National evidence-based clinical care guidelines for type 1 diabetes in children, adolescents and adults

Prepared by the Australasian Paediatric Endocrine Group

and the Australian Diabetes Society

for the Australian Government Department of Health and Ageing

Australasian Paediatric Endocrine Group

Australian Diabetes Society

Disclaimer

This document is a general guide to appropriate practice, to be followed subject to the clinician's judgement and the patient's preference in each individual case. The guidelines are designed to provide information to assist decision-making and are based on the best evidence available at the time of compilation (up to December 2010). They are not meant to be proscriptive. The relevance and appropriateness of the information and recommendations in this document depend on the individual circumstances. Each of the parties involved in developing this document expressly disclaims and accepts no responsibility for any undesirable consequences arising from relying on the information or recommendations contained herein.

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Preface

Type 1 diabetes is an increasingly common condition in Australia. Currently, type 1 diabetes is incurable and there is no known way to prevent it. The condition most commonly develops during childhood and adolescence, but can have its onset at any time in life. Following diagnosis, the demands in managing type 1 diabetes have a major effect on the individual's lifestyle in the short and long term, due to the burden of monitoring the disease, taking insulin safely and controlling blood glucose. As the years proceed, especially during adolescence and into adulthood, diabetes end-organ complications become increasingly common in a person with type 1 diabetes; such complications require specific care. Moreover, pregnancy in women with type 1 diabetes demands careful preconception planning, and management throughout gestation. In essence, type 1 diabetes affects nearly every aspect of life for the person with the condition and for their family.

The management of an individual with type 1 diabetes requires a multidisciplinary health-care network delivering integrated clinical care, using a complex array of health-care tools. Through advances in therapy and technology, the quality of life, morbidity and mortality outcomes in people with type 1 diabetes continue to improve in countries with a well-developed health-care system, such as Australia. Demonstrable progress has been made in recent decades and continues to be made, through personalised intensive patient education and self-care, application of new medicines and technologies, and targeted psychosocial support of the person with type 1 diabetes.

This is the first Australian evidence-based guideline for type 1 diabetes that addresses clinical care across the lifespan. Through the collaborative efforts of the Australasian Paediatric Endocrine Group and the Australian Diabetes Society, on behalf of the Australian Government Department of Health and Ageing, this guideline for health-care professionals and consumers addresses key aspects of clinical care for people with type 1 diabetes. The guideline updates the *Clinical practice guidelines: Type 1 diabetes in children and adolescents* (APEG (Australasian Paediatric Endocrine Group) 2005), and extends the scope of that document to address the needs of adults with type 1 diabetes, including pregnancy.

This national evidence-based guideline provides a comprehensive resource for the health-care professional team in the modern clinical care of people with type 1 diabetes in Australia. It should be used in the context of the health-care needs and circumstance of each individual with diabetes.

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Co-chair (APEG)

Professor Stephen Twigg

Co-chair (ADS)

Executive summary

The *National evidence-based clinical care guidelines for type 1 diabetes in children, adolescents and adults* is the first national evidence-based clinical care guideline for type 1 diabetes across the lifespan. This document was developed by an Expert Advisory Group (EAG) representing specialist societies and organisations, with the active participation of consumer groups and the community.

This Executive summary includes:

- a summary of the recommendations that were developed by the EAG, based on evidence from a systematic review of the relevant question; each recommendation is numbered according to the chapter to which it pertains
- a summary of the practice points that were developed by the EAG through consensus decision-making, where the systematic review found insufficient high-quality data to produce evidence-based recommendations but clinicians require guidance to ensure good clinical practice; as with the recommendations, each practice point is numbered according to the chapter to which it pertains.

Details of the systematic review used in the development of these guidelines are given in the technical report that accompanies this document.

After the public consultation, materials relevant to health professionals and consumers will be developed to accompany these guidelines; these materials will be available online and in print.

Summary of recommendations

No	Recommendation
R3.1	No interventions are recommended for use in clinical practice to delay or prevent the onset of type 1 diabetes (Grade A).
R4.1	Clinicians should be aware that the co-occurrence of psychological disorders in type 1 diabetes is common (Grade A).
R4.2	To minimise the impact of diabetes on cognitive function, every effort should be directed toward achieving glycaemic targets (Grade B).
R6.1	Continuous real-time monitoring may be considered for individuals expected to adhere with therapy, but routine use is not currently recommended (Grade C).
R6.2	Continuous glucose monitoring systems are not recommended for routine use to improve glycaemic control or reduce severe hypoglycaemia, but may be considered for paediatric patients (Grade C).
R7.1	Human insulin or insulin analogues may be used as treatment for glycaemic control (Grade C).
R7.2	Nonsensor-augmented CSII should be considered for use in individuals in whom the expected magnitude of benefit is clinically significant in terms of reducing HbA_{1c}, reducing hypoglycaemia, or improving QoL (Grade C).
R7.3	Metformin should not be used in routine clinical practice for type 1 diabetes (Grade C).
R8.1	Paediatric patients presenting with newly diagnosed type 1 diabetes should be managed in an appropriately resourced ambulatory care or inpatient hospital setting (Grade B).
R9.1	Education and psychological support are an essential component of standard diabetes care. Intensified education and psychological support programs should be considered when treatment goals are not being met (Grade B).
R10.1	Matching of meal-time insulin dose to carbohydrate intake should be considered for patients using multiple daily injection therapy (Grade C).
R10.2	Patients with type 1 diabetes should be educated on low-GI diets (Grade A).
R10.3	Diets high in monounsaturated fats should not be used routinely in patients with type 1 diabetes (Grade C).
R12.1	CAM should not be used to treat type 1 diabetes to target metabolic outcomes (Grade C).
R13.1	Females of childbearing age with type 1 diabetes should be aware of the need for pregnancy planning and receive preconception care (Grade B).
R16.1	Risk factors for severe hypoglycaemia should be identified (Grade B).
R16.2	Acute hypoglycaemia (Grade B) and hyperglycaemia (Grade C) should be minimised to maintain optimal cognitive performance.
R16.3	Structured education specifically targeting prevention of severe hypoglycaemia should be provided (Grade B).
R17.1	Blood ketone measurement should be available as part of a comprehensive sick-day management plan (Grade B).
R18.1	Intensive glycaemic control should be implemented to reduce the risk of onset or progression of microvascular and development of macrovascular diabetes complications (Grade B).
R18.2	ACEI therapy should be used to prevent progression of diabetic nephropathy (Grade B).
R18.3	Statins are recommended for use in adults with type 1 diabetes, to reduce total and LDL cholesterol, and to reduce cardiovascular risk (Grade B).
R20.1	Screening for coeliac disease should occur at diagnosis of type 1 diabetes in children and adolescents; individuals with negative tests at diagnosis should be rescreened (Grade B).
R20.2	At diagnosis of type 1 diabetes, patients should be screened for thyroid dysfunction and tested for antibodies to TPO; screening for thyroid dysfunction should be performed regularly thereafter (Grade B).

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BGAT, blood glucose awareness training; BITES, Brief Intervention in Type 1 diabetes, Education for Self-efficacy; CAM, complementary and alternative medicine; CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; DAFNE, dose adjustment for normal eating; DCCT, Diabetes Complications and Control Trial; DKA, diabetic ketoacidosis; GI, glycaemic index; HbA_{1c}, glycated haemoglobin; IQ, intelligence quotient; LDL, low density lipoprotein; MDI, multiple daily injections; NDSS, National Diabetes Services Scheme; QoL, quality of life; RCT, randomised controlled trial; SMBG, self-monitored blood glucose; TPO, thyroid peroxidase; TSH, thyroid stimulating hormone; VLDL, very low density lipoprotein; β-OHB, beta-hydroxybutyrate

Summary of practice points

No	Practice point
PP3.1	Interventions aimed at delaying or preventing the onset of type 1 diabetes should only be used in a research setting.
PP4.1	Consider the co-occurrence of psychological disorders, including eating disorders, when assessing people with type 1 diabetes and suboptimal glycaemic control, insulin omission or recurrent DKA admissions.
PP4.2	In young people with diabetes, the prevalence of psychological disorders is high compared with rates of end-organ complications.
PP4.3	The diabetes team should assess family functioning (including parental psychopathology) and diabetes-related functioning, including communication, parental involvement and support, roles and responsibilities for self-care behaviours (Delamater 2009).
PP4.4	Validated screening tools for psychological disorders in type 1 diabetes are available (see Chapter 9).
PP4.5	It is important to monitor the school performance of children who developed diabetes before age 5–7 years, and those with a history of significant hypoglycaemic episodes or chronic poor control.
PP4.6	Early age of onset of type 1 diabetes is associated with a minor but statistically significant reduction in population IQ. Therefore, children experiencing significant learning difficulties should be referred for psycho-educational or neuropsychological evaluation. If learning disabilities are present, alternative causes should be sought and remedial interventions to address specific deficits implemented.
PP4.7	In children with type 1 diabetes, assessment of developmental progress in all domains of QoL (i.e. physical, intellectual, academic, emotional and social development) should be conducted on a routine basis.
PP6.1	Continuous real-time monitoring could be considered for use by specialist units, in specific patient populations, such as those with hypoglycaemia unawareness, recurrent severe hypoglycaemia or suspected nocturnal hypoglycaemia. In these situations, use of a hypoglycaemia alarm in a real-time monitoring system may help to treat hypoglycaemia in a timely manner and help to prevent severe episodes of hypoglycaemia.
PP6.2	When combined with CSII therapy, evidence from sensor-augmented CSII studies supports use of real-time monitoring systems for metabolic (HbA_{1c}) benefit when they are used at least 70% of the time.
PP6.3	It is essential that individuals using these systems are provided with education in the correct use of the real-time monitoring device and the correct interpretation of results.
PP6.4	Real-time monitoring systems are expensive and are not currently reimbursed by the NDSS or health insurance funds. Given current constraints, they are most likely to be useful over short periods of time, to aid profile setting and trouble shooting in glycaemic control.
PP6.5	Retrospective CGM systems could be considered for use by specialist units, in specific patient populations such as those with suspected nocturnal hypoglycaemia.
PP6.6	Retrospective CGM systems are not currently reimbursed by the NDSS or health insurance funds. These systems are designed to be used continuously over short periods of time (e.g. 3 days continuously), to aid profile setting and trouble shooting in glycaemic control.

No	Practice point
PP7.1	Basal and rapid-acting insulin analogues may reduce the risk of hypoglycaemia compared to human insulin.
PP7.2	Insulin analogues may be useful in people who have a history of recurrent nocturnal or severe hypoglycaemia.
PP7.3	In some people, basal and rapid-acting insulin analogues may improve an individual's HbA_{1c} level without increasing hypoglycaemia.
PP7.4	Rapid-acting insulin analogues may be useful in people who match bolus insulin doses to carbohydrate intake by counting.
PP7.5	Personal preference and quality of life should be considered when individualising insulin therapy, including analogue therapy versus human insulin.
PP7.6	Individuals who may be likely to benefit from CSII pump therapy, as part of intensive diabetes management, are: • some children and adolescents, including infants and young children, and pregnant adolescents (ideally preconception) • individuals with microvascular complications of diabetes • individuals with reduced hypoglycaemia awareness • individuals (or their supervising adults) with desirable motivational factors; for example, those seeking to improve blood glucose control and having realistic expectations • individuals exhibiting desirable CSII treatment-related behavioural factors, including those who: – are able to perform carbohydrate counting – are currently undertaking four or more blood glucose tests per day – have reliable adult supervision (in paediatrics), and a history of good self-management skills (in adults) – are able to master the technical skills of CSII – are reliable in follow-up health care.
PP7.7	Metformin may be considered in individuals who have a high insulin requirement (e.g. overweight or obese subjects with total daily insulin dose at or above 2.0 IU/kg body weight), although the evidence demonstrates only a modest overall reduction in insulin requirement.
PP7.8	Since metformin may contribute to lactic acidosis development in metabolically unstable patients, it is relatively contraindicated in people who are at high risk of developing diabetic ketoacidosis or have high alcohol consumption.
PP7.9	Metformin is not contra-indicated in individuals with type 1 diabetes and co-existing polycystic ovary syndrome, and may be used to help induce ovulation.
PP7.10	Use of metformin in type 1 diabetes is not approved by the Therapeutic Goods Administration and is an 'off-label' indication in Australia. Prescribers should be aware that long-term adverse effects of metformin include an increased risk of vitamin B-12 deficiency, which should be monitored.
PP8.1	Groups for whom inpatient management is necessary at diagnosis include: • individuals with diabetic ketacidosis, significant comorbidities, inadequate social support or mental health issues • children under 2 years of age • those in geographically remote areas • non-English speakers.
PP8.2	In adults, ambulatory care at diagnosis is considered to be routine unless there are specific issues.
PP8.3	Technological mechanisms to support management can be a component of care for rural and remote patients, but should not replace face-to-face clinical care.
PP9.1	Regardless of whether a tool is used, people with a suspected mental health disorder should be referred for appropriate assessment.

No	Practice point
PP9.2	Consideration should be given to the practicality of using specific tools in clinical practice (self versus interviewer or clinician administered; length; complexity), reference to more general tools or screening already undertaken, resourcing issues and labelling (as per mental health in general).
PP9.3	Diabetes care teams should have appropriate access to mental health professionals to support them in the assessment of psychological functioning in people with type 1 diabetes (NICE 2010).
PP9.4	Assessment of developmental progress in all domains of quality of life (i.e. physical, intellectual, academic, emotional and social development) should be conducted on a routine basis in the clinical setting.
PP9.5	Educational and psychological interventions should be culturally, developmentally and age appropriate.
PP9.6	The multidisciplinary diabetes health-care team should aim to maintain consistent contact with people with diabetes and their families or carers.
PP9.7	The multidisciplinary diabetes team should aim to provide preventive interventions for patients and families (include training parents in effective behaviour-management skills) at key developmental stages, including after diagnosis and before adolescence. These interventions should emphasise appropriate family involvement and support in diabetes management, effective problem-solving and self-management skills, and realistic expectations about glycaemic control (Delamater 2009).
PP9.8	Diabetes care teams should have appropriate access to mental health professionals to support them in the delivery of psychological support (NICE 2010).
PP9.9	Flexible intensive insulin therapy programs, such as DAFNE, aim to provide dietary freedom for people with type 1 diabetes (see Chapter 10).
PP10.1	An individualised insulin to carbohydrate ratio should be used for patients using CSII and may be used in those on multiple daily injection therapy.
PP10.2	Adjusting insulin according to carbohydrate quantity has the potential to improve QoL and increase flexibility in food intake in people with type 1 diabetes. However, regularity in meal routines remains important for optimal glycaemic control.
PP10.3	Advice on carbohydrate quantity and distribution should take into account an individual's energy requirements, previous dietary and eating patterns, activity levels and insulin regimen.
PP10.4	In clinical practice, a number of methods for carbohydrate quantification are commonly taught, including 1 g increments, 10 g carbohydrate portions and 15 g carbohydrate exchanges.
PP10.5	Day-to-day consistency in carbohydrate intake is important for patients who are on fixed insulin regimens.
PP10.6	In type 1 diabetes, GI should not be used in isolation, but should be used with a method of carbohydrate quantification or regulation.
PP10.7	Patients should be advised that to lower the glycaemic impact of the meal, high GI food choices should be combined with low GI food choices.
PP10.8	Where possible, high GI food choices should be substituted with moderate or low GI choices.
PP10.9	Food choices for people with type 1 diabetes should not be made solely on the basis of GI, but should also consider the other nutritional aspects of the food, with a focus on lower fat, higher fibre, nutrient-dense foods.
PP10.10	High-protein/low-carbohydrate diets in children and adolescents may have deleterious effects on growth.
PP10.11	High-protein diets, particularly those based on animal protein or red meat, may lead to progression of diabetic nephropathy. Reducing protein intake or replacing red meat with vegetable or soy protein may help to reduce the progression of nephropathy.

No	Practice point
PP10.12	Restricting carbohydrate intake may affect the nutritional adequacy of the diet and may cause hypoglycaemia if insulin therapy is not adjusted accordingly.
PP10.13	High-protein diets result in ketosis, which may affect blood glucose control and result in dehydration, lethargy and loss of lean body mass.
PP10.14	People with type 1 diabetes should be given advice on fat intake, focusing on reducing saturated and trans fat intake, to reduce the risk of cardiovascular disease.
PP10.15	People with type 1 diabetes should be encouraged to substitute saturated and trans fats with monounsaturated or polyunsaturated fats.
PP10.16	Education on carbohydrate quantification should not encourage people to eat high-fat foods, particularly packaged snacks.
PP10.17	Advice to lower energy intake, specifically total fat intake, should be given to people with type 1 diabetes at risk of overweight or obesity.
PP10.18	Diets high in monounsaturated fats are difficult to adhere to in the context of an Australian diet.
PP12.1	Clinicians should ask patients about CAM in a nonjudgmental way, and document their use.
PP12.2	Patients with type 1 diabetes should be aware that there is a lack of evidence for the effectiveness of CAM. While there is evidence for a low rate of adverse events, the possibility of interaction between CAM and conventional medicines should be considered.
PP12.3	Patients who use CAM should be advised not to cease their insulin because of the high risk of diabetic ketoacidosis.
PP13.1	Counselling on contraception, pregnancy planning and preconception care should start during adolescence in females with type 1 diabetes.
PP13.2	At the time of planning pregnancy, females with type 1 diabetes should be referred to a multidisciplinary diabetes care team with expertise in preconception care. This health care delivery approach is described in detail in the 2005 Australasian Diabetes in Pregnancy Position Statement, which provides guidelines for prepregnancy planning and pregnancy care in women with type 1 diabetes (McElduff et al 2005).
PP13.3	Intensive glycaemic management to optimise the HbA_{1c} level in a safe manner is an essential component of preconception care.
PP13.4	There is an increased risk of neural tube defects in pregnancies in type 1 diabetes, and high-dose folic acid supplementation should be started before conception.
PP13.5	Screening for diabetes complications should occur during preconception care, specifically for diabetic retinopathy and nephropathy.
PP13.6	Preconception care should include review of medications. Statins, ACEI and ARBs are contraindicated in pregnancy.
PP13.7	Glycaemic control should be optimised before starting any assisted reproduction procedures.
PP13.8	Ideally, intensive management to achieve and maintain optimal glycaemic control should commence before conception (see Q31).
PP13.9	Intensive management to achieve and then maintain optimal glycaemic control should occur throughout pregnancy.
PP13.10	Management should be by a multidisciplinary team experienced in the management of diabetes in pregnancy

No	Practice point
PP13.11	The potential benefits of tight glycaemic control should be balanced against the risk of severe hypoglycaemia during pregnancy
PP14.1	The relative risk of unplanned pregnancy should be considered against the potential cardiovascular risk associated with hormonal contraceptives.
PP14.2	Nonhormonal contraception methods with high efficacy and are also generally well tolerated (e.g. IUD methods) can be clinically useful.
PP14.3	Contraceptive preferences will often differ across women of reproductive age; for example, between a teenager with type 1 diabetes and a 40–45-year-old woman.
PP14.4	In a stable long-term relationship, male contraception through vasectomy is an effective nonhormonal permanent contraceptive method for a couple who do not desire further conception.
PP15.1	Transition must never be rushed. Rather, it needs to occur in a purposeful, structured, coordinated manner beginning in early adolescence.
PP15.2	Without a structured transition process, many young people are lost to specialist diabetes care after transfer to an adult service (Nakhla et al 2009). The percentage of young people reported as lost to adult care varies from 11% to 24% (Frank 1996; Pacaud et al 2005).
PP15.3	These young people lost from the system are likely to re-present in early adult life with preventable diabetes-related complications as a result of poor diabetes control. The 'drop out' from specialist diabetes care results in preventable morbidity, a potential reduction in both productivity and life expectancy, and additional long-term costs to the health system (Frank 1996; Nakhla et al 2009).
PP15.4	Greater attention to the cohort of adolescents who are not attending clinic regularly and who have poor glycaemic control may improve transition outcomes. Evidence suggests that these factors are predictors of failure in transition to adult care (Frank 1996; Jacobsen et al 1997; Goyder et al 1999).
PP15.5	The transition program must be aimed at engaging the young person in their care and ensuring they have the appropriate knowledge and skills to make informed health decisions (Viner 2001).
PP15.6	As well as dealing with the medical issues of the young person, education needs to include (McDonagh and Viner 2006): • skills training, including diabetes self-management, self-advocacy, and the ability to independently negotiate services and to actively participate in a medical consultation • education about general adolescent health issues, such as drug taking, alcohol use, and mental and sexual health issues • educational and vocational issues, particularly career, work experience and disclosure.
PP15.7	During the transition process, the focus should progressively switch from the parent as the care giver to acknowledging the growing autonomy of the young person.
PP15.8	Successful transition requires an interested and capable adult diabetes service (public or private) and a willingness by the adult health professionals to participate in the transition process.
PP15.9	Both paediatric and adult teams need to be responsive to the needs of young people if transition is to be successful.
PP15.10	The manner in which the young person is prepared for transition to the adult health-care system is crucial to their continued wellbeing and adherence to ongoing health support and treatment.
PP16.1	Minimising occurrence of severe hypoglycaemia is an important target in type 1 diabetes care, including in intensive diabetes management.
PP16.2	Specific management strategies should be implemented for people who have a high risk of severe hypoglycaemia, including those with a history of severe hypoglycaemia or a reduced ability to detect early warning symptoms of hypoglycaemia (i.e. hypoglycaemia unawareness). In cases of hypoglycaemia unawareness, strategies to reduce severe hypoglycaemia include more frequent SMBG, and making sure that any blood glucose below a certain threshold (e.g. <4 mmol/L) is treated as hypoglycaemia, even in the absence of hypoglycaemia symptoms.

No	Practice point
PP16.3	Intensive diabetes management may increase the risk of severe hypoglycaemia; therefore, some people who have a high risk of severe hypoglycaemia may not be suitable for low HbA_{1c} targets. .
PP16.4	Certain risk factors that are known to increase severe hypoglycaemia risk include alcohol abuse and recreational drug abuse, and these should also be addressed in people with type 1 diabetes.
PP16.5	A medical practitioner should carefully assess whether a person with type 1 diabetes is fit to drive a motor vehicle, this is required, in particular, to help reduce the risk of motor vehicle crashes due to severe hypoglycaemia. The AustRoads *Assessing fitness to drive* booklet, should be used as a reference.
PP16.6	Adverse cognitive effects of acute severe hypoglycaemia and acute severe hyperglycaemia should be avoided during tasks requiring high level cognitive function, such as in school, college or university examinations; or in adolescents and adults during potentially dangerous activities involving occupational health, such as operating heavy machinery or during driving. In some cases, the risk or presence of acute severe changes in blood glucose to very low and possibly very high levels may lead to the need for exemption from or avoidance of the cognitively demanding or high-risk activity.
PP16.7	Mild hypoglycaemia and mild hyperglycaemia are common in type 1 diabetes; however, acute severe dysregulation of blood glucose to either extreme that may cause cognitive effects should be avoidable in most people with type 1 diabetes, if due self care is taken.
PP16.8	The blood glucose level at which a person develops cognitive effects from severe hypoglycaemia can vary, related to the degree of chronic glycaemia control and avoidance of severe hypoglycaemia if an episode has occurred during recent weeks to months. In such cases, early warning symptoms of hypoglycaemia that may have been lacking in a person with type 1 diabetes may at least partially return.
PP16.9	Developmentally appropriate structured education programs, such as 'self-study material' video programs and BGAT, can be used to help to reduce rates of severe hypoglycaemia.
PP16.10	Some programs, such as BGAT, can be delivered as individual or group programs.
PP16.11	Where resource constraints apply, structured education should be offered preferentially to individuals at highest risk of and from severe hypoglycaemia; for example, those with a history of recurrent severe hypoglycaemia, and adults who are motor vehicle drivers.
PP16.12	Research into modified programs to prevent severe hypoglycaemia that may require less resource and time input needs to be undertaken. Such research needs documented outcomes, including assessment of optimal time intervals for people to undertake refresher courses.
PP17.1	Blood ketone measurement is strongly preferred, because it gives a more timely result. However, where blood ketone measurement is not available, urine ketone measurement is the alternative test as part of a comprehensive sick-day management plan.
PP17.2	Blood ketone measurement is strongly recommended in people with type 1 diabetes on CSII.
PP17.3	Blood β-OHB monitoring may be especially useful in very young children or when urine specimens are difficult to obtain.
PP17.4	A comprehensive sick-day management plan should include written guidelines and 24-hour access to clinical advice.
PP17.5	The sick-day management plan should be regularly reviewed by the patient and diabetes health-care professional.
PP17.6	Comprehensive sick-day guidelines are available for people with diabetes and their families (ADEA 2006; Ambler and Cameron 2010) and health-care professionals (Brink et al 2009).

No	Practice point
PP18.1	Intensive glycaemic control refers to an implemented strategy of intensive glycaemic management and is only achieved by a 'package' of methods, including MDI or CSII, frequent insulin dose adjustment, blood glucose level monitoring at least four times per day, weekly measurement of 3 am blood glucose levels, formal diabetes education, medical nutrition therapy and physical activity advice.
PP18.2	The generalisability of implementing an intensive glycaemic control strategy may be limited by the strict inclusion criteria in the clinical trials undertaken. The potential benefit of a strategy of intensive glycaemic control needs to be individualised as much as is practical for each person with type 1 diabetes.
PP18.3	Observational data from the DCCT suggest that the greatest absolute benefit from an intensive management approach will be seen in those with higher HbA_{1c} levels if such improved HbA_{1c} levels can be achieved and sustained.
PP18.4	Transient worsening of some diabetes complications, particularly diabetic retinopathy, can occur some months after commencement of intensive glycaemic management, and clinicians should monitor for and manage these complications. Ophthalmologic monitoring before initiation of intensive treatment and at 3-month intervals for 6–12 months thereafter seems appropriate for such patients. In patients whose retinopathy is already approaching the high-risk stage, it may be prudent to delay the initiation of intensive treatment until photocoagulation can be completed, particularly if the HbA_{1c} is high.
PP18.5	A strategy of intensive glycaemic control maintained for some 6–7 years leads to persistent microvascular benefits and new macrovascular benefits 10 years later (so-called 'metabolic memory'); this emphasises the importance of tight glycaemic control relatively early in the disease course to achieve sustained outcomes in minimising long-term complications of diabetes.
PP18.6	While intensive glycaemic control to reduce long-term end-organ diabetes complications is readily justified at a health economics level, it needs to be adequately resourced and appropriately targeted for the benefits observed in the RCTs to be achieved.
PP18.7	For patients who are intolerant of ACEI, ARBs can be used as an alternative treatment for the secondary prevention of nephropathy.
PP18.8	On the basis of the systematic evidence, including data in adolescents (Cook et al 1990), ACEI in type 1 diabetes can control albuminuria in normotensive microalbuminuria; however, there are currently restrictions from the Therapeutic Goods Administration to be considered in their use in this setting of normotension.
PP18.9	Tight control of blood pressure is of critical importance in limiting the progression of retinopathy and nephropathy. The general blood pressure target is <130/80 mmHg and <125/75 mmHg in the presence of 1 g daily or more of proteinuria.
PP18.10	ACEI and ARBs are contraindicated in pregnancy.
PP18.11	A small study has raised concerns that oral contraceptive use in women with type 1 diabetes may limit the efficacy of ACEI and ARB and contribute to macroalbuminuria (Ahmed et al 2005). Large prospective studies are required to further investigate this relationship.
PP18.12	As global macrovascular risk in type 1 diabetes is high in adults, statins should be commenced early in the disease course, at relatively low levels of dyslipidaemia, and before the development of cardiovascular disease.
PP18.13	Statin therapy can be used after Tanner stage II in boys and after menarche in females. In high-risk vascular disease states (e.g. hereditary LDL receptor deficiency), statins may be indicated from the age of 8 years.
PP18.14	Statin therapy is contraindicated in pregnancy, and reliable contraceptive methods should be used in females of reproductive age who are on statin treatment.

No	Practice point
PP18.15	The benefit of statin therapy in people with end-stage renal failure (including in those with type 1 diabetes) has not been confirmed; however, it is prudent to use low-dose statin treatment in this group, which is at particularly high risk of cardiovascular disease.
PP20.1	All adults with newly diagnosed type 1 diabetes should be screened for coeliac disease at diagnosis.
PP20.2	All adults with type 1 diabetes who have not been previously screened should be screened for coeliac disease.
PP20.3	Children and adolescents should be rescreened for coeliac disease at least once in the first 5 years after diagnosis.
PP20.4	Tests for TSH should be repeated at least yearly in those with anti-thyroid antibodies at diagnosis.
PP20.5	Tests for TSH should be repeated at least 2-yearly in all other patients with type 1 diabetes.
PP20.6	Women planning pregnancy should have a test for TSH preconception and in the first trimester.
PP20.7	Women who are TPO positive should be tested postpartum for thyroid dysfunction.

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BGAT, blood glucose awareness training; BITES, Brief Intervention in Type 1 diabetes, Education for Self-efficacy; CAM, complementary and alternative medicine; CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; DAFNE, dose adjustment for normal eating; DCCT, Diabetes Complications and Control Trial; DKA, diabetic ketoacidosis; GI, glycaemic index; HbA_{1c}, glycated haemoglobin; IQ, intelligence quotient; LDL, low density lipoprotein; MDI, multiple daily injections; NDSS, National Diabetes Services Scheme; QoL, quality of life; RCT, randomised controlled trial; SMBG, self-monitored blood glucose; TPO, thyroid peroxidase; TSH, thyroid stimulating hormone; VLDL, very low density lipoprotein; β-OHB, beta-hydroxybutyrate

1 Introduction

1.1 Development of the guidelines

The *Clinical practice guidelines: Type 1 diabetes in children and adolescents* (APEG (Australasian Paediatric Endocrine Group) 2005) were endorsed by the National Health and Medical Research Council (NHMRC) in 2005. The guidelines were aimed at health-care professionals involved in the care of children and adolescents with type 1 diabetes. Although the document included transition to adult care, it did not address the needs of adults with type 1 diabetes. Also, that document was developed at a time when management and technologies were less well-developed than they are today. Thus, revision of the 2005 guidelines was needed because of:

- evolving technologies, including continuous subcutaneous insulin infusion (CSII) and continuous glucose monitoring (CGM) systems (Bergenstal et al 2010; Misso et al 2010)
- greater use of insulin analogues and multiple daily injection (MDI) regimens (Singh et al 2009)
- changes to medical nutrition therapy including increased use of flexible insulin dose adjustment for carbohydrate quantity (Thomas and Elliott 2009)
- increasing evidence base for the importance of blood glucose control for the prevention of macrovascular disease and long-term complications (Nathan et al 2005)
- greater awareness of psychosocial aspects of type 1 diabetes (Northam et al 2010).

In addition, there were no national evidence-based guidelines for management of adults with type 1 diabetes. Therefore, the Australasian Paediatric Endocrine Group (APEG) and the Australian Diabetes Society (ADS), on behalf of the Australian Government Department of Health and Ageing (DoHA), agreed to update the existing guideline, and extend the scope to include adults with type 1 diabetes, including pregnancy.

1.2 Governance structure

A multilevel management structure was established to coordinate the development of the type 1 diabetes guidelines. The structure consists of:

- an executive consisting of co-chairs from APEG and ADS, and executive members responsible for the overall development and governance of the entire project
- an Expert Advisory Group (EAG) responsible for clinical oversight of the guidelines, including appraisal of evidence
- project officers responsible for systematic reviews of the literature
- expert methodological consultants, as required by the NHMRC, to provide advice and mentoring to the systematic reviewers and the EAG; and to ensure that the development process and the guidelines produced comply with NHMRC requirements
- a medical and technical editor.

DoHA provided project funding, while project management was performed by the co-chairs. Appendix A provides details of the membership of the executive and EAG involved in governance. Details of how the guidelines will be implemented and updated are provided in Chapter 22.

1.3 Structure of the document and related materials

1.3.1 The document

The guidelines developers produced recommendations and practice points, as follows:

- *recommendations* – based on evidence from the systematic reviews
- *practice points* – based on consensus decision-making, where the systematic review found insufficient high-quality data to produce evidence-based recommendations, but clinicians require guidance to ensure good clinical practice.

The recommendations and practice points are given in the relevant sections of Chapters 3–20, and summarised in the Executive summary.

The remainder of the document includes:

- an outline of the methods used to develop the clinical research questions, undertake a systematic review of the literature, and develop recommendations and practice points (Chapter 2)
- clinical practice guidance, setting out the main findings of the systematic review and other considerations documented by the EAG; these chapters also give recommendations and practice points, as appropriate (Chapters 3–20)
- recommendations for further research (Chapter 21)
- information on implementing, evaluating and maintaining the guidelines (Chapter 22).

The document also includes appendixes that provide information on membership of the Expert Advisory Group (the governance body for guideline development), a process report, evidence matrixes and useful resources for health professionals and people with type 1 diabetes. Finally, the document contains a list of abbreviations and acronyms, and a list of references.

1.3.2 Related materials

After the public consultation, materials relevant to health professionals and health consumers will be developed to accompany these guidelines; these materials will be available online and in print.

The technical report that underpins this document is also available online. This includes background information and the results of the systematic review pertaining to the clinical questions posed within this guideline, including results of the literature searches, study quality appraisal, NHMRC evidence statement forms and evidence summaries for the individual studies.

2 Methods

The development of evidence-based clinical practice guidelines that meet National Health and Medical Research Council (NHMRC) standards involves developing a set of clinical research questions, systematically reviewing the scientific literature for evidence related to those questions, and then developing and grading recommendations based on a structured assessment of the evidence (NHMRC 1999; NHMRC 2009). The methods used in applying this process to the development of these guidelines are outlined below. A summary of the overall process of guideline development is given in Appendix B (Process report).

2.1 Clinical research questions – development and details

Between July 2009 and March 2010, the clinical research questions were developed, prioritised, combined and refined by the Expert Advisory Group (EAG) and project officers, in consultation expert methodological consultants (Appendix A). The process resulted in different types of questions, as shown in Table 2.1.

Table 2.1 Details of question types

Question type[a]	Answered based on	Uses
Interventional	Systematic review	Used to develop: • recommendations • practice points
Diagnostic accuracy	Systematic review	Used to develop: • recommendations • practice points
Prognostic	Systematic review	Used to develop: • recommendations • practice points
Aetiological	Systematic review	Used to develop: • recommendations • practice points
Background	Background material	Used to: • capture information considered to be outside the scope of the systematic review questions • provide general information for the guidelines.

[a] See Section 2.3 for explanation of question types

The systematic and background questions were developed by the EAG, with the aim of answering clinically relevant areas of uncertainty; however, it was recognised that, in some areas, there would be little or no high-quality published evidence. Such questions were classified as 'background' and systematic reviews were not undertaken. Details of research question criteria are presented in the technical report that accompanies this document.

2.2 Review and research

2.2.1 Systematic review process

Systematic reviews were undertaken with the aim of answering high-priority questions relevant to the care of individuals with type 1 diabetes. To answer these questions, a broad

search strategy was designed, as detailed in the accompanying technical report. Searches were conducted in relevant electronic databases, bibliographies of studies identified as relevant and literature recommended by expert members of the EAG. The systematic review included only data from studies that met the prespecified inclusion criteria, were of adequate quality and were published before December 2010. Identification of relevant evidence and assessment of evidence was conducted in accordance with NHMRC standards and procedures for externally developed guidelines (NHMRC 2007).

2.2.2 Background material

Material relevant to background questions was gathered by the project officers under the supervision of the EAG members. Sources included medical textbooks, published scientific and review articles, and other relevant medical literature; however, systematic review processes were not applied. The questions researched in this manner are listed in the accompanying technical report and noted below each question throughout the guideline.

2.3 Development of evidence statements, recommendations and practice points

For each research question addressed by the systematic review, the body of evidence was consolidated into evidence statements and rated according to the evidence matrix shown in Table 2.2. The matrix considers five domains: evidence base, consistency, clinical impact, generalisability and applicability. For included studies, the first two components were derived directly from the literature identified for each research question; for assessment of the last three components (clinical impact, generalisability and applicability) guidance was provided by the EAG. To ensure that guidelines were based on the best available evidence, studies of higher levels of evidence (i.e. Levels I or II) were included in preference to those presenting lower levels (i.e. Levels III or IV) of evidence. This minimises the potential for bias in the evidence base for each systematically reviewed question. However, lower level studies were reviewed where evidence for any of the primary outcomes was not available in higher level studies.

Table 2.2 Body of evidence matrix

Component	A	B	C	D
	Excellent	**Good**	**Satisfactory**	**Poor**
Evidence base	Several Level I or II studies with low risk of bias	One or two Level II studies with low risk of bias or a systematic review/multiple Level III studies with low risk of bias	Level III studies with low risk of bias, or Level I or II studies with moderate risk of bias	Level IV studies, or Level I to III studies with high risk of bias
Consistency	All studies consistent	Most studies consistent and any inconsistency can be explained	Some inconsistency reflecting genuine uncertainty around a clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	Population/s studied in the body of evidence are the same as the target population for the guideline	Population/s studied in the body of evidence are similar to the target population for the guideline	Population/s studied in the body of evidence are different to the target population but it is clinically sensible to apply this evidence to the target population for the guideline	Population/s studied in the body of evidence are different to the target population and it is hard to judge whether it is sensible to generalise to the target population for the guideline
Applicability	Directly applicable to the Australian health-care context	Applicable to the Australian health-care context with a few caveats	Probably applicable to the Australian health-care context with some caveats	Not applicable to the Australian health-care context

Source: NHMRC (2009)

Evidence statements were only transformed into 'action-oriented' recommendations where:

- the body of evidence was sufficient; that is, wherever the evidence yielded support for recommendations of at least NHMRC grade C (see Table 2.3)
- the question type was interventional (i.e. it evaluated the effectiveness of an intervention).

The recommendations were carefully worded to reflect the strength of the body of evidence.

Table 2.3 Definitions of NHMRC grades for recommendations

Grade	Definition
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendations must be applied with caution

Source: NHMRC (2009)

Where there was insufficient quality or quantity of evidence, it was not possible to develop evidence-based recommendations. In this situation the EAG used an expert consensus-based process to develop practice points to guide clinical practice.

For prognostic and aetiological questions, the evidence base only provided an indication of the risk associated with a particular factor; thus, it was not possible to make an evidence-based recommendation for a change in practice. Instead, the EAG again used a consensus-based process to develop practice points to guide practice.

For background questions where a systematic review had not been undertaken, practice tips were developed to guide practice, as appropriate.

2.4 Description of public consultation

Public consultation was conducted from Monday 7 February to Friday 10 March 2011, during which time the draft guidelines were available on the websites of the Australian Paediatric Endocrine Group (APEG) and Australian Diabetes Society (ADS). Notification was posted in The Australian national newspaper, and a range of stakeholders, committees, working groups and interested people were invited to provide submissions. An electronic feedback form was provided to facilitate submissions.

3 Natural history

3.1 Introduction

The typical clinical course of type 1 diabetes includes a preclinical phase, presentation of diabetes (at which time patients are usually symptomatic of hyperglycaemia), a partial remission or honeymoon phase, and a continuing requirement for insulin therapy (Haller et al 2005). In the absence of insulin therapy, patients with type 1 diabetes will eventually progress to metabolic decompensation and life-threatening diabetic ketoacidosis (DKA) (Balasubramanyam et al 2008). Over the course of time, acute and chronic complications of diabetes occur in most people with type 1 diabetes. On average, the lifespan of people with type 1 diabetes is shorter than that of the general population (Secrest et al 2010a), although there has been improvement across recent decades (Nishmura et al 2001).

3.2 Epidemiology

In most western countries, type 1 diabetes accounts for more than 90% of childhood and adolescent diabetes, although less than half of people with type 1 diabetes are diagnosed before the age of 15 years (Craig et al 2009a). Type 1 diabetes incidence varies greatly between different countries, within countries and between different ethnic populations. Mean annual incidence rates for childhood type 1 diabetes (0–14 years age group) across the world have varied from fewer than 1 per 100 000 patient years to more than 60 per 100 000 patient years in recent decades (Anonymous 2006; Harjutsalo et al 2008; Patterson et al 2009). In Australia, the incidence of childhood diabetes is approximately 22 per 100 000 patient years, with an average increase of 2.8% per year from 2000 to 2006 (Catanzariti et al 2009). The rising incidence of type 1 diabetes is associated with an increased proportion of people with low-risk human leukocyte antigen (HLA) genotypes in Australia (Fourlanos et al 2008). The incidence of type 1 diabetes among indigenous Australian children is similar to that of Caucasian children (Craig et al 2007).

3.3 Preclinical diabetes

In the months or years before clinical presentation of type 1 diabetes, one or more autoantibodies can be detected as markers of β-cell autoimmunity. These include insulin autoantibodies (IAA), glutamic acid decarboxylase (GAD), the insulinoma-associated 2 molecule (IA-2) and zinc transporter 8 (ZnT-8). It is clear from prospective studies of prediabetes that islet autoimmunity can be transient; however, the presence of persistently raised levels of one or more islet antibodies confers an increased and incremental risk of progression to type 1 diabetes (Orban et al 2009).

Genetic risk markers can further assist in quantifying risk of progression to type 1 diabetes. More than 40 type 1 diabetes susceptibility alleles have been identified (Barrett et al 2009); of these, 10 genes can be singled out as strong causal candidates, and there is significant evidence for linkage with the HLA region on chromosome 6p21.3 (LOD score 213.2) (Concannon et al 2009). HLA alleles that confer an increased risk of type 1 diabetes include HLA DRB1 03-DQA1*0501-DQB1* 0201 and HLA DRB1 04-DQA1*0301-DQB1* 0302, while alleles that confer protection include HLA DR02-DQA1*0102-DQB1* 0602. In the absence of such a protective allele, an individual aged under 45 years has a 25–50% 5-year risk of type 1 diabetes in the presence of two or more islet antibodies (Orban et al 2009).

Genetic testing alone cannot be used to predict development of type 1 diabetes, particularly given that the relative frequency of high-risk HLA class II genotypes in Australian children with type 1 diabetes has decreased in recent decades (Fourlanos et al 2008). It is currently accepted that most cases of type 1 diabetes result from an interplay between genetic predisposition or environmental factors; however, the environmental triggers (viral, dietary or chemical) that initiate pancreatic β-cell destruction remain largely unknown. Enterovirus infection has been associated with development of diabetes-associated autoantibodies in some populations (Stene et al 2010; Oikarinen et al 2011; Yeung et al 2011), and enteroviruses have been detected in the islets of people with type 1 diabetes (Richardson et al 2009). Early introduction of cow's milk protein (Knip et al 2010) and weight gain in early life (Couper et al 2009) are also putative triggers for autoimmunity and type 1 diabetes. In the absence of a proven intervention to prevent progression to type 1 diabetes (see Section 3.7 below), screening or intervention in the preclinical phase should be confined to defined clinical studies.

3.4 Interventions to delay or prevent the onset of type 1 diabetes

Question 1

What interventions delay or prevent the onset of type 1 diabetes?

The detailed systematic review of this question is in Chapter 1 of the accompanying technical report, and the evidence matrix is in Section C1 of Appendix C

The aim of intervention before type 1 diabetes onset is to prevent (primary prevention) or arrest (secondary prevention) immune-mediated β-cell destruction, thereby preventing or delaying clinical disease. It is essential to identify people at risk of type 1 diabetes for such interventions. The number of positive autoantibodies is highly predictive of type 1 diabetes (Orban et al 2009). In the presence of impaired first-phase insulin response (FPIR) to intravenous (IV) glucose, and islet autoantibodies, the projected 5-year risk of type 1 diabetes is greater than 50%; even among people with a normal FPIR, the 5-year risk of type 1 diabetes is greater than 25% (Skyler 2008).

Most intervention studies have targeted either islet autoantibody-positive first-degree relatives, or infants born with a first degree relative with type 1 diabetes and/or high -risk HLA type, because of their increased risk of type 1 diabetes compared with the general population. Multicentre randomised controlled trials (RCTs) using nicotinamide, parenteral insulin, oral insulin or intranasal insulin, and the elimination of cow's milk protein from infant feeding have been undertaken in recent years, with the aim of preventing type 1 diabetes. The outcomes of these studies are summarised below.

3.4.1 Insulin

Five RCTs examined progression to type 1 diabetes incidence among autoantibody-positive first-degree relatives after exposure to intranasal, oral, IV or subcutaneous (SC) plus IV insulin (Fuchtenbusch et al 1998; Diabetes Prevention Trial – Type 1 Diabetes Study Group 2002; Harrison et al 2004; Skyler et al 2005; Nanto-Salonen et al 2008). Two of these studies were pilot studies (Fuchtenbusch et al 1998; Harrison et al 2004); the Australian pilot (Harrison et al 2004) was not designed to answer the clinical question asked here. Only one study found a delayed time to development of diabetes (5 years vs 2.3 years, $p<0.03$), but diabetes incidence was not reported, and the study was underpowered to detect a reduction in diabetes risk from 80% to 30% (Fuchtenbusch et al 1998). In a post-hoc analysis of the Diabetes Prevention Trial 1 (DPT-1), of the participants in the oral insulin study with IAA of at least 80 nU/mL (n=263), the proportion who developed diabetes was 6.2% per year in the oral insulin group and 10.4% per year in the placebo group (hazard ratio [HR] 0.57,

95% confidence interval [CI]: 0.36 to 0.89, p=0.015) (Skyler et al 2005). The estimated delay in developing diabetes was 4.5 years. On the basis of this analysis, another large oral insulin prevention study is currently being conducted by the Type 1 Diabetes TrialNet, in relatives with characteristics similar to those of the DPT-1 subgroup (Type 1 Diabetes TrialNet 2010).

3.4.2 Nicotinamide

Four studies have examined the effects of nicotinamide on the development of type 1 diabetes (Lampeter et al 1998; Gale et al 2004; Cabrera-Rode et al 2006; Olmos et al 2006). Three found no difference between treatment and placebo groups, while in the study of 24 participants from Chile (Olmos et al 2006), the 60-month cumulative probability of staying diabetes free was 100% in the nicotinamide group and 62.5% (95%CI: 17 to 100) in the placebo group (p=0.0483). However, this study did not have development of diabetes as an a priori outcome measure. There is currently insufficient evidence to support the use of nicotinamide for the prevention of type 1 diabetes.

3.4.3 Day-care exposure

A systematic review of case–control studies tested the hypothesis that increased early contact with infectious agents, measured by day-care exposure, would decrease the risk of type 1 diabetes in childhood (Kaila and Taback 2001). Day-care exposure appeared to have a protective effect in the subgroup of children diagnosed with type 1 diabetes before the age of 5 years (OR 0.6, 95%CI: 0.5 to 0.8). However, this result was based on only two studies, and the degree of heterogeneity between the other primary studies examined in the review was too high to allow reliable summary results overall.

3.4.4 Vitamin D

The active form of vitamin D – 1,25-dihydroxycholecalciferol – regulates the expression of more than 200 genes, including those related to apoptosis and immune modulation. The gene that encodes 1α hydroxylase, the enzyme that converts 25-hydroxyvitamin D3 (25OHD) to its metabolically active form (1,25 OHD), is a recently described type 1 diabetes susceptibility gene (Bailey et al 2007). It has been suggested that changes in vitamin D intake during recent decades have contributed to the recent trends in the increased incidence of type 1 diabetes. A systematic review of observational studies examined whether vitamin D supplementation in infancy reduced the risk of type 1 diabetes in later life (Zipitis and Akobeng 2008). Meta-analysis of data from the case–control studies showed that the risk of type 1 diabetes was significantly reduced in infants who were supplemented with vitamin D compared to those who were not supplemented (pooled OR 0.71, 95%CI: 0.60 to 0.84). There was also some evidence of a dose–response effect, with those using larger amounts of vitamin D being at lower risk of developing type 1 diabetes. However, the high level of bias in these studies limits the applicability of the results.

3.4.5 Summary

No trial has successfully demonstrated prevention of type 1 diabetes. There is some evidence from post-hoc analysis of DPT-1 that oral insulin may slow progression from pre-type 1 to type 1 diabetes in patients with high-titre IAA. This is currently being addressed by an oral insulin trial (Type 1 Diabetes TrialNet 2010). Several other prevention trials are also underway. INIT-II is an Australian multicentre double-blind, placebo-controlled RCT of intranasal insulin in children and young adults at risk of type 1 diabetes. The Trial to prevent type 1 diabetes in the Genetically at Risk (TRIGR) is an international multicentre trial (including Australia) that aims to establish whether weaning to a highly hydrolysed formula in infancy subsequently reduces the risk of type 1 diabetes in 'at-risk' children (Akerblom

2010). The results of the pilot trial for TRIGR, conducted in Finland, showed that intervention with a hydrolysed formula during infancy halved the risk of development of one or more islet autoantibodies (HR 0.51, 95%CI: 0.28 to 0.91) (Knip et al 2010). However, whether hydrolysed formula or other interventions can prevent progression to type 1 diabetes (as opposed to islet autoimmunity) is presently unknown.

Evidence statement	
Q1	There is no evidence to support the use of any intervention to delay or prevent the onset of type 1 diabetes.
Recommendation	
R3.1	No interventions are recommended for use in clinical practice to delay or prevent the onset of type 1 diabetes (Grade A).
Practice point	
PP3.1	Interventions aimed at delaying or preventing the onset of type 1 diabetes should only be used in a research setting.

3.5 Presentation of diabetes

Clinical presentation at diagnosis can vary widely in people with type 1 diabetes, and age at presentation is an important factor influencing presentation. At one extreme are those presenting with severe DKA who require hospitalisation, intensive rehydration and IV insulin infusion. At the other extreme are those without symptoms of hyperglycaemia, who may be detected incidentally.

There are certain clinical scenarios in which the diagnosis of type 1 diabetes may be delayed, particularly in children:

- very young children may present with severe DKA because of a more rapid onset of severe insulin deficiency, and because the symptoms of polyuria and polydipsia may not be apparent to the parent or clinician
- hyperventilation of ketoacidosis may be misdiagnosed as pneumonia or asthma (cough and breathlessness distinguish these conditions from DKA)
- abdominal pain associated with ketoacidosis may simulate an 'acute abdomen' and lead to referral to a surgeon
- vomiting may be misdiagnosed as gastroenteritis or sepsis
- polyuria and enuresis may be misdiagnosed as a urinary tract infection
- polydipsia may be thought to be psychogenic.

Delayed diagnosis of type 1 diabetes in a child is associated with an increased risk of DKA (Craig et al 2009b).

At the other end of the clinical presentation spectrum, milder degrees of metabolic decompensation can make it difficult to differentiate type 1 from type 2 and other forms of diabetes. In such cases, the absence or presence of signs of insulin resistance will help to clarify the diagnosis; such signs include acanthosis nigrans and overweight or obesity, family

history of type 1 or type 2 diabetes, investigations for the detection of islet cell antibodies, and clinical course after diagnosis (Leslie et al 2008).

3.6 Acute complications

Acute complications of diabetes occur to some degree in most people with type 1 diabetes. The complication most feared by people with type 1 diabetes is hypoglycaemia (Anderbro et al 2010; Barnard et al 2010), which is addressed in Chapter 16. Mild hypoglycaemia occurs about twice a week on average in those on an intensive insulin regimen and with a glycated haemoglobin (HbA_{1c}) level of about 7% (DCCT Research Group 1993). Severe hypoglycaemia (in which a person requires assistance from someone else to deal with their episodes of hypoglycaemia) is much less common, occurring, on average about once every 5 patient years (DCCT Research Group 1993; Jones and Davis 2003; Cryer et al 2009). However, episodes of severe hypoglycaemia tend to be more frequent in certain people (Cryer 2010; Ly et al 2011), particularly those with :

- a history of severe hypoglycaemia (especially over recent months)
- reduced hypoglycaemia awareness
- a lower HbA_{1c} level
- longer duration of diabetes.

3.4.1 Reduced hypoglycaemia awareness

A major challenge in care of people with type 1 diabetes is reduced hypoglycaemia awareness, where symptoms of hypoglycaemia change and usually become more subtle. This change is associated with the development of autonomic neuropathy, and a reduction in the counter-regulatory response to hypoglycaemia (Ly et al 2011). The condition becomes more common over time, especially after 10 or more years of the disease (Cryer 2010). Some series indicate about 25% prevalence of reduced symptomatic awareness in people with type 1 diabetes, including both children and adults (Jones and Davis 2003; Smith et al 2009) Reduced hypoglycaemia awareness requires increased vigilance in blood glucose monitoring and self care to prevent severe hypoglycaemia. In some people, reduced hypoglycaemia awareness may improve with avoidance of hypoglycaemia (Ly et al 2011); this topic is addressed in Chapter 16.

3.4.2 Diabetic ketoacidosis

DKA is another acute complication of type 1 diabetes. It occurs when insulin delivery is insufficient to prevent progressive hyperglycaemia and ketone body formation. Like hypoglycaemia, DKA can occur in anyone with type 1 diabetes, but is more common when there is a precipitant (e.g. infection of the gastrointestinal or respiratory or urinary tract). DKA also occurs more frequently in people with a past history of DKA, or who adhere suboptimally to self-administration of insulin or care of their diabetes (Skinner 2002).

Chapter 17 (on acute complications of diabetes) notes that aiding self-care, adherence to therapy and 'sick day' management can prevent many cases of threatened or mild DKA from worsening and requiring hospitalisation.

3.7 Chronic complications

As with acute complications in type 1 diabetes, chronic complications vary among people and over time in the same person – from subclinical and mild, to end-stage complications. Type 1 diabetes causes both microvascular complications (e.g. retinopathy, nephropathy and

neuropathy) and macrovascular complications (e.g. coronary artery disease, peripheral arterial disease and stroke).

3.7.1 Microvascular complications

The development and progression of microvascular complications of diabetes depend strongly on the duration of diabetes (Brink 2001), and on genetic susceptibility, especially in relation to diabetic retinopathy and nephropathy (Ayodele et al 2004; Wiltshire et al 2008; Wang et al 2010). Nonproliferative diabetic retinopathy eventually occurs in most people with type 1 diabetes (Roy et al 2004; Melendez-Ramirez et al 2010), whereas vision-threatening proliferative retinopathy or maculopathy occurs in a minority (Roy et al 2004). Subclinical diabetic nephropathy as microalbuminuria occurs in up to 20% of children and adolescents with type 1 diabetes (Mohsin et al 2005; Bogdanovic 2008), and in up to 50% of adults after about 20 or more years of diabetes (Nathan et al 2005). In addition, after 20 years of diabetes, overt nephropathy with macroalbuminuria and proteinuria with reduced glomerular filtration occurs in about 20%, and about one-fifth of these patients progress to end-stage renal disease (Ayodele et al 2004). Diabetic peripheral neuropathy occurs to some degree in up to 50% of those with type 1 diabetes (Mohsin et al 2005); in a minority of people, it leads to some form of amputation. Autonomic neuropathy (AN), especially cardiac autonomic neuropathy (Rolim et al 2008), is under-recognised; AN contributes to diabetic gastroparesis (Chang et al), cardiovascular disease (Rolim et al 2008) and erectile dysfunction in men (Vinik et al 2003).

3.7.2 Macrovascular complications

Cardiovascular disease – a macrovascular complication – is the main cause of premature death in people with type 1 diabetes of 20 or more years' duration (Secrest et al 2010a). Other macrovascular complications are cerebrovascular and peripheral vascular disease. Some recent data also suggest that the rate of death from type 1 diabetes may be decreasing, compared with previous decades (Nishmura et al 2001; Secrest et al 2010a); this is likely to be associated with more intensive management of risk factors for diabetic nephropathy and cardiovascular disease (Secrest et al 2010a). Macrovascular and microvascular complications of diabetes are each addressed in Chapter 18.

3.7.3 Weight

A significant subgroup of people with type 1 diabetes is or becomes overweight or obese. This reflects the increased prevalence of overweight and obesity in the general population, and some data suggest that over-treatment of type 1 diabetes may exacerbate overweight, obesity and insulin resistance. Recent Australian and international studies indicate that the clinical combination of type 1 diabetes and the condition known as 'metabolic syndrome' portends a worse prognosis than type 1 diabetes alone (Pambianco et al 2007; McGill et al 2008).

3.8 Prevention of complications

Clinical trial data indicate that intensive control of blood glucose can slow the natural history of microvascular complications (DCCT Research Group 1993) and – to some extent – macrovascular complications of diabetes (Nathan et al 2009). However, intensive blood glucose control needs to be balanced against the concerns of inducing hypoglycaemia (especially severe episodes), and maintaining quality of life and psychological wellbeing. The management sections of this document (Chapters 6 and 16) focus on individualising care in a person with type 1 diabetes to achieve this balance, optimising the prognosis of the disease (Nathan et al 2009). As described in Chapter 18, secondary prevention, including routinely

screening for and detecting key microvascular and macrovascular complications, is also justified (Australian Diabetes Society 2008; Anderbro et al 2010).

4 Characteristics of type 1 diabetes

4.1 Introduction

The impact of type 1 diabetes on psychosocial functioning, particularly among young people, is widely recognised. Evidence from epidemiological studies suggests that psychological difficulties are more common in children and adolescents with diabetes, as well as in those with other chronic medical conditions (Barlow and Ellard 2006). However, whether people of all ages with type 1 diabetes are at greater risk of psychosocial morbidity and mental health disorders is unclear. This systematic review examined the prevalence of psychological disorders including depression, anxiety and eating disorders across the lifespan of people with type 1 diabetes, compared with the nondiabetic population where controlled data were available.

4.2 Psychological disorders in type 1 diabetes

Question 2

Is there an increased prevalence of psychological disorders in people with type 1 diabetes across the lifespan, including clinical depression, anxiety disorder and eating disorder?

The detailed systematic review of this question is in Chapter 2 of the accompanying technical report, and the evidence matrix is in Section C2 of Appendix C

4.2.1 Psychological distress

The systematic review identified one study from the United States that estimated the prevalence of severe psychological distress (SPD) among adults with and without diagnosed diabetes (Li et al 2009). The investigators used the Kessler-6 scale, which provides a brief valid screen for Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV disorders (Kessler et al 2010). Among 713 adults with type 1 diabetes, the prevalence of SPD was 11%, compared with 3.6% among individuals without diabetes. Significant correlates of SPD among those with diabetes were young age, low education levels, low household income, obesity, current smoking, no leisure-time physical activity, presence of one or more microvascular or macrovascular complications, and disability, suggesting that these factors may contribute to the increased prevalence of SPD in diabetes.

4.2.2 Psychological adjustment, wellbeing and functioning

The systematic review identified four studies that examined the outcomes of psychological adjustment, wellbeing and functioning in children and adolescents (Wake et al 2000; Helgeson et al 2007; Nardi et al 2008; Northam et al 2010).

In a cross-sectional survey of parent and adolescent-reported functional health status, using the Child Health Questionnaire by Wake et al (2000), parents reported that children aged 5–18 years with diabetes had poorer health than children in the normative sample across all domains, particularly especially on psychosocial and parent/family scales. Psychosocial wellbeing was markedly lower in those aged 5–11 years with HbA_{1c} above 8.8%, but not in those aged 12–18 years. Parents and clinicians concurred in their ratings of health for those aged 12–18 years but not for those aged 5–11 years, suggesting that clinicians may underrate the impact of diabetes for younger children.

The prospective cohort study by Helgeson et al (2007) compared adolescents with diabetes (n=132) with a healthy comparison group (n=131) on indices of psychosocial functioning annually for 3 years. There were no group differences in depressive symptoms, anxiety, anger or behavioural problems. However, adolescents with diabetes showed greater declines in social acceptance compared with healthy adolescents, and a greater rise in disturbed eating behaviour. Among females in both groups, depressive symptoms and anxiety increased, and self worth decreased over time.

The cross-sectional study of 90 young people with type 1 diabetes (Nardi et al 2008) evaluated self and parent reports of quality of life (QoL) and psychological adjustment compared with controls. There was no difference in psychological adjustment between young people with diabetes and controls. However, parents of children with type 1 diabetes were more worried than those of controls, and adolescents had worse QoL and more frequent psychological problems than controls. HbA_{1c} levels correlated positively with psychological problems ($p<0.05$) and negatively with QoL ($p<0.05$).

The 12-year prospective cohort study by Northam et al (2010) compared functional outcomes in 110 adolescents and young adults with type 1 diabetes, compared to 76 community controls, recruited between 1990 and 1992. Follow-up measures of psychosocial wellbeing were the Youth Self Report and Young Adult Self-Report, which provide scores for internalising (anxiety, withdrawal and somatic concerns) and externalising (aggression and delinquency) problems, and a semistructured interview of functional outcomes. While both cases and controls reported similar levels of current psychosocial wellbeing, people with type 1 diabetes were significantly more likely than controls to have had contact with mental health services (37% vs 18%) at some point since diagnosis. Psychiatric morbidity was associated with poor glycaemic control and failure to transition to tertiary adult diabetes care. There was significant correlation between mental health service use and established functional outcome measures, such as school lower school completion rates.

4.2.3 Psychiatric disorders

Two studies reported psychiatric status according to a DSM-IV diagnosis (Kovacs et al 1997; Northam et al 2005). In a prospective cohort study of Victorian adolescents, Northam et al (2005) found that 15 out of 41 (37%) received a DSM-IV diagnosis, including mood, anxiety, eating and behaviour disorders. Of those who received a diagnosis, 60% met criteria for two or more psychiatric disorders. Although the study was not controlled, this was two to three times higher than concurrent community levels.

The uncontrolled study by Kovacs et al (1997) found 15 of 92 children (16%) had a psychiatric disorder at onset of diabetes, which predated type 1 diabetes onset, while 32% had an adjustment disorder within 3 months of diabetes onset. After 9 years of follow-up, 42% developed at least one episode of psychiatric disorder. The prevalence of major depression was higher than rates in similarly aged cohorts in the general population, and the rate of generalised anxiety disorder (10%) appeared to be higher than the general population rate. An earlier psychiatric disorder increased the risk of later disorder. Initial maternal psychopathology increased the risk of a psychiatric disorder in the young person with type 1 diabetes.

Depression

In an uncontrolled study from the United States, the 26% prevalence of major depression among children, adolescents and young adults was higher than in the general population

(Kovacs et al 1997). Maternal depression was a specific risk factor for depression in the participants.

The prevalence of depression among adults with type 1 diabetes was not significantly different from that of the matched control groups in a meta-analysis by Barnard et al (2006) (weighted odds ratio [OR] 2.4, 95% confidence interval [CI]: –0.7 to 5.4). However, only one of the four included studies was considered to be of adequate methodological rigour (Petrak et al 2003), and in this study there was a significantly higher rate of major depressive episodes in women with diabetes (9.3% in the diabetes group compared with 3.2% in the reference group), but not in men (3.6% type 1 diabetes compared with 2.2% control). Since the study only included cases of newly diagnosed diabetes, the findings may not be generalisable to the wider population of longer term patients. The only primary study published since that date that fulfilled the inclusion criteria reported a significantly increased prevalence of depression, based on the Beck Depression Inventory II (BDI-II), in German adults with type 1 diabetes (mean age 44 years, mean duration 29 years) compared to controls (32% vs 16%) (Gendelman et al 2009). Patients with diabetes also reported using more antidepressant medications.

Anxiety

In a prospective study by Kovacs et al (1997), 20% of young people with type 1 diabetes developed some type of anxiety disorder – most commonly generalised anxiety disorder (12%), only diagnosable with DSM-III after age 18, or an overanxious disorder of childhood (8%). The study was not controlled, but the rate of generalised anxiety disorder appeared to be elevated compared to the general population. In the prospective study by Northam et al (Northam et al 2005), 17% of participants received a DSM-VI diagnosis of anxiety 10 years after disease onset.

An uncontrolled, cross-sectional, multicentre study of 276 adolescents examined the prevalence of anxiety symptoms (rather than a diagnosis of anxiety disorder) using the State-Trait Anxiety Inventory questionnaire (Herzer and Hood 2010). The prevalence of trait anxiety symptoms (17%) and state anxiety symptoms (13%) were comparable to published norms for otherwise healthy children. State anxiety symptoms were associated with less frequent blood glucose monitoring and suboptimal glycaemic control.

A systematic review of the prevalence of clinically significant anxiety in adults with diabetes (Grigsby et al 2002) found two controlled studies, but only one of these examined the prevalence of anxiety disorder (Friedman et al 1998). This study from France reported less anxiety and fewer affective disorders, based on self-report measures, in 69 young adults with type 1 diabetes compared to medical outpatients; however, the lifetime prevalence of generalised anxiety disorder was higher than that reported for the general French population. There was also a high lifetime prevalence of not otherwise specified anxiety disorders (44%), simple phobia (27%), social phobia (25%), and agoraphobia – with and without panic disorder (15%), according to DSM-III-R criteria. Current social phobia, dysthymia and not otherwise specified depressive disorders were associated with impaired glycaemic control.

Eating disorders

Two systematic reviews and meta-analyses on eating disorders met the inclusion criteria. Bulimia nervosa was significantly more common in type 1 diabetes (1.7%) compared to controls (0.7%) (Mannucci et al 2005). In the earlier meta-analysis (Nielsen 2002), the OR for bulimia was about 3, while both eating disorders not otherwise specified and subthreshold

eating disorders were also increased (OR about 2). In contrast, there was no significant difference in the prevalence of anorexia nervosa in adolescent and adult females with type 1 diabetes compared with controls (Nielsen 2002; Mannucci et al 2005). In the prospective study by Northam et al (2005), 17% of participants received a DSM-VI diagnosis of anxiety 10 years after disease onset.

4.2.4 Summary

Meta-analyses reported no difference in the prevalence of depression in adults with type 1 diabetes compared with the nondiabetic population; however, the methodological quality of three of the four included studies in the systematic review on depression was poor. Two primary studies demonstrated a higher prevalence of depression in adults with type 1 diabetes, at onset of diabetes (Petrak et al 2003) and with long-standing diabetes (Gendelman et al 2009). Evidence from one controlled study in adults showed that the lifetime prevalence of generalised anxiety disorder was higher than that reported for the general population, but there was no difference in the prevalence of anxiety and affective disorders based on self-report measures. Pooled analysis showed an increased prevalence of bulimia nervosa, eating disorders not otherwise specified and subthreshold eating disorders in adolescents and adults with diabetes compared with controls, but no difference in the prevalence of anorexia nervosa.

In the paediatric population, data from controlled studies showed that adolescents and young adults with type 1 diabetes were more likely than controls to have had contact with mental health services, and had higher rates of referral to mental health services (Northam et al 2010). Primary uncontrolled data demonstrated a 26% prevalence of major depressive disorder and 20% prevalence of anxiety disorder in young people with type 1 diabetes (Kovacs et al 1997). Uncontrolled data showed that 37% of adolescents met criteria for a DSM-IV psychiatric disorder according to a self-report measure (Northam et al 2005) (two to three times higher than community levels); among these, 60% met criteria for two or more psychiatric disorders. Primary studies examining prevalence of eating disorders in young people reported no significant difference between those with diabetes and control groups regarding the incidence of anorexia nervosa. However, binge eating, intense excessive exercise for weight control, reporting two or more current disturbed eating behaviours, and eating disorders not otherwise specified or subthreshold eating disorders were all significantly more common among girls with diabetes than in their peers without diabetes (Colton et al 2007).

The generalisability of these data may be limited by the varied selection and inclusion criteria, as well as the variability in control group selection. The lack of a control group in some paediatric studies may influence the interpretation of the findings. The studies were mostly conducted in Australia, Europe or North America; therefore, the results are applicable to the Australian population.

Evidence statements	
Q2	Level I evidence shows that the prevalence of depression in people with type 1 diabetes is greater in certain subgroups – women and the newly diagnosed – than in the general population. Level I evidence shows that there is increased prevalence of bulimia nervosa in adults and adolescents with type 1 diabetes compared to the general population. Level II evidence indicates that there are higher referral rates to mental health services in children and young adults with type 1 diabetes, compared with the general population. Level IV evidence shows an increased prevalence of depression and anxiety in young people and adolescents with type 1 diabetes, compared with the general population. Level IV evidence shows that the prevalence of anxiety in adults with type 1 diabetes is high, but similar to that in the general population.
Recommendation	
R4.1	Clinicians should be aware that the co-occurrence of psychological disorders in type 1 diabetes is common (Grade A).
Practice points	
PP4.1	Consider the co-occurrence of psychological disorders, including eating disorders, when assessing people with type 1 diabetes and suboptimal glycaemic control, insulin omission or recurrent DKA admissions.
PP4.2	In young people with diabetes, the prevalence of psychological disorders is high compared with rates of end-organ complications.
PP4.3	The diabetes team should assess family functioning (including parental psychopathology) and diabetes-related functioning, including communication, parental involvement and support, roles and responsibilities for self-care behaviours (Delamater 2009).
PP4.4	Validated screening tools for psychological disorders in type 1 diabetes are available (see Chapter 9).
DKA, diabetic ketoacidosis	

4.3 What is the impact of type 1 diabetes on cognitive outcomes?

Question 3

What is the impact of type 1 diabetes on cognitive performance?

The detailed systematic review of this question is in Chapter 3 of the accompanying technical report, and the evidence matrix is in Section C3 of Appendix C

People with type 1 diabetes are at risk of developing cognitive difficulties; however, results are inconsistent regarding the magnitude and pattern of cognitive difficulties, due to heterogeneity of study sampling and design, the cognitive abilities examined in the studies, and the assessment tools used. Adolescents with type 1 diabetes have poorer functional academic outcomes (e.g. completion of secondary school) than the general population (Dahlquist and Kallen 2007) or controls (Northam et al 2010), suggesting cognitive abilities may be affected by type 1 diabetes.

To address evidence for the impact of type 1 diabetes on cognitive performance, a systematic review was performed to identify Level I and II studies examining measures of cognitive abilities on cognitive performance in children and adults with type 1 diabetes. The review identified two meta-analyses in children and adolescents, and one in adults (Brands et al 2005; Gaudieri et al 2008; Naguib et al 2009), and four Level II (case–control and

cohort) studies (DCCT/EDIC Research Group 2007; Musen et al 2008; Kent et al 2009; Northam et al 2009) that met the inclusion criteria.

4.3.1 Children

Of the two meta-analyses in young people, only one is reported here (Gaudieri et al 2008), because the review by Naguib et al (2009) did not add any additional information. In the meta-analysis sample of 2144 children (1393 with type 1 diabetes and 751 controls) from 19 studies, type 1 diabetes was associated with slightly lower overall intelligence. There were small differences compared with control subjects across a broad range of specific domains, excluding learning and memory, where performance was similar for type 1 diabetes and healthy controls. Greater effects on verbal and visual learning and memory were observed in children with early onset diabetes compared to healthy controls and to those with late-onset diabetes. A history of seizures was associated with a negligible overall cognition effect size (Gaudieri et al 2008).

A study by Musen et al (2008) examined cognitive performance 18 years later in 249 adolescents aged 13–17 years at entry into the Diabetes Complications and Control Trial (DCCT). The study found no significant effect of treatment assignment or cumulative number of hypoglycaemic events on any cognitive domain. However, higher values of glycated haemoglobin (HbA_{1c}) were associated with modest declines in psychomotor and mental efficiency ($p<0.01$). A 3-year longitudinal study of young people aged 9–17 years found no significant effect of glycaemic control on verbal memory, but the predicted effect of metabolic control on visual memory using growth curve modelling was significant ($p<0.01$) (Kent et al 2009). There were no effects of disease duration, age of onset, or severe hypoglycaemia on visual or verbal memory. In the Australian longitudinal cohort study of 106 young people with type 1 diabetes, verbal and full-scale intelligence quotient (IQ) (Northam et al 2009) and working memory (Lin et al. 2010) were significantly lower 12 years after diabetes diagnosis compared with controls (Northam et al 2009). A history of severe hypoglycaemia was predictive of lower verbal IQ (VIQ), and early onset of diabetes predicted lower performance IQ (PIQ). Magnetic resonance spectroscopy and imaging suggested several neuropathological processes including gliosis, demyelination and altered osmolarity may explain the neurocognitive changes observed. The findings from this study contrast with those of an Australian case–control study, which found that episodes of seizure or coma (even those occurring in very early childhood) did not result in broad cognitive dysfunction or specific memory difficulties in children and adolescents with early onset type 1 diabetes compared with their peers (Strudwick et al 2005).

None of the included studies in children examined the effect of hyperglycaemia on cognitive function. However, a crossover study of experimental hyperglycaemia in 12 children demonstrated that acute hyperglycaemia impaired complex cognitive function (Davis et al 1996). In the prospective cohort study of young people in Victoria with type 1 diabetes, those with type 1 diabetes performed more poorly than controls on working memory, and poorer working memory was significantly associated with hyperglycemia (Lin et al 2010).

4.3.2 Adults

The systematic review of 33 studies of adults with type 1 diabetes demonstrated significantly lower performance on six cognitive domains (intelligence, speed of information processing, psychomotor efficiency, visual and sustained attention, cognitive flexibility and visual perception) compared with controls. While learning and memory appeared to be spared, the authors concluded that even mild forms of cognitive dysfunction had the potential to affect everyday activities. Lower cognitive performance in patients with

diabetes appeared to be associated with the presence of microvascular complications, but not with severe hypoglycaemia or with poor glycaemic control (Brands et al 2005).

In the DCCT and Epidemiology of Diabetes Interventions and Complications (EDIC) study, neither treatment assignment nor frequency of severe hypoglycaemia were associated with a decline in any cognitive domain. Higher HbA_{1c} values were significantly associated with moderate declines in motor speed ($p=0.001$) and psychomotor efficiency ($p<0.001$) (DCCT/EDIC Research Group 2007).

4.3.3 Summary

This systematic review of evidence for the impact of type 1 diabetes on the cognitive function of children, adolescents and adults is based on three Level II studies (two of low risk of bias and one of moderate risk of bias), and two meta-analyses at high risk of bias. Most of the studies included in the meta-analyses were of cross-sectional design, making casual inferences problematic. When compared with healthy controls, children and adolescents demonstrated marginal negative effects on several cognitive domains, excluding learning and memory, and scored marginally lower on IQ. Cognitive effects were most pronounced and pervasive for children with early onset diabetes, with moderately lower performance compared with controls. Adults demonstrated a small-to-moderate negative impact on several cognitive domains, excluding learning and memory.

Where the association between occurrence of severe hypoglycaemia and its impact on cognitive function was examined, a significant negative effect was reported in one prospective cohort of children, with severe hypoglycaemia predicting lower VIQ. No other significant effects were reported. Where the association between glycaemic control and impact on cognitive function was examined, significant negative effects were reported in one prospective cohort including adults and adolescents, and in one prospective cohort including children older than 9 years. No significant effects on IQ were reported in one prospective cohort of Australian children, and no significant effects were reported in a qualitative analysis of studies included in a meta-analysis in adults. Early onset diabetes was associated with lower performance and full-scale IQ, verbal and visual learning and memory skills, and attention or executive function skills.

One study was undertaken in Australia, and the remainder in countries with a well-developed health-care system. Thus, the findings are appropriate to the Australian health-care context. Appropriate exclusions were reported in the studies, including diabetes complications, history of head injury and depression. The absence of clear and consistent associations across the studies may reflect methodological limitations in measuring hypoglycaemia and hyperglycaemia accurately, rather than an absence of association.

Evidence statement	
Q3	Evidence from Level I and II studies show a longitudinal association between glycaemic control and some aspects of cognitive function. The magnitude of this effect is greatest in children with early onset type 1 diabetes.
Recommendation	
R4.2	To minimise the impact of diabetes on cognitive function, every effort should be directed toward achieving glycaemic targets (Grade B).
Practice points	
PP4.5	It is important to monitor the school performance of children who developed diabetes before age 5–7 years, and those with a history of significant hypoglycaemic episodes or chronic poor control.
PP4.6	Early age of onset of type 1 diabetes is associated with a minor but statistically significant reduction in population IQ. Therefore, children experiencing significant learning difficulties should be referred for psycho-educational or neuropsychological evaluation. If learning disabilities are present, alternative causes should be sought and remedial interventions to address specific deficits implemented.
PP4.7	In children with type 1 diabetes, assessment of developmental progress in all domains of QoL (i.e. physical, intellectual, academic, emotional and social development) should be conducted on a routine basis.
IQ, intelligence quotient; QoL, quality of life	

4.4 Growth and physical development

Question 4 (background question)

What is the impact of type 1 diabetes on physical development?

Question 4 was a background question and therefore was not systematically reviewed

Among the primary goals of diabetes management in children and adolescents are the maintenance of normal growth, physical and pubertal development, and ideal body weight. In general, children and young people with optimal blood glucose control will grow and develop normally. In an Australian study of adolescents with type 1 diabetes, growth hormone secretion paralleled that seen in normal adolescents during puberty, and growth hormone secretion was not affected by glycaemic control (Batch and Werther 1992). The National Institute of Clinical Excellence (NICE) guidelines found no randomised controlled trials (RCTs) that investigated growth and puberty among children and young people with type 1 diabetes (NICE 2010). Due to the limited evidence base in this area, a systematic review was not performed for this question. Data from cross-sectional and cohort studies of growth in young people with type 1 diabetes are described below.

A number of studies demonstrating a negative impact of type 1 diabetes on linear growth included patients diagnosed more than 20 years ago, at a time when glycaemic targets were higher and the use of intensive management was less common in young people. In a cohort study of 152 children with type 1 diabetes, a linear relationship between HbA_{1c} and growth rate was observed, and patients with total HbA_{1c} above 16% had the greatest growth deceleration (Wise et al 1992). Several groups have reported a reduction in height standard deviation score (SDS) after diagnosis of type 1 diabetes (Bognetti et al 1998; Gunczler and Lanes 1999; Donaghue et al 2003), and a relationship between loss of height and suboptimal

glycaemic control (Gunczler and Lanes 1999; Donaghue et al 2003). In a longitudinal study from Germany, growth reduction was more pronounced in patients diagnosed before the onset of puberty, and final height was significantly lower in patients with prepubertal onset of diabetes compared with later onset (Holl et al 1998). There was a greater loss of height in patients with suboptimal glycaemic control. In a smaller Australian study, the mean near-final height Z score was significantly lower than the mean prepubertal height Z score in boys with type 1 diabetes, but not in girls (Kanumakala et al 2002).

Obesity appears to be an emerging problem in young people with type 1 diabetes, particularly among children with young onset of diabetes (<5 years of age) and females (Libman et al 2003; Kordonouri and Hartmann 2005; Clarke et al 2006). Several studies in Australia and overseas have shown that rapid growth and weight gain precede the onset of type 1 diabetes, and children are taller than their peers at diagnosis (Clarke et al 2006), while overweight and obesity persist after diagnosis, particularly in older children. It is thought that overweight in early childhood may initiate islet autoimmunity (Couper et al 2009) and accelerate beta cell loss (Wilkin 2001). This contrasts with the weight loss that occurs in the weeks or months before diagnosis due to hyperglycaemia. Factors contributing to overweight in type 1 diabetes include the requirement for supraphysiological insulin doses to achieve glycaemic targets, frequent snacking, and excess energy intake to avoid or treat hypoglycaemia. Obesity is an independent risk factor for macrovascular disease in type 1 diabetes (discussed in Chapter 18). Obesity is a also risk factor for microalbuminuria in adolescents with type 1 diabetes (Stone et al 2006).

Practice tips

- The measurement of height, weight and body mass index is an integral component of diabetes care for children and adolescents. Height and weight should be measured in a private room (NICE 2010).
- Anthropometric measurements should be plotted on an appropriate centile chart.
- Changes in growth or significant changes in weight, or pubertal delay, may reflect changing glycaemic control. In such cases, comorbidities such as coeliac disease or thyroid dysfunction should also be considered.
- Dietary advice and meal planning should be revised regularly to meet changes in appetite and insulin regimens, and to ensure optimal growth. Prevention of overweight and obesity is a key strategy in the management of type 1 diabetes (see Chapter 10).
- Regular review and adjustment of insulin doses (and basal rates on pumps) is required in children and adolescents, because insulin requirements can change rapidly with growth and puberty. In particular, significant insulin resistance may occur during puberty, and insulin requirements typically increase (>1 unit/kg/day). Postpubertally, insulin doses usually decline.

4.5 Urban versus rural care

Question 5 (background question)

Does glycaemic control differ between urban and rural patients in Australia?

Question 5 was a background question and therefore was not systematically reviewed

Multidisciplinary teams are not available in many rural and geographically remote areas of Australia that have low population density and small numbers of people with type 1 diabetes, particularly children. In these situations, care may be provided by a local

paediatrician or physician with access to resources, support and advice from a tertiary centre diabetes team. It is not known whether a lack of multidisciplinary team care, or other factors related to living rural locations, influence glycaemic control. A systematic review was not performed for this question, because no RCTs examining the effect of interventions on glycaemic control in urban versus rural patients were identified. Three cross-sectional studies that examined glycaemic control in young people with type 1 diabetes living in rural areas were identified (Handelsman et al 2001; Cameron et al 2002; Goss et al 2010). One of these studies included a control group of urban youth (Cameron et al 2002).

The largest study was an audit of about 1200 children with type 1 diabetes living in New South Wales and the Australia Capital Territory, in which glycaemic control did not differ between those from urban and those from rural areas (Handelsman et al 2001). A Victorian study on clinical and QoL outcomes demonstrated no differences in glycaemic control between youth with type 1 diabetes living in urban and rural locations, despite less reported access to team-based diabetes care in rural centres (Cameron et al 2002). However, rural youth had lower QoL and the greatest deficits were seen in areas of mental health, self esteem, parent impact (emotional) and family cohesion. Following implementation of a multidisciplinary paediatric diabetes clinic in rural Victoria, glycaemic control improved significantly from a median of 9.7% to 7.9%. Although there was no urban comparison group, the level of glycaemic control was comparable with that achieved in patients managed in urban centres (Goss et al 2010).

These findings suggest that the glycaemic control of young people with type 1 diabetes is not influenced by location of residence. Thus, care provided locally in urban centres, or in partnership with outreach services, is likely to be comparable to that in regional centres. However, there is some evidence for lower QoL in rural youth. The management of patients living in rural and remote areas using telemedicine is covered in Chapter 8.

Practice principles

- All people with type 1 diabetes, including those from rural and remote areas, should have access to optimal medical management.
- In rural and geographically remote areas within the Australian health-care system, people with diabetes may be successfully cared for by a local paediatrician or physician, and a multidisciplinary health-care team experienced in diabetes, with access to resources, support and advice from a tertiary centre diabetes team.

4.6 Cost of diabetes

Question 6 (background question)

What is the cost burden to individuals and society of type 1 diabetes?

Question 6 was a background question and therefore was not systematically reviewed

Although this question was not systematically reviewed, a recent review (DiabCo$t Type 1) was identified that described the cost of type 1 diabetes in direct health-system costs, indirect costs and QoL (Colagiuri et al 2009).

DiabCo$t Type 1 was a retrospective, cross-sectional, self-reported survey of people with type 1 diabetes, aged 5 years and older, in Australia. Participants were randomly selected from the National Diabetes Services Scheme (NDSS) register, with appropriate permission and compliance with privacy regulations. A stratified random sample of 10 000 people was sent a survey in August 2006. Parents, guardians or carers were asked to assist with

completing the survey when it was sent to children. The respondents were anonymous to both the study investigators and the administrators of the NDSS. The survey comprised two structured, self-administered questionnaires, one for people with diabetes and another for their carers. The questionnaires were designed to elicit information on costs incurred over the previous 3 months. In addition, QoL for people with type 1 diabetes was assessed using the EuroQuol (EQ-5D), an instrument for measuring health-related quality of life states that consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression).

The DiabCo$t Type 1 survey collected direct health-care costs, non-health care costs and indirect costs for people with type 1 diabetes, costs to carers, and an assessment of the impact of type 1 diabetes on the individual's QoL. The survey measured total health costs for the study respondents. It was not intended or possible to separate health-care costs attributable to diabetes and those incurred for non-diabetes related conditions.

The number of evaluable questionnaires returned was 2200 (response rate 22%). The mean age of respondents was 32 years, and time since diagnosis was just over 8 years. Most participants (82.7%) reported no complications. Microvascular complications alone were reported by 12.3%, macrovascular complications alone by 0.7%, and both microvascular and macrovascular complications by 4.3%. Mild hypoglycaemic episodes in the 3 months preceding the survey were reported by 88.7%, with a mean number of just under 16 episodes within that 3-month period. About 19% reported experiencing a mean of almost three severe hypoglycaemic episodes requiring assistance. About one-third of respondents reported having a carer. The mean age of carers was 42.9 years, and 90% were female (Colagiuri et al 2009).

The total average annual cost per person with type 1 diabetes was $4669. This figure comprised $3862 in direct costs ($3640 direct health costs and $222 direct non-health costs) and $807 in indirect costs ($418 related to the person with type 1 diabetes and $389 related to carer costs). Hospitalisation accounted for nearly half of the direct health-care costs. Medications accounted for 32%, with insulin accounting for about 14%. Ambulatory service costs were derived from visits to general practitioners (3.7%), medical specialists (7.7%) and allied health professionals (4.8%) such as diabetes educators, dieticians or nutritionists, podiatrists, psychologists and optometrists. Consumables, blood glucose testing strips and insulin-administering equipment accounted for 4.5% of direct health-care costs (Colagiuri et al 2009).

Costs increased with the presence of complications. The average total annual cost was $3468 for people without complications, $8122 for people with microvascular complications only, $12 105 for people with macrovascular complications only, and $16 698 for people with both macrovascular and microvascular complications.

Nineteen percent of carers reported being retired or currently not working in order to care for the person with diabetes. Carers took an average of almost 3 days off work in the previous 3 months to care for the person with diabetes. The employment situation of 17% of carers had changed to care for the person with diabetes, with an accompanying reduction in income for nearly 70% of these carers, resulting in mean annual lost wages of $7413 per carer (Colagiuri et al 2009). People with type 1 diabetes reported an impact on health-related QoL, particularly for the 'pain/discomfort' and 'anxiety/depression' dimensions. QoL scores were lower in people with complications.

This was the first individual level assessment of the financial and personal impact of type 1 diabetes on the person with diabetes and their carer in Australia. The minimum estimated cost to the nation of type 1 diabetes ranges from $430 to $570 million, depending on the data used to estimate the number of people with type 1 diabetes in Australia. These costs are substantially higher than previous estimates, which were based on administrative rather than patient-level data. The real cost is even higher, since the full impact of indirect costs associated with premature mortality could not be assessed because this was a self-reported questionnaire, and the survey did not evaluate the cost of disability (Colagiuri et al 2009).

These findings have important implications for policy and service delivery for people with type 1 diabetes and their carers. The role of complications as a cost driver underlines the need to ensure access to appropriate standards of care, to prevent or delay the onset of complications.

The cost of type 1 diabetes was also examined in the NICE guidelines (NICE 2010). NICE reviewed the economic analysis of the DCCT, which examined the cost effectiveness of alternative approaches to the management of type 1 diabetes. An economic simulation model was constructed to estimate the life-time costs and outcomes of conventional and intensive insulin therapy. Quality-of-life scores assigned to specific health states were not based on primary research into the social valuations for different health states (as would be normally be expected in health economic evaluation). The simulations showed that the mean annual cost of intensive therapy using multiple daily injections was around $4000, and for continuous subcutaneous insulin infusion (CSII) was $5800. The figure for CSII is approximately three times the mean annual cost of conventional therapy (which is $1700). The model estimated that the cost of the adverse effects of intensive therapy was three times the cost of the adverse effects of conventional therapy, but these costs accounted for only about 5% of the total costs of therapy in both groups. The expected life-time cost per patient was around $100 000 for intensive therapy and $66 000 for conventional therapy at 1996 prices. The analysis concluded that intensive therapy cost $28 661 per year of life gained.

No study has estimated the cost effectiveness of alternative forms of treatment for children and young people. The DCCT model included patients aged 13–39 years, and so the costs and benefits associated with children and young people cannot be estimated from this model. Furthermore, the cost of initiation of intensive therapy was around $2900. More than 85% of this cost was attributable to hospitalisation to initiate intensive therapy, but this level of hospitalisation might not be expected in health-care settings outside a research environment. Further research based on the experience of children and young people accessing conventional and intensive forms of treatment in routine clinical care is required.

5 Role of major trials in advancing clinical care in blood glucose management

Question 7 (background question)

What do the findings from the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications study tell us about the importance of glycaemic control?

Question 7 was a background question and therefore was not systematically reviewed

5.1 Introduction

5.1.1 Diabetes Control and Complications Trial

Blood glucose management in type 1 diabetes is important to prevent acute metabolic deterioration, with life-threatening diabetic ketoacidosis (DKA) or severe hypoglycaemia. The great importance of long-term blood glucose control in preventing the development and worsening of diabetes end-organ complications was established by a definitive randomised controlled trial (RCT) – the Diabetes Control and Complications Trial (DCCT).

The DCCT was a multicentre RCT designed to compare intensive and conventional diabetes therapy, with regard to the effects on the development and progression of the early vascular and neurological complications of diabetes (DCCT Research Group 1986; DCCT Research Group 1993). Two cohorts were studied, to answer two different questions:

- Will intensive therapy prevent the development of diabetic retinopathy in patients with no retinopathy?
- Will intensive therapy affect the progression of early retinopathy?

The primary study outcome was retinopathy. Secondary outcomes were renal, neurologic, cardiovascular and neuropsychological effects, as well as the adverse effects of the two treatment regimens.

The major criteria for eligibility included insulin dependence (as measured by deficient C-peptide secretion); an age of 13–39 years; and the absence of hypertension, hypercholesterolemia and severe diabetic complications or medical conditions.

Intensive therapy was aimed at maintaining blood glucose concentrations close to the normal range while preserving clinical wellbeing, as defined for the standard treatment group. The targets were (DCCT Research Group 1993):

- preprandial blood glucose concentrations between 3.9 mmol/L and 6.7 mmol/L
- postprandial concentrations of less than 10 mmol/L
- weekly 3-am measurement of more than 3.6 mmol/L

- glycated haemoglobin (HbA_{1c}) measured monthly within the normal range (<6.05%)
- a process of weekly clinic visits until the target range was reached, and monthly visits thereafter.

The intensive therapy methods included the subcutaneous administration of insulin three or more times daily by injection or by an external pump infusing insulin (continuous subcutaneous insulin infusion [CSII]). The dosage was adjusted according to the results of self monitoring of blood glucose (SMBG), dietary intake and anticipated exercise. SMBG was performed at least four times per day, with at least weekly 3-am measurement. The patients initially chose either multiple daily injection or CSII therapy, and could change to the other method according to preference or targets. Patients visited the study centre each month, and were contacted even more frequently by telephone for review and dose adjustment. Telephone contacts were maintained at least weekly. The objective of the standard treatment regimen (conventional therapy) was to maintain the clinical wellbeing of the patient. Wellbeing was defined as freedom from symptoms attributable to glycosuria or hyperglycaemia; freedom from frequent or severe hypoglycaemia; absence of ketonuria; normal growth and development in adolescents; and maintenance of ideal body weight in all participants. An upper action limit of 13.11% was set for HbA_{1c}; this value mandated therapeutic intervention (DCCT Research Group 1993).

A total of 1441 patients with age range 13–39 years were recruited across 29 centres from 1983 to 1989. The entire cohort was followed for a mean of 6.5 years, which gave a total of more than 9300 patient years; 99% of patients completed the study. Eleven patients died and 32 were assigned to inactive status.

In baseline characteristics, the mean age was 27±7 (± standard deviation) years in all groups, except for conventional therapy in the primary prevention cohort, where the mean age was 26±8 years. Most participants were classified as being of 'white race' ethnicity. The average duration of diabetes was 2.6±4 years in the primary prevention cohort and 8.6–8.9 years in the secondary intervention cohort. The mean HbA_{1c} was 8.8% in the primary prevention cohort and 8.9–9% in the secondary intervention cohort.

The data safety and quality committee stopped the RCT phase of the DCCT prematurely after a mean follow-up of 6.5 years (DCCT Research Group 1993). The benefits of intensive treatment were deemed incontrovertible, and highly unlikely to be reversed with time. During the closeout period of the study, all participants were encouraged and advised to implement or continue intensive treatment using DCCT staff.

The overall within-participant mean HbA_{1c} levels for the entire DCCT period were 9.1% for the conventional group and 7.2% for the intensive treatment group ($p<0.001$) (Lachin et al 2008). Among those in the intensive group, 50% of participants had a mean HbA_{1c} between 6.5 and 7.5%, compared to 8% of the conventional group. Among those in the conventional group, 31% had a mean HbA_{1c} between 8.5 and 9.5%, compared to 5% of the intensive group (Lachin et al 2008). Forty-four percent of patients receiving intensive therapy achieved the goal HbA_{1c} of 6.05% or less at least once during the study. Less than 5% maintained an average value in this range. The mean value for all glucose profiles in the intensive therapy group was 8.6±1.7 mmol/L. In the conventional group, the mean value was 12.8±3.1 mmol/L ($p<0.001$) (DCCT Research Group 1993).

Microvascular outcomes

In the primary prevention cohort, intensive therapy (where a median HbA_{1c} of 7.3% was achieved) reduced the adjusted mean risk for the development of retinopathy by 76% (95%

confidence interval [CI]: 62% to 85%) compared with conventional therapy (median HbA_{1c} of 9.1%) (DCCT Research Group 1993). These data are summarised in Chapter 43 of the technical report. Those in the primary prevention cohort with duration of diabetes of less than 2.5 years at entry into the trial had 89% reduction in the risk of retinopathy, compared with 70% in patients with duration of more than 2.5 years (p<0.001). In the secondary-intervention cohort, intensive therapy slowed progression of retinopathy by 54% (95%CI: 39% to 66%) and reduced the development of proliferative or severe nonproliferative retinopathy by 47% (95%CI: 14% to 67%) (DCCT Research Group 1993).

In the primary prevention cohort, there was an early worsening of retinopathy (DCCT Research Group 1995). This occurred in 22% of patients in the intensive treatment group, compared with 13% in the conventional group (odds ratio [OR] 2.06, p<0.001) (Anonymous 1998a). The progression consisted of the development of soft exudates or intraretinal microvascular abnormalities. This occurred mainly in the secondary intervention cohort, and was most commonly observed during the first year of intensive therapy (DCCT Research Group 1993). The abnormalities often disappeared by 18 months. The patients with early worsening who were treated intensively ultimately had a 74% reduction (95%CI: 46% to 88%) in the risk of subsequent progression, compared with patients with early worsening who received conventional therapy (p<0.001) (Anonymous 1998a).

In terms of nephropathy, in combined cohorts, intensive therapy reduced the occurrence of microalbuminuria (urinary albumin excretion of ≥40 mg per 24 hours) by 39%. Albuminuria was reduced by 54% (DCCT Research Group 1993). Observational data showed that the risk of developing nephropathy was exponentially related to the mean HbA_{1c}, and for each 10% decrease in HbA_{1c} there was a 25% decrease in the risk of microalbuminuria (DCCT Research Group 1993). No glycaemic threshold for nephropathy was detected above the nondiabetic range of HbA_{1c}. The DCCT found no influence of intensive treatment on glomerular filtration rate; however, these values remained within normal range for most participants during the DCCT.

Intensive therapy reduced the odds of having symptoms and signs of peripheral neuropathy by 64% (p=0.0044) and 45% (p<0.0001) respectively. In the primary intervention cohort who did not have peripheral neuropathy at baseline, intensive treatment reduced the appearance of clinical peripheral neuropathy at 5 years by 69% (to 3%, compared with 10% in the conventional therapy group, p<0.001). In the secondary intervention cohort, intensive treatment also reduced the appearance of clinical peripheral neuropathy at 5 years, by 57% (7% compared with 16%, p<0.001). Autonomic neuropathy signs were also minimised by intensive compared with conventional therapy, by 53% (p=0.04) (DCCT Research Group 1993). Nerve conduction velocities generally remained stable with intensive therapy, but decreased significantly with conventional therapy (1995b).

Macrovascular outcomes

The DCCT was not powered to assess effects of glycaemic control on macrovascular outcomes; however, the development of macrovascular disease was found to favour intensive therapy. The number of combined major macrovascular events was almost twice as high in the conventionally treated group (40 events) than in the intensive treatment group (23 events); a difference in rates that was not statistically significant (DCCT Research Group 1993; Anonymous 1995a).

Adverse events

Mortality did not differ significantly between the treatment groups, nor did overall DKA events. There were also no significant differences between groups with regard to the number of major accidents requiring hospitalisation. The incidence of severe hypoglycaemia, including multiple episodes in some patients, was approximately three times higher in the intensive therapy group than in the conventional therapy group ($p<0.001$), with grade 2 or 3 hypoglycaemia occurring as 62 episodes per 100 patient years in the former, and 19 in the conventional group (DCCT Research Group 1993). Most severe episodes occurred at night. Development of hypoglycaemia unawareness was also more common in the intensive treatment group (Lorenz et al 1991). There were two fatal motor vehicle crashes, one in each group, in which hypoglycaemia may have been a factor. Also, a person not involved in the trial was killed in a motor vehicle accident involving a car driven by a patient in the intensive group who was probably hypoglycaemic (DCCT Research Group 1993).

Quality of life

Despite the higher risk of severe hypoglycaemia with intensive therapy, there was no difference between the two groups in the occurrence of clinically important changes in neuropsychological function, nor were there any significant differences in the mean total scores in the quality of life questionnaire (DCCT Research Group 1993; Anonymous 1996). Thus, by this measure, quality of life was maintained in the intensive treatment group, despite an increase in the rigor of diabetes care. During the DCCT, there was a 33% increase in the mean adjusted risk of becoming overweight in the intensive group, compared with a 9.3% increase in risk in the conventional group. At 5 years' study duration, patients in the intensive group had gained a mean of 4.6 kg more than patients receiving conventional therapy.

5.1.2 Epidemiology of Diabetes Interventions and Complications study

The Epidemiology of Diabetes Interventions and Complications (EDIC) study was a multicentre, longitudinal, observational study that used the DCCT cohort of patients. The aim of the EDIC study was to determine the long-term effects of prior separation of glycaemic levels on multiple microvascular and macrovascular outcomes (Lachin et al 2000; Writing Team for the DCCT/EDIC Research Group 2002). Of the 29 DCCT clinics, 28 opted to participate as EDIC clinical centres. Each participant had a standardised annual history and physical examination. The examination included detailed evaluation of overall health status, diabetes management and occurrence of diabetic complications. Measures of health satisfaction and quality of life were obtained every other year. The study outcomes were to:

- describe the development and progression of cardiovascular (coronary, peripheral and cerebral) disease in type 1 diabetes
- study the effects and interactions of potential risk factors for cardiovascular disease in type 1 diabetes
- examine the long-term effects of differences in prior diabetes treatment (conventional vs intensive) during the DCCT on the subsequent development and progression of cardiovascular disease
- examine the development of abnormal lipid and lipoprotein levels
- relate early degrees of microalbuminuria to the development of nephropathy
- study the rate of development of neuropathy
- examine the transition to retinopathy

- examine long-term effects of differences in prior control on microvascular complications
- examine effects of putative genetic factors
- observe current health care, implementation and maintenance of intensive therapy
- study health related to quality of life.

At the end of EDIC year 1, 95% of the former intensive therapy group and 75% of the former conventional group reported that they were using intensive treatment. The mean HbA_{1c} levels were 7.9% for the former intensive treatment group and 8.3% in the former conventional group. The HbA_{1c} levels converged further, and remained similar during the ensuing 7 years (Writing Team for the DCCT/EDIC Research Group 2002). The overall mean HbA_{1c} levels for the entire EDIC follow-up until 2002 were 8.3% for the former conventional group and 8.1% for the intensive treatment group (Writing Team for the DCCT/EDIC Research Group 2002).

Microvascular outcomes

In EDIC, the microvascular outcomes seen at the DCCT closeout were largely maintained (Lachin et al 2000; Writing Team for the DCCT/EDIC Research Group 2002). A strong positive exponential relationship was found between the risk of retinopathy and the mean HbA_{1c} measured quarterly. For each 10% decrease in HbA_{1c}, there was a 39% decrease in risk of retinopathy over the range of HbA_{1c} values. There was no glycaemic threshold at which the risk of retinopathy was eliminated above the nondiabetic range of HbA_{1c} (4.0–6.05%). For each 10% decrease in HbA_{1c} during the DCCT, there was a 25% decrease in the risk of microalbuminuria. In EDIC, after 4 years, the proportion of patients with progressive retinopathy and nephropathy (as albuminuria) was reduced ($p<0.001$ for each endpoint) in the intensive treatment group of the DCCT compared with the original conventionally treated group. After 5 years, the prevalence of confirmed clinical neuropathy in those without neuropathy at baseline was reduced by 69% in the primary cohort and 57% in the secondary cohort.

In the longer term EDIC follow-up, the original DCCT intensive treatment also reduced the risks of onset and progression of some endpoints assessing autonomic neuropathy. Specifically, for the original intensive treatment group, incident cardiac autonomic neuropathy was reduced by 31% (OR 0.69, 95%CI: 0.51 to 0.93) and incident abnormal cardiac R-R interval variation by 30% (OR 0.70, 95%CI: 0.51 to 0.96) in EDIC year 13–14, compared with those in the original DCCT conventional therapy group (Pop-Busui et al 2009). In contrast, orthostatic hypotension prevalence did not differ between the two groups and, as in the DCCT, in EDIC a decreased awareness of hypoglycaemia was more common in the original intensive treatment group (Anonymous 1998b). Cognitive outcomes were not different between the two groups in EDIC (Jacobson et al 2007); no evidence of substantial long-term declines in cognitive function was found in patients carefully followed for an average of 18 years, despite relatively high rates of recurrent severe hypoglycaemia. Higher HbA_{1c} values were associated with moderate declines in motor speed ($p=0.001$) and psychomotor efficiency ($p<0.001$) (Jacobson et al 2007).

Cardiovascular outcomes

In EDIC, a total of 144 cardiovascular events occurred in 83 patients during the mean 17 years of follow-up; 46 among 31 patients in the intensive treatment group and 98 among 52 patients in the conventional group. The respective event rates were 0.38 and 0.80 per 100 patient years ($p=0.007$) (Nathan et al 2005) The risk of the first occurrence of nonfatal myocardial infarction, stroke or death from cardiovascular disease (CVD) was reduced by

57% with intensive treatment compared with conventional treatment (96%CI: 12% to 79%, p=0.02) (Nathan et al 2005). The presence of diabetic nephropathy was found to mediate about 50% of the effects of glycaemia on cardiovascular outcomes, and blood glucose accounted for well over 90% of the observed effect (rather than lipid or blood pressure levels and their treatments). A study of the surrogate endpoint of carotid intima-media thickness (CIMT) some years earlier had reported in EDIC that between the intensive therapy and conventional group, there was less progression of the intima-media thickness of the common carotid artery to year 6 of the EDIC in intensive treatment groups (Nathan et al 2003). Mean CIMT progression was 0.032 mm in the intensive treatment group and 0.046 mm in the conventional group, with a difference of 0.013 mm (95%CI: 0.003 to 0.24).

5.2 Across the lifespan

Compared with the adults in the DCCT, the adolescent subgroup (n=195, aged 13–17 years) had similar microvascular benefit and similar adverse events in terms of the relative risk of severe hypoglycaemia in intensive and conventional treatment (DCCT Research Group 1994). The benefits did not clearly persist, however, in adolescents who continued into the EDIC (White et al 2010). Nearly 80% of the observed differences in the prolonged treatment effect between adults and adolescents at year 10 of the EDIC were explained by differences in mean A_{1c} during the DCCT between adolescents and adults. This finding indicates that tight glycaemic control is required in adolescence to optimise outcomes into adulthood.

The DCCT and EDIC did not study people with advanced end-stage diabetes end-organ complications, and it is not clear whether tight glycaemic control as a strategy will lead to improved outcomes in this cohort. As the benefits of tight glycaemia control persist across decades, the memory effect (explained below) of elevated glucose reinforces the importance of tight glycaemic control as a method to minimise risk of diabetes microvascular and macrovascular complications in the long term.

5.3 Metabolic control matters – putting glycaemic control into context

The DCCT study provides evidence that intensive diabetes treatment and improved glycaemic control confers a significant risk reduction for microvascular complications compared with conventional treatment. The EDIC study has shown that this positive effect continues after randomisation. This phenomenon has been termed ‘metabolic memory’; the long-term effect of hyperglycaemia on the risk of microvascular complications may be mediated by the generation of advanced glycation end products The EDIC also showed a positive effect of intensive therapy for reduction in macrovascular disease; the beneficial effect of intensive treatment on the risk of CVD may be a result of the reduction in the incidence of microvascular disease. In the EDIC study nephropathy accounted for approximately 50% of the variation in CVD risk (Nathan et al 2005).

More recent studies have confirmed that HbA_{1c} explains virtually all the difference in the risk of complications between the intensive and conventional groups, and a given HbA_{1c} level has similar effects within the two treatment groups (Lachin et al 2008). Other components of hyperglycemia, such as glucose variation, may contribute to the risk of complications, but such factors can only explain a small part of the differences in risk between intensive and conventional therapy over time (Lachin et al 2008).

5.4 Glycaemic target setting

The DCCT was not designed to assign patients to multiple treatment levels of glycaemia. Thus, the question of a glycaemic target that would preserve the benefits of intensive

therapy but reduce the risk of severe hypoglycaemia could not be directly answered by the study. However, the relation between the rate of development of retinopathy and glycaemic exposure (HbA_{1c} over time) was analysed. These secondary analyses showed a continuously increasing risk of sustained progression of retinopathy by three steps with increasing mean HbA_{1c}. The risk of severe hypoglycaemia also increased continuously with lower monthly HbA_{1c} values. Thus, the findings did not support the existence of one specific target value for HbA_{1c} that would maximise benefits and minimise risk. The intensive treatment group achieved, on average, an HbA_{1c} level of below 7.2%; hence, a value below this level is generally set as the generic HbA_{1c} target in adults with type 1 diabetes. In adolescents, achieving tight glycaemic control by intensive therapy is more challenging, with a greater risk-to-benefit ratio due to severe hypoglycaemia (Fenton et al 1999). In Australia, generic HbA_{1c} targets in type 1 diabetes are <7.5% for children and adolescents (Rewers et al 2009) and <7.0% in adults (Cheung et al 2009b).

The average duration of diabetes was only 2.6 years at study entry in the intensive treatment arm of the DCCT, for the average 6.5 years' study duration. Thus, the DCCT and EDIC mainly examined the importance of tight glycaemic control in the first 10 years after type 1 diabetes diagnosis. In contrast, glycaemic control typically becomes more difficult to achieve safely with increasing duration of diabetes, and a lack of hypoglycaemia awareness and severe hypoglycaemia events both become increasingly common.

6 Blood glucose monitoring

6.1 Introduction

Monitoring of blood glucose is an essential aspect of care in people with type 1 diabetes. An integral part of current standard intensive diabetes management is self-monitoring of blood glucose (SMBG). Such monitoring is performed intermittently, four to five times each day, using an accurate, portable blood glucose meter (DCCT Research Group 1993). For an individual with diabetes, personalised education in interpretation of SMBG serial profiles and trends across and between days is necessary. Such education helps the person to accurately match insulin requirements between meals, adjust doses in flexible eating, and target correction insulin boluses appropriately (DAFNE Study Group 2002); (McIntyre 2006).

More frequent SMBG is typically required in certain circumstances. For example, timely targeting of SMBG within a day or at night can help to prevent hypoglycaemic events or detect them early in their course (Allen and Frier 2003). Such targeting also improves safety in planning and undertaking physical activity and cognitively demanding activity; for example, at school (Bui and Daneman 2006), in the work place and when driving (Cox et al 2006). When hypoglycaemia does occur, serial SMBG helps to ensure that it is adequately treated (DCCT Research Group 1993). In addition, in sick day management, when blood glucose may become elevated with developing ketoacidosis, frequent SMBG is necessary, as is ketone measurement (Laffel et al 2006).

Despite being a cornerstone of care in type 1 diabetes, SMBG performed by intermittent capillary blood glucose testing only provides a cross-sectional 'snapshot' of blood glucose levels. This limitation may lead to undetected peaks and troughs in blood glucose occurring between times of SMBG testing, which can lead to erroneous decisions about insulin dosing and carbohydrate intake (Fiallo-Scharer and Diabetes Research in Children Network Study Group 2005). More frequent SMBG testing in intensive diabetes management is a predictor of lower glycated haemoglobin (HbA_{1c}) levels (Schutt et al 2006); however, sampling of blood glucose using a fingerprick device during SMBG is demanding for the person with diabetes, and often the frequency of testing actually performed is suboptimal (Hansen et al 2009).

Continuous glucose monitoring (CGM) systems measure glucose in the interstitial fluid, to provide semicontinuous information about glucose levels. CGM systems may allow detection of fluctuations that would not have been identified with self-monitoring alone. Currently, the regular use of CGM is not common practice in care of people with type 1 diabetes, either within Australia or in other countries with well-developed health-care systems (2007).

6.2 Comparison of continuous monitoring and standard management

Question 8

Does continuous real-time monitoring versus standard management improve HbA_{1c}, minimise fluctuations of blood glucose and reduce severe hypoglycaemia?

Question 9

Does continuous glucose monitoring (retrospective systems) versus standard management improve HbA_{1c}, minimise fluctuations of blood glucose and reduce severe hypoglycaemia?

Question 10 (background question)

What is the cost and cost-effectiveness of real-time monitoring versus standard management?

Question 11 (background question)

What are the cost and cost-effectiveness of CGM systems versus standard management?

HbA_{1c}, glycated haemoglobin; CGM, continuous glucose monitoring

The detailed systematic reviews of these questions are in Chapters 8 and 9 of the accompanying technical report, and the evidence matrixes are in Sections C8 and C9 of Appendix C

Questions 10 and 11 were background questions and thus were not included in the systematic review

For the purposes of this series of questions, standard management includes capillary SMBG at least four times per day, and an HbA_{1c} level undertaken every 3–4 months.

There are two types of CGM systems:

- 'real-time systems' that continuously provide the actual glucose concentration on a display
- so called 'retrospective systems' that measure the glucose concentration during a certain time span; the information is stored in a monitor and can be downloaded later.

The systematic review examined how continuous real-time monitoring compares with conventional management in improving HbA_{1c}, minimising fluctuations of blood glucose and reducing severe hypoglycaemia (SH).

In addressing the real-time monitoring systems (question 8) 13 publications met the inclusion criteria, of which 12 were randomised controlled trials (RCTs) (Chase et al 2003; Chase 2005; Deiss et al 2006; Hirsch et al 2008; JDRF CGM Study Group 2008; Cosson et al 2009; Hermanns et al 2009; JDRF CGM Study Group 2009; Logtenberg et al 2009; O'Connell et al 2009; Peyrot and Rubin 2009; Raccah et al 2009). The search also identified a Cochrane protocol on this topic (Langendam et al 2009). The authors were contacted and provided the final version of this systematic review. Langendam et al (In preparation) (the currently unpublished Cochrane Review) included all of the studies of real-time CGM systems captured by the search. Langendam et al (In preparation) were unable to pool the results and perform a meta-analysis. All RCTs compared CGM with SMBG; there were no head-to-head comparisons between CGM systems. Glycaemic control was an outcome measure in all RCTs, and most studies reported change in HbA_{1c} level. In power analyses, a clinically significant difference of 0.5% HbA_{1c} was often used to calculate sample size. SH and diabetic ketoacidosis (DKA) occurred infrequently; thus, most studies were underpowered to detect differences for these outcomes. Results of the cross-over trial by Logtenberg et al (2009) were excluded, because they included patients from an outpatient clinic who used continuous intraperitoneal insulin infusion (CIPII). At present, CIPII is only available in a few

European countries (mainly France, Sweden and The Netherlands); therefore, it is not relevant to Australia.

In children, an RCT reported in Langendam et al (In preparation) investigated the effectiveness of real-time CGM systems (JDRF CGM Study Group 2008). In this trial the CGM group used three different types of CGM systems, and 114 children (aged 8–14 years) were included. During the 6-month study period, HbA_{1c} levels declined in both the CGM and SMBG groups. The difference in change was not statistically significant (change in HbA_{1c} – 0.37% vs –0.22%, mean difference [MD] –0.15%, 95% confidence interval [CI]: –0.42 to 0.12). However, the proportion of patients who improved their HbA_{1c} level by at least 0.5% was significantly higher in the CGM group (54% vs 31%, relative difference [RD] 23%, 95%CI: 5% to 40%). The occurrence of SH after 6 months of follow-up was lower in the CGM study arm, but the difference was not statistically significant (7% vs 12%, RD –5%, 95%CI: –16% to 6%). At baseline and after 6 months, glucose values were measured with (blinded) CGM in both study arms. The change in mean number of minutes per day with glucose level below 3.9 mmol/L was not different between the CGM and SMBG group (–2 vs 0 minutes, p=–0.29), nor was the change in number of minutes per day with glucose level above 10.0 mmol/L (hyperglycaemia), although the change was larger in the CGM group (–102 vs –36 minutes, p=0.58).

Two RCTs addressed the adolescent population (Hirsch et al 2008; JDRF CGM Study Group 2008). In one RCT (Juvenile Diabetes Research Foundation [JDRF] adolescents) the CGM group used three different CGM devices, and included 110 adolescents (15–24 years of age) (JDRF CGM Study Group 2008). In the other trial (Hirsch et al 2008), patient age was 12–18 years, and all had been previously treated with an insulin pump for at least 6 months. The duration of both studies was 6 months. In each of the two trials, both the CGM group and the SMBG group had lower HbA_{1c} levels after 6 months from baseline, but there was no statistically significant difference in change between the two study arms, and no difference in absolute HbA_{1c} level (8.0% vs 8.2%, MD –0.19, 95%CI: –0.85 to 0.47). Also, the proportion of patients who had improved their HbA_{1c} level by at least 0.5% was equal in both groups. SH and DKA events were infrequent, and there were no significant differences between the groups. At baseline and after 6 months, glucose values were measured with CGM in both groups in JDRF (2008). The number of minutes per day with glucose level <3.9 mmol/L (hypoglycaemia) and with glucose level >10.0 mmol/L (hyperglycaemia) decreased for both groups between the two time points, but with largely the same amount (JDRF CGM Study Group 2008).

In adults, the effectiveness of real-time CGM systems was investigated in six trials (Hirsch et al 2008; JDRF CGM Study Group 2008; Cosson et al 2009; Hermanns et al 2009; Logtenberg et al 2009; Peyrot and Rubin 2009). One of these trials included patients from 12 years of age, and reported the results for HbA_{1c} for adults separately (Hirsch et al 2008). The detailed outcome of these trials is provided in the technical document. In summary, shorter term (<6 months duration) studies showed no statistically significant differences in glycaemic control for the real-time CGM systems, although one study found a relatively large and clinically relevant difference in change in HbA_{1c} (0.69%) between the CGM and SMBG groups (2009). Longer term (≥6 months) glycaemic control outcomes showed conflicting results: one RCT (with low risk of bias) showed a statistically and clinically significant greater improvement in HbA_{1c} for the CGM group (MD in change –0.52%, 95%CI: –0.72 to –0.32) (JDRF CGM Study Group 2008) while in another RCT (moderate risk of bias), there was no difference (Hirsch et al 2008).

In patients with poorly controlled diabetes (HbA_{1c} >8.0%), three RCTs using real-time CGM were performed (Deiss et al 2006; Cosson et al 2009; Raccah et al 2009). There was limited evidence for improved glycaemic control. The change in HbA_{1c} was larger in the CGM group than in the SMBG group in all three RCTs, but statistically significant in only one high-quality RCT (MD in change –0.60%, 95%CI: –1.00 to –0.20) (Deiss et al 2006). In one of these RCTs (Raccah et al 2009), a subgroup of patients who were fully protocol-compliant (including CGM sensor wear ≥70% of the time) was analysed according to a prespecified analysis. Fully compliant CGM users showed a larger improvement in HbA_{1c} than CGM users in the total group (mean change in 6 months –0.96%, standard deviation [SD] 0.93 vs –0.81%, SD 1.09%). In this per-protocol analysis, the difference in improvement between the CGM and SMBG groups was statistically significant (p-value for difference between study arms = 0.004), in contrast to the intention-to-treat analysis (Raccah et al 2009).

In conclusion, there is some evidence favouring the effectiveness of real-time CGM use to improve HbA_{1c} levels, including in those with poorly controlled diabetes. Against intuitive expectations, real-time CGM systems are not associated with lower incidence of severe hypoglycaemia in type 1 diabetes, although most studies were underpowered to detect a difference in this endpoint, and studies that include patients with hypoglycaemia unawareness are lacking.

In addressing question 9, a total of nine publications met the inclusion criteria in examining retrospective CGM systems, compared with standard management. Of these, two were systematic reviews (Chetty et al 2008; Golicki et al 2008) and seven were RCTs (Chase et al 2001; Chico et al 2003; Ludvigsson and Hanas 2003; Tanenberg et al 2004; Lagarde et al 2006; Yates et al 2006; Deiss et al 2006b); with two in adults alone (Chico et al 2003; Tanenberg et al 2004); four in children alone (Chase et al 2001; Ludvigsson and Hanas 2003; Lagarde et al 2006; Deiss et al 2006b); and one in adults and children (Yates et al 2006). The search also identified a Cochrane protocol on this topic (Langendam et al 2009); the authors were contacted and provided the final version of this systematic review (In preparation). This unpublished Cochrane review included all of the studies of CGM systems captured by our search, and here, we report only on the evidence from RCTs in retrospective CGM systems. The seven studies included in Langendam's systematic review were also included in the previous systematic review conducted by Chetty et al (2008).

The technical report addresses and tabulates the findings. In summary, Chetty et al (2008) found that, compared with SMBG, retrospective CGM systems were associated with a nonsignificant reduction in HbA_{1c} (0.22%; 95%CI: –0.439% to 0.004%; p=0.055). Sensitivity analysis using the three high-quality studies gave similar results (0.044%; 95%CI: –0.35% to 0.26%; p=0.775). When the paediatric population was analysed separately, a significant reduction in HbA_{1c} in favour of CGM systems was observed (0.37%; 95%CI: –0.71% to –0.02%; p=0.036). The authors concluded that there is insufficient evidence to support CGM systems as more beneficial than intensive SMBG in improving HbA_{1c} in patients with type 1 diabetes. There may be a benefit in the paediatric population. Langendam et al (2009), in adults, reported results that were consistent with Chetty et al (2008), showing no clear benefit of retrospective CGM systems. However, Langendam et al (2009) found the evidence for retrospective CGM systems in children to be conflicting: significantly lower in some studies (Ludvigsson and Hanas 2003; Lagarde et al 2006), and significantly higher in another (Chase et al 2001). HbA_{1c} levels for the CGM group at the end of the study were reported. In one RCT, the difference in change after 3 months was not statistically significant (Deiss et al 2006). In another RCT, the absolute HbA_{1c} level was significantly lower in the CGM group, but the difference in change in HbA_{1c} did not reach significance (Lagarde et al 2006). In terms of patients poorly controlled at study entry, three RCTs (retrospective CGM systems) were

performed with commencing HbA_{1c} >8.0%; the evidence for improved glycaemic control was conflicting. There was no definite evidence for any effect of retrospective CGM systems on SH rates or variability in blood glucose levels.

In summary, use of retrospective CGM systems compared with current standard monitoring does not provide clear metabolic benefit. The exception to this finding may be in the paediatric population.

In terms of addressing cost-effectiveness (question 10): a systematic search identified one study (Eastman et al 2003) that examined the cost-effectiveness (preliminary analysis) for the use of GlucoWatch Biographer. This study was also identified by Langendam et al in their systematic review. Because the GlucoWatch Biographer is no longer available in Australia, we have not summarised the findings of this study. The JDRF et al (2008) study (included in the systematic review for question 8), has planned a cost-effectiveness study of real-time CGM, but this analysis has not yet been published. Thus, no conclusions could be drawn or recommendations made, especially in the context of current limited demonstrable effectiveness of real-time blood glucose monitoring.

Evidence statements	
Q8	There is insufficient evidence to support routine use of continuous real-time monitoring to improve HbA_{1c} and reduce severe hypoglycaemia.
Q9	There is insufficient evidence to support routine use of continuous retrospective blood glucose monitoring systems to improve HbA_{1c} and reduce severe hypoglycaemia.
Recommendations	
R6.1	Continuous real-time monitoring may be considered for individuals expected to adhere with therapy, but routine use is not currently recommended (Grade C).
R6.2	Continuous glucose monitoring systems are not recommended for routine use to improve glycaemic control or reduce severe hypoglycaemia, but may be considered for paediatric patients (Grade C).
Practice points	
PP6.1	Continuous real-time monitoring could be considered for use by specialist units, in specific patient populations, such as those with hypoglycaemia unawareness, recurrent severe hypoglycaemia or suspected nocturnal hypoglycaemia. In these situations, use of a hypoglycaemia alarm in a real-time monitoring system may help to treat hypoglycaemia in a timely manner and help to prevent severe episodes of hypoglycaemia.
PP6.2	When combined with CSII therapy, evidence from sensor-augmented CSII studies supports use of real-time monitoring systems for metabolic (HbA_{1c}) benefit when they are used at least 70% of the time.
PP6.3	It is essential that individuals using these systems are provided with education in the correct use of the real-time monitoring device and the correct interpretation of results.
PP6.4	Real-time monitoring systems are expensive and are not currently reimbursed by the NDSS or health insurance funds. Given current constraints, they are most likely to be useful over short periods of time, to aid profile setting and trouble shooting in glycaemic control.
PP6.5	Retrospective CGM systems could be considered for use by specialist units, in specific patient populations such as those with suspected nocturnal hypoglycaemia.
PP6.6	Retrospective CGM systems are not currently reimbursed by the NDSS or health insurance funds. These systems are designed to be used continuously over short periods of time (e.g. 3 days continuously), to aid profile setting and trouble shooting in glycaemic control.

CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; HbA_{1c}, glycated haemoglobin; NDSS, National Diabetes Services Scheme

7 Insulin and pharmacological therapies

7.1 Introduction

When regular human insulin is administered subcutaneously, it is present in multimeric forms, leading to delayed and variable absorption. Therefore, altered forms of human insulin – known as insulin analogues – have been developed to deliver therapeutic insulin in a way that better reflects bolus physiological insulin requirements, both prandial (i.e. at meal times) and basal (i.e. between meals, including overnight). Adjunctive therapy with metformin in type 1 diabetes can slightly reduce insulin requirements.

The systematic review investigated a range of insulin analogues for their effectiveness in reducing glycated haemoglobin (HbA_{1c}) levels and hypoglycaemia. The analogues reviewed were the rapid-acting analogues, insulin lispro, insulin aspart and insulin glulisine; and the basal analogues, insulin glargine and insulin detemir. The analogues were compared with rapid-acting human or regular insulin, and basal-acting neutral protamine Hagedorn (NPH) insulin zinc.

7.2 Insulin analogues versus human insulin

Question 12

How effective are insulin analogues versus human insulin at reducing hypoglycaemia and HbA_{1c}?

Question 13

What is the relative effectiveness of insulin analogues on hypoglycaemia rates and HbA_{1c}?

Question 14

What are the cost and cost-effectiveness of insulin analogues on hypoglycaemia rates and HbA_{1c}?

$HbA_{1c,}$ glycated haemoglobin

The detailed systematic reviews of these questions are in Chapters 12–14 of the accompanying technical report, and the evidence matrixes are in Sections C12–C14 of Appendix C

7.2.1 Comparison of insulin analogues and human insulin in reducing hypoglycaemia and HbA_{1c}

In comparing insulin analogues with human insulin, the literature search identified 15 Level I studies in type 1 diabetes, three of which were comprehensive and were included for analysis (Banerjee et al 2007; Tran et al 2007; Singh et al 2009). Three, more recent, Level II studies were included in the analysis for rapid-acting analogues (Chatterjee et al 2007; Bartley et al 2008; Chase et al 2008). The studies covered paediatric, adolescent and adult populations. In general, the randomised controlled trials (RCTs) were limited by the lack of blinding in treatment assignment, and the lack of reported blinding of outcome assessor, patient and care giver. Most of the included trials were multicentre and were sponsored by industry, and many were also multinational.

Adults, rapid-acting and basal-acting analogues

In adults, compared with regular human insulin, use of insulin lispro resulted in an HbA_{1c} lower by 0.09% units and a 20% lower risk of severe hypoglycaemia (Singh et al 2009). The rate of total hypoglycaemia was similar between groups. Subgroup analysis by method of administration did not reveal substantial differences in treatment effects between patients using multiple daily injections (MDI) and those using continuous subcutaneous insulin infusion (CSII). Insulin aspart also resulted in a slightly lower mean HbA_{1c} concentration (0.13%) compared with regular human insulin (Singh et al 2009). However, there were no differences between groups in the risk of severe hypoglycaemia or the rate of overall hypoglycaemia.

In adults, compared with NPH insulin, use of insulin glargine resulted in a significantly lower HbA_{1c} (by 0.11% units and, more recently, by 0.19%) (Chatterjee et al 2007). There was a high degree of heterogeneity regarding hypoglycaemia, which was largely negated when the study of shortest duration (4 weeks) was removed from the meta-analysis; this study had demonstrated the largest risk reduction in favour of insulin glargine. Overall, no differences were found in HbA_{1c} between insulin detemir and NPH insulin (Singh et al 2009); however, a more recent single study (Bartley et al 2008) reported an HbA_{1c} lower by 0.22% with insulin detemir. In these studies, the risk of severe hypoglycaemia was statistically and clinically reduced (significantly – by 26% (Singh et al 2009) and 69% (Bartley et al 2008)) with use of insulin detemir compared with NPH insulin; overall hypoglycaemia was similar in the two groups.

Children and adolescents, rapid-acting and basal-acting analogues

In children and adolescents, the data demonstrated few metabolic advantages of insulin analogues compared with human insulin. In children, pooled analysis of trials comparing insulin lispro with regular human insulin found no significant difference in HbA_{1c} or hypoglycaemia (Singh et al 2009). In adolescents, one study found that nocturnal hypoglycaemia was significantly reduced by 39% (Singh et al 2009). Another study compared insulin aspart and human insulin in children, and found no differences. Similarly, no differences were found in a trial comparing insulin aspart and human insulin in patients aged 6–18 years. Furthermore, no differences in HbA_{1c} or hypoglycaemia were found between insulin glargine and the conventional insulins (mostly NPH insulin) in children or adolescents (Chase et al 2008). Regarding insulin detemir and NPH insulin in adolescents, one trial showed no difference in HbA_{1c} and a small but significant effect in favour of insulin detemir in nocturnal hypoglycaemia (reduced by 15%) and overall hypoglycaemia (Singh et al 2009).

Summary

Overall, insulin analogues appear to offer relatively few clinical advantages over conventional insulins in the management of most people with type 1 diabetes, although high-quality RCTs are needed to confirm these findings. The clearest advantage for insulin analogues is in adults, where some studies show a slight advantage in HbA_{1c} (0.1–0.2%) and others show reduced hypoglycaemia, particularly in nocturnal hypoglycaemia and severe hypoglycaemia in some studies. This advantage in hypoglycaemia is notable, because many clinical trials excluded people with a history of recurrent severe hypoglycaemia.

A recent report of combined phase III and IV studies Mullins et al (2007) found that, compared with NPH insulin, use of insulin glargine in type 1 diabetes reduced either HbA_{1c} or hypoglycaemia. Although systematic, this study appeared to be highly selective and biased in terms of the study series included for analysis. The study demonstrated an inverse relationship between HbA_{1c} and severe hypoglycaemia, and after adjusting for study

endpoint HbA_{1c}, there was some evidence for a reduction in symptomatic and severe hypoglycaemia in patients treated with glargine compared with NPH.

7.2.2 Comparisons of insulin analogues

The review identified one Level 1 study of fair quality (Singh et al 2009), which included two RCTs (Bode et al 2002; Pieber et al 2007); it also identified three further RCTs (Dreyer et al 2005; Weinzimer et al 2008; Heller et al 2009). Populations studied included children, adolescents and adults, and the studies were multicentre and multinational.

None of five studies showed a significant difference in mean change from baseline HbA_{1c} when different insulin analogues were compared. One study showed a lower relative risk of all nocturnal, all severe and symptomatic nocturnal hypoglycaemia for insulin detemir compared with insulin glargine (Pieber et al 2007). However, another study found no difference in frequency of any types of hypoglycaemia between these insulins (Heller et al 2009).

In CSII therapy, one study found no significant difference in HbA_{1c} between aspart, regular and lispro insulin in adults (Bode et al 2002). Another study of CSII therapy found no significant difference between insulin aspart and insulin lispro in HbA_{1c} or hypoglycaemia (Weinzimer et al 2008).

Some people with type 1 diabetes will prefer certain insulin types and regimens to others, even though a consistent metabolic advantage may be difficult to demonstrate. Also, some insulins may have other relative advantages; for example, insulin detemir has been shown in some high-level longer term studies to cause less weight gain than regimens using other basal insulins (especially NPH insulin) (Bartley et al 2008).

7.2.3 Cost-effectiveness studies

Twelve studies addressed the cost effectiveness of insulin analogues compared with human insulins. These studies included one meta-analysis (Tran et al 2007), three studies of rapid-acting insulin analogues (Banerjee et al 2007; Reviriego et al 2008; Pratoomsoot et al 2009), and seven studies of long-acting insulin analogues (Palmer et al 2004; Grima et al 2007; Palmer et al 2007; Brixner and McAdam-Marx 2008; Cameron and Bennett 2009; Gschwend et al 2009; Tunis et al 2009). As severe hypoglycaemia has a significant impact on the total cost of diabetes, the studies found that the use of insulin analogues may be associated with reductions in annual costs by reducing the frequency of severe hypoglycaemia. However, the overall financial effect may be cost neutral or cost saving when total costs are considered, because insulin analogues cost more. Studies of quality-adjusted life years and quality-adjusted life expectancy in developed countries generally demonstrate that insulin analogues are economically justified in the treatment of type 1 diabetes.

Evidence statements	
Q12	In adults, Level I studies of insulin analogues show a small (0.1–0.2%) but statistically significant reduction in HbA_{1c} with insulin analogues compared to human insulin; this effect is not seen in children.
Q12	Compared with human insulin, insulin analogues have no effect on overall hypoglycemia, but lead to a slight reduction in severe and nocturnal hypoglycemia in adults. Compared with human insulin, insulin detemir shows a small but significant benefit with respect to nocturnal and overall hypoglycemia in children and adolescents.
Q13	Level II evidence is consistent in showing no significant difference between insulin analogues in relation to their effect on HbA_{1c}.
Q13	Overall, Level II evidence shows no significant difference between insulin analogues in relation to reduction of hypoglycemia.
Recommendation	
R7.1	Human insulin or insulin analogues may be used as treatment for glycaemic control (Grade C).
Practice points	
PP7.1	Basal and rapid-acting insulin analogues may reduce the risk of hypoglycaemia compared to human insulin.
PP7.2	Insulin analogues may be useful in people who have a history of recurrent nocturnal or severe hypoglycaemia.
PP7.3	In some people, basal and rapid-acting insulin analogues may improve an individual's HbA_{1c} level without increasing hypoglycaemia.
PP7.4	Rapid-acting insulin analogues may be useful in people who match bolus insulin doses to carbohydrate intake by counting.
PP7.5	Personal preference and quality of life should be considered when individualising insulin therapy, including analogue therapy versus human insulin.
HbA_{1c}, glycated haemoglobin	

7.3 Continuous subcutaneous infusion pumps versus multiple daily injections

Question 15

How effective are modern pumps versus MDI at reducing hypoglycaemia and HbA_{1c} and improving QoL (DQOL or SF-36 or others)?

Question 15a

How effective are sensor-augmented insulin-infusion pumps versus MDI at reducing hypoglycaemia and HbA_{1c}, and improving QoL?

Question 16

What are the costs (upfront plus ongoing) and cost effectiveness of treatment with CSII pumps versus MDI?

CSII, continuous subcutaneous insulin infusion; DQOL, diabetes quality of life; $HbA_{1c,}$ glycated haemoglobin; MDI, multiple daily injections; QoL, quality of life

MDI is defined as three injections per day for adults, and at least three injections per day for children; modern pumps are defined as those that are available in Australia or overseas, and are not obsolete.

The detailed systematic reviews of these questions are in Chapters 15 and 16 of the accompanying technical report, and the evidence matrixes are in Sections C15 and 16 of Appendix C

Intensive diabetes management can be delivered using either MDI as part of a basal-bolus insulin approach, or rapid-acting insulin in insulin pump therapy as CSII. Since the Diabetes Control and Complications Trial publication in the early 1990s, MDI has included three or more injections of subcutaneous insulin each day for adults; CSII therapy has also progressively improved. Thus, for the purposes of this question, MDI is defined as three or more injections per day; modern CSII pump therapy is defined as those pumps that are available in Australia or overseas and have not become obsolete.

The systematic literature review addressing question 15 identified three systematic reviews (Fatourechi et al 2009; Pankowska et al 2009; Misso et al 2010) and two additional RCTs (Opipari-Arrigan et al 2007; Bolli et al 2009). Ten of the studies included in the meta-analysis of HbA_{1c} by Misso et al (2010) were published before 2000, and they were therefore excluded from our modern CSII and MDI criterion. We reanalysed the data from the remaining studies that met our inclusion criteria, with the addition of the study by Bolli et al (2009). A random-effects model was used, and results were reported as weighted mean difference at endpoint.

In terms of HbA_{1c} outcomes, the studies included in this analysis were in children and adults with type 1 diabetes, with 697 people (CSII n=351, MDI n=346), 204 of whom were younger than 18 years and 493 of whom were older than 18 years. Overall, the mean difference at treatment end between CSII and MDI in HbA_{1c} was –0.2% in favour of CSII (95% confidence interval [CI]: –0.28 to –0.12, $p<0.00001$) with low heterogeneity across the studies. In adults, the mean difference in HbA_{1c} was –0.16% ($p=0.06$) in favour of CSII. In children, the mean difference in HbA_{1c} was –0.25% ($p=0.01$) in favour of CSII. This is in keeping with the meta-analysis by Pankowska and colleagues, which showed a significantly lower HbA_{1c} value in the children treated with CSII compared with MDI group by –0.24% ($p<0.001$) (Pankowska et al 2009).

In assessing hypoglycaemia, Misso et al (2010) suggested that data from the 17 studies in their meta-analysis reporting on hypoglycemia indicated that there was no relevant benefit of one intervention over the other for reducing nonsevere hypoglycaemic events. However,

the authors suggested that CSII may be better than MDI for reducing the incidence of severe hypoglycaemic events. Pankowska et al (2009) only assessed episodes of severe hypoglycaemia: four included studies reported episodes of severe hypoglycemia, and meta-analysis showed no significant difference between CSII and MDI, with a pooled relative risk and 95%CI of 0.87 (0.06 to 11.66); p=0.87. When Fatourechi et al (2009) undertook a meta-analysis of hypoglycaemia, the authors found a nonsignificant reduction in severe hypoglycaemia (pooled odds ratio [OR] 0.48, 95%CI: 0.23 to 1.00) and no evidence for a reduction in nocturnal hypoglycaemia (pooled OR 0.82, 95%CI: 0.33 to 2.03). Adolescents and adults enrolled in crossover trials also had nonsignificantly fewer minor hypoglycemia episodes per patient week (p=0.06) with CSII than MDI, whereas children enrolled in parallel trials had significantly more episodes with CSII (p=0.03). The authors noted that the main limitation of their study was the paucity of data in patients with a history of severe hypoglycaemia and patients with hypoglycaemia unawareness (Fatourechi et al 2009). However, Bolli et al (2009) found the incidence of total hypoglycaemia, nonsevere hypoglycaemia, symptomatic hypoglycaemia and asymptomatic hypoglycaemia was similar in both groups; only two participants in both groups experienced one severe hypoglycaemic event. It is noteworthy that the event rates for hypoglycaemia were low in all these studies, which affects the power to detect between group differences. The studies were not powered for the outcome of severe hypoglycaemia.

In terms of quality of life (QoL), Misso et al (2010) reported that, while QoL was measured by different instruments in 15 of the included studies, the data suggested that most participants were more satisfied with CSII than MDI. Of the studies from this paper that met our inclusion criteria, eight measured QoL using validated measurement tools. Four studies used the validated Diabetes Treatment Satisfaction Questionnaire (DTSQ); two of these studies enrolled people younger than 18 years. In all four studies, the CSII group scored higher (representing better treatment satisfaction) than the MDI group. This difference was statistically significant in two of the four studies. Of the two studies that used the validated diabetes QoL youth scale, one study in adults reported a higher score, representing better QoL in the CSII group than the MDI group. The other study, which enrolled people younger than 18 years, did not report scores but noted that there was no difference between the groups. Two studies that used the validated diabetes QoL scale (DQOL) found that the MDI group scored lower (representing better QoL than the CSII group), but this was not statistically significant. The SF-12 questionnaire, SF36 general health perceptions scale, and the paediatric QoL inventory (PedsQL) revealed that CSII was favoured over MDI for perception of better mental health, perception of better general health, and better QoL, respectively.

Pankowska et al (2009) analysed the results of QoL measures reported in four of the included studies. In one study, DTSQ scores were significantly higher in patients treated with CSII (30.6±3.7 vs 21.9±3.8, p<0.001). In a second study, DQOL from baseline to end of study was significantly better in the CSII group (–0.24±0.25 vs –0.08±0.19, p=0.03). In a third study, DQOL was measured separately in mothers and fathers, with mothers of patients on MDI reporting a greater negative impact of diabetes on family life, and fathers in the MDI group reporting significantly higher scores on the stress index. There was no difference in DQOL scores between groups in the fourth study. Bolli et al (2009) found a significant increase in DTSQ treatment satisfaction score in the CSII group compared with the MDI group (3.1, 95%CI: 0.1 to 6.1, p=0.042). Opipari-Arrigan et al (2007) measured diabetes-related QoL with a validated tool – the PedsQL. They found a significant improvement in diabetes symptoms in both groups compared with baseline, and a significant decrease in diabetes related worry in the CSII group.

In summary, there is evidence from the studies reviewed suggesting that, on average, there is some advantage for CSII over MDI in terms of HbA_{1c} levels, especially in the paediatric population, and QoL advantages for many people receiving CSII compared with MDI. Hypoglycaemia outcomes appear to be similar for CSII and MDI, although people at the highest risk of severe hypoglycaemia, who had a history of severe hypoglycaemia or a lack of hypoglycaemia awareness, were often excluded from these studies.

For intensive insulin diabetes regimens to be effective, whether using CSII or MDI, individuals need to be motivated, prepared to routinely undertake carbohydrate counting and frequent self-measures of blood glucose (SMBG), and to make correction dosage adjustments to insulin therapy. The studies varied in terms of whether the CSII group received more intensive education in SMBG, bolus correction and carbohydrate counting than the MDI group. Thus, the intensive diabetes-management approach, rather than CSII alone, may account for some of the observed advantages of CSII over MDI. To achieve sustained outcomes in intensive diabetes management, reliable follow-up in health care by the person with type 1 diabetes with their multidisciplinary diabetes health care team is highly desirable. This helps to ensure that self-management – including target setting – remains appropriate, and that patients continue to be motivated to optimise their health outcomes through self care.

In addressing sensor-augmented pumps, one study met the inclusion criteria (Bergenstal et al 2010). In this multicentre (n=30) study of fair study quality, 485 patients (n=329 adults, n=156 children) were randomised to receive either sensor-augmented CSII or the MDI approach (which did not include any real-time sensor component). Inclusion criteria were HbA_{1c} 7.4–9.5%, at least 3 months of MDI before enrolment, and monitoring of blood glucose levels at least four times per day. Exclusions included CSII in past 3 years, age under seven years, two or more severe hypoglycaemic episodes per year before enrolment, or current pregnancy. Baseline characteristics in both groups were similar. The primary outcome was change from baseline in HbA_{1c}, with the rate of severe hypoglycaemia as the secondary outcome. Follow-up measures occurred progressively at 3-month intervals for 12 months. Finally, for reasons of technical device training, patients in the pump therapy group received more contact with clinical staff members than did patients in the injection-therapy group during the first 5 weeks of the study.

Study outcomes at 1 year showed that the mean HbA_{1c} level had decreased from the baseline of 8.3% in all groups, to 7.5% in the sensor-augmented CSII group, compared to an average level of 8.1% in the MDI group ($p<0.001$ for difference between groups). Significant differences were seen by 3 months of the trial and were maintained across the 12 months. The proportion of patients who reached the target of less than 7.0% HbA_{1c} was also greater in the pump-therapy group (27%) as a whole than in the injection-therapy group (10%) ($p<.001$), and was significantly greater in adults alone. Post-hoc analysis showed that, in the sensor-augmented CSII group, the increased use of the sensor was associated with a greater reduction in HbA_{1c} at 12 months in the entire group ($p=0.003$). There was no significant difference between groups in the rate of severe hypoglycaemia, which was at a low rate in both groups. QoL was not assessed.

7.3.1 Cost-effectiveness studies

Campbell et al (2008) reported cost effectiveness as the incremental cost per severe hypoglycaemic attack avoided over 6 years. The analysis projected costs saved per severe hypoglycaemic attack, but the authors noted that the current evidence regarding reduction in severe hypoglycaemic events in patients treated with CSII compared to MDI was equivocal. The total additional costs of using CSII relative to improvements seen in glycaemic

control, and the reduction in consequent diabetic complications, were considered and modelled by Cohen et al (2007), Roze et al (2005) and St Charles (2009), based on a lifetime horizon. All three studies used a base case of a 1.2% reduction in HbA_{1c} in the patients treated with CSII compared to MDI. In Cohen et al (2007), the mean discounted lifetime direct medical costs associated with CSII was projected to be $A123 402±2113 in Australian adults compared with $A88 760±2055 for MDI (and in adolescents, $A148 918±2498 vs $A107 139±2320). The authors reported the incremental difference in costs of A$34 642 translated into a cost per life-year gained (LYG) of $A88 220 with CSII versus MDI in adults, and in the incremental difference of A$41 779 translated into a cost per LYG of $A77 851. These results are both near the threshold value of $A76 000/LYG considered to represent good value for money in Australia. All three studies (Cohen et al (2007), Roze et al (2005) and St Charles (2009)) also presented sensitivity analyses based on a reduction of HbA_{1c} of 0.51%, which is much closer to the reduction of HbA_{1c} of 0.2% reported in the systematic review of the clinical effectiveness of CSII versus MDI associated with this report. Costs were substantially higher for the smaller reduction in HbA_{1c}. However, the economic models did not include any reduction in the long-term complications of diabetes that may occur due to improved glycaemic control; nor did they include the associated costs, quality of life or survival implications.

Evidence statements	
Q15	Across all individuals with type 1 diabetes, Level II evidence shows that CSII has a minor benefit for HbA_{1c} levels compared to MDI. Level I evidence demonstrates a small but statistically significant reduction in HbA_{1c} with CSII compared to MDI.
Q15	There is no evidence to support a reduction in hypoglycaemia in adults. There is Level I evidence of a slight, but statistically significant increase in mild hypoglycaemia in children using CSII. There is no statistically significant evidence to support a reduction in severe and nocturnal hypoglycaemia in adults and children.
Q15	Level II evidence shows an improvement in QoL with CSII compared to MDI. Level II evidence consistently shows improved treatment satisfaction with CSII compared to MDI.
Recommendation	
R7.2	Nonsensor-augmented CSII should be considered for use in individuals in whom the expected magnitude of benefit is clinically significant in terms of reducing HbA_{1c}, reducing hypoglycaemia, or improving QoL (Grade C).
Practice points	
PP7.6	Individuals who may be likely to benefit from CSII pump therapy, as part of intensive diabetes management, are: • some children and adolescents, including infants and young children, and pregnant adolescents (ideally preconception) • individuals with microvascular complications of diabetes • individuals with reduced hypoglycaemia awareness • individuals (or their supervising adults) with desirable motivational factors; for example, those seeking to improve blood glucose control and having realistic expectations • individuals exhibiting desirable CSII treatment-related behavioural factors, including those who: – are able to perform carbohydrate counting – are currently undertaking four or more blood glucose tests per day – have reliable adult supervision (in paediatrics), and a history of good self-management skills (in adults) – are able to master the technical skills of CSII – are reliable in follow-up health care.
CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections; QoL, quality of life	

7.4 Metformin as an adjunct to insulin

Question 17

How effective is metformin plus insulin versus insulin alone at achieving glycaemic control (HbA_{1c} targets), reducing body weight, and reducing insulin requirement?

HbA_{1c}, glycated haemoglobin

Question 18 (background question)

What are the costs and cost-effectiveness of adding metformin to insulin?

The detailed systematic reviews of question 17 is in Chapter 17 of the accompanying technical report, and the evidence matrix is in Sections C17 of Appendix C

Question 18 was a background question and therefore was not systematically reviewed

Metformin is a biguanide that is commonly used in the treatment of type 2 diabetes, where it improves glycaemic control without causing weight gain. Metformin lowers glucose by reducing hepatic glucose production (by inhibiting gluconeogenesis), and increasing insulin-

stimulated glucose uptake in skeletal muscle and adipocytes. The effect of metformin on glucose metabolism is independent of residual β-cell activity; thus, the drug may have potential for use in patients with type 1 diabetes (Jacobsen et al 2009).

A systematic review and meta-analysis published in 2010 (Vella et al 2010) aimed to capture all published data from RCTs that involved using metformin in people of any age with type 1 diabetes. The review found five studies with relevant outcomes. Based on these studies, the overall effect on %HbA_{1c} was a standardised mean difference (SMD) between treatment groups of −0.10, favouring metformin added to insulin (95%CI: SMD reduction of –0.36 to 0.15, p=0.42) (not statistically significant). As there was some suggestion of heterogeneity (p=0.175), the authors carried out a sensitivity analysis of the four smaller and shorter studies. Excluding the largest study (Lund et al 2008), the overall effect on %HbA_{1c} was an SMD between treatment groups of −0.30 (i.e. 0.30 standardised units lower in the metformin than in the placebo groups; 95%CI: SMD of −0.64 to 0.037, p=0.081). This translates into an absolute difference in HbA_{1c} of 0.28% lower in the metformin than in the placebo groups (difference not statistically significant), with little evidence of heterogeneity (p=0.35).

The meta-analysis also analysed insulin dose in the five relevant studies (Vella et al 2010). The longest of these studies (up to 12 months duration) found a statistically significant reduction in daily insulin dose with metformin. The overall measure of effect was an SMD between treatment groups of –0.65 (i.e. 0.65 standardised units lower in the metformin than in the placebo groups; 95%CI: SMD of –0.92 to –0.39 units, p<0.001). This translates into an absolute difference in insulin-dose requirement of 6.6 U/day less in the metformin than in the placebo groups. The $\chi 2$ test of heterogeneity was not statistically significant (p=0.41).

Seven studies were of sufficient duration to report data on changes in weight or BMI. Metformin reduced weight by 1.7–6.0 kg in two studies (Lund et al 2008; Jacobsen et al 2009), but had no effect on weight in three others (Meyer et al 2002; Särnblad et al 2003; Khan et al 2006). A sustained and statistically significant reduction (mean 1.74 kg) was reported in the largest study, which was also of the longest duration (Lund et al 2008). There were insufficient data on weight for a formal meta-analysis of this outcome (Vella et al 2010).

There have been no rigorous, prospective studies of metformin in type 1 diabetes, in relation to diabetes complications outcomes. In type 2 diabetes, metformin is the agent of first choice. In a long-term Level II clinical trial of metformin in type 2 diabetes (UKPDS Group 1998a), metformin reduced microvascular and cardiovascular events in overweight people, and reduced diabetes-related death and all-cause mortality in this population. Metformin is known to have clinical value in women who have polycystic ovarian syndrome, where it may induce ovulation and aid fertility (Tang et al 2010).

Evidence statements	
Q17	Level I evidence demonstrates a small but not statistically significant reduction in HbA_{1c} with metformin plus insulin compared to insulin alone.
Q17	Level II evidence shows no consistent effect of metformin plus insulin versus insulin alone on reduction in BMI or body weight.
Q17	Level I evidence demonstrates a small but statistically significant reduction in insulin requirement with metformin plus insulin compared to insulin alone.
Recommendation	
R7.3	Metformin should not be used in routine clinical practice for type 1 diabetes (Grade C).
Practice points	
PP7.7	Metformin may be considered in individuals who have a high insulin requirement (e.g. overweight or obese subjects with total daily insulin dose at or above 2.0 IU/kg body weight), although the evidence demonstrates only a modest overall reduction in insulin requirement.
PP7.8	Since metformin may contribute to lactic acidosis development in metabolically unstable patients, it is relatively contraindicated in people who are at high risk of developing diabetic ketoacidosis or have high alcohol consumption.
PP7.9	Metformin is not contra-indicated in individuals with type 1 diabetes and co-existing polycystic ovary syndrome, and may be used to help induce ovulation.
PP7.10	Use of metformin in type 1 diabetes is not approved by the Therapeutic Goods Administration and is an 'off-label' indication in Australia. Prescribers should be aware that long-term adverse effects of metformin include an increased risk of vitamin B-12 deficiency, which should be monitored.

8 Health-care delivery

8.1 Introduction

Multidisciplinary care is established practice for the management of individuals of all ages with type 1 diabetes. The specialist multidisciplinary diabetes care team includes:

- the person with diabetes and their family or carer
- a paediatric or adult endocrinologist or physician trained in the care of children, adolescents or adults with diabetes
- a diabetes educator
- a dietitian
- a psychologist or social worker with knowledge of diabetes and chronic illness.

The specialist health-care professional team leads and takes responsibility for diabetes care, including initiation of and changes to diabetes management, regular reviews, screening for complications and management of diabetes 'sick days'. The patient's general practitioner (GP) should be involved in care, including management of inter-current medical conditions and preventive health issues, such as immunisation schedules. The GP may also have an important role in psychosocial support, and in ensuring additional access to allied health services via Medicare for the person with type 1 diabetes. To ensure consistency and continuity of care, when a patient has been seen by the specialist team, the team then needs to inform the GP in in a timely manner of any changes to diabetes management, and the rationale for the changes. This is particularly important if the changes are significant.

During pregnancy, the diabetes care team should also include an obstetrician. Depending on the health-care needs of the person with diabetes, other members of a team may include:

- a podiatrist
- an exercise physiologist
- an optometrist
- medical specialists, including an ophthalmologist, psychiatrist, nephrologist, cardiologist, gastroenterologist, dermatologist, adolescent physician and geriatrician, as appropriate.

The family's importance as members of a child's care team should be emphasised from the day of diagnosis (Pihoker et al 2009). Care provided by a multidisciplinary team results in fewer days in hospital, a higher level of participation in diabetes self-care practices, decreased re-admission rates, lower glycated haemoglobin (HbA_{1c}) levels and delayed development of complications (Levetan et al 1995; Zgibor et al 2000; Zgibor et al 2002).

The health-care needs of Aboriginal and Torres Strait Islander peoples and culturally and linguistically diverse people should be specifically considered and professional support from indigenous health-care workers included as part of multidisciplinary care.

The multidisciplinary team may not be available in rural and remote areas, particularly those with low population density. In such circumstances, primary care may be provided by a locally based paediatrician or physician, or a GP. These practitioners should have ready access to facilities and advice provided by the diabetes care team in regional centres.

Telemedicine is an option for delivery of health care to remote and geographically isolated sites.

Diabetes is primarily managed in the outpatient or ambulatory setting. Regular and continuing ambulatory diabetes care assessment is essential for maintaining optimal glucose control and monitoring for risk factors for acute and chronic complications.

After hours, patients should have access to the multidisciplinary diabetes specialist care team. For example, the team should be available to provide support in sick day care or when severe hypoglycaemia occurs, and to advise on the need for acute care hospital assessment.

8.2 Ambulatory care

Question 19

What is the effectiveness of ambulatory care versus hospital inpatient care of patients with newly diagnosed disease?

The detailed systematic review of this question is in Chapter 19 of the accompanying technical report, and the evidence matrix is in Section C19 of Appendix C

8.2.1 At diabetes onset

Approaches to the initial management of patients newly diagnosed with diabetes who are not acutely unwell include:

- home management; this may involve one or two visits daily by a diabetes nurse for 2–3 days, followed closely by subsequent outpatient care (Dougherty et al 1999)
- ambulatory care; this involves initial insulin therapy and education being delivered in an outpatient setting, and commonly involves up to 1 week of diabetes self-care education and review every day or every second day, initially (Clar et al 2007)
- hospital inpatient admission.

Outpatient care is standard for adults with newly diagnosed type 1 diabetes who are not unwell, whereas, in children and adolescents, both inpatient and ambulatory care are practised.

A systematic review of routine hospital admission versus outpatient or home care in children at diagnosis of type 1 diabetes (Clar et al 2007) included two randomised controlled trials (RCTs) and five cohort studies, involving 626 children and adolescents. Of these, 298 received ambulatory care at diagnosis, either on an outpatient basis or at home, or in a combination of these types of care. Of the studies included in the review, only one was regarded as of good quality and of low risk of bias (Dougherty et al 1999). This was an RCT of 62 Canadian children who received traditional hospitalisation and outpatient follow-up or home management. The study found a significant between-group difference in glycaemic control at 2 and 3 years follow-up, with the ambulatory care group having a 0.7% lower HbA_{1c} (Dougherty et al 1999). None of the other studies found differences in glycaemic control between groups. Three studies measured patient knowledge, and found no significant difference between groups (Dougherty et al 1999; Siminerio et al 1999; Srinivasan et al 2004). The two studies that reported adverse events (diabetic ketoacidosis [DKA] and severe hypoglycaemia) found no difference between groups in either of these outcomes (Chase et al 1992; Dougherty et al 1999). Other psychosocial outcomes examined did not differ between groups; they included treatment adherence, family impact, coping and stress, treatment satisfaction, quality of life, child behaviour and sociability (Clar et al 2007).

There is Level IV evidence supporting a benefit of ambulatory care in terms of hospital re-admission rates (Swift et al 1993). In a 10-year retrospective cohort study from the United Kingdom of children with type 1 diabetes aged under 15 years, 138 of 236 children were managed in the home or outpatient setting. Significantly fewer children who received home management were re-admitted for diabetes-related reasons (p=0.004). There was no difference in glycaemic control between the groups.

8.2.2 After diabetes onset

After the initial period of diagnosis and education (when frequent contact with the diabetes care team is usually required), individuals with diabetes should be reviewed regularly, at least 3–4 times per year. The reviews should include one major annual review with the multidisciplinary team, which in children should include regular assessment of growth , blood pressure, puberty, associated conditions, nutrition and complications. All patients should have a GP who is regularly kept informed of the diabetes management.

As a chronic and complex disease, type 1 diabetes places a substantial and often relentless burden of treatment demands on the person with diabetes and their family. This burden can lead to reduced adherence to therapy, and may limit the capacity of the person with diabetes to fully participate in diabetes self-care (May et al 2009). An increasingly appreciated concept in chronic disease is to deliver health care that is minimally disruptive to the patient's lifestyle; this strategic approach aims to optimise quality of life, patient engagement in therapy and metabolic outcomes. Termed 'minimally disruptive medicine', the approach is facilitated by interdisciplinary coordination in clinical practice, and by personalising the health care delivered. For example, the health professional and patient share decision making, and set care priorities from the perspective of the person with diabetes (insert new ref x). These aspects of health-care delivery can be practised in an organised diabetes ambulatory care setting.

Evidence statements	
Q19	Ambulatory care, delivered by a multidisciplinary team in a tertiary referral diabetes service, at diagnosis of type 1 diabetes in children over 2 years of age: results in a lower HbA_{1c} (0.7%) at 3 years follow-up compared to in-hospital care at diagnosis does not increase the risk of severe hypoglycaemia or diabetic ketoacidosis, or result in poorer levels of diabetes knowledge at 2 years follow-up compared to in-hospital care at diagnosis.
Recommendation	
R8.1	Paediatric patients presenting with newly diagnosed type 1 diabetes should be managed in an appropriately resourced ambulatory care or inpatient hospital setting (Grade B).
Practice points	
PP8.1	Groups for whom inpatient management is necessary at diagnosis include: • individuals with diabetic ketacidosis, significant comorbidities, inadequate social support or mental health issues • children under 2 years of age • those in geographically remote areas • non-English speakers.
PP8.2	In adults, ambulatory care at diagnosis is considered to be routine unless there are specific issues.
HbA_{1c}, glycated haemoglobin	

8.3 Telemedicine

Question 20

What is the effectiveness of telemedicine and other technology-based delivery methods for rural and remote individuals?

The detailed systematic review of this question is in Chapter 20 of the accompanying technical report, and the evidence matrix is in Section C20 of Appendix C

Australia is geographically large, but most of the population is concentrated in the southeast of the country. In many parts of Australia, the population density is low and health-care services are provided in regional sites some hundreds of kilometres away. This is often the case in type 1 diabetes, where multidisciplinary health-care services across a specialist team are typically desired and are necessary to optimise health care. Telemedicine, defined as the use of electronic information and communication technologies to provide and support health care when distance separates the participants (Field 1996), is one potential method by which health-care could be delivered in a personalised, patient-specific manner to remote and geographically isolated sites.

The systematic review identified a total of four relevant publications: two RCTs (Level II) (Ahring et al 1992; Biermann et al 2002), a comparative study (Level III-2) (Corriveau et al 2008), and a case-series study (Level IV) (Liesenfeld et al 2000). Technology methods used in the intervention included: telephone modems, telemanagement and internet-based systems, and in some cases subsequently included health professional consultation and advice.

All four studies reported changes in HbA_{1c} as an outcome measure. They were based in North America and in European countries, with study duration 1–8 months. Of the four studies, only one (Ahring et al 1992), reported a statistically significant reduction in HbA_{1c} level compared with a control group, and another (Corriveau et al 2008) showed improvement in HbA_{1c} compared with baseline in patients using an internet-based insulin pump monitoring system. One other study (Biermann et al 2002) reported cost and time savings of a telemedicine intervention. The authors developed a cost-analysis scenario that showed a saving of €650 (~AUD $900) per year per patient in achieving HbA_{1c} outcomes.

Telemedicine has the potential to aid in medical care in type 1 diabetes for rural and remote individuals; however, there have been few studies of this, especially in an Australian context. The four included studies reported were from international sources and were of limited methodological quality, involving small numbers of participants (42–94 per study).

Evidence statement	
Q20	There is insufficient evidence to determine the effect of telemedicine and other technology-based delivery methods for rural and remote individuals on glycaemic control or time and cost savings.
Practice point	
PP8.3	Technological mechanisms to support management can be a component of care for rural and remote patients, but should not replace face-to-face clinical care.

9 Education and psychological support

9.1 Introduction

It is widely recognised that psychological and behavioural problems affect the outcomes and management of type 1 diabetes. The systematic review that examined the prevalence of psychological disorders (see Chapter 2 of the technical report) provided evidence for an increased prevalence of depression and anxiety in young people with type 1 diabetes. However, the evidence base to guide the use of screening tools for psychological disorders in type 1 diabetes is limited. Therefore, a systematic review was undertaken to examine the diagnostic performance of screening tools for psychological disorders in type 1 diabetes, to inform clinical practice. The results of this review are summarised in Section 9.2.

It is also widely recognised that intensive educational input and continuing support, frequently and at high levels, are key components of effective diabetes self management. The Diabetes Control and Complications Trial (DCCT) provided unequivocal evidence that intensification of management reduces microvascular complications. More than 20 years after the DCCT was conducted, it is now clear that education is a fundamental component of diabetes care for people with type 1 diabetes. Educational and psychological interventions are frequently combined to improve knowledge, skills and self efficacy across various aspects of diabetes self management (Swift 2009). Therefore, it is difficult to ascertain the effectiveness of the educational component on metabolic and psychological outcomes. To address this issue, a systematic review examined the effects of educational and psychological interventions on metabolic and psychological outcomes. The results of this review are summarised in Section 9.3.

9.2 Psychological screening tools

Question 21

What is the diagnostic performance of the following screening tools: CDI, BASC, EDE, CHQ, BAI, BDI, HADS, EDI, ADS, ATT19?

ADS, Appraisal of Diabetes Scale, ATT19, Diabetes Integration Scale; BAI, Beck Anxiety Inventory; BASC, Behaviour Assessment System for Children; BDI, Beck Depression Inventory; CDI, Children's Depression Inventory; CHQ, Child Health Questionnaire; EDE, Eating Disorders Examination; EDI, Eating Disorder Inventory; HADS, Hospital Anxiety and Depression Scale

The detailed systematic review of this question is in Chapter 21 of the accompanying technical report, and the evidence matrix is in Section C21 of Appendix C

A wide range of tools are available to screen for psychological disorders (including depression, anxiety and eating disorders) and behavioural problems in patients with type 1 diabetes and other chronic conditions. The tools examined in this systematic review were the Behaviour Assessment System for Children (BASC), the Children's Depression Inventory (CDI), the Child Health Questionnaire (CHQ) and the Eating Disorders Examination (EDE). The tools studied in adults were the Appraisal of Diabetes Scale (ADS), the Beck Anxiety Inventory (BAI), the Beck Depression Inventory (BDI), the Diabetes Integration Scale (ATT19), the Eating Disorder Inventory (EDI) and the Hospital Anxiety and Depression Scale (HADS).

The systematic review examined the diagnostic performance of these screening tools in patients with type 1 diabetes. Outcomes examined were the diagnosis of anxiety, depression or eating disorder. The systematic review identified three studies: Cameron et al (2003), Hermanns et al (2006) and Lustman et al (1997).

The CHQ, evaluated by Cameron et al (2003), is a generic health status questionnaire that measures functional health and wellbeing in children aged 5–18 years, in the context of their family and social environments. In particular, the CHQ assesses the burden imposed by health problems on functional health and wellbeing of children (Landgraf et al 1996). In a study of 103 children in Victoria with type 1 diabetes and aged 7–12 years, Cameron et al (2003) assessed the validity of the CHQ as a screening tool for detecting 'at-risk' emotional and behavioural maladjustment in children with diabetes, compared with the BASC. The investigators found significant correlations between the CHQ Global Behaviour and Mental Health scales, and the BASC Externalizing and Internalizing scales, respectively. They concluded that sequential use of the CHQ, as a screening tool, followed by an established mental health measure such as BASC, may help to identify children with diabetes who are at risk for chronic maladjustment and poor health outcomes.

The study by Hermanns et al (2006) assessed the screening performance of different measures of depression, including the BDI, and the Problem Areas in Diabetes (PAID) questionnaire. This German study involved 372 adults with diabetes, of whom 142 had type 1 diabetes. Patients who were positive on one of the depression questionnaires subsequently participated in the Composite International Diagnostic Interview (CIDI). The BDI measures the severity and depth of depression symptoms, whereas the PAID is designed to identify negative emotional responses related to various aspects of diabetes.

In the subgroup of patients with type 1 diabetes, the prevalence of clinical depression was 30%, and a further 31% were diagnosed with subclinical depression. In the total study group, the authors found that the BDI was the most sensitive assessment method for detecting clinical depression (as defined by the International Statistical Classification of Diseases and Related Health Problems 10th Revision – ICD-10), with a good balance between sensitivity (87%) and specificity (81%), using receiver operating characteristic (ROC) analysis. This was higher than the PAID questionnaire's ability to screen for clinical depression, with a sensitivity of 81% and a specificity of 74%. Positive predictive values for both tools were low (BDI 43% and PAID 34%), while negative predictive values were high (97% and 96% respectively). The BDI was also more sensitive than the CIDI. All methods had low sensitivity for the detecting diabetes-specific emotional problems. None of the analyses were specific to patients with type 1 diabetes (Hermanns et al 2006).

The BDI was also evaluated as a screening tool for major depression in diabetes in a United States study of 172 adults with diabetes, 59 of whom had type 1 diabetes (Lustman et al 1997). The BDI was compared with a diagnostic interview (the National Institute of Mental Health Diagnostic Interview Schedule), according to *Diagnostic and statistical manual of mental disorders* (DSM)-III-R criteria, using ROC analysis. The BDI effectively discriminated depressed participants from nondepressed participants, using the full 21-item BDI, the cognitive items alone, or the somatic items alone – although the cognitive items were more effective than the somatic items. The authors also found that a cut-off score of 16 or more provided a sensitivity of 70% and positive predictive value of 70%. They concluded that the BDI is an effective screening test for major depression in adults with diabetes.

Summary

A single study suggested that the CHQ may be useful as a screening tool in children with type 1 diabetes (Cameron et al 2003). Two studies indicate that the BDI may be useful in screening for depression in adults with either type 1 or type 2 diabetes (Lustman et al 1997; Hermanns et al 2006).

Evidence statement	
Q21	There is one Level II and one Level III study demonstrating the diagnostic accuracy of the BDI in a mixed population of type 1 and type 2 diabetes. There is one Level II study examining the diagnostic accuracy of the CHQ administered to the parents of children with type 1 diabetes. No evidence was identified for the performance of other psychological screening tools in type 1 diabetes.
Practice points	
PP9.1	Regardless of whether a tool is used, people with a suspected mental health disorder should be referred for appropriate assessment.
PP9.2	Consideration should be given to the practicality of using specific tools in clinical practice (self versus interviewer or clinician administered; length; complexity), reference to more general tools or screening already undertaken, resourcing issues and labelling (as per mental health in general).
PP9.3	Diabetes care teams should have appropriate access to mental health professionals to support them in the assessment of psychological functioning in people with type 1 diabetes (NICE 2010).
PP9.4	Assessment of developmental progress in all domains of quality of life (i.e. physical, intellectual, academic, emotional and social development) should be conducted on a routine basis in the clinical setting.
BDI, Beck Depression Index; CHQ, Child Health Questionnaire	

9.3 Education and psychological support programs

Question 22

What is the effectiveness of education and/or psychological support programs in type 1 diabetes:

a) on metabolic outcomes

b) on psychological outcomes?

Question 23 (background question)

What are the cost and cost effectiveness of different education programs?

The detailed systematic review of this question is in Chapter 22 of the accompanying technical report, and the evidence matrix is in Section C22 of Appendix C

Question 23 was a background question and was not systematically reviewed.

For the purpose of this review, education and psychological programs were defined as interventions that are delivered in either a group or one-on-one format, and are focused on changing either knowledge, behaviour or self-management skills; or have a psychological focus, such as coping skills, problem solving or family communication. Outcomes included in the search were metabolic (glycaemic control, severe hypoglycaemia, diabetic ketoacidosis [DKA]) and psychological (knowledge, self-management behaviours, psychosocial and quality of life [QoL]).

A total of 11 studies were included in this review (DAFNE Study Group 2002; Loveman et al 2003; Winkley et al 2006; Channon et al 2007; Viklund et al 2007; Couch et al 2008; George et al 2008; Snoek et al 2008; Amsberg et al 2009; Grey et al 2009; Ismail et al 2010). Of these, three were Level I studies. Couch et al (2008) is a comprehensive report from the Agency for Healthcare Research and Quality, evaluating the effectiveness of diabetes education programs in children and adolescents younger than 18 years. Loveman et al (2003) is a health technology assessment report on the effectiveness of diabetes self-

management education in adults (including type 1 and type 2 diabetes), with a subanalysis on results in studies of type 1 diabetes. Winkley et al (2006) is a systematic review and meta-analysis of the effect of psychological interventions in both children and adults with type 1 diabetes. These three reviews had a low risk of bias; however, the included studies were predominantly at high risk of bias. Of the eight Level II studies, six had a low risk of bias and two had a moderate risk of bias. Further details regarding the studies included in these three systematic reviews, and characteristics of the Level II studies, are provided in the technical document.

9.3.1 Metabolic outcomes

Glycaemic control

In the most recent systematic review, the effect on HbA_{1c} of education programs for children and their families was reported in 33 randomised controlled trials (RCTs) (Couch et al 2008). HbA_{1c} levels decreased significantly in eight studies, three of which were categorised as family therapy, four as cognitive–behavioural therapy (CBT) and one as general diabetes education. In 9 studies, either the intervention group or both intervention group and control group reported a nonsignificant change in HbA_{1c}; in the remaining 16 studies, there was no difference between groups. The authors concluded that, due to the heterogeneity across the studies and the low methodological quality overall, there was insufficient evidence to determine whether any interventions were more effective than standard care for improving diabetes control. In contrast, the meta-analysis by Winkley et al (2006), which included 21 studies (10 in children and adolescents), found that HbA_{1c} was significantly reduced in those who had received a psychological intervention compared with those in the control group (absolute reduction 0.48% in children and 0.22% in adults). However, there was significant heterogeneity across studies. In the meta-analysis by Loveman et al (2003), education resulted in significant and long-lasting improvements in glycaemic control in adults with type 1 diabetes.

Loveman et al (2003) evaluated the clinical and cost effectiveness of educational interventions in adults with type 1 diabetes. Interventions that included a focus on diabetes self management were included. Two RCTs in adults with type 1 diabetes met our inclusion criteria and both were of low quality (Terent et al 1985; Reichard et al 1996). The Stockholm Diabetes Intervention Study found significant differences between groups at all time points during follow-up to 10 years (Reichard et al 1996). However, the intervention in this study also involved the intensification of diabetes management, potentially confounding the effects of the education. The other RCT, which was small, found that formal education compared with self monitoring of blood glucose did not improve glycaemic control (Terent et al 1985). Given that blood glucose monitoring is standard today, the applicability of these results to current management is questionable.

In the two primary studies testing the effectiveness of training in flexible intensive insulin management, one reported a significant reduction of 1% in HbA_{1c} in the intervention group at 6 months (DAFNE Study Group 2002), and the second reported no difference between groups at any time point up to 12 months' follow-up (George et al 2008). The latter study involved a brief (2.5 days) psycho-educational intervention; it is possible that the shorter duration and or nature of the intervention may explain the lack of effect on HbA_{1c}. In the three primary studies testing the effectiveness of psychological interventions, CBT reduced HbA_{1c} by about 0.5% at 48 weeks' follow-up in one study (Amsberg et al 2009), and had no effect on HbA_{1c} in two studies (Snoek et al 2008; Ismail et al 2010). However, CBT in combination with motivational enhancement therapy significantly reduced HbA_{1c} (by 0.45%) compared with usual care (Ismail et al 2010).

Severe hypoglycaemia

In the systematic review by Couch et al (2008), three of the six included RCTs reported a significant effect of an intervention on rates of severe hypoglycaemia in children and adolescents. One of the RCTs used a general diabetes education intervention (Svoren et al 2003), one a CBT intervention (Grey et al 2000), and one a skills-based intervention (Nordfeldt and Ludvigsson 2002). The authors concluded that there was no clear evidence that educational interventions had an effect on short-term complications (Couch et al 2008). However, they noted most studies did not have high enough rates of DKA to show significant differences. Furthermore, it is possible that both standard care and standard diabetes education reduce the incidence of hypoglycaemia, making it difficult to demonstrate differences across these educational interventions. One systematic review in adults reported hypoglycaemia as an outcome; however, the authors did not specifically report results for severe hypoglycaemia (Loveman et al 2003). The two primary studies in which severe hypoglycaemia was reported as an outcome both found no significant effect on the rate of severe hypoglycaemia (DAFNE Study Group 2002; George et al 2007).

Diabetic ketoacidosis

In the systematic review by Couch et al (2008), one RCT reported a significant effect of CBT on rates of DKA (Grey et al 2000) and one RCT found no effect. Only one of the included studies by Loveman et al (2003) reported DKA as an outcome, and this study found no difference between the intervention and control groups (Terent et al 1985). It is likely, however, that these studies were not sufficiently powered to detect a between-group difference in rates of DKA.

9.3.2 Psychological outcomes

Knowledge

The systematic review by Couch et al (2008) included 11 RCTs in children and adolescents that assessed the impact of interventions on knowledge. The interventions included general diabetes education (n=5), CBT (n=3) and diabetes camps (n=3). The results of studies were inconsistent, with three studies of low quality reporting a statistically significant increase in knowledge, four studies (one of low quality and three of moderate quality) reporting knowledge gains that were not statistically significant, and four studies (three of low quality and one of high quality) reporting no change. In the one study in adults reporting knowledge as an outcome, a diabetes knowledge test demonstrated no significant change as a result of an educational intervention, the Brief Intervention in Type 1 diabetes, Education for Self-efficacy (BITES) (George et al 2008).

Self-management behaviours

There were 15 RCTs from the review by Couch et al (2008) that assessed self management and regimen adherence in young people with type 1 diabetes; one study of moderate quality and seven of low quality reported significant improvement in self management in the intervention group. Successful interventions included general diabetes education (n=3), CBT (n=3) and family therapy (n=2). The remaining studies did not show a significant change.

Psychosocial

There were 21 RCTs from the review by Couch et al (2008) that examined one or more psychosocial outcomes in young people with type 1 diabetes, including family or social relationships, family or social support, social skills, coping, self perception, self efficacy, stress, depression and anxiety. The authors concluded that diabetes education was effective in improving several psychosocial outcomes; however, study quality was generally low and

there was considerable heterogeneity across interventions, time points and measures used. The meta-analysis by Winkley et al (2006) reported a significant reduction in psychological distress with psychological therapy in children and adolescents (pooled estimate –0.46, 95% confidence interval [CI]: –0.83 to –0.10, p=0.013), based on four studies, while in adults there was some evidence for a reduction in psychological distress with therapy, but this did not reach statistical significance (pooled estimate –0.25, 95%CI: –0.51 to 0.01, p=0.059).

Primary studies in children, adolescents and adults also provide evidence for an effect of educational and psychological interventions on psychosocial outcomes. Motivational interviewing was associated with significant benefits on various psychosocial measures in adolescents after 12 months, including more positive wellbeing, less depression and anxiety, and differences in personal models of illness (Channon et al 2007). In the two studies of adults that tested the effectiveness of educational training, one reported a beneficial effect of flexible intensive insulin management on dietary freedom (DAFNE Study Group 2002), and the other found that the brief educational intervention (BITES) led to significant improvements in treatment satisfaction and empowerment for up to 12 months, but no significant changes on the Illness Perception Questionnaire and Hypoglycaemia Fear Scale (George et al 2008). In three RCTs examining psychological interventions in adults, CBT had a significant effect on wellbeing, diabetes-related distress, frequency of blood glucose level testing, avoidance of hypoglycaemia, perceived distress, anxiety and depression in one study (Amsberg et al 2009); CBT had no effect on psychosocial outcomes in a second study (Ismail et al 2010); and in the third study, which compared CBT with blood glucose awareness training, both interventions resulted in fewer depressive symptoms during 12 months of follow up (Snoek et al 2008).

Quality of life

The systematic review by Couch et al (2008) reported that the results of the included RCTS were mixed, and concluded that there was limited evidence for the effect of educational interventions on QoL. The RCT by Laffel et al (2003) found no difference in QoL scores between the family therapy group and control group. One study of moderate quality found that adolescents who received coping skills training, together with intensive diabetes management, experienced less negative impact on QoL compared to controls (Grey et al 2000). In the RCT by Channon et al (2007), there was a significant improvement in QoL (as measured by the diabetes QoL) for the group receiving motivational interviewing in measures of satisfaction, impact of diabetes and worries.

None of the RCTs in adults reported by Loveman et al (2003) used validated QoL measurement tools; therefore, results were not reported in this review.

9.3.3 Summary

This systematic review examining the effectiveness of education or psychological interventions in reducing HbA_{1c}, severe hypoglycaemia and DKA, and improving psychological outcomes, is based on three Level I studies of low risk of bias, and eight Level II studies, six of which were of low risk of bias and two of moderate risk of bias. The studies included in the three Level I studies were predominantly of high risk of bias.

In children and adolescents, the effects of educational or psychological interventions were heterogeneous, and results were inconsistent in their effect on HbA_{1c}, severe hypoglycaemia, DKA, knowledge, self-management behaviours and psychological outcomes. Two studies examining refinements to intensive therapy education suggested that educational interventions may increase the effects of intensive diabetes management on

reducing HbA_{1c}. A pooled analysis of 10 studies found a 0.5% reduction in HbA_{1c} following psychological interventions, but with significant heterogeneity in the study results. Psychological distress was significantly lower following psychological interventions in children and adolescents.

In adults, self-management education significantly lowered HbA_{1c} (by 0.5–1.0%) when delivered in conjunction with intensive diabetes management, but this was not a consistent finding, reflecting heterogeneity of interventions and study quality. Specific psychological interventions (e.g. CBT) also significantly reduced HbA_{1c} (by about 0.5%), whereas a pooled analysis of psychological interventions found no significant effect on HbA_{1c}, with significant heterogeneity reported. Self-management education in the context of intensive insulin management consistently resulted in significant improvements in a number of psychological outcomes, including QoL.

One primary study was carried out in Australia, the rest were conducted in countries with a well-established health-care system; thus, the results are applicable to the Australian health-care system.

9.3.4 Cost effectiveness

In the systematic review by Loveman et al (2003), economic evaluations comparing education with usual care or other educational interventions were not identified. Cost analysis and information from sponsor submissions indicated that, where costs associated with patient education were in the region of 500–600 pounds sterling per patients, the benefits over time would have to be very modest to offer an attractive cost-effectiveness profile. The other two systematic reviews did not report cost effectiveness (Winkley et al 2006; Couch et al 2008).

Evidence statement	
Q22	There is some evidence from Level I and II studies for a beneficial effect of psychological support programs and education on glycaemic control in children and adolescents. There is insufficient evidence to identify a particular intervention that is more effective than standard care to improve glycaemic control. There is Level I and II evidence that educational or psychological interventions improve some psychological outcomes, including psychological distress and self-management behaviours in young people with type 1 diabetes. The evidence base shows that the intensified education programs delivered in Reichard et al (1996) and the DAFNE Study Group (2002) are associated with reductions in HbA_{1c} compared with usual care. However, the intensified education programs delivered in the BITES program and by Terent et al (1985) were not associated with reductions in HbA_{1c} compared with usual care. There is Level II evidence that educational and psychological interventions improve some psychological outcomes (including psychological wellbeing, diabetes-related distress, self-care behaviours, distress, anxiety and depression) in adults.
Recommendation	
R9.1	Education and psychological support are an essential component of standard diabetes care. Intensified education and psychological support programs should be considered when treatment goals are not being met (Grade B).
Practice points	
PP9.5	Educational and psychological interventions should be culturally, developmentally and age appropriate.
PP9.6	The multidisciplinary diabetes health-care team should aim to maintain consistent contact with people with diabetes and their families or carers.
PP9.7	The multidisciplinary diabetes team should aim to provide preventive interventions for patients and families (include training parents in effective behaviour-management skills) at key developmental stages, including after diagnosis and before adolescence. These interventions should emphasise appropriate family involvement and support in diabetes management, effective problem-solving and self-management skills, and realistic expectations about glycaemic control (Delamater 2009).
PP9.8	Diabetes care teams should have appropriate access to mental health professionals to support them in the delivery of psychological support (NICE 2010).
PP9.9	Flexible intensive insulin therapy programs, such as DAFNE, aim to provide dietary freedom for people with type 1 diabetes (see Chapter 10).
BITES, Brief Intervention in Type 1 diabetes, Education for Self-efficacy; DAFNE, dose adjustment for normal eating; HbA_{1c}, glycated haemoglobin	

10 Nutrition

10.1 Introduction

Nutritional management is fundamental to diabetes care and education. Dietary recommendations for individuals with type 1 diabetes are based on healthy eating recommendations suitable for all children and adults, and thus for the whole family. Nutritional advice should be adapted to cultural, ethnic and family traditions, as appropriate. The main aims of nutritional management in type 1 diabetes are to (Smart et al 2009):

- encourage appropriate eating behaviour and healthy lifelong eating habits, while preserving social, cultural and psychological wellbeing
- encourage people to eat three balanced meals a day, with appropriate healthy snacks (if necessary), to supply all essential nutrients, maintain a healthy weight, prevent binge eating, and provide a framework for regular monitoring of blood glucose levels
- provide sufficient and appropriate energy intake and nutrients for optimal growth, development and good health
- achieve and maintain an appropriate body mass index (BMI) and waist circumference (this includes the need to undertake regular physical activity)
- achieve a balance between food intake, metabolic requirements, energy expenditure and insulin action profiles, to attain optimum glycaemic control
- prevent and treat acute complications of diabetes, such as hypoglycaemia, hyperglycaemia, illness and exercise-related problems
- reduce the risk of microvascular and macrovascular complications
- maintain and preserve quality of life (QoL)
- develop an enabling, trusting, empathic, supportive relationship, to facilitate behaviour change and consequent positive dietary modifications.

There is evidence for the nutritional requirements of young people; however, the evidence base for many aspects of dietary management of diabetes is limited and is often not of high quality. This chapter outlines the evidence to support carbohydrate quantification, insulin-to-carbohydrate ratios, use of the glycaemic index (GI), and modification of dietary fat and protein. Further evidence-based information on the nutritional management of type 1 diabetes, including age group specific advice, can be found in the guidelines from the International Society for Pediatric and Adolescent Diabetes (Smart et al 2009) and the American Diabetes Association (American Diabetes Association 2008).

People with type 1 diabetes should have access to an accredited practising dietitian who is skilled in the nutritional management of the condition. However, all team members should have a thorough understanding of the principles of nutritional management of type 1 diabetes.

Refer to Chapters 9–11, 16 and 20 for evidence statements and recommendations regarding physical activity, psychosocial disorders (including eating disorders), hypoglycaemia, coeliac disease and type 1 diabetes.

10.2 Carbohydrate quantification

Question 24

What are the efficacy and safety of (i) regulating or quantifying dietary carbohydrate and (ii) insulin-to-carbohydrate ratios in type 1 diabetes?

The detailed systematic review of this question is in Chapter 24 of the accompanying technical report, and the evidence matrix is in Section C24 of Appendix C

Nutritional guidelines for the Australian population recommend that carbohydrate intake makes up 45–65% of energy intake, predominantly from wholegrain breads and cereals, legumes, fruit, vegetables and low-fat dairy products (except for children under 2 years) (NHMRC 2006). These recommendations do not differ for people with type 1 diabetes; however, the distribution of carbohydrate intake is more important. Individualised advice regarding carbohydrate amount and distribution should consider usual appetite, food intake patterns, exercise, insulin regimen and energy requirements.

Carbohydrate can be regulated or quantified in different ways:

- **Consistent carbohydrate intake:** For those receiving fixed meal-time doses of insulin, this approach is used; it involves day-to-day consistency in carbohydrate intake, where a consistent intake of carbohydrate is encouraged using serves or exchange lists of measured quantities of food.
- **Flexible carbohydrate intake:** Carbohydrate counting is a meal-planning approach that focuses on improving glycaemic control and allowing flexibility of food choices. This can be achieved with individualised insulin-to-carbohydrate ratios for patients using intensive insulin therapy.

Four Level II studies have examined carbohydrate-based interventions in type 1 diabetes. One study used a flexible low-GI diet, but did not include the use of insulin-to-carbohydrate ratios (Gilbertson et al 2003), and three studies used flexible intake of carbohydrate with adjustment of insulin based on insulin-to-carbohydrate ratios (Kalergis et al 2000; DAFNE Study Group 2002; Scavone et al 2010). Only one study included children (Gilbertson et al 2003) and was of good quality. Most participants (n=104, aged 8–13 years) were treated with twice-daily insulin, and their diabetes management did not include the use of insulin-to-carbohydrate ratios. The intervention group was prescribed a flexible low-GI diet, and the control group received a fixed quantity of dietary carbohydrate. At 12 months, children in the low-GI group had lower HbA_{1c} levels than those in the carbohydrate-exchange group (8.1% vs 8.6%, p=0.05). The flexible low-GI diet was associated with better QoL for both children and parents. The study was conducted at a time when conventional insulin therapy was used more frequently in children with type 1 diabetes and before continuous subcutaneous insulin infusion (CSII) was widely used. Therefore, the results of this study may not be directly applicable to treatment regimens that are more commonly used in children with type 1 diabetes (CSII and multiple daily injections [MDI]). No studies that examined flexible diet or the use of insulin-to-carbohydrate ratios in adolescents were identified.

The three studies that examined insulin-to-carbohydrate ratios were all conducted in adults receiving MDI therapy (n=446) (Kalergis et al 2000; DAFNE Study Group 2002; Scavone et al 2010), and one was of good quality (DAFNE Study Group 2002). The DAFNE study group (DAFNE Study Group 2002) found a lower HbA_{1c} in the intervention group (8.4% vs 9.4% at 6 months, p<0.0001) compared with no change in the control group (9.3% vs 9.4%), while HbA_{1c} was not different between groups in the other studies. QoL, measured using a validated tool was better in the intervention group than in the control group in the DAFNE

study (DAFNE Study Group 2002). There were no between-group differences in weight, BMI or severe hypoglycaemia. There is some evidence to suggest an improvement in both HbA_{1c} and QoL in adults who have received education on the use of insulin-to-carbohydrate ratios to enable a liberalised carbohydrate intake.

Evidence statement	
Q24	Level II evidence (from three studies) shows that the use of insulin-to-carbohydrate ratios in multiple daily injection therapy reduces HbA_{1c} but has no clinically significant effect on weight, QoL or severe hypoglycaemia.
Recommendation	
R10.1	Matching of meal-time insulin dose to carbohydrate intake should be considered for patients using multiple daily injection therapy (Grade C).
Practice points	
PP10.1	An individualised insulin to carbohydrate ratio should be used for patients using CSII and may be used in those on multiple daily injection therapy.
PP10.2	Adjusting insulin according to carbohydrate quantity has the potential to improve QoL and increase flexibility in food intake in people with type 1 diabetes. However, regularity in meal routines remains important for optimal glycaemic control.
PP10.3	Advice on carbohydrate quantity and distribution should take into account an individual's energy requirements, previous dietary and eating patterns, activity levels and insulin regimen.
PP10.4	In clinical practice, a number of methods for carbohydrate quantification are commonly taught, including 1 g increments, 10 g carbohydrate portions and 15 g carbohydrate exchanges.
PP10.5	Day-to-day consistency in carbohydrate intake is important for patients who are on fixed insulin regimens.
CSII, continuous subcutaneous insulin infusion; HbA_{1c}, glycated haemoglobin; QoL, quality of life	

10.3 Glycaemic index and glycaemic load

Question 25

What are the efficacy and safety of low glycaemic index or high-fibre diets in type 1 diabetes?

The detailed systematic review of this question is in Chapter 25 of the accompanying technical report, and the evidence matrix is in Section C25 of Appendix C

GI is a ranking of foods based on their acute glycaemic impact compared to the reference standard glucose (Wolever et al 1991). Carbohydrates with a low GI result in a slower and more gradual rise in blood glucose levels, and reduce the postprandial glycaemic response compared to carbohydrates with a higher GI. Low-GI food sources include wholegrain breads; legumes; pasta; wholegrains such as oats, barley and quinoa; many fruits (temperate, citrus, most stone fruit and berries); and dairy foods. Many factors may influence a food's glycaemic response; however, the ranking of foods on the basis of their GI value is generally consistent (Wolever et al 1991).

Glycaemic load (GL) is another method of predicting the postprandial blood glucose response, which takes into account both the GI of the food and the portion size (Salmeron et al 1997). Low-GL diets are usually high in dietary fibre. There has been no assessment of the efficacy of low-GL diets in children and adolescents. A recent systematic review of 11

randomised controlled trials (RCTs) assessed the effects of low-GI or low-GL diets on glycaemic control in people with diabetes (Thomas and Elliott 2009). Four RCTs involved 186 patients with type 1 diabetes (Collier et al 1988; Fontvieille et al 1992; Giacco et al 2000; Gilbertson et al 2001); of these, two were paediatric studies, including one RCT of 104 Australian children aged 8–13 years (Gilbertson et al 2001). The results of this study are discussed in Section 10.2, above. Two studies reported HbA_{1c} as an outcome — one that involved children (Gilbertson et al 2001) and the other adults (Giacco et al 2000); pooled analysis showed a significant difference in HbA_{1c} in the low-GI group versus the conventional or high-GI group (weighted mean difference [WMD] –0.5%, 95% confidence interval [CI]: –0.9 to 1.0, p=0.02). Hypoglycaemia was reported in two studies (Giacco et al 2000; Gilbertson et al 2001); the mean rate of any hypoglycaemic event per month was lower in adults randomised to a low-GI diet (0.7 vs 1.5 in the high-GI group, p<0.01) (Giacco et al 2000). Improved QoL was reported for both children and parents in one study (Gilbertson et al 2001), based on a higher rate of diabetes never limiting the type of family activities pursued (53% vs 27%, p=0.02).

Evidence statement	
Q25	Level I evidence shows that a low GI diet has a beneficial effect on glycaemic control in adults and children. There is insufficient evidence to determine the effect of low-GI diets on body mass index, weight, severe hypoglycaemia or QoL in children, adolescents or adults with type 1 diabetes.
Recommendation	
R10.2	Patients with type 1 diabetes should be educated on low-GI diets (Grade A).
Practice point	
PP10.6	In type 1 diabetes, GI should not be used in isolation, but should be used with a method of carbohydrate quantification or regulation.
PP10.7	Patients should be advised that to lower the glycaemic impact of the meal, high GI food choices should be combined with low GI food choices.
PP10.8	Where possible, high GI food choices should be substituted with moderate or low GI choices.
PP10.9	Food choices for people with type 1 diabetes should not be made solely on the basis of GI, but should also consider the other nutritional aspects of the food, with a focus on lower fat, higher fibre, nutrient-dense foods.
GI, glycaemic index; QoL, quality of life	

10.4 Protein

Question 26

What are the efficacy and safety of modifying protein diets in type 1 diabetes?

The detailed systematic review of this question is in Chapter 26 of the accompanying technical report, and the evidence matrix is in Section C26 of Appendix C

Nutritional guidelines for the Australian population recommend that protein should comprise up to 25% of total daily energy intake (NHMRC 2006). Sources of vegetable protein, such as legumes, should be encouraged. Sources of animal protein also recommended include fish, lean cuts of meat and low-fat dairy products.

In the presence of persistent microalbuminuria or established nephropathy, excessive protein intake may be detrimental to renal function (NHMRC 2006). There is also evidence that vegetable or soy protein may be preferable to animal protein, particularly red meat,

with respect to reducing the progression of renal disease (Robertson et al 2009c). However, the evidence base for modification of other outcomes in type 1 diabetes is limited.

One systematic review of eight RCTs examined the effect of low-protein diets in adults with type 1 or 2 diabetes-related renal diseases. Four studies involved 70 adults with type 1 diabetes (Pan et al 2008). In this subgroup, change in HbA_{1c} from baseline to study end did not differ between the intervention and control groups (WMD: 0.04%, 95%CI: –0.53 to 0.61, I^2=0%, p=0.89). Other outcomes relevant to diabetes (e.g. BMI, weight, QoL and rates of severe hypoglycaemia) were not examined in the systematic review.

There is no Level I or II evidence for the efficacy and safety of low-protein diets in children and adults with type 1 diabetes and normal renal function. There is no evidence for the efficacy and safety of high-protein diets versus normal diets in children and adults with type 1 diabetes and normal renal function.

Evidence statement	
Q26	There is insufficient evidence to determine the effect of modifying protein intake in individuals with type 1 diabetes.
Practice points	
PP10.10	High-protein/low-carbohydrate diets in children and adolescents may have deleterious effects on growth.
PP10.11	High-protein diets, particularly those based on animal protein or red meat, may lead to progression of diabetic nephropathy. Reducing protein intake or replacing red meat with vegetable or soy protein may help to reduce the progression of nephropathy.
PP10.12	Restricting carbohydrate intake may affect the nutritional adequacy of the diet and may cause hypoglycaemia if insulin therapy is not adjusted accordingly.
PP10.13	High-protein diets result in ketosis, which may affect blood glucose control and result in dehydration, lethargy and loss of lean body mass.

10.5 Fat

Question 27

What are the efficacy and safety of modifying dietary fat intake in type 1 diabetes?

The detailed systematic review of this question is in Chapter 27 of the accompanying technical report, and the evidence matrix is in Section C27 of Appendix C

Nutritional guidelines for the Australian population recommend that fat should comprise about 20–35% of total daily energy intake (NHMRC 2006). The recommended targets for fat intakes do not differ for people with diabetes; however, studies have shown that children, young people and adults with diabetes consume fat and saturated fat above dietary recommendations (Helgeson et al 2006; Overby et al 2007; Snell-Bergeon et al 2009). Recent guidelines (Smart et al 2009) recommend the following composition of dietary fat:

- less than 10% of energy from saturated fat and trans fats
- less than 10% of energy from polyunsaturated fat
- more than 10% of energy from monounsaturated fat.

Five Level II studies examined modification of dietary fat intake in 118 people with type 1 diabetes (Donaghue et al 2000; Georgopoulos et al 2000; Strychar et al 2003; Rosenfalck et

al 2006; Strychar et al 2009). Four were RCTs or crossover studies in adults, and one was a randomised parallel study in 25 adolescents (Donaghue et al 2000). Four studies assessed the effect of high monounsaturated fat diets and one randomised crossover study in 10 adults examined the effect of a low-fat (25%) isoenergetic diet (Rosenfalck et al 2006).

In the four studies that examined a high monounsaturated fat diet, there was no difference in HbA_{1c} between the intervention and control groups. One study reported a statistically significant, but modest, increase in weight (2%) in the intervention group (Strychar et al 2009).

In the study that examined a low-fat diet, insulin sensitivity improved significantly in the intervention group, but there was no difference in HbA_{1c}, weight or BMI (Rosenfalck et al 2006). The effect on lipid profiles was variable across the five studies. There was a significant improvement in LDL-cholesterol following the monounsaturated diet intervention in one RCT (Strychar et al 2003), and in total triglycerides (TG), very low density lipoprotein (VLDL) TG and VLDL-cholesterol in the subgroup of participants who had adhered to required dietary targets. There were no significant differences in lipid profiles in the two other RCTs (Georgopoulos et al 2000; Strychar et al 2009).

Two studies reported low dietary adherence rates, suggesting that adherence to high monounsaturated fat diets in patients with type 1 diabetes may be poor (Donaghue et al 2000; Strychar et al 2003). QoL and severe hypoglycaemia were not measured as outcomes in any of these studies.

No RCTs have been published on the effect of modifications of other types of dietary fat (saturated and polyunsaturated) in people with type 1 diabetes.

Evidence statement	
Q27	Level II evidence (from one, good-quality study, small sample size) shows that, in nonobese adults with well-controlled, uncomplicated type1 diabetes, a diet high in monounsaturated fats can have a beneficial effect on LDL-cholesterol, triglycerides, VLDL-triglycerides and VLDL-cholesterol.
Q27	There is insufficient evidence to determine any effect on weight, body mass index, quality of life and severe hypoglycaemia of diets high in monounsaturated fat in children, adolescents or adults with type 1 diabetes.
Recommendation	
R10.3	Diets high in monounsaturated fats should not be used routinely in patients with type 1 diabetes (Grade C).
Practice points	
PP10.14	People with type 1 diabetes should be given advice on fat intake, focusing on reducing saturated and trans fat intake, to reduce the risk of cardiovascular disease.
PP10.15	People with type 1 diabetes should be encouraged to substitute saturated and trans fats with monounsaturated or polyunsaturated fats.
PP10.16	Education on carbohydrate quantification should not encourage people to eat high-fat foods, particularly packaged snacks.
PP10.17	Advice to lower energy intake, specifically total fat intake, should be given to people with type 1 diabetes at risk of overweight or obesity.
PP10.18	Diets high in monounsaturated fats are difficult to adhere to in the context of an Australian diet.
LDL, low density lipoprotein; VLDL, very low density lipoprotein	

11 Exercise

11.1 Introduction

Question 28 (background question)

How should insulin type, dose, and mode of delivery and diet be varied for exercise?

Question 28 was a background question and therefore was not systematically reviewed

Physical activity is an expected part of daily activity; it is important for cardiovascular and metabolic fitness, and general wellbeing (Laaksonen et al 2000; D'hooge et al 2010). Incidental daily physical activity can generally be managed in a person with type 1 diabetes, and does not pose an unexpected major caloric deficit (Robertson et al 2009b). In contrast, structured bouts of physical activity (as exercise) do require planning. There are well-known cases of elite athletes with type 1 diabetes, indicating that type 1 diabetes is not an impediment to optimal performance during exercise (Robertson et al 2009b).

A number of studies in people with type 1 diabetes have shown that structured exercise does not improve chronic glycaemic control, whereas blood glucose levels may be acutely unstable at the time of exercise (Ligtenberg et al 1999; Rabasa-Lhoret et al 2001; Särnblad et al 2005). The main concern with exercise in people with type 1 diabetes is that hypoglycaemia may be precipitated during or after the exercise (Tuominen et al 1995). Exercise consumes energy and improves insulin sensitivity; thus, increased carbohydrate intake, reduced insulin dosage, or a combination of the two are generally required around the time of the exercise, to minimise the risk of immediate (Rabasa-Lhoret et al 2001) or delayed hypoglycaemia (McMahon et al 2007). Exercise-induced hypoglycaemia is especially likely during exercise that is of long duration (>60 minutes) or persistent and intense (Robertson et al 2009b). In contrast, in different clinical settings, exercise may exacerbate or cause metabolic instability in the form of acute hyperglycaemia (Mitchell et al 1988).

The profile of blood glucose response to any type of exercise is difficult to predict in different people with type 1 diabetes (Robertson et al 2009b). However, an initial approach using some guiding principles may be used to help keep blood glucose levels reasonably safe during exercise. Subsequently, a more personalised and detailed plan can be developed. This involves the person with type 1 diabetes carefully documenting their initial exercise strategy – including exercise type, intensity and timing – relative to meals and related exercise insulin regimen chosen, carbohydrate intake and blood glucose profile (Toni et al 2006; Robertson et al 2009b; Ambler and Cameron 2010).

11.2 General principles in initial exercise planning

11.2.1 Carbohydrate requirement

The intensity and duration of the exercise will affect the amount of energy consumed due to the exercise, and thus the estimated amount of carbohydrate required. Data are readily accessible to estimate the calories (including carbohydrate) expended in differing activities (Pendergast et al 2010). For example, in a child weighing 40 kg, 30 minutes of basketball will consume an estimated 120 kilocalories (508 kJ) of carbohydrate (Robertson et al 2009b).

More predictable blood glucose responses to exercise will occur in a person who has ongoing cardiovascular fitness, has better controlled HbA_{1c} levels, and undertakes the

exercise in a set routine, including in its timing, each day or every second day (Robertson et al 2009b).

The type of exercise, and its timing relative to meals and administration of rapid-acting insulin, is likely to affect the approach to modifying carbohydrate intake and insulin dosage. Carbohydrate and insulin therapy may be modified following some of the guidelines below (Toni et al 2006).

- **Ensure adequate energy stores before exercise**. A meal containing carbohydrates, fats and protein should be consumed about 3–4 hours before exercise, to maximise endogenous energy stores. Glycogen stores can be optimised if carbohydrate is consumed; for example, as a beverage with 1–2 g carbohydrate/kg body weight (Robertson et al 2009b).
- **Supplemental carbohydrate.** If supplemental carbohydrate is taken during exercise (which is usually required if the exercise lasts more than 30 minutes), 6% oral solutions with rapidly absorbed (high glycaemic index [GI]) carbohydrate appear to be most efficient (Riddell and Iscoe 2006). If the insulin dosage is not reduced, then the carbohydrate intake amount should be matched as far as possible with the predicted requirement of carbohydrate. As a guide, during the time of peak insulin action, the typical amount of carbohydrate required is 1.0–1.5 g of carbohydrate per kg of body weight per hour (Riddell and Iscoe 2006).
- **Reduce insulin doses before exercise**. If the planned exercise is to be more than 60 minutes in duration, then a reduction in bolus insulin using insulin changes as described above, combined with progressive supplemental carbohydrate every 30–40 minutes, is indicated (Robertson et al 2009b).

Detailed guidelines for carbohydrate intake in children and adolescents, varying with the duration and intensity of exercise, are available (Ambler and Cameron 2010).

11.2.2 Insulin therapy

Multiple daily injection and insulin pump (continuous subcutaneous insulin infusion [CSII]) therapy-based regimens provide the greatest flexibility in insulin adjustment for exercise. The highest risk time for initial hypoglycaemia after exercise using rapid acting insulin analogues is 40–90 minutes, and for regular (soluble) insulin, is 2–3 hours (Tuominen et al 1995). Therefore, the dose of insulin that is acting at the time of the exercise (especially rapid or short acting) may need to be reduced. Suggested changes to insulin doses based on the time of day and duration of exercise are outlined below:

- Exercise performed early in the morning, before breakfast:
  - reduce the previous evening basal (intermediate or long-acting) insulin dose by 20–50%
  - reduce the pre-breakfast bolus (rapid-acting) insulin dose after exercise by 30–50%
  - reduce the evening dose of basal insulin on the day of exercise.
- Exercise performed in the postprandial phase:
  - preferably delay exercise until at least 1–2 hours after the meal
  - reduce the pre-meal bolus insulin dose by 20–75%, related to duration and intensity of exercise.

- Prolonged exercise:
  - reduce the pre-meal bolus insulin dose by 30–50% if exercise lasts up to 4 hours; for all-day exercise, reduce all meal bolus doses across the day by 30–50%
  - reduce the previous evening basal insulin by 50%, and the basal insulin dose by 10–20% up to 24 hours after all-day exercise, such as walking.
- Intermittent high-intensity exercise (team sports):
  - reduce the pre-meal bolus insulin by 70–90% if exercise commences within 1–3 hours of the meal.
- For CSII therapy, decrease the basal rate by 30–50% for the duration of the exercise; and, if exercise is planned, reduce the basal rate for 1–2 hours before exercise. Alternatively, CSII may be suspended for up to 2 hours. Consider supplemental bolus insulin either before or 1 hour into exercise. In either case, a reduction in the overnight basal rate may also be needed by 20–30% or sometimes more, after vigorous and prolonged exercise.

11.2.3 Glycaemic control

Suboptimal glycaemic control with HbA_{1c} levels above 7.5% can reduce aerobic exercise capacity, and increase fatigue rate. Thus, reasonably good chronic glycaemic control is desirable to aid exercise capacity (Komatsu et al 2005).

Situations that may lead to severe hyperglycaemia around the time of the exercise, rather than hypoglycaemia in response to exercise, include (Mitchell et al 1988; Robertson et al 2009b):

- a person being insulin deficient before exercise
- the intensity of the exercise being repeated and of high intensity, such as that above maximum oxygen uptake of 80%
- the exercise causing mainly anaerobic metabolism.

These situations will lead to release of high levels of noradrenaline. In addition, excessive emotional stress or excess carbohydrate intake can contribute to hyperglycaemia related to exercise (Robertson et al 2009b). If the blood glucose level is above 14 mmol/L, then it is recommended that exercise not be undertaken (Robertson et al 2009b).

11.3 Fine tuning an initial exercise regimen through monitoring

Once an initial exercise plan has been developed with the person with diabetes, it useful to carefully monitor and document the blood glucose profile during and after exercise episodes, to help in fine tuning the regimen (Toni et al 2006). This iterative approach allows progressive documentation of reproducibility of the blood glucose response with exercise.

Further strategies to prevent hypoglycaemia related to exercise and its severity due to exercise are outlined below.

11.3.1 Sprinting

A recent publication from Australian data has indicated that a 10-second sprint at the end of a bout of exercise can help to prevent hypoglycaemia some 2 hours after the exercise (Bussau et al 2007). This preventive role appears to be the case for certain types of exercise, such as consistent, moderate-intensity aerobic physical activity.

11.3.2 Preventing nocturnal hypoglycaemia

Severe, nocturnal hypoglycaemia is more prone to occur up to 24 hours after a bout of at least moderate physical activity undertaken for at least 1 hour (Robertson et al 2009b). In one study in adolescents, the rate of nocturnal hypoglycaemia was about double (48% of participants had events) on nights of exercise days compared with nights when no exercise had been undertaken during the day (Tsalikian et al 2005). The effect appears to be mainly due to increased insulin sensitivity through induction of glucose transporter type 4 in skeletal muscle (Gulve and Spina 1995). In addition, data indicate that counter-regulatory hormone and autonomic nervous system responses to hypoglycaemia may be blunted following a significant bout of exercise (Sandoval et al 2004).

The following strategies have been suggested to help prevent nocturnal hypoglycaemia due to exercise undertaken within the past 24 hours:

- reduce the long-acting insulin dose overnight after the exercise undertaken that day; for example, the dose of long-acting insulin could be reduced from 10–20% (Taplin et al 2010), and in some cases up to 50% (Toni et al 2006)
- ensure blood glucose is above 7 mmol/L before going to bed (Whincup and Milner 1987; Tansey et al 2006)
- always consume at least 10–15 g carbohydrate before bed after a day of exercise (Whincup and Milner 1987), preferably as a low-GI food or with a mixed meal, such as a glass of milk, to aid a slow but persisting rate of glucose absorption into the blood stream
- in higher risk settings after days of unusually intense or long-duration physical activity, consider setting the bedroom alarm clock in the early morning hours to check blood glucose at those times, and to supplement with carbohydrate as required
- monitor blood glucose continuously, to help in recognising asymptomatic hypoglycaemia (monitoring can include both retrospective and real-time systems) (Riddell and Perkins 2009); real-time monitoring systems often have a hypoglycaemia alarm triggered by a threshold blood glucose level, to help avoid severe hypoglycaemia.

11.3.3 Hypoglycaemia and recreational sport

Scuba diving is currently contraindicated in people with type 1 diabetes, because of the complications posed by hypoglycaemia occurring under deep water, and the difficulty in monitoring blood glucose in that setting (Australian Diabetes Society 1994). The sport is conditionally supported for some people in some developed countries, and there are highly specific guidelines for it to be undertaken (Lormeau et al 2005). However, scuba diving can be associated with mishap in people with type 1 diabetes, and it can cause major swings in blood glucose levels (Dear Gde et al 2004). Other studies have shown that, in people without hypoglycaemia unawareness or major diabetes complications, scuba diving can be safe (Edge et al 2005). The field is evolving (Lormeau et al 2005), including in blood glucose monitoring technology underwater (Adolfsson et al 2009; Bonomo et al 2009; Pollock 2009). It may eventuate that Authorities in Australia will support conditional approval for people with type 1 diabetes to scuba dive on a case-by-case assessment basis.

11.3.4 Preventing hypoglycaemia in children

Parents and carers of children must ensure ready access to carbohydrates, particularly in young children, to help prevent hypoglycaemia related to physical activity. During increased physical activity beyond the usual amount, the carer or parent should be highly suspicious

that hypoglycaemia may occur. At school and sporting activities, it is particularly important for teachers or others responsible for the child with diabetes to be aware of the risk of hypoglycaemic episodes with exercise, and they should know how to recognise and treat such episodes.

In a research setting, the β 2 agonist terbutaline taken orally at bedtime prevented nocturnal hypoglycaemia related to exercise in children with type 1 diabetes; however, terbutaline often induces hyperglycaemia and is not recommended (Taplin et al 2010). Appropriate oral carbohydrate and glucagon should be ready accessible to the primary carer, as required, to help prevent or treat severe hypoglycaemia episodes. Treatment of hypoglycaemia is addressed in Chapter 16.

11.3.5 Preventing hypoglycaemia in adolescents and adults when exercise is combined with alcohol

Moderate or large consumption of alcohol is well known to cause delayed hypoglycaemia after 6–12 hours (Plougmann et al 2002; Cryer et al 2003). Alcohol reduces gluconeogenesis (Robertson et al 2009b), and particular care should be taken when it is combined with exercise; for example, at 'big nights out' or dance parties. In these situations, severe hypoglycaemia may also be mistaken for effects of alcohol, or other mood and mind-altering drugs. Severe hyperglycaemia and diabetic ketoacidosis may also occur in these settings(Lee et al 2009). With due care in diabetes self-management, outcomes in managing blood glucose during social events – including those involving physical activity – may be positive (Ramchandani et al 2000). Specific advice to reduce the risk of hypoglycaemia and adverse outcomes includes:

- eat carbohydrate beforehand, during the period of drinking, and afterwards
- consider reducing overnight insulin to avoid overnight hypoglycaemic episodes after drinking alcohol
- arrange for a responsible person to wake the person the next morning at an appropriate time, to see that all is well.

12 Complementary and alternative medicines

12.1 Introduction

A range of complementary medicines – herbal medicines, antioxidants, vitamins and heavy metals are used by people with diabetes, although most clinical research addressing complementary and alternative medicines (CAM) has been performed in people with type 2 diabetes (Yeh et al 2003). A systematic review examined the effectiveness of CAM in achieving targets in type 1 diabetes.

12.2 Effectiveness, cost and cost effectiveness of complementary therapies and alternative medicines

Question 29 (interventional)

What is the effectiveness of complementary and alternative medicines at achieving metabolic targets?

Question 30 (interventional cost effectiveness)

What are the costs and cost effectiveness of complementary and alternative medicines at achieving metabolic targets?

The detailed systematic reviews of these questions are in Chapters 29 and 30 of the accompanying technical report, and the evidence matrixes are in Sections C29 and C30 of Appendix C

Four systematic reviews met the inclusion criteria in examining complementary medicines in type 1 diabetes (Pozzilli et al 1996; Yeh et al 2003; Pilkington et al 2007; Baker et al 2008). The studies captured by these Level I studies were supplemented by Level II studies that were published after the Level I studies (Pozzilli et al 1996; Visalli et al 1999; Ludvigsson et al 2001; Crinò et al 2004; Manuel et al 2004; Pena et al 2004; Engelen et al 2005; Pitocco et al 2006; Giannini et al 2007; Huang and Gitelman 2008). A number of trials studied the effect of herbs (Sharma et al 1990; Serraclara et al 1998) and vitamin supplements (Crinò et al 2004; Manuel et al 2004; Engelen et al 2005; Giannini et al 2007).

12.2.1 Effectiveness of complementary and alternative medicines

Glycaemic control was an outcome measure in 10 studies (Pozzilli et al 1996; Serraclara et al 1998; Visalli et al 1999; Ludvigsson et al 2001; Crinò et al 2004; Pena et al 2004; Pitocco et al 2006; Altschuler et al 2007; Giannini et al 2007; Huang and Gitelman 2008). All the included studies found no difference in glycated haemoglobin (HbA_{1c}). A meta-analysis conducted by Pozzilli et al (1996), which looked at nicotinamide treatment in patients with recent-onset type 1 diabetes, reported no differences in HbA_{1c} values between nicotinamide and control patients.

Insulin dose was an outcome measure in nine studies (Sharma et al 1990; Pozzilli et al 1996; Serraclara et al 1998; Visalli et al 1999; Ludvigsson et al 2001; Crinò et al 2004; Pitocco et al 2006; Altschuler et al 2007; Huang and Gitelman 2008). Of these, eight studies found no difference in overall insulin requirement. The study by Serraclara et al (1998) showed a reduction in insulin dose (12% lower in the intervention group) (no raw data were provided in the study), and there was a decline in mean capillary glycaemia ($p<0.05$). However, this study was graded as being of poor quality (Yeh et al 2003). The meta-analysis of 10

randomised controlled trials (RCTs) by Pozzilli et al (1996) also reported no difference in insulin dose required between nicotinamide and control patients.

Lipid targets were an outcome in two studies, both of which examined the effect of vitamin E compared to conventional treatment (Manuel et al 2004; Engelen et al 2005). A combination of vitamin E plus fenofibrate or atorvastatin did not improve lipid levels compared to fenofibrate or atorvastatin alone.

Overall, adverse event rates were low in the studies.

In summary, no consistent efficacy of complementary and alternative therapies in type 1 diabetes was found.

12.2.2 Cost-effectiveness studies

As no efficacy could be demonstrated, no evidence of cost effectiveness was found.

12.2.3 Summary

None of the 4 reviews or 13 primary studies of CAM in type 1 diabetes provided evidence for effects on glycaemic control. Similarly, there was insufficient evidence for other outcomes. The search strategy included only Level I and II studies; therefore, lower level studies at higher risk of bias were not considered. The outcome of studies using CAM may be influenced by the quality of the preparation studied; for example, in the case of herbal medicines, the part of the plant used and how it was prepared. The inclusion criteria for the studies varied, which limits the generalisability of the systematic review's findings for some outcomes. The studies were conducted in Australia and in countries with a well-developed health-care system, and are therefore applicable to the Australian health-care context.

Cinnamon was examined in only one RCT in adolescents with type 1 diabetes; however, it has been used for centuries in Chinese and Ayurvedic medicine, mostly to treat type 2 diabetes. Two main species are used: *Cinnamomum cassia*, which appears to be the preferred species; and *C. vera* or *C. zeylanicum*. The species have a similar chemical content, but with enough divergence to explain different clinical effects.

The systematic review did not include diabetes complications as an outcome, as was the case for the four Level I studies identified. However, there was one Level II study (a double-blind RCT) of gamma-linolenic acid in adults with type 1 and type 2 diabetes with distal diabetic polyneuropathy, confirmed both clinically and by objective nerve function studies. The intervention was associated with a significant improvement in sensory and motor nerve function, and in symptom score after 6 months. The study intervention, gamma-linolenic acid, is a constituent of evening primrose oil (*Oenothera biennis*).

No serious adverse events were reported in the included studies. However, CAM use was associated with deaths in children (Lim et al 2010); these deaths were ascribed to a failure to use conventional medicine in favour of a CAM therapy. There were 35 other reports of adverse events associated with CAM use in children. In one case, naturopathy for diabetes and a reduction in insulin dose was associated with symptomatic hyperglycaemia.

Evidence statement	
Q29	There is Level I evidence for a low rate of adverse events with nicotinamide, and Level II evidence for a low rate of adverse events with vitamin E and cinnamon. All studies showed no efficacy of complementary and alternative medicines in glycaemic control in type 1 diabetes. There is insufficient evidence to determine the efficacy of complementary and alternative medicines on lowering insulin dose in type 1 diabetes. There is insufficient evidence to determine an effect of complementary and alternative medicines on lipid levels in type 1 diabetes.
Recommendation	
R12.1	CAM should not be used to treat type 1 diabetes to target metabolic outcomes (Grade C).
Practice points	
PP12.1	Clinicians should ask patients about CAM in a nonjudgmental way, and document their use.
PP12.2	Patients with type 1 diabetes should be aware that there is a lack of evidence for the effectiveness of CAM. While there is evidence for a low rate of adverse events, the possibility of interaction between CAM and conventional medicines should be considered.
PP12.3	Patients who use CAM should be advised not to cease their insulin because of the high risk of diabetic ketoacidosis.
CAM, complementary and alternative medicine	

13 Maternal pregnancy and foetal outcomes

13.1 Introduction

Elevated blood glucose levels are toxic to the developing foetus. There is a positive relationship between high levels of glycated haemoglobin (HbA_{1c}) early in pregnancy in women with type 1 diabetes and the risk of congenital malformations; rates may be many times those occurring in nondiabetic pregnancies (Ylinen et al 1984). Congenital malformations that are associated with type 1 diabetes include major anomalies such as cardiac and neural tube defects, and malformations of the renal and urinary tract, gastrointestinal and skeletal systems (Miodovnik et al 1988). There is also an association between poor glycaemic control early in pregnancy and perinatal mortality. In addition, adverse maternal outcomes, such as severe hypoglycaemia, are not uncommon in type 1 diabetes pregnancies (Robertson et al 2009a), and are increased in the first trimester compared with pre-pregnancy (Nielsen et al 2009). Preconception care typically includes a strong focus on intensive blood glucose control, but also includes complications screening, medication review, folate supplementation, and discussion of smoking and alcohol intake.

13.2 Effectiveness of preconception care

Question 31

What is the effectiveness of preconception care in women with type 1 diabetes on improving maternal and foetal outcomes?

The detailed systematic review of this question is in Chapter 31 of the accompanying technical report, and the evidence matrix is in Section C31 of Appendix C

This question considered the effectiveness of preconception care on improving pregnancy outcomes for the foetus and the mother. The systematic literature search identified one systematic review and 10 cohort studies examining the effectiveness of preconception care in women with type 1 diabetes. The systematic review (Ray et al 2001) included 16 cohort studies (8 prospective and 8 retrospective). Most of the studies, including those in the systematic review, were of a low level of evidence. The nature of the question does not lend itself to a randomised controlled trial (RCT) study design, and no RCTs were identified. Most of the studies were of fair quality and some of poor quality. Limitations in some studies included an unclear description of the preconception care intervention or the number of people who received preconception care, largely due to the studies being retrospective. One study included a mixed population, with participants were recruited during either preconception or first trimester.

The systematic review by Ray et al (2001) reported a significantly lower rate of major congenital anomalies among preconception care recipients compared with nonrecipients. Among 2561 offspring (14 studies), the pooled rate of major anomalies was 2.1% in recipients compared with 6.5% in nonrecipients (relative risk [RR] 0.36, 95% confidence interval [CI]: 0.22 to 0.59). In nine studies (2104 offspring) the risk for major and minor anomalies combined was also lower among women who received preconception care (RR 0.32, 95%CI: 0.17 to 0.59). In seven studies, early first trimester HbA_{1c} values were lower in the preconception care group (pooled mean difference: 2.3%, 95%CI: 2.1 to 2.4), but there was heterogeneity for this pooled estimate ($p<0.20$).

Of the 10 additional cohort studies identified, results were mixed across various outcomes. Most of the studies found a reduced risk of an adverse foetal outcome with preconception care: five studies reported a reduced rate of perinatal mortality (McElvy et al 2000; Boulot et al 2003; Temple et al 2006; Pearson et al 2007; Tripathi et al 2010) and six studies found fewer congenital malformations (Goldman et al 1986; McElvy et al 2000; Boulot et al 2003; Temple et al 2006; Pearson et al 2007; Tripathi et al 2010). There was no significant effect of preconception care on maternal outcomes, including the rate of hypoglycaemia (Goldman et al 1986), the risk of severe hypoglycaemia (Temple et al 2006; Heller et al 2010), or the risk of pre-eclampsia (McElvy et al 2000; Temple et al 2006).

The evidence demonstrates that preconception care in reduces the risk of congenital malformations and perinatal mortality among women with type 1 diabetes. Preconception care also appears to be effective at reducing HbA_{1c} levels at or around the time of conception. Many of the studies, including the systematic review of 16 cohort studies, only examined congenital malformations and perinatal mortality, and did not consider other maternal and foetal outcomes (e.g. birth weight, macrosomia, pre-eclampsia or the risk of severe hypoglycaemia).

Evidence statement	
Q31	Level III evidence shows that preconception care is effective at reducing congenital malformations, perinatal mortality and HbA_{1c} levels in women with type 1 diabetes.
Recommendation	
R13.1	Females of childbearing age with type 1 diabetes should be aware of the need for pregnancy planning and receive preconception care (Grade B).
Practice points	
PP13.1	Counselling on contraception, pregnancy planning and preconception care should start during adolescence in females with type 1 diabetes.
PP13.2	At the time of planning pregnancy, females with type 1 diabetes should be referred to a multidisciplinary diabetes care team with expertise in preconception care. This health care delivery approach is described in detail in the 2005 Australasian Diabetes in Pregnancy Position Statement, which provides guidelines for prepregnancy planning and pregnancy care in women with type 1 diabetes (McElduff et al 2005).
PP13.3	Intensive glycaemic management to optimise the HbA_{1c} level in a safe manner is an essential component of preconception care.
PP13.4	There is an increased risk of neural tube defects in pregnancies in type 1 diabetes, and high-dose folic acid supplementation should be started before conception.
PP13.5	Screening for diabetes complications should occur during preconception care, specifically for diabetic retinopathy and nephropathy.
PP13.6	Preconception care should include review of medications. Statins, ACEI and ARBs are contraindicated in pregnancy.
PP13.7	Glycaemic control should be optimised before starting any assisted reproduction procedures.
ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; HbA_{ic}, glycated haemoglobin	

13.3 Effectiveness of blood glucose control

Question 32

What is the effectiveness of blood glucose control during pregnancy in women with type 1 diabetes in achieving blood glucose targets and improving maternal and foetal outcomes?

The detailed systematic review of this question is in Chapter 32 of the accompanying technical report, and the evidence matrix is in Section C32 of Appendix C

The most readily demonstrable benefit of intensive blood glucose control in pregnancies of women with type 1 diabetes occurs in preconception care (as described in Section 13.2). Question 32 considered whether blood glucose control *during* pregnancy can lead to improved pregnancy outcomes for the mother with type 1 diabetes and her foetus.

The systematic review found only one Level I study that met the inclusion criteria (Middleton et al 2010). This Cochrane review was of high quality. The authors used a rigorous and detailed search methodology that was updated monthly until May 2010. The review included three RCTs, two from the United States and one from Saudi Arabia, with a total of 223 women and babies. There was a high risk of bias for all three trials due to unclear allocation concealment methods and a lack of blinded outcome assessment, as well as a high risk of selective outcome reporting bias. The Cochrane review divided the studies into different categories of targeted glycaemic control: 'very tight' (fasting blood glucose [FBG] level <5 mmol/L), 'tight' (<6 mmol/L), 'moderate' (<7 mmol/L) and 'loose' (<9 mmol/L). In pooled analysis of two of the trials (Demarini et al 1994; Sacks et al 2006) glycaemic control was significantly better in the very tight target group compared with a tight–moderate group in the first (mean difference [MD] –1.23 mmol/L, 95%CI: –2.19 to –0.27) and second (MD –0.99 mmol/L, 95%CI: –1.64 to –0.34), but not the third trimesters (MD –0.66 mmol/L, 95%CI: –1.60 to 0.28). Few differences in outcome for mother or foetus were seen across these two trials. The single trial involving 60 women and babies that compared tight (≤5.6 mmol/L), moderate (5.0–6.7 mmol/L) and loose (6.7–8.9 mmol/L) glycaemic control targets found few differences between tight and moderate groups (Farrag 1987). In the loose control group, there were significantly more pre-eclampsia events, caesarean sections, neonates with respiratory distress syndrome, and cases of birth weight greater than the 90th percentile.

Thus, based on limited evidence, there were few differences in outcomes between very tight and tight–moderate glycaemic control targets in pregnant women with type 1 diabetes, including the actual level of glycaemic control achieved. There was some evidence of harm (increased pre-eclampsia, caesareans, respiratory distress syndrome and birth weight greater than 90th percentile) for loose glycaemic control (FBG above 6.7 mmol/L).

The systematic review did not include data from the Diabetes Control and Complications Trial (DCCT) because it was not designed to examine the effect of glycaemic control on pregnancy outcomes. It is noteworthy that maternal and fetal outcomes were better in those randomised to the intensive treatment arm of the DCCT and who received preconception care.

In gestational diabetes mellitus, regimens targeting very tight blood glucose control before and after meals in the third trimester reduced adverse maternal and foetal outcomes (Crowther et al 2005). In type 1 diabetes, however, the potential benefit of setting very tight glycaemic targets needs to be balanced against the risk of severe hypoglycaemia occurring in the pregnant woman.

Evidence statement	
Q32	During pregnancy in women with type 1 diabetes, there is some evidence of harm for fasting blood glucose targeted at 6.7–8.9 mmol/L, compared to below 6.7 mmol/L.
Practice points	
PP13.8	Ideally, intensive management to achieve and maintain optimal glycaemic control should commence before conception (see Q31).
PP13.9	Intensive management to achieve and then maintain optimal glycaemic control should occur throughout pregnancy.
PP13.10	Management should be by a multidisciplinary team experienced in the management of diabetes in pregnancy
PP13.11	The potential benefits of tight glycaemic control should be balanced against the risk of severe hypoglycaemia during pregnancy

13.4 Effectiveness of insulin pumps and CGMS during pregnancy

Question 33 (background question)

How effective are insulin pumps during pregnancy in achieving blood glucose targets and improving maternal and foetal outcomes?

Question 34 (background question)

How effective is CGMS during pregnancy in achieving blood glucose targets and improving maternal and foetal outcomes?

Question 35 (background question)

How and how often should complications (specified as retinopathy, CVD/hypertension and kidney functioning) be monitored during pregnancy?

CGMS, continuous glucose monitoring systems; CVD, cardiovascular disease

Questions 33–35 were background questions and thus were not systematically reviewed

It is beyond the scope of this document to address every aspect of clinical care in pregnancy in type 1 diabetes. Type 1 diabetes pregnancy related items not addressed in this current guideline include schedules of care and monitoring of the progressive wellbeing of mother and foetus, management of delivery and its timing, and postpartum management. A summary consensus approach to managing diabetes in pregnancy is provided in the Australasian Diabetes in Pregnancy Society (ADIPS) publication in the *Medical Journal of Australia* (McElduff et al 2005). Comment is provided, below, related to the questions 33–35.

13.4.1 CSII, CGMS, real-time blood glucose monitoring and sensor-augmented CSII therapy in pregnancy

Currently, there is no high-level evidence to address whether insulin delivery by continuous subcutaneous insulin infusion (CSII) therapy has any different effect on outcomes for the pregnant mother or foetus from the use of multiple daily injections (MDI) of insulin, in either preconception care or during pregnancy. RCTs with a subsequent meta-analysis in a Cochrane systematic review have not shown any difference in glycaemic control or other outcomes between MDI and CSII strategies (Farrar et al 2007).

Use of continuous glucose monitoring systems (CGMS) in type 1 diabetes pregnancy may aid clinical decision making in pregnancy and is well tolerated (McLachlan et al 2007). However,

there is no Level I or II evidence assessing whether CGMS or real-time blood glucose monitoring may improve pregnancy outcomes in type 1 diabetes. As described in Chapter 7 (question 15), the combination of CSII and continuous real-time monitoring of blood glucose (as sensor-augmented CSII therapy) was shown in one recent RCT to improve HbA_{1c} levels in type 1 diabetes outside of pregnancy (Bergenstal et al 2010). Such studies have not yet been undertaken in type 1 diabetes and pregnancy.

13.4.2 Diabetes complications monitoring during pregnancy

During pregnancy in type 1 diabetes, microvascular complications – specifically retinopathy (Vestgaard et al 2010) and nephropathy – may worsen in an accelerated manner (Yogev et al 2010), especially in the overweight. The cause for this deterioration may be related to rapidly improved glycaemic control leading into and during pregnancy, the haemodynamic stress of pregnancy, and effects of various placentally derived and other hormones and growth factors during pregnancy (Kaaja 2009). Women with vision-threatening retinopathy should, ideally, receive photocoagulation therapy before conception. Patients with microalbuminuria before pregnancy are at increased risk of developing pre-eclampsia (Ekbom et al 2001). If renal function is significantly impaired related to marked overt diabetic nephropathy (serum creatinine >0.2 mmol/L) (Biesenbach et al 1992), there is an increased risk of progression to dialysis during pregnancy. Therefore, chronic kidney disease stages 3B or higher should be considered a contraindication to pregnancy (McElduff et al 2005). The presence of autonomic neuropathy resulting in gastroparesis, orthostatic hypotension or hypoglycaemic unawareness may severely complicate the management of pregnancy in type 1 diabetes; however, these conditions are not generally viewed as contraindications to pregnancy. Evidence of macrovascular disease should be sought through detailed history and examination, and investigated if suspected. Pre-existing heart disease, including coronary heart disease, requires cardiological review before pregnancy, and significant coronary artery stenosis should be treated before conception (McElduff et al 2005).

There are no Level I or II studies that address the nature and timing of diabetes complications monitoring during pregnancy in type 1 diabetes. For complications, screening recommendations from professional bodies such as the ADIPS (McElduff et al 2005) indicate that, in women without a known history of microvascular complications, screening at least once during the pregnancy should occur for the diabetes microvascular complications of retinopathy and nephropathy, using standard methods. Such screening should preferably be undertaken in the first trimester, especially if complications screening has not recently been done. Those with known diabetic retinopathy or nephropathy before pregnancy are at high risk. In such cases, monitoring during pregnancy and related management should be individualised by the health care professional multidisciplinary unit supporting the pregnancy. For example, retinopathy monitoring and nephropathy monitoring (including assessment of albuminuria and determination of estimated glomerular filtration rate) could be undertaken each trimester. It is also recommended, as a guide, that formal eye review for diabetic retinopathy should be undertaken at least 3-monthly if baseline retinopathy is present, if there is a rapid improvement in glycaemic control, or if there has been a long duration of pre-existing diabetes (McElduff et al 2005). More frequent monitoring of complications status may be indicated for pregnant women who have required recent photocoagulation therapy, have systemic hypertension or overt diabetic retinopathy (Kaaja 2009). Recent data from women with diabetic nephropathy before pregnancy indicate that strict control of blood pressure and blood glucose can lead to improved pregnancy outcomes, compared with historic controls (Nielsen et al 2009).

13.4.3 Practice tips

- Screening for diabetes complications, specifically diabetic retinopathy and nephropathy, should not only occur as part of preconception care, but also during pregnancy, preferably in the first trimester.
- Vision-threatening diabetic retinopathy detected before pregnancy should be managed before conception, especially as retinopathy will often worsen during pregnancy.
- The presence of significant chronic kidney disease is a relative contraindication to pregnancy in type 1 diabetes; the risks of pregnancy in this setting should be discussed before conception.
- In women who have diabetic retinopathy or nephropathy before pregnancy, processes for monitoring these complications throughout pregnancy should be individualised, as scheduled by the multidisciplinary high-risk pregnancy diabetes health professional care team.
- Periodic use of CGMS or real-time blood glucose monitoring during pregnancy may aid modification of intensive insulin therapy regimens during pregnancy.
- Intensive diabetes management during pregnancy should routinely include multidisciplinary specialist care and may involve the use of CSII.
- Insulin requirements fall rapidly during labour and in the puerperium. At this time, close monitoring and adjustment of insulin therapy is necessary.
- Level 3 neonatal nursing facilities may be required and should be anticipated when birth occurs before 36 weeks, or if there has been poor glycaemic control.

14 Contraception

14.1 Introduction

Question 36

What is the effectiveness of hormonal versus nonhormonal contraception in type 1 diabetes?

The detailed systematic review of this question is in Chapter 36 of the accompanying technical report, and the evidence matrix is in Section C36 of Appendix C

Reliable methods of contraception are needed in women with type 1 diabetes, not least because planned pregnancy is necessary to optimise fetal and maternal outcomes in pregnancy. The options in contraception are broadly divided into hormonal and nonhormonal methods. Both efficacy and potential adverse effects, including those related to diabetes, need to be assessed to examine effectiveness.

In a review of the published literature, one systematic review (Visser et al 2006) met the inclusion criteria, and had been updated in 2009. This systematic review aimed to capture all published data from randomised controlled trials (RCTs) and quasi-randomised trials that compared differences between progestogen-only contraceptive methods, combined oestrogen/progesterone contraceptives, and nonhormonal contraceptives in women with diabetes. The comparisons were in terms of effectiveness in preventing pregnancy, effects on carbohydrates and lipid metabolism, and long-term outcomes such as vascular complications.

The four RCTs in the systematic review differed in terms of the contraceptives studied, participant characteristics and methodological quality (Radberg et al 1982; Skouby et al 1986; Rogovskaya et al 2005; Grigoryan et al 2006); thus, data could not be combined in a meta-analysis. The trial results were examined on an individual quantitative basis and narrative summaries were reported. The hormonal contraceptives included differing doses (low and higher dose) of oestrogen, androgenic and nonandrogenic progestogens (either alone or with oestrogen), and intrauterine devices (IUDs) that contain copper or release levonorgestrel. Outcomes of interest included metabolic outcomes (e.g. glycaemia, insulin requirements, lipid profiles), as well as body weight and effects on blood pressure.

No unintended pregnancies occurred during any of the included trials. Since pregnancy is a rare event in contraceptive users, the sample size and duration of the included trials were too small and too short, respectively, to detect differences among the various contraceptives. From large trials conducted among contraceptive users in the general population, we know that, with proper use of contraceptives (as occurred in the included trials), combined oral and progesterone-only contraceptives give a 0.3% chance of an unintended pregnancy within the first year. This chance is 0.6% for copper IUDs and 0.1% for progestogen-releasing IUDs (WHO 2004). It is expected that the chance of an unintended pregnancy is similar for women with diabetes relative to women without diabetes when such contraception is used.

In relation to metabolic outcomes, the studies did not show benefit or adverse effect on glycaemia. The three studies that reported lipid levels, including cholesterol subsets, gave conflicting results, although all lipid levels were within normal range before and after contraceptive use. The studies that examined blood pressure (Radberg et al 1982; Skouby et

al 1986) found no change in this parameter across the 6-month study duration, nor did body weight change (Skouby et al 1986). The RCTs had some limitations, including poor reporting of study methods and poor methodological quality. Three of the four included studies did not describe the method of generating the allocation sequence, the method of concealing the treatment allocation sequence, or the use of blinding. At 12 months' maximal duration, none of the studies were of adequate duration to assess for any direct effect on diabetes end-organ complications.

14.2 Summary

Overall, the data did not provide sufficient evidence to assess whether progesterone-only or combined oral contraceptives differ from nonhormonal contraceptives in their effects on diabetes control, lipid metabolism and long-term diabetes-related complications. Unintended pregnancies were not observed during any of the studies. Three of the four studies were of limited methodological quality and described surrogate outcomes.

Evidence statements	
Q36	The four RCTs included in this systematic review provided insufficient evidence to assess whether progesterone-only and combined oral contraceptives differ from nonhormonal contraceptives in their impact on glycaemic control.
Q36	The four RCTs included in this systematic review provided insufficient evidence to assess whether progesterone-only and combined oral contraceptives differ from nonhormonal contraceptives in their impact on lipid metabolism.
Practice points	
PP14.1	The relative risk of unplanned pregnancy should be considered against the potential cardiovascular risk associated with hormonal contraceptives.
PP14.2	Nonhormonal contraception methods with high efficacy and are also generally well tolerated (e.g. IUD methods) can be clinically useful.
PP14.3	Contraceptive preferences will often differ across women of reproductive age; for example, between a teenager with type 1 diabetes and a 40–45-year-old woman.
PP14.4	In a stable long-term relationship, male contraception through vasectomy is an effective nonhormonal permanent contraceptive method for a couple who do not desire further conception.
ACEI, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; IUD, intrauterine device; RCT, randomised controlled trial	

15 Transition and care across the individual's lifespan

15.1 Introduction

The most useful definition for transition comes from the American Society for Adolescent Medicine, where it is described as 'the purposeful planned movement of adolescents and young adults with chronic physical and medical conditions from child-centred to adult-orientated health care systems' (Blum et al 1993). This chapter is based on contemporary guidelines (Court et al 2009) and expert consensus from the Expert Advisory Group. The chapter also draws extensively on the *Best practice guidelines for health professionals* for the effective transition of young people with diabetes from paediatric to adult care (Lang 2008).

Question 37 (background question)

What are the essential elements in transitional care models in type 1 diabetes from adolescence to adulthood?

Question 37 was a background question and therefore was not systematically reviewed

15.2 Key elements for effective transitional care

The key elements required for effective transitional care, discussed below, are:

- flexible timing of transfer
- flexibility in provision of health services
- a 'transition case manager' for each person
- a preparation period
- a choice of adult provider
- a coordinated transfer
- joint consultations
- accessible medical documentation
- maintaining contact after transfer
- psychosocial support.

Flexible timing of transfer

There is no 'set' or 'right' time for transition. Each person should be viewed as an individual and consideration should be given to the person's developmental and health status, and also to what is happening in their life. However, establishing a target transfer age is useful for planning by the care team, and for preparing the young person for an anticipated change. Young people should not be transferred to a new service or clinic at a time when they are experiencing major life changes or are in 'crisis'.

Flexibility in provision of health services

Health services need to be flexible and designed to suit the needs of young people; examples include evening clinics and young adult clinics.

A 'transition case manager' for each person

Each young person should be assigned a transition case manager from within the multidisciplinary diabetes care team. The role of the manager includes monitoring and documenting the young person's progress through the transition process. The manager can either intervene where necessary, or arrange appropriate interventions from other members of the care team; for example, if the young person fails to attend a clinic appointment or has evidence of poor glycaemic control. The transition case manager becomes the primary contact for the young person.

A preparation period

A preparation period is necessary to help young people develop the necessary knowledge and skills to enable them to cope with the responsibilities of taking charge of their own diabetes health care.

A choice of adult provider

Where possible, young people should be given a choice of adult care provider, and should be reassured that it may take more than one visit to a doctor or service to find someone that they feel comfortable with. Options should include care in the private sector.

A coordinated transfer

Young people should be given an anticipated transfer date or an age of transfer to adult services. Ideally, before transfer, there should be at least one joint visit with the adult service or clinic.

Accessible medical documentation

A comprehensive medical and psychological history, along with a treatment summary, should accompany the young person when they are transferred to an adult service. Documentation of education and skills acquisition should also be included. The young person's consent needs to be obtained for the release of this information (Viner 1999).

Maintaining contact after transfer

The transition case manager should maintain contact with the young person after transfer, to ensure that their needs are being met by the adult diabetes service to which they have been transferred. Young people need to be supported in finding an adult diabetes service that they feel comfortable with. Contact should be maintained until the young person has successfully engaged with an adult diabetes service.

Psychosocial support

During the transition process, the psychosocial needs of the young person must be proactively anticipated and managed (Royal College of Physicians of Edinburgh Transition Steering Group 2008). Additional psychological support is likely to be required as the time of transfer to adult care approaches.

The paediatric care team must also be aware of the prevalence of depression in young people with diabetes. Behavioural problems and declining school performance can be specific markers of underlying psychological distress in adolescence (Department of Health Western Australia 2009).

15.3 Adult diabetes health service

Adult health care differs significantly from paediatric care in relation to the type and level of support, decision making, consent processes and family involvement. These factors may contribute to the decrease in attendance by young people after transfer to the adult care system.

Health professionals tend to focus on future benefit from current treatment, whereas young people tend to be focused on the 'here and now'. A process of active negotiation with the young person may help them to take ownership of, and responsibility for, their health care (Royal College of Physicians of Edinburgh Transition Steering Group 2008).

Elements of adult diabetes care that contribute to successful transition include providing adequate psychological support, tailoring treatment and maintaining confidentiality.

In 2005, a survey of young people with diabetes investigated what young people want from an adult diabetes service (Dovey-Pearce et al 2005). Given the high proportion of young people with diabetes who 'drop out' of conventional adult care, adult services should consider adopting some, if not all, of the following practices, to meet the specific needs of young people:

- ensuring that the young person sees the same staff at each consultation or clinic visit
- providing definite appointment times
- providing capacity for 'drop in' visits
- holding clinics and consultations out of working hours (including weekends)
- providing specific clinics for young adults
- encouraging questions during clinics and consultations
- taking an interest in the patient as a person
- providing information relevant to the young person
- providing resources (e.g. list of appropriate websites, booklets, videos)
- providing regular updates (e.g. through a newsletter)
- encouraging telephone or email contact with staff
- sending SMS reminders for appointments
- implementing a patient feedback process.

15.4 The role of the general practitioner

The general practitioner (GP) has an important role as a partner in the management of all young people with diabetes, and should be the primary point of contact for the young person and their family for day-to-day health issues. The diabetes care team has a responsibility to keep the GP informed of the young person's progress and current treatment.

The GP has a critical role in ensuring continuity of care, particularly during transition. In the absence of a suitable adult diabetes service, the GP may become responsible for the young person's diabetes management after transfer from paediatric care. It is essential that the GP screens for diabetes complications, and immediately refers the young person to a diabetes specialty service if any of the following apply:

- there are any abnormal findings on the annual diabetes complication screen
- the HbA_{1c} is above 9% on two or more occasions in one year
- there is continued and significant weight loss
- the body mass index is below 18 kg/m^2 or above 25 kg/m^2
- the young person is experiencing difficulty adhering to the treatment regimen (or is noncompliant)
- the young person is pregnant or is considering becoming pregnant
- the young person has been admitted to hospital for a diabetes-related condition (e.g. ketoacidosis or severe hypoglycaemia)
- there is a diagnosis of one or more coexisting diseases
- there are any mental health issues.

Practice points	
PP15.1	Transition must never be rushed. Rather, it needs to occur in a purposeful, structured, coordinated manner beginning in early adolescence.
PP15.2	Without a structured transition process, many young people are lost to specialist diabetes care after transfer to an adult service (Nakhla et al 2009). The percentage of young people reported as lost to adult care varies from 11% to 24% (Frank 1996; Pacaud et al 2005).
PP15.3	These young people lost from the system are likely to re-present in early adult life with preventable diabetes-related complications as a result of poor diabetes control. The 'drop out' from specialist diabetes care results in preventable morbidity, a potential reduction in both productivity and life expectancy, and additional long-term costs to the health system (Frank 1996; Nakhla et al 2009).
PP15.4	Greater attention to the cohort of adolescents who are not attending clinic regularly and who have poor glycaemic control may improve transition outcomes. Evidence suggests that these factors are predictors of failure in transition to adult care (Frank 1996; Jacobsen et al 1997; Goyder et al 1999).
PP15.5	The transition program must be aimed at engaging the young person in their care and ensuring they have the appropriate knowledge and skills to make informed health decisions (Viner 2001).
PP15.6	As well as dealing with the medical issues of the young person, education needs to include (McDonagh and Viner 2006): • skills training, including diabetes self-management, self-advocacy, and the ability to independently negotiate services and to actively participate in a medical consultation • education about general adolescent health issues, such as drug taking, alcohol use, and mental and sexual health issues • educational and vocational issues, particularly career, work experience and disclosure.
PP15.7	During the transition process, the focus should progressively switch from the parent as the care giver to acknowledging the growing autonomy of the young person.
PP15.8	Successful transition requires an interested and capable adult diabetes service (public or private) and a willingness by the adult health professionals to participate in the transition process.
PP15.9	Both paediatric and adult teams need to be responsive to the needs of young people if transition is to be successful.
PP15.10	The manner in which the young person is prepared for transition to the adult health-care system is crucial to their continued wellbeing and adherence to ongoing health support and treatment.

16 Hypoglycaemia

16.1 Introduction

Hypoglycaemia occurs when the blood glucose level falls below normal and the person experiences related symptoms that resolve after the blood glucose returns to normal (Cryer et al 2009). Hypoglycaemia in type 1 diabetes results from a clinically significant mismatch between the insulin administered and the insulin required for the person's lifestyle requirements (Cryer et al 2009).

Hypoglycaemia is considered mild (or moderate) when the person is able to treat themselves. The common definition used for severe hypoglycaemia (also known as grade 2 or 3 hypoglycaemia), is that the episode requires assistance from a third party to treat the hypoglycaemia (DCCT Research Group 1993). Severe hypoglycaemia is defined as unconsciousness or seizures. Severe hypoglycaemia may be life threatening; for example, by causing injury or precipitating cardiac events (Cryer 2010). It is a major endpoint to target in the professional care of type 1 diabetes (DCCT Research Group 1993). Hypoglycaemia of all forms is generally feared by people with diabetes and their immediate carers and family (Anderbro et al 2010; Barnard et al 2010). Fear of hypoglycaemia and its consequences is often the greatest barrier to optimal glycaemic control (Pearson 2008).

Mild hypoglycaemia remains a regular occurrence in most people with type 1 diabetes; for example, in the intensive management group of the Diabetes Control and Complications Trial (DCCT), mild hypoglycaemia occurred about twice weekly (DCCT Research Group 1993), and may adversely affect quality of life. In contrast, severe hypoglycaemia occurs on average once every three or more years in type 1 diabetes (Jones and Davis 2003). There is marked individual variation in the rate of severe hypoglycaemia, with some people never experiencing it and others experiencing it multiple times a year, despite intensive diabetes management in multidisciplinary diabetes health-care units (DCCT Research Group 1997). Nocturnal hypoglycaemia accounts for close to half of the episodes of severe hypoglycaemia (Allen and Frier 2003).

Risk factors for severe hypoglycaemia and acute effects are discussed in Section 16.2; cognitive effects that can occur due to severe hypoglycaemia in Section 16.3; and efficacy and safety of treatments for hypoglycaemia in Section 16.4.

16.2 Predictive factors for severe hypoglycaemia

Question 38

i) What are the predictive factors for severe hypoglycaemia?

ii) What is the effect of intensive diabetes management on the incidence of severe hypoglycaemia?

The detailed systematic review of this question is in Chapter 38 of the accompanying technical report, and the evidence matrix is in Section C38 of Appendix C

Severe hypoglycaemia is about 10 times more common in people with type 1 diabetes than in those with type 2 diabetes (DCCT Research Group 1991; UKPDS Group 1998b; DCCT Research Group 2009). In severe hypoglycaemia, the person with diabetes is unable to treat themselves, and the hypoglycaemia may lead to accident and precipitate medical emergencies. Methods to identify risk factors for severe hypoglycaemia in a person with

type 1 diabetes, and to minimise the occurrence of severe hypoglycaemia, are therefore of high priority. Severe hypoglycaemia may be more common in settings where attempts to reduce risk of long-term end-organ complications of diabetes are instituted.

The risk factors for severe hypoglycaemia include those that are inherent in the individual with diabetes and those that are a consequence of treatment of diabetes. This question was divided into two parts to examine the evidence for these factors separately.

16.2.1 Predictors of severe hypoglycaemia

In addressing question 38(i), the systematic review was subdivided into children or adolescents and adults, because predictors of severe hypoglycaemia may differ across the life span.

Children and adolescents

The systematic review identified Level II (prospective cohort) studies, which ranged from 61 (Gonder-Frederick et al 2008) to more than 7605 person years of follow-up (Bulsara et al 2007). In addition, three cross-sectional studies were identified, each of which surveyed more than 2000 young people with type 1 diabetes (Mortensen and Hougaard 1997; Danne et al 2001). In adults, the highest level evidence came from a randomised control trial (RCT) – the DCCT (DCCT Research Group 1993). Two analyses of this population were included (DCCT Research Group 1991; DCCT Research Group 1997), with a follow-up time of more than 9000 person years. Six adult cross-sectional studies were also identified (Chaturvedi et al 1995; Stephenson et al 1996; Buyken et al 1998; Salti et al 2004; Hirai et al 2007; Pedersen-Bjergaard et al 2008). Overall, studies were mostly of good or fair quality.

Study outcomes are summarised and tabulated in the technical document. Age was an independent risk factor for severe hypoglycaemia in children and adolescents; severe hypoglycaemia was more common in children younger than 6 years compared with older children (Davis et al 1998; Bulsara et al 2004; Bulsara et al 2007). Increasing duration of diabetes, especially after more than 9 years, was positively associated with severe hypoglycaemia (Bulsara et al 2004; Bulsara et al 2007) and the risk increased progressively with each 5 years of diabetes in the paediatric age group (Rewers et al 2002).

Lower glycated haemoglobin (HbA_{1c}) level was also consistently a risk factor for severe hypoglycaemia across seven studies reported, including in the DCCT (DCCT Research Group 1994). In one study, for each 2% reduction in HbA_{1c} level, the severe hypoglycaemia risk increased 1.5 fold (95% confidence interval [CI]: 1.2 to 2.0) (Allen et al 2001), reflecting a similar finding in one Australian study across the HbA_{1c} range of 7–9% (Davis et al 1998). Other factors associated with increased risk of severe hypoglycaemia were the conditions of reduced hypoglycaemia awareness (i.e. reduced ability to detect early warning symptoms of hypoglycaemia) (Gonder-Frederick et al 2008) and psychiatric illness (Rewers et al 2002), although these conditions were not well examined, due to exclusion criteria in many studies. For teenagers, being male was implicated as a risk factor in one study (Bulsara et al 2004), but not another (Rewers et al 2002). Social disadvantage (Bulsara et al 2004), higher insulin dose and serum angiotensin converting enzyme (ACE) level, were also risk factors in one study. In the DCCT, adolescents in both the conventionally and intensively managed groups had a higher rate of severe hypoglycaemia compared with adults in the trial (DCCT Research Group 1994). Across all the risk factors in children and adolescents, significant odds ratios (ORs) for severe hypoglycaemia were generally in the range 1.5–3.0, with the most robust associations being found for longer diabetes duration, age less than 6 years and lower HbA_{1c} level.

Adults

Risk factors for severe hypoglycaemia included increasing diabetes duration (DCCT Research Group 1997), lower HbA_{1c} level (DCCT Research Group 1997) and male sex (DCCT Research Group 1997), in keeping with evidence from studies in young people. The original DCCT report indicated a continuous, apparently exponential, increase in severe hypoglycaemia risk with lower HbA_{1c} levels (DCCT Research Group 1993). A more recent publication using the DCCT cohort reported a hazard ratio of 0.93 for a higher HbA_{1c} and severe hypoglycaemia ($p<0.001$); the study also suggested that mean blood glucose and standard deviation add to the risk, independently of HbA_{1c} level (Kilpatrick et al 2007). A previous history of severe hypoglycaemia was also an independent risk factor for severe hypoglycaemia (Kilpatrick et al 2007). The ORs for severe hypoglycaemia were generally in the range 1.5–3.0 with the higher ratios being observed in those with a longer diabetes duration, lower HbA_{1c} level or previous severe hypoglycaemia. In addition, in various studies, risk factors for severe hypoglycaemia were found to include hypoglycaemia unawareness (Pedersen-Bjergaard et al 2008), presence of autonomic neuropathy (Hirai et al 2007), current smoking (Hirai et al 2007), angiotensin 2 receptor allele genotype, a higher serum ACE level (Pedersen-Bjergaard et al 2008) and prolonged fasting in those with type 1 diabetes who practise Ramadan (Salti et al 2004). Increasing age in adults was an independent risk factor for severe hypoglycaemia in one study (Pedersen-Bjergaard et al 2008) but not in another (Kilpatrick et al 2007).

16.2.2 The effect of intensive diabetes management on the incidence of severe hypoglycaemia

The systematic review identified two meta-analyses that examined the risk of adverse effects of intensified treatment in insulin-dependent diabetes. Wang et al (1993b) was published before the DCCT, and was of fair quality. The meta-analysis by Egger et al (1997b) included the results of the DCCT and was of good quality. These two studies provided Level I evidence that intensified diabetes management significantly increased the risk of severe hypoglycaemia.

In the meta-analysis by Egger et al, examining a total of 2067 patients, the incidence of severe hypoglycaemia ranged from 0 to 66.6 (median 7.9) episodes per 100 patient years among the intensively treated patients, and from 0 to 33.3 (median 4.6) episodes per 100 patient years among conventionally treated patients. The combined OR reported by Egger et al (1997b) was 2.99 ($p<0.0001$) for intensively treated patients, with some evidence for heterogeneity across studies ($p=0.06$). The DCCT trial reported a relative risk of 3.28 for severe hypoglycaemia in patients from the intensive treatment arm compared to the conventional group. The meta-analysis published before the DCCT results showed a trend towards an increase in severe hypoglycaemia with intensively treated patients; however, this was not statistically significant (Wang et al 1993b) – the estimated difference between arms being 9.1 (95%CI: –1.4 to 19.6). These results were pooled from six small studies (with numbers ranging from 20 to 94 participants), with overall low incidence rates of severe hypoglycaemia.

The definition of severe hypoglycaemia varied somewhat in the studies included in this systematic review. Most studies followed the DCCT definition of severe hypoglycaemia, as hypoglycaemia requiring the assistance of a third party (DCCT Research Group 1993). Some defined severe hypoglycaemia further as that resulting in seizure or coma or hospital admission, or requiring parenteral therapy. Therefore, these studies may underestimate the prevalence of any severe hypoglycaemia requiring third-party help. In addition, the threshold at which children need assistance from a third party may differ from that of adults. Davis et al (1998) attempted to address this by including only episodes accompanied by

obvious neuroglycopaenia. In addition, the issue of recurrent severe hypoglycaemia was not always addressed in the included studies and was not included as an outcome for this report. People with a history of prior severe hypoglycaemia were often excluded from the studies addressing severe hypoglycaemia. In adults, severe hypoglycaemia tends to recur and 'cluster' in certain high-risk individuals (e.g. people with more than 10 years of type 1 diabetes, with past history of severe hypoglycaemia and reduced hypoglycaemia awareness), especially if chronic behavioural or psychological disorders exist that can reduce adherence to matching insulin doses to lifestyle needs and in monitoring blood glucose.

Evidence statements	
Q38	Level II evidence indicates that younger age, longer duration of diabetes and hypoglycaemia unawareness are associated with higher risk of severe hypoglycaemia.
Q38	Level I evidence from studies published before 1997 (including the DCCT) shows that intensive management is associated with a higher risk of severe hypoglycaemia.
Recommendation	
R16.1	Risk factors for severe hypoglycaemia should be identified (Grade B).
Practice points	
PP16.1	Minimising occurrence of severe hypoglycaemia is an important target in type 1 diabetes care, including in intensive diabetes management.
PP16.2	Specific management strategies should be implemented for people who have a high risk of severe hypoglycaemia, including those with a history of severe hypoglycaemia or a reduced ability to detect early warning symptoms of hypoglycaemia (i.e. hypoglycaemia unawareness). In cases of hypoglycaemia unawareness, strategies to reduce severe hypoglycaemia include more frequent SMBG, and making sure that any blood glucose below a certain threshold (e.g. <4 mmol/L) is treated as hypoglycaemia, even in the absence of hypoglycaemia symptoms.
PP16.3	Intensive diabetes management may increase the risk of severe hypoglycaemia; therefore, some people who have a high risk of severe hypoglycaemia may not be suitable for low HbA_{1c} targets. .
PP16.4	Certain risk factors that are known to increase severe hypoglycaemia risk include alcohol abuse and recreational drug abuse, and these should also be addressed in people with type 1 diabetes.
PP16.5	A medical practitioner should carefully assess whether a person with type 1 diabetes is fit to drive a motor vehicle, this is required, in particular, to help reduce the risk of motor vehicle crashes due to severe hypoglycaemia. The AustRoads *Assessing fitness to drive* booklet, should be used as a reference.
DCCT, Diabetes Control and Complications Trial; HbA_{1c}, glycated haemoglobin; SMBG, self-monitored blood glucose	

16.3 Acute effects of severe hypoglycaemia

Question 39

What are the acute effects of hypoglycaemia and hyperglycaemia on cognitive function?

The detailed systematic review of this question is in Chapter 39 of the accompanying technical report, and the evidence matrix is in Section C39 of Appendix C

The systematic review identified 31 studies that met the search criteria for this question, three of which were prospective cohort studies in a naturalistic environment (Cox et al 1999; Cox et al 2005; Gonder-Frederick et al 2009). The other studies were labour-intensive laboratory studies with small participant numbers, where blood glucose levels were manipulated artificially by use of the insulin clamp method. All studies were undertaken in

well-developed health-care systems, including one paediatric study in Australia (Davis et al 1996).

The prospective cohort studies collectively included 289 adults and 61 primary school aged children, and were of moderate risk of bias. Cox et al (1999) and (2005) examined adults with recent severe hypoglycaemia and current hyperglycaemia, respectively. Gonder-Frederick et al (2009) studied effects of hypoglycaemia and hyperglycaemia in school-aged children using a field procedure to test the hypothesis that naturally occurring episodes of hypoglycaemia and hyperglycaemia are associated with deterioration in cognitive function. The insulin clamp studies were predominately carried out in adults (total n=398), with only two being in children or adolescents (total n=48) (Gschwend et al 1995; Davis et al 1996). Studies were heterogeneous in terms of the methodologies used, including glycaemic thresholds at which cognitive function was assessed, the tests that were used to measure cognitive function, the timeframe in which assessment was undertaken, and the outcomes measured. The studies were mainly of moderate risk of bias.

In the cohort studies, both hypoglycaemia and hyperglycaemia were associated with impaired cognitive function (Cox et al 1999; Cox et al 2005; Gonder-Frederick et al 2009). In adults, acute hyperglycaemia (defined as blood glucose level >15 mmol/L) had a significant impact on cognition, with slowing in all cognitive performance tests ($p<0.02$) and an increased number of mental subtraction errors (Cox et al 2005). In children, during blood glucose extremes (defined as <3.0 mmol/L and >22.2 mmol/L), cognitive function was significantly affected, as demonstrated by longer time taken to complete mental mathematics and choice reaction time (Gonder-Frederick et al 2009). However, the studies each reported large differences between individuals in the degree of impairment occurring at different blood glucose levels (Cox et al 2005; Gonder-Frederick et al 2009). Abnormal test results in hyperglycaemia were observed in about 50% of adults studied and Cox et al (2005) reported that exploratory analyses undertaken to determine the basis of these individual differences demonstrated an association between cognitive impairment and greater exposure to blood glucose readings above 15 mmol/L and higher HbA_{1c} (Cox et al 2005).

In adults, the negative impact on cognitive function when blood glucose level was less than 3.9 mmol/L was significantly greater when compared with the impact on those without a recent history of severe hypoglycaemia (Cox et al 1999). In children, demographic variables such as age and sex were not associated with individual differences; however, a relationship was demonstrated between higher HbA_{1c}, frequency of severe hypoglycaemia and greater cognitive impairment when blood glucose levels were high (Gonder-Frederick et al 2009). The reported limitations of these studies included the relatively small number of participants, most of whom were Caucasian (Gonder-Frederick et al 2009). In addition, the participants were studied over a relatively short period of time, yielding a limited number of extreme blood glucose readings (Gonder-Frederick et al 2009). The authors suggested that the results, especially those on acute hyperglycaemia, be considered preliminary and be interpreted with caution. Large individual differences were found, and numerous, unidentified variables were likely to have affected the impact of acute blood glucose extremes on cognitive function.

Among the insulin clamp studies, in those measuring the effect of hypoglycaemia on cognitive function, significant effects on both simple and more complex cognitive tasks were demonstrated compared to measures of cognitive function during euglycaemia. Decreases in psychomotor function, motor speed and reaction time, attention, verbal function, memory, visual spatial skills and auditory information processing were demonstrated in response to acute hypoglycaemia. Gonder-Fredrick et al (1994) found that glycaemic thresholds for, and

recovery from, cognitive dysfunction varied greatly across individuals, ranging from glucose levels below 2.6 mmol/L to above 3.6 mmol/L (Gonder-Frederick et al 1994). Hypoglycaemia unawareness was associated with more profound and longer lasting cognitive dysfunction (Gold et al 1995), and recent occurrence of nocturnal hypoglycaemia was associated with lower glycaemic thresholds for cognitive dysfunction (Fanelli et al 1998). Lower HbA_{1c} was also associated with lower glycaemic thresholds for cognitive dysfunction in one study (Ziegler et al 1992), but not in another (Maran et al 1995). Where the effects of hyperglycaemia were studied, assessment of cognitive function was undertaken during plasma glucose levels ranging from 16.7 mmol/L to as high as 30 mmol/L.

There was inconsistency in the results reported concerning the effects of acute hyperglycaemia on cognitive function in the two studies in children. Davis et al (1996) found a significant impact on performance intelligence quotient (IQ) in a group of 12 Australian children. Gschwend et al (1995) found no impact of acute hyperglycaemia on cognitive performance, as measured by choice reaction time and the trail-making test, in a series of 10 teenagers (Gschwend et al 1995). This inconsistency may be due to the different methodologies used and the outcomes measured. No effect on cognitive function was reported in two studies that assessed the impact of acute hyperglycaemia on cognitive function in adults (Hoffman et al 1989; Draelos et al 1995). Subtle trends towards poorer performance during hyperglycaemia were reported in three studies by Holmes et al (1983; 1984; 1986).

Thus, acute hypoglycaemia and acute hyperglycaemia may adversely affect cognitive function in children and adults. Data are less well established for acute hyperglycaemia, and there is much individual variation in threshold for effects and rate of recovery, only some of which may be explained by currently known variables.

Evidence statements	
Q39	Level II evidence shows that acute hypoglycaemia causes a temporally related impairment in cognitive performance. Level III evidence shows that acute hyperglycaemia may cause cognitive impairment in children and adults. One Level II study shows that acute hyperglycaemia above 22 mmol/L in children is associated with a comparable impairment to acute hypoglycaemia (<3 mmol/L).
Recommendation	
R16.2	Acute hypoglycaemia (Grade B) and hyperglycaemia (Grade C) should be minimised to maintain optimal cognitive performance.
Practice points	
PP16.6	Adverse cognitive effects of acute severe hypoglycaemia and acute severe hyperglycaemia should be avoided during tasks requiring high level cognitive function, such as in school, college or university examinations; or in adolescents and adults during potentially dangerous activities involving occupational health, such as operating heavy machinery or during driving. In some cases, the risk or presence of acute severe changes in blood glucose to very low and possibly very high levels may lead to the need for exemption from or avoidance of the cognitively demanding or high-risk activity.
PP16.7	Mild hypoglycaemia and mild hyperglycaemia are common in type 1 diabetes; however, acute severe dysregulation of blood glucose to either extreme that may cause cognitive effects should be avoidable in most people with type 1 diabetes, if due self care is taken.
PP16.8	The blood glucose level at which a person develops cognitive effects from severe hypoglycaemia can vary, related to the degree of chronic glycaemia control and avoidance of severe hypoglycaemia if an episode has occurred during recent weeks to months. In such cases, early warning symptoms of hypoglycaemia that may have been lacking in a person with type 1 diabetes may at least partially return.

16.4 Efficacy and safety of treatments

Question 40 (background question)

What are the efficacy and safety of treatments for mild or severe hypoglycaemia?

Question 40 was a background question and was therefore not systematically reviewed

Treatment for mild to moderate and severe hypoglycaemia is well established and effective for children and adults (Pearson 2008; Endocrinology Expert Group 2009). The amount of glucose needed to treat a hypo depends on the person's size, insulin plan, recent insulin doses and recent exercise. Bigger, older children and adults require the larger amount and occasionally more.

Treatment options for mild to moderate hypoglycaemia in a cooperative child include (Ambler and Cameron 2010):

- glucose tablets 10–20 g (not in children under 5 years)
- ordinary soft drink or cordial 125–250 mL
- fruit juice 125–250 mL
- sugar or honey (two to four teaspoons)
- jelly beans – 3 to 6 large or 6 to 12 small jelly beans (not in children under 5 years).

In general, the fast-acting carbohydrate (above) is followed with an exchange or serve of slow-acting carbohydrate, such as bread, milk, biscuits, apple or banana. This is not always required, particularly for those on pumps.

Treatment of mild to moderate hypoglycaemia in adults may be treated with readily available glucose containing food with 20–25 g of glucose. This should be promptly followed up by a food that has more slowly absorbed carbohydrate, such as a sandwich or dried fruit (Endocrinology Expert Group 2009).

Severe hypoglycaemia in children who are not in hospital should be treated with glucagon subcutaneous (SC) or intramuscular (IM), as 0.5 mg (age less than 5 years), or 1 mg (age 5 years or more), given by the responsible parent or carer. Children with severe hypoglycaemia in hospital should initially be given 10% glucose at 2 mL/kg as an intravenous (IV) bolus, 0.45% sodium chloride with 5% glucose at maintenance rates to keep the blood glucose level above 4 mmol/L (Endocrinology Expert Group 2009; Ambler and Cameron 2010).

Severe hypoglycaemia in adults should be treated with glucagon 1 mg SC or IM, administered to patients by their partners or relatives; this is often also the choice of therapy used by paramedics. In the hospital setting, IV bolus glucose as 50%, 20–30 mL, is given through a secure cannula, then some form of maintenance glucose, such as 5% dextrose at 100 mL per hour, is often provided (Endocrinology Expert Group 2009).

The methods described above to treat hypoglycaemia are highly efficacious in resolving symptoms of hypoglycaemia and returning blood glucose to the normal range. Factors that may limit efficacy of treating moderate hypoglycaemia are if the glucose is not swallowed or if gastroparesis is present (e.g. due to diabetic gastroparesis in those with long-standing diabetes or intercurrent illness such as gastroenteritis). Even though gastric motility is stimulated during low blood glucose, in people with diabetic gastroparesis, gastric motility may not be normalised during hypoglycaemia (Kong and Horowitz 1999). In all cases of hypoglycaemia, close monitoring in follow-up is required, and the person should usually cease complex tasks or physical activity when moderate hypoglycaemia occurs, and instead focus on treating the moderate hypoglycaemia. The glucose provided orally as described above would typically not be part of a mixed meal with significant amounts of fat, such as a chocolate bar, because the fat in the chocolate will reduce the rate of gastric emptying and, potentially, the rate of glucose absorption from the upper gastrointestinal tract (Kong and Horowitz 1999). In moderate hypoglycaemia, the autonomic symptoms of low blood glucose should begin to resolve within 5–15 minutes, and blood glucose should be above 4 mM at 15 minutes or more after self treatment. If symptoms and blood glucose have not improved, then a re-treatment of oral glucose may be required, and possibly even parenteral therapy by glucagon, if there is concern that the oral glucose is not being absorbed.

In severe hypoglycaemia, the parenteral treatments are also typically highly efficacious (Collier et al 1987; Namba et al 1993), and it is rewarding as a health-care professional to observe the usual rapid improvement in level of consciousness as glucose is being administered IV during severe hypoglycaemia. However, it can take more than 60 minutes for the more subtle adverse cognitive effects of severe hypoglycaemia to fully resolve (Fanelli et al 2003). Glucagon administration is said to be underused as a versatile therapy for severe hypoglycaemia (Pearson 2008). Glucagon as therapy does require adequate glycogen stores to be present in the liver for glucagon to mobilise glucose from the glycogen, into the blood stream. Thus, in cases of prolonged fasting preceding severe hypoglycaemia, it would be predicted that glucagon would be less efficacious, and parenteral glucose would

be the therapy of choice (Pearson 2008). In some cases, initial efficacy will be lost in severe hypoglycaemia after parenteral therapy, and this can occur, for example, if the insulin administered is much greater than physiological requirements. In such cases, re-treatment with IV bolus glucose may be required, and higher rates of infusion and greater concentrations of glucose (e.g. in adults, up to 50% via a central vein site) may be required.

Side effects due to therapy for hypoglycaemia may also limit effectiveness. For example, glucagon often induces nausea and vomiting on regaining consciousness (Pearson 2008), and safe practice is to have the patient initially in the coma position before waking, and a vomit bag or bucket at the ready on its administration. Also, in severe hypoglycaemia, administration of 50% glucose IV is contraindicated in children, because it has been associated with contributing to death due to hyperosmolality (Endocrinology Expert Group 2009). As described above, to treat severe hypoglycaemia in children, 10% glucose only is recommended.

Once the episode of hypoglycaemia has been treated, it is important to carefully consider possible causes. Hypoglycaemia can often be explained by an imbalance between insulin type and dosage and lifestyle factors, such as carbohydrate intake and timing, and degree of physical activity (Cryer et al 2009). Any episode of severe hypoglycaemia should lead to a fundamental reassessment of the treatment regimen of the type 1 diabetes in the individual (Cryer et al 2009), including active involvement and consultation by the treating multidisciplinary health professional team to define, as far as possible, the precipitating and predisposing factors leading to the severe hypoglycaemia, to help prevent its recurrence. An adult driver who has experienced an episode of severe hypoglycaemia should not drive again until their medical carer has provided formal clearance to do so; in Australia, this will typically be the treating endocrinologist. Some insulin regimens, such as use of insulin analogues and continuous subcutaneous insulin infusion (CSII) pump therapy, may help to reduce the risk of severe hypoglycaemia in some cases. Nevertheless, it is the overall diabetes management package in intensive diabetes management, including lifestyle factors (e.g. diet and exercise) and blood glucose target setting and monitoring that will help to minimise the risk of hypoglycaemia events, including severe hypoglycaemia (Cryer et al 2009).

Changes in management that may be required after severe hypoglycaemia include target setting in blood glucose in the individual, modified physical activity and carbohydrate or alcohol intake, and varying insulin regimens (Cryer et al 2009). Closer attention to carbohydrate counting, and frequency and timing of blood glucose monitoring may also be required. Rarely, severe hypoglycaemia may also occur due to onset of new medical complications, which may induce hypoglycaemia in people with type 1 diabetes. Such complications include primary glucocorticoid deficiency of Addison's disease (primary cortisol deficiency) as described in an Australian paediatric case series (Thomas et al 2004). Although rare, Addison's disease is more common in people with type 1 diabetes; in Australia, it is most commonly caused by an autoimmune disease, and may present with hypoglycaemia, including in type 1 diabetes (Thomas et al 2004).

People with hypoglycaemia unawareness are at increased risk of developing severe hypoglycaemia (Cryer 2010). Some degree of hypoglycaemia unawareness is common in type 1 diabetes, with up to one-third of children and adults experiencing it. The condition may resolve with time and by avoidance of hypoglycaemia (Cryer 2010; Ly et al 2011), but in many cases it becomes chronic and is thought to be a form of autonomic failure related to type 1 diabetes (Cryer 2010; Ly et al 2011). Methods to help prevent severe hypoglycaemia in those with hypoglycaemia unawareness include more frequent timing of blood glucose

level checks and also treatment of any low capillary blood glucose levels (e.g. <4 mM), even in the absence of any symptoms of hypoglycaemia at the time of the low blood glucose occurring. In addition, real-time blood glucose monitoring with an in-built hypoglycaemia alarm in one recent Australian study improved counter-regulatory adrenaline responses to induced hypoglycaemia (Ly et al 2011).

In rare cases, despite the best efforts of all concerned, nonpreventable recurrent severe hypoglycaemia that is life-threatening occurs many times each year in a person with type 1 diabetes. The clinical scenario may be a person with more than 10 years of type 1 diabetes, who has hypoglycaemia unawareness and unstable, brittle diabetes with intercurrent end-organ complications, such as diabetic gastroparesis, which makes treatment of hypoglycaemia more difficult. Such patients could be formally assessed for forms of pancreas transplantation, including being enrolled in clinical trial programs of islet cell transplantation (Meloche 2007). While transplantation of the endocrine pancreas and related immunosuppression has its own inherent risks, it is recognised as a highly effective method to reduce the frequency of, or even abolish, recurrent life-threatening episodes of severe hypoglycaemia (O'Connell et al 2006).

Practice tips

- While acute treatment of hypoglycaemia is usually highly effective, its therapy does differ somewhat in children and adults, including doses of glucose and other agents used.
- In all cases of hypoglycaemia, even in moderate hypoglycaemia, occurrence should lead to consideration of the cause by the person with type 1 diabetes, in attempt to avoid recurrence.
- In cases where severe hypoglycaemia has occurred, a fundamental reassessment of the type 1 diabetes treatment regimen is required to identify precipitating and predisposing factors that have contributed to the severe hypoglycaemia. The person with diabetes will need to work closely with the treating multidisciplinary diabetes care team of health professionals to reduce severe hypoglycaemia risk of recurrence.
- While some insulin regimens, such as insulin analogues use and SCII pump therapy, may in some cases help to reduce severe hypoglycaemia risk, it is the overall diabetes management package, including lifestyle factors (such as diet, exercise) and blood glucose target setting and monitoring, that will help to minimise the risk of hypoglycaemia events including severe hypoglycaemia.
- In people with a lack of hypoglycaemia awareness or 'hypoglycaemia unawareness', specific education programs to help regain symptoms of hypoglycaemia and also to reduce further severe hypoglycaemia may be implemented and should be considered.
- In rare cases of nonpreventable recurrent severe hypoglycaemia, referral for assessment for pancreas transplantation – either the whole organ or islet cell transplantation – should be considered.

16.5 Prevention of severe hypoglycaemia

Question 41 (background question)

How can severe hypoglycaemia be prevented?

The detailed systematic review of this question is in Chapter 41 of the accompanying technical report, and the evidence matrix is in Section C41 of Appendix C

The objective of this question was to evaluate the evidence for any intervention primarily designed to prevent, reduce or avoid severe hypoglycaemia. The potential reduction of severe hypoglycaemia as a secondary outcome of specific interventions has been addressed by other systematic reviews in this series (see Chapter 7). The search strategy for this question focused on educational interventions.

Five studies met the criteria set for this question, with three of these being RCTs (Nordfeldt et al 2003; Nordfeldt et al 2005; Schachinger et al 2005) (Level II evidence). The other two studies were case series with outcomes before and after testing (Level IV evidence) and with significant potential for bias (Cox et al 2001; Broers et al 2005). Each study examined the effect of educational interventions on the reduction of severe hypoglycaemia. In all studies, severe hypoglycaemia was defined as an episode of hypoglycaemia requiring assistance. Participants' reports of severe hypoglycaemia were confirmed by blood glucose level diary in one study (Schachinger et al 2005). The two studies by Nordfeldt et al (2003; 2005) reported the results derived from the same study, with the article published in 2005 reporting results after the 24-month follow-up. Four studies were of fair quality and one was of poor quality (Broers et al 2005) – the population sample studied in the case series by Broers et al (2005) had participated in a research project by the same authors published 3 years previously. The subpopulation of people with type 1 diabetes and hypoglycaemia unawareness was of particular interest for this question; however, no studies were found that fulfilled inclusion criteria in this search. One study of a population with impaired hypoglycaemia awareness was excluded because it was a pilot study with no power calculations (Thomas et al 2007).

The intervention 'self-study material' in Nordfeldt et al (2003) examined children with type 1 diabetes and their parents. Those in the intervention group (n=222) received two video programs consisting of interview clips of young patients and their parents regarding diabetes treatment and prevention of hypoglycaemia, including comments from a consultant physician diabetologist. A self-study brochure mailed out 1 month later contained frequently asked questions on aspects of severe hypoglycaemia management. The control group (n=110) were provided material as a video of general diabetes information and corresponding brochure. The yearly incidence of severe hypoglycaemia was obtained by postal surveys at baseline and 12 months later.

The three other studies examined the intervention, blood glucose awareness training (BGAT), with slight differences in edition and language. For example, in Schachinger et al (2005), the German version of BGATIII was delivered by a physician–psychologist team to groups of 5–12 participants in 8 weekly sessions, with each session lasting 2 hours. The sessions focused on internal cues, disruptions in cognitive and motor performance, and mood changes. Patients were taught to use these signals to recognise when their blood glucose level was too high or low. Exogenous cues such as insulin dose, food and exercise were reviewed subsequently. Weekly homework and preparatory readings were required. The control group participated in 3-monthly sessions by one physician; focus topics were set out, with participants determining the specific issues and timing. Further details of the study interventions and control methods are described in the technical document.

All studies reported a significant reduction in severe hypoglycaemia after intervention. The largest study, which was an RCT of fair quality, reported a reduction of severe hypoglycaemia in the intervention group compared with control. The difference in incidence of severe hypoglycaemia at 24 months between the two groups was –15% (95%CI: –1 to –29): there were 20 episodes of severe hypoglycaemia in the intervention group compared with 34 in the control group (Nordfeldt et al 2005). While the 12-month results of the same study showed no difference between intervention and control groups (95%CI: –4 to 24), a

difference in change from baseline was seen in the intervention group (–15%, 95%CI: 1 to 29, p=0.039) but not the control group (+3%, 95%CI: –11 to 17) (Nordfeldt et al 2003). The RCT published by Schachinger et al (2005) reported that BGAT also led to a decrease in severe hypoglycaemia episodes, with a time-group interaction of p=0.04, and also a reduction in severe hypoglycaemia episodes per 6 months in the BGAT group compared to baseline (p=0.0). Change from post-exposure to baseline was also significant in the nonrandomised study by Broers et al (2005): the number of severe hypoglycaemia episodes decreased after intervention (p=0.001); there were 7.9 episodes per year at baseline reported in the BGAT group participants, and 1.7 at 12 months of follow-up. Cox et al (2001) reported that severe hypoglycaemia was reduced by about one-third across the first and last 6 months of follow-up compared with baseline (p<0.002), with mean episodes per month of 1.6 at baseline, 1.2 at 6 months and 1.1 at 12 months. As these case series by Broers et al (2005) and Cox et al (2001) did not have a control group, the observed change may not have been attributable to the intervention alone.

The populations recruited varied across the different studies, potentially affecting generalisability. The participants in the paediatric study by Nordfeldt et al (2003) were a broad, nonselected population with type 1 diabetes, because all consenting subjects with paediatric type 1 diabetes in a defined geographic catchment area were recruited. In the RCT by Schachinger et al (2005), the selection of the population studied was biased towards those with a history of recurrent severe hypoglycaemia, who also had a longer diabetes duration and were older than is generally the case in a population with type 1 diabetes. Thus, the results of that study are most relevant to adults with type 1 diabetes who had previously experienced severe hypoglycaemia.

Evidence statement	
Q41	Level II and Level IV evidence shows that specific educational interventions (in particular, BGAT) reduce the rate of severe hypoglycaemia.
Recommendation	
R16.3	Structured education specifically targeting prevention of severe hypoglycaemia should be provided (Grade B).
Practice points	
PP16.9	Developmentally appropriate structured education programs, such as 'self-study material' video programs and BGAT, can be used to help to reduce rates of severe hypoglycaemia.
PP16.10	Some programs, such as BGAT, can be delivered as individual or group programs.
PP16.11	Where resource constraints apply, structured education should be offered preferentially to individuals at highest risk of and from severe hypoglycaemia; for example, those with a history of recurrent severe hypoglycaemia, and adults who are motor vehicle drivers.
PP16.12	Research into modified programs to prevent severe hypoglycaemia that may require less resource and time input needs to be undertaken. Such research needs documented outcomes, including assessment of optimal time intervals for people to undertake refresher courses.
BGAT, blood glucose awareness training	

17 Acute complications – diabetic ketoacidodsis and sick-day management

17.1 Introduction

Diabetic ketoacidosis (DKA) is a life-threatening acute complication of type 1 diabetes. Treatment of patients with DKA uses significant health-care resources, and accounts for one out of every four dollars spent on direct medical care for adult patients with type 1 diabetes in the United States (Umpierrez and Kitabchi 2003). The mortality rate for DKA is less than 5% (Nyenwe et al 2010), but higher rates are observed in elderly patients and those with concomitant life-threatening illnesses. Infection is the most common precipitating cause for DKA, present in up to half of all cases, with urinary tract infection and pneumonia accounting for most infections. Other precipitating causes include surgery, trauma, myocardial ischaemia, psychological stress, and noncompliance or omission of insulin therapy.

Successful treatment of DKA requires frequent monitoring of the patient; fluid replacement and insulin to correct hypovolaemia, acidosis and hyperglycaemia; replacement of electrolyte losses; and careful investigation to determine the precipitating cause. Since most DKA cases occur in patients with a known history of diabetes, DKA should be largely preventable through frequent monitoring of blood glucose (BG) levels, early detection of ketosis and adequate replacement of insulin, together with education of patients, health-care professionals and the general public. The frequency of hospitalisations for DKA has been reduced following implementation of diabetes education programs, improved follow-up care and access to medical advice.

This chapter specifically addresses the effectiveness of blood ketone monitoring for preventing DKA. Management of sick days and DKA are covered in Sections 17.3 and 17.4, below.

17.2 Ketone monitoring

Question 42

Does ketone monitoring prevent ketoacidosis or hospital admission?

The detailed systematic review of this question is in Chapter 42 of the accompanying technical report, and the evidence matrix is in Section C42 of Appendix C

Ketone monitoring is used at times of hyperglycaemia for the detection of severe insulin deficiency in the diagnosis of DKA, and to guide insulin replacement during sick days. Ketone bodies can be measured in two ways: from beta-hydroxybutyrate (β-OHB) in capillary blood samples, or from acetoacetic acid measured by a urine dipstick test. Quantitative measurement of β-OHB, the major circulating ketone during DKA, is correlated with the degree of acidosis in patients with DKA (Sheikh-Ali et al 2008; Turan et al 2008). Evidence suggests that β-OHB correlates better with changes in acid–base status than acetoacetate during the course of treatment for DKA (Laffel 1999). Capillary β-OHB is more sensitive than urinary ketone levels for detecting ketosis (Turan et al 2008). A systematic review examined the effectiveness of blood ketone monitoring versus urine ketone monitoring in preventing DKA or hospital admission.

The systematic review identified no Level I studies and one Level II study (Laffel et al 2006). Laffel et al (2006) was a prospective, two-centre study that assessed sick-day management using blood β-OHB monitoring compared with traditional urine ketone testing. Participants (n=123, aged 3–22 years) were randomised to receive either a BG monitor that also measured blood β-OHB, or a monitor plus urine ketone strips. Participants were encouraged to check ketones during acute illness or stress, when glucose levels were consistently elevated (≥13.9 mmol/L on two consecutive readings), or when symptoms of DKA were present. After 6 months, participants in the blood ketone group checked ketones significantly more during sick days (91%) than participants in the urine ketone group (61%, p<0.001). The incidence of hospitalisation and emergency assessment was lower in the blood ketone group (38/100 patient years) than in the urine ketone group (75/100 patient years, p=0.05). Blood ketone monitoring during sick days appeared acceptable to, and was preferred by, young people with type 1 diabetes. The authors concluded that routine implementation of blood β-OHB monitoring for managing sick days and impending DKA could potentially reduce hospitalisation and emergency assessment compared with urine ketone testing.

The evidence for the effectiveness of blood ketone monitoring versus urine ketone monitoring for preventing DKA or hospital admission is therefore based on one randomised controlled trial with a low risk of bias. No studies were found in adults older than 22 years. The study was conducted in the United States, which has a well-developed health-care system; therefore, the results are applicable to the Australian health-care setting.

Evidence statement	
Q42	Blood ketone measurement compared with urine ketone measurement, as part of a sick-day management plan, reduces the rate of emergency presentations and hospitalisations.
Recommendation	
R17.1	Blood ketone measurement should be available as part of a comprehensive sick-day management plan (Grade B).
Practice points	
PP17.1	Blood ketone measurement is strongly preferred, because it gives a more timely result. However, where blood ketone measurement is not available, urine ketone measurement is the alternative test as part of a comprehensive sick-day management plan.
PP17.2	Blood ketone measurement is strongly recommended in people with type 1 diabetes on CSII.
PP17.3	Blood β-OHB monitoring may be especially useful in very young children or when urine specimens are difficult to obtain.
PP17.4	A comprehensive sick-day management plan should include written guidelines and 24-hour access to clinical advice.
PP17.5	The sick-day management plan should be regularly reviewed by the patient and diabetes health-care professional.
PP17.6	Comprehensive sick-day guidelines are available for people with diabetes and their families (ADEA 2006; Ambler and Cameron 2010) and health-care professionals (Brink et al 2009).
β-OHB, beta-hydroxybutyrate; CSII, continuous subcutaneous insulin infusion	

17.3 Sick-day management

People whose diabetes is well controlled should not experience more illness or infections than those without diabetes (Brink et al 2009), although there is some evidence of impaired leukocyte function in poorly controlled diabetes (Bagdade et al 1974). Some illnesses, particularly those associated with fever, raise BG levels because of higher levels of stress

hormones promoting gluconeogenesis and insulin resistance, while ketone body production increases due to relative or absolute insulin deficiency. Illness associated with vomiting and diarrhoea (e.g. gastroenteritis) may lower BG levels and result in hypoglycaemia rather than hyperglycaemia. Decreased food intake, poor absorption and slower emptying of the stomach during gastroenteritis may also contribute to hypoglycaemia. Insulin requirements are sometimes increased during the incubation period of an infection for a few days before the onset of the illness. The increased need for insulin may persist for a few days after the illness has passed, due to insulin resistance.

17.3.1 Practice principles for sick-day management

- More frequent monitoring:
  - BG levels should be monitored regularly, initially every 2 hours, particularly if ketones are present.
  - Urinary or fingerprick blood ketone tests help to guide sick-day management. Ketone testing should always be performed if the BG level is above 15 mmol/L.
- Never stop insulin:
  - Insulin doses may need to be increased or decreased, depending on the illness.
  - If the BG level is above 15 mmol/L and ketones are increased, additional rapid or short-acting insulin is needed. The dose and frequency of injection will depend on the level and duration of hyperglycaemia, and the severity of ketosis.
  - If there is hyperglycaemia with negative or small amounts of ketones, an additional 5–10% of total daily dose (TDD) (or 0.05–0.1 U/kg) should be given as rapid or short-acting insulin. This may be repeated every 2–4 hours based on results of BG level monitoring; see Table 17.1, adapted from ADEA guidelines (ADEA 2006) and Ambler and Cameron (2010).
  - If there is hyperglycaemia and more marked ketonaemia or ketonuria (moderate to high), an additional 10–20% of TDD (usually not more than 0.1 U/kg) may need to be given as rapid or short-acting insulin. This dose should be repeated every 2–4 hours; based on frequent BG levels and ketone results.
  - Patients on continuous subcutaneous insulin infusion (CSII) use only rapid-acting insulin; therefore, DKA can develop rapidly. Episodes of hyperglycaemia must be taken seriously, especially if associated with positive urine or blood ketones (or both). Correction doses should be given through the pump if there are no ketones, or with a syringe or pen injection if ketones are present.
- Maintain hydration:
  - Hyperglycaemia, fever, excessive glycosuria and ketonuria increase fluid losses.
  - Elevated levels of ketones, whether associated with low BG (starvation) or high BG (insulin deficiency), contribute to nausea and vomiting, leading to decreased food and fluid intake, further elevated levels of ketones, and dehydration and ketoacidosis.
  - Liquids for hydration should contain salt and water and not just plain water if there are ongoing losses due to vomiting or diarrhoea.
  - In young children with diabetes, intravenous (IV) fluids may be required if nausea, vomiting or diarrhoea are persistent.
  - When vomiting occurs in a person with diabetes, it should always be considered a sign of insulin deficiency until proven otherwise.

- Treat the underlying illness:
  - The underlying illness should be treated as it would be for a person without diabetes.

Table 17.1 Guidelines for sick day management

Blood glucose level (mmol/L)	Ketones – blood (mmol/L)[a] or urine	Supplemental insulin dose (can be given up to 2 hourly)[b]	Timing of review	Fluid intake
<4.0	<1.0 Negative	Insulin dose reduction may be required. Consider mini dose glucagon to prevent hypoglycaemia if vomiting, diarrhoea or reduced carbohydrate intake	Check every 20–30 minutes until BGL >4. Supervised medical care required if ketones remain positive and BGL remains low	Take sweetened fluids or quick-acting carbohydrate (or both); hospital admission for IV fluids may be needed if BGL cannot be maintained.
	≥1.0 Positive	Priority is to increase BGL with fluid and carbohydrate		
4–8	< 1.0 Negative/ trace	No change to insulin	Two hourly	Give sweetened fluids or extra carbohydrate to maintain or increase BGL
	1.0–1.4 Small	No change to insulin. Ketones indicate carbohydrate and insulin deficiency.	Two hourly	
	>1.5 Moderate/ Large	5% supplemental insulin may be required	Two hourly	
8–15	<1.0 Negative/ trace	May fall without extra insulin. If persistently elevated, consider 5 % supplemental insulin	Two hourly	Sweetened fluids recommended
	1.0–1.4 Small	If persistently elevated ketones, consider 5–10% supplemental insulin	Two hourly	
	>1.5 Moderate/ large	10% supplemental insulin dose	Hourly	
>15	<1.0 Negative/ trace	5–10% supplemental insulin dose	Hourly	Unsweetened fluids recommended
	1.0–1.4 Small	10–15% supplemental insulin dose	Hourly	
	>1.5 Moderate/ large	15–20% supplemental insulin dose	Hourly	

BGL, blood glucose level; IV, intravenous

[a] blood 3β-hypdroxybutyrate

[b] Refers to percentage of total daily insulin dosage given as rapid or fast-acting supplemental insulin dose. Exercise caution with supplemental insulin doses in the presence of BGL <8 mmol/L – advise increasing sweetened fluid intake first.

17.4 Diabetic ketoacidosis

17.4.1 Background

DKA is characterised by the triad of uncontrolled hyperglycaemia, metabolic acidosis and increased total body ketone concentration. DKA results from absolute or relative deficiency of circulating insulin, and the effects of increased levels of the counter-regulatory hormones (i.e. catecholamines, glucagon, cortisol and growth hormone) (Foster and McGarry 1983; Kitabchi et al 2006). The combination of low serum insulin and high counter-regulatory hormone concentrations causes an accelerated catabolic state, with increased glucose production by the liver and kidneys, and impaired peripheral glucose use. This leads to hyperglycaemia, hyperosmolality, increased lipolysis and ketogenesis, causing hyperketonaemia and metabolic acidosis. Hyperglycaemia and hyperketonaemia cause osmotic diuresis, dehydration and loss of electrolytes, which often is aggravated by vomiting. If these metabolic derangements are not arrested and corrected with exogenous insulin and fluid and electrolyte therapy, then fatal dehydration and metabolic acidosis will ensue. Ketoacidosis may be aggravated by lactic acidosis from poor tissue perfusion or sepsis.

Patients with DKA have severe depletion of water and electrolytes from both the intracellular and extracellular fluid compartments. Despite their dehydration, patients continue to maintain normal blood pressure, and have considerable urine output until extreme volume depletion and shock occurs, leading to a critical decrease in renal blood flow and glomerular filtration. At presentation, the magnitude of specific deficits in an individual patient varies depending on the duration and severity of illness, the extent to which the patient was able to maintain intake of fluid and electrolytes, and the content of food and fluids consumed before coming to medical attention. Consumption of fluids with a high carbohydrate content exacerbate the hyperglycaemia.

DKA at diagnosis is more common in younger children (<5 years of age), and in children whose families do not have ready access to medical care for social or economic reasons. The risk of DKA in established type 1 diabetes is 1–10% per patient per year (Wolfsdorf et al 2009). The risk of DKA is increased in people with poor glycaemic control or previous episodes of DKA; peripubertal and adolescent girls; children with psychiatric disorders, including those with eating disorders; children with difficult or unstable family circumstances; children with limited access to medical services; and people who omit insulin and CSII (because only rapid insulin is used, interruption of insulin delivery for any reason rapidly leads to insulin deficiency).

17.4.2 Definition of diabetic ketoacidosis

The biochemical criteria for the diagnosis of DKA are:

- hyperglycaemia (BG level >11 mmol/L)
- venous pH <7.3 or bicarbonate <15 mmol/L
- ketonaemia and ketonuria.

17.4.3 Management

Successful management of DKA requires meticulous monitoring of the patient's clinical and biochemical response to treatment, so that timely adjustments in treatment can be made when indicated by the patient's clinical or laboratory data. Clinical observations, IV and oral medications, fluids and laboratory results should be documented on a flow chart each hour.

People of all ages with severe DKA should receive care in an intensive care unit or comparable high-intensity unit. In DKA, timely rehydration and correction of the acidosis and electrolyte disturbances are priorities in care (Kitabchi et al 2006).

Consensus guidelines for managing DKA have been published elsewhere; the guidelines below are adapted from these (Kitabchi et al 2006; Wolfsdorf et al 2009).

Children and adolescents with DKA should be managed in a unit that has (Wolfsdorf et al 2009):

- experienced nursing staff trained in monitoring (of vital signs and neurological status) and management
- a paediatric endocrinologist, consultant paediatrician or paediatric critical care specialist with training and expertise in the management of DKA, who can direct inpatient management; where such expertise is not available onsite, telephone advice should be sought from the appropriate specialists
- access to laboratories for frequent and timely evaluation of biochemical variables
- written guidelines for DKA management in young people.

A. Emergency assessment

- Perform a clinical evaluation to confirm the diagnosis and determine its cause. Look for evidence of infection.
- Weigh the patient and use this weight for calculations.
- Assess clinical severity of dehydration.
- Assess level of consciousness (using the Glasgow coma scale).
- Obtain a blood sample for laboratory measurement of serum or plasma glucose; electrolytes (including bicarbonate or total carbon dioxide [CO_2]); blood urea nitrogen; creatinine; osmolality; venous (or arterial in critically ill patient) pH; pCO_2; full blood count; and calcium, phosphorus and magnesium concentrations.
- Perform a urinalysis or blood test for ketones (or point-of-care measurement on a fingerprick blood sample using a bedside meter if available). There is some evidence that serum β-OHB levels >3.0 mmol/L in children and >3.8 mmol/L adults are more reliable measures of DKA than serum bicarbonate (Sheikh-Ali et al 2008).
- Obtain appropriate specimens for culture (blood, urine or throat) and consider performing a chest X-ray to exclude infection, unless there is a clear alternative explanation for the DKA.
- If laboratory measurement of serum potassium is delayed, perform an electrocardiogram for baseline assessment of potassium status (see details of electrocardiographic [ECG] features below under section E, below).

B. Supportive measures

- Secure the airway and empty the stomach by continuous nasogastric suction, to prevent pulmonary aspiration in the unconscious or severely obtunded patient.
- Put in place a peripheral IV catheter for convenient and painless repetitive blood sampling.
- Use a cardiac monitor for continuous electrocardiographic monitoring to assess T-waves for evidence of hyperkalaemia or hypokalaemia.

- Give oxygen to patients with severe circulatory impairment or shock.
- Give antibiotics to febrile patients after obtaining appropriate cultures of body fluids.
- Catheterise the bladder if the patient is unconscious or unable to void on demand (e.g. in infants and very ill young children).

C. Fluid replacement

- For patients who are severely volume depleted but not in shock, begin volume expansion (resuscitation) immediately with 0.9% saline, to restore the peripheral circulation.
  - The volume and rate of administration depends on circulatory status and, where it is clinically indicated, the volume administered for children is typically 10 mL/kg/hour over 1–2 hours, and may be repeated if necessary. For adults, 1 L statim, followed by a second 1 L of 0.9% saline during the first hour is a typical regimen (Kitabchi et al 2006).
- In the rare patient with DKA who presents in shock, rapidly restore circulatory volume with isotonic saline. For children, administer 20 mL/kg boluses, infused as quickly as possible through a large bore cannula, with reassessment after each bolus.
  - Intraosseous access should be considered after multiple attempts to gain IV access have failed.
  - Fluid management (deficit replacement) should be with 0.9% saline for at least 4–6 hours. Thereafter, deficit replacement should be with a solution that has a tonicity equal to or greater than 0.45% saline with added potassium chloride, potassium phosphate or potassium acetate (see below under potassium replacement).
  - The rate of fluid (IV and oral) should be calculated to rehydrate evenly over 48 hours (see Table 17.2).

Table 17.2 Example of volumes of maintenance +10% deficit, to be given evenly over 48 hours

Weight (kg)	Infusion rate (mL/kg/hour)
4–9	6
10–19	5
20–49	4
50–59	3.5
60–80	3

Example

A 6-year-old boy weighing 20 kg will be given 80 mL per hour, or a total volume of 1920 mL per 24 hours for 2 days.

- The severity of dehydration may be difficult to determine and is frequently underestimated or overestimated; therefore, infuse fluid each day at a rate rarely in excess of 1.5–2 times the usual daily maintenance requirement based on age, weight or body surface area.
- Do not routinely add urinary losses to the calculation of replacement fluid, although this may be advisable in rare circumstances.
- When oral fluid is tolerated, reduce IV fluid accordingly so that the total amount of fluid given to the patient per hour does not exceed the calculated hourly rehydration volume.

- The sodium content of the fluid may need to be increased if measured serum sodium is low and does not rise appropriately as the plasma glucose concentration falls.
- For adults, the subsequent approach to fluid replacement is similar to that used in children. If hypernatraemia occurs in adults, then changing the hydration fluid to 0.45% saline is appropriate (Kitabchi et al 2006).

D. Insulin therapy

- Start insulin infusion after the patient has received initial volume expansion.
- Correct insulin deficiency as follows:
  - **Dose:** 0.1 unit/kg/hour (e.g. dilute 50 units regular [soluble] insulin in 50 mL normal saline, 1 unit=1 mL).
  - **Route of administration:** An IV bolus is unnecessary in children and should not be used at the start of therapy. In adults, an IV bolus of insulin at 0.1 IU/kg of body weight is recommended in some DKA protocols (Kitabchi et al 2006).
- In general, keep the dose of insulin at 0.1 unit/kg/hour, at least until resolution of DKA (pH >7.30, bicarbonate >15 mmol/L or closure of the anion gap); this invariably takes longer than normalisation of blood glucose concentrations.
- If the patient demonstrates marked sensitivity to insulin (e.g. some young children with DKA and patients with hyperglycaemic hyperosmolar state), the dose may be decreased to 0.05 unit/kg/hour or less, provided that metabolic acidosis continues to resolve.
- During initial volume expansion, the plasma glucose concentration falls steeply. Thereafter, the plasma glucose concentration typically decreases at a rate of 2–5 mmol/L/hour, depending on the timing and amount of glucose administration.
- To prevent an unduly rapid decrease in plasma glucose concentration and hypoglycaemia, add 5% glucose to the IV fluid (e.g. 5% glucose in 0.45% saline) when the plasma glucose falls to 15 mmol/L, or sooner if the rate of fall is precipitous.
- If necessary, use 7.5–10% dextrose to prevent hypoglycaemia while continuing to infuse insulin to correct the metabolic acidosis.
- If BG falls very rapidly (>5 mmol/L/hour) after initial fluid expansion, consider adding glucose even before plasma glucose has decreased to 15 mmol/L.
- If biochemical parameters of DKA (pH and anion gap) do not improve, reassess the patient, review insulin therapy, and consider other possible causes of impaired response to insulin (e.g. infection or errors in insulin preparation). In adults, in nonresponding cases, a doubling of the hourly insulin administration amount as a bolus may be indicated each hour to reverse the acidosis (Kitabchi et al 2006).

E. Potassium replacement

- Potassium-replacement therapy is required during therapy for DKA. This is because a total body deficit of potassium occurs in DKA and correction of the acidosis in the absence of potassium therapy will usually rapidly make this apparent through the development of hypokalaemia. Patients may have hyperkalaemia, hypokalaemia or normokalaemia at presentation, depending on the total body potassium deficit and the degree of acidosis.
- If the patient is hypokalaemic, this indicates a severe deficit of total body potassium. Start potassium replacement at the time of initial volume expansion and before starting insulin therapy. Otherwise, start replacing potassium after initial volume expansion and

concurrent with starting insulin therapy. If the patient is hyperkalaemic, defer potassium replacement therapy until urine output is documented.

- If immediate serum potassium measurements are unavailable, an ECG may help to determine whether the patient has hyperkalaemia or hypokalaemia. Flattening of the T wave, widening of the QT interval, and the appearance of U waves indicate hypokalaemia. Tall, peaked, symmetrical, T waves and shortening of the QT interval are signs of hyperkalaemia.
- The starting potassium concentration in the infusate should be 40 mmol/L. Subsequent potassium replacement therapy should be based on serum potassium measurements. If potassium is given with the initial rapid volume expansion, a concentration of 20 mmol/L should be used.
- Potassium phosphate may be used together with potassium chloride or acetate (e.g. 20 mmol/L potassium chloride and 20 mmol/L potassium phosphate, or 20 mmol/L potassium phosphate and 20 mmol/L potassium acetate).
- Potassium replacement should continue throughout IV fluid therapy.
- The maximum recommended rate of IV potassium replacement is usually 0.5 mmol/kg/hour.
- If hypokalaemia persists despite a maximum rate of potassium replacement, then the rate of insulin infusion can be reduced.

F. Phosphate

- Prospective studies have not shown clinical benefit from phosphate replacement.
- Severe hypophosphataemia in conjunction with unexplained weakness should be treated.
- Potassium phosphate salts may be safely used as an alternative to, or combined with, potassium chloride or acetate, provided serum calcium is monitored carefully to avoid hypocalcaemia.

G. Acidosis

- Progressive monitoring and correction of acidosis is a key element of care in DKA. In adults with DKA, acidosis is the main factor that lowers consciousness (Nyenwe et al 2010).
- The metabolic acidosis in DKA will usually resolve with the treatment regimen of rehydration and insulin therapy.
- Bicarbonate therapy may cause a paradoxical brain acidosis, and its administration is not recommended unless the acidosis is profound and likely to affect adversely the action of adrenaline (epinephrine) during resuscitation.
- If bicarbonate is considered necessary, cautiously give 1–2 mmol/kg over 60 minutes.

H. Introduction of oral fluids and transition to subcutaneous insulin injections

- Oral fluids should be introduced only when substantial clinical improvement has occurred (mild acidosis or ketosis may still be present).
- When oral fluid is tolerated, IV fluid should be reduced.
- To prevent rebound hyperglycaemia, the first subcutaneous injection should be given 15–30 minutes (with rapid-acting insulin) or 1–2 hours (with regular insulin) before stopping the insulin infusion, to allow sufficient time for the insulin to be absorbed. With

intermediate-acting or long-acting insulin, the overlap should be longer and the IV insulin gradually lowered. For example, for the patient on a basal-bolus insulin regimen, the first dose of basal insulin may be administered in the evening and the insulin infusion stopped the next morning.

I. Cerebral oedema

This complication of DKA therapy is a major concern in children.

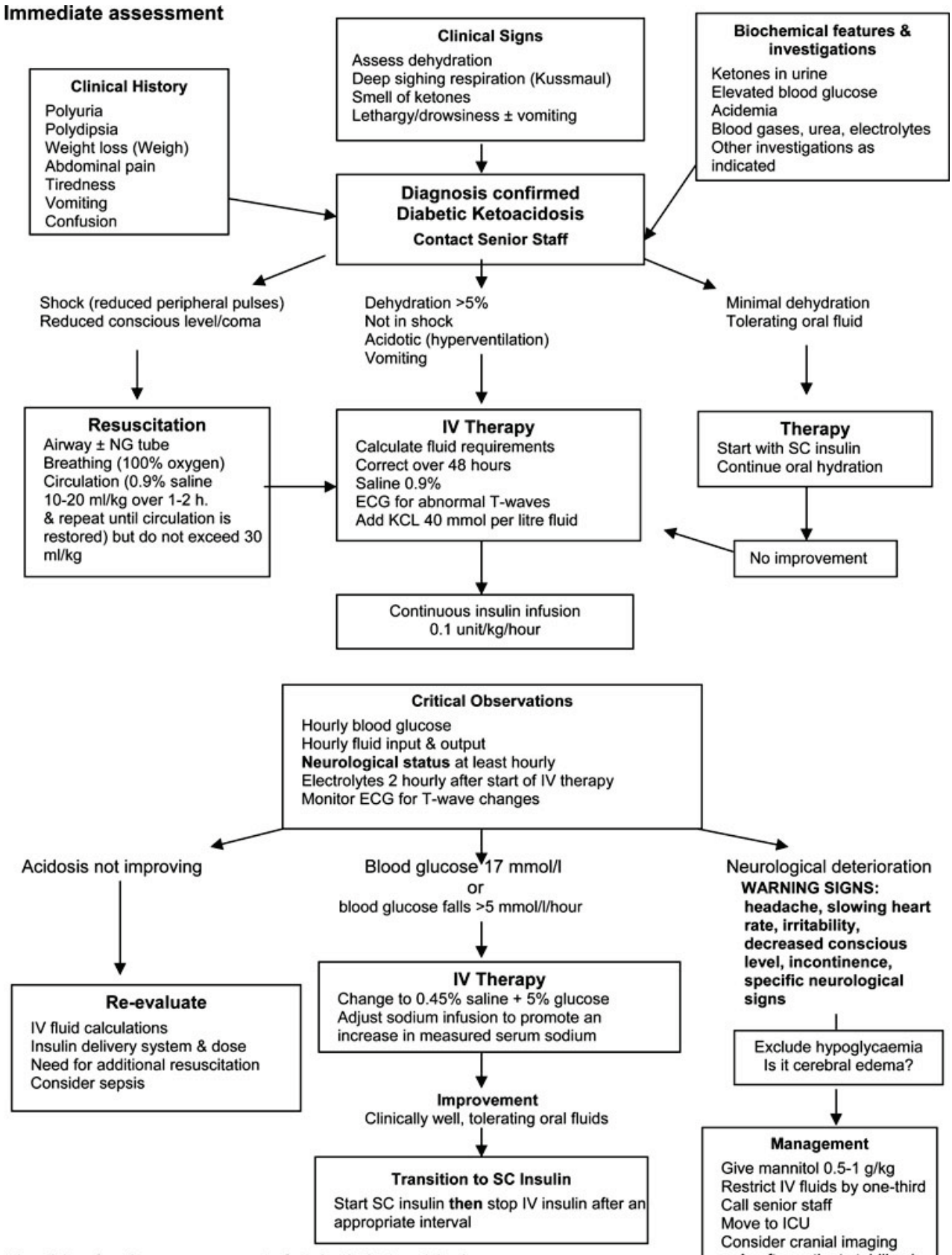
- Warning signs and symptoms of cerebral oedema include:
  - headache and slowing of heart rate
  - change in neurological status (restlessness, irritability, increased drowsiness, incontinence)
  - specific neurological signs (e.g. unreactive pupils or cranial nerve palsies)
  - rising blood pressure
  - decreased O_2 saturation.
- Treatment of cerebral oedema:
  - Initiate treatment as soon as the condition is suspected.
  - Reduce the rate of fluid administration by one-third.
  - Give mannitol 0.5–1 g/kg IV over 20 minutes and repeat if there is no initial response in 30 minutes to 2 hours.
  - Consider using hypertonic saline (3%), 5 mL/kg over 30 minutes, as an alternative to mannitol, especially if there is no initial response to mannitol.
  - Make sure that mannitol or hypertonic saline is available at the bedside.
  - Elevate the head of the bed.
  - Intubation may be necessary for the patient with impending respiratory failure, but aggressive hyperventilation (to a pCO_2 <2.9 kPa [22 mmHg]) has been associated with poor outcomes and is not recommended.
  - After treatment for cerebral oedema has been started, take a cranial computed tomography scan to rule out other possible intracerebral causes of neurologic deterioration (≈10% of cases), especially thrombosis or haemorrhage, which may benefit from specific therapy.

17.4.4 Summary and key points

- DKA is caused by either relative or absolute insulin deficiency.
- Patients with DKA should be managed in centres experienced in its treatment, and where vital signs, neurological status and laboratory results can be monitored frequently.
- Fluid replacement should begin before insulin therapy is started.
- Volume expansion (resuscitation) is required only if needed to restore peripheral circulation.
- Subsequent fluid administration (including oral fluids) should rehydrate evenly over 48 hours at a rate rarely in excess of 1.5–2 times the usual daily maintenance requirement.

- Insulin therapy should start at 0.1 U/kg/hour, 1–2 hours *after* starting fluid replacement therapy.
- There is no single generally recommended algorithm to manage DKA in adults. For a consensus approach algorithm in managing DKA in adults from the American Diabetes Association, see Kitabchi et al (2006).

Figure 17.1 Algorithm for managing diabetic ketoacidosis in children and adolescents



Algorithm for the management of diabetic ketoacidosis
Source: adapted from Dunger et al. Karger Publ. 1999

NG, nasogastric; SC, subcutaneous.

18 Microvascular and macrovascular complications

18.1 Introduction

The long-term vascular complications of diabetes include retinopathy (leading to visual impairment and blindness), nephropathy (resulting in hypertension and renal failure), neuropathy (manifesting as pain, paraesthesiae, muscle weakness and autonomic dysfunction) and macrovascular disease (cardiac disease, peripheral vascular disease and cerebrovascular disease). Although clinical evidence of microvascular and macrovascular complications is uncommon in childhood and adolescence, early functional and structural abnormalities may be present a few years after the onset of type 1 diabetes (Cho et al in press).

It is now more than 20 years since the Diabetes Complications and Control Trial (DCCT) provided clear evidence that intensive diabetes treatment and improved glycaemic control significantly reduce the risk of microvascular complications compared with conventional treatment. The follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study demonstrated a continued benefit for randomised groups, together with a risk reduction for macrovascular disease. In parallel with changes in clinical treatment goals and management – for example, increased use of multiple daily injections (MDI) and continuous subcutaneous insulin infusion (CSII), identification of risk factors, regular complication screening and more aggressive treatment of early abnormalities – there is evidence for a declining incidence of some complications, such as retinopathy, in young people (Mohsin et al 2005) and adults (Nathan et al 2009) with type 1 diabetes.

Systematic reviews have examined the evidence for the efficacy of intensive glycaemic management, antihypertensive agents and statins on microvascular or macrovascular complications. A systematic review also addressed the effectiveness of antihypertensive agents at controlling blood pressure in type 1 diabetes. Cost effectiveness of these interventions and optimal frequency for screening were subsequently addressed as background questions.

18.2 Effect of intensive glycaemic management on complications

Question 43

What is the effect of intensive glycaemic management on microvascular and macrovascular complications?

The detailed systematic review of this question is in Chapter 43 of the accompanying technical report, and the evidence matrix is in Section C43 of Appendix C

Question 43 addressed the effects of intensive glycaemic control (referred to here as intensive management), as implemented by the DCCT study. Intensive glycaemic control was defined in that study as the maintenance of glycaemic control as close as possible to the normal range.

As described in detail in Chapter 5, the DCCT and its epidemiological follow-up – the EDIC study – demonstrated that a management program of intensive blood glucose control reduced the microvascular and macrovascular end-organ complications of diabetes (DCCT Research Group 1993). The systematic literature review provided further support for the

effects of an intensive treatment strategy (see Chapter 43 of the technical report) on these outcomes and identified a meta-analysis of microvascular outcomes (Wang et al 1993a) and two meta-analyses of macrovascular disease that included data from the DCCT/EDIC (Lawson et al 1999; Stettler et al 2006).

18.2.1 Microvascular complications

As described in Chapter 5, data from the DCCT indicated that new onset and progression of diabetic retinopathy, nephropathy, and peripheral and autonomic neuropathy were reduced by intensive treatment compared with conventional treatment (DCCT Research Group 1993). The observational data showed that, for every 1.0% unit decrease in glycated haemoglobin (HbA_{1c}), there was a 39% decrease in retinopathy risk over the range of HbA_{1c} values studied. For nephropathy, for every 1.0% unit decrease in HbA_{1c}, there was a 25% decrease in the risk of microalbuminuria. For each microvascular outcome, no glycaemic threshold for risk reduction was detected above the nondiabetic range of HbA_{1c}.

A meta-analysis that preceded the DCCT identified 16 studies with duration of follow-up ranging from 8 to 60 months (Wang et al 1993a). Most of the studies included patients with normal albumin excretion or microalbuminuria and normal serum creatinine at baseline. All but one of these studies achieved better or near normal glycaemic control with intensive treatment. The between-group difference in HbA_{1c} by study end was –1.4% (95% confidence interval [CI]: –1.8 to –1.1).

After 2–5 years of intensive treatment, the risk of retinopathy progression was significantly reduced (odds ratio [OR] 0.49, 95%CI: 0.28 to 0.85, p=0.01), and there was no heterogeneity across pooled studies (p=0.89). Progression to background retinopathy is clinically different from progression to proliferative retinopathy. Therefore, some studies also reported these outcomes separately, noting that intensive treatment significantly slowed retinopathy progression to more severe states, such as proliferative retinopathy, or changes requiring laser treatment (OR 0.44, 95%CI: 0.22 to 0.87, p=0.02) without heterogeneity (p=0.99). For nephropathy, intensive treatment significantly reduced the risk of nephropathy progression (OR 0.34, 95%CI: 0.2 to 0.58, p<0.001) without heterogeneity (p=0.99).

18.2.2 Macrovascular complications

A meta-analysis examined six randomised controlled trials (RCTs), each running for more than 2 years, from which data on cardiovascular events were pooled (Lawson et al 1999). With a total of 1732 participants, the number of first major macrovascular events was reduced, with a relative risk ratio (RRR) of 0.55 (95%CI: 0.35 to 0.88, p=0.02), but not the number of patients developing macrovascular disease. Given that the risk of a macrovascular event is highest in those who have already had one event, the benefit of intensive therapy over conventional therapy on the number of macrovascular events, but not on the number of patients, suggests that intensive therapy decreases the likelihood of a patient having multiple types of events. In 2006, this was updated with another meta-analysis of data from 1800 people with type 1 diabetes. The total number of recorded events was small: 134 events in 11 293 person years (Stettler et al 2006). Nevertheless, the risk of any macrovascular event (RRR 0.38, 95%CI: 0.26 to 0.56), cardiac event (RRR 0.41, 95%CI: 0.19 to 0.87) or peripheral vascular event (RRR 0.39, 95%CI: 0.25 to 0.62) was significantly reduced, while the risk of cerebrovascular events was not significantly reduced (Stettler et al 2006). Assuming a typical incidence of one macrovascular event per 100 person years, 16 patients would need to receive intensified treatment for 10 years to prevent one macrovascular event (Stettler et al 2006). The DCCT was included in the 1999 macrovascular meta-analysis, and the DCCT and EDIC were included in the 2006 macrovascular meta-analysis. The

systematic reviews found no heterogeneity in the findings of the six RCTs (Lawson et al 1999) or the eight RCTs (Stettler et al 2006) examining macrovascular outcomes in type 1 diabetes. In both those meta-analyses, data from the DCCT and EDIC dominated the participant numbers examined.

18.2.3 Glycaemic control

The intensive glycaemic control approach in the DCCT aimed to maintain blood glucose concentrations close to the normal range while preserving clinical wellbeing, as defined by the conventional or standard treatment group (DCCT Research Group 1993). The blood glucose targets are detailed in Chapter 5. The intensive treatment methods across each study included in the meta-analyses used a similar intensive treatment approach to the DCCT and EDIC. The consistent key elements of intensive treatment were the frequency of insulin treatment administration, the frequency of self-monitored blood glucose and the provision of strong support from a coordinated multidisciplinary team of health professionals. The support included frequent contact with diabetes educators, dieticians, psychologists and social workers, as well as with diabetologists skilled in intensified management. Processes included frequent study centre visits, telephone contacts each month, and even more frequent contact by telephone for review and dose adjustment. In the DCCT, quality of life was maintained in the intensive treatment group when assessed by questionnaire, compared with the conventional group.

18.2.4 Adverse events

A fair-quality Level I study (Egger et al 1997a) examined the adverse events associated with this intensity of glucose control in terms of severe hypoglycaemia, diabetic ketoacidosis (DKA) and death. Fourteen RCTs were identified that contributed 16 comparisons, with a total of 1028 patients allocated to intensified treatment and 1039 patients allocated to conventional treatment. A total of 26 patients died, 846 suffered at least one episode of severe hypoglycaemia, and 175 experienced DKA. The pooled OR for hypoglycaemia was 2.99 (95%CI: 2.45 to 3.64). The risk of DKA depended on the type of intensified treatment used; the OR was 7.20 (95%CI: 2.95 to 17.58) for exclusive use of pumps; 1.13 (95%CI: 0.15 to 8.35) for MDI; and 1.28 (95%CI: 0.90 to 1.83) (p=0.004 for interaction) for trials offering a choice between the two. Mortality associated with 5 deaths attributed to DKA, and two sudden deaths, was significantly increased (p=0.007) whereas mortality due to macrovascular causes was not significantly (p=0.16) decreased (three vs eight deaths for intensive vs conventional treatment).

18.2.5 Cost effectiveness

Cost-effectiveness studies found that the annual cost of intensive treatment was approximately three times the cost of conventional treatment. Such studies indicate that a strategy of Intensive glycaemic control in people with type 1 diabetes with the characteristics of those included in the DCCT, is strongly justified to reduce the long-term complications of diabetes; the incremental cost per year of life gained by intensive treatment is US$28 661. Through simulation and extrapolation of projected cumulative incidences by age 70 years, intensive treatment would prevent all stages of microvascular and macrovascular complications. In addition, the end-stage severe diabetes complications, including blindness, end-stage renal disease and lower extremity amputation, would be markedly reduced (by 50% or more). Total and cardiovascular mortality would also be reduced. Incorporating hypoglycaemia into the model was reported to have little or no effect on the results. Thus, over a lifetime, DCCT-defined intensive treatment would reduce complications, improve quality of life, and could be expected to increase length of life (Nathan et al 2005). Other studies using intensive treatment, including the Stockholm

Diabetes Intervention Study (Reichard et al 1999), found similar cost effectiveness to the DCCT.

Evidence statements	
Q43	Intensive glycaemic control in adolescents and adults with type 1 diabetes reduces the risk of microvascular outcomes.
Q43	Intensive glycaemic control in adolescents and adults with type 1 diabetes reduces the risk of cardiovascular disease.
Recommendation	
R18.1	Intensive glycaemic control should be implemented to reduce the risk of onset or progression of microvascular and development of macrovascular diabetes complications (Grade B).
Practice points	
PP18.1	Intensive glycaemic control refers to an implemented strategy of intensive glycaemic management and is only achieved by a 'package' of methods, including MDI or CSII, frequent insulin dose adjustment, blood glucose level monitoring at least four times per day, weekly measurement of 3 am blood glucose levels, formal diabetes education, medical nutrition therapy and physical activity advice.
PP18.2	The generalisability of implementing an intensive glycaemic control strategy may be limited by the strict inclusion criteria in the clinical trials undertaken. The potential benefit of a strategy of intensive glycaemic control needs to be individualised as much as is practical for each person with type 1 diabetes.
PP18.3	Observational data from the DCCT suggest that the greatest absolute benefit from an intensive management approach will be seen in those with higher HbA_{1c} levels if such improved HbA_{1c} levels can be achieved and sustained.
PP18.4	Transient worsening of some diabetes complications, particularly diabetic retinopathy, can occur some months after commencement of intensive glycaemic management, and clinicians should monitor for and manage these complications. Ophthalmologic monitoring before initiation of intensive treatment and at 3-month intervals for 6–12 months thereafter seems appropriate for such patients. In patients whose retinopathy is already approaching the high-risk stage, it may be prudent to delay the initiation of intensive treatment until photocoagulation can be completed, particularly if the HbA_{1c} is high.
PP18.5	A strategy of intensive glycaemic control maintained for some 6–7 years leads to persistent microvascular benefits and new macrovascular benefits 10 years later (so-called 'metabolic memory'); this emphasises the importance of tight glycaemic control relatively early in the disease course to achieve sustained outcomes in minimising long-term complications of diabetes.
PP18.6	While intensive glycaemic control to reduce long-term end-organ diabetes complications is readily justified at a health economics level, it needs to be adequately resourced and appropriately targeted for the benefits observed in the RCTs to be achieved.
CSII, continuous subcutaneous insulin infusion; DCCT, Diabetes Complications and Control Trial; HbA_{1c}, glycated haemoglobin; MDI, multiple daily injection; RCT, randomised controlled trial	

18.2.6 Summary

The DCCT and EDIC clearly demonstrated that intensive glycaemic control in adolescents and adults with type 1 diabetes reduced the risk of onset or progression of microvascular complications and development of macrovascular disease. The potential benefit of intensive glycaemic control needs to be individualised. Specifically, the benefit of intensive glycaemic control needs to be weighed against the risk of severe hypoglycaemia, in particular in young children, elderly patients, those with major comorbidities, and patients with autonomic neuropathy. In each of these cases, increased risk of severe hypoglycaemia and complications developing may necessitate modification of glycaemic targets set and the use of strategies to achieve the targets safely. People with end-stage diabetes complications, such as end-stage renal failure, heart failure or extensive cardiovascular disease, were not

enrolled in the DCCT; therefore people with these complications may not benefit to the same degree from intensive glycaemic control as those who were studied in the DCCT.

18.3 Frequency of screening for complications

Question 44 (background question)

How frequently should patients with type 1 diabetes be screened for microvascular and macrovascular complications?

Question 44 was a background question and therefore was not systematically reviewed

Subsequent to the diagnosis of diabetes, most people with type 1 diabetes will develop some microvascular end-organ complications in their lifetime (Roy et al 2004; Melendez-Ramirez et al 2010). Some people will also develop clinically significant and more severe progressive complications, such as vision-threatening retinopathy, diabetic nephropathy, or painful or insensate peripheral neuropathy (Roy et al 2004; Nathan et al 2005). As the decades progress, many people will also develop cardiovascular disease (CVD) – as coronary heart disease (CHD), cerebrovascular or peripheral arterial disease – with a CVD mortality rate in this group of approximately 40% (Secrest et al 2010b). However, recent studies have reported that frequencies of severe complications in patients with type 1 diabetes are lower compared with those reported historically, especially when the disease is treated intensively (Hovind et al 2003; Nathan et al 2005).

18.3.1 Mortality rates

Diabetes-related complications account for the excess deaths reported in people with type 1 diabetes. Nevertheless, mortality trends over recent decades in international prospective studies indicate that both men and women with type 1 diabetes are, on average, living longer than in the past (Nishmura et al 2001; Secrest et al 2010a). This improvement is consistent with:

- in the 1980s, increased use of HbA_{1c} testing and home blood glucose monitoring, as well as improved blood pressure therapy
- in the 1990s, increased use of lipid-lowering therapy and further reductions in cigarette smoking.

However, compared with the general population, much higher mortality rates (13-fold for women and fivefold for men), continue to be reported in cohorts with type 1 diabetes (Secrest et al 2010a). This suggests a continuing major excess in mortality, ascribed mainly to renal and CVD (Secrest et al 2010b). In Australia, death rates in people with insulin-treated diabetes, which includes those with type 1 diabetes, remain three-fold higher than the general population (Australian Institute of Health and Welfare 2009). The cause of death in long-term prospective series of people with type 1 diabetes varies with diabetes duration and age. In one study of childhood-onset type 1 diabetes, in the first 10 years after diagnosis, the leading cause of death was acute diabetes complications (73.6%), while during the subsequent 10 years, deaths were fairly evenly attributed to acute (15%), cardiovascular (22%), renal (20%) or infectious (18%) causes. After 20 years of diabetes, chronic diabetes complications (cardiovascular, renal or infectious) accounted for more than 70% of all deaths (Secrest et al 2010b). In addition to the presence of diabetes complications, other factors that predict mortality are higher waist:hip ratio, and elevated levels of cholesterol other than high-density lipoprotein (HDL) cholesterol (Soedamah-Muthu et al 2008). In contrast, longevity in type 1 diabetes is predicted by higher HDL cholesterol levels and more normal body habitus or body mass index (Bain et al 2003).

18.3.2 Value of screening

The value of screening for chronic diabetes organ complications is that:

- detecting early complication changes may help to better identify those who may benefit from intensive control of blood glucose and early targeting of other surrogate vascular risk factors (e.g. blood pressure) (Marcovecchio and Chiarelli 2010)
- additional interventions have been shown to help prevent end-stage complications.

These interventions include laser photocoagulation therapy for proliferative diabetic retinopathy or macular oedema, angiotensin converting enzyme inhibitor (ACEI) therapy for diabetic nephropathy, and preventive foot care for people with peripheral neuropathy (Melendez-Ramirez et al 2010). Normoalbuminuric people with type 1 diabetes have a mortality risk over subsequent decades that is similar to the general population without diabetes, emphasising the importance of preventing diabetic nephropathy (Orchard et al 2010).

18.3.3 Screening methods

Consensus guidelines indicate that adults with type 1 diabetes should undergo microvascular screening for diabetic retinopathy, nephropathy and peripheral neuropathy, using standard methods, on an annual basis, from 5 years after the diagnosis of their diabetes (Canadian Diabetes Association 2008; 2011). These methods include fundoscopy and visual acuity; albuminuria (spot albumin to creatinine ratio or timed urine collection for albumin excretion rate) and determination of estimated glomerular filtration rate (GFR); and assessment of ankle reflexes, feet vibration perception, and ability to detect the 10 g 5.07-gauge Semmes-Weinstein monofilament (Canadian Diabetes Association 2008). Australian research has indicated that early evidence of microvascular complications of diabetes (retinopathy prevalence of 12%) are found when diabetes onset occurs in childhood and adolescence, and nonproliferative diabetic retinopathy can occur within 2 years of diagnosis in type 1 diabetes (Cho et al 2010). Retinopathy screening for diabetes that has had its onset in childhood and adolescence is recommended 2 years after diabetes diagnosis (for pubertal-onset type 1 diabetes), and after 5 years (or after age 9 years,) for prepubertal onset diabetes (APEG 1996; Donaghue et al 2009).

18.3.4 Current recommendations for screening

In general, Australian and international consensus recommendations indicate that, once screening for microvascular complications has started in type 1 diabetes, it should then occur yearly for diabetic nephropathy and every 1–2 years for retinopathy (Australian Diabetes Society 2008; Hanas et al 2009; American Diabetes Association 2010). In lower risk cases, the frequency of subsequent screening for diabetic retinopathy could be reduced from once a year to once every 2 years on the advice of an experienced eye care professional (Donaghue et al 2009; American Diabetes Association 2010).

18.3.5 Emerging screening technologies

The development of new sensitive methods to detect more subtle, subclinical diabetes complications in people with shorter duration type 1 diabetes is an area of ongoing intensive clinical research (Marcovecchio et al 2010). To date, noninvasive approaches (including in children) of corneal confocal microscopy to detect early structural tissue changes of diabetic neuropathy, vascular and B mode ultrasound to examine blood vessel and cardiac function, and pupillometry to screen for autonomic neuropathy (Cho et al 2010). Standard field retinal fundus photography analysing retinal vascular dilatation (Cheung et al 2008) and branching

(Cheung et al 2009a) can predict impending classical diabetic retinopathy. In one study, cystatin C levels detected early abnormalities of glomerular filtration (Premaratne et al 2008). Other studies also estimate that up to half of the susceptibility to microvascular complications of diabetes is due to common genetic polymorphisms (Wiltshire et al 2008; Barrett et al 2009; Wang et al 2010). It is envisaged that these technologies to better define microvascular complication risk and early change will continue to be developed, and that some will become routine screening approaches for detecting early microvascular pathology.

There are no agreed universal recommendations for screening macrovascular disease in people with type 1 diabetes, other than in adults, where screening involves undertaking a thorough history and performing a detailed examination annually, and possibly a resting electrocardiogram (ECG) yearly or every 2 years (Canadian Diabetes Association 2008; American Diabetes Association 2010). The clinical assessment includes taking a history for new onset symptoms of ischaemic heart disease, including typical or atypical chest pain or unexplained dyspnoea on exertion, and examining for carotid bruits and lower limb pulses (Canadian Diabetes Association 2008). The American Diabetes Association indicates that, in people with type 1 or type 2 diabetes, candidates for cardiac stress testing include those with typical or atypical cardiac symptoms, or an abnormal resting ECG (American Diabetes Association 2010). The Canadian Diabetes Association includes as candidates for testing those with known cerebrovascular or peripheral arterial disease (Canadian Diabetes Association 2008). Dynamic screening investigations to be considered for CVD include stress echocardiography or nuclear medicine (SestaMIBI) heart study, depending on local expertise (Canadian Diabetes Association 2008). Therefore, certain less traditional risk factors should be considered to help stratify risks and identify people who may need screening for cardiovascular complications of diabetes, in addition to the conventional risk factors of severe hypertension, dyslipidaemia or smoking. These additional risk factors include diabetes duration (>15 years), a first-degree family history of premature cardiovascular disease, presence of active diabetic retinopathy, and occupations with a relatively high risk (e.g. occupations that involve driving a commercial motor vehicle regularly) (Canadian Diabetes Association 2008).

18.3.6 Individualised follow-up

Once a diabetes complication has developed, follow-up should be individualised to treat and monitor the complication. This will usually involve more frequent examinations of the complication after specific therapies have been started, and possibly also intensified general risk-factor management of blood glucose, blood pressure and lipids, and possibly antiplatelet therapy (Canadian Diabetes Association 2008). The safety of intensive glucose control has not been established in people with symptomatic CHD. Therefore, it may not be appropriate to intensify blood glucose control to minimise the risk of severe hypoglycaemia and precipitant cardiac events. In addition, in people with more severe end-stage complications (e.g. chronic kidney disease stages 3–5, or dense insensate peripheral neuropathy), there is no evidence that intensified blood glucose control will improve outcomes; glycaemic targets should therefore be individualised for each patient, taking into account the burden and severity of comorbidities (Canadian Diabetes Association 2008). In people with diabetes and CHD, revascularisation in the form of coronary stenting may help to relieve symptoms of CHD, and revascularisation in the form of coronary artery by-pass may also be indicated for prognosis where triple vessel or left main coronary artery disease exist (Schwartz 2009).

18.3.7 Other complications

Other complications of type 1 diabetes have been described, in addition to the classical microvascular and macrovascular complications. Associated autoimmune clusters can occur, so screening for coeliac disease and autoimmune thyroid disease are addressed in Chapter 20. Addison's disease is rare but occurs with increased frequency in type 1 diabetes; testing should be performed as clinically indicated. Psychological conditions, impact on physical development and chronic cognitive effects are addressed in Chapter 4. These diabetes complications are not, at present, universally or routinely screened for, but may be detected at regular clinical review, or as part of clinical research protocols. Type 1 diabetes can also cause cheiroarthropathy with limited joint mobility (Kordonouri et al 2009), lipohypertrophy at insulin injection sites (Overland et al 2009a), Charcot's arthropathy (Armstrong et al 1997), diabetic mastopathy (Ely et al 2000), and subclinical pulmonary disease (Wheatley et al 2010). Diabetic cardiomyopathy (Suys et al 2004) and the rare but devastating condition 'dead in bed syndrome' (Tu et al 2010) are also well recognised. Autoimmune skin conditions that are more common in type 1 diabetes include necrobiosis lipoidica diabeticorum, vitiligo and granuloma annulare (Edidin 1985). Finally, certain infections, such as localised cutaneous or mucosal infections, or systemic fungal and bacterial infections, may be exacerbated by poor glycaemic control (de Leon et al 2002) and are not uncommon. Diabetes may also affect mortality and morbidity outcomes from sepsis (Yende and van der Poll 2009). A specific type of life-threatening fungal infection in type 1 diabetes is mucormycosis, which is more common in children (Simmons et al 2005). Increased periodontal disease prevalence is also reported and may lead to improvement in glycaemic control when treated (Simpson et al 2010).

18.4 Effectiveness of antihypertensive agents at controlling blood pressure

Question 45

How effective are antihypertensive agents at controlling blood pressure in type 1 diabetes?

The detailed systematic review of this question is in Chapter 45 of the accompanying technical report, and the evidence matrix is in Section C45 of Appendix C

Hypertension is a pathogenic factor in macrovascular and microvascular events in diabetes (Jandeleit-Dahm and Cooper 2002). Systemic hypertension occurs most commonly in type 1 diabetes as essential hypertension in the presence or absence of the metabolic syndrome and in the setting of diabetic nephropathy (Jandeleit-Dahm and Cooper 2002). The renin–angiotensin–aldosterone system has long been implicated in mediating adverse effects on diabetic nephropathy through systemic blood pressure-dependent and independent mechanisms (Jandeleit-Dahm and Cooper 2002).

Three RCTS met the inclusion criteria to examine the effectiveness of antihypertensive agents in type 1 diabetes (Parving et al 1989; Gerdts et al 1998; Andersen et al 2000). The studies varied in duration from about 7–12 months, and examined ACEI or angiotensin receptor blocker (ARB) therapy in one study arm. Participants generally had some degree of diabetic nephropathy, and all had mild-to-moderate systemic hypertension. Casual clinic blood pressure readings or 24-hour ambulatory blood pressure were study endpoints. Some studies followed up-titration and treat-to-target protocols. The studies collectively indicated that antihypertensive therapy, with the introduction of a single agent, reduced systolic blood pressure by about 6–12 mmHg and diastolic blood pressure by about 5–9 mmHg. Mean 24-hour blood pressure readings in the study group were 5–9 mmHg lower than in the placebo group. When different agents were compared, there were no differences in blood pressure

control. Overall, adverse events ascribed to the active therapy during the studies were reported to be few.

In summary, these short-term, small studies demonstrate that antihypertensive agents are effective in type 1 diabetes in lowering blood pressure, similar to the effects seen in the general population. ACEI and ARB therapy, which were studied in these clinical trials, are preferred first-line agents in adults with diabetes in international guidelines (National High Blood Pressure Education Program 2004). ACEI are recommended for use in children with hypertension; they have been effective and safe in children in short-term studies (Donaghue et al 2009). In all patients with elevated blood pressure, nonpharmacological strategies and ongoing motivation for adherence to antihypertensive therapies are necessary (National High Blood Pressure Education Program 2004). Recent data from Australia indicate that antihypertensive agents, mainly ACEI and ARBs, are commonly used in adults with type 1 diabetes (Department of Health and Ageing 2009).

In people with nephropathy due to diabetes, systemic hypertension is common, and multiple agents are often required to achieve blood pressure targets (Andros et al 2006). Recent discussion has focused on whether there should be one blood pressure target for most adults with type 1 diabetes, or whether factors such as calculated cardiovascular risk should also play a role (Cooper-Dehoff et al 2011). At present, most guidelines recommend a blood pressure target of less than 130/80 mmHg, and in the presence of 1 g daily or more of proteinuria, less than 125/75 mmHg (National High Blood Pressure Education Program 2004).

18.5 Effectiveness of antihypertensive agents at reducing complications

Question 46

How effective are antihypertensive agents at reducing or preventing retinopathy, nephropathy, neuropathy and autonomic neuropathy?

The detailed systematic review of this question is in Chapter 46 of the accompanying technical report, and the evidence matrix is in Section C46 of Appendix C

The evidence base for this question was one Level I study of good quality and seven Level II studies, mostly of good quality.

The nephropathy studies were heterogeneous regarding study type and their baseline population proteinuria status. The ACEI in Diabetic Nephropathy Trialists Group meta-analysis included 12 Level II studies, with a total of 698 microalbuminuric participants without hypertension, who were given active treatment for at least 1 year. The studies consistently observed beneficial treatment effects of ACEI (ACEI Trialist Group 2001). In patients receiving ACEI, progression to macroalbuminuria was reduced (OR 0.38, 95%CI: 0.25 to 0.57) and regression to normoalbuminuria was increased (3.07, 95%CI: 2.15 to 4.44). When the 2-year data were estimated, the albumin excretion rate was 54% lower in patients receiving ACEI than in those receiving placebo (95%CI: 37% to 66%). The magnitude of the effect on lowering albumin excretion was related to baseline levels: 74% for those whose baseline albumin excretion rates were at the upper boundary of microalbuminuria (200 ug/min), compared with 18% in those whose baseline microalbuminuria was at the lower boundary (20 ug/min) (p=0.04).

Primary prevention studies are the DIRECT and RASS. One study (DIRECT-renal) examined the development of new onset microalbuminuria, in normotensive patients and found no

effect with ARB (Bilous et al 2009). In the RASS study, there was no reduction in new onset of microalbuminuria with ACEI (Mauer et al 2009).

An earlier study by Lewis et al (1993) was in a proteinuric population; thus, the measurement of disease progression differed from the other studies as the degree of nephropathy at study enrolment was more advanced. The ACEI, captopril, significantly reduced the time to doubling of serum creatinine ($p<0.007$), with a 48% risk reduction in the captopril group compared with placebo; and significantly reduced combined death or dialysis and transplantation ($p<0.006$). An aggregate analysis over the 4 years of the study revealed significantly less proteinuria in the captopril group ($p=0.001$). The efficacy was better than that achieved by blood pressure control alone in the placebo group. The generalisability of the body of evidence is limited by the inclusion of only adults in all trials. Although the baseline hypertensive status of populations varied between trials, as did the proteinuric state, benefit was seen across all stages of diabetic nephropathy examined. Regarding applicability, populations were drawn from multiple study sites in multiple countries, including America, Australia, Europe and New Zealand.

The body of evidence for retinopathy as an outcome consisted of three large Level II studies addressing prevention of retinopathy onset and progression. Two of these studies were of good quality: DIRECT-Prevent/DIRECT-Protect (Chaturvedi et al 2008) and RASS (Mauer et al 2009); the third – EUCLID – was of fair quality (Chaturvedi et al 1998). EUCLID examined normotensive patients, but did not assess new retinopathy as a primary outcome. Only one study examined incidence of retinopathy: in the DIRECT-prevent study, patients treated with ARBs had reduced incidence of retinopathy onset (hazard ratio for candesartan vs placebo 0.82, 95%CI: 0.67 to 1.00, $p=0.05$). The studies were conflicting in relation to progression of retinopathy; the DIRECT-protect study showed no effect (Chaturvedi et al 2008), the RASS study showed a reduction for ACEI (OR 0.35) and ARB (OR 0.3), and the EUCLID study showed a significant reduction in the progression of retinopathy, using a completers analysis method rather than intention to treat. In EUCLID, after 2 years of treatment with lisinopril, the progression of diabetic retinopathy by one level was reduced by 50% (95%CI: 28% to 89%, $p=0.02$). Progression to proliferative diabetic retinopathy was reduced in the lisinopril group by 82% (OR 0.18, 95%CI: 0.04 to 0.82, $p=0.03$). The authors concluded that the EUCLID findings would need to be confirmed before changes to clinical practice could be advocated. The generalisability was limited, because only adults were studied. Patients were normotensive and varied according to baseline retinopathy status. These studies were multicentre and included populations from America, Europe and the United Kingdom.

For cardiac autonomic neuropathy, the body of evidence consisted of two small, short-term Level II studies of poor and good quality (Ebbehøj et al 2002; Lanza et al 2007). The risk of bias was high. The studies were consistent in showing a statistically significant improvement in various aspects of cardiac autonomic neuropathy measurement; however, apart from reduced heart rate variability and an increase in RR interval in both studies, measurements showing improvement differed between studies and therefore cannot be compared. As neither study examined clinical endpoints, the clinical impact of these studies is small. The small size and short-term nature of the studies limit their generalisability. Both studies were conducted at single sites in Europe. Studies of antihypertensive therapy in peripheral neuropathy were not identified.

Overall, there is evidence that ACEI prevent progression of pre-existing nephropathy. Evidence of their effect on the onset of nephropathy or retinopathy is lacking, and evidence on prevention of progression of retinopathy or autonomic neuropathy is inconclusive or limited.

Evidence statements	
Q45	Level II evidence shows that antihypertensive agents are effective at lowering blood pressure.
Q46	**Primary prevention**: In normotensive normoalbuminuric patients with type 1 diabetes, there is consistent evidence that neither ACEI nor ARB prevent the onset of microalbuminuria. **Secondary prevention (progression)**: There is evidence that the use of ACEI prevents the progression from microalbuminuria to macroalbuminuria. There is evidence that ACEI attenuates or delays the progression from macroalbuminuria to doubling of creatinine or end-stage renal disease (combined death, dialysis and transplantation).
Q46	**Primary prevention**: In normotensive patients with type 1 diabetes and no retinopathy, there is insufficient evidence to determine the effect of ACEI or ARB on the onset of retinopathy. **Secondary prevention**: In normotensive patients with type 1 diabetes and nonproliferative diabetic retinopathy, ACEI or ARB reduce the progression of retinopathy. Prespecified outcomes were two grades of retinopathy progression on the ETDRS scale (DIRECT and RASS) or one grade (EUCLID), thus with differing study outcome measures.
Recommendation	
R18.2	ACEI therapy should be used to prevent progression of diabetic nephropathy (Grade B).
Practice points	
PP18.7	For patients who are intolerant of ACEI, ARBs can be used as an alternative treatment for the secondary prevention of nephropathy.
PP18.8	On the basis of the systematic evidence, including data in adolescents (Cook et al 1990), ACEI in type 1 diabetes can control albuminuria in normotensive microalbuminuria; however, there are currently restrictions from the Therapeutic Goods Administration to be considered in their use in this setting of normotension.
PP18.9	Tight control of blood pressure is of critical importance in limiting the progression of retinopathy and nephropathy. The general blood pressure target is <130/80 mmHg and <125/75 mmHg in the presence of 1 g daily or more of proteinuria.
PP18.10	ACEI and ARBs are contraindicated in pregnancy.
PP18.11	A small study has raised concerns that oral contraceptive use in women with type 1 diabetes may limit the efficacy of ACEI and ARB and contribute to macroalbuminuria (Ahmed et al 2005). Large prospective studies are required to further investigate this relationship.
ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker	

18.6 Effectiveness of statin therapy in reducing complications

Question 47 (interventional)

What is the effect of statins on lipid levels and cardiovascular outcomes in type 1 diabetes?

The detailed systematic review of this question is in Chapter 47 of the accompanying technical report, and the evidence matrix is in Section C47 of Appendix C

In type 1 diabetes, a diet that is low in saturated fat and high in fruit and vegetables, a healthy body weight, and regular physical activity are crucial for reducing macrovascular risks. These factors constitute the usual lifestyle prescription to lower macrovascular risk. Such nonpharmacological treatment is routinely desirable in type 1 diabetes. Glycaemic control can improve some lipid levels, especially circulating high triglycerides and low HDL-cholesterol in people with type 1 diabetes in whom HbA_{1c} levels have been elevated (Perez et al 2000).

There is a strong evidence base for the effectiveness of 3-hydroxy-3-methylglutaryl-coenzyme reductase inhibitors (termed *statins* as a class) in reducing total and low-density lipoprotein (LDL) cholesterol and cardiovascular events in people with type 2 diabetes, whether or not they have macrovascular disease (Marshall et al 2004). However, cardiovascular endpoint studies involving statin administration in type 1 diabetes have been more limited.

In terms of vascular outcomes, the Cholesterol Treatment Trialists analysed the data from 18 686 individuals with diabetes from a previously published prospective meta-analysis of statins on CHD and other major vascular events (CTT Collaborators 2008). The aim of this large, fair-quality meta-analysis was to examine effects of statins on major coronary and major vascular events in patients with diabetes. Studies included in the meta-analysis were those that had an intervention that modified lipid levels, and that aimed to recruit 1000 or more participants, with treatment duration of at least 2 years.

Of the 14 studies in the meta-analysis, 11 provided data on middle-aged to older adult patients with type 1 diabetes. Trial participants were considered to have diabetes if they had a recorded history of diabetes at randomisation. Subdivision of diabetes type was done according to the definitions used in the individual trials. Of 90 056 participants, 18 686 (20%) had diabetes. Further subdivision showed that 1466 (1.6% of the 20%) of these participants had type 1 diabetes. Baseline characteristics of patients presenting with type 1 diabetes included a mean age of 55.1 years, 21% smokers and 56% with a history of any vascular disease (previous heart attack or CHD, stroke or peripheral arterial disease). The mean blood pressure was 140/78 mmHg. The mean total cholesterol was 5.7 mmol/L, LDL 3.4 mmo/L, and HDL 1.3 mmol/L.

The percentage of participants with type 1 diabetes was small in the original trials, which may have increased the risk of allocation bias. The interventions studied included simvastatin 20–40 mg, pravastatin 40 mg, lovastatin 40–80 mg, fluvastatin 40–80 mg and atorvastatin 10 mg. In participants with type 1 diabetes, the mean (standard error) differences in plasma lipid concentrations at 1 year in participants exposed to statins and controls were as follows:

- total cholesterol –1.04 mmol/L (0.08)
- LDL –0.96 mmol/L (0.15)
- triglycerides –0.09 mmol/L (0.08).

There was no change in HDL. Regarding adverse events, there were too few cases of rhabdomyolysis reported in patients with diabetes for meaningful analysis.

Results indicated that there was some evidence of benefit in the 1466 people with type 1 diabetes (RR 0.79, 99%CI: 0.62 to 1.01, p=0.01) in terms of proportional reduction per mmol/L LDL cholesterol. Also reported was a reduction in the incidence of major vascular events by about 20% per mmol/L LDL cholesterol reduction in all prognostic subgroups of participants with diabetes that were examined. After 5 years of treatment, 42 fewer patients per thousand had a vascular events per mmol/L cholesterol reduction. This benefit was greater for those with a history of vascular disease (57 per 1000) than those without (36 per 1000).

The remaining nine Level II studies were consistent in reporting a statistically significant reduction in total cholesterol and LDL with statin use in adults. The order of magnitude of statistically significant difference in total cholesterol ranged from –1.2 to –2.1 mmol/L

treatment (compared to placebo) at the end of each study. The percentage reduction in total cholesterol from baseline to end of treatment in the statin groups ranged from –21% to –33%. Regarding LDL, the magnitude of difference ranged from –0.85 to –1.7 mmol/L treatment compared to placebo. In terms of percentage reduction in the treatment groups from baseline to study end, the range was –29 to –48%. Five studies showed a nonsignificant effect of statins on triglyceride levels (Hommel et al 1992; Kjaer et al 1992; Zhang et al 1995; Mullen et al 2000; Fried et al 2001). Two studies (Rustemeijer et al 1997; Noutsou and Georgopoulos 1999) reported a significant reduction in triglycerides and one (de Vries et al 2005) showed a significant reduction in triglycerides with doses of 20–40 mg but not 10 mg simvastatin. A statistically significant increase in HDL with statins was also reported (de Vries et al 2005) with all doses of simvastatin. One study (Manuel et al 2003) also showed a significant improvement in LDL cholesterol, but this was not replicated in any of the other studies.

Overall, in type 1 diabetes, the evidence indicates a consistent biological effect of statins on circulating lipids, as seen in the general population. A meta-analysis of subgroup data showed that cardiovascular risk was also attenuated with statin use in type 1 diabetes. Studies underway, such as the Adolescent type 1 Diabetes Cardio-renal Intervention Trial (AdDIT), may provide further definitive evidence for the future use of statins in young adults and children (AdDIT Research Group 2009).

Evidence statement	
Q47	Level I and II evidence demonstrates that statins are effective at reducing total and LDL cholesterol in adults with type 1 diabetes. Level I evidence demonstrates that statins reduce cardiovascular events in adults with type 1 diabetes.
Recommendation	
R18.3	Statins are recommended for use in adults with type 1 diabetes, to reduce total and LDL cholesterol, and to reduce cardiovascular risk (Grade B).
Practice points	
PP18.12	As global macrovascular risk in type 1 diabetes is high in adults, statins should be commenced early in the disease course, at relatively low levels of dyslipidaemia, and before the development of cardiovascular disease.
PP18.13	Statin therapy can be used after Tanner stage II in boys and after menarche in females. In high-risk vascular disease states (e.g. hereditary LDL receptor deficiency), statins may be indicated from the age of 8 years.
PP18.14	Statin therapy is contraindicated in pregnancy, and reliable contraceptive methods should be used in females of reproductive age who are on statin treatment.
PP18.15	The benefit of statin therapy in people with end-stage renal failure (including in those with type 1 diabetes) has not been confirmed; however, it is prudent to use low-dose statin treatment in this group, which is at particularly high risk of cardiovascular disease.
LDL, low-density lipoprotein	

18.7 Cost and cost effectiveness of antihypertensive agents and statins

Question 48 (background question)

What are the cost and cost effectiveness of antihypertensive agents at controlling blood pressure in type 1 diabetes?

Question 49 (background question)

What are the cost and cost effectiveness of antihypertensive agents at reducing or preventing retinopathy, nephropathy, neuropathy and autonomic neuropathy?

Question 50 (background question)

What are the cost and cost effectiveness of statins at correcting dyslipidaemia in type 1 diabetes?

Questions 48–50 were background question and therefore were not systematically reviewed

One review was identified that examined cost effectiveness of ACEI in patients with type 1 diabetes (Swislocki and Siegel 2001). The review included four studies and concluded that treatment of hypertensive patients with type 1 diabetes is cost effective. An Australian study used Markov modelling to compare intensive management with usual care for patients with suboptimally managed type 1 and type 2 diabetes and hypertension (Howard et al 2010). This study found that treating all known patients with diabetes with ACEI was both less costly (an average lifetime saving of $A825 per patient) and more effective than current treatment (resulting in 0.124 additional quality-adjusted life years [QALYs] per patient). Several studies limited to patients with type 2 diabetes have demonstrated cost effectiveness for antihypertensive therapy. Intensive blood pressure control in hypertensive patients with type 2 diabetes reduced costs and improved health outcomes relative to moderate hypertension control (CDC Diabetes Cost-effectiveness Group 2002). Similarly, Markov modelling demonstrated that a hypertension management program in patients with type 2 diabetes was cost effective, and achieved greater gains in QALYs compared with standard care (Ly et al 2009).

A systematic review of cost effectiveness of interventions to prevent and control diabetes, which included 56 studies, found evidence that antihypertensive agents, and statin therapy (for the secondary prevention of cardiovascular disease), were cost saving and cost effective in type 2 diabetes (Li et al 2010). None of the included studies examined these therapies in patients with type 1 diabetes. ACEI therapy for intensive hypertension control compared with standard hypertension control; ACEI or ARB therapy to prevent end-stage renal disease compared with no ACEI or ARB treatment; and early irbesartan therapy (at the microalbuminuria stage) to prevent end-stage renal disease compared with later treatment (at the macroalbuminuria stage) were all cost saving in type 1 diabetes.

18.8 Predictive ability of Framingham equation

Question 51 (background question)

What is the predictive ability of the Framingham multiple cardiovascular disease risk factor equation in type 1 diabetes?

Question 51 was a background question and therefore was not systematically reviewed

In the course of a lifetime, many people with type 1 diabetes will develop clinically significant CHD (Sibal et al 2006). Risk factor algorithms have been developed, from long-term prospective cohort studies, to assess absolute risk of CHD and mortality. For the general population, the most widely used models for a first CHD event have been based on

data from the Framingham Heart Study (Wilson et al 1987; Poole et al 2009). Some risk factor score methods, including the Framingham and the UKPDS Risk Factor Engine, have been validated in populations with type 2 diabetes (Stevens et al 2001; Nuevo et al 2009; van der Heijden et al 2009); however, they have not been shown to perform well in populations with type 1 diabetes (Zgibor et al 2006).

Two important issues for coronary heart disease (CHD) in type 1 diabetes are as follows (Sibal et al 2006):

- CHD events often occur earlier in life in type 1 diabetes than for people with type 2 diabetes or in the general community (due to the often earlier age onset of type 1 diabetes)
- diabetic nephropathy as albuminuria or proteinuria, or reduced GFR, are common and major factors that contribute to CHD events that occur in type 1 diabetes.

In the EDIC study, the average age of onset of CHD events was 39 years (interquartile range 34–44 years), and renal disease was thought to contribute to about half of the CHD events that occurred (Nathan et al 2005). In contrast, in the general population, the age of onset of CHD events is the late 60s and early 70s (Carney et al 2009). The risk factor engines have not been designed for people in the 20 to mid-40s age group and do not include renal disease parameters. It is therefore not surprising that the risk factor engines performed poorly in predicting CHD events in people with type 1 diabetes (Zgibor et al 2006). Each risk factor engine markedly underestimated risk of first CHD events in people with type 1 diabetes.

Currently, there are no risk factor engines for CHD events in type 1 diabetes. Such tools would be desirable to help identify individuals at highest event risk. If developed from populations with type 1 diabetes, they are likely to include parameters of diabetes duration and renal status (estimated GFR and albuminuria status), as well as those of age, blood pressure and lipid status (Sibal et al 2006).

19 Foot ulcers and Charcot's arthropathy

19.1 Introduction

National evidence-based guidelines for the prevention, identification and management of foot complications in type 2 diabetes have been developed and were submitted to the National Health and Medical Research Council in late 2010 (AIHW 2008). The guidelines inform clinicians of best practice for preventing, identifying and managing foot disease in adults with type 1 or 2 diabetes, in both urban and rural or remote primary care, and in specialist foot centres. The guidelines are equally relevant for type 1 diabetes. In view of the availability of these contemporary guidelines, the literature on the prevention, identification and management of foot complications in type 1 diabetes was not systematically reviewed here.

19.2 Foot complications in young people with type 1 diabetes

Children and adolescents with type 1 diabetes usually do not display the severe foot problems observed in older people with diabetes. Nevertheless, young people are at greater risk than their peers without diabetes of structural and functional foot abnormalities (Barnett et al 1995). In a prospective study of young people with type 1 and type 2 diabetes, most of the foot problems observed were potentially modifiable disorders of the skin and nails (69%), while a significant proportion (31%) were structural musculoskeletal disorders requiring referral to a podiatrist or orthotist (Rasli and Zacharin 2008).

Foot abnormalities not specific to diabetes – including deformity, plantar callus and high plantar pressure – may contribute to soft-tissue breakdown and ulceration. Structural changes that are specific to diabetes – including soft-tissue thickening and limited joint mobility in the foot – may alter the mechanics of the foot, leading to high plantar pressure and ulceration. Functional abnormalities (see Box 19.1, below) can result in abnormal pressure changes on the plantar surface of the foot, or abnormal pressure from footwear (AIHW 2008).

Box 19.1 Paediatric foot abnormalities that may lead to abnormal plantar pressure

- Significant leg length discrepancy (>1 cm).
- Genu varum (normal up to the age of 2 years) or genu valgum (normal between 2 and 7 years).
- Internal or external knee position.
- Varus or valgus foot position (a small degree of valgus alignment is normal up to 7 years).
- In-toeing or out-toeing.
- Abnormal shoe wear patterns – the heel should wear to the centre or slightly laterally; the sole should show even wear; and the upper of the shoe should not be deformed.
- Inadequate shoe fit – either too small or too large.

Plantar callus and increased plantar pressure have been observed more commonly in young people with type 1 diabetes (Duffin et al 2003). Plantar callus can increase plantar pressure, which may damage underlying soft tissue; in adults with diabetes, this is a reliable predictor

of subsequent ulceration (Murray et al 1996). Plantar pressure is evaluated by using pressure analysis equipment, which is available at most high-risk foot clinics and diabetes complications assessment clinics.

Thickening of the plantar aponeurosis – which indicates loss of elasticity and thickening of the dermis, and is a marker of tissue collagen glycation and oxidation – has been observed in one-third of young people with type 1 diabetes (Duffin et al 2002). Thickening of the plantar aponeurosis was associated with increased forefoot plantar pressure and limited joint mobility in a study of adults with type 1 and 2 diabetes (D'Ambrogi et al 2003), and with limited subtalar joint mobility in young people with type 1 diabetes (Duffin et al 2002). Thickening of the plantar fascia is also a risk factor for subsequent development of microvascular complications, including peripheral neuropathy (Craig et al 2008).

Limited joint mobility has also been detected in the feet of young people with diabetes (Barnett et al 1995; Duffin et al 2002), affecting the ankle, subtalar, first metatarsophalangeal and interphalangeal joints. Joint limitation in the first metatarsophalangeal joints increases plantar pressure under the hallux, an area at great risk of developing a plantar ulcer (Duffin et al 2003). Limited joint mobility increases plantar pressure, which in turn may lead to tissue breakdown and ulceration, although this is rarely observed in young people with diabetes. Limited joint mobility at the first metatarsophalangeal joint is indicated by dorsiflexion (in a weight-bearing position) of less than 60 degrees, and warrants further assessment.

19.3 Foot complications in adults with type 1 diabetes

The spectrum of diabetes-related complications that affect the foot in adults is different from that observed in young people. In adults, complications include ulceration, deformity, ischaemia, infection (including osteomyelitis) and Charcot's neuroarthropathy (CNA). The pathophysiology of foot ulceration is complex and multifactorial. Peripheral neuropathy, peripheral vascular disease, foot deformity, trauma, skin infection, impaired healing and limited self-care, may all contribute to foot ulceration or failure of ulcer healing. Failure of foot ulcers to heal can lead to foot amputation.

Peripheral neuropathy, foot deformity and external trauma are all common causes of foot ulceration in diabetes, together with peripheral vascular disease and peripheral oedema (Boulton 2008). In a population-based sample of Australian adults with diabetes aged 25 years or more (the Australian Diabetes, Obesity, and Lifestyle Study) (Tapp et al 2003), a substantial proportion (about 20%) were at risk of foot ulceration, which is a leading cause of hospitalisation for people with diabetes (AIHW 2008). Diabetes is the most common cause of nontraumatic lower limb amputation in Australia (Barr et al 2006). The 5-year survival for those who have had limb amputation is poor, with mortality rates ranging from 39% to 80% (Moulik et al 2003).

The risk of foot ulceration and amputation is increased in patients with previous foot ulceration or previous amputation, peripheral neuropathy, peripheral vascular disease and foot deformity (including hallux deformity, hammer or claw toe, callus, previous amputation, flattened arches, abnormally wide feet and CNA). Older age is a significant risk factor for diabetes-related foot complications; in addition, evidence suggests that visual impairment, kidney disease, poor glycaemic control, ill-fitting footwear and socioeconomic disadvantage are also risk factors (Baker IDI Heart and Diabetes Institute et al 2010).

CNA is a noninfectious, degenerative disease of the bones and joints, particularly weight-bearing joints such as the foot and ankle. The condition is characterised by joint dislocation,

fractures and deformities. In extreme cases, it may significantly disrupt the bony architecture of the affected joint. In developed countries, CNA typically manifests most commonly in patients with long-standing diabetes and peripheral neuropathy. About half of patients with CNA experience some pain, however the severity of the pain may be less than clinical signs and symptoms would seem to indicate. Specific clinical signs indicating the presence of CNA include unilateral swelling and joint deformity, an increase in local skin temperature (generally about 3^{o}C higher in the affected extremity), erythema, joint effusion or oedema, absence of sweating, bounding pedal pulses, an insensate foot and bone resorption. Instability, loss of joint function and concomitant ulceration may also be evident.

Suspected CNA of the foot is considered an emergency and should prompt immediate referral to a dedicated multidisciplinary foot care service. Early management aims to eliminate further trauma or stress to the foot by preventing weight bearing, thus preventing progression of the disease. Offloading with a total contact cast – widely accepted as the most effective treatment for patients with CNA – protects the foot, and reduces foot temperature and bone activity. Complications that may arise from inadequate or delayed treatment include foot deformity, chronic ulceration, infection and osteomyelitis.

Prevention of foot complications in people with diabetes should include (Baker IDI Heart and Diabetes Institute et al 2010):

- podiatry
- hygiene maintenance (advice to inspect and wash feet daily)
- appropriate footwear and hosiery
- protective shoes (avoid constrictive footwear)
- clinic contact initiated by the patient, if concerned.

19.4 Screening for foot complications in type 1 diabetes

Question 52 (background question)

How and how often should children, adolescents and adults with type 1 diabetes be screened for foot complications?

The detailed systematic review of this question is in Chapter 52 of the accompanying technical report, and the evidence matrix is in Section C52 of Appendix C

No studies have evaluated the effectiveness of screening for foot complications in children and adolescents. Similarly, no studies have addressed the optimal frequency of screening.

Screening for foot problems in adults is associated with a reduction in ulceration and reduction in major and total amputation. One large randomised controlled trial examined the effects of a two-stage foot-screening program followed by a foot-protection program for those classified as high risk for foot ulceration compared to standard care (Lemaster et al 2008). Patients classified as high risk were entered into a foot-protection program that included foot care (podiatry and hygiene maintenance), support hosiery and protective shoes. Those classified as low risk received no further special treatment. A significant reduction in major and total amputation was demonstrated in the intervention group, and there was a trend to increased ulcer healing. Nonrandomised, observational studies have demonstrated that other commonly used clinical assessments are effective in predicting foot ulceration or amputation. Tools for assessing neuropathy, circulation and foot deformity are shown in Box 19.2.

Box 19.2 Tools for assessing neuropathy, circulation and foot deformity

Neuropathy

- 10 g monofilament sensitivity.
- Vibration perception (tuning fork or biothesiometer).
- Neuropathy Disability Score – tendon reflexes and the sensory modalities of pinprick, light touch, vibration and temperature perception.

Circulation

- Palpation of peripheral pulses.
- Ankle-brachial index.

Foot deformity

- Assessment for foot deformity.

Six-point scale: *small muscle wasting, *Charcot foot deformity, *bony prominence, *prominent metatarsal heads, *hammer or claw toes and *limited joint mobility

Low-risk group = score of 0–2, high-risk group = score of 3–6

Practice principles (Baker IDI Heart and Diabetes Institute et al 2010)

- Foot care education should be provided to all people with diabetes to assist with prevention of foot complications.
- Podiatry review is an important component of a foot-protection program. However, in settings where this is not possible, a suitably trained, alternative health-care worker may undertake a review of the feet.
- In people identified as having low-risk feet (where no risk factors or previous foot complications have been identified), foot examination should occur annually.
- In people identified as having intermediate-risk or high-risk feet (without current foot ulceration), foot examination should occur at least every 3–6 months.
- People identified as having intermediate-risk or high-risk feet should be offered a foot-protection program that includes foot education, podiatry review and appropriate footwear.
- People with plantar callus, high plantar pressures or limited joint mobility need to be monitored closely for foot complications.
- People with diabetes-related foot ulceration are best managed by a multidisciplinary foot-care team.
- Given the limited access to multidisciplinary foot-care teams, at a minimum, the following factors should always precipitate referral to such a team:
  - deep ulcers (probe to tendon, joint or bone)
  - ulcers not reducing in size after 4 weeks, despite appropriate treatment
  - the absence of foot pulses
  - ascending cellulitis
  - CNA.

- If access to a multidisciplinary foot-care team is limited, foot ulceration or foot complications other than those listed above should be managed by a general practitioner, together with either a podiatrist or a wound-care nurse.
- Remote expert consultation with digital imaging should be made available to people with diabetic foot ulceration living in remote areas who are unable to attend a multidisciplinary foot-care team or service for management.

20 Other complications and associated conditions

20.1 Introduction

Individuals with type 1 diabetes are at increased risk of detectable organ-specific autoantibodies (e.g. thyroid and adrenal), and the development of autoimmune diseases such as thyroid and coeliac disease. This chapter examines the evidence for screening for these two conditions in children, adolescents and adults with type 1 diabetes.

20.2 Coeliac disease

20.2.1 Epidemiology

Coeliac disease is more common in patients with type 1 diabetes than in the general population. Prevalence ranges from 0.8% to 6.4% in adults, and 0.6% to 16.4% in children with type 1 diabetes (Bruno et al 2003; Cerutti et al 2004; Kordonouri et al 2009). In Australia, the prevalence in children is about 5% (Pham et al 2010), with an incidence of 0.72 per 100 patient years (Glastras et al 2005). In patients with diabetes, coeliac disease commonly presents as a silent disease, with few if any symptoms (Larsson et al 2008). Established risk factors include younger age at diagnosis of type 1 diabetes (Cerutti et al 2004), shorter duration of diabetes (Larsson et al 2008) and human leukocyte antigen (HLA) DQ2 (Doolan et al 2005). Younger children (aged <5 years) are more likely to be diagnosed with coeliac disease after longer diabetes duration compared with older children and adolescents, and are more likely to seroconvert after being negative on screening at diabetes diagnosis (Pham et al 2010).

Complications of seropositivity to coeliac antigens in children with type 1 diabetes include adverse effects on bone mineral density, weight standard deviation scores (SDS) (Artz et al 2008), body mass index (BMI) (Simmons et al 2007) and growth (Kaspers et al 2004). There are no data regarding these outcomes in the adult population.

20.2.2 Screening

Antibody screening tests for coeliac disease include those for antigliadin antibodies (AGA), either IgA or IgG; antireticulin antibodies (ARA), IgA; antiendomysium antibodies (EMA), IgA; and anti-tissue transglutaminase (tTGA and tTGG). These tests can give a false-negative result in IgA-deficient populations; therefore, a measure of total IgA is recommended at the time of screening.

Recommendations regarding screening for coeliac disease in patients with type 1 diabetes are not consistent. There are currently two issues; the type of screening tests to use and the timing of testing including frequency. The National Institute of Health and Clinical Excellence (NICE) guidelines recommend using IgA tTGA as the initial test; IgA EMA if the result of the tTGA test is equivocal; IgA deficiency if serology is negative; and IgG tTGA or IgG EMA (or both) for people with confirmed IgA deficiency (NICE 2009). This guidance is based on a report from the Agency for Healthcare Research and Quality (AHRQ), which concluded that the IgA tTGA and IgA EMA tests show higher levels of sensitivity and specificity than the AGA tests. Inclusion criteria for all study participants, including controls, included a reference test of small bowel biopsy.

In regards to timing of screening, the current International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines (Kordonouri et al 2009) advocate screening at diagnosis in all children with type 1 diabetes, with repeat annual screening for the first 5 years after diagnosis, and every 2 years thereafter. This is based on the reduced risk of coeliac disease with increasing diabetes duration. The guidelines do not stratify screening intervals by age.

In the presence of an elevated antibody level, a small bowel biopsy is required to confirm the diagnosis of coeliac disease by demonstrating subtotal villus atrophy, according to Marsh criteria (Marsh and Crowe 1995).

20.2.3 Management

Following introduction of a gluten-free diet, mucosal changes reverse and antibody titres return to normal; however, there is insufficient evidence to demonstrate improvement in glycaemic control. The aims of treatment with a gluten-free diet are to reduce the risk of subsequent gastrointestinal malignancy and conditions associated with subclinical malabsorption (osteoporosis, iron deficiency and growth failure). Patients with proven coeliac disease should be referred to a gastroenterologist, and receive education and support from a dietitian. Educational materials for patients and families should be made available.

Question 53

How and how often should patients with type 1 diabetes be screened for coeliac disease?

The detailed systematic review of this question is in Chapter 53 of the accompanying technical report, and the evidence matrix is in Section C53 of Appendix C

The systematic review identified seven longitudinal cohort studies (Barera et al 2002; Crone et al 2003; Cerutti et al 2004; Glastras et al 2005; Poulain et al 2007; Larsson et al 2008; Salardi et al 2008). Five of these were prospective studies, all of medium risk of bias, and two were retrospective, both of medium risk of bias. All of the studies were in children and adolescents (n=6506), with no prospective or retrospective, longitudinal studies found in adults. The findings of the studies were consistent in demonstrating the high prevalence of antibodies for coeliac disease or biopsy-proven coeliac disease, mostly detected at the time of diagnosis of type 1 diabetes or within 2–4 years post diagnosis.

All studies were of fair quality, but only one included adults. The included studies demonstrated a high prevalence of antibodies for coeliac disease or of biopsy-proven coeliac disease in children and adolescents with type 1 diabetes and a decreasing trend in prevalence with duration of diabetes, with most cases being detected by screening at diagnosis of diabetes or up to 2–4 years post diagnosis (Barera et al 2002; Crone et al 2003; Cerutti et al 2004; Larsson et al 2008; Salardi et al 2008). Cerutti et al (2004) concluded from their data that coeliac disease is rarely found after 10 years duration of diabetes (Cerutti et al 2004). There are also some subgroups of patients for whom the risk of developing coeliac disease may be higher, with female sex and age of less than 4 years at diagnosis of type 1 diabetes being independently associated with the risk for having both coeliac disease and diabetes (Cerutti et al 2004). Additionally, positive antibodies at diagnosis are highly predictive of future disease (Glastras et al 2005), suggesting the need for closer surveillance of patients falling into these subgroups.

The results therefore provide the rationale for routine screening at the time of diagnosis of type 1 diabetes and repeated at follow-up until the risk declines, although none of the studies were designed to address the optimal frequency of screening.

Evidence statements	
Q53	There is an increased risk of coeliac disease in children and adolescents with type 1 diabetes compared to general population historical rates. The number of new cases detected 1 and 2 years after diagnosis is similar to the number of cases at diagnosis. The number of new cases detected after 10 years of diabetes duration is similar to the general population.
Recommendation	
R20.1	Screening for coeliac disease should occur at diagnosis of type 1 diabetes in children and adolescents; individuals with negative tests at diagnosis should be rescreened (Grade B).
Practice points	
PP20.1	All adults with newly diagnosed type 1 diabetes should be screened for coeliac disease at diagnosis.
PP20.2	All adults with type 1 diabetes who have not been previously screened should be screened for coeliac disease.
PP20.3	Children and adolescents should be rescreened for coeliac disease at least once in the first 5 years after diagnosis.

20.3 Thyroid disease

20.3.1 Epidemiology

Thyroid disease is the most common autoimmune disease in patients with type 1 diabetes; it occurs more commonly in children and adults than in the general population (Mantovani et al 2007; Volzke et al 2007; Somers et al 2009). At diagnosis of type 1 diabetes, 8–15% of young people have positive thyroid peroxidase (TPO) antibodies (Glastras et al 2005; Kordonouri et al 2005) and the cumulative incidence of thyroid autoimmunity ranges from 10% to 22% after up to 10 years of diabetes (Kordonouri et al 2005; Severinski et al 2009). Among 28 671 patients aged under 30 years with type 1 diabetes from Germany and Austria, thyroid autoimmunity was found in 20% (Warncke et al 2010). The prevalence of primary hypothyroidism ranges from 3% to 8% in young people (Hansen et al 2003; Severinski et al 2009). Hyperthyroidism is less common than hypothyroidism in association with type 1 diabetes (Umpierrez et al 2003), but is still more common than in the general population.

Among children and adolescents with type 1 diabetes, the prevalence of thyroid autoimmunity is associated with female gender, older age and longer diabetes duration (Kordonouri et al 2005; Karavanaki et al 2009; Severinski et al 2009; Warncke et al 2010). The risks of thyroid autoimmunity and thyroid disease are also higher in adult women (Perros et al 1995; Umpierrez et al 2003). The risk of developing thyroid disease (hypothyroidism or hyperthyroidism) is greater among those who have evidence of thyroid autoimmunity at diagnosis of type 1 diabetes (Umpierrez et al 2003; Glastras et al 2005; Kordonouri et al 2005), particularly if thyroid autoantibody titres are high (Kordonouri et al 2005).

20.3.2 Clinical features

Autoimmune thyroid disease may present as a subclinical disease, with few if any symptoms or signs. Clinical features may include the presence of a painless goitre, increased weight gain, growth retardation (in children), tiredness, lethargy, cold intolerance and bradycardia. Notably, goitre was less common in adults with type 1 diabetes than in the general population (Volzke et al 2007). Glycaemic control may not be significantly affected, although insulin requirements may be lower in hypothyroidism due to reduced insulin degradation. Hyperthyroidism may be associated with worsening glycaemic control and increased insulin requirements.

20.3.3 Screening and investigation

Screening tests for thyroid disease include measures of antibodies against TPO (TPOA) and thyroglobulin (TGA), and thyroid function tests (thyroid stimulating hormone [TSH], free T4 and T3). In the population without diabetes, TPOA is more specific than TGA, and TSH is recommended as the screening test for thyroid disease. Hypothyroidism is confirmed by demonstrating a low free T4 level and a raised TSH concentration. Compensated hypothyroidism may be detected in an asymptomatic individual with a normal thyroxine level and a modestly increased TSH.

20.3.4 Management

Treatment of thyroid disease in type 1 diabetes is the same as that used in the general population. Hypothyroidism is treated with oral L-thyroxine sufficient to normalise TSH levels. Treatment of hyperthyroidism is usually with anti-thyroid drugs such as carbimazole or propylthiouracil; carbimazole is the preferred treatment in children due to the increased risk of liver failure in patients treated with propylthiouracil (Rivkees and Mattison 2009). Beta-adrenergic blocking drugs are helpful during the acute phase of thyrotoxicosis, to control tachycardia and agitation. Treatment options for persistent or recurrent hyperthyroidism include surgery or radioactive iodine.

Question 54

How and how often should patients with type 1 diabetes be screened for thyroid disease?

The detailed systematic review of this question is in Chapter 54 of the accompanying technical report, and the evidence matrix is in Section C54 of Appendix C

The literature search identified six publications describing longitudinal screening for thyroid disease. These studies involved a total of 1127 children and adolescents and 464 adults with type 1 diabetes ,screened on multiple occasions for thyroid disease and followed for up to 18 years (Perros et al 1995; Umpierrez et al 2003; Kordonouri et al 2004; Glastras et al 2005; Kordonouri et al 2005; Severinski et al 2009). Five of the studies were of moderate risk of bias and one of high risk of bias.

The method of screening included measurement of thyroid function (TSH, T4 and T3) in combination with measures of autoantibodies (TPOA and TGA) at diagnosis of type 1 diabetes. Follow-up screening with thyroid function tests alone was carried out in one study (Glastras et al 2005), and in combination with antibody testing in five studies (Perros et al 1995; Umpierrez et al 2003; Kordonouri et al 2004; Kordonouri et al 2005; Severinski et al 2009). Transient autoimmunity was only reported in one study in five children; in all cases, the initial TPOA and TGA titres were only slightly elevated (<100U/ml) (Kordonouri et al 2004). In the studies measuring thyroid antibodies at multiple time points, most patients

with positive thyroid antibodies were detected at the initial screening (Umpierrez et al 2003; Kordonouri et al 2004; Kordonouri et al 2005; Severinski et al 2009).

The studies demonstrated a high prevalence of thyroid autoimmunity and thyroid disease in type 1 diabetes. The prevalence of thyroid autoimmunity ranged from 5.4% to 15.5% in children and adolescents, and the prevalence of hypothyroidism was 8.1% in the study by Severinski (2009). In adults, the prevalence of thyroid disease, including subclinical disease, was reported as 12.4% in males and 31.4% in females (Perros et al 1995). In a cohort of Australian children, the incidence was 0.9 per 100 patient years (Glastras et al 2005). By duration of diabetes, the cumulative incidence of autoimmune thyroiditis was reported as 14% after 10 years duration in children (Kordonouri et al 2005) and as high as 22% after 6 years duration in a group of Croatian children (Severinski et al 2009). In both studies, the cumulative incidence in girls was significantly greater than in boys. In adults, the annual incidence of thyroid disease was reported as 6.5% in males and 12.3% in females, including subclinical forms (Perros et al 1995).

Three studies, two in children and one in adults, reported statistically significant differences in the probability of developing thyroid disease between patients negative for thyroid antibodies at diagnosis of diabetes and those positive for antibodies; patients with a positive screen were 17–18 times more likely to develop thyroid disease (Umpierrez et al 2003; Glastras et al 2005; Kordonouri et al 2005). Given the higher risk associated with the presence of autoantibodies, it may be appropriate to undertake a higher level of surveillance for this subgroup of patients.

The results of these studies provide the rationale for screening for thyroid disease at diagnosis of type 1 diabetes. The authors of these studies consistently recommendedscreening for thyroid disease at diagnosis of type 1 diabetes by measurement of thyroid function and thyroid autoantibodies.

For follow-up screening, three authors recommended annual thyroid function tests, particularly in those patients with an initial positive thyroid autoantibody test (Perros et al 1995; Umpierrez et al 2003; Glastras et al 2005); one study recommended bi-annual thyroid function tests in those initially negative to thyroid autoantibodies(Glastras et al 2005). Kordonouri et al (2005) recommended a combination of both thyroid function tests and thyroid autoantibody tests annually in those with a positive thyroid autoantibody test at diagnosis, and annually from onset of puberty in those with an initial negative thyroid autoantibody test. Severinski et al recommend annual screen with a thyroid autoantibody test with thyroid function tests in those with a positive result (Severinski et al 2009).

The evidence is generalisable to both children and adults with type 1 diabetes with the only exclusions reported as those patients who had developed thyroid disease prior to the diagnosis of diabetes. The results are applicable to the Australian population with one study carried out in a cohort of Australian children and all other studies carried out in countries with a well-developed health-care system.

Evidence statements	
Q54	Thyroid dysfunction is common in type 1 diabetes, and positive antibodies are strongly predictive of thyroid dysfunction.
Recommendation	
R20.2	At diagnosis of type 1 diabetes, patients should be screened for thyroid dysfunction and tested for antibodies to TPO; screening for thyroid dysfunction should be performed regularly thereafter (Grade B).
Practice points	
PP20.4	Tests for TSH should be repeated at least yearly in those with anti-thyroid antibodies at diagnosis.
PP20.5	Tests for TSH should be repeated at least 2-yearly in all other patients with type 1 diabetes.
PP20.6	Women planning pregnancy should have a test for TSH preconception and in the first trimester.
PP20.7	Women who are TPO positive should be tested postpartum for thyroid dysfunction.
TPO, thyroid peroxidase; TSH, thyroid stimulating hormone	

21 Future research

The systematic reviews for these guidelines highlighted a lack of high-quality evidence in a number of areas related to clinical care of people with type 1 diabetes. In particular, many of the studies lacked statistical power to detect treatment effects, or had other methodological weaknesses. For many questions, there was no high-level evidence (Level II or III studies). Further research is needed to provide a stronger evidence base.

This chapter:

- describes the evidence gaps identified for questions and suggests areas for future research
- identifies topics that were not systematic reviewed, but may be considered in future revisions of these guidelines.

21.1 Evidence gaps and areas of future research

21.1.1 Natural history of type 1 diabetes

Question 1

What interventions delay or prevent the onset of type 1 diabetes?

There is no evidence to support the use of any intervention to delay or prevent the onset of type 1 diabetes. Further studies are needed to investigate the effectiveness of therapies targeting both primary and secondary prevention. In particular, characterisation of subgroups of individuals with type 1 diabetes, by their genetic predisposition or environmental triggers, and identification of biomarkers in the prediabetes phase, may assist in targeted prevention strategies.

21.1.2 Characteristics of type 1 diabetes

Question 2

Is there an increased prevalence of psychological disorders in people with type 1 diabetes across the lifespan, including clinical depression, anxiety disorder and eating disorder?

There is Level I evidence demonstrating that the prevalence of depression in people with type 1 diabetes is greater in certain subgroups (women and the newly diagnosed), and an increased prevalence of bulimia nervosa in adults and adolescents with type 1 diabetes, compared to the general population. Thus, longitudinal cohort studies, with appropriate controls, are needed to better understand the incidence of and risk factors for psychological morbidity among people with type 1 diabetes.

21.1.3 Blood glucose monitoring

Question 8

Does continuous real-time continuous glucose monitoring versus standard management improve HbA_{1c}, minimise fluctuations of blood glucose and reduce severe hypoglycaemia?

There is insufficient evidence to support routine use of continuous glucose monitoring (CGM) systems to improve glycated haemoglobin (HbA_{1c}) and reduce severe hypoglycaemia, although there is some evidence for a benefit in those with poorly controlled diabetes. In

this era of rapidly evolving technology, future studies should address the benefits of real-time CGM in specific patient populations, such as those with hypoglycaemia unawareness, recurrent severe hypoglycaemia or suspected nocturnal hypoglycaemia. Cost-effectiveness should also be addressed.

21.1.4 Insulin and pharmacological therapies

Question 15

How effective are modern pumps versus multiple daily injections at reducing hypoglycaemia and HbA_{1c} and improving quality of life?

Question 15a

How effective are sensor-augmented insulin-infusion pumps versus multiple daily injections at reducing hypoglycaemia and HbA_{1c}, and improving quality of life?

There is no evidence to support a reduction in severe or nocturnal hypoglycaemia in children or adults. Many of the studies excluded individuals with a history of severe hypoglycaemia. Overall, the rate of severe hypoglycaemia and patients with hypoglycaemia unawareness is low, and the studies were not powered for the outcome of severe hypoglycaemia. Future studies should be powered to address the outcomes of severe and nocturnal hypoglycaemia.

Only one study was identified that examined the effectiveness of sensor-augmented pumps on metabolic outcomes. The study was not powered to address the outcome of severe hypoglycaemia, and quality of life (QoL) was not assessed. Future studies should examine the effects of sensor-augmented pumps on other outcomes relevant to individuals with type 1 diabetes, and whether they are of particular benefit to specific populations (e.g. young children, pregnant women).

Question 17

How effective is metformin plus insulin versus insulin alone at achieving glycaemic control (HbA_{1c} targets), reducing body weight, and reducing insulin requirement?

Level I evidence demonstrates a small but not statistically significant reduction in HbA_{1c} with metformin plus insulin compared to insulin alone; however, there was significant heterogeneity between studies. There have been no rigorous, prospective studies of metformin in type 1 diabetes, in relation to diabetes complications outcomes. Future studies should address the effects of metformin in specific populations (e.g. those with high insulin requirements), and the effect on microvascular and cardiovascular events and mortality in overweight people with type 1 diabetes.

21.1.5 Health care delivery

Question 20

What is the effectiveness of telemedicine and other technology-based delivery?

The systematic review found there is insufficient evidence to determine the effect of telemedicine and other technology-based delivery methods for rural and remote individuals on glycaemic control or time and cost savings. The included studies reported were from international sources and were of limited methodological quality, involving small numbers of participants. Future studies should be relevant to the Australian health care system, relevant to contemporarily available technology and address outcomes for other populations, as well as rural and remote individuals.

21.1.6 Education and psychological support

Question 21

What is the diagnostic performance of the following screening tools: CDI, BASC, EDE, CHQ, BAI, BDI, HADS, EDI, ADS, ATT19?

ADS, Appraisal of Diabetes Scale; ATT19, Diabetes Integration Scale; BAI, Beck Anxiety Inventory; BASC, Behaviour Assessment System for Children; BDI, Beck Depression Inventory; CDI, Children's Depression Inventory; CHQ, Child Health Questionnaire; EDE, Eating Disorders Examination; Eating Disorder Inventory, EDI, HADS, Hospital Anxiety and Depression Scale

The systematic review found few studies that address this question, and the Expert Advisory Group (EAG) concluded that there is insufficient evidence to recommend any specific tool for psychological screening. Future studies should examine the diagnostic performance of screening tools in young people and adults with type 1 diabetes, and the benefits of screening on glycaemic control and psychosocial outcomes.

21.1.7 Complementary and alternative medicines

Question 29 (interventional)

What is the effectiveness of complementary and alternative medicines at achieving metabolic targets?

Only four randomised controlled trials (RCTs) were identified that examined the effectiveness of complementary and alternative medicine (CAM) on metabolic outcomes and diabetes complications were not included as an outcome. Given the wide use of CAM in the community, future versions of this guideline should examine the effects of CAM on complications (e.g. gamma-linolenic acid on neuropathy). Future RCTs should study effectiveness on glycaemic control and diabetes complications, for types of CAM that have demonstrated benefit in short-term studies as potent insulin sensitisers or agonists.

21.1.8 Maternal pregnancy and foetal outcomes

Question 31

What is the effectiveness of preconception care in women with type 1 diabetes on improving maternal and foetal outcomes?

The systematic review found Level III evidence that preconception care is effective at reducing congenital malformations, perinatal mortality and HbA_{1c} levels in women with type 1 diabetes. Future studies should consider other maternal and foetal outcomes (e.g. birth weight, macrosomia, pre-eclampsia or the risk of severe hypoglycaemia).

Question 32

What is the effectiveness of blood glucose control during pregnancy in women with type 1 diabetes in achieving blood glucose targets and improving maternal and foetal outcomes?

There is insufficient evidence to make recommendation about the effectiveness of blood glucose control during pregnancy in achieving outcomes. Future studies need to address the benefit-to-risk ratio of very tight and less tight glycaemic control during pregnancy.

21.1.9 Contraception

Question 36

What is the effectiveness of hormonal versus nonhormonal contraception in type 1 diabetes?

The systematic review did not identify sufficient evidence to assess whether progesterone-only or combined oral contraceptives differ from nonhormonal contraceptives in their effects on glycaemia control, lipid metabolism and long-term diabetes-related complications. Further studies are needed to address these issues and the effects of hormonal contraception on diabetes complications.

21.1.10 Acute effects of hypoglycaemia and hyperglycaemia

Question 39

What are the acute effects of hypoglycaemia and hyperglycaemia on cognitive function?

The systematic review concluded that data are not well-established for the effects of acute hyperglycaemia on cognitive function, and there is much individual variation in threshold for effects and rate of recovery. Future research examining the specific effects of acute hyperglycaemia on cognitive function will inform future guidelines, particular in educational and work settings, and for driving.

Question 41

How can severe hypoglycaemia be prevented?

The systematic review identified Level II and Level IV evidence that specific educational interventions (e.g. blood glucose awareness training [BGAT]) reduce the rate of severe hypoglycaemia. However, the recommendation based on this evidence is most relevant to adults with type 1 diabetes who had previously experienced severe hypoglycaemia. In addition, no formal educational programs such as BGAT for those at high risk of severe hypoglycaemia, have been reported in Australia. Future studies should evaluate strategies for prevention of hypoglycaemia among all individuals with type 1 diabetes across their lifespans.

21.1.11 Sick day management and diabetic ketoacidosis

Question 42

Does ketone monitoring prevent ketoacidosis or hospital admission?

The evidence for the effectiveness of blood ketone monitoring versus urine ketone monitoring for the prevention of diabetic ketoacidosis (DKA) or hospital admission is based on one RCT in children. No studies were found in adults aged over 22 years. The effectiveness of home blood ketone measurement in adults with type 1 diabetes on these outcomes, or ketone measurement in specific populations with type 1 diabetes (e.g. use of continuous subcutaneous insulin infusion [CSII]), could be addressed by future research.

21.1.12 Diabetes complications

Question 46

How effective are antihypertensive agents at reducing or preventing retinopathy, nephropathy, neuropathy and autonomic neuropathy?

The systematic review found evidence that angiotensin converting enzyme inhibitors (ACEI) prevent progression of pre-existing nephropathy; however, evidence of their effect on the onset of nephropathy or retinopathy is lacking, and evidence on prevention of progression of retinopathy or autonomic neuropathy is inconclusive or limited. Future guidelines should address the effectiveness of ACEI for these other outcomes among individuals with type 1 diabetes, including adolescents.

Question 47

What is the effect of statins on lipid levels and cardiovascular outcomes in type 1 diabetes?

Level I and II evidence demonstrates that statins are effective at reducing total and low density lipoprotein (LDL) cholesterol in adults with type 1 diabetes. Future guidelines should include the effectiveness of statins on markers of early cardiovascular disease in adolescents, and help to better define the appropriate age of commencement of statins in people with type 1 diabetes.

Question 53

How and how often should patients with type 1 diabetes be screened for coeliac disease?

The systematic review identified evidence to support routine screening at the time of diagnosis of type 1 diabetes in children and repeated at follow up until the risk declines, although none of the studies were designed to address the optimal frequency of screening. No studies were performed in adults. Future guidelines should address the role and frequency of screening for coeliac disease in adults.

21.2 Topics for future consideration

21.2.1 Screening for type 1 diabetes

Interventions to delay or prevent the onset of type 1 diabetes were addressed by the systematic review for question 1; however, screening for type 1 diabetes was not covered in this guideline. Most people who develop type 1 diabetes do not have a first-degree relative with the disease, and the prevalence of positive islet autoantibodies among such individuals is generally less than 5%; thus, screening is not currently performed outside the research setting. If successful primary or secondary prevention therapies become available in the future, then the role of screening would be relevant to future clinical care guidelines for type 1 diabetes.

21.2.2 Experimental therapies aimed at curing type 1 diabetes

The guidelines did not address experimental therapies for type 1 diabetes, such as islet cell transplant, which are currently only used in a research setting. As this field evolves, and if stem cell therapy becomes a therapeutic option, such treatment may become established in regular clinical care.

21.2.3 Maternal pregnancy and fetal outcomes

The guidelines did not address every aspect of clinical care in pregnancy in type 1 diabetes. Future guidelines should examine the evidence for care (e.g. use of CSII) and monitoring (e.g. CGM) of the mother and foetus, optimal frequency for complications screening during pregnancy, management of delivery and its timing, and postpartum management of the mother and infant.

21.2.4 Transition care

Transition care was not addressed in the guidelines due to the publication of best practice guidelines for transition (Lang 2008). However, further guidelines should address the optimal timing for transition of young people to adult care and models to improve uptake and continuity of care following transition.

21.2.5 Hypoglycaemia unawareness

As people with hypoglycaemia unawareness are at high risk of recurrent severe hypoglycaemia, research into the mechanism of its development, methods to efficiently screen for its presence in the clinic, and approaches to minimising its impact should be addressed in future studies and guidelines.

21.2.6 Complications

The optimal frequency of complications screening was not addressed by a systematic review. Future research that examines tailoring of screening based on risk profiling (e.g. genetic or metabolic) would inform current guidelines, which are predominantly evidence based.

Systematic review of technologies to better define microvascular complication risk and preclinical markers may enable recommendations for complications screening to be individualised.

Medications that demonstrate benefit in complications in type 2 diabetes such as fenofibrate and metformin, should be clinically trialled in people with type 1 diabetes, for effects on diabetes microvascular and macrovascular outcomes.

There are no evidence-based recommendations for screening for macrovascular disease in people with type 1 diabetes; as this is an evolving area of research, future guidelines should address the optimal methods and frequency of screening.

There are no predictive tools based on risk-factor profiles for cardiovascular outcomes in type 1 diabetes. Such tools would be desirable to help identify individuals at highest risk and should include diabetes, renal status, age, blood pressure and lipid status.

21.2.7 Foot care

The foot guidelines (Baker IDI Heart and Diabetes Institute et al 2010) identified a number of areas for future research about foot care in people with diabetes. Of these, most are relevant to individuals with type 1 diabetes, in particular:

- drugs for the improvement of microvascular blood flow
- the effect of herbal or nutritional supplements on ulcer healing or amputation
- thermal wound therapy in addition to standard wound care
- educational programs for the prevention of ulcer recurrence and amputation.

22 Implementing, evaluating and maintaining the guidelines

22.1 Guidelines dissemination

The Expert Advisory Group (EAG), together with the Australian Diabetes Society (ADS) and the Australasian Paediatric Endocrine Group (APEG), developed an initial strategy to guide appropriate communication on the implementation of this guideline. The strategy identifies target audiences for the guidelines, plans and tools for effective implementation, communication channels and key messages. These are the first national, evidence-based guidelines to address the needs of individuals with type 1 diabetes across the lifespan. Thus, it will be important to engage societies of related disciplines (e.g. Australian Diabetes Educators Association, Australian Diabetes In Pregnancy Society, Dietitians Association of Australia, Royal Australian College of General Practitioners and Royal Australian College of Physicians) and consumer groups (e.g. Australian Diabetes Council, Diabetes Australia, Juvenile Diabetes Research Foundation and Type 1 Diabetes Network). These organisations will be asked to endorse the guidelines and to provide a link to the document from their websites.

The public consultation process will help in formulating the plan for dissemination of the guidelines. The feedback proforma provided in the public consultation includes a request for comment on dissemination of the guidelines (including suggested methods, other organisations to target in dissemination and key topics for dissemination).

Following public consultation, the implementation and dissemination plan for the guidelines will be as set out below.

- Confirm which recommendations should have priority for implementation (questions that have been systematically reviewed and led to evidence-based recommendations will take priority over background questions).
- Address any recommendations that will affect or deviate from current clinical practice. Overall, the evidence-based recommendations in the draft guidelines would not lead to significant changes in clinical care (including new technologies). However, the recommendations and practice points given in the draft guidelines are likely to enhance aspects of care in areas such as psychological care of children and youth, metformin in type 1 diabetes, indications for statin therapy and blood glucose awareness training for those at high risk of severe hypoglycaemia.
- Address where there are resource implications with the new recommendations and cost-effectiveness data, and indicate where a change in service delivery will be required as a result of a recommendation. Economic issues were considered when formulating the evidence-based recommendations, and they are unlikely to have major cost implications. Thus, cost is not expected to be a barrier to implementation of the recommendations.
- Determine the methods of dissemination, including through the health professional organisations and type 1 diabetes related consumer organisations noted above.

All of the above will be further canvassed, and a detailed plan for dissemination will be formally confirmed at the EAG meeting after public consultation.

22.2 Guidelines effectiveness assessment

Once the guidelines have been disseminated, continued re-evaluation will be necessary to monitor the impact of the guidelines, reduce variation in practice patterns and optimise effectiveness of clinical care. After public consultation, if funding is provided on the basis of a business case, a plan will be designed to evaluate implementation of the guidelines and to determine:

- the extent to which the guidelines influence changes in clinical practice and health outcomes
- what factors (if any) contribute to noncompliance with the guidelines.

The results of the evaluation will be used to inform future review of the guidelines.

22.3 Guidelines review and updating

The guidelines will be reviewed and amended in 5 years' time, unless an issue arises (e.g. new clinical evidence relevant to practice) that triggers a need to review the document earlier.

APEG and ADS plan to convene a group of experts to undertake the review. In the intervening period, the co-chairs, via the secretariats of APEG and ADS, will be the contacts for major issues, events or practice changes.

To provide feedback and inform future reviews of these guidelines, comments on its content or implementation, or on the accompanying materials, should be sent to:

APEG Secretariat, PO Box 180, Morisset NSW 2264
Email: apeg@willorganise.com.au or Tel: 02 4973 6573

or

ADS Secretariat, 145 Macquarie Street, Sydney NSW 2000
Email: suzie@diabetessociety.com.au Tel: 02 9256 5462

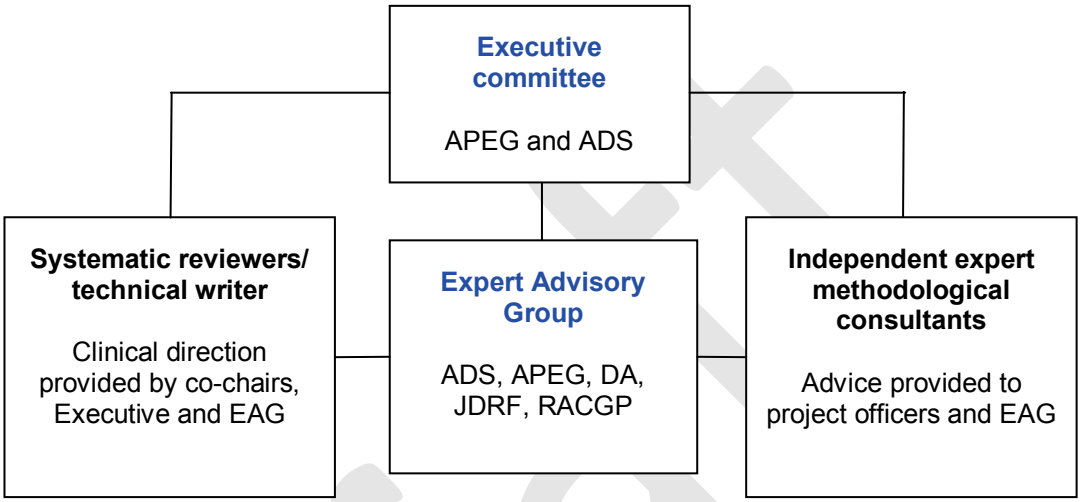
A list of colleges and societies that endorse the guidelines will be available on the APEG and ADS websites.

Appendix A: Governance

A1 Management structure for guideline development

Figure A1 illustrates the management structure for the development of the guidelines.

Figure A1 Management framework for development of the guidelines



ADS, Australian Diabetes Society; APEG, Australian Paediatric Endocrine Group; DA, Diabetes Australia; EAG, Expert Advisory Group; JDRF, Juvenile Diabetes Research Foundation; RACGP, Royal Australian College of General Practitioners

A2 Terms of reference

Executive

The Executive was established to provide coordination and direction for development of the guidelines. It was co-chaired by representatives from the Australian Diabetes Society (ADS) and the Australian Paediatric Endocrine Group (APEG). The role of the Executive was to:

- develop and oversee the project plan for the guidelines, and ensure that the development process meets National Health and Medical Research Council (NHMRC) requirements
- recommend the membership of the Expert Advisory Group (EAG), in consultation with APEG and ADS
- ensure effective communication and consultation with all relevant stakeholders for the duration of the project
- provide regular updates on the project to APEG and ADS councils and the Australian Government Department of Health and Ageing (DoHA)
- review resources that are dedicated to the project, to ensure that they are sufficient for the project to meet its deadlines

- review and approve revisions to the project plan
- address other matters as raised by members of the EAG.

Expert Advisory Group

The EAG was formed to determine the scope and structure of the guidelines, and to determine the focus of the systematic review of the evidence-based literature. The group's terms of reference were to:

- consider the scope of the project and proposed structure of the guidelines, as referred by the Executive and, if necessary, to present to the Executive recommendations for revisions
- formulate the clinical questions to be answered by the literature review, under the guidance of the independent expert methodological consultants
- provide clinical oversight for the development of the content of the guidelines, in particular, ensuring that:
  - the research undertaken is comprehensive
  - the quality of the revised guidelines will meet with clinical approval
- ensure appropriate engagement by consumers at all relevant points
- assist in the development or review of tools and strategies to support the implementation and audit of the guidelines and review their uptake
- facilitate consultation and the uptake of the guidelines
- respond to any additional requirements to ensure compliance with the NHMRC guidelines development processes.

Systematic reviewers and technical writer

Project officers were appointed by APEG and ADS to conduct systematic reviews of the scientific literature, and to produce technical reports for the technical document. A technical writer was appointed to provide medical and technical editing.

Expert methodological consultants

Two guideline method advisors were appointed by the executive to provide advice and mentoring to the project officers and the EAG, and to ensure that the development process and guidelines complied with NHMRC requirements.

Executive and operational support

The EAG secretariat was provided jointly by APEG and ADS. The secretariats provided support in communication, coordination of meetings, minute-taking and other administrative roles.

A3 Membership of bodies involved in governance of the guidelines

Co-chairs

Associate Professor Maria Craig	Australasian Paediatric Endocrine Group
Professor Stephen Twigg	Australian Diabetes Society

Executive

Professor Fergus Cameron	Australasian Paediatric Endocrine Group
Dr N Wah Cheung	Australian Diabetes Society
Dr Jenny Conn	Australian Diabetes Society
Professor Kim Donaghue	Australasian Paediatric Endocrine Group
Associate Professor Alicia Jenkins	Australian Diabetes Society
Professor Martin Silink	Australasian Paediatric Endocrine Group

Expert Advisory Group

Dr Linda Beeney	Psychologist	Independent psychological expert
Professor Stephen Colagiuri	Endocrinologist Medical Advisor	Australian Diabetes Society
Dr Louise Conwell	Paediatric endocrinologist	Australasian Paediatric Endocrine Group
Prof Jenny Couper	Paediatric endocrinologist	Australian Diabetes Society
Ms Nuala Harkin	Nurse practitioner	Australasian Paediatric Endocrine Group, Australian Diabetes Educators Association
Professor Mark Harris	General practitioner	Royal Australian College of General Practitioners
Ms Heather Hart	Credentialed diabetes educator	Australian Diabetes Society, Australian Diabetes Educators Association
Dr Jane Holmes-Walker	Endocrinologist	Australian Diabetes Society
Dr Craig Jefferies	Paediatric endocrinologist	Australasian Paediatric Endocrine Group

Dr Tony Lafferty	Paediatric endocrinologist	Australasian Paediatric Endocrine Group
Ms Eunice Lang	Credentialed diabetes educator	Australasian Paediatric Endocrine Group
Clinical Professor Tim Jones	Paediatric endocrinologist	Australasian Paediatric Endocrine Group
Ms Kate Marsh	Accredited Practising Dietitian	Australian Diabetes Society
Dr Alison Nankervis	Endocrinologist	Australian Diabetes Society, Australian Diabetes in Pregnancy Society
Dr Mark Pascoe	Paediatrician	Australasian Paediatric Endocrine Group
Associate Professor Christine Rodda	Paediatric endocrinologist	Australasian Paediatric Endocrine Group
Dr Tony Russell	Endocrinologist	Australian Diabetes Society
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Conflict of interest

All members of the EAG declared any conflicts of interest before starting work on the guidelines. Conflicts of interest were also reviewed and updated at the commencement of all EAG meetings and at completion of the guidelines. Declarations were made to the Co-chairs of the EAG through the guideline secretariats. Written guidelines for declaring conflicts of interest were provided to the EAG members, who were informed of the responsibility of the individual to identify and disclose any real or potential conflict of interest in relation to their involvement with the NHMRC process with regard to the content of the guidelines or guideline recommendations.

A5 Acknowledgements

The ADS and APEG received funding from DoHA to review and update the guidelines for the care of children and adolescents with type 1 diabetes, and to extend the guidelines to address the needs of adults with type 1 diabetes.

The EAG also wishes to acknowledge editorial assistance provided by Ms Trisha Dunning and Dr Elizabeth Northam, and input during the guideline development process from Ms Kate Gilbert, on behalf of the Type 1 Diabetes Network.

Appendix B: Process report

B1 Development process

Due to a lack of national evidence-based guidelines for management of type 1 diabetes across the lifespan, the Australasian Paediatric Endocrine Group (APEG) and the Australian Diabetes Society (ADS) agreed to review and update the type 1 diabetes guidelines in children and adolescents (APEG 2005) and to extend the guidelines to address the needs of adults with type 1 diabetes, on behalf of the Australian Government Department of Health and Ageing (DoHA). In 2009, an Executive Advisory Group (EAG) was formed to oversee development of the guidelines. Members of the EAG were nominated by APEG and ADS councils to represent APEG, ADS, the Australian Diabetes Educators Association (ADEA), the Australian Diabetes In Pregnancy Society (ADIPS) and the Dietitians Association of Australia (DAA). Representation from the Royal Australian College of General Practitioners (RACGP) and consumer organisations – Diabetes Australia (DA) and the Juvenile Diabetes Research Foundation (JDRF) – were also invited. Further details of the governance framework are provided in Section 1.2 and Appendix A.

B2 Research phase

Relevant clinical research questions were developed, prioritised, combined and refined by the EAG from July 2009 to March 2010, and further refined through consultation among the systematic reviewers and expert methodological consultants. A technical report, which contained the systematic reviews, was developed before the writing of the guidelines.

B3 Methodology

Methods are outlined in Chapter 2, with greater detail given of each systematic review in the accompanying technical report. Briefly, the clinical research questions for systematic review were structured according to PICO ('population, intervention, comparator and outcome' for intervention questions), PPO ('population, predictor and outcome' for prognostic questions) or PRO ('population, risk factor and outcome' for aetiological questions) criteria. Three main strategies were identified potentially relevant literature: electronic database searching, manual searching and literature recommended by expert members of the EAG. The primary databases searched were EMBASE, Medline and the Cochrane Library Database. Additional searches were conducted of Cumulative Index to Nursing and Allied Health Literature and Australasian Medical Index. The electronic searches included articles published between June 1966 and December 2010.

Inclusion criteria were determined from the PICO, PPO or PRO criteria that formed the basis of the systematically reviewed research questions. Non-English publications were excluded. Studies that were eligible for inclusion were evaluated according to National Health and Medical Research Council (NHMRC) levels of evidence hierarchy, dimensions of evidence, and quality assessment criteria (NHMRC 2009). An NHMRC evidence statement form was completed for each systematically reviewed research question (see Appendix C) Where there was sufficient evidence to formulate a recommendation, NHMRC grading criteria were applied to indicate the strength of the body of evidence underpinning the recommendation (NHMRC 2009). Where it was not possible to develop evidence-based recommendations because no evidence was identified, or where additional information was required to supplement recommendations and guide clinical practice, the EAG developed practice points through a consensus-based process.

Material relevant to background questions was gathered by the project officers under the supervision of the EAG members. Sources included medical textbooks, published scientific and review articles, and other relevant medical literature; however, systematic review processes were not applied. The questions researched in this manner are listed in the technical report and noted below each question throughout the guideline.

B4 Public consultation

Public consultation was conducted from Monday 7 February to Friday 11 March 2011, during which time the draft guidelines were available on the APEG and ADS websites. Notification was posted in *The Australian* national newspaper, and the APEG and ADS invited a range of stakeholders, committees, working groups and interested people to provide submissions.

B5 Finalising the guidelines

To be completed after public consultation

Appendix C: Evidence matrixes

C1 Question 1

Question 1 – nicotinamide

Q1	What interventions delay or prevent the onset of type 1 diabetes?	
Evidence statement	There is no evidence to support the use of any intervention to delay or prevent the onset of type 1 diabetes.	
Evidence base	A	Four RCTs, all of good quality.
Consistency	A	Studies consistent in showing no effect.
Clinical impact	NA	Given that nicotinamide is not used routinely to delay or prevent type 1 diabetes, the clinical impact of this intervention is not applicable.
Generalisability	C	The target population was people without type 1 diabetes. The evidence base included only high-risk populations (but with differences in definitions), who represent only 10% of people who develop type 1 diabetes.
Applicability	A	The studies included one from Australia; the remainder were from countries with well-established health-care systems.
Other factors	None identified.	
Details	For full systematic review, see Chapter 1 of the accompanying technical report	

RCT, randomised controlled trial

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 1 – insulin

Q1	What interventions delay or prevent the onset of type 1 diabetes?	
Evidence statement	There is no evidence to support the use of any intervention to delay or prevent the onset of type 1 diabetes.	
Evidence base	A	Five RCTs – three of low risk of bias, one of moderate risk of bias and one of high risk of bias.
Consistency	A	All studies reporting diabetes as an outcome were consistent (excluding the one poor-quality study).
Clinical impact	NA	Given that insulin is not used routinely to delay or prevent type 1 diabetes, the clinical impact of this intervention is not applicable.
Generalisability	C	The target population was people without type 1 diabetes. The evidence base included only high-risk populations (but with differences in definitions), who represent only 10% of people who develop type 1 diabetes.
Applicability	A	The studies included one from Australia; the remainder were from countries with well-established health-care systems.
Other factors	None identified.	
Details	For full systematic review, see Chapter 1 of the accompanying technical report	

RCT, randomised controlled trial

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

C2 Question 2

Q2	Is there an increased prevalence of psychological disorders in people with type 1 diabetes across the life span, including clinical depression, anxiety disorder and eating disorder?	
Evidence statement	Level I evidence shows that the prevalence of depression in people with type 1 diabetes is greater in certain subgroups – women and the newly diagnosed – than in the general population. Level I evidence shows that there is increased prevalence of bulimia nervosa in adults and adolescents with type 1 diabetes compared to the general population. Level II evidence indicates that there are higher referral rates to mental health services in children and young adults with type 1 diabetes, compared with the general population. Level IV evidence shows an increased prevalence of depression and anxiety in young people and adolescents with type 1 diabetes, compared with the general population. Level IV evidence shows that the prevalence of anxiety in adults with type 1 diabetes is high, but similar to that in the general population.	
Evidence base	A	• Eating disorders: Two Level I, one Level II and two Level IV studies, (adolescent and adult). • Depression: One Level I and one Level IV studies (adults); one Level II study (paediatric) (no control group). • Anxiety: One Level I study (adults), two Level IV studies (one paediatrics, one adult). • Psychosocial: One Level IV study (adults), two Level II studies and one Level IV study (paediatrics).
Consistency	B	• Psychosocial: Increased rate of referral to mental health services in paediatrics and adolescents (one Level II study); no differences in psychological adjustment and psychosocial difficulty in one Level II and one Level IV study in paediatrics and adolescents. • Depression: No difference in Level I study, but a significant difference in Level IV study (adults). • Anxiety: Not applicable (adults, one study only); studies uncontrolled (paediatrics). • Eating disorders: Anorexia – no difference in both Level I studies; bulimia – increased in both Level I studies (adults and adolescents); Level IV studies showed increase prevalence of disordered traits in type 1 diabetes, but no difference in diagnosed eating disorders (adolescents).
Clinical impact	C	Adults.
	A	Children and adolescents.
Generalisability	A	Paediatric, adolescent and adult populations were delineated in most studies.
Applicability	B	Studies were from North America and Europe; thus, they were from countries with well-established health-care systems.
Other factors	None identified.	
Details	For full systematic review, see Chapter 2 of the accompanying technical report	

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

C3 Question 3

Q3	What is the impact of type 1 diabetes on cognitive performance?	
Evidence statement	Evidence from Level I and II studies show a longitudinal association between glycaemic control and some aspects of cognitive function. The magnitude of this effect is greatest in children with early onset type 1 diabetes.	
Evidence base	B	Three Level II studies (two of low risk of bias, one of moderate risk of bias), and two Level IV studies, both of high risk of bias.
Consistency	B	Compared with healthy controls, children and adolescents demonstrated marginal effect on several domains and scored marginally lower on IQ, but with no effect on learning and memory. Adults demonstrated a small-to-moderate effect on several cognitive domains, again with no effect on learning and memory. Hypoglycaemia predicts a lower verbal IQ in children (one study), with no other significant effect reported. In relation to metabolic control, a higher HbA_{1c} is associated with a negative impact on cognitive function (reported in two studies including children >9 years, adolescents and adults). One study reported no significant effect on IQ. In early-onset diabetes, a negative association was reported in one prospective study and one meta-analysis.
Clinical impact	A	Children.
	B	Adolescents and adults.
Generalisability	B	Studies included children, adolescents and adults. Exclusions included diabetes complications, history of head trauma and depression. There is no evidence from the older adult or the elderly population (especially with respect to dementia).
Applicability	A	One study was in Australian children, two were from the United States (i.e. a country with a well-established health-care system).
Other factors	The mechanism is not known.	
Details	For full systematic review, see Chapter 3 of the accompanying technical report	

HbA_{1c}, glycated haemoglobin; IQ, intelligence quotient

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

C4 Question 4

This question was not systematically reviewed.

C5 Question 5

This question was not systematically reviewed.

C6 Question 6

This question was not systematically reviewed.

C7 Question 7

This question was not systematically reviewed.

C8 Question 8

Question 8 – HbA_{1c}

Q8	Does continuous real-time monitoring versus standard management improve HbA_{1c}, minimise fluctuations of blood glucose and reduce severe hypoglycaemia?	
Evidence statement	There is insufficient evidence to support routine use of continuous real-time monitoring to improve HbA_{1c} and reduce severe hypoglycaemia.	
Evidence base	A	Level I evidence with a low risk of bias. Systematic review comprised nine RCTs with a low or moderate risk of bias.
Consistency	C	There was significant clinical and methodological heterogeneity across the nine RCTs, but some consistency regarding the magnitude and direction of effect. There was a nonsignificant advantage to real-time monitoring, with the direction fairly consistent across studies. Children – limited evidence (two RCTs). Adolescents – two RCTs. Adults – consistent up to 6 months, but inconsistent beyond that time, possibly due to lack of adherence (six RCTs). All age groups – (five RCTs).
Clinical impact	D	
Generalisability	C	Studies included children and adolescents, or adults, but some had a small sample size.
Applicability	B	The studies included one Australian study.
Other factors	Continuous real-time monitoring is not used routinely in Australia, but is a rapidly developing technology. The clinical role of real-time blood glucose monitoring is expected to increase with time; therefore, the current evidence statement may become outdated.	
Details	For full systematic review, see Chapter 8 of the accompanying technical report	

HbA_{1c}, glycated haemoglobin; RCT, randomised controlled trial

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 8 – hypoglycaemia

Q8	Does continuous real-time monitoring versus standard management improve HbA_{1c}, minimise fluctuations of blood glucose and reduce severe hypoglycaemia?	
Evidence statement	There is insufficient evidence to support routine use of continuous real-time monitoring to improve HbA_{1c} and reduce severe hypoglycaemia.	
Evidence base	A	
Consistency	C	There were no reports of severe hypoglycaemia; there was insufficient evidence on this outcome, because studies lacked power due to low event rates.
Clinical impact	D	
Generalisability	C	
Applicability	B	
Other factors	None identified.	
Details	For full systematic review, see Chapter 8 of the accompanying technical report	

HbA_{1c}, glycated haemoglobin

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

C9 Question 9

Question 9 – HbA_{1c}

Q9	Does continuous glucose monitoring (retrospective systems) versus standard management improve HbA_{1c}, minimise fluctuations of blood glucose and reduce severe hypoglycaemia?	
Evidence statement	There is insufficient evidence to support routine use of continuous retrospective blood glucose monitoring systems to improve HbA_{1c} and reduce severe hypoglycaemia.	
Evidence base	A	Level I evidence with a low risk of bias, comprising seven RCTs: three with a low risk of bias and four with a moderate risk of bias.
Consistency	C	There was a nonsignificant reduction in this outcome. A sensitivity analysis of the high-quality studies reduced the magnitude of the effect. A subgroup analysis of the paediatric group found a significant effect, but results in adults were conflicting.
Clinical impact	D	The magnitude of change in the meta-analysis was –0.4%.
Generalisability	B	
Applicability	B	The studies included one Australian study in children.
Other factors	None identified.	
Details	For full systematic review, see Chapter 9 of the accompanying technical report	

HbA_{1c}, glycated haemoglobin; RCT, randomised controlled trial

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 9 – hypoglycaemia

Q9	Does continuous real-time monitoring versus standard management improve HbA_{1c}, minimise fluctuations of blood glucose and reduce severe hypoglycaemia?	
Evidence statement	There is insufficient evidence to support routine use of continuous retrospective blood glucose monitoring systems to improve HbA_{1c} and reduce severe hypoglycaemia.	
Evidence base	A	
Consistency	C	There were no reports of severe hypoglycaemia; there was insufficient evidence on this outcome, because studies lacked power due to low event rates.
Clinical impact	D	
Generalisability	B	
Applicability	B	
Other factors	None identified.	
Details	For full systematic review, see Chapter 9 of the accompanying technical report	

HbA_{1c}, glycated haemoglobin

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

C10 Question 10

This question was not systematically reviewed.

C11 Question 11

This question was not systematically reviewed.

C12 Question 12

Question 12 – HbA_{1c}

Q12	How effective are insulin analogues versus human insulin at reducing HbA_{1c}?	
Evidence statement	Compared with human insulin, insulin analogues have no effect on overall hypoglycemia, but lead to a slight reduction in severe and nocturnal hypoglycemia in adults. Compared with human insulin, insulin detemir shows a small but significant benefit with respect to nocturnal and overall hypoglycemia in children and adolescents.	
Evidence base	C	One good-quality systematic review (Level I evidence) was selected from 15 identified systematic reviews. The selected study was based on Level II evidence (17 RCTs) that was of poor quality (i.e. lack of double blinding and of ITT reporting). In addition, 3 RCTs (Level II) were included, all of which were of fair quality.
Consistency	B	The RCTs included in the Level I study were mostly consistent, as were findings across all the Level I studies identified.
Clinical impact	D	The reduction in HbA_{1c} was *statistically* significant, but was below the level commonly accepted as *clinically* significant (0.5% change in HbA_{1c}). Impact on patient satisfaction (which is considered to be a key benefit of analogues) was not captured by the Level I study selected.
Generalisability	B	Patients characteristics were HbA_{1c} 6–11% at baseline, with some exclusions of HbA_{1c} below 10% or 11%. Many studies excluded patients for severe hypoglycaemia.
Applicability	A	Studies included populations form Australia, Europe, South Africa and the United States and were thus from countries with well-established health-care systems.
Other factors	None identified.	
Details	For full systematic review, see Chapter 12 of the accompanying technical report	

HbA_{ic}, glycated haemoglobin; ITT, intention to treat; RCT, randomised controlled trial

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 12 – hypoglycaemia

Q12	How effective are insulin analogues versus human insulin at reducing hypoglycaemia?	
Evidence statement	Compared with human insulin, insulin analogues have no effect on overall hypoglycemia, but lead to a slight reduction in severe and nocturnal hypoglycemia in adults. Compared with human insulin, insulin detemir shows a small but significant benefit with respect to nocturnal and overall hypoglycemia in children and adolescents.	
Evidence base	C	One good quality systematic review (Level I evidence) was identified, but the study was based on poor-quality Level II evidence (i.e. lack of double blinding and lack of ITT reporting).
Consistency	C	The definitions of hypoglycaemia used in individual trials were not consistent. There was also variation in the units of measurement between trials. This resulted in high heterogeneity and it was thus not possible to make summary estimates for specific subgroups.
Clinical impact	D	The clinical impact of hypoglycaemia is significant. However, evidence on the clinical impact was lacking, apart from in one subtype of hypoglycemia. Impact on patient satisfaction (which is considered to be a key benefit of analogues) was not captured by the Level I study selected.
Generalisability	B	Patient characteristics: HbA_{1c} 6–11% at baseline, with some exclusions of HbA_{1c} <10 or <11. Many studies excluded patients for severe hypoglycaemia.
Applicability	A	Studies included populations from Australia, Europe, South Africa and the United States.
Other factors	Impact of hypoglycaemia (and the associated disutility) not fully captured in the studies. Evidence base is missing the patient perspective.	
Details	For full systematic review, see Chapter 12 of the accompanying technical report	

HbA_{ic}, glycated haemoglobin; ITT, intention to treat

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

C13 Question 13

Question13 – HbA_{1c}

Q13	What is the relative effectiveness of insulin analogues on HbA_{1c}?	
Evidence statement	Level II evidence is consistent in showing no significant difference between insulin analogues in relation to their effect on HbA_{1c}.	
Evidence base	C	One good-quality systematic review was identified that included two RCTs (Level II evidence) of fair and poor quality; three RCTs (Level II) of fair quality were also identified.
Consistency	A	Different agents were compared; thus, the results could not be pooled.
Clinical impact	D	The studies did not capture patient satisfaction or preference.
Generalisability	B	The population was aged 20–40 years, HbA_{1c} was 7–8% at baseline, and severe hypoglycaemia was an exclusion criterion in most studies.
Applicability	A	No Australian studies or sites were included in the studies, but the results are considered applicable to the Australian health-care context.
Other factors	Based on a literature review of economic evaluations of analogues, the EAG concluded that analogues are unlikely to be cost effective at the published prices in Australia. However, the true cost effectiveness has probably not been captured, because none of the published economic analyses captured the patient perspective.	
Details	For full systematic review, see Chapter 13 of the accompanying technical report	

EAG, Expert Advisory Group; HbA_{1c}, glycated haemoglobin; RCT, randomised controlled trial

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question13 – hypoglycaemia

Q13	What is the relative effectiveness of insulin analogues at reducing hypoglycaemia?	
Evidence statement	Level II evidence is consistent in showing no significant difference between insulin analogues in relation to their effect on HbA_{1c}.	
Evidence base	C	One good-quality systematic review was identified that included two RCTs (Level II evidence) of fair and poor quality; three RCTs (Level II) of fair quality were also identified.
Consistency	C	One Level II study showed a significant difference in hypoglycemia rate between insulin analogues; the remaining four studies did not show a significant different. The agents compared were different in all but two studies; thus, consistency was limited across the body of evidence.
Clinical impact	D	The studies did not capture patient satisfaction or preference.
Generalisability	B	Population was aged 20–40 years; HbA_{1c} was 7–8% at baseline; severe hypoglycaemia was an exclusion criterion in most studies.
Applicability	A	No Australian studies or sites were included in the studies, but the results are considered applicable to the Australian health-care context.
Other factors	Based on a literature review of economic evaluations of analogues, the EAG concluded that analogues are unlikely to be cost effective at the published prices in Australia. However, the true cost effectiveness has probably not been captured, because none of the published economic analyses captured the patient perspective.	
Details	For full systematic review, see Chapter 13 of the accompanying technical report	

EAG, Expert Advisory Group; HbA_{1c}, glycated haemoglobin; RCT, randomised controlled trial

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

C14 Question 14

This question was not systematically reviewed.

C15 Question 15

Question 15 – HbA_{1c}

Q15	How effective are modern CSII versus MDI at reducing HbA_{1c}?	
Evidence statement	Across all individuals with type 1 diabetes, Level II evidence shows that CSII has a minor benefit for HbA_{1c} levels compared to MDI. Level I evidence demonstrates a small but statistically significant reduction in HbA_{1c} with CSII compared to MDI.	
Evidence base	C	One good-quality systematic review (Level I) was identified, but the study was based on Level II studies with a moderate to high risk of bias. Also, the systematic review included evidence with pumps that are now obsolete. The systematic review undertaken for these guidelines was updated and was limited to modern pumps; however, many of the included studies had a moderate risk of bias.
Consistency	B	The included studies were fairly consistent in relation to changes in HbA_{1c}, showing a statistical difference in favour of CSII.
Clinical impact	D	The accuracy of HbA_{1c} measurement is 0.2%; hence, the magnitude of the observed changes in adults was within the bounds of measurement error, but this was not the case for children and adolescents younger than 18 years.
Generalisability	B	The meta-analysis conducted for the current systematic review included 697 patients. However, the individual studies were small, and the total sample for children younger than 5 years was very small. Exclusions included severe hypoglycaemia, hypoglycaemia unawareness and complications of diabetes.
Applicability	B	No studies were conducted in Australia. However, all studies were undertaken in countries with an established health-care system.
Other factors	A systematic search of the literature for published economic evaluations of insulin pumps found that pumps are typically only cost effective when the magnitude of change in HbA_{1c} is at least 0.51%. This sensitivity analysis is modelled on reductions in consequent diabetes complications over a lifetime horizon. A second cost-effectiveness analysis was based on the incremental costs per severe hypoglycaemia attack avoided over 6 years.	
Details	For full systematic review, see Chapter 15 of the accompanying technical report	

CSII, continuous subcutaneous infusion pumps; HbA_{1c}, glycated haemoglobin; MDI, multiple daily injections

Notes: MDI is defined as three injections per day for adults, and three or more injections per day for children and adolescents; modern pumps are defined as those that are available in Australia or overseas and are not obsolete.

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 15 – hypoglycaemia

Q15	How effective are modern CSII versus MDI at reducing hypoglycaemia?	
Evidence statement	There is no evidence to support a reduction in hypoglycaemia in adults. There is Level I evidence of a slight, but statistically significant increase in mild hypoglycaemia in children using CSII. There is no statistically significant evidence to support a reduction in severe and nocturnal hypoglycaemia in adults and children.	
Evidence base	C	One good-quality systematic review (Level I) was identified, but the study was based on Level II studies with a moderate to high risk of bias. Also, the systematic review included evidence with pumps that are now obsolete. The systematic review undertaken for these guidelines was updated and was limited to modern pumps; however, many of the included studies had a moderate risk of bias.
Consistency	C	Definitions of hypoglycaemia varied between studies, making comparisons difficult. In one systematic review, an evaluation of individual studies indicated no difference in nonsevere hypoglycaemia between groups, and a tendency towards less severe hypoglycaemia in the CSII group. In two other reviews, a meta-analysis of studies showed no difference between groups in relation to severe hypoglycaemia. In one systematic review, a meta-analysis of studies showed significantly more episodes of hypoglycaemia in children treated with CSII.
Clinical impact	D	The clinical impact is unclear.
Generalisability	B	The meta-analysis conducted for the current systematic review included 697 patients. However, the individual studies were small, and the total sample for children younger than 5 years was very small. Some of the studies included in this systematic review had hypoglycaemia unawareness and one or more recent severe hypoglycaemia episodes as exclusion criteria.
Applicability	B	No studies were conducted in Australia. However, all studies were undertaken in countries with an established health-care system.
Other factors	A systematic search of the literature for published economic evaluations of insulin pumps found that pumps are typically only cost effective when the magnitude of change in HbA_{1c} is at least 0.51%. This sensitivity analysis is modelled on reductions in consequent diabetes complications over a lifetime horizon. A second cost-effectiveness analysis was based on the incremental costs per severe hypoglycaemia attack avoided over 6 years.	
Details	For full systematic review, see Chapter 15 of the accompanying technical report	

CSII, continuous subcutaneous infusion pumps; HbA_{1c}, glycated haemoglobin; MDI, multiple daily injections

Notes: MDI is defined as three injections per day for adults, and three or more injections per day for children and adolescents; modern pumps are defined as those that are available in Australia or overseas and are not obsolete.

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 15 – quality of life

Q15	How effective are modern CSII versus MDI at improving QoL?	
Evidence statement	Level II evidence shows an improvement in QoL with CSII compared to MDI. Level II evidence consistently shows improved treatment satisfaction with CSII compared to MDI.	
Evidence base	C	One good-quality systematic review (Level I) was identified, but the study was based on Level II studies with a moderate to high risk of bias. Also, the systematic review included evidence with pumps that are now obsolete. The systematic review undertaken for these guidelines was updated and was limited to modern pumps; however, many of the included studies had a moderate risk of bias. QoL was poorly reported, and was measured using a variety of instruments. Results were not pooled.
Consistency	D	The results of the Level II studies were inconsistent in relation to QoL: • 7 studies (n=425) found statistical difference in favour of CSII • four studies (n=85) found no statistical differences between MDI and CSII. The results of the Level II studies were consistent where: • PedsQL was used • treatment satisfaction was measured.
Clinical impact	D	The clinical impact is unclear.
Generalisability	B	The meta-analysis conducted for the current systematic review included 697 patients. However, the individual studies were small, and the total sample for children younger than 5 years was very small.
Applicability	B	No studies were conducted in Australia. However, all studies were undertaken in countries with an established health-care system.
Other factors	A systematic search of the literature for published economic evaluations of insulin pumps found that pumps are typically only cost effective when the magnitude of change in HbA_{1c} is at least 0.51%. This sensitivity analysis is modelled on reductions in consequent diabetes complications over a lifetime horizon. A second cost-effectiveness analysis was based on the incremental costs per severe hypoglycaemia attack avoided over 6 years.	
Details	For full systematic review, see Chapter 15 of the accompanying technical report	

CSII, continuous subcutaneous infusion pumps; HbA_{1c}, glycated haemoglobin; MDI, multiple daily injections; PedsQL, Pediatric Quality of Life Inventory; QoL, quality of life

Notes: MDI is defined as three injections per day for adults, and three or more injections per day for children; modern pumps are defined as those that are available in Australia or overseas and are not obsolete; QoL is defined as DQoL, SF–36 or others.

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

C16 Question 16

This question was not systematically reviewed.

C17 Question 17

Question 17 – HbA_{1c}

Q17	How effective is metformin plus insulin versus insulin alone at achieving HbA_{1c} targets?	
Evidence statement	Level I evidence demonstrates a small but not statistically significant reduction in HbA_{1c} with metformin plus insulin compared to insulin alone.	
Evidence base	C	One systematic review was identified that included nine RCTs (with a meta-analysis of five of the RCTs). Change in HbA_{1c} was an outcome reported in the meta-analysis.
Consistency	B	Most studies reporting this outcome were consistent. The authors of the systematic review conducted a sensitivity analysis of the four smaller RCTs, excluding the largest RCT because of issues of heterogeneity. The outcome was confirmed in both analyses.
Clinical impact	D	Benefit is small and therefore will have a restricted impact on clinical management. In addition, due to the small sample size, safety could not be adequately addressed.
Generalisability	B	Adults.
	C	Children and adolescents (the evidence base is limited by age and weight, and there is no evidence in children under 16 years of age).
Applicability	B	There were no studies from Australia; however, all the studies were undertaken in countries with an established health-care system.
Other factors	Metformin is not TGA-approved for use in type 1 diabetes, so any current use is off label. There are likely to be issues with compliance, and with safety (especially lactic acidosis). There are no publications on cost effectiveness of metforminin type 1 diabetes, but metformin is a low-cost drug.	
Details	For full systematic review, see Chapter 17 of the accompanying technical report	

HbA_{1c}, glycated haemoglobin; RCT, randomised controlled trial; TGA, Therapeutic Goods Administration

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 17 – body-mass index

Q17	How effective is metformin plus insulin versus insulin alone at reducing BMI or weight?	
Evidence statement	Level II evidence shows no consistent effect of metformin plus insulin versus insulin alone on reduction in BMI or body weight.	
Evidence base	C	One systematic review was identified that included nine RCTs with a moderate risk of bias; six of these RCTs reported changes in BMI or body weight.
Consistency	D	Metformin plus insulin versus insulin alone was associated with weight loss of 1.7–6.0 kg (mean of 1.74 kg in longest duration study), but three studies found no difference in weight. There were insufficient data on weight for the authors to conduct a formal meta-analysis of this outcome.
Clinical impact	D	Benefit is small and therefore will have a restricted impact on clinical management. In addition, due to the small sample size, safety could not be adequately addressed.
Generalisability	B	Adults.
	C	Children and adolescents (the evidence base is limited by age and weight, and there is no evidence in children under 16 years of age).
Applicability	B	There were no studies from Australia; however, all the studies were undertaken in countries with an established health-care system.
Other factors	Metformin is not TGA-approved for use in type 1 diabetes, so any current use is off-label. There are likely to be issues with compliance, and with safety (especially lactic acidosis). There are no publications on economic populations in type 1 diabetes, but metformin is a low-cost drug.	
Details	For full systematic review, see Chapter 17 of the accompanying technical report	

BMI, body-mass index; RCT, randomised controlled trial; TGA, Therapeutic Goods Administration

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 17 – insulin requirements

Q17	How effective is metformin plus insulin versus insulin alone at reducing insulin requirements?	
Evidence statement	Level I evidence demonstrates a small but statistically significant reduction in insulin requirement with metformin plus insulin compared to insulin alone.	
Evidence base	C	One systematic review that included nine RCTs (with a meta-analysis of five of the RCTs). Insulin dose was an outcome reported in the meta-analysis.
Consistency	A	All five studies reporting this outcome were consistent; overall, they showed a mean reduced insulin requirement of 6.6 U/day. The authors of the systematic review conducted a sensitivity analysis of the four smaller RCTs, excluding the largest RCT because of issues of heterogeneity. The outcome was confirmed in both analyses.
Clinical impact	D	Benefit is small and therefore will have a restricted impact on clinical management. In addition, due to the small sample size, safety could not be adequately addressed.
Generalisability	B	Adults.
	C	Children and adolescents (the evidence base is limited by age and weight, and there is no evidence in children younger than 16 years).
Applicability	B	There were no studies from Australia; however, all the studies were undertaken in countries with an established health-care system.
Other factors	Metformin is not TGA-approved for use in type 1 diabetes, so any current use is off label. There are likely to be issues with compliance, and with safety (especially lactic acidosis). There are no publications on economic populations in type 1 diabetes, but metformin is a low-cost drug.	
Details	For full systematic review, see Chapter 17 of the accompanying technical report	

RCT, randomised controlled trial; TGA, Therapeutic Goods Administration

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

C18 Question 18

This question was not systematically reviewed.

C19 Question 19

Q19	What is the effectiveness of ambulatory care versus hospital inpatient care of patients with newly diagnosed disease?	
Evidence statement	Ambulatory care, delivered by a multidisciplinary team in a tertiary referral diabetes service, at diagnosis of type 1 diabetes in children over 2 years of age: results in a lower HbA_{1c} (0.7%) at 3 years follow-up compared to in-hospital care at diagnosis does not increase the risk of severe hypoglycaemia or diabetic ketoacidosis, or result in poorer levels of diabetes knowledge at 2 years follow-up compared to in-hospital care at diagnosis.	
Evidence base	A	One Level II study (of low risk of bias) in children older than 2 years. One Level IV study (of high risk of bias) in children. One Level IV systematic review of low level of bias (included five studies in addition to the Level II study above – four of high risk of bias, one of medium risk of bias).
Consistency	B	• HbA_{1c} – one Level II study demonstrated 0.7% difference between groups in favour of home care. All other studies found no significant difference. • Severe hypoglycaemia – no significant difference (consistent). • Diabetic ketoacidosis – no significant difference (consistent). • Patient knowledge – no significant difference (consistent).
Clinical impact	B	Ambulatory care is as effective as inpatient care in terms of glycaemic targets, rates of severe hypoglycaemia and diabetic ketoacidosis, and diabetes knowledge.
Generalisability	C	No adults in evidence base, no children younger than 2 years
Applicability	C	Setting – One study was conducted in Australia, and the others in countries with an established health-care system. Evidence was from tertiary centres only, and may not be applicable to rural and remote settings.
Other factors	From Dougherty et al (1999): Parents in the home-based group spent significantly fewer hours on diabetes care and incurred significantly lower out-of-pocket expenses during the first month. Health-care sector costs were significantly higher. Hospital costs were $889 higher, and government costs $890 higher per child. Social (total) costs were only $48 higher per case (nonsignificant) with home care, when parents' time was valued at $11.88 per hour. Implementation issues: infrastructure, demographically appropriate.	
Details	For full systematic review, see Chapter 19 of the accompanying technical report	

HbA_{1c}, glycated haemoglobin

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

C20 Question 20

Q20	What is the effectiveness of telemedicine and other technology-based delivery methods for rural and remote individuals?	
Evidence statement	There is insufficient evidence to determine the effect of telemedicine and other technology-based delivery methods for rural and remote individuals on glycaemic control or time and cost savings.	
Evidence base	D	Four studies: two Level II studies, one Level III study and one Level IV study; all with high risk of bias, in which telemedicine replaced standard care.
Consistency	C	One RCT found a significant reduction; three showed no effect.
Clinical impact	C	If compared to tertiary outreach.
Generalisability	B	Three in adults, one in children.
Applicability	C	In the study by Biermann et al (2000), the definition of remote was only 50 minutes to clinic. Most studies were either old or out of date.
Other factors	None identified.	
Details	For full systematic review, see Chapter 20 of the accompanying technical report	

RCT, randomised controlled trial

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

C21 Question 21

Q21	Psychological screening tools	
Evidence statement	There is one Level II and one Level III study demonstrating the diagnostic accuracy of the BDI in a mixed population of type 1 and type 2 diabetes. There is one Level II study examining the diagnostic accuracy of the CHQ administered to the parents of children with type 1 diabetes. No evidence was identified for the performance of other psychological screening tools in type 1 diabetes.	
Evidence base	C	Two Level II studies (diagnostic accuracy) of fair quality and one Level III-II study (diagnostic accuracy) of fair quality.
Consistency	B	Studies were broadly consistent, with difference related to instruments.
Clinical impact	C	
Generalisability	B	One study in children with type 1 diabetes and two studies in adults (both with type 1 and type 2 diabetes).
Applicability	A	One Australian study (in children). The adult studies were in Germany and the United States.
Other factors	None identified.	
Details	For full systematic review, see Chapter 21 of the accompanying technical report	

CHQ, Child Health Questionnaire

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

C22 Question 22

Question 22 – children and adolescents: metabolic outcomes

Q22	**What is the effectiveness of education and/or psychological support programs in type 1 diabetes?**	
Evidence statement	There is some evidence from Level I and II studies for a beneficial effect of psychological support programs and education on glycaemic control in children and adolescents. There is insufficient evidence to identify a particular intervention that is more effective than standard care to improve glycaemic control.	
Evidence base	C	Two Level I studies with a low risk of bias. HbA_{1c} – Level II studies – 25 with a high risk of bias, 5 with a moderate risk of bias and 3 with a low risk of bias. Severe hypoglycaemia – Level II studies – 3 with a high risk of bias and 3 with a low risk of bias. Diabetic ketacidosis – Level II studies – 2 with a moderate risk of bias.
Consistency	D	HbA_{1c} (meta-analysis – 0.5% difference in HbA_{1c} – significant heterogeneity) – findings inconsistent. Severe hypoglycaemia and diabetic ketacidosis – findings inconsistent.
Clinical impact	C	
Generalisability	B	Exclusions were not reported.
Applicability	A	One study was conducted in Australia, the others in countries with a well-established health-care system.
Other factors	None identified.	
Details	For full systematic review, see Chapter 22 of the accompanying technical report	

HbA_{1c}, glycated haemoglobin

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 22 – children: psychological outcomes

Q22	What is the effectiveness of education and/or psychological support programs in type 1 diabetes?	
Evidence statement	There is Level I and II evidence that educational or psychological interventions improve some psychological outcomes, including psychological distress and self-management behaviours in young people with type 1 diabetes.	
Evidence base	A	Two Level I studies of low risk of bias (most studies of low or moderate risk of bias) and three Level II studies (one of moderate risk of bias and two of low risk of bias).
Consistency	D	(Couch et al 2008) Knowledge – inconsistent (5/11 significant difference). Self-management behaviour – inconsistent (6/15 significant effect, 4/15 positive effect not significant, 5/15 not significant). Psychosocial – inconsistent (7/15 significant effect). QoL – inconsistent (1/2 positive effect). (Winkley et al 2006) Psychological interventions – significant effect on psychological distress. Level II studies. QoL – significant improvement in one study, no effect in two studies.
Clinical impact	D	The findings are unlikely to alter current clinical practice.
Generalisability	B	Exclusions were not reported.
Applicability	A	One study was conducted in Australia, the others in countries with a well-established health-care system.
Other factors	None identified.	
Details	For full systematic review, see Chapter 22 of the accompanying technical report	

QoL, quality of life

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 22 – adults: education and psychological interventions on metabolic outcomes

Q22	What is the effectiveness of education and/or psychological support programs in type 1 diabetes?	
Evidence statement	The evidence base shows that the intensified education programs delivered in Reichard et al (1996) and the DAFNE Study Group (2002) are associated with reductions in HbA_{1c} compared with usual care. However, the intensified education programs delivered in the BITES program and by Terent et al (1985) were not associated with reductions in HbA_{1c} compared with usual care.	
Evidence base	B	One Level I study with a low risk of bias (including two Level II studies with a high risk of bias), and two Level II studies with a low risk of bias.
Consistency	B	• HbA_{1c}–Results from the Level I study were inconsistent. In the larger study with a long intervention involving phone calls, etc, and a long follow-up, the intervention had a significant effect in combination with intensification of therapy. In the smaller study that was of poor quality and involved a relatively brief intervention, there was no effect. The Level II studies found a significant effect in one study but not in the other. • Severe hypoglycaemia was not reported (NA). • Diabetic ketacidosis was reported in one study, which showed no effect (NA).
Clinical impact	B/C	HbA_{1c} – B Psychological outcomes – C
Generalisability	B	Reported exclusions included pregnancy, non-English speaking, mental illness and diabetes complications.
Applicability	A	The studies were in countries with an established health-care system.
Other factors	The heterogeneity of interventions contributed to differences in findings. The focus here is on the incremental benefit associated with intensified education compared to standard education. However, issues around how to define standard education may affect interpretation. It is taken as given that education is an effective and critical component of care.	
Details	For full systematic review, see Chapter 22 of the accompanying technical report	

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 22 – adults: psychological outcomes

Q22	What is the effectiveness of education and/or psychological support programs in type 1 diabetes?	
Evidence statement	There is Level II evidence that educational and psychological interventions improve some psychological outcomes (including psychological wellbeing, diabetes-related distress, self-care behaviours, distress, anxiety and depression) in adults.	
Evidence base	B	One Level I study with a low risk of bias (most included studies were of moderate and high risk of bias) and three Level II studies (two with a low risk of bias and one of moderate risk of bias).
Consistency	C	• Educational interventions and psychological outcomes – both Level II studies reported a significant effect in terms of dietary freedom, quality of life, diabetes empowerment and treatment satisfaction (B). • Psychological outcomes – the meta-analysis found no significant effect on psychological distress; of the Level II studies, one found a significant effect on wellbeing, diabetes-related distress, self-care behaviours, distress, anxiety and depression; the other two studies found no significant effect on psychological outcomes.
Clinical impact	D	The findings are unlikely alter current clinical practice.
Generalisability	B	Reported exclusions included pregnancy, non-English speaking, mental illness and diabetes complications.
Applicability	A	The studies were conducted in countries with an established health-care system.
Other factors	None identified.	
Details	For full systematic review, see Chapter 22 of the accompanying technical report	

HbA_{1c}, glycated haemoglobin

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

C23 Question 23

This question was not systematically reviewed.

C24 Question 24

Q24	What is the efficacy and safety of following a meal plan with a fixed carbohydrate intake versus a liberalised intake of dietary carbohydrate and/or matching insulin to estimated carbohydrate in type 1 diabetes?	
Evidence statement	Level II evidence (from three studies) shows that the use of insulin-to-carbohydrate ratios in multiple daily injection therapy reduces HbA_{1c} but has no clinically significant effect on weight, QoL or severe hypoglycaemia.	
Evidence base	C	Three Level II studies – one with a low risk of bias and two with a high risk of bias.
Consistency	C	HbA_{1c} – two studies were positive; 1% with the DAFNE Study Group (2002), 0.4% with Scavone et al (2010) (one study of high quality), and one study was negative (small sample size and high risk of bias).
	A	BMI/weight – no change in this outcome in two studies.
	D	QoL – reported in two studies, one showing a positive change and the other study (small sample size and high bias) showing no significant change.
	NA	Severe hypoglycaemic episodes – reported in one study.
Clinical impact	C	$HbA_{1c.}$
	D	BMI/weight.
	C	QoL.
	D	Severe hypoglycaemic episodes.
Generalisability	C	Studies included adults only, and excluded people with non-English speaking, psychiatric illness, pregnancy, complications and hypoglycaemia unawareness. The studies did not include children or the elderly, and may have included dietary naive subjects.
Applicability	B	Studies were conducted in Canada, Italy and the United Kingdom.
Other factors	None identified.	
Details	For full systematic review, see Chapter 24 of the accompanying technical report	

BMI, body mass index; HbA_{1c}, glycated haemoglobin; QoL, quality of life; RCT, randomised controlled trial

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

C25 Question 25

Q25	What is the efficacy and safety of low glycaemic index/high-fibre diets in type 1 diabetes?	
Evidence statement	Level I evidence shows that a low GI diet has a beneficial effect on glycaemic control in adults and children. There is insufficient evidence to determine the effect of low-GI diets on body mass index, weight, severe hypoglycaemia or QoL in children, adolescents or adults with type 1 diabetes.	
Evidence base	A	One Level I study with a low risk of bias, comprising four Level II studies – one with a low risk of bias, one with a moderate risk of bias, and two with a high risk of bias. The rating is based on the Level I study, not the individual studies within it.
Consistency	A	HbA_{1c} – only reported in two studies, which together showed a pooled improvement of 0.5%.
	N/A	BMI – not reported in the systematic review.
	N/A	Weight – not reported in the systematic review.
	N/A	QoL – none of the studies used a validated tool.
	N/A	Severe hypoglycaemic episodes – not reported in the systematic review.
Clinical impact	C	For outcome of $HbA_{1c.}$
Generalisability	C	Evidence based on studies in children aged 8–13 years and adults; no studies included children aged under 8 years or those with complications. The studies from 1988 and 1992 are not relevant to current practice, because different regimens are now used.
Applicability	A	Studies were performed in countries with well-established health-care systems, including one Australian study.
Other factors	None identified.	
Details	For full systematic review, see Chapter 25 of the accompanying technical report	

BMI, body mass index; GI, glycaemic index; HbA_{1c}, glycated haemoglobin; QoL, quality of life; RCT, randomised controlled trial

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

C26 Question 26

Q26	What are the efficacy and safety of a high-protein diet in type 1 diabetes?	
Evidence statement	There is insufficient evidence to determine the effect of modifying protein intake in individuals with type 1 diabetes.	
Evidence base	NA	
Consistency	NA	
Clinical impact	NA	
Generalisability	NA	
Applicability	NA	
Other factors	NA	
Details	For full systematic review, see Chapter 26 of the accompanying technical report	

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

C27 Question 27

Q27	What are the efficacy and safety of a high monounsaturated fat diet in type 1 diabetes?	
Evidence statement	Level II evidence (from one, good-quality study, small sample size) shows that, in nonobese adults with well-controlled, uncomplicated type1 diabetes, a diet high in monounsaturated fats can have a beneficial effect on LDL-cholesterol, triglycerides, VLDL-triglycerides and VLDL-cholesterol. There is insufficient evidence to determine any effect on weight, body mass index, quality of life and severe hypoglycaemia of diets high in monounsaturated fat in children, adolescents or adults with type 1 diabetes	
Evidence base	C	Four Level II studies – one of low quality, two of moderate quality and one of high quality.
Consistency	A	HbA_{1c} – all studies found no between-group differences.
	C	Weight and BMI – one study found a significant increase in favour of intervention; all other studies found a nonsignificant difference.
	NR	QoL – not reported.
	NR	Severe hypoglycaemic episodes – not reported.
	D	Results for lipids were variable – two studies showed no difference in lipids; one study (in adolescents) showed a significant increase in HDL in the comparator group and an inverse correlation between total cholesterol and LDL-cholesterol and dietary monounsaturated fat content in both groups; another study (in adults) showed a significant decrease in LDL in the intervention group.
Clinical impact	D	Slight or restricted impact for outcomes of HbA_{1c}, weight and BMI, and lipids.
Generalisability	C	The study groups was small (n=108 total), and participants found it difficult to follow the diet due to its difference from most western-style diets. The studies only included adults and adolescents.
Applicability	B	Studies were performed in countries with well-established health-care systems, and included one Australian study.
Other factors	None identified.	
Details	For full systematic review, see Chapter 27 of the accompanying technical report	

BMI, body mass index; HbA_{1c}, glycated haemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein; QoL, quality of life; RCT, randomised controlled trial; VLDL, very low density lipoprotein

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

C28 Question 28

This question was not systematically reviewed.

C29 Question 29

Question 29 – complementary and alternative medicines: adverse effects

Q29	Complementary and alternative medicines and outcome/population adverse effects	
Evidence statement	There is Level I evidence for a low rate of adverse events with nicotinamide, and Level II evidence for a low rate of adverse events with vitamin E and cinnamon. All studies showed no efficacy of complementary and alternative medicines in glycaemic control in type 1 diabetes. There is insufficient evidence to determine the efficacy of complementary and alternative medicines on lowering insulin dose in type 1 diabetes. There is insufficient evidence to determine an effect of complementary and alternative medicines on lipid levels in type 1 diabetes.	
Evidence base	C	One systematic review, of poor quality; eight Level II studies (seven with a low risk of bias; one with a high risk of bias).
Consistency	C	Five Level II studies (four with a low risk of bias; one with a high risk of bias) reported no adverse events. The systematic review reported that 6 of 291 patients treated with nicotinamide experienced an adverse effect. One study reported seven adverse events in the intervention (vitamin E) group, but this group was not statistically different from the other groups, and the adverse events were not considered serious. One study reported one adverse event (n=72; cinnamon intervention). One study reported one adverse event (n=82; vitamin E intervention).
Clinical impact	D	Interventions unlikely to be used in clinical practice.
Generalisability	A	Two studies were in adults – one study (fig leaf) reported no adverse events; one study (vitamin E) reported seven adverse events, but no statistically significant difference between groups. Four studies were in adolescents – two studies reported no adverse events; one study (cinnamon) reported one adverse event; one study (vitamin E) reported one adverse event. One study was in children (antioxidants) and reported no adverse events. One study was in children and adults (vitamin E + nicotinamide), and reported no adverse events.
Applicability	A	One study was conducted in Australia, five studies were in Europe and two were in the United States.
Other factors	None of the studies were powered to address adverse events.	
Details	For full systematic review, see Chapter 29 of the accompanying technical report	

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 29 – complementary and alternative medicines: glycaemic control

Q29	Complementary and alternative medicines and outcome/population – glycaemic control combined	
Evidence statement	There is Level I evidence for a low rate of adverse events with nicotinamide, and Level II evidence for a low rate of adverse events with vitamin E and cinnamon. All studies showed no efficacy of complementary and alternative medicines in glycaemic control in type 1 diabetes. There is insufficient evidence to determine the efficacy of complementary and alternative medicines on lowering insulin dose in type 1 diabetes. There is insufficient evidence to determine an effect of complementary and alternative medicines on lipid levels in type 1 diabetes.	
Evidence base	C	One systematic review of poor quality and 10 Level II studies (8 with a moderate risk of bias and 2 with a high risk of bias).
Consistency	A	Studies were consistent. All included studies found no difference in HbA_{1c} (cinnamon, vitamin E + nicotinamide, vitamin E, alpha-lipoic acid, antioxidants, folate, vitamin D + nicotinamide, vitamin E + nicotinamide, fig leaf, and nicotinamide). Systematic review/meta-analysis (nicotinamide) showed no difference between intervention and control.
Clinical impact	D	Results of studies unlikely to influence current clinical practice.
Generalisability	B	Seven studies in adolescents (cinnamon, alpha-lipoic acid, vitamin D + nicotinamide, vitamin E + nicotinamide, nicotinamide, folate, and vitamin E). One study in children and adolescents (vitamin E + nicotinamide). One study in children (antioxidants). One study in adults (fig leaf). A systematic review: age range 10–26 (nicotinamide).
Applicability	A	One Australian study, two studies from the United States, and seven European studies.
Other factors	None identified.	
Details	For full systematic review, see Chapter 29 of the accompanying technical report	

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 29 – complementary and alternative medicines: insulin dose

Q29	Complementary and alternative medicines and outcome/population insulin dose	
Evidence statement	There is Level I evidence for a low rate of adverse events with nicotinamide, and Level II evidence for a low rate of adverse events with vitamin E and cinnamon. All studies showed no efficacy of complementary and alternative medicines in glycaemic control in type 1 diabetes. There is insufficient evidence to determine the efficacy of complementary and alternative medicines on lowering insulin dose in type 1 diabetes. There is insufficient evidence to determine an effect of complementary and alternative medicines on lipid levels in type 1 diabetes.	
Evidence base	C	One systematic review/meta-analysis of poor quality. Nine Level II studies, seven of low risk of bias, two of high risk of bias.
Consistency	B	Systematic review (nicotinamide) and eight Level II studies (cinnamon, vitamin E+ nicotinamide, alpha-lipoic acid, antioxidants, vitamin D + nicotinamide, nicotinamide + vitamin E, fenugreek, and nicotinamide) showed no difference in insulin dose. One study (fig leaf) showed a decrease in insulin requirement, but the study was of poor quality and of high risk of bias.
Clinical impact	D	Results of studies unlikely to influence current clinical practice.
Generalisability	A	Systematic review (nicotinamide) – age range 10–26 years. Five studies in adolescents (cinnamon, alpha-lipoic acid, vitamin D + nicotinamide, vitamin E + nicotinamide, and nicotinamide). One study in children (antioxidants). One study in adults (fig leaf). One study in adolescents and adults (fenugreek). One study in children and adolescents (vitamin E + nicotinamide).
Applicability	A	Six studies were conducted in Europe, two in the United States and one in India.
Other factors	None identified.	
Details	For full systematic review, see Chapter 29 of the accompanying technical report	

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 29 – complementary and alternative medicines: lipid targets

Q29	Complementary and alternative medicines and outcome/population – lipid targets	
Evidence statement	There is Level I evidence for a low rate of adverse events with nicotinamide, and Level II evidence for a low rate of adverse events with vitamin E and cinnamon. All studies showed no efficacy of complementary and alternative medicines in glycaemic control in type 1 diabetes. There is insufficient evidence to determine the efficacy of complementary and alternative medicines on lowering insulin dose in type 1 diabetes. There is insufficient evidence to determine an effect of complementary and alternative medicines on lipid levels in type 1 diabetes.	
Evidence base	C	Two Level II studies of low risk of bias.
Consistency	A	Studies were consistent – both found no effect of the intervention (vitamin E) in lowering lipids.
Clinical impact	D	Results of studies unlikely to influence current clinical practice.
Generalisability	C	Both studies were in adults. Exclusion criteria were only reported in one study; they were hypertension (systolic BP >140 mmHg or diastolic BP >90 mmHg), creatinine level ≥15 mg/L or positive microalbuminuria, total cholesterol >300 mg/dl or triglycerides >500 mg/dl, pregnancy, breast feeding, women of childbearing age without adequate contraception, recent or unstable cardiovascular or cerebrovascular disease.
Applicability	C	Both studies were conducted in Belgium.
Other factors	None identified.	
Details	For full systematic review, see Chapter 29 of the accompanying technical report	

BP, blood pressure

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

C30 Question 30

This question was not systematically reviewed.

C31 Question 31

Q31	What is the effectiveness of preconception care in women with type 1 diabetes in improving maternal and foetal outcomes?	
Evidence statement	Level III evidence shows that preconception care is effective at reducing congenital malformations, perinatal mortality and HbA_{1c} levels in women with type 1 diabetes,	
Evidence base	C	One systematic review (included 16 cohort studies – 8 prospective and 8 retrospective) and 10 cohort studies. Level III and IV evidence with a moderate risk of bias.
Consistency	A	Studies were generally consistent in their findings, particularly in regard to the primary outcomes (congenital malformations, perinatal mortality and HbA_{1c}).
Clinical impact	A	Results expected to affect clinical management.
Generalisability	A	For females of childbearing age.
Applicability	A	No studies from Australia, but studies undertaken in countries with a well-established health system.
Other factors	Question is not suitable for study by RCT.	
Details	For full systematic review, see Chapter 31 of the accompanying technical report	

HbA_{1c}, glycated haemoglobin; RCT, randomised controlled trial

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

C32 Question 32

Q32	What is the effectiveness of blood glucose control during pregnancy in women with type 1 diabetes in achieving blood glucose targets and improving maternal and foetal outcomes?	
Evidence statement	During pregnancy in women with type 1 diabetes, there is some evidence of harm for fasting blood glucose targeted at 6.7–8.9 mmol/L, compared to below 6.7 mmol/L.	
Evidence base	D	One Level I study that included three RCTs of high risk of bias, due to unclear allocation concealment methods, lack of blinded outcome assessment and high risk of selective outcome reporting bias.
Consistency	NA	Only one study was available.
Clinical impact	C	
Generalisability	B	
Applicability	A	No studies from Australia, but the studies were undertaken in countries with a well-established health system
Other factors	None identified.	
Details	For full systematic review, see Chapter 32 of the accompanying technical report	

RCT, randomised controlled trial

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

C33 Question 33

This question was not systematically reviewed.

C34 Question 34

This question was not systematically reviewed.

C35 Question 35

This question was not systematically reviewed.

C36 Question 36

Question 36 – HbA_{1c}

Q36	What is the metabolic effect of hormonal versus nonhormonal contraceptives in women with type 1 diabetes?	
Evidence statement	The four RCTs included in this systematic review provided insufficient evidence to assess whether progesterone-only and combined oral contraceptives differ from nonhormonal contraceptives in their impact on glycaemic control.	
Evidence base	D	Level 1 evidence comprising four RCTs, three of high risk of bias and one of moderate risk of bias.
Consistency	A	HbA_{1c} – only two studies reported this outcome, and no difference was found in either study. No safety outcomes were reported.
Clinical impact	D	Results of studies unlikely to influence current clinical practice.
Generalisability	D	Sample size was small (n=62), and studies were not recent.
Applicability	C	All studies were conducted in Europe.
Other factors	None identified.	
Details	For full systematic review, see Chapter 36 of the accompanying technical report	

HbA_{1c}, glycated haemoglobin; RCT, randomised controlled trial

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 36 – lipids

Q36	What is the metabolic effect of hormonal versus nonhormonal contraceptives in women with type 1 diabetes?	
Evidence statement	The four RCTs included in this systematic review provided insufficient evidence to assess whether progesterone-only and combined oral contraceptives differ from nonhormonal contraceptives in their impact on lipid metabolism.	
Evidence base	D	Level I evidence comprising four RCTs, three of high risk of bias and one of moderate risk of bias.
Consistency	C	Lipids – results were conflicting; one study reported a significant increase and three studies reported changes that were not clinically meaningful (i.e. they were within the normal range). No safety outcomes were reported.
Clinical impact	D	Results of studies unlikely to influence current clinical practice.
Generalisability	D	Sample size was small (n=62), and studies were not recent.
Applicability	C	All studies were conducted in Europe.
Other factors	None identified.	
Details	For full systematic review, see Chapter 36 of the accompanying technical report	

RCT, randomised controlled trial

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

C37 Question 37

This question was not systematically reviewed.

C38 Question 38

Question 38 – predictive factors for hypoglycaemia

Q38	What are the predictive factors for severe hypoglycemia	
Evidence statement	Level II evidence indicates that younger age, longer duration of diabetes and hypoglycaemia unawareness are associated with higher risk of severe hypoglycaemia.	
Evidence base	B	Younger age is associated with increased risk (e.g. OR 2.2): four Level II studies and one Level IV study in children; one Level II study in older children. Longer duration is associated with increased risk: (e.g. IRR 5.3, RR 1.39/5 years), four Level II studies in children and two Level II studies in adults. Lower HbA_{1c}: (RR 1.2 per 1%), three Level II studies in children; one Level IV study in children showing no relationship; three Level II studies and one Level IV study in adults. Sex: one Level I study in males; one Level I study showing no effect and one Level I study in adults. Psychological disorder: (RR1.56), one Level II study in children. Decreased hypoglycaemic awareness: one Level II study in children (RR4.6), one Level II and one Level IV study in adults. Prior hypoglycaemia: (HR 1.98) one Level I study and one Level IV study in adults.
Consistency	B	Generally consistent.
Clinical impact	B	
Generalisability	A	Populations were mostly clearly defined as paediatric or adult.
Applicability	A	Large Australian studies as well as American and European.
Other factors	None identified.	
Details	For full systematic review, see Chapter 38 of the accompanying technical report	

HR, hazard ratio; IRR, incidence rate ratio; OR, odds ratio; RR, rate ratio

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 38 – incidence of hypoglycaemia

Q38	What is the effect of intensive diabetes management on the incidence of hypoglycaemia?	
Evidence statement	Level I evidence from studies published before 1997 (including the DCCT) shows that intensive management is associated with a higher risk of severe hypoglycaemia.	
Evidence base	A	Two Level I studies one with a low risk of bias and one with a moderate risk of bias.
Consistency	B	Direction of effect is consistent, but magnitude of effect varies when the results from DCCT are excluded: OR of experiencing one or more severe hypoglycaemic episode, 2.99 changed to 1.59. Significant interaction between effect and HbA_{1c}.
Clinical impact	C	Limitations regarding currency of evidence.
Generalisability		Intensity of control may not be replicable. All studies included adults or adolescents, with a mean age of 18–42 years across included studies. No studies in children.
	B	Adults.
	C	Children.
Applicability	C	Studies in America, Europe and North America (DCCT). Management practices have changed, so current delivery of care may be different from that in the evidence base.
Other factors	None identified.	
Details	For full systematic review, see Chapter 38 of the accompanying technical report	

DCCT, Diabetes Control and Complications Trial; HbA_{1c}, glycated haemoglobin; OR, odds ratio

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

C39 Question 39

Q39	What are the acute effects of hypoglycaemia and hyperglycaemia on cognitive function?	
Evidence statement	Level II evidence shows that acute hypoglycaemia causes a temporally related impairment in cognitive performance. Level III evidence shows that acute hyperglycaemia may cause cognitive impairment in children and adults. One Level II study shows that acute hyperglycaemia above 22 mmol/L in children is associated with a comparable impairment to acute hypoglycaemia (<3 mmol/L).	
Evidence base	B/C	Three Level II studies of moderate risk of bias (n=289 adults, n=61 primary school aged children) and 27 Level II or III studies, predominately of moderate risk of bias (clamp studies) (n=398 adults, n=48 children aged >6 years). B for hypoglycaemia. C for hyperglycaemia.
Consistency	A/C	BG level below 3.9 mmol/L and above 15 mmol/L in adults has a negative impact on cognition. BG level below 3.0 mmol/L and above 22.2 mmol/L in children has a negative impact on cognition. In adults, a recent history of severe hypoglycaemia attenuates the effect of hypoglycaemia, and higher HbA_{1c} and greater exposure to BG levels above 15 mmol/L are associated with a greater level of impairment during hyperglycaemia. In children, higher HbA_{1c} and frequency of severe hypoglycaemia are associated with a degree of impairment at BG levels above 22.2 mmol/L. Effects of hyperglycaemia and hypoglycaemia were highly individualised. A for hypoglycaemia. C for hyperglycaemia.
Clinical impact	A/C	'Hyperglycaemia resulted in increased errors and slower responses when performing basic verbal and mathematical tasks, which are important to numerous daily functions, such as balancing cheque books, calculating insulin dosing, and school and work performance.' (Cox et al 2005) Individual scores indicated that performance declines by more than 1 SD during hypoglycaemia and hyperglycaemia for more than 20% of children (Gonder-Frederick et al 2009). Group scores – during hypoglycaemia and hyperglycaemia there was, on average, a 20% decrease in speed (Gonder-Frederick et al 2009). A for hypoglycaemia. C for hyperglycaemia.
Generalisability	B	No studies in children younger than 6 years. Reported exclusions included diabetes duration of less than 1 year, inability to read English, psychiatric disorder, substance abuse and pregnancy.
Applicability	A	One study was in Australia; the rest were from countries with a well-established health-care system.
Other factors	N/A	
Details	For full systematic review, see Chapter 39 of the accompanying technical report	

BG, blood glucose; HbA_{1c}, glycated haemoglobin; SD, standard deviation

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

C40 Question 40

This question was not systematically reviewed.

C41 Question 41

Q41	How can severe hypoglycaemia be prevented?	
Evidence statement	Level II and Level IV evidence shows that specific educational interventions (in particular, BGAT) reduce the rate of severe hypoglycaemia.	
Evidence base	C	Two Level II studies (1 with 12 months follow-up) with moderate risk of bias, and two Level IV studies; one with low risk of bias and one with high risk of bias.
Consistency	B	Reduction of severe hypoglycemia –the 24-month and 12-month results from the same study were conflicting (no effect at 12 months and a significant effect at 24 months). This may be explained by length of follow-up and the overall effect being positive. The other Level II study found a significant effect compared to control. The two Level II studies were consistent in reporting significant improvement compared to baseline. (Different definitions of severe hypoglycaemia and reporting methods were used.)
Clinical impact	A	Level II studies used a method not described in detail. Level IV studies used published BG awareness training methodology.
Generalisability	B	Populations were representative with studies in adolescents and adults. Compliance of the populations may vary. Children were not represented.
Applicability	A	Studies were set in Europe and North America.
Other factors	One study reported the cost of intervention per 100 patients at €1000, and the yearly socioeconomic cost for severe hypoglycaemia at €17 440. Issues regarding language. Cost effectiveness should be considered with regard to implementation.	
Details	For full systematic review, see Chapter 41 of the accompanying technical report	

BG, blood glucose; BGAT, blood glucose awareness training

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

C42 Question 42

Q42	How effective is blood ketone monitoring versus urine ketone monitoring in prevention of diabetic ketoacidosis or hospital admission?	
Evidence statement	Blood ketone measurement compared with urine ketone measurement, as part of a sick-day management plan, reduces the rate of emergency presentations and hospitalisations.	
Evidence base	B	One Level II study of low risk of bias.
Consistency	N/A	Blood ketone monitoring resulted in a significant reduction (about 50%) in the incidence of hospitalisation and emergency assessment.
Clinical impact	A	This is an important clinical procedure that is easy to do at home.
Generalisability	B	Participants aged 3–22 years, and population not defined in terms of ethnicity. Exclusions included 'known emotional problems' and recurrent episodes of DKA.
Applicability	A	The study was undertaken in the United States, which has a well-developed health-care system.
Other factors	None identified.	
Details	For full systematic review, see Chapter 42 of the accompanying technical report	

DKA, diabetic ketoacidosis

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable.

C43 Question 43

Question 43 –macrovascular

Q43	What is the effect of intensive glycaemic management on macrovascular complications?	
Evidence statement	Intensive glycaemic control in adolescents and adults with type 1 diabetes reduces the risk of cardiovascular disease.	
Evidence base	A	Level I evidence – two systematic reviews of low risk of bias and the DCCT/EDIC studies (Level II/III).
Consistency	A	Any cardiovascular event – a statistically significant difference was observed in all studies.
Clinical impact	A	
Generalisability	B	The DCCT was a large trial (n=1441). Children were not included in the DCCT; the age at baseline was 13–39 years. The age in the two systematic reviews was 18–42 years.
Applicability	A	The studies were not conducted at sites in Australia (the DCCT/EDIC studies were in the United States), but did include some rural and remote centres.
Other factors	None identified.	
Details	For full systematic review, see Chapter 43 of the accompanying technical report	

DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 43 – microvascular

Q43	What is the effect of intensive glycaemic management on microvascular complications?	
Evidence statement	Intensive glycaemic control in adolescents and adults with type 1 diabetes reduces the risk of microvascular outcomes.	
Evidence base	B	One Level II study of low risk of bias (DCCT), plus the long-term follow-up of the DCCT cohort (EDIC).
Consistency	NA	Only one study.
Clinical impact	A	
Generalisability	B	The DCCT was a large trial (n=1441). Children were not included in the DCCT; the age at baseline was 13–39 years.
Applicability	A	The studies were conducted in the United States, but did include some rural and remote centres.
Other factors	Intensive management in the DCCT referred to intensive glycaemic management, through a package of methods including MDI or CSII, frequent insulin dose adjustment, blood glucose monitoring at least four times per day and a weekly 3-am BG level, formal diabetes education, medical nutrition therapy, and physical activity advice. Such a package is not necessarily available at all centres in Australia. The incremental cost per life year gained was US$28 661, but this is not necessarily informative for the Australian setting (see Chapter 4 of the guidelines on costs of diabetes).	
Details	For full systematic review, see Chapter 43 of the accompanying technical report	

BG, blood glucose; CSII, continuous subcutaneous insulin infusion; DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; MDI, multiple daily injections

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

C44 Question 44

This question was not systematically reviewed.

C45 Question 45

Q45	How effective are antihypertensives at reducing blood pressure in type 1 diabetes?	
Evidence statement	Level II evidence shows that antihypertensive agents are effective at lowering blood pressure.	
Evidence base	B	Three RCTs, two of high risk of bias and one of low risk of bias.
Consistency	A	The studies were consistent in magnitude and direction.
Clinical impact	C	A 10 mmHg reduction in systolic pressure and a 5 mmHg reduction in diastolic pressure. The impact is most applicable to the adult population; this evidence has already been incorporated into clinical practice.
Generalisability	C	The studies had small sample sizes (n=16–35) and were in people with diabetes, with complications.
Applicability	B	All studies were conducted in northern Europe.
Other factors	None identified.	
Details	For full systematic review, see Chapter 45 of the accompanying technical report	

ACE, Angiotensin converting enzyme; RCT, randomised controlled trial

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

C46 Question 46

Question 46 – retinopathy

Q46	How effective are antihypertensives at reducing or preventing retinopathy, nephropathy, neuropathy and autonomic neuropathy?	
Evidence statement	Primary prevention: In normotensive patients with type 1 diabetes and no retinopathy, there is insufficient evidence to determine the effect of ACEI or ARB on the onset of retinopathy. Secondary prevention: In normotensive patients with type 1 diabetes and nonproliferative diabetic retinopathy, ACEI or ARB reduce the progression of retinopathy. Prespecified outcomes were two grades of retinopathy progression on the ETDRS scale (DIRECT and RASS) or one grade (EUCLID), thus with differing study outcome measures.	
Evidence base	B	Two Level II studies with combined low risk of bias.
Consistency	B	All studies were consistent in showing no effect on incidence of retinopathy. Evidence was conflicting about the progression of retinopathy. RASS: reduction with ACE (OR 0.35) and ARB (OR 0.3). DIRECT: No effect on predefined progression (2 steps), signify effect on post hoc analysis of three steps. No effect on proliferative retinopathy. EUCLID: Underpowered, and retinopathy not a primary outcome of this study.
Clinical impact	D	
Generalisability	B	Large, good or fair-quality trials in normotensive, normoalbuminuric and microalbuminuric patients. All adult participants.
Applicability	B	Both large multicentre studies undertaken in Europe, the United Kingdom and the United States.
Other factors	None identified.	
Details	For full systematic review, see Chapter 46 of the accompanying technical report	

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; OR, odds ratio; RASS, Renin Angiotensin System Study

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 46 – nephropathy

Q46	How effective are antihypertensives at reducing or preventing retinopathy, nephropathy, neuropathy and autonomic neuropathy?	
Evidence statement	Primary prevention: In normotensive normoalbuminuric patients with type 1 diabetes, there is consistent evidence that neither ACEI nor ARB prevent the onset of microalbuminuria. Secondary prevention (progression): There is evidence that the use of ACEI prevents the progression from microalbuminuria to macroalbuminuria. There is evidence that ACEI attenuates or delays the progression from macroalbuminuria to doubling of creatinine or end-stage renal disease (combined death, dialysis and transplantation).	
Evidence base	B	Primary.
	A	Secondary.
Consistency	B	Primary (results inconsistent for ACEI and ARB).
	A	Secondary – ACEI.
	B	Secondary – ARB.
Clinical impact	D	Primary.
	A	Secondary.
Generalisability	B	Large, good to fair-quality trials in normotensive, normoalbuminuric and microalbuminuric patients. All adult participants.
Applicability	A	Both large multicentre studies undertaken in Europe, the United Kingdom and the United States.
Other factors	Children and adolescents are not represented in the evidence base.	
Details	For full systematic review, see Chapter 46 of the accompanying technical report	

ACEI; angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; OR, odds ratio

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

C47 Question 47

Q47	How effective are statins at correcting dyslipidaemia in type 1 diabetes?	
Evidence statement	Level I and II evidence demonstrates that statins are effective at reducing total and LDL cholesterol in adults with type 1 diabetes. Level I evidence demonstrates that statins reduce cardiovascular events in adults with type 1 diabetes.	
Evidence base	A	Level I study with inclusion criteria (>1000 patients) that ensure a low risk of bias. The Level II studies included four of low risk of bias, four of moderate risk of bias and two of high risk of bias.
Consistency	A	LDL/total cholesterol –all studies show a statistically significant effect on lowering total cholesterol and LDL-cholesterol. Two studies showed a statistically significant increase in HDL, in contrast to the other studies.
	B	HDL/triglycerides.
Clinical impact	A	There was a large effect size and the finding has the potential to affect all patients with type 1 diabetes.
Generalisability	B	Systematic review was large (n=1466 total). Numbers in individual studies were 8–82. Children and young adults were not represented in the evidence base.
Applicability	A	Studies were conducted in Europe or the United States.
Other factors	PBS prescribing restrictions limit access to statins (e.g. microalbuminuria, Indigeneous). PBS guidelines use total cholesterol as the indicator, whereas paediatric guidelines recommend LDL cholesterol as the indication for therapy.	
Details	For full systematic review, see Chapter 47 of the accompanying technical report	

HDL, high density lipoprotein; LDL, low density lipoprotein; PBS, Pharmaceutical Benefits Scheme

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

C48 Question 48

This question was not systematically reviewed.

C49 Question 49

This question was not systematically reviewed.

C50 Question 50

This question was not systematically reviewed.

C51 Question 51

This question was not systematically reviewed.

C52 Question 52

This question was not systematically reviewed.

C53 Question 53

Q53	How often should individuals with type 1 diabetes be screened for coeliac disease?	
Evidence statement	There is an increased risk of coeliac disease in children and adolescents with type 1 diabetes compared to general population historical rates. The number of new cases detected 1 and 2 years after diagnosis is similar to the number of cases at diagnosis. The number of new cases detected after 10 years of diabetes duration is similar to the general population.	
Evidence base	C	Five Level II studies of moderate risk of bias, and two Level III studies of moderate risk of bias.
Consistency	B	Prevalence of coeliac disease by duration was similar across the studies; it ranged from 1.6% to 8.1%. All studies demonstrated an increased risk of coeliac disease in type 1 diabetes. The direction of the effect was consistent, but the magnitude varied.
Clinical impact	B	Detection of coeliac disease will have a major impact on patients.
Generalisability	B	Most of the evidence is in children and adolescents. Only study in adults was a cross-sectional study not a longitudinal study.
Applicability	A	
Other factors	None identified.	
Details	For full systematic review, see Chapter 53 of the accompanying technical report	

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

C54 Question 54

Q54	How and how often should patients with type1 diabetes be screened for thyroid disease?	
Evidence statement	Thyroid dysfunction is common in type 1 diabetes, and positive antibodies are strongly predictive of thyroid dysfunction.	
Evidence base	C	Five Level III studies with a moderate risk of bias, and one Level III study with a high risk of bias.
Consistency	B	Consistent findings included the following: • A significant difference in the cumulative incidence of thyroid disease in patients positive to thyroid antibodies at diagnosis versus those negative to thyroid antibodies at diagnosis (four studies). • In studies measuring thyroid antibodies at multiple time-points, most patients were found to be positive at diagnosis of type 1 diabetes, rather than at follow-up testing (four studies). • Transient autoimmunity was not found in any patients who had highly positive thyroid antibody screen (>100 U/mL) (four studies). • Children and adults should be screened for thyroid disease and autoimmunity at diagnosis of type 1 diabetes (six studies). • Annual screening is suggested in antibody-positive patients, with less frequent screening in antibody negative patients (five studies).
Clinical impact	B	Thyroid dysfunction is common in type 1 diabetes, and often requires treatment. Antibodies to TPO or TG are predictive of development of hypothyroidism.
Generalisability	A	There is evidence in both children (n=1127) and adults (n=464) with type 1 diabetes. Follow-up was of 18 years' duration.
Applicability	A	One study was conducted in a group of Australian children younger than 15 years; all other studies were undertaken in countries with a well-developed health-care system.
Other factors	N/A	
Details	For full systematic review, see Chapter 54 of the accompanying technical report	

TG, thyroglobulin; TPO, thyroid peroxidase

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Appendix D: Other resources

D1 Consumer reading materials

Publication details	Notes
Children and adolescents	
Caring for diabetes in children and adolescents : a parent's manual (Ambler and Cameron 2010) http://www.rch.org.au/diabetesmanual/index.cfm?doc_id=2352	A joint project of The Children's Hospital at Westmead and the Royal Children's Hospital. The resource takes into account the current guidelines from the NHMRC and ISPAD, and shows how these guidelines can be applied. The book will be useful to parents, grandparents, friends and other carers, as well as to young people with diabetes.
Adults	
Straight to the point – a guide for adults living with type 1 diabetes (Overland et al 2009b) http://www.jdrf.org.au/shop/products/Straight-to-the-Point.html	A useful resource for any adult living with type 1 diabetes, whether they are adjusting to life with the disease or are already familiar with living with it. The book covers everything from day-to-day management (including tips on food and exercise), to managing the disease at work and play, using real-life stories to illustrate the points made.
A starter kit for recently diagnosed adult diabetes (Reality Check 2005) www.realitycheck.org.au/starterkit/	A user friendly starter kit for adults with diabetes. With funding from the Federal Government's Department of Health and Ageing, a 40-page book for Adults who are newly-diagnosed with type 1 diabetes has been developed. The resource has been critically reviewed and endorsed for clinical accuracy by 30 diabetes-specialist health care professionals from around Australia. More than 250 diabetes centres and specialist practices are using the Kits to aid in education of their newly-diagnosed patients.
Sick day management	
Guidelines for sick day management for people with type 1 diabetes (ADEA 2006) http://www.adea.com.au/asset/view_document/979316048	This document has been produced in different versions for consumers and health-care professionals, and is currently under review.
Nutrition therapy	
The new traffic light guide to food (Diabetes Education and Assessment Programme 1997) http://catalogue.nla.gov.au/Record/2054756	A useful guide that will increase confidence about choosing foods and eating in a relaxed way.
Continuous subcutaneous insulin infusion (CSII) pump therapy	
I'm considering an insulin pump (Diabetes Australia VIC 2009) http://www.diabetesvic.org.au/type-1-diabetes/insulin-therapy-and-pumps/insulin-pump-information	A useful introduction for those considering an insulin pump and are just starting to find out about it as an option in therapy.
Guidelines for continuous subcutaneous insulin infusion (CSII) pump therapy (Victorian CSII Working Party 2009) http://www.diabetesccre.unimelb.edu.au/professionals/documents/CSIIguidelinesJuly2009-FINAL.pdf	A highly practical, advanced guide to insulin pump therapy.

D2 Health professional reading materials

Publication details	Organisation
Australian guidelines	
Guidelines for the management of diabetic retinopathy (Australian Diabetes Society 2008) http://www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/di15.pdf	NHMRC Clinical care guideline, prepared by the Australian Diabetes Society
Clinical practice guidelines: Type 1 diabetes in children and adolescent (APEG 2005)	NHMRC Clinical care guideline, prepared by the Australasian Paediatric Endocrine Group
Consensus guidelines for the management of type 1 and type 2 diabetes in relation to pregnancy (McElduff et al 2005)	Australasian Diabetes in Pregnancy Society (ADIPS)
Position statement of the Australian Diabetes Society: individualisation of glycated haemoglobin targets for adults with diabetes mellitus. (Cheung et al 2009b)	The Australian Diabetes Society
International guidelines	
Clinical practice consensus guidelines (ISPAD 2009) http://www.ispad.org/FileCenter.html?CategoryID=5	International Society for Pediatric and Adolescent Diabetes (ISPAD)
Type 1 diabetes: Diagnosis and management of type 1 diabetes in children, young people and adults (NICE 2010) http://www.nice.org.uk/nicemedia/live/10944/29390/29390.pdf	National Institute for Health and Clinical Excellence (NICE) (United Kingdom)
Clinical guidelines for the management of type 1 diabetes in childhood and adolescence – currently under review (ISPAD (International Society for Pediatric and Adolescent Diabetes) 2000) http://www.idf.org/node/1145?node=550	International Diabetes Federation (IDF)
Standards of medical care in diabetes (American Diabetes Association 2010)	American Diabetes Association (ADA)

Abbreviations and acronyms

A_{1c}	glycated haemoglobin
ACE	angiotensin converting enzyme
ACEI	angiotensin converting enzyme inhibitor
ADA	American Diabetes Association
ADC	Australian Diabetes Council
ADDQoL	audit of diabetes-dependent quality of life
ADEA	Australian Diabetes Educators Association
ADIPS	Australasian Diabetes in Pregnancy Society
ADS	Australian Diabetes Society
AER	albumin excretion rate
AHT	antihypertensive
AN	autonomic neuropathy
ANOVA	analysis of variation
APEG	Australasian Paediatric Endocrine Group
APS	autoimmune polyglandular syndrome
APS	Australian Psychological Society
ARA	antireticulin antibodies
ARB	angiotensin II receptor blocker
AUC	area under the glucose curve
BAI	Beck Anxiety Inventory
BASC	Behaviour Assessment System for Children
BDI	Beck Depression Inventory
BG	blood glucose

BGAT	blood glucose awareness training
BGL	blood glucose level
BMI	body mass index
BP	blood pressure
BRFSS	Behavioural Risk Factor Surveillance System
C	cholesterol
CACTI	coronary artery calcification in type 1 diabetes
CAN	cardiac autonomic neuropathy
CBGM	continuous blood glucose monitoring
CBCL	child behaviour check list
CBT	cognitive behavioural therapy
CCB	calcium channel blocker
CCF	congestive cardiac failure
CDI	Children's Depression Inventory
CFRD	cystic fibrosis related diabetes
CGM	continuous glucose monitoring
CGMS	continuous glucose monitoring systems
CHD	coronary heart disease
CHO	carbohydrate
CI	confidence interval
CIDI	Composite International Diagnostic Interview
CIMT	carotid intima-media thickness
CIPII	continuous intraperitoneal insulin infusion
CNS	central nervous system
CORE	Center for Outcomes Research

CRP	C-reactive protein
CSII	continuous subcutaneous insulin infusion
CT	conventional treatment
CVA	cardiovascular accident
CVD	cardiovascular disease
DA	Diabetes Australia
DAA	Dietitians Association of Australia
DAFNE	dose adjustment for normal eating
DARE	database of abstracts of reviews of effects
DCCT	Diabetes Control and Complications Trial
df	degrees of freedom
DIDMOAD	diabetes insipidus diabetes mellitus optic atrophy deafness
DIMD	Diagnostic Interview for Mental Disorders
DIS	Diagnostic Interview Schedule
DKA	diabetic ketoacidosis
DPT	Diabetes Prevention Trial
DQOL	diabetes quality of life
DSG	desogestrel
DSM	*Diagnostic and statistical manual of mental disorders*
E2	17ß-estradiol
EDE	Eating Disorders Examination
EDI	Eating Disorder Inventory
EDIC	Epidemiology of Diabetes Interventions and Complications
ED-NOS	eating disorders not otherwise specified
EDTRS	Early Treatment Diabetic Retinopathy Study

EE2	ethinyl-estradiol
ELISA	enzyme linked immunosorbent assay
EMA	antiendomysial antibodies
ENDIT	European Nicotinamide Diabetes Intervention Trial
EOD	early onset diabetes
ES	effect score
FBG	fasting blood glucose
FPG	fasting plasma glucose
FPIR	first phase insulin response
FSIQ	full scale intelligence quotient
GAD	glutamic acid decarboxylase
GADA	glutamic acid decarboxylase antibodies
GFR	glomerular filtration rate
GI	glycaemic index
GSD	gestodene
HADS	Hospital Anxiety and Depression Scale
HbA_{1c}	glycated haemoglobin
HDL	high density lipoprotein
HF	high frequency
HLA	human leukocyte antigen
HMG CoA	3-hydroxy-3-methylglutaryl-coenzyme
HNF	hepatic nuclear factor
HR	hazard ratio
HSCL	Hopkins Symptom Checklist
HRV	heart rate viability

HTA	health technology assessments
IA-2	insulinoma-associated 2 molecule
IAA	insulin autoantibodies
IAsp	insulin aspart
ICA	islet cell antigen
ICER	incremental cost-effectiveness ratio
IDDM	Insulin dependent diabetes mellitus
IDF	International Diabetes Federation
IFG	impaired fasting glycaemia
IGT	impaired glucose tolerance
IIS	individual impairment score
IM	Intramuscular
INAHTA	International Network of Health Technology Assessment
IQ	intelligence quotient
IQR	interquartile range
IRR	incidence rate ratio
ISCA	Interview Schedule for Children and Adolescents
IT	intensive treatment
ITT	intention to treat
IUD	intrauterine device
IV	intravenous
IVGTT	intravenous glucose tolerance test
JDFU	Juvenile Diabetes Foundation Unit
JDRF	Juvenile Diabetes Research Foundation
K6	Kessler 6 scale

LADA	latent autoimmune diabetes of the adult
LDL	low density lipoprotein
LF	low frequency
LNG	levonorgestrel
LOD	late onset diabetes
LY	life year
LYN	lynoestrenol
M-CIDI	Munchener Composite International Diagnostic Interview
MD	mean difference
MDI	multiple daily injections
MET	motivational enhancement therapy
MF	metformin
MHC	major histocompatibility complex
MI	myocardial infarction
MNSI	Michigan Neuropathy Screening Instrument
MODY	maturity onset diabetes in the young
mono	monounsaturated
MOS	Medical Outcomes Survey
MRDM	malnutrition related diabetes mellitus
mtDNA	mitochondrial DNA
NA	not available
NATA	National Association of Testing Authorities
NICE	National Institute for Clinical Excellence
NIDDM	non-insulin dependent diabetes mellitus
NHMRC	National Health and Medical Research Council

NHS	National Health Service
NPH	neutral protamine Hagedorn
NR	not reported
NS	not significant
OR	odds ratio
OCP	oral contraceptive pill
PAID	Problem Areas in Diabetes program
PedsQL	Pediatric Quality of Life Inventory
PG	plasma glucose
PGL	plasma glucose levels
PIQ	performance intelligence quotient
PL	placebo
poly	polyunsaturated
PPG	program project grant
PSE	present state examination
PTSD	post-traumatic stress disorder
OGTT	oral glucose tolerance test
QALE	quality-adjusted life expectancy
QALY	quality-adjusted life years
QoL	quality of life
QUAL	qualitative
QUANT	quantitative
RACP	Royal Australian College of Physicians
RACGP	Royal Australian College of General Practitioners
RAS	renin-angiotensin system

RCFA	red cell fatty acids
RCMAS	Revised Children's Manifest Anxiety Scale
RCT	randomised controlled trial
RD	risk difference
ROC	receiver operating characteristic
RR	relative risk
S-ACE	serum angiotensin converting enzyme
SADS	Schedule for Affective Disorders and Schizophrenia
SADS-LA	Schedule for Affective Disorders and Schizophrenia Lifetime Version
SC	subcutaneous
SCL-90R	Symptom Checklist–90R
SD	standard deviation
SDS	standard deviation score
SE	standard error
SES	socioeconomic status
SH	severe hypoglycaemia
SIMP	simplified
SMBG	self-monitoring of blood glucose
SPD	severe psychological distress
SPPC	self-perception profile for children
SR	systematic review
STAI	State-Trait Anxiety Inventory
TG	trigylceride
TPOA	thyroperoxidase antibodies
TRIGR	Trial to Prevent Type 1 Diabetes in the Genetically at Risk

TSH	thyroid stimulating hormone
tTG	anti-tissue transglutaminase
tTGA	anti-tissue transglutaminase antibody
UKPDS	United Kingdom Prospective Diabetes Study
VIQ	verbal intelligence quotient
VLDL	very low density lipoprotein
WHO	World Health Organization
WMD	weighted mean difference
YASR	Young Adult Self Report
YSR	Youth Self Report
ZnT-8	zinc transporter 8

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