Guidance concerning the use of glycated haemoglobin for the diagnosis of Diabetes Mellitus

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Introduction.

The measurement of glycated haemoglobin (HbA1c) has been accepted for Medicare reimbursement in Australia for the diagnosis of diabetes mellitus. A positive test suggesting the diagnosis of diabetes mellitus is an HbA1c $\geq$ 48 mmol/mol (6.5%). This test provides an alternative to traditional glucose based methods for diagnosis. It does not replace them. The correct use of the test may facilitate the earlier diagnosis of patients with elevated mean blood glucose levels at increased risk of long term diabetes-specific microvascular complications. It will be used predominantly for the diagnosis of type 2 diabetes mellitus.

It is important that medical practitioners who elect to use the test for diagnosis understand the nature of the test, its limitations as well as its benefits. The major benefits of using glycated haemoglobin for diagnosis were outlined in the position paper of the HbA1c Committee of the Australian Diabetes Society recently published in this Journal (1). Practitioners are recommended to read that paper in conjunction with this implementation document.

The Medicare Wording for Reimbursement.

The wording for reimbursement states that the test is for “Quantitation of HbA1c (glycated haemoglobin) performed for the diagnosis of diabetes in asymptomatic patients at high risk. “ The test when used for diagnosis can be performed not more than once in a 12 month period (2). The brevity of this statement raises certain issues that need to be considered.

1. Identification of patients at high risk.

The intent of the statement is that the only patients at high risk of having un-diagnosed diabetes should be tested. As outlined in the original position statement, there are two

groups of patients at high risk: (i) those with an underlying medical condition or ethnic origin associated with high rates of type 2 diabetes, and (ii) those patients having a number of characteristics placing them at increased risk of diabetes (1, 3). The latter group of patients are best identified using the AUSDRISK score available at http://www.health.gov.au/internet/main/publishing.nsf/Content/diabetesRiskAssessmentTool. Patients considered to be at high risk have a score $\geq$ 12.

The HbA1c should not be used to randomly or systematically screen un-differentiated groups of patients for diabetes. Without prior knowledge of the medical status of patients, the test may not correctly diagnose patients as having diabetes (see below, section 5). It also represents a more expensive approach to screening compared with using blood glucose levels (BGLs) based on current costs (2).

2. Asymptomatic patients.

The wording for reimbursement states that only asymptomatic patients should be considered for this test. Many of the symptoms in isolation are not specific for diabetes mellitus. For example, there may be many reasons for the development of tiredness or blurred vision as isolated symptoms. The committee recommends that these patients be considered asymptomatic and are suitable for the test, but only if they fulfil the high risk requirement as outlined above. If one or more symptoms are present in a patient at low risk, blood glucose should be used if diabetes is suspected.

Patients who have multiple symptoms highly suggestive of diabetes mellitus (weight loss, polyuria, polydypsia, blurred vision etc) are not asymptomatic and should have diabetes confirmed by measurement of blood glucose. These patients would be expected to have very high BGLs. There is the theoretical possibility that a patient with rapidly evolving

diabetes could become symptomatic yet have a normal glycated haemoglobin as BGLs have not been elevated for a significant duration of time. Thus, it may not be clinically appropriate to measure HbA1c for diagnosis in symptomatic patients, especially if symptoms have been present for a short period of time.

3. Re-measurement.

A result less than 48 mmol/mol (6.5%) suggests that the patient does not have diabetes mellitus. As the test has been performed in a patient at high risk of developing diabetes in the next 5 years, the test should be repeated 12 months later as recommended in the National Health and Medical Research Council (NHMRC) guidelines for diagnosis of type 2 diabetes (3), irrespective of the HbA1c result. This cost will be reimbursed. These persons are at high risk of developing diabetes in the future and should be given lifestyle advise to reduce their risk of development of diabetes (4, 5).

People having a result just less than 48 mmol/mol (6.5%) do not need to have the test repeated in less than 12 months unless there is a significant change in their medical condition eg sudden change of weight, development of symptoms suggestive of diabetes etc. The Committee does not recommend labelling these people as having “pre-diabetes” based on having an HbA1c just less than 48 mmol/mol (6.5%) consistent with the position of the World Health Organisation (6).

However, prudent clinical practice would suggest that people having an HbA1c of 42-47 mmol/mol; 6.0-6.4%) are at an even higher risk for developing diabetes than that based on their AUSDRISK score alone. The HbA1c result may not fulfil the criteria for diagnosis but these individuals will have a degree of dysglycaemia that increases their risk of cardiovascular disease (7, 8). They should be counselled about lifestyle measures (weight

loss, dietary changes, exercise) as well as being assessed for other modifiable cardiovascular risk factors (hypertension, dyslipidaemia, smoking). Unless symptomatic, these people should not have additional blood glucose measurements performed to diagnose diabetes. It is possible that many people having a non-diagnostic HbA1c may have blood glucose levels that would be consistent with impaired fasting glucose, impaired glucose tolerance or diabetes. However, the HbA1c result is below the threshold for diagnosis which implies that these people are at minimal risk of developing microvascular complications (9). The HbA1c should be repeated 12 months later.

4. Confirmation of Diabetes Mellitus.

The NHMRC guidelines suggest that an abnormal blood glucose in an asymptomatic patient should be confirmed before the diagnosis of diabetes mellitus is established. However, a confirmatory HbA1c is not reimbursed by Medicare. A single elevated HbA1c result is accepted by Medicare as evidence of established diabetes. However, other organisations such as the World Health Organization and the American Diabetes Association recommend that diagnoses made by HbA1c be confirmed (6, 10).

Diabetes is a life long condition and there are employment, insurance, financial and lifestyle implications of being diagnosed with diabetes. It is important that the diagnosis is correct. Although HbA1c is a more reliable laboratory measure of mean blood glucose (1), it does have a small coefficient of variation even in the best laboratories. Additionally, handling errors can occur. In consideration of all these issues, the Committee recommends that a confirmatory test is performed on another day. Ideally, this test should be performed as soon as possible before any lifestyle or pharmacological interventions are commenced. If delayed, a subsequent normal result may simply reflect the improvement in glycaemia

following changes in management. If the result is below 48 mmol/mol (6.5%), then the diagnosis of diabetes has not been confirmed. In general, the patient should be advised that they do not have diabetes but they are at high risk of its development, and managed as outlined above in section 3.

Practically, this creates conflict between prudent clinical practice and the regulatory recommendations. According to Medicare, a single elevated HbA1c establishes the diagnosis and the patient is entitled to four monitoring HbA1c tests per year. The Committee has recommended that a confirmatory test be performed. Is the confirmatory test recommended by the Committee a monitoring test from the regulatory perspective? Can the first monitoring test be considered a confirmatory test? It would need to be performed before any management or lifestyle changes are made. If less than 48 mmol/mol, does this invalidate the original biochemical diagnosis and entitle the patient to further HbA1c tests for diagnosis annually? For the individual patient, these issues are reconciled by having a clear understanding of the timing and interpretation of the tests. In summary, the Committee simply recommends that a confirmatory test be considered. If performed appropriately and less than 48 mmol/mol, the patient should not be considered to have diabetes and should have a diagnostic HbA1c performed in 1 year.

5. Abnormal glycated haemoglobin measurements.

In the context of establishing the diagnosis of diabetes based on the HbA1c, an inappropriately low result is the major concern as the diagnosis will be missed. In all patients having an HbA1c performed, the possibility that the patient may have an

associated medical condition that may render the HbA1c measurement invalid should be considered. These conditions have been previously discussed (1). In summary, HbA1c may not be the appropriate test in patients with any significant chronic medical disease, any anaemia or any abnormality of red blood cell structure (Box 1). This possibility should certainly be considered in any patient who has a high AUSDRISK score with an unexpectedly low HbA1c. A full blood count (FBC) may reveal red blood cell abnormalities suggestive of a haemoglobinopathy or haemolytic anaemia but a normal FBC does not exclude the possibility. Certain ethnic communities are more likely to have an underlying abnormality of haemoglobin. In these people, the possibility should be discussed with the laboratory. Newer methodologies are minimising this problem.

Summary.

The use of the HbA1c for diagnosis overcomes many practical problems associated with traditional blood glucose measurements. However, the test is not without its own limitations of which the medical practitioner needs to be aware. The possibility of having a medical condition that may interfere with the test should always be considered, even though these are rare in most Australian communities. Appropriately used, it should provide a cost-effective, efficient and simple tool for the early diagnosis of type 2 diabetes.

References.

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Box 1.

Conditions that may reduce glycated haemoglobin.

A. Increased erythropoiesis.

Iron administration, Vitamin B12/ Folate administration, Erythropoietin therapy, Chronic liver disease, Reticulocytosis

B. Abnormal Haemoglobin

Haemoglobinopathies, Haemoglobin F, methaemoglobin

C. Decreased Glycation

Aspirin, Vitamin C and E, certain haemoglobinopathies, increased intra-erythrocyte pH.

D. Increased Erythrocyte Destruction.

Haemoglobinopathies, splenomegaly, rheumatoid arthritis, drugs eg antiretrovirals, ribavirin and dapsone.

E. Assay Issues.

Haemoglobinopathies*, hypertriglyceridaemia.

*The common heterozygote haemoglobinopathies do not cause problems with most currentassays but for further information contact your laboratory. Adapted from Gallagher et al (11)

Box 2.

Summary of Implementation Recommendations.

- The HbA1c should be consider in patients considered at high risk having an AUSDRISK score >12 or a pre-existing high risk condition.
- If one or more symptoms are present in a patient at low risk, blood glucose should be used for diagnosis.
- Patients who have multiple symptoms suggestive of diabetes mellitus are not asymptomatic and should have diabetes confirmed by measurement of blood glucose.
- A result equal to or above 48 mmol/mol (6.5%) suggests that the patient does have diabetes mellitus.
- A result less than 48 mmol/mol (6.5%) suggests that the patient does not have diabetes mellitus. As the test has been performed in a high risk patient the test should be repeated 12 months later
- A confirmatory test should be considered and performed on another day, ideally as soon as possible before any lifestyle or pharmacological interventions are commenced.
- Be aware of conditions which may invalidate the test.

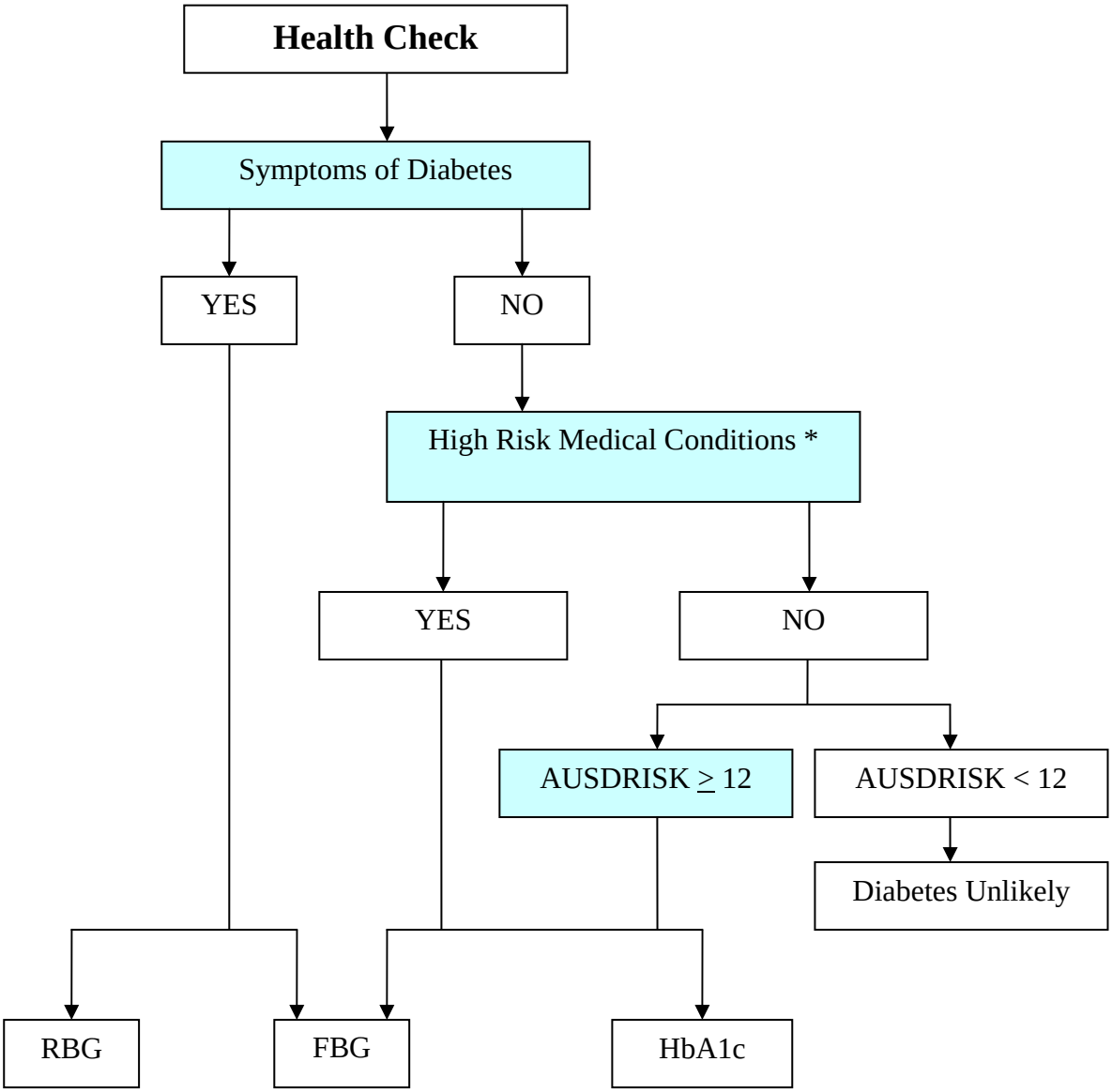

Figure 1. Pathway for Diagnosis of Diabetes Mellitus.

RBG = Random Blood Glucose. Diabetes is confirmed if BGL ≥11.1mmol/l
FBG = Fasting Blood Glucose. Diabetes is confirmed in a symptomatic patient if BGL ≥ 7.0 mmol/l. Diabetes is suggested if BGL ≥ 7.0 mmol/l in an asymptomatic patient and should be confirmed. Impaired Fasting Glucose is present if FBG 6.0 to 6.9 mmol/l. An oral glucose tolerance test is rarely required.
HbA1c ≥ 48 mmol/mol (6.5%) suggests diabetes (see article).
* High risk conditions include cardiovascular disease, prior gestational diabetes mellitus, impaired glucose tolerance or impaired fasting glucose, polycystic ovarian disease, and patients on antipsychotic medication.