ADS Position Statements

1996
Diabetes and Hypertension

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This position statement has been published: Med J Aust 1995;163:372-375

ABSTRACT
This position statement summarises the importance of hypertension associated with diabetes mellitus. It must be emphasised that although the principles of management of hypertension in the diabetic patient resemble those in a hypertensive individual without diabetes, important issues in terms of associated medical problems and choice of different classes of antihypertensive drugs need to be considered. The association of hypertension with a range of micro and macrovascular diabetic complications and the treatment of hypertension in patients with diabetes is reviewed with emphasis on the appropriate choice of antihypertensive drugs. In addition, treatment of early and overt diabetic nephropathy in the absence and presence of systemic hypertension is discussed. Finally, this statement outlines core facts and makes specific recommendations for the management of the patient with diabetes and hypertension.

INTRODUCTION
Over the last decade there has been increasing interest in the clinical association of hypertension with diabetes (1-3). Although a recent Consensus statement has provided guidelines for the management of hypertension in Australia (4) the present report focusses specifically on the management of hypertension in the diabetic patient. Hypertension is at least twice as prevalent in diabetic as in non-diabetic individuals (1). Furthermore, it has been clearly shown that hypertension in the patient with diabetes is associated with accelerated progression of both microvascular [retinopathy and nephropathy] (5) and macrovascular [atherosclerosis] complications (3). Macrovascular disease accounts for the majority of deaths in patients with non-insulin dependent (type II) diabetes and the presence of hypertension in this type of diabetes is associated with a 4-5 fold increase in mortality, predominantly from coronary artery disease and stroke (6).

DIABETIC RENAL DISEASE
Hypertension is associated with microvascular complications and in particular nephropathy (5). Diabetic nephropathy is now the leading cause of end-stage renal failure in the Western World with a similar number of insulin dependent (type I) and type II diabetic patients entering end-stage renal failure programmes (7). In type I diabetes, nephropathy affects about one third of patients (8) and antihypertensive treatment has been shown to retard its progression (9). In type II diabetic patients, hypertension is not as closely linked to renal disease and often antedates the diagnosis of diabetes (10). Data on the long-term effects of antihypertensive drugs on nephropathy in type II diabetes are still pending.

In type I diabetes, elevation of blood pressure is closely linked to renal disease (5). Longitudinal studies have shown that blood pressure is already rising in type I patients with diabetes before the development of overt proteinuria, in the phase known as microalbuminuria (11). Microalbuminuria is defined as an elevated urinary albumin excretion rate **(30-300mg/24hours or 20-200µg/minute)** when conventional dipstick tests for proteinuria such as Albustix, are still negative (12) and is now regarded as an early phase of nephropathy. In type I patients with diabetes the presence of micro-albuminuria or overt proteinuria predicts cardiovascular disease (13). The increase in cardiovascular disease is approximately threefold in microalbuminuric type I diabetic patients when compared to age and duration matched normoalbuminuric patients with diabetes (14).

This increase in cardiovascular disease is even higher in patients with overt proteinuria (13).

INSULIN RESISTANCE OR METABOLIC SYNDROME

Type II diabetes and hypertension commonly co-exist and may be part of the insulin resistance or metabolic syndrome (10). This syndrome describes a constellation of clinical and biochemical features which are strongly associated with accelerated atherosclerosis (12). These features include obesity, mixed dyslipidemia (raised triglycerides and low HDL-cholesterol) and hyperinsulinaemia as well as hypertension. The underlying mechanism for the association of hypertension with diabetes in this syndrome remains unknown. It is possible that endothelial dysfunction as a result of both hypertension and diabetes could be an important factor in the high incidence of vascular disease in individuals with both conditions (15).

ANTIHYPERTENSIVE THERAPY AND DIABETIC RENAL DISEASE

Hypertension should be treated aggressively in diabetic patients particularly if there is evidence of renal disease. The aim of blood pressure reduction includes retardation of the progression and prevention of diabetic complications. Many studies have been performed over the last decade to evaluate the efficacy of antihypertensive agents on the progression of diabetic nephropathy, with particular emphasis on type I diabetic patients (16). Recently, Lewis et al. reported that in type I diabetic patients with overt proteinuria, the ACE inhibitor, captopril, not only reduced proteinuria but delayed the onset of end-stage renal failure (17). Studies in microalbuminuric type I diabetic patients have shown that antihypertensive therapy, even in the absence of systemic hypertension, will reduce albuminuria and postpone the development of overt (Albustix positive) proteinuria (18,19). Long-term effects on renal function in this group of microalbuminuric type I diabetic patients remain to be determined. The role of other antihypertensive drugs and in particular calcium channel blockers in influencing the progression of diabetic renal disease has not been as clearly delineated (20). Comparisons between ACE inhibitors and other classes of antihypertensive drugs have been performed in diabetic patients (21,22). However, these studies have generally been short in duration, have concentrated on type I diabetes or have included heterogeneous groups of patients, including both forms of diabetes, both hypertensive and normotensive patients or patients with different stages of renal disease. At present, a significant number of large trials are in progress in both type I and type II diabetic patients focussing not only on different antihypertensive drugs but also on different goal blood pressures (23,24).

The role of ACE inhibitors in type II diabetic patients with albuminuria has not been as extensively investigated as in type I diabetes. However, in a study of patients with type II diabetes and microalbuminuria, Ravid et al demonstrated that the ACE inhibitor enalapril prevented the rise in albuminuria and decline in renal function observed in the placebo group (25). Recent meta-analyses have suggested that ACE inhibitors are superior to other classes of antihypertensive agents in reducing proteinuria in diabetic patients (21,22). A recently completed study by Lacourciere et al indicated that in microalbuminuric type II diabetic patients, captopril was superior to metoprolol or hydrochlorothiazide in reducing urinary albumin excretion (26). More detailed reviews of the various studies comparing the different classes of antihypertensive drugs in type I and

type II diabetic patients have been recently published (20-22). Retinopathy is closely associated epidemiologically with hypertension (27). However, the role of anti-hypertensive therapy in preventing this diabetic complication remains unknown. It is of interest that in the study by Ravid et al ACE inhibition was associated with the development of less retinopathy (25).

ANTIHYPERTENSIVE DRUGS - SIDE EFFECTS

The choice of antihypertensive drug should be determined by the drug's capacity to lower blood pressure, to protect the diabetic kidney from ongoing injury and also on its side effect profile (28). Antihypertensive drugs such as beta blockers and thiazide diuretics may influence glycaemic control in a deleterious manner (29). These agents can also have unfavourable effects on lipids by increasing triglyceride levels and decreasing HDL-cholesterol levels. Beta blockers may exacerbate symptoms of peripheral vascular disease, a condition which is more prevalent in diabetic patients (28). In type I diabetic patients who are at a high risk of hypoglycaemia, beta blockers may reduce awareness of hypoglycaemia and inhibit the metabolic counter-regulatory response. Recently, it has been shown that the deleterious effects of thiazide diuretics on lipid and glucose metabolism are dose related and do not generally occur if low doses are used (30). The alpha blockers such as prazosin and the calcium channel blockers do not have adverse effects on glucose or lipid levels. ACE inhibitors have been shown to enhance insulin sensitivity (31). However, these modest effects on insulin resistance do not appear to be associated with a dramatic improvement in glycaemic control in diabetic patients. Nevertheless, this class of agent, like calcium channel and alpha blockers, does not adversely affect lipid or glucose levels. ACE inhibitors are commonly used in diabetic patients with nephropathy (17-19). However, these agents may uncommonly be associated with life-threatening hyperkalaemia (32), particularly in the setting of hyporeninaemic hypoaldosteronism, a condition that is often associated with renal impairment and autonomic neuropathy in diabetes. Renal artery stenosis should always be considered in the setting of recent onset hypertension in a diabetic patient. This is particularly relevant if there is bilateral renal artery stenosis which is often associated with rapid deterioration of renal function if ACE inhibitors are administered (33).

RECENT GUIDELINES IN THIS AREA

Recently, there has been a proliferation in guidelines for the mangement of hypertension. In some of these reports, specific recommendations for the treatment of the diabetic patient with hypertension have been included (4, 34-36). In addition, several of the organisations which advise on the management of diabetes have developed their own set of guidelines for treating hypertension in the diabetic patient (37,38). Finally, the recent results suggesting renal protection in diabetic patients with antihypertensive drugs and in particular ACE inhibitors in the setting of a “normal” blood pressure and evidence of early or overt nephropathy has led to specific recommendations on the use of antihypertensive agents in the absence of hypertension (39).

This position statement outlines the opinion of the Australian Diabetes Society in this area and has in particular reviewed the guidelines of the Australian Consensus statement on hypertension (4) as well as recent guidelines from the American Diabetes Association (37) and the report by an Ad-Hoc Committee to the Scientific Advisory Board of the National

Kidney Foundation of the United States (39). In all these reports it has been commented that ACE inhibitors may have a specific role in diabetic patients with proteinuria. However, the reports have varied as to whether ACE inhibitors are considered the drugs of first choice in the clinical situation of diabetes, hypertension and proteinuria.

CONCLUSION

Individuals with both hypertension and diabetes are at high risk for both vascular and renal disease. Such individuals should be treated with appropriate antihypertensive drugs and must be carefully monitored in terms of satisfactory blood pressure control and prevention and management of end-organ complications.

CORE FACTS IN DIABETES AND HYPERTENSION

1. Hypertension is twice as prevalent in diabetic compared with non-diabetic subjects.

2. The co-existence of hypertension with diabetes is associated with accelerated progression of both atherosclerotic cardiovascular disease and microvascular complications.

3. Both hypertension and diabetes are risk factors for stroke.

4. Overt diabetic nephropathy which is often accompanied by hypertension is associated with up to a 30 fold increase in mortality, mostly from cardiovascular disease.

5. Antihypertensive therapy in patients with diabetic nephropathy reduces the rate of decline in renal function and decreases proteinuria.

6. In patients with type I diabetes, hypertension is usually absent at diagnosis and its development is associated with nephropathy.

7. In patients with type I and type II diabetes, the prevalence of hypertension increases from normoalbuminuria to microalbuminuria to macroalbuminuria.

8. Type II diabetes and hypertension frequently co-exist as part of the so-called Insulin Resistance or Metabolic Syndrome that additionally includes hyperinsulinaemia, obesity, increased VLDL triglyceride, decreased HDL cholesterol and atherosclerotic vascular disease.

9. Thiazides may lead to sexual dysfunction, worsened glycaemic control and dyslipidaemia. However, the metabolic side effects are less prominent with low doses of these agents.

10. Beta blockers are associated with increased VLDL triglyceride, reduced HDL cholesterol, sexual dysfunction, exacerbation of symptoms of peripheral vascular disease and a reduction in hypoglycaemic awareness and its rate of recovery.

11. Angiotensin converting enzyme (ACE) inhibitors may decrease proteinuria and preserve renal function to a greater extent than other antihypertensive agents. ACE inhibitors may have a renoprotective action in the normotensive patient with microalbuminuria (urinary albumin excretion rate 30-300mg/24hrs). These drugs do not have deleterious effects on lipid and glucose levels but may lead to deterioration in renal function in the presence of bilateral renal artery stenosis and to hyperkalaemia in the setting of hyporeninaemic hypoaldosteronism.

12. Calcium channel blockers are effective antihypertensive agents in diabetes and do not have any deleterious metabolic side effects. Their role as renoprotective agents in diabetes has not been clearly demonstrated.

PRACTICE RECOMMENDATIONS IN DIABETES AND HYPERTENSION

1. Blood pressure should be measured in the supine position after 5 minutes rest at every visit in all patients with diabetes. Since postural hypotension related to autonomic neuropathy is common in diabetes, regular measurement of standing blood pressure should also be considered.

2. The appropriate cuff size (bladder length should be at least 80% and bladder width at least 40% of the arm circumference) should be used for measuring blood pressure. This is particularly relevant in type II diabetes with its high prevalence of obesity.

3. In patients with hypertension, the presence of all long-term complications, especially nephropathy and vascular disease, should be suspected and formally evaluated.

4. Assessment of diabetic nephropathy should include measurement of creatinine clearance and urinary protein excretion including screening for microalbuminuria.

5. In this group of patients with a high risk of vascular disease a fasting lipid profile (total and HDL-cholesterol and triglycerides) should be performed.

6. Hypertension in diabetes should be defined as equal to or greater than 140/90 in individuals less than 40 years old. In individuals more than 60 years old, hypertension is defined as blood pressure equal to or greater than 160/90. These levels of blood pressure to start treatment should be considered as minimal criteria. Introduction of therapy at lower blood pressure levels should be considered in patients with diabetes if there is evidence of microalbuminuria or overt renal disease.

7. In diabetic children, the definition of hypertension is a blood pressure greater than the 90th percentile for age.

8. Ambulatory and home blood pressure monitoring may be useful in individuals with suspected "whitecoat" hypertension (elevated in the office setting but normal at home), labile hypertension, or orthostatic hypotension with supine hypertension, as is commonly observed in diabetic patients with autonomic neuropathy.

9. The choice of antihypertensive drug therapy in diabetic patients requires careful consideration of the advantages and disadvantages of each class of agent with particular regard to their beneficial and deleterious effects on glucose and lipid metabolism.

10. In individuals with evidence of renal disease, either microalbuminuria or overt proteinuria, ACE inhibitors should be considered the first choice of antihypertensive agent.

11. Regular monitoring of plasma potassium and creatinine concentrations must be instituted in all diabetic patients on ACE inhibitors. Measurements must be performed before and within 2 weeks of commencing therapy.

12. In hypertensive diabetic patients with angina an appropriate choice of antihypertensive drug would be a beta blocker or calcium channel blocker whereas in the setting of congestive cardiac failure an appropriate choice would be an ACE inhibitor.

13. The target blood pressure with antihypertensive therapy in diabetic patients is as yet unknown. However, the use of drugs, particularly ACE inhibitors should be considered in normotensive diabetic patients if they have evidence of persistent microalbuminuria, particularly if they are less than 40 years old and urinary albumin excretion is increasing. In such individuals, a goal blood pressure of less than 130/85 should be considered.

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Flow chart indicating strategy for management of hypertension in a diabetic patient.