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Diabetes and Hypertension: Pathogenesis, Prevention and Treatment†

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ABSTRACT

Hypertension occurs in approximately 30% of patients with type 1 diabetes and from 50 to 80% of patients with type 2 diabetes. Although the pathogenesis of hypertension is distinct in each type, hypertension markedly enhances the already high risk of cardiovascular and renal disease in types 1 and 2 and implications for treatment are similar in both. The threshold for blood pressure treatment in diabetic patients is generally agreed to be 140/90 mm/hg with a target BP of < 130/80. So-called ''lifestyle modifications'' play an important role in therapy, particularly in type 2 patients, by decreasing blood pressure and improving other risk factors for cardiovascular disease. Indeed non-pharmacologic interventions have been demonstrated to prevent the development of type 2 diabetes in patients at high risk to develop the disease. Aggressive anti-hypertensive drug treatment is warranted given the high risk associated with the combination of diabetes and hypertension and the demonstrated effectiveness of anti-hypertensive treatment in reducing cardiovascular morbidity and mortality in this group of patients. ACE inhibitors and ARBs are the cornerstones of pharmacologic management, in no small part because of the renoprotective effects of these agents in antagonizing the development and

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progression of diabetic renal disease. Multiple agents, including diuretics, will usually be required to attain target blood pressure levels.

Key Words: Diabetes; Hypertension; Microalbuminuria; Nephropathy; Cardiovascular risk factors.

INTRODUCTION: INCIDENCE AND PATHOGENESIS

Type 1 Diabetes Mellitus

In patients with type 1 diabetes, absolute failure of insulin secretion follows autoimmune destruction of the pancreatic beta cells. In type 1 patients, hypertension develops after a substantial latent period and is related, at least in part, to blood glucose control. Hypertension follows the development of diabetic renal disease, as signified by the presence of microalbuminuria (30 to 300 mg albumin excretion per day; over 300 mg day is macroalbuminuria, or proteinuria, measured by standard laboratory techniques). A classic microvascular complication, renal disease develops in approximately 30% of type 1 patients (1,2). The presumption is that the renal disease causes the hypertension, although recent studies (3) have raised the possibility that subtle increases in blood pressure (loss of normal nocturnal fall in BP) may play a role in the genesis of microalbuminuria and hence diabetic renal disease. It is clear that elevated blood pressures have a detrimental effect on renal function and protein excretion. In addition to their blood pressure lowering effects Angiotensin Converting Enzyme (ACE) inhibitors have been demonstrated to have further selective benefit in diminishing microalbuminuria and preventing or delaying the progression of diabetic nephropathy (1). These agents are therefore indicated in all type 1 patients with microalbuminuria even when the blood pressure is normal. Presumably angiotensin receptor blockers (ARBs) have a similar effect in type 1 patients (as has been demonstrated for type 2 patients, see below), although this has not been conclusively established.

Type 2 Diabetes Mellitus

Over 90% of patients with diabetes mellitus in the US have the type 2 variety. Hypertension is also more common in type 2 as compared with type 1 patients, occurring in 50 to 80% of type 2 patients. In contrast to type 1 patients, hypertension is frequently present at the time of diagnosis of type 2 diabetes, although it is important to note that the onset of type 2 disease, being insidious, is difficult to identify with certainty. The time course of development, and the fact that hypertension is much more common than nephropathy in type 2 patients, indicate that, in distinction to type 1 patients, the nephropathy is not the cause of the elevated blood pressure. Nonetheless, hypertension has important adverse effects on nephropathy in type 2 patients and needs aggressive treatment.

Most patients with type 2 diabetes, at least in western populations, are obese with a central or abdominal fat distribution; in Asia, although obesity is less commonly associated with type 2 diabetes than in the west, the association with abdominal fat

accumulation, as indicated by the waist to hip ratio, has been documented. The fundamental pathogenetic features of type 2 diabetes are insulin resistance coupled with an inherited limitation of pancreatic beta cell insulin secretory reserve. In the face of impaired insulin action on skeletal muscle glucose uptake, glucose levels rise, insulin secretion increases, and plasma insulin levels rise, partially compensating for the impairment in glucose metabolism. Over time, in predisposed individuals, insulin secretion cannot keep pace and impaired glucose tolerance followed by overt type 2 diabetes mellitus develops.

It appears likely that the pathogenesis of hypertension in type 2 diabetic patients resembles that in obese patients with the metabolic syndrome. A recently described factor in the elusive pathogenesis of central or abdominal fat localization may be the expression of 11 beta-hydroxysteroid dehydrogenase type 1 in central abdominal fat cells. This enzyme can form active cortisol from inactive cortisone thereby amplifying the biologic effects of glucocorticoids and contributing to an expansion of the intra-abdominal fat mass that is associated with hypertension (4). Central obesity, insulin resistance, hyperinsulinemia, increased leptin, sympathetic nervous system stimulation, and adipocyte production of angiotensinogen with consequent activation of the renin-angiotensin-aldosterone system (5) all appear to be involved in the pathogenesis of the increased blood pressure and the generation of other commonly associated cardiovascular risk factors. The hypertension in type 2 diabetes may be considered part of a continuum with obesity related hypertension (6).

Several large, prospective, randomized trials have recently demonstrated that in addition to their blood pressure lowering effects, ARBs have selective further benefit in reducing the rate of progression of renal disease (7). This class of drugs should always be part of any therapeutic regimen for patients with Type 2 diabetes and albuminuria. Data are limited, however, with the use of ACE inhibitors in patients with Type 2 diabetes but they may have similar beneficial effects (7).

RISK OF CARDIOVASCULAR EVENTS AND DIABETIC NEPHROPATHY

Myocardial Infarction and Stroke

The clinical importance of the association of diabetes and hypertension is directly related to the magnitude of the cardiovascular risk imposed when these two common diseases occur concomitantly. Diabetes doubles the risk for major cardiovascular events including myocardial infarction and stroke in hypertensive patients already at increased risk (8). The risk associated with high blood pressure in diabetic patients is demonstrable as a continuous variable across a broad range of blood pressure levels extending well into the normal range. This enhanced risk, plus the fact that treatment has a more pronounced effect to reduce cardiovascular end points in diabetic as compared with non-diabetic hypertensives, forms the basis for aggressive antihypertensive recommendations. Furthermore, patients with nephropathy in both types of diabetes are at considerably increased risk for coronary heart disease (9,10) and the presence of microalbuminuria is now considered to be a risk factor for coronary artery disease (11).

Diabetic Nephropathy

Diabetes is the most common cause of renal failure in the world (12). While hyperglycemia contributes to the development of diabetic nephropathy (1,2), hypertension accelerates the progression of the disease. Blockade of the renin angiotensin system with ACE inhibitors or ARBs, even in the presence of normal levels of blood pressure decreases microalbuminuria and slows the progression of renal failure (1).

TREATMENT AND PREVENTION

Effect of Lifestyle Intervention and Insulin Sensitizing Drugs on the Incidence of Type 2 Diabetes

It is well established that an intensive program of lifestyle modification can delay or prevent the development of type 2 diabetes (13–15). The recently published results of the Diabetes Prevention Program (DPP) (13) clearly demonstrated that low energy, low fat diets, in conjunction with moderate exercise for at least 150 minutes per week, reduced the incidence of diabetes by 58%, in a population at high risk for the development of type 2 diabetes. The results were so impressive that the monitoring board stopped the study one year early. The cumulative incidence of diabetes at three years was 28.9% in the control group and 14.4% in the intervention group (13). This beneficial change was associated with an average weight loss of only 4 to 5 kilograms. Lifestyle intervention, moreover, was more effective than treatment with the anti-hyperglycemic agent, metformin, although the latter exerted a beneficial effect in comparison with placebo (13).

The DPP did not address the mechanisms involved in the beneficial effect of lifestyle changes. Since the three interventions, decreased caloric intake with weight loss, lowered fat intake, and physical exercise all increase insulin sensitivity, it is a reasonable inference that diminishing insulin resistance plays a role. Consistent with this interpretation is a recent study (16) demonstrating that troglitazone, an insulin-sensitizing drug of the thiazolidinedione class, reduced the incidence of diabetes by over 50%. This effect, moreover, persisted for at least eight months after the drug was discontinued, and was most marked in those subjects who responded with the greatest increase in insulin sensitivity. Troglitazone has been removed from the market because of hepatic toxicity but other drugs of this class (pioglitazone, rosiglitazone) are in current usage in the treatment of type 2 diabetes.

It is thus clear that pharmacologic and non-pharmacologic strategies are available for the prevention of type 2 diabetes in high-risk groups. In addition, intensive interventions to reduce risk factors (hyperglycemia, hypertension, hypercholesterolemia) in type 2 diabetic patients have been demonstrated to reduce microvascular and macrovascular complications by 50% (17).

Thresholds and Targets for Drug Treatment

There is general agreement that that the threshold for drug treatment of hypertension in diabetic patients is 140/90 mm/hg and that the therapeutic goal is 130/80 or below (11,18,19). This target is predicated on the continuous relationship

between cardiovascular risk and blood pressure and the absence of a demonstrated lower limit of benefit in published trials. Based on a meta-analysis of multiple studies of patients with diabetic nephropathy, an even lower goal of 125/75 or below has been recommended for those with progressing nephropathy (19). It is also generally recognized, however, that achieving these lower goals may be difficult, particularly on the systolic side. As a consequence multiple agents will frequently be necessary (7,11,18,19).

Specific Agents: Primacy of ACE Inhibitors and ARBs

It is worth emphasizing that blood pressure reduction *per se* is the major goal. Some regimens, however, appear to offer distinct benefits, while others are associated with untoward outcomes in diabetic patients. As noted above, the renoprotective effects of ACE inhibitors and ARBs confer an important advantage in delaying or preventing the development of diabetic nephropathy and every diabetic patient with microalbuminuria, even if normotensive, should be on one of these agents. There is also some evidence that these agents have an advantage in reducing overall cardiovascular risk in diabetics (20,21). A further advantage of ACE inhibitors and ARBs is a beneficial impact on carbohydrate metabolism in comparison with beta blocker based regimens (22,23). The latter have been shown to increase the development of diabetes in populations at risk.

Since combination therapy will be required in almost all diabetic hypertensives to achieve goal, the addition of diuretics, selective beta-1 blockers, and calcium channel blockers (CCBs), will usually be required to attain goal BP. Low dose thiazide diuretics can be used initially but in the face of deteriorating carbohydrate metabolism or renal insufficiency low doses of long acting loop diuretics are preferable. Although the ALLHAT study suggested that chlorthalidone was equal in efficacy to ACE inhibitors for type 2 diabetes (24), the weight of evidence suggests that drugs affecting the renin-angiotensin system are preferable, particularly in patients with increased urinary albumin excretion (25,26). As most patients will require two or more drugs, this issue generally is moot. Potassium levels should be monitored in all diabetics on ACE inhibitors and ARBs. Although beta blockers are not agents of first choice in patients with diabetes, they are effective at lowering the BP, and clearly indicated for their cardioprotective effects in the presence of ischemic heart disease. Caution is needed in using beta blockers in patients with type 1 diabetes who are prone to hypoglycemia, as they may mask the symptoms of hypoglycemia as well as inhibit glycogen breakdown. CCB's may also be effective but the use of dihydropyridine CCB's is controversial in diabetic patients (26).

CONCLUSIONS

Current therapeutic strategies in the management of hypertensive type 2 diabetic patients, or patients at risk for the development of type 2 diabetes, are highly effective. Intensive lifestyle interventions including weight loss and moderate exercise delay or prevent the development of overt type 2 diabetes, and reduce the cardiovascular and microvascular complications of diabetes. Aggressive antihypertensive regimens employing ACE inhibitors or ARBs delay or prevent the development of diabetic nephropathy and lower overall cardiovascular risk. Usually two or more drugs are required

for effective control of blood pressure to the recommended level of < 130/80 mmHg and diuretics should generally be included in most regimens. Although the impact of antihypertensive treatment on cardiovascular risk in people with diabetes is greater than that of glucose control (26), an aggressive approach in treating all cardiac risk factors is warranted in these high risk individuals, including LDL cholesterol lowering, smoking cessation, and use of aspirin.

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