Treatment of Obesity Hypertension and Diabetes Syndrome

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Abstract—Obesity has been shown to be an independent risk factor for coronary heart disease. The insulin resistance associated with obesity contributes to the development of other cardiovascular risk factors, including dyslipidemia, hypertension, and type 2 diabetes. The coexistence of hypertension and diabetes increases the risk for macrovascular and microvascular complications, thus predisposing patients to cardiac death, congestive heart failure, coronary heart disease, cerebral and peripheral vascular diseases, nephropathy, and retinopathy. Body weight reduction increases insulin sensitivity and improves both blood glucose and blood pressure control. Metformin therapy also improves insulin sensitivity and has been associated with decreases in cardiovascular events in obese diabetic patients. Antihypertensive treatment in diabetics decreases cardiovascular mortality and slows the decline in glomerular function. However, pharmacological treatment should take into account the effects of the antihypertensive agents on insulin sensitivity and lipid profile. Diuretics and \( \beta \)-blockers are reported to reduce insulin sensitivity and increase triglyceride levels, whereas calcium channel blockers are metabolically neutral and ACE inhibitors increase insulin sensitivity. For the high-risk hypertensive diabetic patients, ACE inhibition has proven to confer additional renal and vascular protection. Because hypertension and glycemic control are very important determinants of cardiovascular outcome in obese diabetic hypertensive patients, weight reduction, physical exercise, and a combination of antihypertensive and insulin sensitizers agents are strongly recommended to achieve target blood pressure and glucose levels. (Hypertension. 2001;38[part 2]: 705-708.)

Key Words: obesity ■ diabetes ■ drug therapy

Hypertension is very frequent among obese type 2 diabetic patients.\(^1,2\) In contrast with hypertension in type 1 diabetes,\(^3\) hypertension in type 2 diabetes develops even without renal involvement. The risk of type 2 diabetes and hypertension are strongly related to obesity and central distribution of fat.\(^3,5\) The constellation of abnormalities that include obesity, hypertension, type 2 diabetes, and also dyslipidemia is called metabolic syndrome. Insulin resistance with hyperinsulinemia is characteristic of the metabolic syndrome, and this condition has been associated with high cardiovascular risk, morbidity, and mortality.\(^6\) Hyperinsulinemia may lead to hypertension and also to an abnormal lipid profile, thereby predisposing patients to atherosclerosis. The rise in plasma insulin levels may elevate blood pressure levels by a variety of mechanisms, including increased sympathetic activity and sodium retention.\(^7,8\) Obesity-induced changes in the renal medulla, resulting in activation of the renin-angiotensin system, may also contribute to sodium retention and hypertension in visceral obese subjects.\(^9\)

Treatment of Hypertension in Diabetic Patients

The occurrence of diabetes and hypertension are multiplicative risk factors for macro- and microvascular disease, resulting in increased risk of cardiac death, coronary heart disease, congestive heart disease, cerebrovascular disease, and peripheral vascular disease.\(^1\) Macrovascular complications account for the majority of deaths in diabetics, and absence of hypertension is associated with increased survival.\(^10\)

Because hypertension is a major determinant of cardiovascular events in type II diabetes, tight blood pressure control is a must in these patients. In fact, in type 2 diabetic patients, the benefits of tight blood pressure control may be even greater than the benefits of a more intensive glycemic control, as shown in the UK Prospective Diabetes Study (UKPDS) study.\(^11\) Nevertheless, clinicians should pursue both blood pressure and glycemic control, as tightly as possible.

Nonpharmacological Treatment

When obese patients with diabetes present with mild hypertension, nonpharmacological measures should be encouraged.\(^12\) Among these are body weight reduction, increased physical activity, decrease in dietary sodium intake, cessation of smoking, and avoidance of excess alcohol ingestion. Body weight reduction and increased physical activity will ameliorate glucose control by decreasing insulin resistance. However, despite all of the apparent cardiovascular benefits associated with weight reduction in obese patients, which

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include reductions in blood pressure, reductions in left ventricular mass, and improvement in lipid profile, there is no evidence that these changes are associated with decreases in mortality.

**Pharmacological Treatment**
The choice of pharmacologic agents to treat obese patients with hypertension and diabetes has to take into account the effects on body weight, metabolic disturbances, and complications of diabetes and/or hypertension.

**Antidiabetic Therapy**
Among the oral antidiabetic agents used in type 2 diabetes, metformin and the thiazolidinediones have been shown to improve glucose tolerance by enhancing insulin sensitivity and to lower blood pressure. The UKPDS study was designed to compare the effects of intensive blood glucose control though different treatment regimens (diet, sulfonylureas, metformin, and insulin) with conventional treatment on the micro- and macrovascular complications of diabetes in ≈4000 patients with type 2 diabetes. Over 10 years, the average glycosylated hemoglobin was 7% in the intensive-treated group compared with 7.9% in the conventional group. This resulted in a 12% reduction in any diabetes-related end point and a 10% in any diabetes-related death (P=0.34) in the intensive-treated group. Most of the risk reduction in this group was due to a 25% risk reduction in microvascular endpoints (P=0.009). There was no reduction in macrovascular disease. A 16% decrease in myocardial infarction did not reach statistical significance (P=0.052). A subset of 1700 overweight patients (>120% ideal body weight) recruited to the UKPDS were included in a separate treatment arm that compared intensive blood glucose control with metformin to conventional therapy. A secondary analysis compared 342 patients allocated to metformin with 951 patients receiving intensive therapy with sulfonylureas or insulin. Over 10 years, the average glycosylated hemoglobin was 7.4% in the metformin-treated group compared with 8.0% in the conventional group. Treatment with metformin resulted in risk reduction of 32% in any diabetes-related end points, 42% in diabetes-related death, and 36% in all-cause mortality. Compared with the group on intensive therapy with sulfonylureas or insulin, the metformin-treated group also showed a greater reduction in any diabetes-related end point, all-cause mortality, and stroke (P<0.0034). Compared with sulfonylureas or insulin therapy, metformin therapy was also associated with less weight gain, fewer hypoglycemic attacks, and lower insulin plasma levels. It is not clear, however, if the improvement in insulin sensitivity induced by metformin confers long-term cardiovascular benefit compared with that of other drugs that reduce blood pressure or blood glucose.

**Antihypertensive Therapy**
As a general rule, the most important objective is to reduce blood pressure to as near the normal values as possible. The goal of blood pressure in type 2 diabetes, as suggested by the Hypertension Optimal Treatment (HOT) trial, should be diastolic blood pressure of ≤80 mm Hg; 85 mm Hg was shown to be less cardioprotective. Similar results have been published in the UKPDS. In this latter study, 1148 patients treated with either captopril or atenolol were randomized to a goal blood pressure <150/85 mm Hg (tight group) or <180/105 mm Hg (less-tight group). At the end of the study, blood pressure levels in the 2 groups were 144/82 mm Hg and 154/87 mm Hg, respectively. After a follow-up of 8 to 9 years, patients in the lower blood pressure group showed a 24% reduction in diabetes-related end points, including microvascular disease; 44% less strokes; and 32% reduction in deaths related to diabetes. They also showed 34% less occurrence of deterioration in retinopathy compared with that of the higher blood pressure group. It is important to stress that 29% of patients in the tight blood pressure control group required ≥3 antihypertensive drugs.

**Antihypertensive Agents**

**ACE Inhibitors and Ang II Antagonists**
This family of agents offers a number of advantages, probably reflecting a major role of angiotensin (Ang) II in the deterioration of renal function and development of atherosclerosis. In type 1 diabetics, ACE inhibitors (ACE-Is) have been proven to reduce the velocity of progression to renal failure and are the only antihypertensive agents that lower protein excretion even when blood pressure is not lowered. Clinically, ACE-Is may not be sufficient to lower blood pressure, and in addition, other antihypertensive agents may be needed. ACE-Is have synergistic actions with diuretics and calcium blockers. Also they have no deleterious effects on lipid metabolism and may even lower lipid levels through the improvement of carbohydrate metabolism. The mechanism of the improvement in glucose utilization may involve increases in kinin formation by ACE-I. One possible explanation is that increases in blood flow induced by kinins may influence insulin sensitivity by promoting better insulin delivery and glucose uptake by the tissues. In normal rats, we have demonstrated that the use of a bradykinin inhibitor may decrease insulin sensitivity.

A cardioprotective effect of converting enzyme inhibition was recently shown by the Hope Study, which was designed to assess the cardiovascular benefits of ramipril in 9297 patients, age ≥55 years, who had a previous cardiovascular event or diabetes plus 1 other cardiovascular risk factor. The primary outcome was a composite of myocardial infarction, stroke, or death from cardiovascular causes. Over a mean period of 5 years, the relative risk of any primary end point was 0.78 (P<0.001) in the ramipril-treated group. In the 3577 diabetic patients without clinical proteinuria included in this study, ramipril lowered the risk of the combined primary outcome by 25% (P=0.0004), myocardial infarction by 22% (P=0.01), stroke by 33% (P=0.074), cardiovascular death by 37% (P=0.0001), total mortality by 24% (P=0.004), and overt nephropathy by 24% (P=0.027). The benefits of ramipril in this study were greater than those that would be expected from the observed effects in blood pressure. The inhibition of Ang II formation or the increase in bradykinin concentrations are possibly some of the mechanisms involved in the protective effect of the ACE-I on the arterial wall.
Close monitoring of potassium levels in the blood is warranted when patients have decreased renal function. Hyperkalemia is a frequent cause of suspension of ACE-I in patients with diabetic nephropathy. Diabetic patients appear to be more prone to develop hyperkalemia probably because of a decrease in aldosterone production.26 Blockade of the renin-angiotensin system with Ang II blockers, from both experimental and clinical data, appear to be equally protective as ACE-I. Ongoing clinical trials in type 2 diabetics will give us a more definite answer as to their role in clinical practice.27

**Diuretics**

These agents, together with salt restriction, are most frequently needed to control blood pressure in diabetic obese patients. The association with ACE-I enhances the antihypertensive effect and reduces the chances of hypokalemia that may worsen insulin resistance.28 More recently, the use of low-dose (12.5 to 25 mg) thiazide therapy has been shown to reduce metabolic disturbances consequent to diuretic therapy.30 Results from the Systolic Hypertension in the Elderly Patient (SHEP) study have shown that chlorthalidone therapy (doses 12.5 to 25 mg) was twice as effective in preventing cardiovascular events in diabetics than in nondiabetic hypertensive patients.31 In clinical practice, it is almost impossible to control blood pressure in diabetic patients without the use of diuretics. Most frequently, thiazides have to be replaced by more potent loop diuretics to control blood pressure, especially when renal damage progresses.

**β-Blockers**

Increases in insulin resistance in obese patients occur during β-blocker therapy.32 However, in clinical practice, β-blockers are frequently used to control tachycardia, to help lower blood pressure, and to assist in secondary prevention of myocardial infarction. In the UKPDS, despite being associated with cardiovascular events in diabetics than in nondiabetic hypertensive patients.31 In clinical practice, it is almost impossible to control blood pressure in diabetic patients without the use of diuretics. Most frequently, thiazides have to be replaced by more potent loop diuretics to control blood pressure, especially when renal damage progresses.

**Calcium Channel Blockers**

Calcium channel blockers are very efficacious in lowering blood pressure and are metabolically neutral for glucose and lipid profiles. The HOT trial showed a cardiovascular protective effect of the long-acting dihydropyridine calcium blocker felodipine.17 In this large study (≈19 000 subjects), patients were randomized to 3 target diastolic blood pressures: ≤90 mm Hg, ≤85 mm Hg, and ≤80 mm Hg. In a subset of 1501 diabetic hypertensive patients, the relative risk of a cardiovascular event was reduced in the ≤80 mm Hg group compared with the ≤90 mm Hg group (relative risk, 0.49).

The placebo-controlled Systolic Hypertension in Europe Trial (Syst-Eur Trial)18 analyzed the effect of nitrindipine in systolic hypertension in the elderly. In the diabetic patients (n=492; 10% of total patients studied), blood pressure was 8.6/3.9 mm Hg lower in the nitrindipine group than in the placebo group. After a median follow-up of 2 years, active treatment reduced cardiovascular events by 69%, cardiovascular mortality by 76%, and overall mortality by 55%. These reductions were greater than those observed in the nondiabetic patients in the study. However, according to the results of Fosinopril Amlodipine Cardiovascular Events Trial (FACET) and Appropriate Blood Pressure Control in Diabetics (ABCD) clinical trials,25,36 calcium channel blockers do not appear to be as protective against coronary disease as ACE-Is.

Because high blood pressure levels are important determinants of cardiovascular outcomes in obese diabetic hypertensive patients, a more strict control of blood pressure is strongly recommended. In diabetic patients with normal renal function, goal systolic blood pressure should be <130 mm Hg; a goal diastolic blood pressure, <85 mm Hg.3,19–21 However, if patients have renal insufficiency and excrete >1 to 2 grams protein/24 hours, goal blood pressure control should be 120/75 mm Hg.22 For renal and vascular protection of the hypertensive diabetic patients, the blockade of the renin-angiotensin system seems to be important. Because poor glycemic control has proven to contribute to vascular lesions, for the insulin resistant obese patients, the administration of insulin-sensitizer agents are preferred. The goal of therapy should be the reduction of glycosylated hemoglobin to values <7% when the upper limit of the method of determination is near 6%. Because these targets are difficult to achieve, body weight reduction, physical exercise, and a combination of several antihypertensive and antidiabetic agents are usually necessary.

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