Insulin Resistance and Hypertension

Theodore A. Kotchen

Resistance to insulin-stimulated glucose uptake is associated with increased risk for cardiovascular disease [1]. Risk factors for cardiovascular disease tend to cluster within individuals, and insulin resistance may be the link between hypertension and dyslipidemia. Depending on the populations studied and methodologies used for defining insulin resistance, approximately 25% to 40% of nonobese nondiabetic patients with hypertension are insulin-resistant [2]. Insulin resistance also has been observed in genetic and acquired animal models of hypertension. A constellation of insulin resistance, reactive hyperinsulinemia, increased triglycerides, decreased high-density lipoprotein cholesterol, and hypertension was designated as syndrome X by Reaven in 1988 [3].

Although a number of putative mechanisms have been proposed, it is unclear whether insulin resistance or reactive hyperinsulinemia, or both, actually cause hypertension. The recent observations that insulin-sensitizing agents attenuate the development of hypertension lend credence to this hypothesis [4]. As discussed subsequently, however, these agents may lower blood pressure by different mechanisms. Whatever mechanism may be involved, the observation that a single agent may have the capacity to both increase insulin sensitivity and lower blood pressure is potentially of considerable clinical significance.

Non-insulin-dependent diabetes mellitus represents an extreme of insulin resistance. Among diabetics, a two- to threefold increased prevalence of hypertension exists. Hypertension is associated with a fourfold increase in mortality among patients with non-insulin-dependent diabetes, and antihypertensive drug therapy has a beneficial impact on both macrovascular and microvascular disease [5]. Despite the potential concern that diuretics may augment insulin resistance, diabetic patients benefit from antihypertensive therapy with diuretics. The renal protective effect of antihypertensive drugs varies among different classes of agents. Angiotensin-converting enzyme inhibitors decrease proteinuria and retard the progression of renal insufficiency in diabetic patients with normal blood pressure and hypertension.
This benefit is independent of an effect on blood pressure and may be related specifically to the capacity of these agents to dilate the efferent renal arteriole. Results of studies evaluating the effects of calcium antagonists on the progression of diabetic nephropathy are varied. Some studies suggest that dihydropyridine calcium antagonists accelerate the progression of diabetic nephropathy, particularly in the short term. Additional studies are required to evaluate the antihypertensive potential of insulin-sensitizing agents in patients with non-insulin-dependent diabetes.

**FIGURE 5-1**

Hyperlipidemia and hypertension. **A**, Epidemiologic studies document an association between serum cholesterol and blood pressure in men and women. **B**, Based on data from the National Health and Nutrition Examination Survey II, persons with hypertension have a high prevalence of hyperlipidemia and vice versa [6]. (Panel A from Bonna and Thelle [7]; with permission.)

**FIGURE 5-2**

Insulin resistance and hypertension. **A**, Genetic and nutritional factors contribute to insulin resistance and resultant hyperinsulinemia. In addition to obesity and type II diabetes, hyperlipidemia and hypertension also may be associated with insulin resistance. Insulin resistance may account for the association of hyperlipidemia with hypertension. **B**, Insulin resistance is associated with hypertension in a number of clinical and experimental settings. (Panel A from Ferrari and Weidmann [8]; with permission.)
Insulin Resistance and Hypertension

**FIGURE 5-3**
Insulin resistance based on glucose and insulin responses to glucose load. In response to an oral glucose load of 75 g, compared with persons with normal blood pressure, patients with hypertension tend to have higher plasma glucose and insulin levels. These data suggest that patients with hypertension are insulin resistant. (From Ferrannini and coworkers [9]; with permission.)

**FIGURE 5-4**
Salt sensitivity. Persons who have salt-sensitive hypertension tend to show more insulin-resistant than are those who are salt-resistant. That is, patients who are salt-sensitive have higher plasma glucose and insulin responses to a glucose load than do those who are salt-resistant. (From Bigazzi and coworkers [10]; with permission.)

**FIGURE 5-5**
Insulin sensitivity. Insulin sensitivity also may be assessed using the euglycemic insulin clamp technique. The frequency distribution for insulin-mediated glucose disposal during euglycemic insulin clamping (M value) differs in persons with normal blood pressure and those with hypertension. The percentage of persons with hypertension considered insulin-resistant depends on the definition of insulin resistance. In this study, 27% of patients with hypertension were classified as being insulin-resistant based on an M value over two SDs above the mean for persons with normal blood pressure. (From Lind and coworkers [2]; with permission.)

**SYNDROME X AND ASSOCIATED CONDITIONS**

- Hypertension
- Hyperinsulinemia
- Increased triglycerides
- Decreased high-density lipoprotein cholesterol
- Increased low-density lipoprotein cholesterol
- Decreased plasminogen activator
- Increased plasminogen activator inhibitor
- Increased blood viscosity
- Increased uric acid
- Increased fibrinogen (?)

**FIGURE 5-6**
As originally defined, syndrome X includes hypertension, hyperinsulinemia, increased plasma triglycerides, and decreased HDL cholesterol. The syndrome also may be associated with clustering of additional cardiovascular disease risk factors.