Diabetes Mellitus and Hypertension

Murray Epstein and James R. Sowers

Diabetes mellitus and hypertension are common diseases that coexist at a greater frequency than chance alone would predict. Hypertension in the diabetic individual markedly increases the risk and accelerates the course of cardiac disease, peripheral vascular disease, stroke, retinopathy, and nephropathy. Our understanding of the factors that markedly increase the frequency of hypertension in the diabetic individual remains incomplete. Diabetic nephropathy is an important factor involved in the development of hypertension in diabetics, particularly type I patients. However, the etiology of hypertension in the majority of diabetic patients cannot be explained by underlying renal disease and remains “essential” in nature. The hallmark of hypertension in type I and type II diabetics appears to be increased peripheral vascular resistance. Increased exchangeable sodium may also play a role in the pathogenesis of blood pressure in diabetics. There is increasing evidence that insulin resistance/hyperinsulinemia may play a key role in the pathogenesis of hypertension in both subtle and overt abnormalities of carbohydrate metabolism. Population studies suggest that elevated insulin levels, which often occurs in type II diabetes mellitus, is an independent risk factor for cardiovascular disease. Other cardiovascular risk factors in diabetic individuals include abnormalities of lipid metabolism, platelet function, and clotting factors. The goal of antihypertensive therapy in the patient with coexistent diabetes is to reduce the inordinate cardiovascular risk as well as lowering blood pressure. (Hypertension 1992;19:403–418)

KEY WORDS • diabetes mellitus • diabetic nephropathy • essential hypertension • kidney failure

Rather, we will emphasize selective issues that we believe are timely and have recently attracted increased attention and investigative interest. First, we will examine and highlight newer avenues of investigation, focusing on the role of abnormalities in vascular smooth muscle cation metabolism and the possibility that hyperglycemia may contribute to the hypertension. Evidence will be considered suggesting that hyperinsulinemia and insulin resistance may participate in the pathogenesis of hypertension by acting at the level of smooth muscle tissue. A possible role for elevated blood glucose levels as well as primary hemodynamic abnormalities as pathogenetic factors will also be surveyed. The next section of this review will reconsider the pivotal role of diabetic nephropathy in the hypertension of diabetes. It is well appreciated both that coexisting hypertension exacerbates diabetic nephropathy and that diabetic nephropathy somehow results in a markedly increased risk of hypertension. The final section of this review will consider briefly the growing controversy relating to the possibility that specific classes of antihypertensive agents may confer beneficial effects on renal function above and beyond those attributable solely to blood pressure reduction.

Prevalence of Concomitant Hypertension and Diabetes

The prevalence of hypertension in diabetic individuals appears to be approximately twofold that in the nondiabetic population.23–27 This is clearly the case for type I diabetes and is probably valid for type II diabetes as well, although the relation is somewhat more controversial with regard to the latter.28–31 A minority of
studies have failed to discern an association between hypertension and diabetes. 22,33 It has been suggested 24 that the explanation for the apparent lack of an increased frequency of diabetes in some studies is an improper selection of controls. As discussed below, there are important differences between the two types of diabetes relating to age and to the presence and stage of diabetic nephropathy.

The prevalence of hypertension in diabetic patients is more frequent in men than in women before the fifth decade and more frequent in women thereafter. 1 The prevalence of these coexistent conditions is higher in blacks compared with whites; both diseases are more common among the socioeconomically disadvantaged. 2,3,4-6 In addition to race, age, and sex, greater body mass, a longer duration of diabetes, and the presence of persistent proteinuria are major determinants of elevated blood pressure, especially systolic pressure, in the diabetic population. 1,3,5,21-38 Both systolic and diastolic blood pressures have been observed to be greater in adolescent type I diabetics than in their non diabetic siblings. 39 Thus, in addition to duration of diabetes, other poorly understood factors likely contribute to the higher prevalence of hypertension in individuals with diabetes mellitus.

**Demographic Differences Regarding Hypertension in Type I Versus Type II Diabetes**

**Type I**

Unless they have an unrelated cause of hypertension, patients with type I diabetes have normal blood pressure before the development of persistent proteinuria (Table 1) (albumin excretion rate greater than 300–500 mg/day, clinically detectable by dipstick). If nephropathy does not develop, these patients usually remain normotensive. 21 At the time of recognition of microalbuminuria (albumin excretion rate of more than 30–70 mg/day, but less than 300 mg/day, detectable only by special techniques), the blood pressure in type I patients, and possibly in type II patients, 40 is increased, although often within the normal range, and tends to increase in parallel with the extent of microalbuminuria. 31-41 In addition, a marked increase in systolic blood pressure during exercise, disproportionate to that observed in normal individuals (i.e., unmasking of hyperresponsiveness in systolic blood pressure) seems to be a characteristic feature of longstanding diabetes and of incipient nephropathy. 42,43 Once persistent proteinuria develops in type I patients, their systolic blood pressure begins to rise at a rate that has been suggested to average about 1 mm Hg per month. 10,51 This phenomenon possibly occurs in type II diabetic patients as well. 52

Slight elevation of blood pressure, microalbuminuria, decreased creatinine clearance (or supranormal glomerular filtration rate), and perhaps increased renal vascular resistance 53 are interrelated markers for incipient diabetic nephropathy. 42,47,53-55 Recently, Chavers and her colleagues 55 have shown that microalbuminuria must be present together with either hypertension or decreased creatinine clearance, or both, to be a consistent indicator of glomerular structural abnormalities in type I patients.

With the onset of established diabetic nephropathy, clear-cut hypertension is common in type I diabetes. 19,41,44,51,53,56-59 It has been suggested that without treatment, mean blood pressure increases at a yearly rate of about 5–8% in overt diabetic nephropathy. 60

**Type II**

At least two studies have shown that type II diabetics have increased blood pressures that are, in part, independent of body weight. 70,80 Whereas patients with type I diabetes are usually normotensive until overt renal disease develops, about 28% of type II patients are already...
Hypertension at the time of diagnosis of diabetes (probably representing essential hypertension and relating in part to obesity). The prevalence of hypertension increases markedly in the proteinuric state. In a Japanese study of type II diabetics, 161 of 374 (43%) diabetic patients versus 215 of 1,197 (18%) control subjects were hypertensive. Of the diabetics, hypertension was observed in 71% of those with proteinuria, 48% of those with retinopathy, 61% with an abnormal electrocardiogram, and 54% with dyslipidemia.

In summary, hypertension tends to be a relatively late finding in type I diabetics, usually implying the existence of established diabetic renal disease. In contrast, hypertension commonly occurs in patients with type II diabetes before the onset of overt diabetic nephropathy.

Coexisting Factors That Affect the Medical Risks of Hypertension

Coexisting Diabetes and Hypertension

The presence of hypertension in patients with diabetes markedly enhances development of macrovascular and microvascular disease in these individuals. Peripheral vascular disease is also increased in the presence of hyper tension in the diabetic patient. Both hypertension and diabetes mellitus are major independent risk factors for accelerated atherosclerosis and ischemic heart disease. Overall, the risk of cardiovascular death in diabetic patients is nearly doubled in the presence of hypertension.

Coexistence of hypertension and diabetes is also associated with acceleration of diabetic retinopathy. A relation between both systolic and diastolic blood pressure and both background factors and proliferative retinopathy has been reported. Hypertension also accelerates the development of diabetic nephropathy. Both the onset of microalbuminuria and the progression of renal disease after the onset of proteinuria are accelerated by hypertension.

Hyperinsulinemia and Hypertension

Over the past several years increased attention has been given to the possible role of insulin resistance and hyperinsulinemia in linking obesity, diabetes, and hypertension to increased atherosclerotic vascular risk. Several possible factors may help explain the epidemiological relation between elevated plasma insulin levels and cardiovascular disease. Insulin resistance and hyperinsulinemia are closely linked to elevated plasma triglyceride levels, low high density lipoprotein levels, and to a lesser extent, with elevated total and low density lipoprotein–cholesterol levels. Insulin resistance and hyperinsulinemia may also affect atherosclerotic vascular risk by interfering with fibrinolysis. A positive correlation exists between plasma insulin levels and those of fibrinogen and plasminogen activator inhibitor. In experimental animal models, insulin promotes the development of diet-induced vascular atherosclerosis and overrides the protective effect of estrogen against atherosclerosis. Insulin stimulates subintimal smooth muscle and fibroblast proliferation in cell culture, increases the uptake and esterification of lipoprotein-cholesterol by smooth muscle cells, and exerts other actions that promote the atherosclerotic process (Table 2). Thus, the hyperinsulinemia existing in disorders of carbohydrate tolerance, such as in hypertension associated with type II diabetes mellitus and obesity, could accelerate atherosclerosis both directly and secondarily by promoting hypertension.

Obesity and Hypertension

Obesity appears to be an important factor linking hypertension to impaired carbohydrate metabolism. The relation between obesity and hypertension is often apparent in childhood. The fact that blood pressure rises in concert with body weight and increased adiposity, even at an early age, suggests that obesity is an important factor in the development of hypertension. Fat distribution appears to be important because central or android obesity is much more strongly linked to insulin resistance and type II diabetes, hypertension, and dyslipidemia than is peripheral or gynecoid obesity.

Lifestyle Changes and Hypertension

A sedentary lifestyle also appears to be associated with both diabetes mellitus and hypertension. For example, men who do not engage in regular aerobic exercise are at increased risk for the development of hypertension. Insulin sensitivity improves in obese individuals who accomplish a significant increase in maximal oxygen consumption during physical training, even when only minor changes in body weight and fat composition occur. It has been suggested, therefore, that physical training exerts at least a portion of its favorable effect on blood pressure via improved insulin sensitivity. Thus, it is clear that obesity and a sedentary lifestyle are likely important contributors to high blood pressure in type II diabetic individuals.

Pathophysiology of Hypertension Associated With Diabetes Mellitus

Hypertension in diabetic individuals has characteristics suggestive of hypertension in the elderly. The hallmark of the hypertensive state in both instances is increased vascular resistance, and isolated systolic hypertension is observed in young diabetic patients as well as in the elderly. Premature atherosclerosis in diabetic individuals with hypertension probably contributes to premature aging changes of the vasculature. This premature aging in diabetics probably plays a key role in the relatively high prevalence of isolated systolic hypertension and decreased baroreceptor sensitivity in

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**TABLE 2. Effects of Insulin on Vascular Tissue That May Promote Atherosclerosis**

<table>
<thead>
<tr>
<th>Effect of Insulin on Vascular Tissue</th>
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<tbody>
<tr>
<td>1. Proliferation of vascular smooth muscle cells and fibroblasts.</td>
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<tr>
<td>2. Increase uptake and esterification of LDL-cholesterol by subintimal smooth muscle cells and macrophages.</td>
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<tr>
<td>3. Increases release of platelet-derived growth factor and insulin-like growth factors as well as other growth factors.</td>
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<tr>
<td>4. Increase in connective tissue synthesis.</td>
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<tr>
<td>5. Decrease in deesterification and removal of cholesterol from foam cells in the subintimal region of the vessel.</td>
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LDL, low density lipoprotein.
Enhanced Vascular Smooth Muscle Contractility

vascular contractility in the diabetic state is unclear. Both insulinopenic 124 and insulin-resistant rats 123-126 also display exaggerated vasoconstrictive responses to various agonists. The precise reason for the enhanced vascular smooth muscle contractility responses to agonists such as norepinephrine and angiotensin II appears to be the hallmark of hypertension in both type I and type II diabetic individuals.4-33-115 Vessels from young diabetics.116 Decreased baroreceptor reflex sensitivity as well as altered cardiac innervation may partially explain the marked variability of blood pressure and the propensity toward orthostatic hypotension observed in diabetics with hypertension.3,116,117 These latter characteristics, also seen in elderly hypertensive patients,8 suggest premature aging of the cardiovascular system in diabetic individuals with coexistent hypertension. In addition to premature vascular aging and its effect on vascular rigidity and resistance, other factors contribute to the pathophysiology of hypertension in diabetes, and these are reviewed below and listed in Table 3.

**Increased Exchangeable Sodium**

Diabetic hypertension is related both to an increase in total peripheral vascular resistance and to increased exchangeable sodium.3,115,118 On the average, exchangeable sodium is increased by about 10%, even in normotensive diabetics.118 Diabetics have an impaired ability to excrete an intravenous saline load,119 and they fail to augment urinary sodium excretion normally in response to water immersion.120 Plasma volume may be higher than normal, even in the absence of hyperglycemia.121 The mechanism (or mechanisms) for renal sodium retention in diabetes has not been established. One concept is that increased tubular reabsorption of glucose simply results in the cotransport of greater amounts of sodium.121,122 It has also been postulated that sodium retention in diabetics might be related to a decreased ability to release natriuretic factors (including dopamine, prostaglandins, and kallikrein)3,123 and to the tubular effects of insulin (see below).

**Enhanced Vascular Smooth Muscle Contractility**

Increased peripheral vascular resistance and enhanced vascular smooth muscle contractility responses to agonists such as norepinephrine and angiotensin II appear to be the hallmark of hypertension in both type I and type II diabetic individuals.4,105-115 Vessels from both insulinopenic124 and insulin-resistant rats125,126 also display exaggerated vasoconstrictive responses to various agonists. The precise reason for the enhanced vascular contractility in the diabetic state is unclear. However, several possible abnormalities may explain this phenomenon. The role of accelerated atherosclerosis and increased vascular rigidity has previously been noted. Other factors related to alterations in vascular smooth muscle cation transport may play a key role in this enhanced vascular resistance.3,35 These alterations in cation transport could result in an increase in vascular smooth muscle cytoplasmic free calcium ([Ca\(^{2+}\)]), which is a major determinant of vascular smooth muscle contractility.177,178 We will explore some of the evidence indicating that decreased insulin action, due to either insulin deficiency or resistance, could account for this increased vascular resistance.

Insulin appears to play an important role in regulation of two important membrane pumps, the Ca\(^{2+}\)-ATPase128-131 and the Na\(^+\),K\(^+\)-ATPase pump132 (Figure 1). Accordingly, insulin deficiency or insulin resistance could result in decreased activity of these pumps. Decreased activity of either the Ca\(^{2+}\)-ATPase pump128-131 or the Na\(^+\),K\(^+\)-ATPase pump132 could result in increases in [Ca\(^{2+}\)]. Decreased activity of erythrocyte membrane Ca\(^{2+}\)-ATPase has been observed in diabetic patients134 as well as in those patients with type II diabetes and coexistent hypertension.135,136 Increased cell levels of Ca\(^{2+}\) have been observed in skeletal muscle cells, in bone cells, and in erythrocytes in association with reduced membrane Ca\(^{2+}\)-ATPase activity in insulin-resistant rats.128,137 Decreased activity of the Na\(^+\),K\(^+\)-ATPase cell membrane pump has been observed in rat models of diabetes mellitus128,138 and obesity.140,141 Thus, abnormalities in vascular smooth muscle cation metabolism and in states of decreased cellular insulin action may play an important role in the increased peripheral vascular resistance that characterizes hypertension in diabetic patients (Figure 1).

Another cell membrane pump that is affected by insulin is the Na\(^-\)H\(^+\) exchanger,142-146 which is stimulated by physiological levels of insulin156 (Figure 1). Very recently Canessa et al147 have demonstrated that young blacks with mild hypertension, hyperinsulinemia, and insulin resistance, as determined by the euglycemic hyperinsulinemic clamp technique, had elevation of red blood cell Na\(^-\)H\(^+\) exchange activity when compared with normotensive and hypertensive subjects without hyperinsulinemia and insulin resistance. These data...
suggest that insulin resistance and the accompanying hyperinsulinemia are associated with enhanced Na\(^+-\)H\(^+\) exchange (Figure 1).

The Na\(^+-\)H\(^+\) antipporter is a ubiquitous transport system that is involved in regulation of intracellular pH, cell volume, and cell growth and is linked to Ca\(^2+\) exchange.\(^{146,149}\) It has been postulated that enhanced Na\(^+-\)H\(^+\) antipporter activity may account for increased cell [Ca\(^2+\)], in essential hypertensive subpopulations.\(^{146}\) An increase in [Ca\(^2+\)], as a result of enhanced Na\(^+-\)H\(^+\) antipporter activity could then account for the increased vascular hypertension associated with insulin resistance and associated hyperinsulinemia.\(^{115,125,126}\) Increased Na\(^+-\)H\(^+\) exchange activity would also lead to intracellular alkalinization, which is a known stimulator of protein synthesis and cell proliferation,\(^{148,149}\) which could promote vascular remodeling, hypertrophy, and accelerated atherosclerosis.\(^{82,148,150}\) Further, Na\(^+-\)H\(^+\) exchange may represent a transmembrane signal for various growth factors,\(^{151-152}\) known to be stimulated by insulin.\(^{153}\) Thus, hyperinsulinemia accompanying insulin resistance and exogenous administration of insulin may contribute to enhanced cellular Na\(^+-\)H\(^+\) exchange, abnormal vascular smooth muscle [Ca\(^2+\)], metabolism, enhanced vascular reactivity, and accelerated atherosclerosis, all of which occur in states of hypertension associated with diabetes mellitus.

**Renin-Angiotensin Axis**

The role of the renin-angiotensin axis in the pathogenesis of diabetic hypertension remains controversial.\(^{59,118,154,155}\) Reports of plasma renin activity (PRA) levels in diabetes mellitus have been highly variable, with some investigators finding low values,\(^{156,157}\) many reporting normal values,\(^{158-161}\) and a few noting high PRA levels. Presumably these inconsistencies are attributable to the complex interplay of several modulating influences, including diet and age.\(^{154}\)

Most investigators have reported that PRA is low in patients with diabetic nephropathy and retinopathy.\(^{156,157,162,163}\) Nevertheless, one study actually noted high levels of PRA in diabetic patients with retinopathy.\(^{164}\) Suppression of PRA is probably related, at least in part, to volume expansion and may also relate to an increase in [Ca\(^2+\)], which is also a factor modulating vasoconstriction and hypertension. PRA is also decreased in diabetic patients with established autonomic neuropathy, which suggests that neural control of renin release is altered in this disorder.\(^{165-168}\) In contrast to the above observations, normal levels of PRA have been found in most studies of diabetic patients who had no clinical evidence of microvascular complications, including nephropathy.\(^{158-161}\) Collectively, these findings suggest that changes in the renin-angiotensin system may be linked in part to the onset of microvascular complications in diabetes mellitus.

It has been suggested that because of a high level of angiotensin converting enzyme in diabetics (possibly reflecting microvascular damage in retina and kidney),\(^{169}\) angiotensin II levels may not be low, even when PRA is suppressed.\(^{56}\) On the other hand, some investigators have observed low concentrations of angiotensin II despite high levels of converting enzyme.\(^{59}\) As discussed below, it has been suggested that angiotensin II, as a consequence of its proteinuric effects\(^{170,171}\) and its enhancement of the mesangial movement of macromolecules,\(^{172}\) is a factor independent of hypertension that predisposes to or accelerates diabetic nephropathy.\(^{173}\) Indeed, there is substantial but inconclusive evidence that by multiple actions, angiotensin II exerts detrimental renal effects contributing to the progression of renal failure.

Abnormalities in renin processing may contribute to the changes in PRA levels described in diabetes mellitus. Increased levels of inactive renin have been noted in several studies of diabetic patients, which suggests an inability to normally activate renin.\(^{174-177}\) High levels of inactive renin have been noted consistently in diabetes with microvascular complications. In this regard, Luetscher and his colleagues\(^{178}\) have reported a close
association between a high level of plasma inactive renin and the presence of microvascular complications.

In summary, the available evidence suggests that when corrected for sodium intake and age, PRA and angiotensin II in diabetic patients tend to be low as compared with nondiabetic subjects. Finally, it has been suggested that elevated levels of plasma inactive renin may correlate with the presence of microvascular complications in diabetic subjects.

Role of Hyperglycemia in the Pathogenesis of Hypertension

Chronic hyperglycemia likely contributes to the genesis of hypertension in diabetic individuals through several mechanisms. One such hypertensive effect engendered by hyperglycemia is that of sodium retention and the increased renal excretion of sodium that has been observed in diabetic hypertensive individuals.179 Hyperglycemia results in glomerular hyperfiltration of glucose, which in turn, stimulates the proximal tubular glucose-Na+ cotransporter.180,181 This mechanism is insulin independent182 and is rapidly operative, as evidenced by elevated proximal tubular cell Na+ concentration and Na+,K+-ATPase activity within 4 days of streptozotocin-induced hyperglycemia in rats.183 Thus, sodium retention occurs in association with mild-to-moderate hyperglycemia and likely contributes to increased total exchangeable Na+ and blood pressure elevations in diabetic hypertensive patients.

Chronic hyperglycemia may also contribute to increased vascular rigidity by promoting vascular structural changes. At high concentrations, glucose appears to have a direct toxic effect on endothelial cells,184 which may result in decreased endothelial-mediated vascular relaxation, increased constriction, promotion of vascular smooth muscle cell hyperplasia, and vascular remodeling.

High glucose levels mimicking the diabetic hyperglycemic state have also been shown to induce fibroenectin and collagen IV overexpression in cultured human vascular endothelial cells.185 Enhanced expression of fibroenectin and collagen IV may further contribute to endothelial dysfunction. Fibroenectin is a glycoprotein that has a complex role in cell matrix interactions,185 and its increased expression has been associated with thickened glomerular basement membranes and mesangium.185 Thus, hyperglycemia-induced local synthesis of fibroenectin by endothelial cells may contribute directly to endothelial dysfunction as well as indirectly to increases in basement membrane production.

There is considerable evidence that hyperglycemia accelerates formation of nonenzymatic advanced glycosylation products, which accumulate in vessel wall proteins.186 The rate of this accumulation is proportional to the time-integrated blood glucose level over long periods of time. A highly significant correlation has been noted between accumulation of increased levels of advanced glycosylation end products and vascular complications.187 Vlassara et al188 have identified a membrane-associated macrophage receptor that specifically recognizes proteins to which advanced glycosylated end products are bound. The binding of proteins with advanced glycosylation end products to macrophage receptors induces the synthesis and secretion of tumor necrosis factors and interleukin-1.189 These cytokines, in turn, stimulate other cells to increase protein synthesis and to proliferate. Interleukin-1 causes vascular smooth muscle cells, mesangial cells, and endothelial cells to proliferate and increases glomerular Type IV collagen synthesis.190 Interleukin-1 and tumor necrosis factors induce the expression of the protooncogenes c-myc and c-fos.190 Further, the growth-promoting effects of tumor necrosis factors and insulin are synergistic.190,191 Tumor necrosis factors appear to stimulate platelet-derived growth factor-like mitogens from both aggregating platelets and endothelial cells by causing thrombosis-promoting alterations in the endothelial cell surface.186,192 As extensively reviewed,186 these alterations include induction of a tissue factor-like procoagulant, suppression of the anticoagulant protein C pathway, and synthesis of an inhibitor of plasminogen activator. The thrombotic changes may then induce release of platelet-derived growth factor from aggregating platelets and from endothelial cells through receptor-mediated thrombin stimulation.192 Thus, prolonged hyperglycemia could lead to excessive production of extracellular matrix and proliferation of vascular smooth muscle cells as a result of an increase in the number of highly cross-linked proteins with advanced glycosylated end products, with resulting hypertrophy and vascular remodeling. This could, in turn, contribute to the enhanced vascular constriction and accelerated atherosclerosis characteristic of diabetic vasculature.

The observation that chronic hyperglycemia is associated with decreased elasticity of connective tissues in arterial walls192,193 may also be related, in part, to increased advanced glycosylation. In addition to irreversible nonenzymatic glycosylation of structural protein, hyperglycemia leads to glycosylation of apolipoproteins, which may increase the atherogenicity of lipoprotein molecules, as recently reviewed.194

Hyperinsulinemia and Insulin Resistance

Hyperinsulinemia associated with insulin resistance in obese individuals with type II diabetes could contribute to elevated blood pressure by several mechanisms. Insulin has been demonstrated to cause sodium reabsorption at both proximal and distal tubular sites.195,196 Data from studies conducted by Rocchini et al197,198 suggest that obese adolescents are sensitive to the sodium-retaining consequences of hyperinsulinemia produced by the acute euglycemic clamp procedure.197 This sodium sensitivity could be attenuated by weight reduction and by the accompanying reduction in insulin levels.198 However, other investigations of obese adults199,200 have demonstrated that weight reduction is accompanied by blood pressure reduction, even when normal salt intake is maintained. Furthermore, Hall et al201 recently found that inducing hyperinsulinemia in dogs by chronic insulin infusion did not induce hypertension in spite of salt retention. Thus, the role of insulin-induced sodium retention in the pathogenesis of hypertension needs further investigation.

It has been suggested that hyperinsulinemia, which exists in nonobese, nondiabetic persons with hypertension,202-208 as well as in obese insulin-resistant patients with hypertension,5,93-112 could elevate blood pressure by stimulating sympathetic nervous system activity209-213 (Figure 2). Nevertheless, acute or subacute insulin
infusions that simulate physiological hyperinsulinemia have recently been shown to decrease peripheral vascular resistance despite increasing sympathetic nerve activity. Further, insulin administration causes hypotension in the absence of a compensatory rise in sympathetic nervous system activity, and glucose ingestion associated with accompanying hyperinsulinemia has been observed to lower blood pressure. These observations suggest that hyperinsulinemia per se does not acutely cause hypertension in spite of its relatively acute or subacute effects on the sympathetic nervous system. However, prolonged hyperinsulinemia may play a role in the pathogenesis of sustained hypertension in type II diabetics through promotion of atherosclerosis, vascular remodeling, and other mechanisms that have not been thoroughly explored.

Insulin resistance in the type II diabetic individual may play a role in the pathogenesis of hypertension. The crucial role of insulin in maintenance of normal cation transport activity has previously been discussed in this review (Figure 1). Insulin resistance at the level of vascular smooth muscle tissue could interfere with normal activity of Na⁺,K⁺-ATPase and Ca²⁺-ATPase, which could result in increased [Ca²⁺]. Recent work by Standley et al has demonstrated that insulin attenuates vascular smooth muscle Ca²⁺ influx by both receptor- (Figure 3) and voltage-operated channels (Figure 4). Thus, decreased action of insulin on vascular smooth muscle tissue could result in decreased ability to modulate [Ca²⁺], responses to vasoconstrictive agonists and to voltage-mediated inward activity, leading to increased [Ca²⁺] and enhanced peripheral vascular resistance. Clearly, more investigative work needs to be performed to better define the role of insulin resistance in mediating the hypertension associated with type II diabetes mellitus.

A relation of alterations in skeletal muscle morphology and vascular rarefaction to the pathogenesis of decreased insulin sensitivity associated with hypertension is suggested by a number of observations. Lillioja et al carried out a landmark study in which they performed muscle biopsies and glucose clamp studies in 64 men. Insulin-induced glucose uptake was positively related to the capillary density and the percent of slow twitch fibers. The slow twitch fibers contain myoglobin (red fibers), have a high oxidative and a low glycolytic capacity, and a relatively rich capillary supply. These red fiber muscles are characterized by high insulin binding, high insulin sensitivity, and high basal glucose uptake. The fast twitch fibers (white fibers) have a relatively high glycolytic and low oxidative capacity and a relatively poor capillary supply. These fast twitch white fibers have low insulin binding, sensitivity, and glucose uptake. Thus, the observations of Lillioja et al are consistent with the concept that insulin sensitivity is integrally related to skeletal muscle blood flow and relative skeletal muscle fiber type. There is evidence that physical training, which enhances insulin sensitivity, also causes an increase of slow twitch red skeletal muscle fibers and increased capillary/fiber ratio. The importance of skeletal muscle capillary density is evidenced by the fact that skeletal muscle glucose delivery is an important determinant of skeletal muscle fiber type. There is evidence that physical training, which enhances insulin sensitivity, also causes an increase of slow twitch red skeletal muscle fibers and increased capillary/fiber ratio. The importance of skeletal muscle capillary density is evidenced by the fact that skeletal muscle glucose delivery is an important determinant of skeletal muscle fiber type.

A recent report by Baron et al supports the importance of skeletal muscle blood flow for glucose use. Obese
individuals had high postprandial glucose and insulin levels but did not increase their postprandial skeletal muscle blood flow. In contrast, lean individuals had lower insulin and glucose values and an associated increase in postprandial muscle blood flow. When this investigative team compared obese and nonobese subjects with type II diabetes with and without hypertension, they observed greater insulin resistance if hypertension was present in subjects with type II diabetes provided the subjects were lean but not if they were obese. This could indicate that the etiology of insulin resistance in obese and lean subjects with type II diabetes mellitus is different in the presence of hypertension or that the insulin resistance of obesity and hypertension are one and the same. Natali et al demonstrated that forearm skeletal muscle showed significant insulin resistance, which was selective for nonoxidative glucose metabolism, likely related to impaired glucose conversion to glycogen. These investigators suggested that this skeletal muscle insulin resistance resulted from a post-receptor defect in insulin action. However, they also suggested the possibility that this resistance could be related, in part, to a maldistribution of muscle blood flow, a qualitative difference in fiber insulin sensitivity, or both (i.e., relatively increased fast twitch white fibers displaying decreased insulin sensitivity).

In summary, it is apparent that the etiology of insulin resistance seen in essential hypertension is incompletely understood. It is likely that there is more than one abnormality. Insulin insensitivity at the level of skeletal muscle, which accounts for most of the peripheral glucose use, probably involves various combinations of abnormalities of skeletal muscle fiber type and blood flow as well as post-receptor defects in insulin action such as membrane glucose transport, decreased activity/concentration of glycogen synthase (the rate-limiting enzyme for glycogen synthesis), or both.231

Diabetic Nephropathy and Its Relation to Hypertension

Diabetic nephropathy is a devastating complication accounting for an important part of the excess mortality of diabetics, perhaps even more so than hypertension.243

For both type I and type II individuals, diabetic nephropathy is currently believed to be the most impor-

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**Figure 4.** Effect of insulin on voltage-dependent inward current. Panel A: Representative current–voltage curves for a control and an insulin-treated cell (100 milliunits/ml for 1.5 hours preceding recording). Holding potential, —80 mV. Graphs show peak inward current elicited by 60-nsec pulses to the indicated membrane potentials. Note particularly the membrane potential at which inward current began to activate (insets). Current recordings of the responses elicited by depolarization to —40 mV and —10 mV in the two representative cells. Panel B: Summary of current–voltage curves from 18 cells (nine insulin-treated, nine control). Currents were normalized by dividing each cell’s current–voltage curve by its maximum elicited current, to reduce the variance between cells caused by differences in cell size and channel density. Normalized responses at each clamp potential were then averaged for all cells in each treatment group. *p<0.03, MANOVA univariate tests comparing normalized control response to normalized insulin-treated response at each depolarization. All nonsignificant points had *p>0.05. Significantly different from no response (0 is outside the 95% confidence limit of the mean). Considering all responses together in a repeated-measures MANOVA, the significance level of the insulin by voltage interaction was less than 0.05. Reproduced with permission from Standley et al.217
The intimate relation between diabetic nephropathy and hypertension mandates consideration in any review of hypertension and diabetes mellitus. First, as the available data strongly suggest that diabetic nephropathy is exacerbated by coexisting hypertension. Persistent microalbuminuria presages diabetic nephropathy in about 80% of type I and perhaps 25% of type II patients. Microalbuminuria is, along with marginally elevated systolic blood pressure and decreased creatinine clearance (or perhaps supranormal glomerular filtration rate at an earlier stage?), one of the major predictors of diabetic nephropathy and early mortality in both type I and type II patients. It also heralds the development of cardiovascular disease.

Determining whether microalbuminuria signifies diabetic nephropathy or is attributable to hypertension per se is unclear. In essential hypertension, elevated urinary albumin excretion may result from systolic blood pressure greater than 170 or 180 mm Hg or diastolic blood pressure greater than 100 mm Hg. Christensen and his associates have shown that plotting urinary albumin excretion against blood pressure differentiates between patients with hypertension associated with either overt or incipient diabetic nephropathy ("diabetic hypertension") and nondiabetic (and diabetic) individuals with essential hypertension. At a mean arterial pressure of 125 mm Hg, diabetics had an average albumin excretion approximately a hundredfold greater than patients with essential hypertension. Similarly, at an average albumin excretion rate of 100 µg/min, mean pressure was about 70 mm Hg higher in the nondiabetic patients with essential hypertension than in patients with diabetic hypertension. In summary, microalbuminuria may occur in patients with essential hypertension, but marked elevations in blood pressure are required.

As diabetic nephropathy progresses, the prevalence of hypertension increases dramatically in both type I and type II patients. That established proteinuria heralds an increasing likelihood of hypertension is strongly supported by the data of Baba et al from Japan. These investigators showed that, over a 10-year follow-up period, 38% of those type II diabetics who initially were normotensive and later became hypertensive had proteinuria when first examined. Only 3% of those who were initially normotensive and remained so had proteinuria when initially examined. Seventy-three percent of those with proteinuria when initially examined became hypertensive, whereas only 13% of those without proteinuria when first examined became hypertensive.

The available data convincingly demonstrate that diabetic nephropathy somehow results in a markedly increased risk of hypertension. As emphasized above, the other side of the coin, the exacerbation of diabetic nephropathy by coexisting hypertension, is equally, if not even more, important. Based on information from numerous studies of type I and type II patients and from experimental animals, the consensus emerges that hypertension markedly accelerates the deterioration of glomerular filtration rate in patients with diabetic renal disease. However, there is some evidence that this might not be the case for diastolic blood pressures of less than 100 mm Hg. Although medication-specific effects on glomerular capillary hydrostatic pressure, independent of changes in systemic blood pressure may be important, the well-established beneficial effect of antihypertensive therapy on diabetic nephropathy (see below) provides strong support for this relation.

The pathogenesis of diabetic nephropathy has been the subject of several recent reviews and will not be considered here. It seems probable that several etiologic factors act in concert to promote the development of diabetic nephropathy and end-stage renal disease. Patients with a genetic predisposition for diabetes, hypertension, or both, appear to be more vulnerable to vascular damage in the presence of mild-to-moderate hyperglycemia than in patients with the same degree of hyperglycemia but without genetic predisposition. Presumably such genetic predisposition is most likely abetted by several risk factors, including smoking and race. Figure 5 is a schema depicting known and putative pathogenic mechanisms whereby genetic predisposition acting in concert with diverse metabolic factors, defective regulation of preglomerular resistance vessels, and systemic hypertension lead to glomerular injury and progression of diabetic nephropathy.

**Pharmacotherapy**

Considerable controversy exists regarding the use of antihypertensive therapy in the diabetic. Thus, the final report on the diagnostic and therapeutic recommendations of The Working Group on Hypertension in Diabetes was followed by an article by Kaplan and his colleagues providing a therapeutic viewpoint differing considerably from that of The Working Group. Kaplan et al objected to the stepped-care approach and recommended proceeding to full doses of one drug before considering a second and substituting another medication for one that has proved ineffective rather than adding a second agent to the first. Furthermore, they emphasized both the disadvantages of the use of
diuretics or β-blockers, or both, as initial agents in diabetic patients and the advantages of using α-1 blockers, calcium antagonists, or angiotensin converting enzyme (ACE) inhibitors. It is clear that many other workers have shown either no effect at all or an actual worsening of the proteinuria. It must be emphasized that these studies were all of a short duration, thereby confounding their interpretation. In contrast, The Melbourne Diabetic Nephropathy Study Group has recently reported the 12-month results of their prospective, randomized study comparing the effects of the ACE inhibitor perindopril with those of the calcium antagonist nifedipine on blood pressure and microalbuminuria. Other studies have shown either no effect at all or an actual worsening of the proteinuria.

It is readily apparent that calcium antagonists may also be beneficial in this clinical setting. These studies have been reviewed recently. In a number of recent studies, these investigators have sought to compare calcium antagonists with ACE inhibitor therapy in conferring beneficial effects on glomerular permeability to proteins and, in a few instances, in attenuating progression in patients with established diabetic glomerular disease. The reports have been widely divergent. Although calcium antagonist therapy has been found to diminish proteinuria significantly in some studies, others have shown either no effect at all or an actual worsening of the proteinuria.

It must be emphasized that these studies were all of a short duration, thereby confounding their interpretation. In contrast, The Melbourne Diabetic Nephropathy Study Group has recently reported the 12-month results of their prospective, randomized study comparing the effects of the ACE inhibitor perindopril with those of the calcium antagonist nifedipine on blood pressure and microalbuminuria. After 12 months of therapy, the investigators observed that both drug regimens were equally efficacious in reducing blood pressure and albumin excretion in hypertensive patients. The reasons for these apparently discrepant findings have not been delineated. Additional studies will be required to elucidate the determinants of these varying responses. Apart from the relative antiproteinuric efficacy of these differing classes of drugs, what must be determined is the long-term effects of ACE inhibitors and calcium antagonists on the natural course of decline of glomerular filtration rate. Finally, the demonstration in several studies that calcium antagonists ameliorated proteinuria raises important questions regarding the mechanisms whereby these agents confer their renal protective effects. Presumably, because calcium antagonists preferentially reduce the resistance of the afferent arteriole, an increase in glomerular capillary pressure should eventuate. The apparent ability of calcium antagonists to ameliorate proteinuria despite a failure to reduce glomerular capillary pressure suggests an important role for nonhemodynamic factors in affording renal protection.

**Future Considerations**

In summary, it is apparent that the hypertension of diabetes mellitus constitutes a fascinating clinical constel-
lation with a complex and multifactorial pathophysiology. In addition to established mediators of increased peripheral vascular resistance and increased exchangeable sodium, increasing attention centers on the possible role of insulin resistance and hyperinsulinemia in mediating hypertension, and linking obesity, diabetes, and hypertension to increased atherosclerotic vascular risk.

Elevated insulin levels have been associated epidemiologically with increased coronary heart disease. Hyperinsulinemia may accelerate the atherosclerotic process by interfering with fibrinolysis, by stimulating proliferation of smooth muscle cells and fibroblasts, by increasing the incorporation of low density lipoprotein–cholesterol into smooth muscle cells in the vascular intima, and by promoting an increase in triglycerides and a reduction in high density lipoprotein–cholesterol. The precise mechanisms by which hyperinsulinemia promotes atherosclerosis warrants further consideration.

Hyperinsulinemia and insulin resistance likely contribute to hypertension by mechanisms that remain incompletely defined. In recent short-term studies, hyperinsulinemia did not appear to be associated with the development of hypertension. However, more long-term effects of hyperinsulinemia on blood pressure need to be clarified. For example, it is quite likely that hyperinsulinemia may contribute, in the long term, to development of hypertension via effects of vascular remodeling and atherosclerotic changes. One mechanism by which deficient vascular smooth muscle cellular insulin action may contribute to the increased peripheral vascular resistance, characteristic of hypertension in diabetic states, is via the resultant abnormalities in cellular cation metabolism. However, mechanisms by which insulin regulates cellular cation transport and intracellular calcium metabolism require further elucidation to more precisely define the role of insulin deficiency and resistance in contributing to the development of hypertension.

Increasing investigation should also focus on identifying appropriate antihypertensive agents that not only lower blood pressure but also reduce cardiovascular risk and retard the rate of progression of diabetic renal disease. In light of recent proposals that ACE inhibitors and possibly calcium antagonists on the natural course of decline of proteinuria may contribute, in the long term, to development of hypertension via effects of vascular remodeling and atherosclerotic changes. Aside from the antiproteinuric effects of these different classes of drugs, what must be determined is the long-term effects of ACE inhibitors and calcium antagonists on the natural course of decline of glomerular filtration rate and, if possible, on the progression of anatomic abnormalities.

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