*Brief Review*

# 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**

Diabetes mellitus and hypertension are two of the most common diseases in Westernized, industrialized civilizations, and the frequency of both diseases increases with increasing age.[1–9] An estimated 2.5 to 3 million Americans have both diabetes and hypertension.[10] Although diabetes mellitus is associated with a considerably increased cardiovascular risk,[11–18] the presence of hypertension in the diabetic individual markedly increases morbidity and mortality.[5,10,19] From data drawn from death certificates, hypertension has been implicated in 44% of deaths coded to diabetes, and diabetes is involved in 10% of deaths coded to hypertension.[20] It has been estimated that 35–75% of diabetic complications can be attributed to hypertension.[10] In contrast, the absence of hypertension is the usual finding in long-term survivors of diabetes.[21,22] Thus, the coexistence of these two diseases likely contributes substantially to overall mortality in industrialized societies. Despite the critical importance of the coexistence of these two diseases, much information regarding their interaction remains unclear and controversial. Nevertheless, much information of theoretical and practical relevance is available, and there is considerable ongoing research exploring the relation between carbohydrate intolerance and hypertension.

It is not our intent to compile an exhaustive survey of the interrelation of hypertension and diabetes mellitus. 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

From the Medical Services, Department of Veterans Affairs Medical Centers, Miami, Fla., and Detroit, Mich., and the Departments of Medicine, University of Miami School of Medicine, Miami, Fla., and Wayne State University School of Medicine, Detroit, Mich.

Address for reprints: Murray Epstein, MD, Professor of Medicine, Nephrology Section (111c1), Veterans Affairs Medical Center, 1201 N.W. 16th Street, Miami, FL 33125.

Downloaded from http://ahajournals.org by on February 28, 2023

TABLE 1. Albuminuria, Hypertension, and Renal Failure in Type I Versus Type II Diabetes

| | Type I | Type II |
|---|---|---|
| Is hypertension present before development of persistent proteinuria? | No | In about 20–30% |
| Is hypertension present at onset of established diabetic nephropathy? | 50% or more | 50% or more |
| Is hypertension present at time of end-stage renal failure? | Virtually 100% | Virtually 100% |
| Does microalbuminuria presage diabetic nephropathy? | In about 80% | In about 25% |
| Does microalbuminuria presage progressive renal insufficiency? | Yes | Not necessarily, and the rate of deterioration of renal function tends to be slower |
| Is microalbuminuria a predictor of cardiovascular disease and early mortality? | Yes | Yes |
| Is persistent proteinuria present at time of diagnosis of diabetes? | No | In about 10% |
| Of Americans entering dialysis programs because of diabetic nephropathy? | Approximately 50% | Approximately 50% |
| Does hypertension exacerbate diabetic nephropathy? | Yes | Yes |
| Does control of hypertension retard the progression of diabetic nephropathy? | Yes | Yes |

Reproduced with permission from Oster et al.[1]

studies have failed to discern an association between hypertension and diabetes.[32,33] 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.[3,34–36] 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 nondiabetic 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.[41–48] 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.[49,50] 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.[29,30] Whereas patients with type I diabetes are usually normotensive until overt renal disease develops, about 28% of type II patients are already

Downloaded from http://ahajournals.org by on February 28, 2023

hypertensive at the time of diagnosis of diabetes (probably representing essential hypertension and relating in part to obesity).[24,27,30,56,61] The prevalence of hypertension increases markedly in the proteinuric state.[57,61-63] In a Japanese study of type II diabetics,[31] 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 diabetes, 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.[39,64-71] Diabetic individuals with coexisting hypertension have a much greater prevalence of stroke and transient ischemic episodes than do normotensive diabetics.[3,64] Peripheral vascular disease is also increased in the presence of high blood pressure in the diabetic patient.[3,39,64-66] Both hypertension and diabetes mellitus are major independent risk factors for accelerated atherosclerosis and ischemic heart disease.[11-18,37,38,65,72-78] Overall, the risk of cardiovascular death in diabetic patients is nearly doubled in the presence of hypertension.[65,78] 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[67,68] and proliferative[67,79] retinopathy has been reported. Hypertension also accelerates the development of diabetic nephropathy.[69-71,80] Both the onset of microalbuminuria[70,80] and the progression of renal disease after the onset of proteinuria[69] 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.[37,38,73-75,81-84] 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.[81,85-87] Insulin resistance and hyperinsulinemia may also affect atherosclerotic vascular risk by interfering with fibrinolysis.[88] A positive correlation exists between plasma insulin levels and those of fibrinogen and plasminogen activator inhibitor.[88,89] In experimental animal models, insulin promotes the development of diet-induced vascular atherosclerosis and overrides the protective effect of estrogen against atherosclerosis.[82,90-92] 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[90-92] (Table 2). Thus, the hyperinsulinemia existing in disorders of carbohydrate tolerance, such as that in hypertension associated with type II diabetes mellitus and obesity, could accelerate atherosclerosis both directly and secondarily by promoting hypertension.

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

1. Proliferation of vascular smooth muscle cells and fibroblasts.
2. Increase uptake and esterification of LDL-cholesterol by subintimal smooth muscle cells and macrophases.
3. Increases release of platelet-derived growth factor and insulin-like growth factors as well as other growth factors.
4. Increase in connective tissue synthesis.
5. Decrease in deesterification and removal of cholesterol from foam cells in the subintimal region of the vessel.

LDL, low density lipoprotein.

### *Obesity and Hypertension*

Obesity appears to be an important factor linking hypertension to impaired carbohydrate metabolism.[6,35,85,86,93-104] The relation between obesity and hypertension is often apparent in childhood.[102-104] 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.[105-112]

### *Lifestyle Changes and Hypertension*

A sedentary lifestyle also appears to be associated with both diabetes mellitus and hypertension.[86,113,114] For example, men who do not engage in regular aerobic exercise are at increased risk for the development of hypertension.[113] 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.[114] It has been suggested, therefore, that physical training exerts at least a portion of its favorable effect on blood pressure via improved insulin sensitivity.[86] 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.[8] The hallmark of the hypertensive state in both instances is increased vascular resistance,[3,8,115] and isolated systolic hypertension is observed in young diabetic patients[3] as well as in the elderly. Premature atherosclerosis in diabetic individuals with hypertension probably contributes to premature aging changes of the vasculature.[3,77] This premature aging in diabetics probably plays a key role in the relatively high prevalence of isolated systolic hypertension and decreased baroreceptor sensitivity in

Downloaded from http://ahajournals.org by on February 28, 2023

TABLE 3. Typical Profile of Blood Pressure Regulatory Mechanisms in the Hypertensive Diabetic Patient

| Factor | Typical findings in hypertensive diabetics |
|---|---|
| Total exchangeable sodium | Typically increased |
| Plasma renin activity | Low normal to low |
| Plasma norepinephrine | Usually normal in nonazotemic nonketotic patients |
| Plasma aldosterone | Low to normal low |
| Baroreceptor sensitivity | Typically decreased |
| Vascular compliance | Typically decreased |
| Peripheral vascular resistance | Typically increased |
| Vascular pressor responses | Typically increased |
| Evidence of renal dysfunction | Typically present in type I patients |
| Central adiposity | Often increased in type II patients |
| Insulin resistance | Typically increased in type II patients |
| Abnormal cation transport mechanisms | Often present in both type I and II diabetic states |

young diabetic individuals.[116] The latter occurs before the development of clinical neurological disease in 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.[4,35,115] Vessels from both insulinopenic[124] and insulin-resistant rats[125,126] 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 ($[Ca^{2+}]_i$), which is a major determinant of vascular smooth muscle contractility.[127,128] 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 $Ca^{2+}$-ATPase[128–131] and the $Na^+,K^+$-ATPase pump[132] (Figure 1). Accordingly, insulin deficiency or insulin resistance could result in decreased activity of these pumps. Decreased activity of either the $Ca^{2+}$-ATPase pump[128–131] or the $Na^+,K^+$-ATPase pump[133] could result in increases in $[Ca^{2+}]_i$. Decreased activity of erythrocyte membrane $Ca^{2+}$-ATPase has been observed in diabetic patients[134] 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 mellitus[138,139] 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 insulin[146] (Figure 1). Very recently Canessa et al[147] 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

Downloaded from http://ahajournals.org by on February 28, 2023

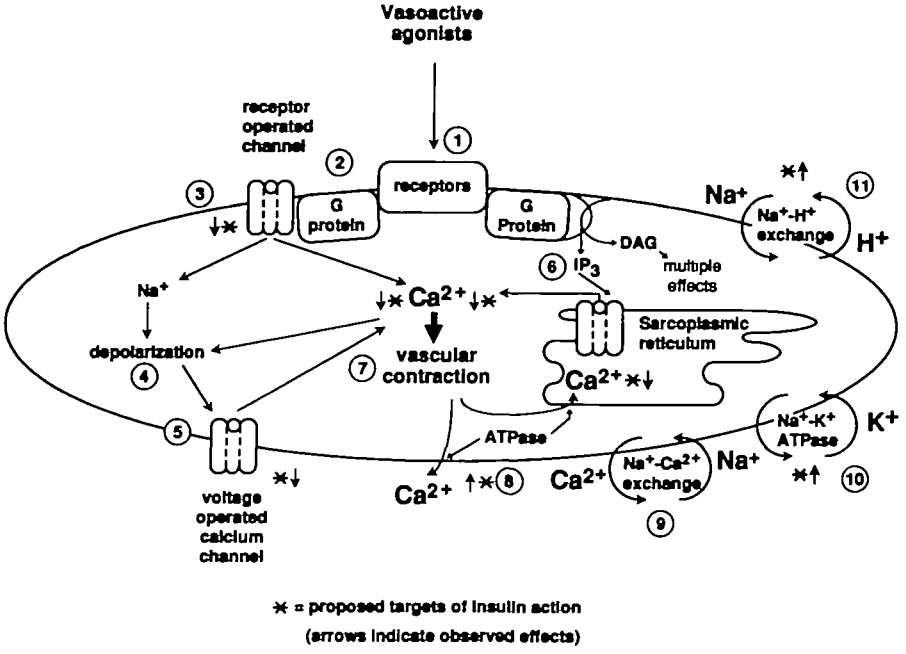



FIGURE 1. *Schematic diagram depicting mechanisms regulating contraction in vascular smooth muscle cells and proposed targets of insulin action. Pivotal steps in regulation of contraction are indicated by circled numbers.*

suggest that insulin resistance and the accompanying hyperinsulinemia are associated with enhanced $Na^+$-$H^+$ exchange (Figure 1).

The $Na^+$-$H^+$ antiporter 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.[148,149] It has been postulated that enhanced $Na^+$-$H^+$ antiport activity may account for increased cell $[Ca^{2+}]_i$ in essential hypertensive subpopulations.[148] An increase in $[Ca^{2+}]_i$ as a result of enhanced $Na^+$-$H^+$ antiport 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] 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 $[Ca^{2+}]_i$ 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 $[Ca^{2+}]_i$, 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 diabetics with microvascular complications. In this regard, Luetscher and his colleagues[178] have reported a close

Downloaded from http://ahajournals.org by on February 28, 2023

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 increase in exchangeable body 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 independent[182] 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 fibronectin and collagen IV overexpression in cultured human vascular endothelial cells.[185] Enhanced expression of fibronectin and collagen IV may further contribute to endothelial dysfunction. Fibronectin 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 fibronectin 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 al[188] 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.[186,190] 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.[190] 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 walls[192,193] 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 al[197,198] suggest that obese adolescents are sensitive to the sodium-retaining consequences of hyperinsulinemia produced by the acute euglycemic clamp procedure.[197] This salt-sensitivity could be attenuated by weight reduction and by the accompanying reduction in insulin levels.[198] However, other investigations of obese adults[199,200] have demonstrated that weight reduction is accompanied by blood pressure reduction, even when normal salt intake is maintained. Furthermore, Hall et al[201] 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,[85,93–112] could elevate blood pressure by stimulating sympathetic nervous system activity[209–213] (Figure 2). Nevertheless, acute or subacute insulin

Downloaded from http://ahajournals.org by on February 28, 2023

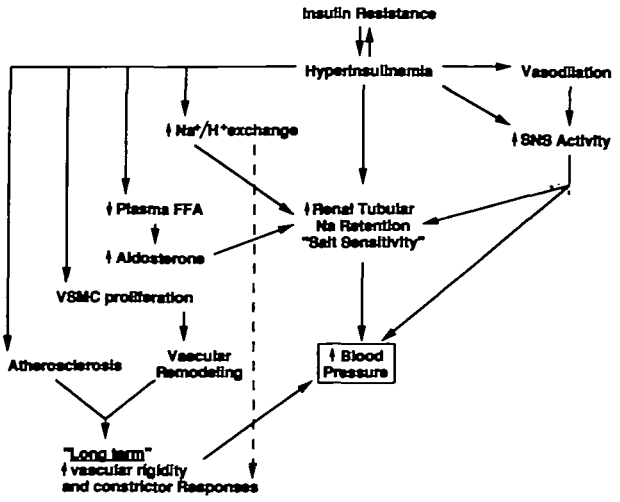



FIGURE 2. *Schematic diagram of the proposed mechanisms by which hyperinsulinemia may contribute to hypertension. SNS, sympathetic nervous system; FFA, free fatty acids; VSMC, vascular smooth muscle cell.*

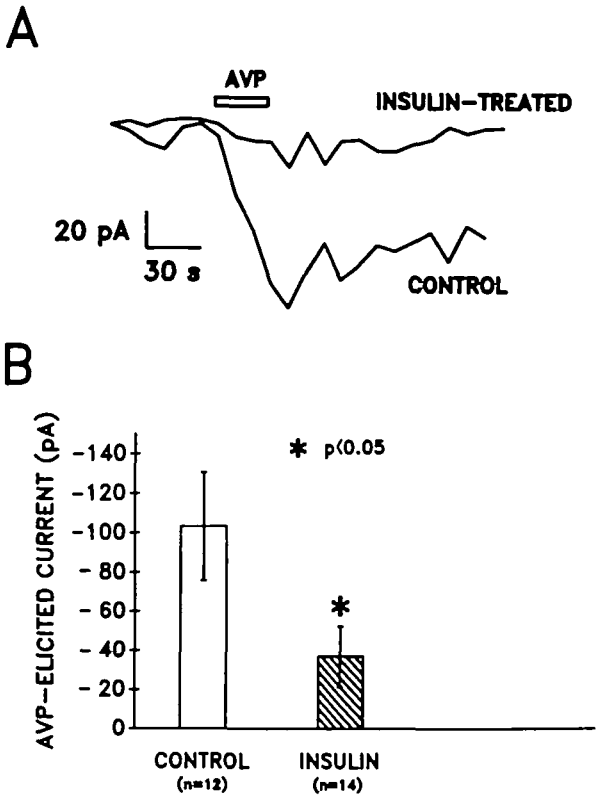



FIGURE 3. *Effect of insulin on arginine vasopressin (AVP)-induced inward current.* Panel A: *Representative recordings of the response to 100 nM AVP in control and insulin-treated cells (100 milliunits/ml for 1.5 hours preceding recording and 100 milliunits/ml in the recording medium). Illustrated recordings are of digitized data averaged for 20-msec periods every 10 seconds.* Panel B: *Maximal AVP-induced inward current from 12 control and 14 insulin-treated cells.* *$p<0.05$, *t test. Reproduced with permission from Standley et al.*[217]

infusions that simulate physiological hyperinsulinemia have recently been shown to decrease peripheral vascular resistance despite increasing sympathetic nerve activity.[214] Further, insulin administration causes hypotension in the absence of a compensatory rise in sympathetic nervous system activity,[215] and glucose ingestion associated with accompanying hyperinsulinemia has been observed to lower blood pressure.[216] 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.[35]

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[129-132] 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 $Ca^{2+}$-ATPase, which could result in increased $[Ca^{2+}]_i$.[35] Recent work by Standley et al[217] has demonstrated that insulin attenuates vascular smooth muscle $Ca^{2+}$ 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 $[Ca^{2+}]_i$ responses to vasoconstrictive agonists and to voltage-mediated inward activity, leading to increased $[Ca^{2+}]_i$ 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[218] 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,[219,220] and a relatively rich capillary supply.[221,222] These red fiber muscles are characterized by high insulin binding, high insulin sensitivity, and high basal glucose uptake.[219,220,223] The fast twitch fibers (white fibers) have a relatively high glycolytic and low oxidative capacity[219,220] and a relatively poor capillary supply.[221,222] These fast twitch white fibers have low insulin binding, sensitivity, and glucose uptake.[219,220] Thus, the observations of Lillioja et al[218] 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.[224-226] The importance of skeletal muscle capillary density is evidenced by the fact that skeletal muscle glucose delivery is an important determinant of skeletal muscle glucose uptake.[227]

A recent report by Baron et al[228] supports the importance of skeletal muscle blood flow for glucose use. Obese

Downloaded from http://ahajournals.org by on February 28, 2023

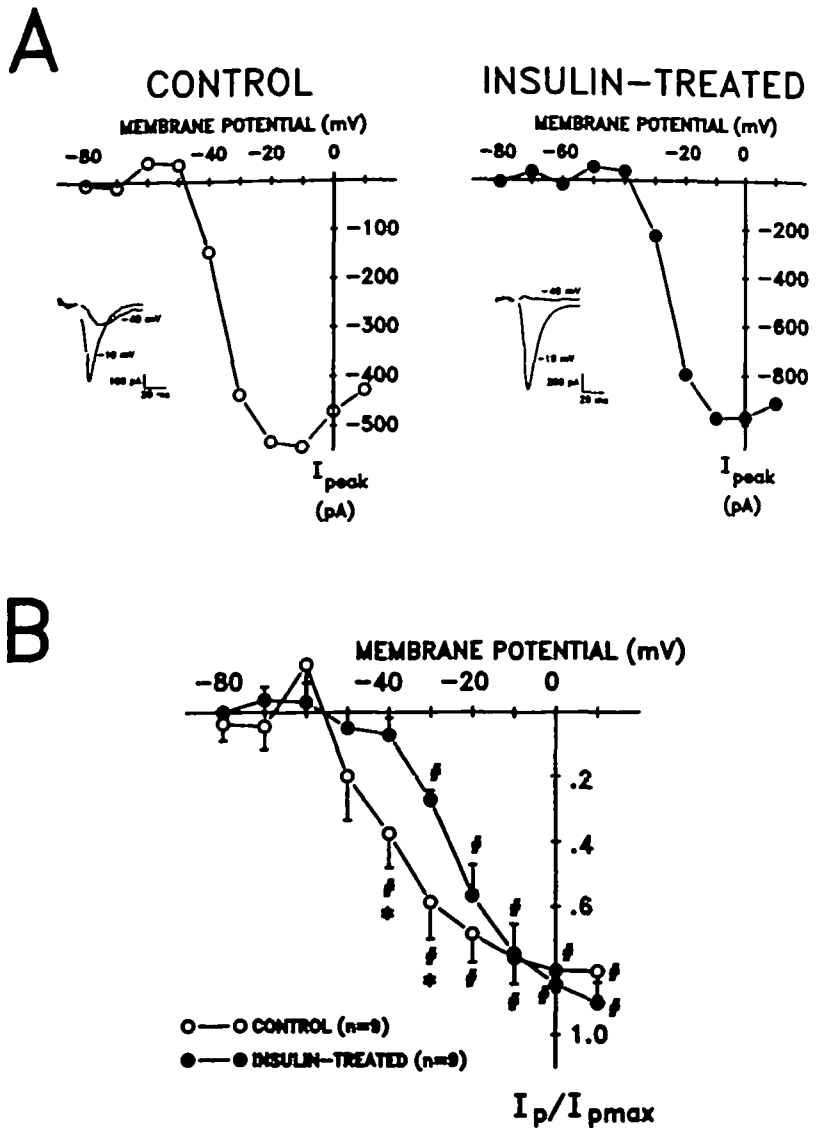



FIGURE 4. *Effect of insulin on voltage-dependent inward current.* Panel A: *Representative current–voltage curves for a control and an insulin-treated cell (100 milliunits/ml for 1.5 hours preceding recording). Holding potential, −80 mV. Graphs show peak inward current elicited by 60-msec pulses to 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]

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[229] 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[230] 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[42,55,232–242] 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[244] and type II[243] individuals, diabetic nephropathy is currently believed to be the most impor-

Downloaded from http://ahajournals.org by on February 28, 2023

tant cause of morbidity and mortality. For example, in type I patients with persistent proteinuria, mortality is 37 to 80 or more times that of the nondiabetic general population.[48,244,245] This relates both to cardiovascular disease and to end-stage renal failure.[48]

Approximately 20–30% of patients with type II, and 30–40% of those with type I diabetes develop diabetic nephropathy; the incidence in the latter peaks after 16–20 years.[89,242–246] In the United States, diabetic nephropathy accounts for approximately 30% of new patients placed on dialysis.[239]

The intimate relation between diabetic nephropathy and hypertension mandates consideration in any review of hypertension and diabetes mellitus. First, as diabetic nephropathy progresses, the prevalence of hypertension increases dramatically. Concomitantly, 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.[247] 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.[42,47,54,55,235,247–251] It also heralds the development of cardiovascular disease.[91,132]

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[60] or diastolic blood pressure greater than 100 mm Hg.[252,253] Christensen and his associates[60] 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 $\mu$g/min, mean pressure was about 70 mm Hg higher in the nondiabetic patients with essential hypertension than in patients with diabetic hypertension.[43] 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[51] and type II[37] patients. That established proteinuria heralds an increasing likelihood of hypertension is strongly supported by the data of Baba et al[31] 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.[17]

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,[57,163,234,254] 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.[255,256] 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[257] 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 a 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.

## Therapy

It appears to be universally accepted that the treatment of hypertension reduces cardiovascular risk and slows the rate of progression of diabetic renal disease. Indeed, Hasslacher et al[57] have proposed that the apparent reduced prevalence of azotemia in diabetics during the period 1978–1983 compared with 1966–1971 might be accounted for by better control of blood pressure.

The therapy of hypertension in the diabetic patient represents a challenge both to lower the blood pressure and to concomitantly avoid or minimize the side effects, metabolic and otherwise, that are alleged[171] to occur more commonly than in the nondiabetic population.

### *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[258] was followed by an article by Kaplan and his colleagues[259] providing a therapeutic viewpoint differing considerably from that of The Working Group. Kaplan et al[259] 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

Downloaded from http://ahajournals.org by on February 28, 2023

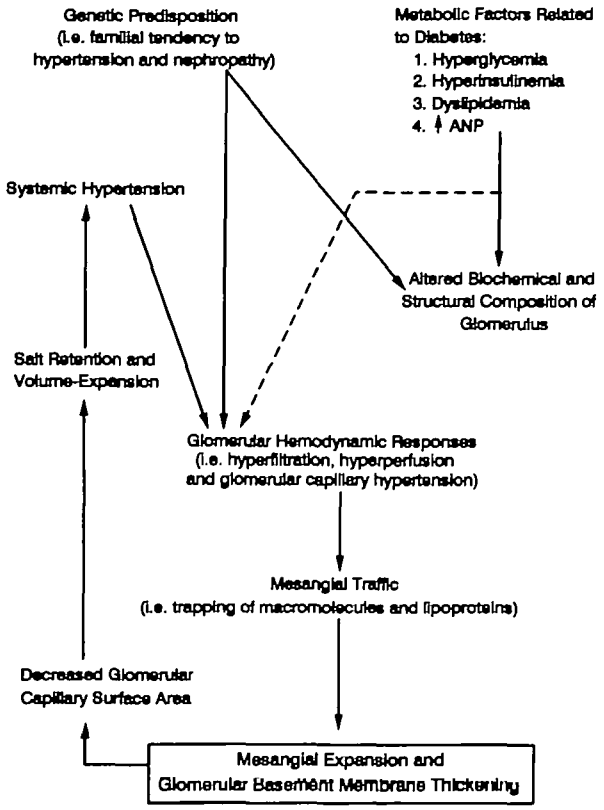



FIGURE 5. *Schematic diagram of the proposed mechanisms whereby diverse metabolic factors and genetic predisposition to hypertension coupled with defective regulation of preglomerular resistance vessels and systemic hypertension lead to glomerular injury and progression of diabetic nephropathy.*

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[4,260,261] are in agreement with the recommendations of Kaplan and his colleagues.

There are many recent articles on the appropriate choice of antihypertensive agents in the patient with diabetes.[3,4,258–265] Much attention has centered on the potential adverse effects of these agents in the diabetic patient. Although a correlation has been observed between arterial hypertension and the risk of diabetes developing, it appears that certain antihypertensive medications rather than the hypertensive state per se predispose to diabetes.[4,266]

Much recent attention has focused on the controversy relating to the formulation that specific classes of antihypertensive agents may confer beneficial effects on renal function above and beyond those attributable solely to blood pressure reduction per se. This topic has been considered in a number of recent articles[267,268] and will be considered only briefly in this review. In brief, ACE inhibitors have been advocated as being advantageous in the management of patients with diabetic nephropathy. The observations from Brenner's laboratory[269–271] have provided a theoretic framework for therapeutic interventions with an ACE inhibitor in patients with diabetes mellitus. These investigators have demonstrated that by virtue of their ability to obviate the effects of angiotensin II primarily at the level of the efferent arteriole, ACE inhibitors can normalize the glomerular capillary hydraulic pressure without reducing the glomerular filtration rate in rats with diabetes mellitus. Consequently, maintenance of normal glomerular capillary hydraulic pressure was associated with markedly reduced development of proteinuria and glomerular structural lesions. These results have been interpreted as indicating that therapy directed at reducing the glomerular capillary pressure effectively retards the progressive loss of renal function in rats with diabetes mellitus. These theoretical observations, coupled with the relative paucity of side effects of these agents, have culminated in an impressive number of preliminary observations suggesting that ACE inhibitors may have a beneficial effect in patients with diabetic nephropathy.

A number of investigators recently examined the possibility that calcium antagonists may also be beneficial in this clinical setting.[271–279] These studies have been reviewed recently.[279] 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.[273–277] The reports have been widely divergent. Although calcium antagonist therapy has been found to diminish proteinuria significantly in some studies,[272–276] others have shown either no effect at all or an actual worsening of the proteinuria.[277,278]

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.[275] 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. Aside 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.[279]

## Future Considerations

In summary, it is apparent that the hypertension of diabetes mellitus constitutes a fascinating clinical constel-

Downloaded from http://ahajournals.org by on February 28, 2023

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 may be advantageous in conferring renal protection in diabetic nephropathy, prospective long-term studies will be needed to further delineate and corroborate these actions. 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.

Downloaded from http://ahajournals.org by on February 28, 2023

## Acknowledgments

Portions of this article are adapted with permission from *Cardiovascular Risk Factors* 1990;1:25–46.

We thank Elsa V. Reina and Diane Jones for secretarial assistance.

## References

1. Oster JR, Materson BJ, Epstein M: Diabetes mellitus and hypertension. *Cardiovasc Risk Factors* 1990;1:25–46
2. Reaven GM, Hoffman BB (eds): Symposium on diabetes and hypertension. *Am J Med* 1989;87(suppl 6A):1S–42S
3. Sowers JR, Levy J, Zemel MB: Hypertension and diabetes. *Med Clin N Am* 1988;72:1399–1414
4. Sowers JR, Zemel MB: Clinical implications of hypertension in the diabetic patient: A Review. *Am J Hypertens* 1990;3:415–424
5. Fuller JH: Epidemiology of hypertension associated with diabetes mellitus. *Hypertension* 1985;2:113–117
6. Stamler J, Rhomberg P, Schoenberg JA, Shekelle RB, Dyer A, Shekelle S, Stamler R, Wannamaber J: Multivariate analysis of the relationship of seven variables to blood pressure: Findings of the Chicago Heart Association Detection Project in Industry, 1967–1972. *J Chron Dis* 1975;28:527–548
7. Mogensen CE: Diabetes and hypertension. *Lancet* 1979;1: 388–389
8. Sowers JR: Hypertension in the elderly. *Am J Med* 1987;82 (suppl 1B):1–8
9. Harris MI, Hadden WC, Knowler WC, Bennett PH: Prevalence of diabetic and impaired glucose tolerance and plasma glucose levels in the US population aged 20–74 years. *Diabetes* 1987;36:523–534
10. Bild D, Teutsch SM: The control of hypertension in persons with diabetes: A public health approach. *Public Health Rep* 1987;102: 522–529
11. Kannel WB, McGee DL: Diabetes and cardiovascular risk factors: The Framingham study. *Circulation* 1979;59:8–13
12. Fuller JH, Shiley MJ, Rose G, Jarrett RJ, Keen H: Coronary heart disease risk and impaired glucose tolerance: The Whitehall Study. *Lancet* 1980;1:1373–1376
13. Pan WH, Cedres LB, Liu K, Dyer A, Schoenberger JA, Shekelle RB, Stamler R, Smith D, Collette P, Stamler J: Relationship of clinical diabetes and asymptomatic hyperglycemia to risk of coronary heart disease mortality in men and woman. *Am J Epidemiol* 1986;123:504–516
14. Barrett-Connor E, Wingard DL: Sex differential in ischemic heart disease mortality in diabetics: A prospective population-based study. *Am J Epidemuol* 1983;118:489–496
15. Butler WJ, Ostrander LD Jr, Carman WJ, Lamphier DE: Mortality from coronary heart disease in the Tecumseh study, long-term effect of diabetes mellitus, glucose tolerance and other risk factors. *Am J Epidemiol* 1985;121:541–547
16. Cruz-Vidal M, Garcia-Palmieri MR, Costas R Jr, Sorlie PD, Havlik RJ: Abnormal blood glucose and coronary heart disease: The Puerto Rico Heart Health Program. *Diabetes Care* 1983;6:556–561
17. Abbott RD, Donahue RP, MacMahon SW, Reed DM, Yano K: Diabetes and the risk of stroke, the Honolulu heart program. *JAMA* 1987;257:949–952
18. Pyorala K, Laakso M, Uusitupa M: Diabetes and atherosclerosis: An epidemiologic view. *Diabetes/Metabolism Rev* 1987;3:463–524
19. Christlieb AR, Warram JH, Królewski AS, Busick EJ, Ganda OP, Asmal AC, Soeldner JS, Bradley RF: Hypertension: The major risk factor in juvenile-onset insulin-dependent diabetics. *Diabetes* 1981;30:90–96
20. Horan MJ: Diabetes and hypertension, in National Diabetes Data Group: *Diabetes in America: Diabetes Data Compiled 1984.* US Dept of Health and Human Services, publication No. (NIH) 85-1468, 1985, chap XVII, pp XVII-1–XVII-21
21. Oakley WG, Pyke DA, Tattersall RB, Watkins PJ: Long-term diabetes: A clinical study of 92 patients after 40 years. *Q J Med* 1974;43:145–156
22. Borch-Johnson K, Nissen RN, Nerup J: Blood pressure after 40 years of insulin-dependent diabetes. *Nephron* 1985;4:11–12
23. Klein BEK, Klein R, Moss SE: Blood pressure in a population of diabetic persons diagnosed after 30 years of age. *Am J Public Health* 1984;74:336–339
24. Pell S, D'Alonzo CA: Some aspects of hypertension in diabetes mellitus. *JAMA* 1967;202:104–110
25. Halperin M, Dodson DL, Beasley J: *Diabetes in Michigan: 1980 Survey Results.* Michigan Department of Public Health, Division of Chronic Disease Control, Lansing, Michigan, September, 1983
26. Vaishnava H, Bhasin RC: Hypertension in Indian diabetics. *J Chron Dis* 1969;21:691–702
27. Teuscher A, Egger M, Herman JB: Diabetes and hypertension: Blood pressure in clinical diabetic patients and a control population. *Arch Intern Med* 1989;149:1942–1945
28. Jarrett RJ: Hypertension in diabetic patients and differences between insulin-dependent diabetes mellitus and non–insulin-dependent diabetes mellitus. *Am J Kidney Dis* 1989;13:14–16
29. Jarrett RJ, Keen H, McCartney M, Fuller JH, Hamilton PJS, Reid DD, Rose G: Glucose tolerance and blood pressure in two population samples: Their relation to diabetes mellitus and hypertension. *Int J Epidemiol* 1978;7:15–24
30. Barrett-Connor E, Criqui MH, Klauber MR, Holdbrook M: Diabetes and hypertension in a community of older adults. *Am J Epidemiol* 1981;113:276–284

31. Baba T, Murabyashi S, Aoyagi K, Sasaki K, Imamura K, Kudo M, Takebe K: Prevalence of hypertension in diabetes mellitus its relation to diabetic nephropathy. *Tohoku J Exp Med* 1985;145: 167–173
32. Freedman P, Moullon R, Spencer AG: Hypertension and diabetes mellitus. *Q J Med* 1958;27:293–305
33. Keen H, Track NS, Sowry GSC: Arterial pressure in clinically apparent diabetics. *Diabete Metab* 1975;1:159–178
34. Pacy PJ, Dodson PM, Beevers M, Fletcher RF, Taylor KG: Prevalence of hypertension in white, black and Asian diabetics in a district hospital diabetic clinic. *Diabetic Med* 1985;2:225–230
35. Sowers JR: Relationship between hypertension and subtle and overt abnormalities of carbohydrate metabolism. *J Am Soc Nephrol* 1990;1:S39–S47
36. Harris MI: Noninsulin-dependent diabetes mellitus in black and white Americans. *Diabetes/Metabolism Rev* 1990;6:71–90
37. Cambien F, Warnet JM, Eschwege E, Jacqueson A, Richard JL, Rossilin G: Body mass, blood pressure, glucose, and lipids: Does plasma insulin explain their relationship? *Arteriosclerosis* 1987;7: 197–202
38. Haffner SM, Stern MP, Hazuda HP, Mitchell BD, Patterson JK: Cardiovascular risk factors in confirmed prediabetic individuals: Does the clock for coronary heart disease start ticking before the onset of clinical diabetes? *JAMA* 1990;263:2893–2898
39. Cruckshanks KA, Orchard TJ, Becker DJ: The cardiovascular risk profile of adolescents with insulin-dependent diabetes mellitus. *Diabetes Care* 1985;8:118–123
40. Kelleher CC, Ferriss JB, Cole M, O'Sullivan DJ: Enalapril and micro-albuminuria in diabetic and non-diabetic hypertension. *J Hum Hypertens* 1987;1:181–183
41. Parving HH, Andersen AR, Smidt UM, Oxenboll B, Edsberg B, Christiansen JS: Diabetic nephropathy and arterial hypertension. *Diabetologia* 1983;24:10–12
42. Viberti G, Bonding JJ: Early diabetic nephropathy: Detection and prevention. *Adv Nephrol* 1988;17:101–112
43. Mathiesen ER, Saurbrey N, Hommel E, Parving H-H: Prevalence of microalbuminuria in children with type 1 (insulin-dependent diabetes mellitus). *Diabetologia* 1986;29:640–643
44. Parving H-H, Hommel E, Mathiesen E, Skott P, Edsberg B, Bahnsen M, Lauritzen M, Hougaard P, Lauritzen E: Prevalence of microalbuminuria, arterial hypertension, retinopathy, and neuropathy in patients with insulin dependent diabetes. *Br Med J* 1988;296:156–160
45. Marre M, Chatellier G, Leblanc H, Guyene TT, Menard J, Passa P: Prevention of diabetic nephropathy with enalapril in normotensive diabetics with microalbuminuria. *Br Med J* 1988;297: 1092–1095
46. Parving H-H, Andersen AR, Smidt UM, Christiansen JS, Oxenboll B, Svendsen PA: Diabetic nephropathy and arterial hypertension: The effect of antihypertensive treatment. *Diabetes* 1983; 32(suppl 2):83–87
47. Wiseman M, Viberti G, Mackintosh D, Jarrett RJ, Keen H: Glycemia, arterial pressure and micro-albuminuria in type I (insulin-dependent) diabetes mellitus. *Diabetologia* 1988;26: 401–405
48. Parving H-H, Hommel E, Nielsen MD, Giese J: Effect of captopril on blood pressure and kidney function in normotensive insulin dependent diabetics with nephropathy. *Br Med J* 1989;299: 533–536
49. Christensen CK: Abnormal albuminuria and blood pressure rise in incipient diabetic nephropathy induced by exercise. *Kidney Int* 1984;25:819–823
50. Karlefors T: Exercise tests in male diabetics: II. Heart rate and systolic blood pressure. *Acta Med Scand* 1966;449:19–43
51. Parving H-H, Smidt UM, Friisberg B, Bonnevie-Nielsen V, Andersen AR: A prospective study of glomerular filtration rate and arterial blood pressure in insulin-dependent diabetics with diabetic nephropathy. *Diabetologia* 1981;20:457–461
52. Kikkawa R, Haneda M, Togawa M, Koya D, Ebata K, Arimura T, Maeda S, Shigeta Y: Microalbuminuria associated with a rise in blood pressure in non-insulin-dependent diabetes. *J Diab Comp* 1989;3:99–102
53. Christensen CK, Mogensen CE: The course of incipient diabetic nephropathy: Studies of albumin excretion and blood pressure. *Diabetic Med* 1985;2:97–102
54. Viberti GC, Hill RD, Jarrett RJ, Argyropoulos A, Mahmud U, Keen H: Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. *Lancet* 1982;1:1430–1432
55. Chavers BM, Bilous RW, Ellis EN, Steffes MW, Mauer SM: Glomerular lesions and urinary albumin excretion in type 1 diabetes without overt proteinuria. *N Engl J Med* 1989;320: 966–970
56. Ritz E, Hasslacher C, Tschöpe W, Koch M, Mann JFE: Hypertension in diabetes mellitus. *Contr Nephrol* 1987;54:77–85
57. Hasslacher C, Ritz E, Tshöpe W, Gallasch G, Mann JFE: Hypertension in diabetes mellitus. *Kidney Int* 1988;34(suppl 25): 133S–137S
58. Feldt-Rasmussen B, Borch-Johnsen K, Mathiesen ER: Hypertension in diabetes as related to nephropathy: Early blood pressure changes. *Hypertension* 1985;7(suppl II):II-18–II-20
59. Feldt-Rasmussen B, Mathiesen ER, Deckert T, Giese J, Christensen NJ, Bent-Hansen L, Nielsen MD: Central role for sodium in the pathogenesis of blood pressure changes independent of angiotensin, aldosterone and catecholamines in type I (insulin-dependent) diabetes mellitus. *Diabetologia* 1987;30:610–617
60. Christensen CK, Krusell LR, Mogensen CE: Increased blood pressure in diabetes: Essential hypertension or diabetic nephropathy? *Scand J Clin Lab Invest* 1987;47:363–370
61. Schnack C, Scheithauer W, Gisinger C, Winkler J, Schernthaner G: Prevalence of microalbuminuria in maturity onset primarily non–insulin-requiring diabetes mellitus: Effect of disease duration, glycemic control, and mean systemic blood pressure. *J Diabetic Complications* 1987;1:132–136
62. Fabre J, Balant LP, Dayer PG, Fox HM, Vernet AT: The kidney in maturity onset diabetes mellitus: A clinical study of 510 patients. *Kidney Int* 1982;21:730–738
63. Reubi FC, Franz KA, Horber F: Hypertension as related to renal function in diabetes mellitus. *Hypertension* 1985;7(suppl II): II-21–II-28
64. Janka HU, Standle E, Mehnett H: Peripheral vascular disease in diabetes mellitus and its relationship to cardiovascular risk factors: Screening with doppler ultrasonic techniques. *Diabetes Care* 1980;3:207–213
65. Kannel WB: Diabetes and cardiovascular disease. The Framingham Study: 18-year follow-up. *Cardiol Dig* 1976;5:11–15
66. McMillan D: Diabetic angiopathy—Its lessons in vascular pathology. *Am Heart J* 1978;96:401–403
67. Knowler WC, Bennett PJ, Ballentine EJ: Increased incidence of retinopathy in diabetics with elevated blood pressure. *N Engl J Med* 1980;302:645–650
68. Chahal P, Inglesby DV, Slightholm M, Kohner EM: Blood pressure and the progression of mild background retinopathy. *Hypertension* 1985;7(suppl II):II-79–II-83
69. Hasslacher C, Steck W, Wahl P, Ritz E: Blood pressure and metabolic control as risk factors for nephropathy in type I (insulin-dependent) diabetes. *Diabetologia* 1985;28:6–16
70. Wiseman M, Viberti G, MacKintosh D: Glycaemia, arterial pressure and micro-albuminuria in type I (insulin-dependent) diabetes mellitus. *Diabetologia* 1984;26:401–405
71. Krowlewski AS: Predisposition to hypertension and susceptibility to renal disease in insulin diabetes mellitus. *N Engl J Med* 1988;318:140–145
72. Kannel WB, Gordon T, Castelli WP: Obesity lipids and glucose intolerance in the Framingham study. *Am J Clin Nutr* 1979;2: 131–141
73. Pyorala K: Relationship of glucose tolerance and plasma insulin to the incidence of coronary heart disease: Results from two population studies in Finland. *Diabetes Care* 1979;2:131–141
74. Welborn TA, Wearne K: Coronary heart disease incidence and cardiovascular mortality in Busselton with reference to glucose and insulin concentrations. *Diabetes Care* 1979;2:154–160
75. Ducimetiere P, Eschwege E, Papoz L, Richard JL, Claude JR, Rosselin G: Relationship of plasma insulin levels to the incidence of myocardial infarction and coronary heart disease mortality in a middle-aged population. *Diabetologia* 1980;19:205–210
76. Multiple Risk Factor Intervention Trial Research Group: Risk factor changes and mortality results. *JAMA* 1982;248:1465–1477
77. Schonfeld G: Diabetes, lipoproteins, and atherosclerosis. *Metabolism* 1985;34:45–50
78. Ritz E, Strumpf C, Katz F, Wing AJ, Quillhorts E: Hypertension and cardiovascular risk factors in hemodialyzed diabetic patients. *Hypertension* 1985;7(suppl II):II-118–II-124
79. Klein R, Klein BE, Moss SE: The Wisconsin epidemiologic study of diabetic retinopathy: II. Prevalence and risk of diabetic retinopathy when age of diagnosis is less than 30 years. *Arch Ophthalmol* 1981;102:520–526
80. O'Hare JA, Feriss JB, Twomey B: Poor metabolic control, hypertension and microangiopathy independently increase the transcapillary escape rate of albumin in diabetes. *Diabetologia* 1983;25:260–266


Downloaded from http://ahajournals.org by on February 28, 2023

81. Zavaroni I, Bonora E, Pagliara M, Dall'Aglio E, Luchetti L, Giuseppe B, Bonati PA, Bergonzani M, Gnudi L, Passeri M, Reaven G: Risk factors for coronary artery disease in healthy persons with hyperinsulinemia and normal glucose tolerance. *N Engl J Med* 1989;320:702–706
82. Stolar MW: Atherosclerosis in diabetics: The role of hyperinsulinemia. *Metabolism* 1988;37:1–9
83. Reaven GM: Role of insulin resistance in human disease. *Diabetes* 1988;37:1595–1607
84. Foster DW: Insulin resistance—A secret killer? *N Engl J Med* 1989;320:733–734
85. Modan M, Kalkin H, Almog S, Lusky AL, Eskol A, Shefi M, Shitrit A, Fuchs L: Hyperinsulinemia: A link between hypertension and obesity and glucose intolerance. *J Clin Invest* 1985;75: 809–817
86. Flack JM, Sowers JR: Epidemiologic and clinical aspects of insulin resistance and hyperinsulinemia. *Am J Med* 1991;91(suppl 1A):11S–20S
87. Modan M, Halkin H, Lusky A, Segal P, Fuchs Z, Chetrit A: Hyperinsulinemia is characterized by jointly disturbed plasma VLDL, LDL, and HDL levels. *Arteriosclerosis* 1988;8:227–236
88. Landin K, Stigendal L, Eriksson E, Krotkiewski M, Risberg B, Tengborn L, Smith U: Abdominal obesity is associated with an impaired fibrinolytic activity and elevated plasminogen activator inhibitor-1. *Metabolism* 1990;39:1044–1048
89. Landin K, Tengborn L, Smith U: Elevated fibrinogen and plasminogen activator inhibitor (PAI-1) in hypertension are related to metabolic risk factors for cardiovascular disease. *J Intern Med* 1990;227:273–278
90. Cruz AB, Amatuzio DS, Grande F, Hay LJ: Effect of intra-arterial insulin on tissue cholesterol and fatty acids in alloxan-diabetic dogs. *Circ Res* 1961;9:39–43
91. Oppenheimer MJ, Sundquist K, Bierman EL: Down-regulation of high-density lipoprotein receptor in human fibroblasts by insulin and IGF-I. *Diabetes* 1989;38:117–122
92. Capron L, Jarnet J, Kazandjian S, Housset E: Growth-promoting effects of diabetes and insulin on arteries. *Diabetes* 1986;35: 973–978
93. Christlieb AR, Krolewski AS, Warram JH, Soeldner JS: Is insulin the link between hypertension and obesity? *Hypertension* 1985; 7(suppl II):II-54–II-57
94. Haffner SM, Fong D, Hazuda HP, Pugh JA, Patterson JK: Hyperinsulinemia, upper body adiposity, and cardiovascular risk factors in nondiabetics. *Metabolism* 1988;37:338–345
95. Lucas CP, Estigarribia JA, Darga LL, Reaven GM: Insulin and blood pressure in obesity. *Hypertension* 1985;7:702–706
96. Manicardi V, Camellini L, Bellodi G, Coscelli C, Ferrannini E: Evidence for an association of high blood pressure and hyperinsulinemia in obese man. *J Clin Endocrinol Metab* 1986;62: 1302–1304
97. Kaplan NM: The deadly quartet: Upper body obesity, glucose intolerance, hypertriglyceridemia and hypertension. *Arch Intern Med* 1989;149:1514–1520
98. Florey C, Du V, Uppal S, Lowery C: Relationship between blood pressure, weight, and plasma sugar and serum insulin levels in school children aged 9–12 years in Westland, Holland. *Br Med J* 1976;1:1368–1371
99. Voors AW, Radhakrishnamurthy B, Srinavasan SE, Webber LS, Berrenson GS: Plasma glucose level related to blood pressure in 272 children, ages 7–15 years, sampled from a total biracial population. *Am J Epidemiol* 1981;113:347–356
100. Williams RR, Hung SC, Hopkins PN, Stults BM, Wu LL, Hasstedt SJ, Barlow GK, Stephenson SH, Laloulel JM, Kuida H: Familial dyslipidemic hypertension: Evidence from 58 Utah Families for syndrome present in approximately 12% of patients with obesity hypertension. *JAMA* 1988;259:3579–3586
101. Baumgartner RN, Roche AF, Chumlea WC, Siervogel RM, Glueck CJ: Fatness and fat patterns: Associations with plasma lipids and blood pressures in adults, 18 to 57 years of age. *Am J Epidemiol* 1987;126:614–628
102. Shear CL, Freedman DS, Burke GL, Harsha DW, Berenson GS: Body fat patterning and blood pressure in children and young adults: The Bogalusa Heart Study. *Hypertension* 1987;9:236–244
103. Garrison RJ, Kannel WB, Stokes J III, Castelli WP: Incidence and precursors of hypertension in young adults: The Framingham Offspring Study. *Prev Med* 1987;16:235–251
104. Julius S, Jamerson K, Mejia A, Krause L, Schork MA, Jones K: The association of borderline hypertension with target organ changes and higher coronary risk: Tecumseh Blood Pressure Study. *JAMA* 1990;264:354–358
105. Feldman R, Sender AJ, Siegelaub AB: Difference in diabetic and nondiabetic fat distribution pattern by skinfold measurements. *Diabetes* 1969;18:478–486
106. Berglund G, Ljungman S, Hartford M, Wilhelmsen L, Bjorntorp P: Type of obesity and blood pressure. *Hypertension* 1982;4: 692–696
107. Blair D, Habicht JP, Sims EAH, Sylvester D, Abraham S: Evidence for an increased risk for hypertension with centrally located body fat and the effect of race and sex on the risk. *Am J Epidemiol* 1984;199:526–540
108. Stern MP, Haffner SM: Body fat distribution and hyperinsulinemia as risk factors for diabetes and cardiovascular disease. *Arteriosclerosis* 1986;6:123–130
109. Haffner SM, Stern MP, Hazuda HP, Pugh J, Patterson JK: Do upper body and centralized adiposity measure different aspects of regional body-fat distribution? Relation to non-insulin-dependent diabetes mellitus, lipids, and lipoproteins. *Diabetes* 1987;36: 43–51
110. Peiris AN, Sothmann MS, Hoffman RG, Hennes MI, Wilson CR, Gustafson AB, Kissebah AH: Adiposity, fat distribution and cardiovascular risk. *Ann Intern Med* 1989;110:867–872
111. Peiris AN, Sothmann MS, Hennes MI, Lee MB, Wilson CR, Gustafson AB, Kissebah AH: The relative contribution of obesity and body fat distribution to alterations in glucose insulin homeostasis. *Am J Clin Nutr* 1989;49:758–764
112. Kanai H, Matsuzawa Y, Kotani K, Keno Y, Kobatake T, Nagai Y, Fujioka S, Tokunaga K, Tarui S: Close correlation of intraabdominal fat accumulation to hypertension in obese women. *Hypertension* 1990;16:484–490
113. Paffenbarger RS Jr, Wing AL, Hyde RT, Jung DL: Physical activity and incidence of hypertension in college alumni. *Am J Epidemiol* 1983;117:245–257
114. Bjorntorp P, DeJounge K, Sjostrom L, Sullivan L: The effect of physical training on insulin production in obesity. *Metabolism* 1970;19:631–638
115. Weidman P, Beretta-Piccoli C, Trost BN: Pressor factors and responsiveness in hypertension accompanying diabetes mellitus. *Hypertension* 1985;79(suppl II):II-33–II-42
116. Eckberg DL, Harkins SW, Fritsch JM, Musgrave GE, Gardner DF: Baroreflex control of plasma norepinephrine and heart period in healthy subjects and diabetic patients. *J Clin Invest* 1986;78:366–374
117. Wiegmann TB, Herron KG, Chonko AM, MacDougall ML, Moore WV: Recognition of hypertension and abnormal blood pressure burdened with ambulatory blood pressure recordings in type I diabetes mellitus. *Diabetes* 1990;39:1556–1560
118. Beretta-Piccoli C, Weidmann P. Body-sodium-blood volume state in nonazotemic diabetes mellitus. *Min Electrolyte Metab* 1982;7: 36–37
119. Roland JM, O'Hare JP, Walters G, Corrall RJM: Sodium retention in response to saline infusion in uncomplicated diabetes mellitus. *Diabetes Res* 1986;3:213–215
120. O'Hare JP, Roland JM, Walters GF, Corrall RJM: Impaired sodium excretion in response to volume expansion induced by water immersion in insulin-dependent diabetes mellitus. *Clin Sci* 1986;71:403–409
121. Borchner-Mortensen J: Glomerular filtration rate and extracellular fluid volume during normoglycemia and moderate hyperglycemia in diabetes. *Scand J Clin Lab Invest* 1973;32:311–316
122. Anderson S, Brenner BM: Influence of antihypertensive therapy on development and progression of diabetic glomerulopathy. *Diabetes Care* 1988;11:846–849
123. Baba T, Murabayashi S, Ishizaki T, Ido Y, Aoyagi K, Takebe K: Renal kallikrein in diabetic patients with hypertension accompanied by nephropathy. *Diabetologia* 1986;29:162–167
124. Reddy S, Shehin S, Sowers JR, Dardas G, Zemel M: Aortic $^{45}Ca$ flux and blood pressure regulation in streptozotocin-induced diabetic rats. *J Vasc Med Biol* 1990;2:47–51
125. Zemel MB, Reddy S, Shehin SE, Lockette W, Sowers JR: Vascular reactivity in Zucker obese rats: Role of insulin resistance. *J Vasc Med Biol* 1990;2:81–85
126. Shehin SE, Sowers JR, Zemel MB: Impaired vascular smooth muscle $^{45}Ca$ efflux and hypertension in Zucker obese rats. *J Vasc Med Biol* 1989;1:278–282
127. Borle AB: Control, modulation and regulation of cell calcium. *Rev Physiol Biochem Pharmacol* 1981;90:113–153
128. Levy J, Zemel MB, Sowers JR: Role of cellular calcium metabolism in abnormalities in glucose metabolism and diabetic hypertension. *Am J Med* 1989;87(suppl 6A):7–16


Downloaded from http://ahajournals.org by on February 28, 2023

129. Goewert RR, Klaven NB, McDonald JM: Direct effect of insulin on the binding of calmodulin to rat adipocyte plasma membranes. *J Biol Chem* 1983;258:9995–9999
130. Wong EC, Sacks DB, Laurino JP, McDonald JM: Characteristics of calmodulin phosphorylation by the insulin receptor kinase. *Endocrinology* 1988;123:1830–1836
131. Graves CB, Gale RD, Laurino JP, McDonald JM: The insulin receptor and calmodulin: Calmodulin enhances insulin-mediated receptor kinase activity and insulin stimulates phosphorylation of calmodulin. *J Biol Chem* 1986;261:10429–10438
132. Lytton J, Lin JC, Guidotti G: Identification of two molecular forms of ($Na^+$, $K^+$)-ATPase in rat adipocytes: Relation to insulin stimulation of the enzyme. *J Biol Chem* 1985;260:1177–1184
133. Matlib M, Schwartz A, Yamorii Y: A $Na^+$-$Ca^{2+}$ exchange process in isolated sarcolemmal membranes of mesenteric arteries from WKY and SHR rats. *Am J Physiol* 1985;249:C166–C171
134. Shaefer W, Priessen J, Mannhold R, Gries AF: $Ca^{2+}$-$Mg^{2+}$-ATPase activity of human red blood cells in healthy and diabetic volunteers. *Klin Wochenschr* 1987;65:17–21
135. Zemel MB, Bedford BA, Zemel PC, Marwah O, Sowers JR: Altered cation transport in non–insulin-dependent diabetic hypertension: Effects of dietary calcium. *J Hypertens* 1988;6: S228–S230
136. Bedford-Johnson BA, Sowers JR, Zemel PC, Luft FC, Zemel MB: Increased sodium-lithium countertransport in black non–insulin-dependent diabetic hypertensives. *Am J Hypertens* 1990;3: 563–565
137. Levy J, Sowers JR, Zemel MB: Abnormal $Ca^{2+}$-ATPase activity in erythrocytes of non–insulin-dependent diabetic rats. *Horm Metab Res* 1990;22:138–142
138. Levy J, Avioli LV, Roberts ML, Roberta ML, Gavin JR: ($Na^+$,$K^+$)-ATPase activity in kidney basolateral membranes of non–insulin-dependent diabetic rats. *Biochem Biophys Res Commun* 1986;139:1313–1319
139. El-Seilfi S, Friberg JM, Kinsella JH, Cheng L, Sactor B: Na-H exchange and Na-dependent transport systems in streptozotocin diabetic rat kidneys. *Am J Physiol* 1987;252:R40–R47
140. DeLuise M, Blackburn GL, Flier JS: Reduced activity of red-cell sodium-potassium pump in human obesity. *N Engl J Med* 1980; 303:1017–1022
141. Sowers JR, Whitfield LA, Beck F, Catunia RA, Tuck M, Dornfeld L, Maxwell M: Role of enhanced sympathetic nervous system activity and reduced $Na^+$,$K^+$-dependent adenosine triphosphatase activity in maintenance of elevated blood pressure in obesity: Effects of weight loss. *Clin Sci* 1982;63:121S–124S
142. Moore RD, Fidelman ML, Seeholzer SH: Correlation between insulin action upon glycolysis and change in intracellular pH. *Biochem Biophys Res Commun* 1979;1:905–910
143. Moore RD, Gupta RK: Effect of insulin on intracellular pH observed by phosphorus-31, NMR spectroscopy. *Int J Quantum Chem Symp* 1986;7:83–92
144. Moore RD: Stimulation of Na:H exchange by insulin. *Biophys J* 1981;33:203–210
145. Putnam RW: Effect of insulin on intracellular pH in frog skeletal muscle fibers. *Am J Physiol* 1985;248:C330–C336
146. Pontrememali R, Rivera A, Canessa M: Insulin and cytosolic $Ca^{++}$ ($Ca_i$) modulate the human red cell Na/H exchanger (EXC). (abstract) *Clin Res* 1991;39:192A
147. Canessa M, Falkner B, Hulman S: Red blood cell Na/H exchanger (EXC) activity is elevated in young hypertensive blacks. (abstract) *Hypertension* 1991;18:378
148. Aviv A, Livne A: The $Na^+/H^+$ antiport, cytosolic free $Ca^{2+}$ and essential hypertension: A hypothesis. *Am J Hypertens* 1988;1: 410–413
149. Erne P, Hermsmeyer K: Intracellular vascular muscle $Ca^{2+}$ modulation in genetic hypertension. *Hypertension* 1989;14:145–151
150. Wray S: Smooth muscle intracellular pH: Measurement, regulation, and function. *Am J Physiol* 1988;254:C213–C225
151. Berk BC, Brock JA, Webb RC, Taubman MB, Atkinson WJ, Gimbrone MA, Alexander RW: Epidermal growth factor, a vascular smooth muscle mitogen, induces rat aortic contraction. *J Clin Invest* 1985;75:1083–1086
152. Berk BC, Aronow MS, Brock TA, Cragoe E, Gimbrone MA, Alexander RW: Angiotensin II–stimulated $Na^+/H^+$ exchange in cultured vascular smooth muscle cells. *J Biol Chem* 1987;262: 5057–5064
153. Kleinman KS, Fine LG: Prognostic implications of renal hypertrophy in diabetes mellitus. *Diabetes Metab Rev* 1988;4:179–189
154. Björck S, Delin K, Herlitz H, Larsson O, Aurell M: Renin secretion in advanced diabetic nephropathy. *Scand J Urol Nephrol* 1984;79:53–57
155. Trujillo A, Eggena P, Barret J, Tuck M: Renin regulation in type II diabetes mellitus: Influence of dietary sodium. *Hypertension* 1989;13:200–205
156. Perez GO, Lespier L, Jacobi J: Hyporeninemia and hypoaldosteronism in diabetes mellitus. *Arch Intern Med* 1977;137:852–855
157. Christlieb AR: Nephropathy, the renin system and hypertensive vascular disease in diabetes mellitus. *Cardiovasc Med* 1978;2: 417–431
158. DeChatel R, Wiedmann P, Flammer J, Ziegler WH, Beretta-Piccoli C, Vetter W, Reubi F: Sodium, renin aldosterone, catecholamines and blood pressure in diabetes mellitus. *Kidney Int* 1977;12:412–421
159. O'Hare JA, Ferriss JB, Brady D, Twomey B, O'Sullivan DJ: Exchangeable sodium and renin in hypertensive diabetic patients with and without nephropathy. *Hypertension* 1985;7(suppl II): II-43–II-48
160. Tomita K, Matsudu O, Ideura T, Shiigai T, Takeuchi J: Renin-angiotensin-aldosterone system in mild diabetic nephropathy. *Nephron* 1982;31:361–366
161. Ferris JB, Sullivan PA, Gonggrijp H, Cole M, O'Sullivan DJ: Plasma angiotensin II and aldosterone in unselected diabetic patients. *Clin Endocrinol* 1982;17:261–269
162. Christlieb AR, Kaldany A, D'Elia JA: Plasma renin activity and hypertension in diabetes mellitus. *Diabetes* 1976;25:969–974
163. Mogensen CE: Progression of nephropathy in long-term diabetics with proteinuria and effect of initial antihypertensive treatment. *Scand J Clin Lab Invest* 1976;36:383–388
164. Drury PL, Bodansky HJ: The relationship of the renin-angiotensin system in type I diabetes to microvascular disease. *Hypertension* 1985;7(suppl II):II-84–II-89
165. Christlieb AR, Munichoodappa C, Braaten JT: Decreased responses of plasma renin activity to orthostasis in diabetic patients with orthostatic hypotension. *Diabetes* 1974;23:835–840
166. Campbell IW, Ewing DJ, Anderton JL, Thompson JH, Horn DB, Clarke BF: Plasma renin activity in diabetic autonomic neuropathy. *Eur J Clin Invest* 1976;6:381–385
167. Fernandez-Cruz A Jr, Noth RH, Lassman MN, Hollis JB, Mulrow PJ: Low plasma renin activity in normotensive patients with diabetes mellitus: Relationship to neuropathy. *Hypertension* 1981; 3:87–92
168. Tuck ML, Sambhi MP, Levin L: Selective hyporeninism and hypoaldosteronism in diabetes mellitus: Studies of the autonomic nervous system control of renin release. *Diabetes* 1979;28:237–246
169. Toop MJ, Dallinger KJC, Jennings PE, Barnett AH: Angiotensin-converting enzyme (ACE): Relationship to insulin-dependent diabetes and micro-angiopathy. *Diabetic Med* 1986;3:455–457
170. Kaysen GA: The metabolism of serum proteins in nephrosis. *AKF Nephrol Lett* 1988;5:31–46
171. Bohrer MP, Deen WM, Robertson CR, Brenner BM: Mechanism of angiotensin II–induced proteinuria in the rat. *Am J Physiol* 1977;233:F13–F21
172. Raij L, Keane WF: Glomerular mesangium: Its function and relationship to angiotensin II. *Am J Med* 1985;79(suppl 3C):24–30
173. Walker WG, Hermann J, Codd T, Russell RP: Role of hypertension in diabetic renal disease. *Maryland Med J* 1988;37:363–367
174. DeLeiva A, Christlieb AR, Melby JC, Grahan CA, Day RR, Leutscher JA, Zager PG: Big renin and biosynthetic defect of aldosterone in diabetes mellitus. *N Engl J Med* 1976;295:639–643
175. Hsueh WA, Carlson EJ, Leutscher JA, Grislis G: Activation and characterization of inactive big renin in plasma of patients with diabetic nephropathy and unusual active renin. *J Clin Endocrinol Metab* 1980;51:535–543
176. Franken AA, Derkx FH, Man in't Veld AJ, Hop WC, van Rens GH, Peperkamp E, de Jong PT, Schalekamp MA: High plasma prorenin in diabetes mellitus and its correlation with some complications. *J Clin Endocrinol Metab* 1990;71:1008–1015
177. Misbin RI, Grant MB, Pecker MS, Atlas SA: Elevated levels of plasma prorenin (inactive renin) in diabetic and nondiabetic patients with autonomic dysfunction. *J Clin Endocrinol Metab* 1987;64:964–968
178. Luetscher JA, Kraemer FB, Wilson DM, Schwartz HC, Bryer-Ash M: Increased plasma inactive renin in diabetes mellitus: A marker of microvascular complications. *N Engl J Med* 1985;312: 1412–1417
179. Weidmann P, Ferrari P: Central role of sodium in hypertension in diabetic subjects. *Diabetes Care* 1991;14:220–232


Downloaded from http://ahajournals.org by on February 28, 2023

180. Ulbrich KJ: Renal tubular mechanisms of organic solute transport. *Kidney Int* 1976;9:134–148
181. Crane RK: The gradient hypothesis and other models of carrier-mediated active transport. *Rev Physiol Biochem Pharmacol* 1977; 78:99–159
182. Harris RC, Brenner BM, Seifert JL: Sodium-hydrogen exchange and glucose transport in renal microvillus membrane vesicles from rats with diabetes mellitus. *J Clin Invest* 1986;77:724–733
183. Kumar AM, Gupta RK, Spitzer A: Intracellular sodium in proximal tubules of diabetic rats: Role of glucose. *Kidney Int* 1988;33:792–797
184. Lorenzi M, Cagliero E, Toledo S: Glucose toxicity for human endothelial cells in culture: Delayed replication, disturbed cell cycle and accelerated death. *Diabetes* 1985;34:621–627
185. Roy S, Sala R, Cagliero E, Lorenzi M: Overexpression of fibronectin induced by diabetes or high glucose: Phenomenon with a memory. *Proc Natl Acad Sci* 1990;87:404–408
186. Brownlee M, Cerami A, Vlassara H: Advanced glycosylation end products in tissue and the biochemical basis of diabetic complications. *N Engl J Med* 1988;318(suppl 20):1315–1321
187. Monnier VM, Vishwanath V, Frank KE, Dauchot P, Kohn RR: Relation between complications of type I diabetes mellitus and collagen-linked fluorescence. *N Engl J Med* 1986;314:403–408
188. Vlassara H, Brownlee M, Cerami A: Novel macrophage receptor for glucose-modified proteins is distinct from previously described scavenger receptors. *N Engl J Med* 1986;164:1301–1309
189. Vlassara H, Brownlee M, Manaque K, Pasagian A, Cerami A: Cachectin/TNF and IL-2 synthesis and secretion are induced by glucose-modified protein binding to a high affinity macrophage receptor. *Science* 1988;240(suppl 4858):1546–1548
190. Le J, Vilcek J: Tumor necrosis factor and interleukin 1: Cytokines with multiple overlapping biological activities. *Lab Invest* 1987;56: 234–248
191. King GL, Goodman AD, Buzney S, Moses A, Kahn CR: Receptors and growth-promoting effects of insulin and insulin-like growth factors on cells from bovine retinal capillaries and aorta. *J Clin Invest* 1985;75:1028–1036
192. Maarek B, Simon A, Levenson CJ, Pethosis-Merle I, Bonthier J: Hetergeneity of subclinical damage of large arteries in treated systemic hypertension. *Am J Cardiol* 1987;59:414–417
193. Blankenhorn DH, Kramah DK: Reversal of atherosis and sclerosis, the two components of atherosclerosis. *Circulation* 1989; 79:1–7
194. Cerami A, Vlassara H, Brownlee M: Protein glycosylation and the pathogenesis of atherosclerosis. *Metabolism* 1985;34(suppl 1):37–44
195. DeFronzo RA, Cooke CR, Andres R, Faloona GR, Davis PJ: The effects of insulin on renal handling of sodium, potassium, calcium, and phosphate in man. *J Clin Invest* 1975;55:845–855
196. Baum M: Insulin stimulates volume absorption in the rabbit proxima convoluted tubule. *J Clin Invest* 1987;79:1104–1109
197. Rocchini AP, Katch V, Kresilis D, Moorehead C, Martin M, Lampman R, Gregory M: Insulin and renal sodium retention in obese adolescents. *Hypertension* 1989;14:367–374
198. Rocchini AP, Key J, Bondie D, Chico R, Moorehead C, Katch V, Martin M: The effect of weight loss on the sensitivity of blood pressure to sodium in obese adolescents. *N Engl J Med* 1989; 321(suppl 9):580–585
199. Tuck ML, Sowers JR, Dornfeld L, Kledzik G, Maxwell M: The effect of weight reduction on blood pressure, plasma renin activity and plasma aldosterone levels in obese patients. *N Engl J Med* 1981;304:930–933
200. Sowers JR, Nyby M, Stern N, Beck F, Baron S, Catunia RA, Vlachis N: Blood pressure and hormone changes associated with weight reduction in the obese. *Hypertension* 1982;4:686–691
201. Hall JE, Coleman TG, Mizelle HC: Does chronic hyperinsulinemia cause hypertension? *Am J Hypertens* 1989;2:171–173
202. Fournier AM, Gadia MT, Kubrusly DB, Skyler JS, Sosenko JM: Blood pressure, insulin, and glycemia in nondiabetic subjects. *Am J Med* 1986;80:861–864
203. Shen DC, Shieh SM, Fuh MT, Wu DA, Chen YDI, Reaven GM: Resistance to insulin-stimulated glucose uptake in patients with hypertension. *J Clin Endocrinol Metab* 1988;66:580–583
204. Manolio TA, Savage PJ, Burke GL, Liu KL, Wagenknecht LE, Sidney S, Jacobs DR, Roseman JM, Donahue RP, Oberman A: Association of fasting insulin with blood and lipids in young adults: The Carelia Study. *Atherosclerosis* 1990;10:430–436
205. Swislocki ALM, Hoffman BB, Reaven GM: Insulin resistance, glucose intolerance and hyperinsulinemia in patients with hypertension. *Am J Hypertens* 1989;2:419–423
206. Singer P, Wolfgang G, Siegfried V, Hajdu I, Weiss M: Postprandial hyperinsulinemia in patients with mild essential hypertension. *Hypertension* 1985;7:182–186
207. Ferrannini E, Buzzigoli G, Bonadonna R, Giorico MA, Oleggini M, Graziadei L, Pedrinelli R, Brandi L, Bevilacqua S: Insulin resistance in essential hypertension. *N Engl J Med* 1987;317: 350–357
208. Pollare T, Lithell H, Berne C: Insulin resistance is a characteristic feature of primary hypertension independent of obesity. *Metabolism* 1990;39:167–174
209. Rowe JW, Young JB, Minaker KL, Stevens AL, Pallotta J, Landsberg L: Effect of insulin and glucose infusions on sympathetic nervous system activity in normal man. *Diabetes* 1981;30: 219–225
210. Sims EAH, Berchtold L: Obesity and hypertension mechanisms and implications for management. *JAMA* 1982;247:49–52
211. Landsberg L, Young JB: Insulin-mediated glucose metabolism in the relationship between dietary intake and sympathetic nervous system activity. *Int J Obes* 1985;9:63–68
212. Hwang IS, Ho H, Hoffman BB, Reaven GM: Fructose-induced insulin resistance and hypertension in rats. *Hypertension* 1987;10: 512–516
213. Berne C, Fagius J: Sympathetic response to oral carbohydrate administration: Evidence from microelectrode nerve recordings. *J Clin Invest* 1989;84:1403–1409
214. Anderson EA, Hoffman RP, Balon TW, Sinkey CA, Mark AL: Hyperinsulinemia produces both sympathetic neural activation and vasodilation in normal humans. *J Clin Invest* 1991;87: 2246–2252
215. Mathias CJ, daCosta DF, Fosbraey P, Christesen NJ, Bunmister R: Hypotensive and sedative effects of insulin in autonomic failure. *Br Med J* 1987;295:161–163
216. Jansen RWMM, Pentermen BJM, vanLier HJJ, Hoefnagels WH: Blood pressure reduction after oral glucose loading and its relation to age, blood pressure and insulin. *Am J Cardiol* 1987;60: 1087–1091
217. Standley PR, Zhang Z, Ram JL, Zemel MB, Sowers JR: Insulin attenuates vasopressin-induced calcium transients and voltage-dependent calcium current in vascular smooth muscle cells. *J Clin Invest* 1991;88:1230–1236
218. Lillioja S, Young AA, Culter CL: Skeletal muscle capillary density and fiber type are possible determinants of in vivo insulin resistance in man. *J Clin Invest* 1987;80:415–424
219. Bowen AM, Tan MH, Watson-Wright WM: Insulin binding and glucose uptake differences in rodent skeletal muscles. *Diabetes* 1981;30:702–704
220. James DE, Jenkins AB, Kraegen EW: Heterogeneity of insulin action in individual muscles in vivo: Euglycemic clamp studies in rats. *Am J Physiol* 1985;248:E567–E574
221. Andersen P: Capillary density in skeletal muscle of man. *Am J Physiol* 1985;248:E567–E574
222. Laughlin MH, Armstrong RB: Rat muscle blood flow as a function of time during prolonged slow treadmill exercise. *Am J Physiol* 1983;244:H814–H824
223. Schultz TA, Lewis SB, Westbie DK, Gerich JE, Rushakoff RJ, Wallin JD: Glucose delivery—A clarification of its role in regulating glucose uptake in rat skeletal muscle. *Life Sci* 1977;20: 733–736
224. Saltin B, Henriksson J, Nygaard E, Andersen P: Fiber types and metabolic potentials of skeletal muscles in sedentary man and endurance runners. *Ann N Y Acad Sci* 1977;301:3–29
225. Anderson P, Henriksson J: Capillary supply of the quadriceps femurs muscle of man: Adaptive response to exercise. *J Physiol* (Lond) 1977;270:677–690
226. Krens B, Lithell H: Lipoprotein metabolism influenced by training-induced changes in human skeletal muscle. *J Clin Invest* 1989;83:558–564
227. Julius S, Gudbrandsson T, Jamerson K, Shahab ST, Andersson O: The hemodynamic link between insulin resistance and hypertension. *J Hypertens* 1991;9:983–986
228. Baron AD, Laakso M, Brechtel G, Hoit B, Watt C, Edelman SV: Reduced postprandial skeletal muscle blood flow contributes to glucose intolerance in human obesity. *J Clin Endocrinol Metab* 1990;70:1525–1533
229. Laakso M, Sarlund H, Mykkanen L: Essential hypertension and insulin resistance in non-insulin dependent diabetes. *Eur J Clin Invest* 1989;19:518–526
230. Natali A, Santoro D, Palombo C, Cerri M, Ghione S, Ferrannini E: Impaired insulin action on skeletal muscle metabolism in essential hypertension. *Hypertension* 1991;17:170–178


Downloaded from http://ahajournals.org by on February 28, 2023

231. Bogardus C, Lillioja S, Stone K, Matt D: Correlation between muscle glycogen synthase activity and in vivo insulin action in man. *J Clin Invest* 1984;73:1185–1190
232. Mogensen CE, Christensen CK, Vittingchus E: The stages in diabetic renal disease with emphasis on the stage of incipient diabetic nephropathy. *Diabetes* 1983;32(suppl 2):64–78
233. Mauer SM, Steffes MW, Azar S, Kupcho Sandberg S, Brown DM: The effect of Goldblatt hypertension on development of the glomerular lesions of diabetes mellitus in the rat. *Diabetes* 1978; 27:738–744
234. Steffes MW, Brown DM, Mauer SM: Diabetic glomerulopathy following unilateral nephrectomy in the rat. *Diabetes* 1978;27: 35–41
235. Mogensen CE: Diabetes mellitus and the kidney. *Kidney Int* 1982;21:673–675
236. Rosenstock J, Raskin P: Early diabetic nephropathy: Assessment and potential therapeutic interventions. *Diabetes Care* 1986;9: 529–545
237. Zatz R, Brenner BM: Pathogenesis of diabetic microangiography: The hemodynamic view. *Am J Med* 1986;80:443–453
238. Parving H-H, Viberti GC, Keen H, Christiansen JS, Lassen NA: Hemodynamic factors in the genesis of diabetic nephropathy. *Metabolism* 1983;32:943–949
239. Friedman EA: Diabetic nephropathy: Strategies in prevention and management. *Kidney Int* 1982;21:780–791
240. Hasslacher C, Ritz E, Terpstra J, Gallasch G, Kunowski G, Rall C: Natural history of nephropathy in type I diabetes: Relationship to metabolic control and blood pressure. *Hypertension* 1985; 7(suppl II):II-74–II-78
241. Ballard DJ, Humphrey LL, Melton J III, Frohnert PP, Chu C-P, O'Fallon WM, Palumbo PJ: Epidemiology of persistent proteinuria in type II diabetes mellitus: Population-based study in Rochester, Minnesota. *Diabetes* 1988;37:405–412
242. Kofoed-Enevoldsen A, Borch-Johnsen K, Kreiner S, Nerup J, Decker T: Declining incidence of persistent proteinuria in type I (insulin-dependent) diabetic patients in Denmark. *Diabetes* 1987; 36:205–209
243. Nelson RG, Pettitt DJ, Carraher MJ, Baird HR, Knowler WC: Effect of proteinuria on mortality in NIDDM. *Diabetes* 1988;37: 1499–1504
244. Borch-Johnsen K, Andersen PK, Deckert T: The effect of proteinuria on relative mortality in Type I (insulin-dependent) diabetes mellitus. *Diabetologia* 1985;28:590–596
245. Borch-Johnsen K, Kreiner S: Proteinuria: Value as predictor of cardiovascular mortality in insulin dependent diabetes mellitus. *Br Med J* 1987;294:1651–1654
246. Andersen AR, Sandahl Christiansen J, Andersen JK, Kreiner S, Deckert T: Diabetic nephropathy in type I (insulin-dependent diabetes): An epidemiological study. *Diabetologia* 1983;25: 496–501
247. Consensus Statement: Proceedings from the International Workshop on Preventing the Kidney Disease of Diabetes Mellitus: Public Health Perspectives. *Am J Kidney Dis* 1989;13:2–6
248. Mogensen CE: Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. *N Engl J Med* 1984;310:356–360
249. Mathiesen ER, Oxenboll B, Johansen K, Svendsen PAa, Deckert T: Incipient nephropathy in type I (insulin-dependent) diabetes. *Diabetologia* 1984;26:406–410
250. Mogensen CE, Christensen CK: Predicting diabetic nephropathy in insulin-dependent patients. *N Engl J Med* 1984;311:89–93
251. Parving H-H, Oxenboll B, Svendsen PAa, Sandahl Christiansen J, Andersen AR: Early detection of patients at risk of developing diabetic nephropathy: A longitudinal study of urinary albumin excretion. *Acta Endocrinol* 1982;100:550–555
252. Parving H-H, Jensen HAE, Mogensen CE, Evrin PE: Increased urinary albumin-excretion rate in benign essential hypertension. *Lancet* 1974;1:1190–1192
253. Christensen CK: Rapidly reversible albumin and $\beta_2$-microglobulin hyperexcretion in recent severe essential hypertension. *J Hypertens* 1983;1:45–51
254. Cooper ME, Allen TJ, Macmillan AP, Bach L, Jerums G, Doyle AE: Genetic hypertension accelerates nephropathy in the streptozotocin diabetic rat. *Am J Hypertens* 1988;1:5–10
255. Jones RH, Hayakawa H, Mackay JD, Parsons V, Watkins PJ: Progression of diabetic nephropathy. *Lancet* 1979;1:1105–1106
256. Viberti GC, Bilous RW, Mackintosh D, Keen H: Monitoring glomerular function in diabetic nephropathy. *Am J Med* 1983;74: 256–264
257. Reddi AS, Camerini-Davalos RA: Diabetic nephropathy: An update. *Arch Intern Med* 1990;150:31–43
258. The working group on hypertension in diabetes: Statement on hypertension in diabetes mellitus. *Arch Intern Med* 1987;147: 830–842
259. Kaplan NM, Rosenstock J, Raskin P: A differing view of treatment of hypertension in patients with diabetes mellitus. *Arch Intern Med* 1987;147:1160–1162
260. Houston MC: Treatment of hypertension in diabetes mellitus. *Am Heart J* 1989;118:819–829
261. Frank HJC: Hypertension in the elderly diabetic: Therapeutic aspects. *J Hypertens* 1988;6(suppl 1):S109–S111
262. Bell DSH: Hypertension in the person with diabetes. *Am J Med Sci* 1989;297:228–232
263. Oster JR, Materson BJ: Metabolic side-effects of antihypertensive agents, in *Hypertension: New Aspects*. New York, Cahners Publishing Co, 1989, pp 1–7
264. Trost BM, Weidmann P, Beretta-Piccoli C: Antihypertensive therapy in diabetic patients. *Hypertension* 1985;7(suppl II): II-102–II-108
265. Runyan JW Jr: Diabetes, hypertension, and other associated diseases. *Primary Care* 1988;15:251–276
266. Bengtsson C, Blohmé G, Lapidus L, Lundgren H: Diabetes in hypertensive women: An effect of antihypertensive drugs or the hypertensive state per se? *Diabetic Med* 1988;5:261–264
267. Tolins JP, Raij L: Concerns about diabetic nephropathy in the treatment of diabetic hypertensive patients. *Am J Med* 1989; 87(suppl 6A):29S–33S
268. Mathiesen ER, Hommel E, Giese J, Parving HH: Efficacy of captopril in postponing nephropathy in normotensive insulin dependent diabetic patients with microalbuminuria. *Br Med J* 1991;303:81–87
269. Anderson S, Brenner BM: Pathogenesis of diabetic glomerulopathy: Hemodynamic considerations. *Diabetes Metab Rev* 1988;4: 163–177
270. Hostetter TH, Renneke HG, Brenner BM: The case for intrarenal hypertension in the initiation and progression of diabetic and other glomerulopathies. *Am J Med* 1982;72:375–380
271. Zatz R, Dunn BR, Meyer TW, Anderson S, Renneke HG, Brenner BM: Prevention of diabetic glomerulopathy by pharmacological amelioration of glomerular capillary hypertension. *J Clin Invest* 1986;77:1925–1930
272. Baba T, Ishizaki T, Ido Y, Aoyagi K, Murabayashi S, Takebe K: Renal effects of nicardipine, a calcium entry blocker in hypertensive type II diabetic patients with nephropathy. *Diabetes* 1986;35: 1206–1214
273. Baba T, Murabayashi S, Takebe K: Comparison of the renal effects of angiotensin converting enzyme inhibitor and calcium antagonist in hypertensive Type 2 (non–insulin-dependent) diabetic patients with microalbuminuria: A randomized controlled trial. *Diabetologia* 1989;32:40–44
274. Stornello M, Valvo EV, Scapellato L: Hemodynamic, renal, and humoral effects of the calcium entry blocker nicardipine and converting enzyme inhibitor captopril in hypertensive Type II diabetic patients with nephropathy. *J Cardiovasc Pharmacol* 1989; 14:851–855
275. Doyle AE: Comparison between perindopril and nifedipine in hypertensive and normotensive diabetics with microalbuminuria. Melbourne Diabetic Nephropathy Study Group. *Br Med J* 1991; 302(suppl 6770):210–215
276. Bakris GL: Effects of diltiazem or lisinopril on massive proteinuria associated with diabetes mellitus. *Ann Intern Med* 1990;112: 701–702
277. Mimram A, Insua A, Ribstein J, Monnier L, Bringer J, Mirouse J: Contrasting effects of captopril and nifedipine in normotensive patients with incipient diabetic nephropathy. *J Hypertens* 1988;6: 919–923
278. Demarie BK, Bakris GL: Effects of different calcium antagonists on proteinuria associated with diabetes mellitus. *Ann Intern Med* 1990;113:987–988
279. Epstein M: Calcium antagonists and diabetic nephropathy. *Arch Intern Med* 1991;151:2361–2364


Downloaded from http://ahajournals.org by on February 28, 2023