Hypertension is a major factor that contributes to the development of the vascular complications of diabetes mellitus, which primarily include atherosclerosis, nephropathy, and retinopathy. The mechanism of the pathophysiological effects of hypertension lies at the cellular level in the blood vessel wall, which intimately involves the function and interaction of the endothelial and vascular smooth muscle cells. Both hypertension and diabetes mellitus alter endothelial cell structure and function. In large and medium size vessels and in the kidney, endothelial dysfunction leads to enhanced growth and vasoconstriction of vascular smooth muscle cells and mesangial cells, respectively. These changes in the cells of smooth muscle lineage play a key role in the development of both atherosclerosis and glomerulosclerosis. In diabetic retinopathy, damage and altered growth of retinal capillary endothelial cells is the major pathophysiological insult leading to proliferative lesions of the retina. Thus, the endothelium emerges as a key target organ of damage in diabetes mellitus; this damage is enhanced in the presence of hypertension. An overall approach to the understanding and treatment of diabetes mellitus and its complications will be to elucidate the mechanisms of vascular disease and endothelial cell dysfunction that occur in the setting of hypertension and diabetes. (Hypertension 1992;20:253–263)

KEY WORDS • diabetes mellitus • endothelium, vascular • hypertension, essential

Vascular damage underlies many of the major complications of diabetes mellitus such as atherosclerosis, nephropathy, and retinopathy. Altered blood vessel function may also influence insulin-mediated glucose uptake in the peripheral tissue, which is a potential determinant of insulin sensitivity. Hypertension accelerates all the vascular complications of diabetes and is itself, in the absence of obesity or diabetes, associated with insulin resistance. High blood pressure alters vascular structure, function, and autocrine-paracrine relations within the blood vessel wall; it is these vascular changes that are likely responsible for hypertension's profound impact on diabetic complications.

Endothelial cells and vascular smooth muscle cells are the two major components of the vessel wall. Both hypertension and diabetes mellitus alter the function and interaction of these cells (Figure 1). In normal vessels, endothelial cells provide a mechanical barrier to underlying smooth muscle cells from circulating substances and blood cells and produce local factors that act in a paracrine fashion to alter vascular tone and growth. These factors are listed in Table 1. Endothelial cells are characterized by their production of angiotensin converting enzyme (ACE), which is responsible for the production of the powerful vasoconstrictor angiotensin II (Ang II) and for the degradation of the vasodilator kinins. Endothelin, a 21-amino acid vasoconstrictor and hypertensive agent, also arises from the endothelium. These vasoconstricting actions are balanced by endothelial production of endothelium-derived relaxing factors (EDRF), which are a family of nitric oxides, as well as vasodilating prostaglandins, histamines, and other vasodilators. The vasoconstricting substances tend to promote growth of vascular smooth muscle cells, whereas endothelial vasodilators tend to inhibit smooth muscle growth. Thus, the endothelium is an important modulator of both vascular tone and growth. In addition, the endothelium produces known growth factors, inflammatory substances, and coagulation factors that further modulate growth and vasoconstriction in vascular smooth muscle.

In vivo and in vitro assessments of endothelial cell function suggest it is markedly altered in diabetes mellitus. Diabetic subjects have increased circulating levels of von Willebrand factor and decreased levels of tissue plasminogen activator, which could contribute to their hypercoagulable state. Vascular segments from diabetic animals demonstrate impaired endothelium-dependent relaxation, which can be duplicated when normal vessel segments are incubated with high glucose concentrations. Hyperglycemia activates protein kinase C in the endothelium, which then stimulates endothelial production of vasoconstrictor prostaglandins. Circulating endothelin and ACE levels have also
DIABETES MELLITUS

HYPERTENSION

DIAMAGED ENDOTHELIAL CELL

DAMAGED ENDOTHELIAL CELL

Altered permissive factors

Vasodilation

Growth

Matrix Production

STIMULATED SMOOTH MUSCLE CELL

ATHROCLUSOSIS

GLUMERULOSCLEROSIS

FIGURE 1. Schema illustrates the interrelation between endothelial cell damage and smooth muscle cell response leading to atherosclerosis and glomerulosclerosis.

been reported to be increased in diabetics\textsuperscript{13,14}; high glucose also stimulates aortic endothelial secretion of endothelin.\textsuperscript{15} In addition, hyperglycemia alters endothelial cell matrix production, which may contribute to the generalized basement membrane thickening that occurs in diabetes. High concentrations of glucose enhance endothelial collagen IV and fibronectin production and increase activity of enzymes involved in collagen synthesis.\textsuperscript{16-17} Glucose toxicity also delays replication and accelerates death of cultured human umbilical vein endothelial cells.\textsuperscript{18} Other metabolic derangements that occur in diabetes in addition to hyperglycemia, such as hypertriglyceridemia and enhanced oxidation, glycosylation, and browning reactions are likely to further damage endothelial cells.\textsuperscript{19,20}

Humans and animals with hypertension also exhibit endothelial dysfunction. Hypertension affects blood vessels by altering shear stress, which is related to vascular flow, blood viscosity, and other factors, and by altered production and activity of contractile substances, ions, and ion channels. Patients with essential hypertension display decreased vascular response to acetylcholine, an endothelium-dependent vasodilator, but normal responses to sodium nitroprusside, a direct smooth muscle dilator.\textsuperscript{21} Endothelial abnormalities can develop when hypertension is induced in animal models,\textsuperscript{22,23} and anti-hypertensive treatment can normalize endothelium-dependent vasodilation.\textsuperscript{24} Other endothelial cell modifications due to hypertension include changes in shape, enhanced proliferation, increased intimal permeability to certain substances, and intimal thickening with proteoglycan accumulation (for review, see Reference 25).

A major result of endothelial dysfunction is damage to underlying smooth muscle cell structures that include vascular smooth muscle cells in blood vessels, mesangial cells in renal glomeruli, and pericytes in retinal capillaries. Because of a different milieu in large versus small vessels, and in one organ versus another, endothelial cells from various sources are likely to function and to respond to stress differently and thus, impact differently on the neighboring vascular smooth muscle cells. In blood vessels and kidneys the pathological response of smooth muscle cells includes: hypertrophy and proliferation, enhanced endogenous expression of growth factors, altered extracellular matrix material production, and altered contractile protein gene expression. In retinal capillaries the pericytes disappear. The following focuses on the modified endothelial–smooth muscle cell interaction that may contribute to the complications of diabetes mellitus and on the impact of hypertension to promote these pathological processes.

### Case Report

A 64-year-old Hispanic female presented to the Diabetes Clinic at Los Angeles County and University of Southern California Medical Center with complaints of progressive leg swelling for 2 months and a sudden deterioration in vision in the left eye for 2 weeks.

The patient was first told she had non–insulin-dependent diabetes mellitus (NIDDM) and hypertension at age 44, when she was evaluated for chronic fatigue and polyuria. An oral hypoglycemic agent for control of her blood sugar and a diuretic agent for control of her hypertension were prescribed. She took both medications for about 1 month; however, when her supply of medication was exhausted, she never refilled the prescriptions and did not return to her doctor. Since that time, she has occasionally taken oral hypoglycemic medication, but never for any sustained period of time.

The patient also states that her feet frequently swell on exertion, or chest pain.

Her past medical history is remarkable for 10 pregnancies and eight live-born children. She has had a number of urinary tract infections; the most recent was 5 years ago, at which time she was hospitalized in Mexico and received insulin for a short period of time. There are numerous family members with NIDDM, including the patient’s mother and four of five siblings. The mother died at age 65 of heart disease and one diabetic brother died suddenly at age 50. The patient does not smoke or drink and apart from occasional acetaminophen (Tylenol) does not take medication.

### Table 1. Vasoactive Substances Released by the Endothelium

<table>
<thead>
<tr>
<th>Vasoactive Substance</th>
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<tbody>
<tr>
<td>Angiotensin converting enzyme</td>
</tr>
<tr>
<td>Angiotensin II</td>
</tr>
<tr>
<td>Kinins</td>
</tr>
<tr>
<td>Prostaglandins</td>
</tr>
<tr>
<td>Endothelin</td>
</tr>
<tr>
<td>Endothelium-derived relaxing factor</td>
</tr>
<tr>
<td>Cyclooxygenase-dependent constricting factor</td>
</tr>
<tr>
<td>Histamine</td>
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spots. Visual acuity was limited to light and dark perception on the left and was 20/200 on the right. On examination, the neck was unremarkable, revealing no jugular venous distention. The chest was clear to auscultation and percussion. The heart’s rhythm was regular, without any murmurs, and with no evidence of an S1 or S2. The abdominal examination was unremarkable with a normal-sized liver and spleen and no ascites. The lower extremities demonstrated pitting edema to the groin. On neurological examination, reflexes were diminished globally, and there was diminished sensitivity to pinprick and light touch in a glove-and-stocking distribution.

An electrocardiogram revealed normal sinus rhythm, with deep Q waves in the inferior leads (II, III, and aVF). A chest roentgenogram showed a normal cardiac silhouette, with no evidence of congestive heart failure. Serum electrolytes were normal (meq/l: sodium 135 potassium 4.2, chloride 102, bicarbonate 24, magnesium2+ 1.2); however, the blood urea nitrogen was elevated (40 mg/dl) as was the creatinine (2.0 mg/dl). A fasting blood sugar level was elevated at 395 mg/dl. A complete blood count showed a normal white blood cell and platelet count, but a mild normocytic, normochromic anemia (hemoglobin 10 g/dl, hematocrit 30%, mean corpuscular volume 89 fl). A serum total cholesterol was elevated at 300 mg/dl with a decreased high density lipoprotein (HDL) (47 mg/dl) and a triglyceride level of 320 mg/dl. A urinalysis showed a specific gravity of 1.010, pH 5.0, 3+ proteinuria, and 1+ glucose. A 24-hour urine collection showed a creatinine clearance of 40 ml/min and a protein excretion rate of 3 g/day.

The patient was begun on furosemide (60 mg twice a day) and captopril (12.5 mg twice a day). Eventually the patient required captopril (50 mg twice a day) to control her blood pressure to 135/85 mm Hg. Her serum potassium and magnesium was monitored closely; however, no significant changes were seen after captopril was begun. She was also begun on twice-daily mixed insulin (48 units in the morning and 24 units at night), and on this regimen her blood sugar was well controlled (fasting blood sugar 130 mg/dl, hemoglobin A1C 8.4%). She was begun on a low sodium (2 g/day), low protein (40 g/day), and weight reducing (5,040 J [1,200 calories]/day) diet. On a follow-up visit 12 weeks after discharge, her creatinine clearance was unchanged, whereas her daily urinary protein excretion had fallen to 2.5 g/day. Her repeat total cholesterol was improved (220 mg/dl) as was her total triglyceride level (150 mg/dl), but there was no change in her HDL level (36 mg/dl).

After blood pressure and blood sugar control as well as a moderate reduction in body weight (from 215 to 190 lb), she underwent a cardiac catheterization that demonstrated complete occlusion of the distal right coronary artery, as well as a 50% lesion of the left anterior descending artery. The ejection fraction was normal. After this, the patient underwent a left-sided vitrectomy that resulted in some improvement in her vision; laser surgery therapy was carried out successfully on the right eye.

**Atherosclerosis**

Atherosclerosis is a major complication of diabetes mellitus, contributing to 60% of the mortality in diabetic patients.26 In the Framingham study, the death rate from myocardial infarction was 2.5 times greater among diabetics than nondiabetics.27 Hypertension in the presence of diabetes markedly accelerates the atherosclerotic process.28 Table 2 lists a number of factors that potentially contribute to the development of atherosclerosis in diabetes. Most of these factors are also recognized as independent risk factors for coronary artery disease. Their more common occurrence in the diabetic subject likely accounts for the increased incidence of atherosclerosis in diabetes, since the presence of more than one atherosclerotic risk factor exponentially increases the risk of atherosclerotic heart disease.27

A common denominator of factors 1 through 4 (Table 2) is that they contribute to endothelial dysfunction. Although hyperglycemia and hypertension markedly alter the endothelial cell, hyperglycemia has not conclusively been shown to play a causal role in atherosclerosis.30 Nevertheless, these risk factors lead to abnormal endothelial function such as increased production of clotting factors resulting in enhanced clot formation. In addition, platelets from diabetic subjects produce more thromboxane and thus tend to aggregate more readily compared with platelets from nondiabetics.30 Extracts of platelets from diabetics also exert greater mitogenic effects on vascular smooth muscle than platelets prepared from normal subjects.31

Hyperinsulinemia may further predispose the NIDDM patient to atherosclerosis. Eighty percent of NIDDM subjects are obese. Resistance to insulin’s effect on glucose metabolism due to obesity and genetic factors plays a key pathogenetic role in the development of NIDDM. The resulting hyperinsulinemia affects the atherosclerotic process by altering circulating lipoproteins and altering vascular structure through mitogenic effects on vascular smooth muscle. Elevated circulating very low density lipoprotein (VLDL) triglyceride is common in NIDDM due to enhanced liver production resulting from hyperinsulinemia and elevated plasma free fatty acid (FFA) levels.32 This has been suggested to increase macrophage uptake of VLDL and accumulation of intracellular lipid.33 HDL cholesterol is also decreased in NIDDM, possibly related to the hyperinsulinemia, so that total cholesterol levels, in general, remain unchanged. Low HDL cholesterol, itself, is a well-defined risk factor for atherosclerosis.34 In addition to its impact on circulating lipids, clinical studies further suggest insulin may contribute to atherogenesis independently of lipoprotein abnormalities.35

Epidemiological studies further support a role for insulin in the development of atherosclerosis. Five population studies found higher insulin responses to oral glucose in subjects at greater risk of cardiovascular disease.36-41 Three prospective studies have demonstrated that hyperinsulinemia precedes a coronary artery disease event.36-41 In white male government work-

<table>
<thead>
<tr>
<th>TABLE 2. Factors Contributing to Atherosclerosis in Diabetes Mellitus</th>
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<tbody>
<tr>
<td>Hyperglycemia</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Platelet clotting abnormalities</td>
</tr>
<tr>
<td>Altered circulating lipids</td>
</tr>
<tr>
<td>Obesity, insulin resistance, and hyperinsulinism</td>
</tr>
</tbody>
</table>
ers followed-up for 5–10 years, the incidence of coronary artery disease was significantly greater in subjects who had either higher fasting or 2-hour glucose-stimulated insulin levels.58 In another study that included white men and women, 1-hour glucose-stimulated insulin levels were significantly related to the 6-year incidence of and 12-year mortality from coronary artery disease in men but not in women.41 Zavaroni et al42 performed a meta-analysis of these prospective studies and found that the hyperinsulinemic, insulin-resistant groups tended to have other risk factors for atherosclerosis that included high triglycerides, lower HDL cholesterol, higher total cholesterol, and a greater incidence of hypertension. In fact, Williams and colleagues43 found that these risk factors cocluster in 12% of a white American hypertensive population and in some hypertensive families. The Pima Indian and Mexican-American populations have the highest incidence of NIDDM, but both have a lower incidence of hypertension and cardiovascular disease.44,45 Thus, whether insulin resistance and hyperinsulinemia cocluster with other risk factors for atherosclerosis in all populations remains to be determined. Nondiabetic nonobese patients with essential hypertension have been demonstrated to be insulin resistant and hyperinsulinemic.2 Current studies suggest that the hyperinsulinemic state contributes to an elevated blood pressure;46 the administration of high physiological doses of insulin to normotensive rats causes a rise in blood pressure.47,48 The impact of insulin on blood pressure may be through increased renal sodium reabsorption and enhanced sympathetic nervous system activity.49,50 These studies and clinical studies suggest hyperinsulinemia is an antecedent to hypertension.51–53 Whether hypertension can aggravate the effect of insulin on its target tissue is unknown.54 The first step in insulin action in muscle and fat requires that it be transported by the capillary endothelial cells to interstitial fluids that bathe target tissues. This is associated with capillary vasodilation, which is impaired in obesity, a well-known state of insulin resistance.55 The endothelial cell is rate limiting with regard to insulin transport out of the circulation, since a significant plasma-to-lymph insulin gradient exists, such that lymph insulin levels are only 50–60% of those in plasma.56 Therefore, damage to the endothelial cell by hypertension could potentially alter delivery of insulin to its target tissues. However, some models of hypertension, such as the Goldblatt two-kidney, one clip model of renal vascular hypertension in the rat are not associated with insulin resistance.57

Altered endothelial activity in the blood vessel ultimately leads to proliferation of smooth muscle cells, which is an integral feature of the vascular changes that accompany both hypertension and atherosclerosis.25,58 In both processes, there is intimal infiltration of vascular smooth muscle cells and an increase in fibrous collagen deposition. Vascular smooth muscle cells are the predominant cell type in atherosclerotic fibrous plaques (advanced lesions of atherosclerosis), and their proliferation determines the extent of development of fibrous plaques and whether they will result in clinical sequelae.58 Insulin, in addition to other growth factors derived locally and from the circulation, contributes to mitogenesis of vascular smooth muscle cells.59 Other growth factors demonstrated to affect vascular smooth muscle include platelet-derived growth factor (PDGF), epidermal growth factor (EGF), fibroblast growth factor (FGF), Ang II, norepinephrine, and insulinlike growth factor 1 (IGF-1).60 Many of these such as Ang II, norepinephrine, and endothelin are vasoconstrictive and increase systemic arterial pressure. Most of these factors have paracrine and autocrine, as well as endocrine, mechanisms of action. For example, PDGF, which is a mitogen of vascular smooth cells, is generated locally by activated platelets and can be expressed by vascular smooth muscle cells themselves.60 Inhibitors of growth such as prostaglandins, transforming growth factor β (TGF-β), and heparin are also derived locally and from the circulation.61 Proliferation of smooth muscle is normally controlled by a delicate balance between growth promoters and inhibitors. When the endothelium is damaged, the balance shifts toward enhanced activity of growth promoters.

In animal models, hypertension alone in the presence of low cholesterol does not cause atherosclerosis.62 Thus, the endothelial and vascular smooth muscle cell changes that occur with hypertension do not themselves lead to fatty streak and plaque formation. Increased levels of circulating lipogenic particles such as low density lipoprotein (LDL) or β-VLDL must be present. In rabbits and monkeys, diet-induced hypercholesterolemia leads to atherosclerotic vascular changes; hypertension accelerates the development of these changes.63 The induction of hypertension has a similar effect in the Watanabe hyperlipidemic rabbit (WHHL), which has a genetic defect in cellular LDL receptors and advanced atherosclerosis.63 In human populations with a high incidence of hypertension but generally low levels of plasma cholesterol, there is also a relatively low incidence of atherosclerotic complications. Therefore, lowering blood pressure to decrease the risk of atherosclerosis is important; however, antihypertensive agents must not adversely affect metabolic factors that predispose to atherosclerosis.

**Diabetic Nephropathy**

Diabetic nephropathy is a common and devastating long-term complication of diabetes mellitus. It is currently the most common cause of end-stage renal disease (ESRD) comprising 32% of new cases of ESRD (more than 10,000 cases per year).64 The incidence of ESRD is increasing yearly, especially among ethnic groups with diabetes, such as American Indians, Mexican-Americans, blacks, and Asians.65 In addition, there is an epidemiological association between the development of nephropathy and premature mortality from cardiovascular disease.66 Thus, diabetic patients in whom nephropathy develops are at risk for death from both renal and cardiovascular causes.

Substantial evidence suggests that diabetic nephropathy is a specific manifestation of the widespread endothelial cell dysfunction that exists in diabetes mellitus and that glomerulosclerosis results in part from altered interaction between the glomerular endothelium and mesangium. The glomerular endothelial cell is a long-lived cell that forms a fixed barrier between the blood and cells of the kidney. It is separated from the mesangial cell of the kidney by only its basement membrane; passage of substances between these two cells is easily

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accomplished. The pathophysiological changes that occur with focal and segmental glomerulosclerosis have been likened to those that occur in atherosclerosis, with mesangial changes paralleling changes in vascular smooth muscle cells, including expansion, proliferation, foam cell accumulation, appearance of increased extracellular matrix material (including fibrous collagen), deposits of amorphous debris, and eventual sclerosis.

Hypertension profoundly aggravates glomerular capillary perfusion abnormalities and hastens the development of glomerulosclerosis. In humans, lowering the blood pressure can slow the progression of nephropathy. In insulin-dependent diabetes mellitus (IDDM), a family history of essential hypertension predicts nephropathy; patients with a positive family history have a fourfold greater likelihood of developing diabetic renal disease compared with those with a negative family history. Thus, systemic hypertension associated with genetic factors such as altered sodium-lithium countertransport or low urinary kallikrein excretion may provide a better milieu for development of nephropathy than hypertension alone.

In the presence of systemic hypertension in the normal kidney, the afferent arteriole vasoconstricts to maintain normal glomerular pressure. In the diabetic kidney afferent arteriolar resistance fails to increase, allowing transmission of systemic hypertension into the glomerular capillary, which results in intraglomerular hypertension. Similar to the process in the vasculature, glomerular capillary hypertension alters glomerular endothelial structure and function that are already abnormal due to effects of diabetes mellitus. It is possible that disordered endothelial function in the afferent arteriole, due to diabetes, hypertension, or both, further aggravates its inability to normally alter afferent arteriolar resistance.

Diabetic nephropathy evolves slowly over the course of 10–15 years. The earliest structural change that occurs in the diabetic kidney is an increase in glomerular size and overall kidney size. In patients with IDDM, glomerular hypertrophy can be seen at the time of presentation for diabetes mellitus. After 1–6 years of diabetes, the glomerular size declines somewhat but does not normalize. In patients with NIDDM, glomerular enlargement is not consistently detected, possibly because the time of onset of NIDDM often cannot be established with certainty or because the older diabetic kidney is unable to undergo hypertrophy. The hypertrophy is accompanied by glomerular hyperfiltration (defined as glomerular filtration rate [GFR] in excess of 150 ml/min per 1.73 m²) in both IDDM and NIDDM. The hyperfiltration is associated with an increase in glomerular capillary plasma flow and in mean glomerular capillary hydraulic pressure that is due to an imbalance between afferent and efferent arteriolar resistance as discussed above. Increases in glucose, insulin, glucagon, growth hormone, atrial natriuretic factor, ketone bodies, prostaglandins, dietary protein content, as well as activity of the renin-angiotensin system have been implicated in the etiology of the hyperfiltration (summarized in Reference 77). Regardless of the cause, early in the disease both renal hypertrophy and concomitant hyperfiltration in humans can be reversed with weeks of strict glycemic control.

The next well-documented structural change is the thickening of the glomerular basement membrane. After 1.5–6 years of diabetes in patients with IDDM, it is estimated that 97% of the capillary loops are covered with abnormally thick basement membrane. The thickened basement membrane is elaborated by the endothelial cell. It contains normal basement membrane components, although some structural proteins, such as collagen type IV and V and laminin are increased in amount. The importance of the observed glomerular basement membrane thickening is not entirely clear since there does not appear to be any correlation between basement membrane thickness and renal function. In addition, glomerular basement membrane thickness does not necessarily correlate with basement membrane thickening in other parts of the body.

During this period no functional changes can be seen, although hyperfiltration may persist into this period (the so-called "silent period"). Once urinary microalbuminuria (urinary albumin excretion 20–200 mg/day) is detected, incipient diabetic nephropathy is present. This is the earliest stage at which those patients at risk of developing overt nephropathy can be clinically identified. Over 85% of patients with persistent microalbuminuria will progress to overt nephropathy. Abnormal endothelial cell function potentially plays an important role in the development of microalbuminuria since albumin is lost into the urine through large fenestrated capillary endothelial pores situated in the glomerular basement membrane. In diabetic nephropathy, the charge and size of these fenestrated pores are altered, resulting in passage of albumin through the normally protein-proof pores. Loss of heparan sulfate proteoglycan from the glomerular basement membrane may account for the loss of charge of the basement membrane and subsequent proteinuria. In experimental models of diabetic nephropathy, diabetic animals showed increased loss of heparan sulfate and albumin in the urine, which was prevented by treatment with a converting enzyme inhibitor.

Mesangial cell abnormalities appear usually after 5–15 years of diabetes in patients with IDDM. The most common abnormality seen by light microscope is diffuse intercapillary scarring due to expansion of the mesangial area. The better known nodular intercapillary sclerosis (K-W lesion) is actually less common and is seen in no more than 25% of patients with diabetic nephropathy. The observed mesangial expansion is primarily due to mesangial cell hypertrophy and increased accumulation of mesangial cell matrix. Matrix material consists of components similar to those found in basement membranes, primarily collagens, laminin, and fibronectin. Although type IV collagen and fibronectin appear to be increased in affected mesangial areas in early diabetic nephropathy, there is a nonspecific, "polyclonal" increase in mesangial matrix components. Mesangial expansion can be stopped, but not reversed by normalization of the blood sugar.

The mesangial cell has supportive, filtrative, and synthetic functions. Morphologically, it resembles a smooth muscle cell, from which it is derived. It is capable of contraction, which is important because the mesangial cell binds together capillary loops; contraction of the mesangium in response to agents such as Ang
II (summarized in Reference 90) can alter glomerular capillary flows or pressures. Substances elaborated by the endothelium affect mesangial cell growth, contraction, and protein production. Endothelin increases growth and extracellular matrix production by mesangial cells. EDRF and prostaglandins (such as prostaglandin E2), inhibit mesangial cell growth and contraction. In addition, increased local production of growth factors by stimulated endothelial cells and inflammatory cells results in growth of mesangium. For example, damage to the endothelium can also activate platelets and result in glomerular thrombosis; PDGF and other substances from platelets can enhance mesangial cell proliferation and matrix overproduction. As shown in Table 3, a wide variety of factors have been shown to alter mesangial cell growth, when tested in vitro. Most of the factors listed stimulate mitogenesis. Only Ang II and possibly arginine vasopressin have been demonstrated to induce hypertrophy, which is more prominent in glomerulosclerosis than is proliferation. Ang II also causes hypertrophy and not hyperplasia of vascular smooth muscle cells. The mesangial cell also synthesizes a variety of substances that can affect its own growth, including IGF-1, PDGF, platelet activating factor (PAF), renin, prostaglandins, and interleukin-1 (IL-1). With mesangial expansion overt persistent proteinuria (>0.5 g/24 hr) develops and glomerular closure proceeds. There may be hypertrophy of remaining glomeruli. Without intervention, the GFR falls by about 1 ml/min per month; thus, the approximate time from the first appearance of proteinuria to dialysis is 5 years.

**Diabetic Retinopathy**

Diabetic retinopathy is a major cause of acquired blindness in adults in the United States. Twenty years after diagnosis, 80% of NIDDM patients have retinopathy (approximately 20% with the more severe proliferative retinopathy), and 90% of IDDM patients have retinopathy (50% with proliferative retinopathy). Two factors have consistently been demonstrated to impact on the development of retinopathy: uncontrolled hyperglycemia and hypertension. A major culprit is the capillary endothelial cell, which plays a prominent and direct role in the structural abnormalities of diabetic retinopathy.

There are two types of retinopathy. Nonproliferative ("background") retinopathy consists of microaneurysms, dot-blot hemorrhages, and hard exudates, and occurs in virtually all patients with diabetes. The more severe proliferative retinopathy involves neovascularization, bleeding, chronic scarring, and retinal detachment. In nonproliferative retinopathy, the earliest structural change that may be seen in the retina is vasodilation of the retinal capillaries, which is felt to be due to abnormal tissue oxygenation. The vasodilation is accompanied by retinal hyperperfusion. In addition, capillary permeability increases early in the development of retinopathy in both humans and rats. At this stage, strict diabetic control can reduce capillary permeability toward normal. However, with time capillary endothelial cells become increasingly permeable to larger molecules, and this permeability can no longer be reversed by glycemic control. Another early change is pericyte degeneration. Pericytes elaborate an inhibitory growth factor for endothelial cells. Loss of this inhibitory growth factor early on may allow the endothelial cell to mobilize or proliferate in an abnormal fashion. Other studies suggest IGF-1 is not elevated in serum or vitreous of diabetic patients with proliferative retinopathy, so the role of hormones and growth factor is unclear. These changes in permeability are followed by more obvious structural changes in the retina, including chronic microaneurysm formation, pericyte degeneration, basement membrane thickening, and endothelial cell proliferation. In patients in whom proliferative retinopathy develops, neovascularization with leaky and fragile new capillaries appears. When new retinal vessels form, the endothelial cell first thickens and shows evidence of becoming more synthetically active. There is also degradation of the basement membrane. Endothelial cells then migrate through the vessel walls and begin to proliferate, forming new capillary loops. Vision is compromised when these fragile new capillary loops bleed; retinal detachments can occur when there is chronic scarring, and the fibrous strands put traction on the retina.

The exact mechanism by which hypertension and hyperglycemia affect proliferation is unknown, but as extensively discussed, both affect the endothelial cell. Unlike atherosclerosis and nephropathy, hyperglycemia appears to be a more important factor than hypertension in the development of retinopathy since it commonly occurs in the absence of frank elevations in blood pressure. Hypoxia and ischemia (possibly due to increased red blood cell aggregation in damaged capillaries) are also major contributors to the retinal vessel changes in diabetes. Increased shear stress and changes in rheology associated with hypertension can further accelerate this process.

Hormones are also thought to influence the course of diabetic retinopathy. For example, hypophysectomy has been reported to cause regression of retinopathy. Although growth hormone has direct effects on procollagen I and fibronectin synthesis, as well as on alteration of the synthesis of proteoglycans, IGF-1 probably mediates many of the effects of growth hormone. Modestly elevated local concentrations of IGF-1 in vitreous fluid of diabetics with retinopathy have been described when compared with control subjects without retinopathy; whether this is due to local production of IGF-1 or leakage from the serum into the vitreous is unknown.

**TABLE 3. Substances Affecting Mesangial Cell Growth**

<table>
<thead>
<tr>
<th>Stimulation</th>
<th>Inhibition</th>
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<tbody>
<tr>
<td>Platelet-derived growth factor</td>
<td>Atrial natriuretic factor</td>
</tr>
<tr>
<td>Insulin-like growth factor 1</td>
<td>Heparin</td>
</tr>
<tr>
<td>Insulin</td>
<td>Transforming growth factor β</td>
</tr>
<tr>
<td>Interleukin-1</td>
<td>Prostaglandin I</td>
</tr>
<tr>
<td>Epidermal growth factor</td>
<td>Endothelium-derived relaxing factor</td>
</tr>
<tr>
<td>Transforming growth factor α</td>
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<tr>
<td>Endothelin</td>
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<tr>
<td>Angiotensin II</td>
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<tr>
<td>Arginine vasopressin</td>
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<tr>
<td>Serotonin</td>
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<tr>
<td>Bradykinin</td>
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<td>Epinephrine</td>
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Clinical Discussion

The NIDDM patient described has all of the classic vascular complications of diabetes. The sudden visual deterioration was caused by a retinal hemorrhage due to proliferative retinopathy. Her lower extremity swelling was due to nephrotic syndrome associated with diabetic nephropathy. Coronary artery disease was present, as evidenced by her previous myocardial infarction. Hypertension was diagnosed simultaneously with diabetes, but unfortunately both remained untreated for many years. The uncontrolled diabetes and hypertension created a milieu, extensively described above, favorable to the development of chronic vascular disease and the ensuing diabetic complications. As this patient illustrates, in the presence of diabetes mellitus, hypertension should be treated early and aggressively since it enhances the progression of all of the complications manifested by our patient.

In this obese patient an important and early approach to her treatment should include weight loss and exercise. Both modalities have been demonstrated to decrease blood pressure and to improve insulin action on cellular glucose uptake. For this effect, weight loss need not be excessive; a maintained weight loss of as little as 5 pounds will achieve the goal. However, it must be maintained.

If an antihypertensive agent is needed, one must consider its effect on complications or risk factors for complications in diabetes as well as its efficacy in lowering blood pressure. Indeed, two decades of aggressive antihypertensive therapy in nondiabetic hypertensive populations, largely with diuretics and \( \beta \)-blockers, did not significantly improve the risk of development of coronary artery disease. The explanation may lie in the fact that these agents are known to enhance insulin resistance and glucose intolerance and to alter plasma lipid patterns to a more atherogenic profile. Thus, assessment of these metabolic issues, particularly in the diabetic hypertensive, is critical. ACE inhibition, on the other hand, does not adversely affect lipid profiles.

Captopril has been shown to increase peripheral tissue insulin sensitivity, and ACE inhibition has been demonstrated to be more effective than other agents in decreasing the extent of atherosclerosis in the WHHL rabbit and in preventing myointimal proliferation after aortic balloon catheter injury. Whether some of these direct vascular effects are mediated by mitogenic actions of Ang II on vascular smooth muscle is not known. The \( \alpha \)-adrenergic blockers also enhance insulin sensitivity and lower LDL cholesterol and triglycerides and increase HDL cholesterol. Calcium channel blockers generally do not affect lipid profiles or insulin action.

Intervention with regard to nephropathy includes lowering of systemic blood pressure if hypertension is present, optimizing glucose control, and correcting lipid abnormalities. Current studies suggest a low protein diet may be helpful. ACE inhibitors and certain calcium channel blockers may have protective effects on the glomerulus, as assessed by improved proteinuria, in addition to lowering blood pressure. These agents decrease proteinuria and retard disease progression in animal models of glomerulosclerosis (for review, see Reference 73). Whether they retard or prevent diabetic nephropathy in humans is unknown. Lowering of blood pressure has also been clearly demonstrated to retard the progression of retinopathy, although quite low diastolic pressures must be achieved. Whether one antihypertensive agent accomplishes this better than another also remains to be determined.

This patient required furosemide for diuresis. Captopril was begun for antihypertensive control because of its favorable metabolic effects in diabetic patients and because of its ability to decrease protein excretion. In response to this treatment, the patient had a decrease in serum cholesterol without a change in other lipid parameters and a decrease in protein excretion rate. She did not have evidence of bilateral renal artery stenosis or hyperkalemia, which would have been contraindications to ACE inhibition; this was confirmed when a follow-up test of serum potassium remained normal and creatinine clearance remained unchanged. Serum magnesium was followed-up because diabetic patients often have hypomagnesemia that can be aggravated by loop diuretics. Insulin rather than an oral hypoglycemic was used for control of diabetes in this patient because of the presenting fasting blood sugar of 395 mg/dl and the presence of significant renal insufficiency. In patients with less renal disease, oral agents would be considered before insulin since exogenous insulin in NIDDM aggravates the potential hyperinsulinemia and can stimulate appetite with further weight gain. Future agents that have an even greater impact on increasing peripheral tissue insulin action are currently being developed and tested; these agents should be ideal in NIDDM to decrease hyperinsulinemia and its potential hypertensive and atherogenic effects. Tight glucose control early in the course of retinopathy and nephropathy probably slows the progression of these complications; however, once they are advanced there is no evidence that tight control prevents further decomposition.

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Questions and Answers

Dr. Annette Fitz (University of Iowa, Iowa City): Because Ang II is possibly important to angiogenesis, what do you think of the role of prorenin in the microvascular problems in diabetes?

Dr. Hsueh: We have evidence that it is a potential marker for nephropathy in NIDDM; in fact, Luetscher et al found elevated plasma prorenin in IDDM patients who later developed nephropathy and retinopathy. Derkx et al found elevated prorenin in the vitreous of patients with proliferative retinopathy. I think prorenin can be taken up by the circulation and can activate the renin-angiotensin system, although there is some debate as to that. However, Ang II has been shown to alter the migration of endothelial cells and potentially enhance neovascularization. We added angiotensin I, Ang II, human renin, and prorenin to cultured bovine arterial endothelial cells but couldn't demonstrate any effects. So, at least in our hands, physiological levels of all those didn't seem to change whether they exist or migrate. Thus, there are still some questions about what Ang II does to endothelial cells.
On the other hand, in rat vascular smooth muscle cells, Ang II causes hypertrophy. Our group has shown Ang II causes hypertrophy but not proliferation in cultured murine mesangial cells.

**Dr. Francois M. Abboud (University of Iowa, Iowa City):** What is the mechanism by which ACE inhibitors alleviate proteinuria in diabetes?

**Dr. Hsueh:** We showed Ang II has direct effects on the mesangial cell in terms of hypertrophy. Michael Dunn and his group have shown it causes contraction of mesangial cells. Brian Myers has also suggested and presented evidence that Ang II alters protein sieving in the kidney and actually changes pore size. He has had some animal models of high Ang II with altered protein filtration. His data suggest ACE inhibitors can decrease protein filtration by alteration of glomerular basement membrane pore size. However, does ACE inhibition affect glomerulosclerosis? In animal models it does; the pathology and the protein sieving appear to change in parallel. Whether humans with glomerulosclerosis have parallel changes is presently under debate; until we get more renal biopsies we will be unable to answer those kinds of questions.

**Dr. Allyn L. Mark (University of Iowa, Iowa City):** You mentioned some of the evidence relating to the insulin hypothesis of hypertension, but there is also some evidence that is inconsistent with the role of insulin resistance in pathogenesis of hypertension. For example, the Pima Indians seem to have a high incidence of insulin resistance but do not have an increased instance of hypertension. How do you explain that?

**Dr. Hsueh:** Pima Indians have the highest incidence of NIDDM and insulin resistance of any population ever studied. One of the questions that has intrigued us is whether these people have other mechanisms to protect them from hypertension. It would be interesting to determine if the Pima Indians lack the sympathetic and renal responses to insulin seen in Caucasians that may contribute to hypertension. In the Pima Indians there doesn’t seem to be a relation between insulin and blood pressure levels, whereas this relation exists in almost all Caucasian populations.

**Dr. Mark:** Do you believe that treatment of hypertension in general differs in diabetics and nondiabetics?

**Dr. Hsueh:** I would say in diabetics, we should be much more careful in terms of monitoring renal changes, metabolic changes, and lipids, because of their higher risk for all the vascular complications. Therefore, we may be more sensitive in choosing agents that specifically target those complications. In essential hypertension, one is concerned to a greater extent about issues including quality of life, cost, and other things. We need to individualize hypertensive treatment, but the expense of carrying out studies comparing all classes of antihypertensive therapies in various groups of hypertensive patients will likely preclude obtaining these answers.

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