



Risk Factors for Diabetic Nephropathy

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EPIDEMIOLOGY AND DIABETES TYPE

Diabetic nephropathy can occur in both type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetes mellitus. The following data concerning the epidemiology of renal disease are confounded since they may or may not represent the current “natural history” of the disease; some of the evidence was obtained before the current era of recommended tight glycemic control, aggressive blood pressure and lipid control, and the specific benefit of therapy with angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers.

Type 1 diabetes

The epidemiology of diabetic nephropathy has been best studied in patients with type 1 disease, since the time of clinical onset is usually known. It has been suggested that 25 to 45 percent of these patients will, during their lifetime, develop clinically evident disease (the minimal criterion for which is a persistently positive urine dipstick for protein). Furthermore, the overall incidence of renal disease is substantially higher, since another 20 to 30 percent have subclinical microalbuminuria.

In comparison to these findings, a study from Sweden noted a dramatic reduction in clinically evident diabetic nephropathy to 8.9 percent at 25 years, a presumed reflection of better glycemic control. The average hemoglobin A1c concentration in the later part of this follow-up period was 7.0 percent; patients without overt proteinuria had a lower hemoglobin A1c concentration than those with proteinuria (7.1 versus 8.1 percent).

In addition to the importance of glycemic control, it is likely that more aggressive blood pressure reduction and the use of angiotensin converting enzyme inhibitors will further reduce the incidence of diabetic nephropathy.

The peak onset of nephropathy in type 1 diabetes is between 10 and 15 years after the onset of the disease. Those patients who have no proteinuria after 20 to 25 years have a risk of developing overt renal disease of only about one percent per year.

Type 2 diabetes

In Caucasians, the prevalence of progressive renal disease has generally been lower in type 2 diabetes than in type 1 disease. However, this observation does not apply to all groups with type 2 diabetes, some of whom have a more ominous renal prognosis. As

an example, nephropathy develops in up to 50 percent of diabetic Pima Indians at 20 years, with 15 percent having progressed to end-stage renal disease by this time.

More recent data suggest the renal risk is equivalent in the two types of diabetes. Evidence in support of this hypothesis were the observations in one report that the time to proteinuria from the onset of diabetes and the time to end-stage renal disease from the onset of proteinuria were similar in type 1 and type 2 disease.

Some of the most robust data relating to the development of diabetic nephropathy in a population of predominantly white type 2 diabetics was reported from the United Kingdom Prospective Diabetes Study (UKPDS).¹ The UKPDS was designed to compare the efficacy of different treatment regimens (diet, oral hypoglycemics, insulin, antihypertensive agents, varying blood pressure goals, and other interventions) on glycemic control and the complications of diabetes (including renal failure) in newly diagnosed patients with type 2 diabetes. The details of this study are described separately.

With respect to the development and progression of nephropathy among over 5000 type 2 diabetics enrolled in UKPDS, the following results were reported:¹

- At ten years following diagnosis, the prevalence of microalbuminuria, macroalbuminuria, and either an elevated plasma creatinine concentration (defined as $\geq 175 \mu\text{mol/L}$ [2.0 mg/dL]) or requirement for renal replacement therapy was 25, 5, and 0.8 percent, respectively.
- The yearly rate of progression from diagnosis to microalbuminuria, from microalbuminuria to macroalbuminuria, and from macroalbuminuria to an elevated plasma creatinine or renal replacement therapy was 2.0, 2.8, and 2.3 percent.
- Based upon a statistical model, an estimation of the median time spent in each stage without progression to another nephropathy stage was 19, 11, and 10 years for those with no nephropathy, microalbuminuria, and macroalbuminuria, respectively. Among those with an elevated plasma creatinine concentration ($\geq 2.0 \text{ mg/dL}$ [175 $\mu\text{mol/L}$]), renal replacement therapy was required after a median period of only 2.5 years. This rate of progression is higher than seen in other studies probably because of two factors: appropriate therapy (e.g., angiotensin inhibition and rigorous blood pressure control)

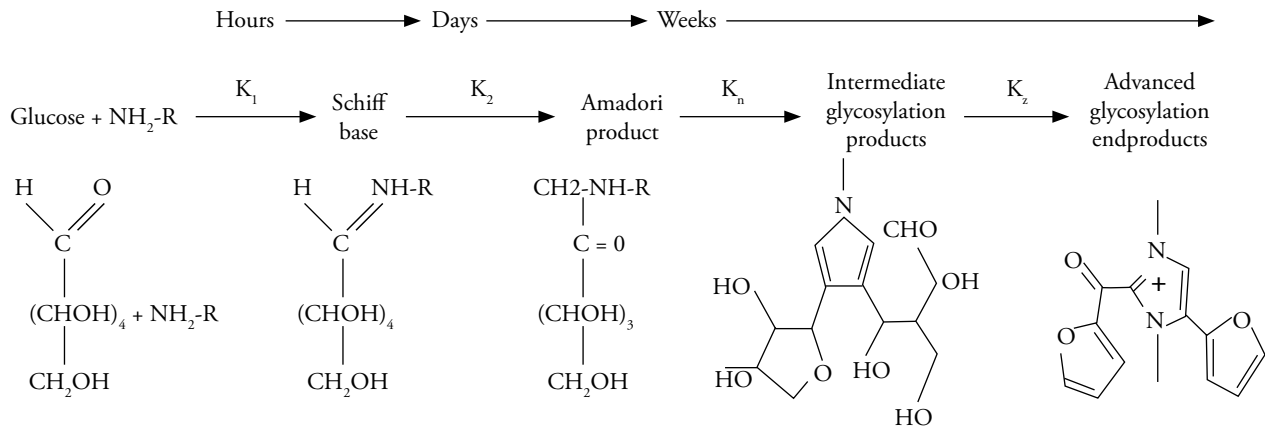


Fig. 1: Formation of advanced glycosylation end-products: Schematic representation of the formation of advanced glycosylation end-products in the presence of persistent hyperglycemia.

was not taken into account; and most of the patients had more advanced renal insufficiency.

PATHOLOGY AND PATHOGENESIS

There are three major histologic changes in the glomeruli in diabetic nephropathy: mesangial expansion, glomerular basement membrane thickening and glomerular sclerosis. The last abnormality, which may have a nodular appearance (the Kimmelstiel-Wilson lesion), is often associated with hyaline deposits in the glomerular arterioles (reflecting the insudation of plasma proteins such as fibrin, immunoglobulins, and complement into the vascular wall) (histology 1A-1C). These different histologic patterns appear to have similar prognostic significance.

The mesangial expansion and glomerulosclerosis do not always develop in parallel, suggesting that they may have somewhat different pathogeneses. Glomerulosclerosis, for example, may result from intraglomerular hypertension induced by renal vasodilatation or from ischemic injury induced by hyaline narrowing of the vessels supplying the glomeruli.

Mesangial expansion, on the other hand, may be directly induced by hyperglycemia, perhaps via increased matrix production or glycosylation of matrix proteins. In vitro studies have demonstrated that hyperglycemia stimulates mesangial cell matrix formation. This process appears to be mediated in part by an increase in the mesangial cell glucose concentration, since similar changes in mesangial function can be induced in a normal glucose milieu by overexpression of glucose transporters, thereby enhancing glucose entry into the cells.

Glycosylation of tissue proteins also may contribute to the development of diabetic nephropathy and other microvascular complications. In chronic hyperglycemia, some of the excess glucose combines with free amino acids on circulating or tissue proteins. This nonenzymatic process initially forms reversible early glycosylation products and later irreversible advanced glycosylation end-products (AGEs) via an Amadori rearrangement (Fig. 1). Circulating AGE levels are increased in diabetics, particularly those with renal insufficiency, since AGEs are normally excreted in the urine. The net effect is tissue accumulation of AGEs, in part by crosslinking with collagen,

which can contribute to the associated renal and microvascular complications.

Hemoglobin is one of the proteins that undergoes irreversible glycosylation. Although this process does not contribute to microvascular disease, it is useful clinically since the glycosylated hemoglobin level is usually a reasonably accurate estimate of long-term glycemic control.

Activation of cytokines and immune-related processes may be other factors involved in the matrix accumulation in diabetic nephropathy.^{2,3} As an example, hyperglycemia increases the expression of transforming growth factor β (TGF- β) in the glomeruli and of matrix proteins specifically stimulated by this cytokine. TGF- β may therefore contribute to both the cellular hypertrophy and enhanced collagen synthesis that are seen in diabetic nephropathy. The following observations support this hypothesis:

- In a gene therapy experiment, a TGF- β RII/Fc chimeric gene (which consists of a fusion of the extracellular domain of the TGF- β type II receptor and IgG-Fc) was introduced into the muscle of streptozotocin-induced diabetic rats. The transfected chimeric protein, which diminishes activation of the native receptor, accumulated in the diabetic kidney since it was secreted into the systemic circulation; these rats showed significant inhibition of diabetes-induced glomerular hypertrophy.
- The administration of an angiotensin converting enzyme inhibitor to patients who have type 1 diabetes and nephropathy lowers serum concentration of TGF- β . An inverse correlation has been found between decreased TGF- β levels and renoprotection, as determined by changes in the glomerular filtration rate over time.
- The combination of an anti-TGF- β antibody plus an ACE inhibitor completely normalized proteinuria in rats with progressive diabetic nephropathy; proteinuria was only partially lessened with an ACE inhibitor alone. There was also histologic benefit in terms of both glomerulosclerosis and tubulointerstitial injury.

Table 1 : Major Risk Factors for Diabetic Nephropathy

- Genetic susceptibility as evidenced by diabetic nephropathy in a sibling
- Hypertension or high-normal blood pressure
- Increased glomerular filtration rate
- Worse glycemic control
- Being black, Mexican-American, or Pima Indian
- Increased plasma prorenin activity
- Increased sodium-lithium and sodium hydrogen countertransport

It has also been proposed that activation of protein kinase C by hyperglycemia contributes to the renal disease and other vascular complications of diabetes.

RISK FACTORS

Studies in patients who have or do not have clinically evident diabetic nephropathy have identified a number of factors as being associated with increased risk of renal involvement (Table 1).

Genetic susceptibility

Genetic susceptibility may be an important determinant of both the incidence and severity of diabetic nephropathy. The likelihood of developing diabetic nephropathy is markedly increased in patients with a diabetic sibling or parent who has diabetic nephropathy; these observations have been made in both type 1 and type 2 diabetes.⁴ One report, for example, evaluated Pima Indian families in which two successive generations had type 2 diabetes. The likelihood of the offspring developing overt proteinuria was 14 percent if neither parent had proteinuria, 23 percent if one parent had proteinuria, and 46 percent if both parents had proteinuria.

The increase in risk cannot be explained by duration of diabetes, hypertension, or degree of glycemic control, although a genetic predisposition to abnormal sodium handling and hypertension may be important. Genetics also may contribute to the influence of race on diabetic nephropathy.

One component of the genetic risk may be the angiotensin converting enzyme (ACE) gene genotype. In patients with type 2 diabetes, the DD polymorphism has been associated with an increased risk for the development of diabetic nephropathy, more severe proteinuria, a greater likelihood of progressive renal failure, and enhanced mortality on dialysis. However, a critical review of nineteen studies examining a possible link between the ACE gene genotype and diabetic nephropathy failed to confirm an association among Caucasians with either type 1 or type 2 diabetes, but could not exclude a possible association in Asians. Unfortunately, due to poor methodology, no definitive conclusions could be drawn. As a result, more rigorous studies are required to definitively ascertain any possible association between a polymorphism of the ACE gene and diabetic nephropathy.

An enhanced risk may also be due to inheritance of one allele of the aldose reductase gene, the rate-limiting enzyme for the polyol pathway. In a controlled study of patients with type 1 diabetes, homozygosity for the Z-2 allele was significantly associated with an odds ratio of 5.25 for the presence of nephropathy.

Blood pressure

Prospective studies have noted an association between the subsequent development of nephropathy and higher systemic pressures, particularly if in the hypertensive range, as well as an increase in nocturnal blood pressure (nondippers). It has also been suggested that a parental history of hypertension identifies subjects at greater risk, although this has not been found in all studies.

The presence of these risk factors for hypertension is particularly important in patients with relatively poor glycemic control (hemoglobin A1 concentration > 12 %) who are at increased risk of overt nephropathy within 20 years. If, however, glycemic control is better, the risk is still greater but the development of renal disease appears to be delayed.

Glomerular filtration rate

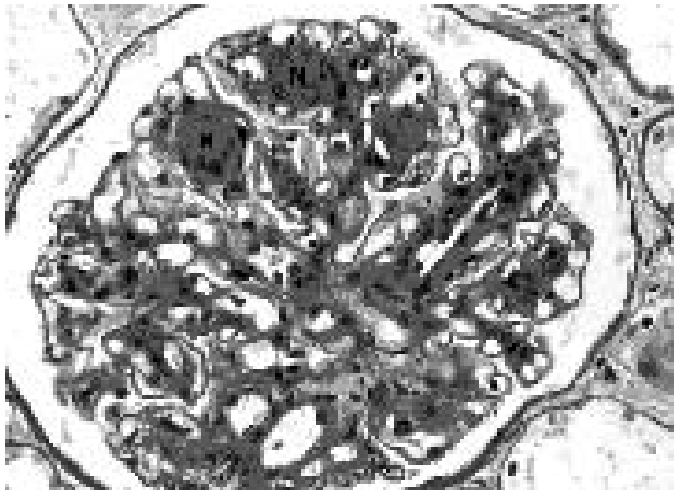
Approximately one-half of patients with type 1 diabetes of less than five years duration have an elevated glomerular filtration rate (GFR) that is 25 to 50 percent above normal. Those patients with glomerular hyperfiltration appear to be at increased risk for diabetic renal disease. This is particularly true for overt nephropathy if the initial GFR is above 150 mL/min; in comparison, lesser degrees of hyperfiltration may have a slower course, with affected patients being at enhanced risk for microalbuminuria.

The glomerular hyperfiltration in type 1 diabetics is typically associated with glomerular hypertrophy and increased renal size. The association between these hemodynamic and structural changes and the development of diabetic nephropathy may be related both to intraglomerular hypertension (which drives the hyperfiltration) and to glomerular hypertrophy (which also increases wall stress). Therapy aimed at reversing these changes – with aggressive control of the plasma glucose concentration early in the course of the disease, dietary protein restriction, and antihypertensive therapy – may slow the rate of progression of the renal disease.

The findings in type 2 diabetes are somewhat different. Up to 45 percent of affected patients initially have a GFR that is more than two standard deviations above age-matched nondiabetic and obese controls. However, the degree of hyperfiltration (averaging 117 to 133 mL/min) is less than that seen in type 1 diabetics. Type 2 diabetics are also older and more likely to have arteriosclerotic vascular disease which will limit increases in both glomerular filtration and glomerular size.

The potential importance of intraglomerular hypertension in the pathogenesis of diabetic nephropathy may explain why systemic hypertension is an important risk factor for the development of diabetic nephropathy. Studies in experimental animals suggest that the diabetic state is associated with impaired renal autoregulation. As a result, raising the systemic pressure does not produce the expected afferent arteriolar vasoconstriction that would minimize transmission of the elevated pressure to the glomerulus. Why this occurs is not clear, but increased production of vasodilator prostaglandins appears to be involved.

It remains unclear whether the changes in renal hemodynamics also occur in other organs, possibly contributing to the development of microvascular disease at these sites. The observation that the intracapillary pressure in skin nail-fold capillaries is elevated early



Histology-1A

in the course of type 1 diabetes is compatible with a systemic abnormality in the regulation of capillary flow.

Glycemic control

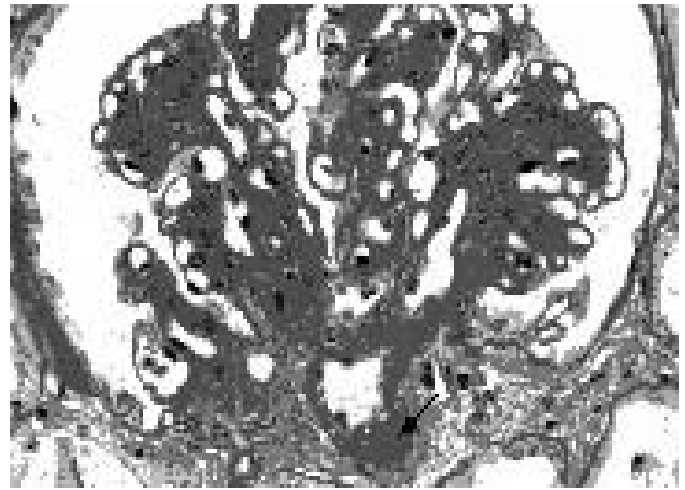
Diabetic nephropathy is more likely to develop in patients with lesser degrees of glycemic control, particularly if the hemoglobin A1c concentration is above 11 percent. Patients with type 1 diabetes whose hemoglobin A1c concentration is maintained below 8.1 percent are at much lower risk for renal disease. In addition, the United Kingdom Prospective Diabetes Study of patients with type 2 diabetes found that fewer patients treated with intensive versus conventional therapy had progression of microalbuminuria (27 versus 39 percent) and proteinuria (7 versus 13 percent) over 15 years of follow-up.

Race

The incidence and severity of diabetic nephropathy are increased in blacks (3- to 6-fold compared to Caucasians), Mexican-Americans, and Pima Indians with type 2 diabetes. This observation in such genetically disparate populations suggests a primary role for socioeconomic factors, such as diet, poor control of hyperglycemia, hypertension, and obesity.⁶

As an example, there appears to be an important association between hypertension and disease progression in black patients with type 2 diabetes. A cross-sectional study found that the GFR was normal in patients who were normotensive; in comparison, hypertension was associated with a decline in renal function, particularly if it developed after the onset of diabetes and the patient had been diabetic for more than 10 years. It is not clear, however, if the hypertension worsened the renal disease or was simply a marker for more severe renal involvement.

However, the importance of genetic influences in the racial propensity to diabetic nephropathy cannot be excluded. Even when adjustments are made for the increased incidence of hypertension and lower socioeconomic status in blacks, there still appears to be as much as a 4.8-fold increase in the risk of end-stage renal disease due to diabetic nephropathy in blacks.⁴⁷ This appears to occur only in type 2 diabetes, with no increase in risk seen with type 1 diabetes.



Histology-1B

Pima Indians, on the other hand, have larger glomeruli than Caucasians, a finding that may represent a specific genetic trait. This increase in glomerular size, via the mechanism described above, could lead to enhanced susceptibility to diabetes-induced glomerular injury. One manifestation of this increased risk is the observation that diabetic Pima Indians with a known duration of disease of less than 3 years already have evidence of glomerular dysfunction (increased albumin excretion due to impaired glomerular size-selectivity). These patients also have a higher GFR (140 vs 122 mL/min) when compared to matched patients without diabetes.

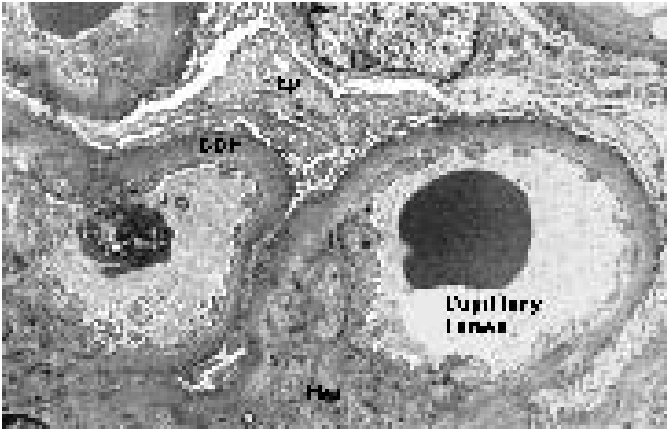
Plasma prorenin activity

Impaired conversion of the precursor prorenin into active renin appears to be relatively common in diabetes, leading to a reduction in the plasma renin activity. Although it is unclear how this occurs, an increase in plasma prorenin activity can often be detected before there is any clinical evidence of microvascular disease. Those patients with elevated prorenin levels are more likely to develop diabetic nephropathy or retinopathy; with regard to renal disease, however, it is unclear if increased prorenin is a risk factor or a marker for early diabetic nephropathy.

This defect in the formation of active renin can also lead to hypoaldosteronism and hyperkalemia in patients with overt renal disease.

Sodium-lithium and sodium-hydrogen countertransport

Many patients with salt-sensitive essential hypertension have an elevation in red cell sodium-lithium countertransport; increased sodium-hydrogen exchange has also been linked to the development of hypertension. These abnormalities are thought to be markers for enhanced sodium transport at sites that might induce a rise in blood pressure, such as the kidney or vascular smooth muscle. Some studies have suggested that type 1 diabetics with nephropathy have higher rates of sodium-hydrogen exchange and red cell sodium-lithium countertransport than those without renal disease. Sodium-hydrogen exchange activity is concordant among type 1 diabetic siblings, suggesting that this



Histology-1C

activity is genetically determined. Thus, a genetic predisposition to hypertension may increase the risk of diabetic nephropathy. This relationship may not be applicable in type 2 diabetes.

Summary

Although each of the above factors increases the risk of developing diabetic nephropathy, none is as yet sufficiently predictive in the individual patient. The earliest detectable sign of diabetic nephropathy is microalbuminuria which, at least in type 1 disease, is associated with a substantial risk of progressive renal damage.

RELATION BETWEEN DIABETIC NEPHROPATHY AND RETINOPATHY

Patients with nephropathy and type 1 diabetes almost always have other signs of diabetic microvascular disease, such as retinopathy and neuropathy. The retinopathy is easy to detect clinically and typically precedes the onset of overt nephropathy in these patients. By the time advanced retinopathy has occurred, there are usually histologic changes in the glomeruli and increased protein excretion that is at least in the microalbuminuric range. There are, however, some patients with advanced retinopathy who have little or no renal disease as assessed from renal biopsy and protein excretion.

The relationship between diabetic nephropathy and retinopathy is less predictable in type 2 diabetes. In one study of 35 patients with diabetes and significant proteinuria (>300 mg/day), 27 (77 percent) were found to have diabetic nephropathy. Diabetic retinopathy was present in 15 of the 27 (56 percent), and in none of the eight individuals without diabetic nephropathy, thereby resulting in a sensitivity and specificity of 40 and 100 percent, respectively. Further analysis of some of these patients plus additional type 2 diabetics with proteinuria found that, among those without retinopathy, approximately 30 percent did not have diabetic nephropathy upon renal biopsy.⁷ Thus, type 2 diabetics with marked proteinuria and retinopathy most likely have diabetic nephropathy, while those without retinopathy have a high incidence of non-diabetic glomerular disease. Data from the third National Health and Nutrition Examination Survey suggests that 30 percent of type 2 diabetics with renal

insufficiency have non-diabetic renal disease, as inferred by the absence of albuminuria and retinopathy in this population.⁸

Some insight into the correlation between nephropathy and retinopathy was provided by a study in which 36 patients with type 2 diabetes and renal involvement underwent renal biopsy. Seventeen biopsies displayed diabetic glomerulosclerosis with Kimmelstiel-Wilson nodules, while 15 revealed changes characteristic of diabetes (mesangial sclerosis) but without classic nodules. Patients with and without nodules did not differ with respect to duration of diabetes or degree of glycemic control. A close correlation was observed between the presence of severe retinopathy and nodules on biopsy: six of seven patients with proliferative retinopathy had such nodules, while seven of eight without retinopathy had mesangial sclerosis. Overall, severe retinopathy was more closely associated with nodules than with mesangial sclerosis. The reason for this association is unknown.

OTHER RENAL DISEASES

Proteinuria in diabetes mellitus is occasionally due to a glomerular disease other than diabetic nephropathy. As examples, membranous nephropathy, minimal change disease, IgA nephropathy, Henoch-Schönlein purpura, thin basement membrane disease, and a proliferative glomerulonephritis have all been described.^{9,10}

The major clinical clues suggesting nondiabetic glomerular disease are:¹⁰

- Onset of proteinuria less than five years from the documented onset of diabetes (since the latent period for overt diabetic nephropathy is usually at least 10 to 15 years); this is more difficult to ascertain in type 2 diabetics in whom the true onset of disease is not known.
- The acute onset of renal disease. Diabetic nephropathy is a slowly progressive disorder characterized by increases in protein excretion and the serum creatinine concentration over a period of years.
- Presence of an active urine sediment containing red cells and cellular casts. Patients with only microscopic hematuria may have thin basement membrane disease, which may affect up to nine percent of the general population, with or without underlying diabetic nephropathy.
- In type 1 diabetes, the absence of diabetic retinopathy or neuropathy. In contrast, lack of retinopathy in type 2 diabetes does not preclude diabetic nephropathy, which remains the most likely diagnosis.

The reported frequency of other renal diseases among patients with diabetes depends upon multiple factors, including ethnicity, geographic location, and biopsy policy. The importance of the last factor was shown in the largest study to date relating to biopsy results in type 2 diabetics.⁹ Nearly 400 renal biopsies were evaluated in centers in Italy with a biopsy policy among type 2 diabetics that was either restricted (in which the procedure was performed for the indications just mentioned and some less stringent criteria) or unrestricted (in which the procedure was performed for much less stringent criteria). Significant disparities were found in the incidence of diabetic glomerulosclerosis (29 and 51 percent for restricted and unrestricted, respectively) and of other renal diseases (57 and 33 percent, respectively).

Nephrosclerosis

In addition to these superimposed glomerular diseases, renal insufficiency and proteinuria may also be induced by other diseases, particularly arteriosclerotic vascular disease (nephrosclerosis) in older type 2 diabetics.^{9,11} This disorder cannot usually be distinguished from diabetic nephropathy without performing a renal biopsy; this is rarely necessary since making this distinction is of no clinical value. One potential clue favoring the presence of nephrosclerosis is a rise in the plasma creatinine concentration, due to interference with renal autoregulation, after institution of an angiotensin converting enzyme inhibitor to treat hypertension or to slow the rate of progression of the renal disease.

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