Overview of diabetic nephropathy

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INTRODUCTION — Diabetic nephropathy occurs in both type 1 (formerly called insulin-dependent or juvenile onset) and type 2 (formerly called non-insulin-dependent or adult onset) diabetes mellitus, including diabetes due to genetic defects of beta-cell function (which was previously called maturity onset diabetes of the young, or MODY). (See "Classification of diabetes mellitus and genetic diabetic syndromes").

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 availability of data supporting the efficacy of tight glycemic control, aggressive blood pressure and lipid control, and the specific benefit of angiotensin converting enzyme (ACE) inhibitors and/or angiotensin II receptor blockers (ARBs).

This topic provides an overview of the epidemiology, pathogenesis, and risk factors for diabetic nephropathy. The importance of microalbuminuria and the treatment of diabetic nephropathy are discussed separately. (See "Microalbuminuria and diabetic nephropathy" and see "Treatment and prevention of diabetic nephropathy").

EPIDEMIOLOGY

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. Approximately 20 to 30 percent will have microalbuminuria after a mean duration of diabetes of 15 years [1,2]. Less than half of these patients will progress to overt nephropathy; microalbuminuria may regress or remain stable in a substantial proportion, probably related to glycemic and blood pressure control. (See
"Microalbuminuria and diabetic nephropathy", sections on Prevalence and Regression of microalbuminuria).

Prior to the current period of intensive monitoring and treatment, it was suggested that 25 to 45 percent of diabetic patients will develop clinically evident disease (the minimal criterion for which is a persistently positive urine dipstick for protein) [1,3,4].

The overall incidence of end-stage renal disease (ESRD) was also substantial, with reported rates of 4 to 17 percent at 20 years from time of initial diagnosis and approximately 16 percent at 30 years [5-7]. In comparison to these findings, subsequent studies have found that the renal prognosis of type 1 diabetes, including the rate of progression to ESRD, has dramatically improved over the last several decades [8,9]: 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 [8]. 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). A similar decline in incidence was not noted in another report in which this degree of glycemic control was not achieved [10]. One study from Finland evaluated the long-term outcomes of 20,005 patients over the period 1965 to 1999 [9]. During the median follow-up period of 17 years (maximum of 37 years), progression to ESRD occurred in only 632 patients, with the cumulative incidence being 2.2 and 7.8 percent at 20 and 30 years, respectively. In addition, the rate of ESRD was relatively lower among patient cohorts diagnosed at later time points, and the incidence of ESRD was lowest among those diagnosed prior to the age of 5 years.

In addition to the importance of glycemic control, more aggressive blood pressure reduction and the use of angiotensin converting enzyme inhibitors has shown to reduce the rate of progression of diabetic nephropathy. (See "Treatment of hypertension in diabetes mellitus").

The onset of overt nephropathy in type 1 diabetes is typically 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 1 percent per year [3].

Type 2 diabetes — In Caucasians, the prevalence of progressive renal disease has
generally been lower in type 2 diabetes than in type 1 disease [11]. 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 ESRD by this time [12].

More recent data suggest the renal risk is equivalent in the two types of diabetes. Evidence in support of this hypothesis includes the observations in one report that the time to proteinuria from the onset of diabetes and the time to ESRD from the onset of proteinuria were similar in type 1 and type 2 disease [13,14].

Some of the most robust data relating to the development of diabetic nephropathy in a population of predominantly white patients with type 2 was reported from the United Kingdom Prospective Diabetes Study (UKPDS) [15]. 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. (See "Glycemic control and vascular complications in type 2 diabetes mellitus" and see "Treatment and prevention of diabetic nephropathy" and see "Treatment of hypertension in diabetes mellitus").

With respect to the development and progression of nephropathy among over 5000 type 2 diabetics enrolled in UKPDS, the following results were reported [15]: At ten years following diagnosis, the prevalence of microalbuminuria, macroalbuminuria, and either an elevated plasma creatinine concentration (defined as 175 µmol/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 concentration 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 (2.0 mg/dL [175 µmol/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 (eg, angiotensin inhibition and rigorous blood pressure control) was not taken into account; and most of the patients had more advanced renal insufficiency.

As with type 1 diabetes, some patients with microalbuminuria due to type 2 diabetes, particularly those with good glycemic control, experience regression of microalbuminuria [16].

PATHOLOGY — Pathologic abnormalities are noted in patients with long-standing diabetes mellitus before the onset of microalbuminuria. There are three major histologic changes in the glomeruli in diabetic nephropathy: mesangial expansion; glomerular basement membrane thickening; and glomerular sclerosis [17,18]. 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, albumin, immunoglobulins, and complement into the vascular wall) (show histology 1A-1C) [17,19]. These different histologic patterns appear to have similar prognostic significance [20].

The mesangial expansion and glomerulosclerosis do not always develop in parallel, suggesting that they may have somewhat different underlying pathogenesis [19].

PATHOGENESIS — There appear to be different pathogenetic processes leading to the abnormalities in diabetic nephropathy.

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 [21]. (See "Mechanisms of glomerular hyperfiltration in diabetes mellitus").

Mesangial expansion, on the other hand, may be directly induced by hyperglycemia, perhaps in part via increased matrix production or glycosylation of matrix proteins. In vitro studies have demonstrated that hyperglycemia stimulates mesangial cell matrix formation [19,22]. 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 [22].
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 (show figure 1). Circulating AGE levels are increased in diabetics, particularly those with renal insufficiency, since AGEs are normally excreted in the urine [23]. The net effect is tissue accumulation of AGEs, in part by crosslinking with collagen, which can contribute to the associated renal and microvascular complications [24]. (See "Glycemic control and vascular complications in type 1 diabetes mellitus", section on Pathogenesis, and see "Estimation of blood glucose control in diabetes mellitus").

The role of glomerular hypertension and hyperfiltration in diabetic nephropathy is reinforced by the apparent benefits of blockade of the renin-angiotensin system. Antagonizing the profibrotic effects of angiotensin II may also be a significant factor in benefits observed with these agents [25]. Support for such profibrotic elements underlying diabetic nephropathy is provided by findings in an animal model of diabetic nephropathy [26]. Transient renin-angiotensin system blockade (for seven weeks) in prediabetic rats reduced proteinuria and improved glomerular structure. (See "Glomerular filtration rate" below and see "Mechanisms of glomerular hyperfiltration in diabetes mellitus").

Activation of cytokines, profibrotic elements, inflammation, vascular growth factors (vascular endothelial growth factor, VEGF), and immune-related processes may be other factors involved in the matrix accumulation in diabetic nephropathy [27-37]. Hyperglycemia stimulates increased VEGF expression (which is mediator of endothelial injury in human diabetes) [28,29], and increases the expression of transforming growth factor β (TGF-β) in the glomeruli and of matrix proteins specifically stimulated by this cytokine [27,38].

The effect of some genetic factors may also be in part mediated by TGF-β [39]. TGF-β may contribute to both the cellular hypertrophy and enhanced collagen synthesis that are seen in diabetic nephropathy, illustrated by the examples below [39-43] (See "Genetic susceptibility" below): The administration of an angiotensin converting enzyme inhibitor to patients who have type 1 diabetes and nephropathy lowers serum
concentrations of TGF-ß [41]. An inverse correlation has been found between decreased TGF-ß levels and renoprotection, as determined by changes in the glomerular filtration rate over time. The combination of an anti-TGF-ß antibody plus an ACE inhibitor completely normalized proteinuria in rats with diabetic nephropathy; proteinuria was only partially lessened with an ACE inhibitor alone [42]. Glomerulosclerosis and tubulointerstitial injury were also improved. The administration of hepatocyte growth factor, which specifically blocks the profibrotic actions of TGF-ß, ameliorates diabetic nephropathy in mice [43].

The renal expression of nephrin may also be impaired in diabetic nephropathy. Congenital mutations in nephrin, a transmembrane protein expressed by podocytes, result in severe congenital nephrotic syndrome of the Finnish type. (See "Congenital and infantile nephrotic syndrome"). When compared with nondiabetic patients with minimal change nephropathy as well as controls, patients with diabetic nephropathy had markedly lower renal nephrin expression and fewer electron dense slit diaphragms [44]. By comparison, the expression of two other important podocyte/slit diaphragm proteins, podocin and CD2AP, was similar among the three groups. Similar decreases in renal nephrin expression have been reported in other studies of diabetic nephropathy [45,46].

Hyperglycemia may upregulate heparanase expression; a decrease in cell surface heparan sulfate may contribute to increased glomerular basement membrane permeability to albumin [47].

Activation of protein kinase C by hyperglycemia, which may contribute to the renal disease and other vascular complications of diabetes [48]. (See "Protein kinase C and the vascular complications of diabetes mellitus").

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 [17,49,50].

Genetic susceptibility — Genetic susceptibility may be an important determinant of both the incidence and severity of diabetic nephropathy [18,48,51]. 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 [52-54]. One report, for example, evaluated Pima Indian families in which two successive generations had type 2 diabetes [53]. 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 the duration of diabetes, hypertension, or the degree of glycemic control, although a genetic predisposition to abnormal sodium handling and hypertension may be important [52]. Genetics also may contribute to the influence of race on diabetic nephropathy (see "Race" below).

The angiotensin converting enzyme (ACE) gene genotype has been considered a potential genetic risk factor. There are conflicting data: 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, greater likelihood of progressive renal failure, and mortality on dialysis [55-57]. 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 [58]. Unfortunately, due to poor methodology, no definitive conclusions could be drawn. An analysis of over 1,000 Caucasian patients with type 1 diabetes found a strong correlation between genetic variation in the ACE gene and the development of nephropathy [59].

Another implicated genetic factor is the angiotensin-II type 2 receptor gene (AT2) on the X-chromosome. Male patients with type 1 diabetes and the AA haplotype of the AT2 gene had a lower glomerular filtration rate than those with the GT haplotype [60]. A similar association was not observed among females.

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 [61]. (See "Aldose reductase inhibitors in the prevention of diabetic complications").

The Genetics of Kidneys in Diabetes Study (GoKinD) has assembled a cohort of individuals and families with type 1 diabetes with and without kidney disease to
facilitate examination of potential genetic factors predisposing to diabetic nephropathy [62].

Age — The impact of age at onset of diabetes on the risk of developing nephropathy and end-stage renal disease is unclear. As an example, among patients with type 2 diabetes, increasing age, along with increasing duration of diabetes, was associated with increased risk for developing albuminuria [50]. In contrast, in a population-based study of 1856 Pima Indians with type 2 diabetes, patients who developed diabetes prior to age 20 had a higher risk of progressing to end-stage renal disease (25 versus 5 per 1000 patient years at risk) [63].

For type 1 diabetes, the risk of developing ESRD is very low for patients diagnosed prior to age 5; at older ages, the relationship of age to progression to ESRD is uncertain [9,64].

Blood pressure — Prospective studies have noted an association between the subsequent development of nephropathy and higher systemic pressures. This is discussed in detail separately. (See "Treatment of hypertension in diabetes mellitus")

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. (See "Mechanisms of glomerular hyperfiltration in diabetes mellitus").

Those patients with glomerular hyperfiltration appear to be at increased risk for diabetic renal disease [49,65]. 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 a lesser risk for microalbuminuria. In one prospective study, for example, patients with type 1 diabetes and a GFR above 125 mL/min had a risk of developing microalbuminuria within 8 years of approximately 50 percent versus only 5 percent in patients with a lower GFR that was similar to that seen in nondiabetics [65].

The glomerular hyperfiltration in type 1 diabetics is typically associated with glomerular hypertrophy and increased renal size [66]. 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 [66], dietary protein restriction, and antihypertensive therapy — may slow the rate of progression of the renal disease. (See "Treatment and prevention of diabetic nephropathy").

The findings in type 2 diabetes are somewhat different. Up to 45 percent of affected patients initially have a GFR that is more than 2 standard deviations above age-matched nondiabetic and obese controls [67,68]. 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 [69].

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 [70]. 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 [71].

Glycemic control — Diabetic nephropathy is more likely to develop in patients with lesser degrees of glycemic control. This is discussed in detail separately. (See "Glycemic control and vascular complications in type 1 diabetes mellitus" and see "Glycemic control and vascular complications in type 2 diabetes mellitus").

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 [12,72,73]. This observation in such genetically disparate populations suggests a primary role for socioeconomic factors, such as diet, poor control of hyperglycemia, hypertension, and obesity [74].

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 [75]. It is not clear, however, if the hypertension worsened the renal disease or was simply a marker for more severe renal involvement. (Blacks are also at increased risk for some other renal diseases, particularly hypertensive nephrosclerosis: see "Hypertensive complications in blacks").

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 [72]. This appears to occur only in type 2 diabetes, with no increase in risk seen with type 1 diabetes.

Pima Indians, on the other hand, have larger glomeruli than Caucasians, a finding that may represent a specific genetic trait [76]. 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) [12,77]. These patients also have a higher GFR (140 versus 122 mL/min) when compared to matched patients without diabetes [77].

Obesity — A high body mass index (BMI) has been associated with an increased risk of chronic kidney disease among patients with diabetes [50,78,79]. In addition, diet and weight loss may reduce proteinuria and improve kidney function among patients with diabetes [80,81]. However, the contribution of obesity (or weight loss) to the risk of nephropathy (independent of diabetes and glycemic control) has not been convincingly demonstrated in these studies.

Others — Additional risk factors may include plasma prorenin activity, and a smoking history [82,83]. A preliminary report suggested a possible association with oral contraceptive use [84].

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 is associated with a
substantial risk of progressive renal damage [49]. (See "Microalbuminuria and diabetic nephropathy").

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 [1,3]. The retinopathy is easy to detect clinically, and typically precedes the onset of overt nephropathy in these patients. The converse is not true. Although many patients with advanced retinopathy have histologic changes in the glomeruli and increased protein excretion that is at least in the microalbuminuric range, a substantial number have little or no renal disease as assessed by renal biopsy and protein excretion [85,86].

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 [87]. 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 [88]. 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 [89].

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 [90]. 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 [69,87,88,91-99].

The major clinical clues suggesting nondiabetic glomerular disease are [87,94,100]: 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 [1,3]. 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 (particularly acanthocytes) 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 [95,101]. (See "Thin basement membrane nephropathy (benign familial hematuria)"). 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 [87].

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 [98]. 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 [14,69,98,102]. 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. (See "Renal effects of ACE inhibitors in hypertension" and see "Treatment and prevention of diabetic nephropathy").

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82. Wilson, DM, Luetscher, JA. Plasma prorenin activity and complications in children
97. Olsen, S. Identification of non-diabetic glomerular disease in renal biopsies from


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