International Journal of
Health Systems and Medical Sciences

ISSN: 2833-7433
Volume 2 | No 12 | Dec -2023

Definition of Diabetic Nephropathy, Diagnosis, Prevention and Treatment

Kodirova Nargizakhon Umarovna [1]

[1] Assistant of department Propadeutics of internal diseases, Bukhara Medical Institute

Abstract: This article analyzes diabetic nephropathy, which is the leading cause of kidney disease in patients starting renal replacement therapy and affects ~40% of type 1 and type 2 diabetic patients. It increases the risk of death, mainly from cardiovascular causes, and is defined by increased urinary albumin excretion (UAE) in the absence of other renal diseases. Diabetic nephropathy is categorized into stages: microalbuminuria (UAE >20 μg/min and ≤199 μg/min) and macroalbuminuria (UAE ≥200 μg/min). Hyperglycemia, increased blood pressure levels, and genetic predisposition are the main risk factors for the development of diabetic nephropathy.

Keywords: diabetic nephropathy, proteinuria, macroalbuminuria, type 1 diabetes, GFR.

Diabetic nephropathy is the leading cause of chronic kidney disease in patients starting renal replacement therapy and is associated with increased cardiovascular mortality. Diabetic nephropathy has been classically defined by the presence of proteinuria >0.5 g/24 h. This stage has been referred to as overt nephropathy, clinical nephropathy, proteinuria, or macroalbuminuria. In the early 1980s, seminal studies from Europe revealed that small amounts of albumin in the urine, not usually detected by conventional methods, were predictive of the later development of proteinuria in type 1 and type 2 diabetic patients. This stage of renal involvement was termed microalbuminuria or incipient nephropathy.

The cumulative incidence of microalbuminuria in patients with type 1 diabetes was 12.6% over 7.3 years according to the European Diabetes (EURODIAB) Prospective Complications Study Group and ~33% in an 18-year follow-up study in Denmark. In patients with type 2 diabetes, the incidence of microalbuminuria was 2.0% per year and the prevalence 10 years after diagnosis 25% in the U.K. Prospective Diabetes Study (UKPDS) Proteinuria occurs in 15–40% of patients with type 1 diabetes, with a peak incidence around 15–20 years of diabetes. In patients with type 2 diabetes, the prevalence is highly variable, ranging from 5 to 20%

Diabetic nephropathy is more prevalent among African Americans, Asians, and Native Americans than Caucasians. Among patients starting renal replacement therapy, the incidence of diabetic nephropathy doubled from the years 1991–2001. Fortunately, the rate of increase has slowed down, probably because of the adoption in clinical practice of several measures that contribute to the early diagnosis and prevention of diabetic nephropathy, which thereby decreases the progression of established renal disease. However, the implementation of these measures is far below the desirable goals. The aim of this article is to discuss the methods for early screening and diagnosis of diabetic nephropathy and the therapeutic strategies that promote reno- and cardioprotection in this high-risk group of patients, in order to reduce the incidence of diabetic nephropathy and its associated cardiovascular mortality.

Diabetic nephropathy has been didactically categorized into stages based on the values of urinary albumin excretion (UAE): microalbuminuria and macroalbuminuria. The cutoff values adopted by the American Diabetes Association (timed, 24-h, and spot urine collection) for the diagnosis of micro- and macroalbuminuria. There is accumulating evidence suggesting that the risk for developing diabetic nephropathy and cardiovascular disease starts when UAE values are still within the normoalbuminuric range. Progression to micro- or macroalbuminuria was more frequent in patients with type 2 diabetes with baseline UAE above the median (2.5 mg/24 h). After 10 years of follow-up, the risk of diabetic nephropathy was 29 times greater in patients with type 2 diabetes with UAE values >10 μg/min. The same was true for patients with type 1 diabetes . This favors the concept that the risk associated with UAE is a continuum, as is the case with blood pressure levels. Possibly, values of UAE lower than those currently used for microalbuminuria diagnosis should be established.

Although microalbuminuria has been considered a risk factor for macroalbuminuria, not all patients progress to this stage and some may regress to normoalbuminuria. The initial studies in the 1980s demonstrated that ~80% of microalbuminuric type 1 diabetic patients progressed to proteinuria over a period of 6–14 years. In more recent studies, only 30–45% of microalbuminuric patients have been reported to progress to proteinuria over 10 years, maybe as a result of more intensive glycemic and blood pressure control strategies.

Screening for diabetic nephropathy must be initiated at the time of diagnosis in patients with type 2 diabetes, since ~7% of them already have microalbuminuria at that time. For patients with type 1 diabetes, the first screening has been recommended at 5 years after diagnosis. However, the prevalence of microalbuminuria before 5 years in this group can reach 18%, especially in patients with poor glycemic and lipid control and high normal blood pressure levels. Furthermore, puberty is an independent risk factor for microalbuminuria. Therefore, in type 1 diabetes, screening for microalbuminuria might be performed 1 year after diabetes diagnosis, especially in patients with poor metabolic control and after the onset of puberty. If microalbuminuria is absent, the screening must be repeated annually for both type 1 and 2 diabetic patients.

The first step in the screening and diagnosis of diabetic nephropathy is to measure albumin in a spot urine sample, collected either as the first urine in the morning or at random, for example, at the medical visit. This method is accurate, easy to perform, and recommended by American Diabetes Association guidelines. Twenty-four–hour and timed urine collections are cumbersome and prone to errors related to collecting samples or recording of time. The results of albumin measurements in spot collections may be expressed as urinary albumin concentration (mg/l) or as urinary albumin-to-creatinine ratio (mg/g or mg/mmol) . Although expressing the results as albumin concentration might be influenced by dilution/concentration of the urine sample, this option is still accurate and cheaper than expression as albumin-to-creatinine ratio. The cutoff value of 17 mg/l in a random urine specimen had a sensitivity of 100% and a specificity of 80% for the diagnosis of microalbuminuria when 24-h timed urine collection was the reference standard.

Diabetic nephropathy develops in, at most, 40% of patients with diabetes, even when high glucose levels are maintained for long periods of time. This observation raised the concept that a subset of patients have an increased susceptibility to diabetic nephropathy. Furthermore, epidemiological and familial studies have demonstrated that genetic susceptibility contributes to the development of diabetic nephropathy in patients with both type 1 and type 2 diabetes. The main potentially modifiable diabetic nephropathy initiation and progression factors in susceptible individuals are sustained hyperglycemia and hypertension Other putative risk factors are glomerular hyperfiltration, smoking, dyslipidemia, proteinuria levels, and dietary factors, such as the amount and source of protein and fat in the diet.

Diabetes causes unique changes in kidney structure. Classic glomerulosclerosis is characterized by increased glomerular basement membrane width, diffuse mesangial sclerosis, hyalinosis, microaneurysm, and hyaline arteriosclerosis. Tubular and interstitial changes are also present. Areas of extreme mesangial expansion called Kimmelstiel-Wilson nodules or nodular mesangial expansion

are observed in 40–50% of patients developing proteinuria. Micro- and macroalbuminuric patients with type 2 diabetes have more structural heterogeneity than patients with type 1 diabetes).

After the diagnosis of micro- or macroalbuminuria is confirmed, patients should undergo a complete evaluation, including a work-up for other etiologies and an assessment of renal function and the presence of other comorbid associations.

Differential diagnosis is usually based on the history, physical examination, laboratory evaluation, and imaging of the kidneys. Renal biopsy is only recommended in special situations. The diagnosis of diabetic nephropathy is easily established in long-term type 1 diabetic patients (>10 years diabetes duration), especially if retinopathy is also present. Typical diabetic nephropathy is also likely to be present in proteinuric type 2 diabetic patients with retinopathy. However, diagnostic uncertainty exists in some patients with type 2 diabetes since the onset of diabetes is unknown and retinopathy is absent in a significant proportion (28%) of these patients.

The presence of symptoms during urination suggests urinary tract disorders such as obstruction, infection, or stones. Skin rash or arthritis may indicate systemic lupus erythematosus or cryoglobulinemia. Presence of risk factors for parenterally transmitted disease may raise the suspicion of kidney disease associated with HIV, hepatitis C, or hepatitis B. History of proteinuria and/or hypertension during childhood or pregnancy may suggest other glomerulonephritis. Also, family history of kidney disease may indicate the presence of polycystic kidney disease or other genetic diseases.

Imaging of the kidneys, usually by ultrasonography, should be performed in patients with symptoms of urinary tract obstruction, infection, or kidney stones or with a family history of polycystic kidney disease.

The criteria for renal biopsy are not well established, but in type 1 diabetes the presence of proteinuria in association with short diabetes duration and/or rapid decline of renal function, especially in the absence of diabetic retinopathy, have been used. In patients with type 2 diabetes, the criteria are less clear. The proportion of nondiabetic renal lesions in proteinuric type 2 diabetic patients seems to vary according to the criteria used to perform the biopsy and to the ethnic background of the patient. When absence of retinopathy was the biopsy criterion in 49 proteinuric Caucasian patients with type 2 diabetes, only 12% had nondiabetic glomerulonephritis. On the other hand, other nephropathies, isolated or superimposed onto diabetic glomerulosclerosis, were observed in 46 and 19%, respectively, of 68 Chinese patients with type 2 diabetes. Proteinuria >1 g/24 h, renal involvement in the absence of retinopathy, or unexplained hematuria were the reasons for performing a biopsy. Patients with nondiabetic glomerulosclerosis had a better prognosis than those with diabetic glomerulosclerosis alone or in association with other nephropathies. However, the real benefit of identifying and treating nondiabetic renal lesions in patients with diabetes remains to be established.

GFR is the best parameter of overall kidney function and should be measured or estimated in micro- and macroalbuminuric diabetic patients. In microalbuminuric patients, GFR may remain stable, but a subset of patients has shown a rapid decline in GFR levels. In type 1 macroalbuminuric patients, GFR declines about 1.2 ml · min^{-1} · $month^{-1}$ without therapeutic interventions. In patients with type 2 diabetes, GFR decline is more variable. One study reported a mean decline of ∼0.5 ml · min^{-1} · $month^{-1}$, although in some patients GFR may remain stable for long periods. Patients with a more rapid GFR decline usually have more advanced diabetic glomerulopathy and worse metabolic control.

Patients should be referred to a nephrologist for evaluation and comanagement when GFR reaches 30 ml· min^{-1} · 1.73 m^{-2}, since there is evidence that nephrologist care may improve morbidity and mortality when patients enter renal replacement therapy.

It is particularly important to investigate retinopathy. Ideally, this should be done by an experienced ophthalmologist, since retinopathy is frequent in the presence of diabetic nephropathy and is a clue for its diagnosis. Prospective studies in type 2 diabetic patients showed that diabetic retinopathy was

a predictor of later development of diabetic nephropathy. Retinopathy is probably a risk marker and not a risk factor in itself, since these microvascular complications (diabetic nephropathy and diabetic retinopathy) share common determinants, such as poor glycemic, blood pressure, and lipid control. Other complications of diabetes, such as peripheral and autonomic neuropathy, should also be evaluated, since they are seen more frequently in patients with diabetic nephropathy and are associated with increased morbidity and mortality.

Patients with diabetic nephropathy, due to their high cardiovascular risk, should be routinely evaluated for the presence of coronary heart disease, independently of the presence of cardiac symptoms. Other atherosclerotic complications, such as carotid disease, peripheral artery disease, and atherosclerotic renal-artery stenosis should also be assessed. Radiocontrast agents used in angiography may cause acute renal failure in up to 35% of diabetic patients, especially in those with decreased renal function. This can be prevented by prior hydration and administration of an iso-osmolar contrast media. Acetylcysteine, a free-radical scavenger, has also been shown to be renoprotective in some studies, but this was not confirmed in a recent study.

Critical renal-artery stenosis (>70%) occurs in ~17% of hypertensive type 2 diabetic patients and may be associated with hypertension and renal insufficiency (ischemic nephropathy). In these patients, the use of ACE inhibitors or angiotensin II type 1 receptor blockers (ARBs) could reduce transcapillary filtration pressure, leading to acute or chronic renal insufficiency, especially if renal-artery stenosis affects both kidneys or the sole functioning kidney. A rise in serum creatinine >50% after use of these agents is a clue for the presence of renal-artery stenosis. Other suggestive features are renal impairment with minimal or absent proteinuria, absent or minimal diabetic retinopathy, presence of macrovascular disease in other sites (coronary, carotid, and peripheral arteries), vascular bruits (especially femoral), and asymmetric kidney shrinkage on renal ultrasound. Magnetic resonance angiography is the method of choice to screen for renal-artery stenosis in diabetic patients. Other options, even though with lower sensitivity, are captopril renal scintigraphy and duplex Doppler ultrasonography imaging of the renal arteries. Captopril renal scintigraphy has limitations in patients with decreased renal function (serum creatinine >2.0 mg/dl), and Doppler ultrasonography is heavily dependent on operator experience. Rarely does renal revascularization cure hypertension, but it may improve or stabilize renal function in patients with chronic kidney disease.

Prevention: normoalbuminuric patients

The basis for the prevention of diabetic nephropathy is the treatment of its known risk factors: hypertension, hyperglycemia, smoking, and dyslipidemia. These are also risk factors for cardiovascular disease and should be vigorously treated.

Intensive blood glucose control

Clinical trials have consistently demonstrated that A1c levels <7% are associated with decreased risk for clinical and structural manifestations of diabetic nephropathy in type 1 and type 2 diabetic patients. In the Diabetes Control and Complications Trial (DCCT), intensive treatment of diabetes reduced the incidence of microalbuminuria by 39%. It is interesting to note that patients randomized to strict glycemic control had a long-lasting reduction of ~40% in the risk for development of microalbuminuria and hypertension 7–8 years after the end of the DCCT. In the UKPDS, a 30% risk reduction for the development of microalbuminuria was observed in the group intensively treated for hyperglycemia. Moreover, in the Kumamoto Study, intensive glycemic control also reduced the rate of development of micro- and macroalbuminuria. Therefore, intensive treatment of glycemia aiming at A1c <7% should be pursued as early as possible to prevent the development of microalbuminuria.

Treatment of hypertension dramatically reduces the risk of cardiovascular and microvascular events in patients with diabetes. Hypertension is common in diabetic patients, even when renal involvement is not present. About 40% of type 1 and 70% of type 2 diabetic patients with normoalbuminuria have blood pressure levels >140/90 mmHg. In the UKPDS, a reduction from 154 to 144 mmHg on systolic blood pressure reduced the risk for the development of microalbuminuria by 29%.

Blood pressure targets for patients with diabetes are lower (130/80 mmHg) than those for patients without diabetes. In the HOT (Hypertension Optimal Treatment) study, a reduction of diastolic blood pressure from 85 to 81 mmHg resulted in a 50% reduction in the risk of cardiovascular events in diabetic but not nondiabetic patients.

The role of ACE inhibitors in the prevention of diabetic nephropathy in patients with type 1 diabetes has not been defined. The use of perindopril during 3 years in normotensive normoalbuminuric type 1 diabetic patients delayed the increase in albuminuria. In patients with type 2 diabetes, ACE inhibitors and ARBs both diminish the risk for diabetic nephropathy and reduce the occurrence of cardiovascular events In the MICRO-HOPE (Heart Outcomes Prevention Evaluation) study, ramipril (10 mg/day) decreased the risk of overt nephropathy by 24% and the risk of cardiovascular death in patients with type 2 diabetes who were >55 years of age with one additional cardiovascular risk factor by 37%. Moreover, ramipril reduced UAE at 1 year and at the end of the study. Therefore, ACE inhibitors have been shown to be beneficial for reno- and cardioprotection in patients with type 2 diabetes.

The goal of treatment is to prevent the progression from micro- to macroalbuminuria, the decline of renal function in patients with macroalbuminuria, and the occurrence of cardiovascular events. The treatment principles are the same as those adopted for the prevention of diabetic nephropathy, although in this case multiple and more intensive strategies must be used..

The effect of strict glycemic control on the progression from micro- to macroalbuminuria and on the rate of renal function decline in macroalbuminuric patients is still controversial. In the DCCT study, intensified glycemic control did not decrease the rate of progression to macroalbuminuria in patients with type 1 diabetes who were microalbuminuric at the beginning of the study. The Microalbuminuria Collaborative Study Group reported similar findings. However, these studies were underpowered to detect an effect of intensified glycemic control on the progression from micro- to macroalbuminuria. Moreover, improvement of glycemic control, especially if associated with lower blood pressure levels, reduced the renal function decline in proteinuric type 1 diabetic patients.

In patients with type 2 diabetes, very few studies analyzed the role of blood glucose control on the progression of diabetic nephropathy. In the Kumamoto Study, a reduction in the conversion from micro- to macroalbuminuria was observed with intensive treatment. Although the effects of strict glycemic control on the progression of diabetic nephropathy are not firmly established, it should be pursued in all these patients.

Some oral antihyperglycemic agents seem to be especially useful. Rosiglitazone, as compared with glyburide, has been shown to decrease UAE in patients with type 2 diabetes. This suggests a beneficial effect in the prevention of renal complications of type 2 diabetes. Also, the use of antihyperglycemic agents in proteinuric type 2 diabetic patients should take renal function into account. Metformin should not be used when serum creatinine is >1.5 mg/dl in men and >1.4 mg/dl in women due to the increased risk of lactic acidosis. Sulfonylureas and their metabolites, except glimepiride, are eliminated via renal excretion and should not be used in patients with decreased renal function. Repaglinide and nateglinide have a short duration of action, are excreted independently of renal function, and have a safety profile in patients with renal impairment. However, at this point, sulfonylureas and insulin secretagogues are usually not very effective due to the low endogenous production of insulin resulting from the long duration of diabetes. Thus, most type 2 diabetic patients with diabetic nephropathy should be treated with insulin.

In microalbuminuric type 1 and type 2 diabetic patients, numerous studies have demonstrated that treatment of hypertension, irrespective of the agent used, produced a beneficial effect on albuminuria. Renin-angiotensin system (RAS) blockade with ACE inhibitors or ARBs confers an additional benefit on renal function. This renoprotective effect is independent of blood pressure reduction and may be related to decreased intraglomerular pressure and passage of proteins into the proximal tubule. A meta-analysis of 12 trials evaluating 698 nonhypertensive microalbuminuric type 1 diabetic patients showed that treatment with ACE inhibitors decreased the risk of progression to macroalbuminuria by 60% and increased the chances of regression to normoalbuminuria. ARBs were

also effective in reducing the development of macroalbuminuria in microalbuminuric type 2 diabetic patients. Irbesartan (300 mg/day) reduced the risk of progression to overt diabetic nephropathy by 70% in a 2-year follow-up study of 590 hypertensive microalbuminuric type 2 diabetic patients. These data reinforce the idea that the antiproteinuric effect of ARBs is blood pressure independent. Although there is no long-term study comparing the effects of ACE inhibitors and ARBs on the progression from microalbuminuria to overt diabetic nephropathy, both agents led to a similar reduction in albuminuria in a 12-week study and a 1-year study. Therefore, the use of either ACE inhibitors or ARBs is recommended as a first-line therapy for type 1 and type 2 diabetic patients with microalbuminuria, even if they are normotensive.

In proteinuric patients, Mogensen was the first to demonstrate, almost 30 years ago, that treatment of hypertension reduced albuminuria and the rate of GFR decline in type 1 diabetic patients. Subsequently, other studies have clearly demonstrated that aggressive treatment of hypertension has a strong beneficial effect in reducing GFR decline in proteinuric type 1 diabetic patients. This reduction in GFR decline was predicted by reduction in albuminuria. According to the MDRD (Modification of Diet in Renal Disease) trial, the lower the blood pressure, the greater the preservation of renal function in nondiabetic patients. Patients with proteinuria >1 g/day and renal insufficiency had slower decline in renal function when blood pressure was <125/75 mmHg. Although this study included mainly nondiabetic patients, this goal also has been recommended for proteinuric diabetic patients. Addition of ACE inhibitors in proteinuric type 1 diabetic patients or ARBs in macroalbuminuric type 2 diabetic patients decreased proteinuria and renal function decline. Although there was no difference in the cardiovascular event rate, a significantly lower incidence of congestive heart failure was observed among patients receiving ARBs. The antiproteinuric effect of ARBs has certain characteristics. It occurs early (within 7 days) after treatment is started and persists stable thereafter, and it is independent of blood pressure reduction and has a dose-response effect beyond the doses needed to control blood pressure. An acute increase in serum creatinine of up to 30–35%, stabilizing after 2 months, might occur in proteinuric patients with creatinine values >1.4 mg/dl starting ACE inhibitors. This raise in creatinine is associated with long-term preservation of renal function, and therefore ACE inhibitors should not be stopped. Greater increases should raise the suspicion of renal-artery stenosis. Inhibition of the RAS, especially with ACE inhibitors, might raise serum potassium levels, particularly in patients with renal insufficiency. For these reasons, albuminuria, serum creatinine, and potassium should be checked monthly during the first 2–3 months after starting treatment with ACE inhibitors or ARBs. Recently, Mogensen et al. developed the new concept of dual blockade of the RAS. ACE inhibitors and ARBs interrupt the RAS at different levels, and the combination of these classes of drugs may have an additive effect on renoprotection. Even though no long-term trials analyzing the benefit of RAS dual blockade in diabetic nephropathy are available, in nondiabetic proteinuric patients the COOPERATE (Combination Treatment of Angiotensin-II Receptor Blocker and Angiotensin-Converting-Enzyme Inhibitor in Nondiabetic Renal Disease) trial has shown that dual therapy was superior to monotherapy at its maximal doses in retarding the progression of renal disease in a 3-year follow-up. The combination of spironolactone, an aldosterone antagonist, with an ACE inhibitor was also more effective in reducing UAE and blood pressure in micro- and macroalbuminuric type 2 diabetic patients than the ACE inhibitor alone.

In the last few years, we have witnessed enormous progress in the understanding of the risk factors and mechanisms of diabetic nephropathy, the stages of renal involvement in diabetes, and the treatment strategies to prevent or interrupt the progression of diabetic nephropathy.

Early detection of diabetic nephropathy, adoption of multifactorial interventions targeting the main risk factors (hyperglycemia, hypertension, dyslipidemia, and smoking), and use of agents with a renoprotective effect (ACE inhibitors and/or ARBs) do indeed reduce the progression of renal disease. Treatment of hypertension is a priority. Attention to these procedures will also ensure the reduction of cardiovascular mortality.

REFERENCES:

1. US Renal Data System: *USRDS 2003 Annual Data Report: Atlas of End-Stage Renal Disease in the United States.* Bethesda, MD, National Institute of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2003
2. Valmadrid CT, Klein R, Moss SE, Klein BE: The risk of cardiovascular disease mortality associated with microalbuminuria and gross proteinuria in persons with older-onset diabetes mellitus.
3. Mogensen CE, Christensen CK: Predicting diabetic nephropathy in insulin-dependent patients. *N Engl J Med*
4. Parving HH, Oxenboll B, Svendsen PA, Christiansen JS, Andersen AR: Early detection of patients at risk of developing diabetic nephropathy: a longitudinal study of urinary albumin excretion. *Acta Endocrinol (Copenh)*
5. Umarovna, K. N. (2023). University of Al-Qadisiyah, College of Pharmacy. *Zien Journal of Social Sciences and Humanities*, *20*, 10-14.
6. Kodirova, Nargizakhon Umarovna (2022). MODERN METHODS OF TREATMENT OF CHRONIC LUNG DISEASES. Oriental renaissance: Innovative, educational, natural and social sciences, 2 (Special Issue 4-2), 983-988.
7. Умаровна, К. Н. (2022). Современные Методы Лечения Хронических Заболеваний Легких. *Central Asian Journal of Medical and Natural Science*, *3*(4), 179-182.
8. Kodirova, N. U. . (2022). MORPHOLOGICAL CHANGES OF THE LUNGS UNDER THE EXPOSURE TO NASVAY. *EUROPEAN JOURNAL OF MODERN MEDICINE AND PRACTICE*, *2*(9), 16–20.
9. Kodirova , N. . (2022). THE EFFECT OF TOBACCO SMOKING ON THE THYROID GLAND. *Евразийский журнал медицинских и естественных наук*, *2*(12), 214–216.
10. Kodirova, N. (2023). AUTOIMMUNE THYROID DISEASES: THE STATE OF THE ISSUE. *International Bulletin of Applied Science and Technology*, *3*(4), 306-312.