Diabetic Nephropathy: Diagnosis, Prevention, and Treatment

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Diabetic nephropathy 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. Elevated serum lipids, smoking habits, and the amount and origin of dietary protein also seem to play a role as risk factors. Screening for microalbuminuria should be performed yearly, starting 5 years after diagnosis in type 1 diabetes or earlier in the presence of puberty or poor metabolic control. In patients with type 2 diabetes, screening should be performed at diagnosis and yearly thereafter. Patients with micro- and macroalbuminuria should undergo an evaluation regarding the presence of comorbid associations, especially retinopathy and macrovascular disease. Achieving the best metabolic control (A1c <7%), treating hypertension (<130/80 mmHg or <125/75 mmHg if proteinuria >1.0 g/24 h and increased serum creatinine), using drugs with blockade effect on the renin-angiotensin-aldosterone system, and treating dyslipidemia (LDL cholesterol <100 mg/dl) are effective strategies for preventing the development of microalbuminuria, in delaying the progression to more advanced stages of nephropathy and in reducing cardiovascular mortality in patients with type 1 and type 2 diabetes.

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DEFINITION AND EPIDEMIOLOGY

— Diabetic nephropathy is the leading cause of chronic kidney disease in patients starting renal replacement therapy (1) and is associated with increased cardiovascular mortality (2). 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 (3–5) and type 2 (6) 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 (7) and ~33% in an 18-year follow-up study in Denmark (8). 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) (9). Proteinuria occurs in 15–40% of patients with type 1 diabetes, with a peak incidence around 15–20 years of diabetes (8,10,11). In patients with type 2 diabetes, the prevalence is highly variable, ranging from 5 to 20% (2,9).

Diabetic nephropathy is more prevalent among African Americans, Asians, and Native Americans than Caucasians (1,12). Among patients starting renal replacement therapy, the incidence of diabetic nephropathy doubled from the years 1991–2001 (1). 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 (13). 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.

STAGES, CLINICAL FEATURES, AND CLINICAL COURSE

— 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 (14) (timed, 24-h, and spot urine collection) for the diagnosis of micro- and macroalbuminuria, as well as the main clinical features of each stage, are depicted in Table 1. There is accumulating evidence suggesting that the risk for developing diabetic nephropathy (15–18) and cardiovascular disease (19,20) starts when UAE values are still within the normoalbuminuric range. Progression to mi-

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Abbreviations: ARB, angiotensin II type 1 receptor blocker; DCCT, Diabetes Control and Complications Trial; GFR, glomerular filtration rate; RAS, renin-angiotensin system; UAE, urinary albumin excretion; UKPDS, U.K. Prospective Diabetes Study.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

cro- or macroalbuminuria was more frequent in patients with type 2 diabetes with baseline UAE above the median (2.5 mg/24 h) (15). 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 (16). The same was true for patients with type 1 diabetes (17). This favors the concept that the risk associated with UAE is a continuum, as is the case with blood pressure levels (21). 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 (22). 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 (3–5). In more recent studies, only 30–45% of microalbuminuric patients have been reported to progress to proteinuria over 10 years (22), maybe as a result of more intensive glycemic and blood pressure control strategies. In fact, a recent study involving type 1 diabetic patients with microalbuminuria reported a UAE reduction of 50% or greater in 56% of the patients (23). This reduction was primarily related to a short duration of microalbuminuria, A1c <8%, systolic blood pressure <115 mmHg, and favorable lipid profile (total cholesterol <198 mg/dl and triglycerides <145 mg/dl).

SCREENING AND DIAGNOSIS

— Screening for diabetic nephropathy must be initiated at the time of diagnosis in patients with type 2 diabetes (14), since ~7% of them already have microalbuminuria at that time (9). For patients with type 1 diabetes, the first screening has been recommended at 5 years after diagnosis (14). 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 (24). Furthermore, puberty is an independent risk factor for microalbuminuria (25). 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 (14).

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 (14). 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) (26,27) or as urinary albumin-to-creatinine ratio (mg/g or mg/mmol) (14,27,28). 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 (26). 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 (29). This value is similar to the cutoff value of 20 mg/l recommended by the European Diabetes Policy Group (27). All abnormal tests must be confirmed in two out of three samples collected over a 3- to 6-month period (14,28), due to the known day-to-day variability in UAE.

Screening should not be performed in the presence of conditions that increase UAE, such as urinary tract infection, hematuria, acute febrile illness, vigorous exercise, short-term pronounced hyperglycemia, uncontrolled hypertension, and heart failure (30). Samples must be refrigerated if they are to be used the same day or the next day, and one freeze is acceptable before measurements (28). Immunoassays routinely used for albumin measurements present adequate diagnostic sensitivity for detection of diabetic nephropathy. However, it was recently demonstrated that conventional immunochemical-based assays did not detect an unreactive fraction of albuminuria, underestimating UAE (31). High-performance liquid chromatography measures total albumin, including immunoreactive and immunounreactive forms, and may allow early detection of incipient diabetic nephropathy.

In situations where specific UAE measurements are not available, semiquantitative dipstick measurements of albuminuria, such as Micral Test II, can be used (14,32). Another alternative is to use a qualitative test for proteinuria (dipstick) (33) or a quantitative measurement of protein in a

Table 1—*Diabetic nephropathy stages: cutoff values of urine albumin for diagnosis and main clinical characteristics*

Stages	Albuminuria cutoff values (ref. 14)	Clinical characteristics (ref. no.)
Microalbuminuria	20–199 μg/min	Abnormal nocturnal decrease of blood pressure and increased blood pressure levels (163)
	30–299 mg/24 h	Increased triglycerides, total and LDL cholesterol, and saturated fatty acids (164, 165)
	30–299 mg/g*	Increased frequency of metabolic syndrome components (166)
		Endothelial dysfunction (167)
		Association with diabetic retinopathy, amputation, and cardiovascular disease (168)
		Increased cardiovascular mortality (2, 169)
		Stable GFR (82)
Macroalbuminuria†	≥200 μg/min	Hypertension (99)
	≥300 mg/24 h	Increased triglycerides and total and LDL cholesterol (170)
	>300 mg/g*	Asymptomatic myocardial ischemia (171, 172)
		Progressive GFR decline (83, 84)

*Spot urine sample. †Measurement of total proteinuria (≥500 mg/24 h or ≥430 mg/l in a spot urine sample) can also be used to define this stage.

spot urine sample (26,28,34). The presence of a positive dipstick (Combur M; Boehring Manheim) or a urinary protein concentration >430 mg/l has a sensitivity of 100% for both tests and a specificity of 82 and 93%, respectively, for the diagnosis of proteinuria (34). An abnormal result should be confirmed by measurement of total protein in a 24-h urine sample. Values >500 mg/24 h confirm the diagnosis of proteinuria. Patients with lower values may still have microalbuminuria, since this method is not sensitive enough to detect small increments in UAE.

Although the measurement of UAE is the cornerstone for the diagnosis of diabetic nephropathy, there are some patients with either type 1 or type 2 diabetes who have decreased glomerular filtration rate (GFR) in the presence of normal UAE (35,36). In patients with type 1 diabetes, this phenomenon seems to be more common among female patients with long-standing diabetes, hypertension, and/or retinopathy (35). For patients with type 2 diabetes in NHANES III (Third National Health and Nutrition Examination Survey; n = 1,197), low GFR (<60 ml · min^{-1} · 1.73 m^{-2}) was present in 30% of patients in the absence of micro- or macroalbuminuria and retinopathy (37). Although renal biopsy was not performed, this observation was probably related to renal parenchymal disease other than classical diabetic glomerulosclerosis. These studies indicate that normoalbuminuria does not protect from a decrease in GFR in type 1 and type 2 diabetic patients. Therefore, GFR should be routinely estimated and UAE routinely measured for a proper screening of diabetic nephropathy.

GFR can be measured by specific techniques, such as inulin clearance, ^{51}Cr-EDTA, ^{125}I-iothalamate, and iohexol (38). The clearance of endogenous creatinine is commonly used, despite its limitations (39). In clinical practice, GFR can be estimated by prediction equations that take into account serum creatinine concentration and some or all of the following variables: age, sex, race, and body size. The recommended (40) equation by the National Kidney Foundation is that of the MDRD (Modified Diet in Renal Disease): GFR (ml · min^{-1} · 1.73 m^{-2}) = 186 × [serum creatinine (mg/dl)$^{-1.154}$ × age (years)$^{-0.203}$ × (0.742 if female) × (1.210 if African American)]. A user-friendly way to use this formula is available online (www.kidney.org/klsprofessionals/gfr_calculator.cfm). The Cockroft-Gault equation: creatinine clearance (ml/min) = [(140 − age (years)] × weight (kg)/[72 × serum creatinine (mg/dl) × (0.85 if female)] is less accurate (40). The reference range of GFR values in young individuals is from 80 to 130 ml · min^{-1} · 1.73 m^{-2}, declining at ~10 ml · min^{-1} · $decade^{-1}$ after 50 years of age (41).

RISK FACTORS AND PATHOGENESIS

— 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 (42) and familial studies (43–47) 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 (17,18,48,49) and hypertension (50–52). Other putative risk factors are glomerular hyperfiltration (53–55), smoking (56,57), dyslipidemia (18,50,58,59), proteinuria levels (60,61), and dietary factors, such as the amount and source of protein (62–64) and fat (65) in the diet.

PATHOLOGY

— 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 (66). Tubular (67) and interstitial (68) 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 (69). Micro- and macroalbuminuric patients with type 2 diabetes have more structural heterogeneity than patients with type 1 diabetes (70,71).

Evaluated by electron microscopy, the severity of glomerular lesions is related to GFR and UAE (72–74) and to diabetes duration (73,75), degree of glycemic control (76), and genetic factors (77,78). Nonetheless, there is an important overlap in mesangial expansion and glomerular basement membrane thickening among normoalbuminuric, microalbuminuric, and proteinuric type 1 and type 2 diabetic patients (73,74), with no clear cutoff to distinguish the groups.

EVALUATION OF PATIENTS WITH DIABETIC NEPHROPATHY

— 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

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 (79).

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 (40).

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 (40).

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 (80). 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 (79). 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 (81). Patients with nondiabetic glomerulosclerosis had a better prognosis than those with diabetic glomerulosclerosis alone or in association with other nephropathies (81). However, the real benefit of identifying and treating nondiabetic renal lesions in patients with diabetes remains to be established.

Monitoring of renal function

GFR is the best parameter of overall kidney function (40) 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 (82). In type 1 macroalbuminuric patients, GFR declines about 1.2 ml · min^{-1} · $month^{-1}$ without therapeutic interventions (83). In patients with type 2 diabetes, GFR decline is more variable. One study reported a mean decline of ~0.5 ml · min^{-1} · $month^{-1}$ (84), although in some patients GFR may remain stable for long periods (85). Patients with a more rapid GFR decline usually have more advanced diabetic glomerulopathy and worse metabolic control (82).

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 (40).

Comorbid associations

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 (16,18). 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 (86,87) 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 (88). This can be prevented by prior hydration and administration of an isoosmolar contrast media (89). Acetylcysteine, a free-radical scavenger, has also been shown to be renoprotective in some studies (90), but this was not confirmed in a recent study (91).

Critical renal-artery stenosis (>70%) occurs in ~17% of hypertensive type 2 diabetic patients (92) 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 (93). 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 (93). 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 (94). Rarely does renal revascularization cure hypertension, but it may improve or stabilize renal function in patients with chronic kidney disease (94).

PREVENTION AND TREATMENT

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% (95). 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 (96). In the UKPDS, a 30% risk reduction for the development of microalbuminuria was observed in the group intensively treated for hyperglycemia (97). Moreover, in the Kumamoto Study, intensive glycemic control also reduced the rate of development of micro- and macroalbuminuria (98). Therefore, intensive treatment of glycemia aiming at A1c <7% should be pursued as early as possible to prevent the development of microalbuminuria.

Table 2—*Strategies and goals for reno- and cardioprotection in patients with diabetic nephropathy*

Intervention	Goal	
	Microalbuminuric	Macroalbuminuric
ACE inhibitor and/or ARB and low-protein diet (0.6–0.8 g · kg wt^{-1} · day^{-1}	Reduction of albuminuria or reversion to normoalbuminuria	Proteinuria as low as possible or <0.5 g/24-h and
	GFR stabilization	GFR decline <2 ml · min^{-1} · year^{-1}
Antihypertensive agents	Blood pressure <130/80 or 125/75 mmHg†	
Strict glycemic control	A1c <7%	
Statins	LDL cholesterol ≤100 mg/dl‡	
Acetyl salicylic acid	Thrombosis prevention	
Smoking cessation	Prevention of atherosclerosis progression	

* Low-protein diet: efficacy not proven in long-term studies in microalbuminuric patients. †Goal: 125/75 mmHg with increased serum creatinine and proteinuria >1.0 g/24-h. ‡LDL cholesterol <70 mg/dl in the presence of cardiovascular disease.

Intensive blood pressure control

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 (99). In the UKPDS, a reduction from 154 to 144 mmHg on systolic blood pressure reduced the risk for the development of microalbuminuria by 29% (100).

Blood pressure targets for patients with diabetes are lower (130/80 mmHg) than those for patients without diabetes (101). 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 (102).

Renin-angiotensin system blockade

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 (103). In patients with type 2 diabetes, ACE inhibitors and ARBs both diminish the risk for diabetic nephropathy (104,105) and reduce the occurrence of cardiovascular events (106). In the MICRO-HOPE (Heart Outcomes Prevention Evaluation) study (106), 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 (106). Therefore, ACE inhibitors have been shown to be beneficial for reno- and cardioprotection in patients with type 2 diabetes.

Treatment: micro- and macroalbuminuric patients

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 strategies and goals are described in Table 2.

Intensive blood glucose control

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 (95,107). The Microalbuminuria Collaborative Study Group reported similar findings (108). However, these studies (107,108) 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 (109).

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 (98). 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 (110). 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 (111). Sulfonylureas and their metabolites, except glimepiride, are eliminated via renal excretion and should not be used in patients with decreased renal function (112). Repaglinide (113) and nateglinide (114) 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.

Intensive blood pressure treatment and renin-angiotensin system blockade

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 (115). 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 (115,116) and may be related to decreased intraglomerular pressure and passage of proteins into the proximal tubule (117). These drugs decrease UAE and the rate of progression from microalbuminuria to more advanced stages of diabetic nephropathy. 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 (118). 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 (119). Additionally, a 38% reduction in UAE was observed, with 34% of patients reversing to normoalbuminuria. It is also interesting to note that UAE was still reduced 1 month after the withdrawal of irbesartan (120). In another trial, valsartan 80 mg/day produced a greater reduction in UAE than amlodipine (44 vs. 8%) with the same degree of blood pressure reduction (116). 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 (121) and a 1-year study (122). 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 (14).

In proteinuric patients, Mogensen (123) 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 (124). This reduction in GFR decline was predicted by reduction in albuminuria (125). 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 (126). Patients with proteinuria >1 g/day and renal insufficiency had slower decline in renal function when blood pressure was <125/75 mmHg (126). Although this study included mainly nondiabetic patients, this goal also has been recommended for proteinuric diabetic patients (127). Addition of ACE inhibitors in proteinuric type 1 diabetic patients (128) or ARBs in macroalbuminuric type 2 diabetic patients (129,130) 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 (129). The antiproteinuric effect of ARBs has certain characteristics. It occurs early (within 7 days) after treatment is started and persists stable thereafter (131), and it is independent of blood pressure reduction (116) and has a dose-response effect beyond the doses needed to control blood pressure (132). 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 (133). 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 (134). 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. (121) 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. The combination of candesartan (16 mg/day) and lisinopril (20 mg/day) was more effective in reducing blood pressure and UAE ratio in hypertensive patients with type 2 diabetes than either drug alone (121). Other studies have also demonstrated that the combination of ACE inhibitors and ARBs had a synergistic effect in blood pressure and UAE reduction in patients with type 1 and type 2 diabetes with diabetic nephropathy. RAS dual blockade is more effective in reducing UAE than maximal recommended doses of ACE inhibitors alone (135). 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 (136). 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 (137).

Strategies of blood pressure treatment in patients with diabetic nephropathy

A detailed discussion of the agents used to treat hypertension in patients with diabetic nephropathy is beyond the scope of this article, and recent guidelines (101,138) and reviews on this subject are available (127,139,140). Therefore, only general guidelines will be discussed here, taking into account the special characteristics of these patients. To reach the blood pressure goal of 130/80 mmHg in diabetic patients in general (101), or 125/75 mmHg in patients with proteinuria >1.0 g/24 h and increased serum creatinine, three to four antihypertensive agents are usually necessary (141). It is more important to reach the blood pressure goals than to use a particular agent, since most patients will require several agents. However, due to the known renoprotective effect of ACE inhibitors and ARBs, treatment should start with either of these agents. Patients with systolic blood pressure 20 mmHg or diastolic blood pressure 10 mmHg above the goal should start treatment with two agents. An ACE inhibitor or ARB and a low-dose thiazide diuretic (12.5–25 mg/day) can be initially used, but loop diuretics (furosemide)

should be used instead of thiazides in patients with GFR <30 ml/min, corresponding to a serum creatinine of 2.5–3.0 mg/dl (101). ARBs are an excellent alternative if ACE inhibitors are not tolerated (cough) and are the preferred agents for type 2 diabetic patients with left ventricular hypertrophy (104) and/or micro- or macroalbuminuria (106,119,129). ARBs and ACE inhibitors can be combined if there is no reduction in albuminuria or if blood pressure target levels are not reached, even before maximizing the dose of each agent. Additional agents should be added as needed. Calcium channel blockers have an additional effect on reducing blood pressure levels. These agents should only be used in combination with an ACE inhibitor and should not be used in patients with a recent coronary event. β-Blockers are especially useful in patients with myocardial ischemia, since these drugs reduce cardiovascular events and mortality in patients with baseline pulse rate >84 bpm (141). Possibly, a metabolic neutral compound, carvedilol, should be used. The combination of β-blockers and nondihydropyridine calcium channel blockers should be used with caution, since both agents have negative chronotropic effects. Blood pressure treatment could be assessed by 24-h ambulatory monitoring in the following situations: in patients with treatment-resistant hypertension, when there is a suspicion of white coat hypertension, or to detect drug-induced or autonomic neuropathy–related hypotensive episodes (138).

Diet intervention

Replacing red meat with chicken in the usual diet reduced UAE by 46% and reduced total cholesterol, LDL cholesterol, and apolipoprotein B in microalbuminuric patients with type 2 diabetes in a 4-week study (142). This was probably related to the lower amount of saturated fat and the higher proportion of polyunsaturated fatty acids found in chicken meat than in red meat. The beneficial effect of polyunsaturated fatty acids on endothelial function (143) could also reduce UAE. A normal protein diet with chicken as the only source of meat may represent an additive strategy for the treatment of microalbuminuric type 2 diabetic patients. However, long-term studies are necessary. According to a meta-analysis (144) of five studies including a total of 108 patients, dietary protein restriction slowed the progression of diabetic nephropathy in patients with type 1 diabetes. More recently, a 4-year randomized controlled trial in 82 patients with type 1 diabetes with progressive diabetic nephropathy showed that a moderately low–protein diet ($0.9\ g \cdot kg^{-1} \cdot day^{-1}$) reduced the risk of end-stage renal disease or death by 76%, although no effect on GFR decline was observed (145). The mechanisms by which a low-protein diet may reduce progression of diabetic nephropathy are still unknown, but might be related to improved lipid profile and/or glomerular hemodynamics.

Dyslipidemia

The goal for LDL cholesterol is <100 mg/dl for diabetic patients in general and <70 mg/dl for diabetic patients with cardiovascular disease (146). The effect of lipid reduction by antilipemic agents on progression of diabetic nephropathy is still unknown. So far, there have been no large trials analyzing whether the treatment of dyslipidemia could prevent the development of diabetic nephropathy or the decline of renal function. However, there is some evidence that lipid reduction by antilipemic agents might preserve GFR and decrease proteinuria in diabetic patients (147). In the Heart Protection Study, 40 mg simvastatin reduced the rate of major vascular events and GFR decline in patients with diabetes, independent of cholesterol levels at baseline, by 25% (148). Moreover, the results of the recently presented CARDS (Collaborative Atorvastatin Diabetes Study), which showed a marked reduction of cardiovascular events in patients with diabetes and at least one additional risk factor for coronary artery disease, suggest that all diabetic patients should be taking statins (www.cardstrial.org).

Anemia

Anemia may occur in patients with diabetic nephropathy even before the onset of advanced renal failure (serum creatinine <1.8 mg/dl), and it has been related to erythropoietin deficiency (149). Furthermore, anemia has been considered a risk factor for progression of renal disease and retinopathy (150). Until the results of the ongoing ACORD (Anemia Correction in Diabetes) study (151) become available, it is recommended to start erythropoietin treatment when Hb levels are <11 g/dl. The target Hb levels should be 12–13 g/dl, and the potential risk of elevation of blood pressure levels with erythropoietin treatment should be taken into account (150).

Use of aspirin

Low-dose aspirin has been recommended for primary and secondary prevention of cardiovascular events in adults with diabetes. This therapy did not have a negative impact on renal function (UAE or GFR) in type 1 and type 2 diabetic patients with micro- or macroalbuminuria (152,153). However, the subgroup analysis of the Primary Prevention Project trial did not show a significant reduction in the occurrence of cardiovascular events in 1,031 diabetic patients using low-dose aspirin (100 mg/day) (154). Although this study was underpowered to analyze the effect on the development of cardiovascular events, these data raise the issue that diabetic patients could be less responsive to aspirin therapy (aspirin resistance). In fact, a recent study demonstrated a reduced response of platelets from diabetic subjects to treatment with aspirin (150 mg/day). This phenomenon was associated with higher levels of A1c, lower concentration of HDL cholesterol, and higher concentration of total cholesterol (155). Therefore, diabetic patients might benefit from aspirin doses >100–150 mg/day or use of other antiplatelet agents such as clopidogrel.

Multifactorial intervention

Patients with microalbuminuria frequently have other cardiovascular risk factors, such as hypertension and dyslipidemia. In the Steno-2 study, multifactorial intervention was compared with conventional treatment in 160 microalbuminuric type 2 diabetic patients (156). The targets were to achieve blood pressure levels <130/80 mmHg, fasting serum cholesterol <175 mg/dl, fasting serum triglycerides <150 mg/dl, and A1c <6.5%. The multifactorial intervention consisted of a stepwise implementation of lifestyle changes and pharmacological therapy, including a low-fat diet, a three to five times a week light-to-moderate exercise program, a smoking cessation program, and prescription of ACE inhibitors or ARBs and aspirin. The intensively treated group had a 61% reduction in the risk of developing macroalbuminuria and a 58 and 63% reduction in the risk of

retinopathy and autonomic neuropathy, respectively. Most importantly, a 55% reduction in the risk for the development of a composite end point consisting of death from cardiovascular causes, nonfatal myocardial infarction, revascularization procedures, nonfatal stroke, and amputation was also observed in the multifactorial intervention group.

NEW POTENTIAL THERAPEUTIC STRATEGIES —

The measures described above might not be effective in some patients with diabetes, and novel therapeutic strategies are warranted. High doses of thiamine and its derivate benfotiamine have been shown to retard the development of microalbuminuria in experimental diabetic nephropathy, probably due to decreased activation of protein kinase C, decreased protein glycation, and oxidative stress (157). Treatment with ALT-711, a cross-link breaker of the advanced glycation end products, has been shown to result in a significant reduction in UAE, blood pressure, and renal lesions in experimental diabetes (158). Treatment with a protein kinase C β inhibitor (ruboxistaurin) normalized GFR, decreased albumin excretion rate, and ameliorated glomerular lesions in diabetic rodents (159). In a rat model of diabetes-induced glomerulosclerosis, administration of a modified heparin glycosaminoglycan prevented albuminuria, glomerular, and tubular matrix accumulation and transforming growth factor β1 mRNA overexpression (160). Very few studies have been conducted in humans. Sulodexide, a glycosaminoglycan, significantly reduced albuminuria in micro- or macroalbuminuric type 1 and type 2 diabetic patients (161). Pimagedine, a second-generation inhibitor of advanced glycation end products, reduced urinary protein excretion and the decline in GFR in proteinuric type 1 diabetic patients in a randomized, placebo-controlled study (162).

CONCLUSIONS —

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.

Note added in proof

In a 5-year prospective study, Barnett et al. (*N ENgl J Med* 351:1952–1961, 2004) observed that telmisartan (80 mg/day) was not inferior to enalapril (20 mg/day) in preventing the progression of decline of GFR in 250 type 2 diabetic patients with microalbuminuria, reinforcing the suggestion that ACE inhibitors and ARBs have a similar effect in protecting the kidney.

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