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Diagnosis and Treatment of Diabetic Nephropathy in Type 1 and Type 2 Diabetes Patients

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Introduction

Diabetic nephropathy (DN) is the leading cause of end-stage renal disease and the care of patients with diabetes and DN contributes significantly to health care costs. Of patients with type 1 diabetes, approx 20%-30% will eventually develop DN [1], whereas about 10%-20% of those with type 2 diabetes will do so [2]. In the past couple of decades, there have been notable advances in our knowledge regarding the DN, including the advent of interventions that can significantly slow or even reverse the course of progressive disease. This review describes the definition and detection of diabetic kidney disease, its natural history, current proven therapies, and potential future therapies.

Definition and Natural History

It is known that DN can be detected before the onset of decreased glomerular filtration rate (GFR) in most patients by detecting abnormal amounts of albumin in the urine. Two stages have been designated: microalbuminuria (defined as urine albumin between 30 and 300 mg/24 h, 20-200 μg/min on a timed sample, or spot urine albumin to creatinine ratio 30-300 mg/g) and albuminuria, also termed clinical albuminuria, macroalbuminuria, and overt nephropathy (>300 mg/24 h, >200 μg/min on a timed sample, or spot urine albumin to creatinine [ACR] ratio >300 mg/g). Short-term hyperglycemia, exercise, urinary tract infections, marked hypertension, heart failure, and acute, febrile illness can cause transient elevations [3]; there is also marked day-to-day variability in albumin excretion, so that at least two three collections done should show elevated levels before a patient is designated as having microalbuminuria.

In type 1 diabetes, microalbuminuria is rarely present at diagnosis, but persistent and untreated microalbuminuria will progress to albuminuria in 30%-80% of individuals over 10-15 yr, and of those, 50%-78% will progress to Diabetic nephropathy over the next 10-18 yr [4]. Hypertension usually develops as a complication of nephropathy. In type 2 diabetes, microalbuminuria and even albuminuria may be present at or soon after diagnosis, in part due to the fact that diabetes has often already been present for years. Left untreated, 20%-40% of such patients will develop overt nephropathy, with only approx 20% of those patients progressing to DN over the next 20 yr [5]. In fact, more patients with albuminuria and type 2 diabetes will die from cardiovascular disease than progress to DN [6,7]. Hypertension is frequently already present at the time of diagnosis of diabetes, often as part of the metabolic syndrome. Based on the current evidence that early intervention may slow the progression of diabetic kidney disease, it is now the standard of care to do annual screening for microalbuminuria, in type 1 diabetes starting at puberty or 5 yr after diagnosis, and in type 2 diabetes beginning at diagnosis [8].

However, cross-sectional studies have found decreased GFR in the absence of increased urine albumin excretion (UAE) in a substantial percentage of adults with type 2 diabetes [9]. In the Third National Health and Nutrition Examination Survey, which collected demographic and health information from a nationally representative sample of the US population, 13% of adults with type 2 diabetes had a GFR <60 mL/min/ 1.73 m^2. Among these, an absence of increased UAE (defined in this study as a spot urine ACR ≥17 mg/g in men and ≥25 mg/g in women) was noted in approx. 40%, whereas absence of both increased UAE and diabetic retinopathy was noted in 30% [9]. Decreased GFR in the absence of increased UAE among adults with both type 1 and 2 diabetes have also been reported in other studies [10]. In follow-up, the rates of decline of GFR in those with type 2 diabetes with initial GFR levels <60 mL/min/1.73 m^2 were similar, regardless of the presence or absence of albuminuria [11]. Thus, these studies demonstrate that substantial declines in GFR may be noted in adults with type 1 and 2 diabetes in the absence of increased UAE. Because these studies did not perform kidney biopsies, investigators can only speculate on the etiology of decreased GFR in the absence of increased UAE. Pathological evidence of DN has been documented in adults with diabetes even in the absence of increased UAE [12,13]. In addition, older patients with type 2 diabetes may also have vascular and tubulo-interstitial changes owing to the presence of comorbid conditions, including long-standing hypertension and renal vascular disease, and potential senescence of glomeruli owing to aging itself [14,15]. Conversely, studies have also reported a range of biopsy findings from normal to typical diabetic changes and frequently other kidney diseases in adults with type 2 diabetes and increased UAE [16]. Therefore, in addition to yearly screening for albuminuria, the yearly measurement of serum creatinine with estimation of GFR using the adjusted modification diet in renal disease (MDRD) [17] or other formulas [18] should also be carried out.

Current Targets for Intervention

Glycemic control

Several large prospective randomized trials have demonstrated the efficacy of improved glycemic control in preventing progression of diabetic kidney disease in persons with type 1 diabetes. A number of observational studies have shown that the development of microalbuminuria is associated with poorer glycemic control [19]. Several small, prospective, interventional studies from the early 1980s showed that improved glycemic control caused a decrease in the development and progression of albuminuria but in most cases, the small sizes of the cohorts precluded statistical significance [20,21]. A meta-analysis of these studies concluded that intensive therapy significantly reduced the risk of nephropathy progression (OR 0.34, 95% CI 0.20-0.58, p<0.001) [22]. The diabetes control and

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complications trial (DCCT) of 1441 subjects with type 1 diabetes showed that an intensive glycemic control regimen compared with a conventional control regimen resulted in a sustained mean hemoglobin (Hb)A1c 2% lower with the intensive regimen [23]. After a mean duration of 9 yr, the intensively treated subjects showed significantly lower rates of microalbuminuria compared with the conventionally treated subjects, in both the primary prevention group (risk reduction 34%) and the secondary prevention group (risk reduction 43%) [24]. In the similarly designed Stockholm study with 102 patients with type-1 diabetes, intensive insulin therapy resulting in a mean HbA1c of 7.1% was associated with albuminuria in only 1 out of 48 patients (2.1%), whereas conventional therapy, resulting in a mean HbA1c of 8.5% was associated with albuminuria in 9 of 54 patients (16.6%) (p=0.01) [25].

Several major intervention studies have also been carried out with type 2 diabetes subjects. Using a similar design as the DCCT, the Kumamoto study separated 110 Japanese subjects with type 2 diabetes into primary prevention and secondary intervention cohorts, randomizing them to intensive (HbA1c 7.1%) or conventional (HbA1c 9.4%) glycemic control with insulin [26]. Over 6 yr, intensively treated subjects sustained a significant reduction in both new onset and progression of nephropathy compared with conventionally treated subjects. In the prevention cohort, 7.7% developed microalbuminuria in the intensive group *vs* 28% in the conventional group (p=0.032). After 8 yr, these percentages were 11.5 and 43.5%. Progression to albuminuria was also reduced (11.5% of intensive *vs* 32% of conventional) [27]. The UK prospective diabetes study (UKPDS) randomly assigned newly diagnosed patients with type 2 diabetes to intensive management using a sulfonylurea or insulin, or to conventional management with diet alone. The average HbA1c for the intensive group was 7% as compared with 7.9% for the conventional group during the study [28]. After 9 yr of intensive therapy, the risk reduction for the development of microalbuminuria was 24% [28]. The degree of risk reduction was similar whether intensive therapy was achieved with sulfonylurea or insulin. However, when better glycemic control was achieved with metformin in the UKPDS, no effect was found on albuminuria [29].

Based on these and other data showing that improving glycemic control reduces the rates of not only nephropathy but also retinopathy and neuropathy, the American Diabetes Association (ADA) recommends for adults with diabetes a goal HbA1c of less than 7%, whereas the American Association of Clinical Endocrinologists and the European Noninsulin-Dependent Diabetes Mellitus (NIDDM) Working Group recommend a treatment goal of less than 6.5% [30,31]. It should be noted that attempts to attain tighter glycemic control may be complicated by an increased frequency of hypoglycemia, especially in patients treated with insulin.

Hypertension/Renin-angiotensin-aldosterone system blockade

Hypertension frequently coexists with diabetes mellitus in adults. The prevalence is greater than 50% in persons with type 2 diabetes mellitus, increasing with age, and approx 25% in those with type 1 diabetes [32]. As mentioned previously, the onset of hypertension in type 1 diabetes appears to be primarily a complication of DN, whereas in type 2 the hypertension is frequently present at the time of the diagnosis of diabetes with both being components of the metabolic syndrome. Despite the possible difference in pathophysiology of hypertension in the two types of diabetes, it is clear that uncontrolled hypertension increases the risk for progressive renal damage in patients with either type.

Treatment of hypertension in diabetes clearly decreases the risk of microvascular and macrovascular complications, including nephropathy. Large prospective, randomized trials (UKPDS and the Appropriate Blood Pressure Control in Diabetes trial) have shown decreased rates of progression of nephropathy with lowering of blood pressure [33]. Based on these and other trials, the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC), the ADA, and the National Kidney Foundation have all redefined the goal blood pressure in individuals with diabetes as <130/80 mmHg [34]. Although the primary goal is blood pressure lowering, the possible differential class effects above and beyond direct effects on blood pressure have been and are continuing to be addressed in large, prospective, and randomized clinical trials. As has been found in multiple clinical trials, the great majority of subjects with diabetes required at least two, and many, even three or more antihypertensive agents in order to reach target blood pressures [35]. Most patients with diabetes on appropriately aggressive therapy, therefore, will ultimately end up taking agents from multiple drug classes. Antihypertensive agents that block the renin-angiotensin-aldosterone system (RAAS) appear to have beneficial effects on the progression of nephropathy above and beyond their blood pressure-lowering effects. They appear to do this by decreasing intraglomerular pressure and by blocking the vasoconstrictive and trophic effects of the RAAS that are thought to be important factors in the pathogenesis of vascular injury in diabetes. Studies have shown angiotensin-converting enzyme (ACE) inhibitors to be of superior benefit in comparison with other classes of antihypertensive agents in decreasing the development of microalbuminuria and albuminuria in patients with type 1 diabetes, including those without hypertension [36]. Currently, there are little data regarding angiotensin receptor blockers (ARBs) in type 1 diabetes and nephropathy, but the efficacy and superiority of ACE inhibitors have generally been extrapolated to ARBs. Until recently, there has been little data from large prospective trials regarding the effectiveness of ACE inhibitors for nephropathy in patients with type 2 diabetes, but again, there have been a presumed extension of their benefits to such patients. A small study of 156 normotensive, normoalbuminuric patients with type 2 diabetes treated with either enalapril or placebo for 6 yr demonstrated a significant risk reduction of 12.5% in the development of microalbuminuria with enalapril as well as a significant attenuation in decline in GFR (mean decrease of 0.025 mL/s/yr with enalapril *vs* 0.04 mL/s/yr with placebo, p=0.040) [37]. In the microalbuminuria, cardiovascular, and renal outcomes-heart outcomes prevention evaluation (MICRO-HOPE) study of 3577 primarily type 2 diabetic subjects, Ramipril showed a statistically significant benefit over placebo in preventing the progression from microalbuminuria to overt nephropathy (24% risk reduction), and a non-significant decrease in development of new microalbuminuria [38].

Protein restriction

A rat model of DN has shown that restriction of dietary protein intake also reduces hyperfiltration and intraglomerular pressure and retards the progression of renal disease [39]. A 4-yr prospective, blinded, and controlled study of 82 subjects with type 1 diabetes and decreasing GFR showed that a low-protein diet (mean 0.89 g/kg/d) compared with usual-protein diet (1.02 g/kg/d) led to a relative risk reduction in diabetic nephropathy or death of 23% after adjustment for baseline cardiovascular disease (p=0.01) [40]. Several small studies in humans with DN have shown that a protein-restricted diet of 0.6 g/kg/d retards the rate of fall of GFR by approx 25% [41].

Lipid-lowering agents

More aggressive lipid-lowering in patients with diabetes has

Therapeutic Interventions in DN		
Intervention	**Goal**	**Therapy**
Hyperglycemia	HbA1c <7%	Insulin or other anti hypergycemic agents
Hypertension	BP <130/80 mm Hg	ACE- inhibitor or ARB
Microalbuminuria/ albuminuria	Urine albumin <500 mg/d	ACE or ARB
Hyperlidemia	LDL <100 mg/d	Statin
Dietary protein	Normal GFR: 0.8 g/kg/d	Nutrition consult

Table 1: Therapeutic intervention in DN.

recently become the standard of care, with the national cholesterol education program (NCEP) designating persons with diabetes as having a coronary heart disease equivalent and recommending a low-density lipoprotein (LDL) target of less than 100 mg/dL [42]. Because of their very high risk for coronary artery disease it may well be that the recently recommended lower goal of less than 70 mg/dL for LDL cholesterol [43] may be more appropriate for patients with established nephropathy. Thus, many patients with diabetes, particularly those with type 2, will require lipid-lowering therapy, frequently with a statin, regardless of their renal status. However, it is interesting to note that animal studies have shown that high-cholesterol diets worsen renal injury, whereas lowering blood lipids by medications ameliorates the renal injury. A relationship between hyperlipidemia and DN has also been suggested by epidemiological studies. A meta-analysis of 12 small, controlled studies in humans concluded that treatment was associated with a lower rate of decline in GFR compared with no treatment -0.156 mL/min/mo *vs* -0.285 mL/min/mo, respectively, p=0.008). This effect did not correlate with either the percent change in cholesterol or with the type of lipid-lowering agent used, although all but two trials utilized statins (the other two, Gemfibrozil, and Probucol). Seven of the trials included only patients with DN [44].

Conclusions

Patients with diabetes who are at high risk of developing diabetic nephropathy can now be identified at a point very early in the course of their development of this complication. A number of therapies (Table 1) have been identified that can slow progression of this Screening and Treatment of Early Diabetic Renal Disease complication, which is associated with a great deal of morbidity and mortality, as well as staggering costs. There is no question in the present day and age that aggressive control of hyperglycemia and hypertension is beneficial in this regard, or that drugs inhibiting RAAS activity are beneficial independent of their blood pressure effects. Protein restriction may also be of benefit in selected patients. Lipid-lowering agents should be used as recommended to attain cholesterol and triglyceride targets, and may contribute a renoprotective effect as well. It is less clear at this time whether reduction of UAE should be a specific goal, and it also remains controversial regarding whether normotensive patients with microalbuminuria or albuminuria should be treated. Although most studies show that current therapies can only slow the progression of disease, it is possible that when instituted very early they may actually halt progression in some patients. Furthermore, a number of promising possibilities are on the horizon. Thus, although the number of people in the world with diabetes is steadily increasing, it may well be that the proportion and possibly the absolute numbers who develop DN will decrease.

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