Diabetic Nephropathy

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Key Points

Both alterations in systemic and glomerular hemodynamics and changes in metabolism due to hyperglycemia are crucial factors in the pathogenesis of diabetic nephropathy.

Microalbuminuria and proteinuria are key markers which identify patients with diabetes mellitus (DM) who have developed diabetic nephropathy. Intensive glycemic control dramatically reduces the risk of developing diabetic nephropathy.

Blood pressure control slows the progression of diabetic nephropathy even after deterioration of renal function starts. Angiotensin-converting enzyme (ACE) inhibition slows the progression of diabetic nephropathy and is indicated for all normotensive or hypertensive diabetic patients who have microalbuminuria or proteinuria.

Diabetic nephropathy is the most common cause of end-stage renal disease (ESRD) in the United States leading to enrollment in the Medicare ESRD program. Patients with DM currently account for 35% of the population requiring renal replacement therapy. Patients with Type II diabetes mellitus (DM) constitute 60% of the diabetic population in the ESRD program. The cost to Medicare for these patients' renal replacement therapy alone exceeds 2 billion dollars per year [1]. In addition to its significant impact on health care costs, diabetic kidney disease significantly shortens the lifespan of the patient with diabetes. It has been estimated that patients with Type I DM and nephropathy (manifested by proteinuria) have a 100-fold greater risk of death relative to a nondiabetic population. Patients with DM without kidney disease have only a 2-fold increase in relative mortality [2].

Epidemiology

The cumulative incidence of nephropathy in patients with Type I DM of 40 years duration is 40%. Several reports suggest that the cumulative incidence of diabetic nephropathy is declining, which may reflect better blood sugar control in the diabetic population as a whole. The annual incidence peaks just before 20 years duration of DM and declines thereafter (Figure 1) [2]. The decline in the annual incidence of diabetic nephropathy over time

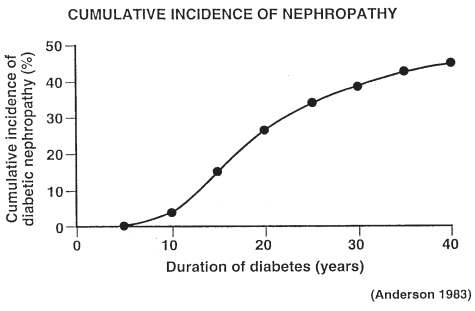

Figure 1. Cumulative incidence of diabetic nephropathy in relation to duration of diabetes in 907 Type I patients.

suggests that the pool of susceptible patients becomes exhausted. Diabetic nephropathy with proteinuria rarely develops before 10 years duration of DM or after 30 years of DM. Thus, the development of diabetic nephropathy is not simply a function of duration of DM nor an inevitable complication in all patients. Rather, the data suggest that only a subset of 40% of patients with Type I DM develop diabetic nephropathy, perhaps because of a genetic susceptibility or an environmental exposure.

Reports of familial clustering of diabetic nephropathy are consistent with a genetic susceptibility to the development of this complication. In families with multiple siblings who have Type I DM, those of a proband with diabetic nephropathy are more likely to have proteinuria and renal insufficiency secondary to diabetic nephropathy than the siblings of duration-matched pro-bands without nephropathy. Similar data supporting genetic susceptibility to diabetic nephropathy have also been reported in families with Type II DM.

Early studies suggested that the cumulative incidence of diabetic nephropathy in patients with Type II DM was less than in patients with Type I DM. However, a recent careful natural history study done in Pima Indians with Type II DM reported a cumulative incidence of diabetic nephropathy comparable to that found in Type I DM patients [3]. Furthermore, in Western Europe it has been reported that up to 40% of patients with Type II DM developed nephropathy, a cumulative incidence quite similar to that found in Type I DM [4]. In part, some of the discrepancies between these reports may reflect the very high mortality rate from atherosclerotic disease in patients with Type II DM and renal disease, resulting in a bias against the progression to ESRD.

For most Type II patients, the age of onset of DM is unknown and may precede the diagnosis by many years. Some patients with Type II DM already have diabetic nephropathy at the time of diagnosis of DM. However, in the Pima Indian study, the age of onset of DM is well documented and precedes proteinuria from diabetic nephropathy by approximately 20 years. Assuming that the natural history of diabetic nephropathy in Pima Indians is representative of all patients with Type II DM, the duration of DM required to develop nephropathy may be similar for Type I and Type II DM.

Finally, there are important racial differences that contribute to the risk of developing diabetic nephropathy. African Americans, Mexican Americans, American Indians, Maori, and Polynesians with DM have a greater risk of developing diabetic nephropathy and a more rapid progression to ESRD than Caucasians [3]. It is not known whether these racial differences are the result of genetic, environmental, or other factors.

Pathogenesis and Risk Factors

Many factors have been postulated to be important in the pathogenesis of diabetic nephropathy. It appears that exposure to both the systemic hemodynamic effects of DM and to the diabetic milieu are critical factors for the development of diabetic kidney disease. In studies with diabetic rats and humans, unilateral renal artery stenosis has been reported to protect the kidney distal to the blocked renal artery from developing the morphologic changes of DM. Thus, exposure to the systemic blood pressure appears to contribute to the development of diabetic kidney disease.

Normal kidneys transplanted into patients with DM develop diabetic lesions over time,

whereas kidneys inadvertently harvested from patients with DM transplanted into non-diabetic ESRD patients showed resolution of their diabetic lesions on microscopy. This suggests that exposure to the diabetic milieu, rather than an intrinsic defect in the kidneys predisposes these patients to the development of diabetic nephropathy.

Hyperglycemia, insulin insufficiency, augmented glucagon and growth hormone levels, and increased ketogenesis have all been implicated in the pathogenesis of diabetic nephropathy. More recently, it has been demonstrated that hyperglycemia results in the glycosylation of long-lived proteins that crosslink to form advanced glycosylation end products (AGEs) [5]. In animal models, the accumulation of AGEs is associated with the end-organ complications of DM. Similarly, in humans the accumulation of AGEs is increased in patients with renal insufficiency. Inhibitors of AGE formation are beneficial in retarding the progression of diabetic nephropathy in experimental animals and are currently being tested in human clinical trials.

Hyperglycemia also leads to the shunting of glucose down the polyol pathway with the accumulation of sorbitol in the lens, nerves, and kidney. In animal models, this pathway has been implicated in the development of diabetic nephropathy, but it is unclear what role it may play in human diabetic kidney disease [6].

Alterations in the renin-angiotensin system also contribute to the development of diabetic nephropathy in animal and human models, as do abnormal intraglomerular pressures in animal models. In the diabetic rat, decreasing intraglomerular pressures by decreasing angiotensin (Ang) II-mediated efferent arteriole resistance preserves glomerular structure and function [7]. Similarly, in humans, interrupting the renin-angiotensin system (see below) slows the progression of diabetic kidney disease. Together, these studies imply that alterations in the renin-angiotensin system play an important role in the pathogenesis of diabetic nephropathy. Additional important factors in this process may be alternations in the production of prostaglandins or kinins.

Identifying the risk factors for development of diabetic nephropathy in humans may help identify important pathogenic mechanisms in the development of this disease [8]. Significant risk factors include a family history of diabetic nephropathy, the presence of hypertension, poor glycemic control, smoking, and increased plasma pro-renin activity. In large population studies, patients with DM have significantly elevated blood pressures compared with non-diabetic controls. The presence of proteinuria in these patients is predictive of the presence of hypertension. Some, but not all, studies suggest that at the time of diagnosis of DM, patients destined to develop diabetic nephropathy have significantly higher mean arterial blood pressures than those patients with DM who never develop nephropathy. Furthermore, patients with both Type I and Type II DM and nephropathy have a predisposition to hypertension, as indicated by elevated sodium-lithium counter transport activity in erythrocytes and a strong parental history of hypertension as compared to diabetic patients without nephropathy. Combined, these data make a compelling arguement that a genetic predisposition to hypertension is a risk factor for developing diabetic nephropathy. However, since it has been reported that up to 25% of patients with Type I DM and established diabetic nephropathy are normotensive, a genetic susceptibility to hypertension cannot be the only risk factor in the development of diabetic nephropathy.

Hyperglycemia is clearly necessary for the development of diabetic nephropathy in animals and humans. Many retrospective clinical studies have documented a relationship be-

tween poor blood sugar control and the subsequent development of diabetic nephropathy. Patients with poor blood sugar control develop diabetic nephropathy earlier. Poor glycemic control also synergistically increases the risk for diabetic nephropathy in patients genetically predisposed to hypertension.

Smoking is a risk factor identified in multiple epidemiological studies for the development and more rapid progression of diabetic nephropathy. The mechanism for the effects of smoking on kidney disease is unclear. Increased plasma pro-renin activity has also been associated with an increased risk of patients developing diabetic retinopathy and nephropathy, although there is considerable overlap in the plasma pro-renin activity between patients with and without complications.

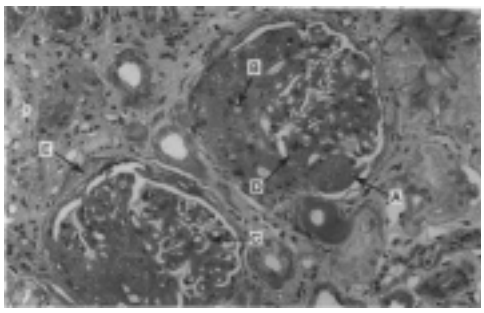

Figure 2. Five distinctive lesions in glomeruli of patients with insulin-dependent diabetes mellitus. A = Kimmelstiel-Wilson nodule; B = intercapillary glomerulosclerosis;C = thickening of glomerular basement membrane; D = mesangial expansion; E = fibrin cap lesion.

Pathology

Renal biopsies are normal in patients at the time of diagnosis of Type I DM. Within as little as 1 – 2 years, however, morphologic changes appear, including glomerular basement membrane thickening, mesangial expansion, nodular and diffuse forms of intracapillary glomerulosclerosis, the capsular drop lesion, and the fibrin cap and arteriolar hyalinosis (Figure 2). Glomerular basement membrane thickening is a sensitive indicator for the presence of DM, but does not predict which patients will develop clinically significant nephropathy. In contrast, mesangial expansion has been demonstrated to correlate with clinically significant diabetic nephropathy [9]. Glomerular filtration rate (GFR), as measured by creatinine clearance, declines linearly with the degree of mesangial expansion. Although DM is primarily a vascular (including glomerular) disease, alterations in the structure and function of the renal tubulointerstitium are also present. The degree of interstitial fibrosis also correlates with the reduction in GFR. Many patients will have morphologic changes in the kidney consistent with the effects of DM but never develop proteinuria or other clinical manifestations of diabetic nephropathy.

The morphologic changes found in patients with Type II DM and diabetic nephropathy were long thought to be indistinguishable from those in patients with Type I DM. Careful prospective biopsy studies have demonstrated that patients with Type I and Type II DM share the nodular form of intracapillary glomerulosclerosis (Kimmelstiel-Wilson-lesions). However, patients with Type II DM have more prominent non-nodular glomerulosclerosis, arteriolar hyalinosis, and other vascular changes.

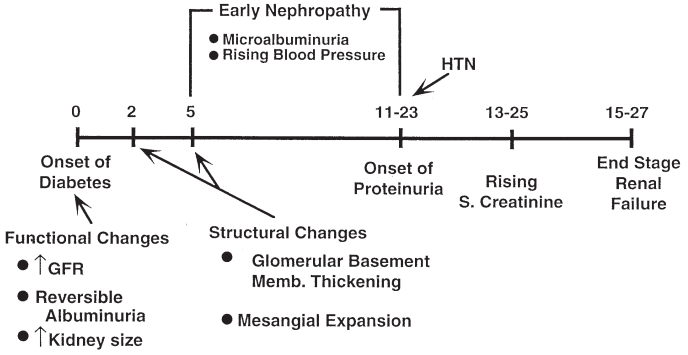

Figure 3. The natural history of diabetic nephropathy.

Natural History

The natural history of diabetic nephropathy is best understood in patients with Type I DM and is illustrated in Figure 3.

At the time of diagnosis of Type I DM, functional changes in the kidney are manifested in virtually all patients [7]. Within a few years, morphologic changes occur in the kidneys of most patients. Glomerular hyperfiltration, elevations in the systemic mean arterial blood pressure, and poor blood sugar control all appear to be important features in this early period. Nephropathy is manifested early by microalbuminuria, with the majority of patients progressing to overt proteinuria. On average, proteinuria is present in the 40% of patients who were destined to develop diabetic nephropathy 10 – 25 years after the onset of Type I DM. Once proteinuria is established, renal function declines inexorably, with 50% of patients reaching ESRD within 7 – 10 years.

Patients with Type II DM frequently have an unknown age of onset of DM and many co-existing illnesses complicating their course. For example, Type II diabetics have a high cardiovascular mortality and often do not survive long enough to develop ESRD from diabetic nephropathy. However, as noted above, studies of the Pima Indians indicate analogous progression in Type II DM compared to Type I [3, 4].

Functional Changes

At the onset of DM, kidney size is increased and albuminuria is present, but these changes usually reverse with blood sugar control. The iniation of insulin therapy also lowers the dramatically increased GFR, although it remains supranormal compared to a nondiabetic population. In both retrospective and prospective studies, higher GFRs at the time of diagnosis of DM predicted the later development of diabetic nephropathy [10]. A GFR of 125 mL/min or less had a negative predictive value of 95% in Type I patients, while a GFR > 125 mL/min had a 53% positive predictive value for the development of nephropathy. However, because of overlap in these patient populations, an early measurement of GFR alone cannot solely predict diabetic renal disease. In patients with Type II DM, reports vary widely about the presence or absence of glomerular hyperfiltration. This may reflect the difficulty in establishing the length of DM in these patients. In the Pima Indians, early glomerular hyperfiltration similar to that reported in patients with Type I DM has been documented.

In animal models of DM, glomerular hyperfiltration is associated with increments in renal flow because of renal dilatation and increases in the glomerular transcapillary hydraulic pressure gradient. These changes lead to accelerated glomerulosclerosis. It is likely that similar glomerular damage associated with glomerular hyperfiltration occurs in humans. Glomerular hyperfiltration has also been associated with increased glomerular surface area and renal hypertrophy.

Microalbuminuria

The presence of microalbuminuria (albumin excretion of 30 – 300 mg/24 hour) in patients with DM is highly predictive of the progression to proteinuria and renal insufficiency in the next 10 – 15 years. The reported prevalence of microalbuminuria in patients with Type I DM varies widely, depending, at least in part, on how the population is selected in terms of DM duration. Overall, approximately 20% of patients with Type I DM will have microalbuminuria in cross-sectional studies. Poor glycemic control and elevations in mean arterial blood pressures also correlate with the development of microalbuminuria [11]. Once present, microalbuminuria is highly predictive of progression to overt proteinuria and renal insufficiency. Between 75% and 100% of patients with documented microalbuminuria go on to proteinuria and declining renal function. The GFR in patients with microalbuminuria is well preserved or increased, but may begin to decrease once the urinary albumin excretion rate exceeds 100 μg/min. Type II patients also develop microalbuminuria, which also predicts progression to proteinuria and ESRD. However, microalbuminuria is associated with a high mortality rate due to atherosclerotic events in these patients, many of whom do not survive to develop proteinuria or ESRD.

Proteinuria and Declining Renal Function

For the vast majority of patients with diabetic nephropathy, proteinuria inevitably progresses to renal decline. In patients with either Type I or Type II DM, the proteinuria typically ranges from 0.5 gm to more than 20 gm/24 hour. In early nephropathy, albuminuria is secondary to a loss of the anionic charge barrier, whereas in established nephropathy, proteinuria results from an increased number of nonselective enlarged pores. Proteinuria typically occurs 17 years (± 6 years) after the onset of Type I DM.

Once proteinuria is established, GFR begins to decline, with an average reported rate of loss between 3 – 12 mL/min/yr. The decline in renal function can be hastened by other diabetic complications such as neurogenic bladder, urinary tract infections, papillary necrosis, and exposure to renal toxins such as IV contrast. Other factors that predict a faster progression include uncontrolled systemic hypertension, uncontrolled blood sugars, higher protein excretion rates, hypercholesterolemia, smoking, and a parental history of DM. Certain racial groups, such as African Americans, Mexican Americans, Native Americans, Polynesians, and Maori, all have a faster rate of progression to ESRD than Caucasians with diabetic nephropathy [4].

End-stage Renal Disease (ESRD)

Once patients with DM reach ESRD, their options include hemodialysis, peritoneal dialysis, or transplantation. ESRD patients with DM have higher mortality rates than nondiabetic ESRD patients. Peritoneal dialysis avoids the problems associated with hemodialysis, such as vascular access, hemodynamic instability, and systemic heparin, but is complicated by increased glucose loads, worsening triglyceride levels, and peritonitis. Hemodialysis provides higher small molecular weight substance clearances. Some studies suggest that higher clearances decrease mortality, particularly in patients with DM and ESRD, although no prospective studies have yet directly compared these two modalities.

Survival is longer for diabetc patients receiving a living related donor transplant compared to patients remaining on dialysis. Two-year renal graft survival and patient survival in Type I DM with living related donor transplants are comparable to survival in nondiabetic ESRD patients. However, Type I DM patients who receive a cadaveric renal transplant have a higher morbidity and mortality than nondiabetic ESRD patients. Patients receiving combined renal and pancreas transplants have a higher morbidity rate than those undergoing renal transplant alone, but have improved hyperglycemia, and both motor and sensory nerve function. No benefits are demonstrable for pancreatic polypeptide secretion, preservation of kidney function, or retinopathy.

The increased morbidity and mortality rates observed in ESRD patients with DM are mainly secondary to complications of atherosclerotic disease. Many investigators have shown that the risk for cardiovascular disease in diabetic patients with renal disease far exceeds that in duration-matched patients with DM without nephropathy. Other morbidity stems from an excessive rate of cerebral and peripheral vascular complications. Low serum albumin and infection also complicate renal replacement therapy for patients with DM. Thus, despite advances malnutrition, infection, and atherosclerotic diseases shorten the life of the patient with DM and ESRD.

Clinical Manifestations and Diagnosis

Microalbuminuria appears to be an important marker for the development of proteinuria and declining renal function. Current recommendations are that all patients with Type I DM of greater than 5 years duration should be screened yearly for microalbuminuria. It is important to specifically order testing for urinary albumin excretion or microalbuminuria, because of the low sensivity of routine urine protein determinations for this condition [10]. Urinary albumin excretion rates exceed 300 mg/day in patients with proteinuria measured either by dipstick or by the traditional 24-hour urine protein assay. With sensitive assays for microalbuminuria, urinary albumin excretions < 30 mg/24 hour can be detected. Patients with normal kidneys have urinary albumin excretion rates < 30 mg/24 hour or 20 μg/min, while microalbuminuria is defined as albumin excretion rates of 30 – 300 mg/24 hour or 20 – 200 μg/min.

The presence of microalbuminuria can be evaluated in a 24-hour urine collection, an overnight urine collection that can be extrapolated to 24 hours, or a spot urine measurement of the albumin-creatinine ratio (Table 1).

Table 1. Measurement of Microalbuminuria

- Test Type I DM patients of greater than 5 years duration every year.
- Test Type II DM patients at the time of diagnosis and every year.
- Rule out causes of transient microalbuminuria: hyperglycemia, UTI, PE, essential HTN, CHF, water loading.
- If the albumin excretion rate is elevated, repeat 3 times over 3 to 6 months to define persistent microalbuminuria.
- Normal albumin excretion: <30 mg/24 hour; microalbuminuria: 30 – 300 mg/24 hour; proteinuria: >300 mg/24 hour.

UTI: urinary tract infection; PE: physical exercise; HTN: hypertension; CHF: congestive heart failure.

Transient causes of microalbuminuria such as hyperglycemia, urinary tract infection (UTI), physical exercise, uncontrolled hypertension, congestive heart failure, or water loading should be considered. Thus, an elevated albumin excretion rate should be repeated on 3 occasions over 3 – 6 months to confirm persistent microalbuminuria. Patients with Type II DM should be screened at the time of diagnosis and yearly thereafter [12]. Identifying patients with microalbuminuria allows measures to be implemented to slow or halt the progression of their kidney disease much earlier, before significant renal insufficiency develops.

Proteinuria in a diabetic patient warrants evaluation. In patients with Type I DM, the onset of proteinuria occurs between 10 and 25 years after diagnosis. Thus, patients who first present with proteinuria before 10 years or after 25 years duration of DM should be suspected of having another cause of kidney disease. In patients with Type I DM, 90 – 95% of patients with diabetic nephropathy have diabetic retinopathy. Therefore, the absence of diabetic retinopathy as determined by either 7 field fundus photos or fluorescein angiography should again suggest the presence of an alternative diagnosis. Only 60 – 65% of patients with Type II DM and diabetic nephropathy have diabetic retinopathy, making it a less helpful factor in their evaluation. All patients with DM and proteinuria should be evaluated carefully for the presence of other systemic diseases that can cause proteinuria, such as a gammopathy, hepatitis B, systemic lupus erythematosus (SLE) or amyloidosis. Abnormalities in the urinalysis, e.g. hematuria or red blood cell casts, should also alert one to the possibility of another kidney disease. A renal ultrasound will rule out anatomic abnormalities and evaluate the patient for kidney size. Most patients with diabetic nephropathy have large kidneys, especially in relation to their decreased GFR.

In a prospective biopsy series in patients with Type I DM and more recently Type II DM, ≤ 10% of the patients who had the typical clinical features noted above were found to have a diagnosis by biopsy other than diabetic nephropathy. Of those patients with an alternate diagnosis, even fewer had a diagnosis identified for which there was a specific therapy indicated. Thus, in the vast majority of patients with DM and proteinuria, a renal biopsy is not necessary. If, however, the patient has any atypical clinical features as outlined above, a renal biopsy should be performed.

There are unique aspects to the management of the patient with DM and progressive renal insufficiency. Insulin requirements decrease in uremia, both because the kidney is responsible for 30 – 40% of the metabolism of insulin and the loss of appetite as renal function declines. Thus, the majority of patients on insulin will have decreased insulin requirements, and many Type II patients will

have decreased oral hypoglycemic requirements as ESRD nears. Further, many oral hypoglycemic agents are excreted by the kidney, and their half-life is prolonged in patients with renal insufficiency. Thus, it is important to counsel both Type I and Type II patients about hypoglycemia and to monitor their oral hypoglycemic or insulin use. Metformin is contraindicated in patients with serum creatinines greater than 1.5 mg/dL and cannot be used in patients with significant renal insufficiency.

DM is the most common cause of Type IV renal tubular acidosis, which results in hyperkalemia and a hyperchloremic metabolic acidosis. Thus, patients with this tubular transport defect can have an electrolyte pattern that is disproportionately abnormal for the degree of renal insufficiency.

Patients who develop nephropathy frequently have gastroparesis resulting from diabetic neuropathy. Symptoms of gastroparesis such as nausea and vomiting can mimic those of uremia.

It is important to evaluate patients with DM frequently to document the onset of diabetic nephropathy to allow optimal management and preventative measures. Avoiding excessive use of nonsteroidal anti-inflammatory agents, the unnecessary use of aminoglycoside antibiotics, and exposure to IV radiocontrast agents is important. Proper interventions for UTI and neurogenic bladder can also help preserve remaining renal function.

Patients with DM appear to require renal replacement therapy earlier than patients with other renal diseases. They have lower GFRs for any given serum creatinine than nondiabetic patients with renal insufficiency, most likely related to lower muscle mass. It is not uncommon for diabetics to be near ESRD with serum creatinines as low as 2 – 3 mg/dL. Diabetic patients have symptoms of uremia and require the initiation of renal replacement therapy at higher GFR levels than do patients with nondiabetic kidney disease. Choosing the best renal replacement therapy for diabetic patients is complex and requires the consideration of many factors, including their body habitus, vasculature, and extent of atherosclerotic disease and heart function. Lastly, patients with DM have a high prevalence of cardiovascular disease. Thus, transplant evaluation in these patients requires careful cardiac testing. Many of these patients with documented cardiovascular disease also have peripheral vascular disease, which can complicate their course. For all these reasons, dialysis teaching and transplant evaluation should begin early in patients with diabetic nephropathy.

Therapeutic Interventions

The major therapeutic interventions that have been evaluated for patients with diabetic nephropathy include antihypertensive therapy, treatment with ACE inhibitors, improved DM control, inhibitors of AGEs formation, the restriction of dietary protein intake, and treatment of dyslipidemia, as well as a variety of less well-studied interventions (Table 2).

Blood Pressure Control

A close correlation exists between the onset and degree of microalbuminuria and the onset and degree of hypertension. Similarly, the presence of hypertension in patients with proteinuria is associated with a more rapid decline in GFR. Multiple studies have shown that reducing the systemic blood pressure in

Table 2. Therapeutic Interventions in Diabetic Nephropathy

Proven Benefit	Possible Benefit
Blood sugar control Blood pressure control ACE inhibition	Low protein diet Treatment of dyslipidemia Smoking cessation Prevention of AGEs formation

diabetic patients with proteinuria and declining renal function slows the rate of decline of renal function and improves survival. These studies primarily used conventional antihypertensive agents, which at the time did not include calcium channel blockers or ACE inhibitors. Although the studies were performed with relatively few numbers of highly selected patients and achieved only modest blood pressure control, a clearly decreased rate of renal decline was observed. Similarly, in studies of patients with microalbuminuria, reducing the mean arterial blood pressure resulted in decreases in urinary albumin excretion rates. Even in normotensive patients with microalbuminuria, the lowering of systemic blood pressure was associated with decreased urinary albumin excretion.

The definition of adequate blood pressure control in patients with diabetic nephropathy has been unclear. The Fifth Joint National Commission defines high normal blood pressure as 140/90 mmHg, and physicians have traditionally used this as a blood pressure goal for patients with hypertension. A number of epidemiological studies indicate that the progression of renal disease correlates closely with increased systemic blood pressure. This effect was linear, with no lower threshold for the benefits of lower blood pressure. Recently, the Collaborative Study Group randomized patients with Type I DM and proteinuria to 2 levels of blood pressure control (a mean arterial blood pressure < 92 mmHg or to a mean arterial blood pressure of 100 – 107 mmHg) to better define the optimal blood pressure for preservation of kidney function. All patients in this study received an ACE inhibitor (Ramipril). Preliminary analysis of these results suggests that the lower blood pressure goal conferred greater benefit. Indeed, many of the patients with the lower blood pressure did not have demonstrable decline in renal function, but rather a regression in their degree of proteinuria, in some cases to near normal ranges. Thus, available data suggest that the blood pressure goals for protecting the kidney against progressive diabetic nephropathy may be lowered to mean arterial blood pressures < 92 mmHg.

In addition a reduction in urinary protein or albumin excretion might be an appropriate end point of antihypertensive therapy independent of its effect on systemic blood pressure. Several major studies in nondiabetic kidney disease demonstrate that an early reduction in urinary protein or albumin excretion predicts a long-term beneficial effect of the intervention. Thus, it has been suggested that antihypertensive therapy should be advanced as tolerated to help reduce urinary protein excretion.

ACE Inhibition

Data from experiments in diabetic rats first suggested that specific antihypertensive agents (ACE inhibitors) could preserve renal function and structure independent of their effect on systemic blood pressure. In these studies, glomerulosclerosis was only partially mitigated by the use of conventional antihypertensive agents, including hydralazine, re-

serpine and hydrochlorothiazide. However, with ACE inhibitors, albuminuria and glomerulosclerosis were ameliorated. The mechanism of protection was postulated to be the reduction of the tonic constrictor effect of Ang II on the efferent arteriole, leading to lower glomerular intracapillary pressures.

A number of studies were then conducted in humans with diabetic nephropathy. A meta-analysis of antihypertensive therapy in patients with diabetic nephropathy, showed only ACE inhibitors decreased proteinuria and preserved GFR independent of changes in systemic blood pressure.

A recently completed clinical trial of ACE inhibitors randomized 409 patients with Type I DM and proteinuria to receive either Captopril three times per day or placebo [13]. Patients enrolled in this trial had urinary protein excretion rates > 500 mg/day and serum creatinine concentrations ≤ to 2.5 mg/dL [13]. The primary outcome of the trial was the time to doubling of serum creatinine (to ≥ 2 mg/dL), representing a halving of the GFR. The use of Captopril led to a risk reduction of 48% for doubling of creatinine compared to the placebo group. Captopril was equally effective in reducing the risk of doubling of serum creatinine in normo- and hypertensive patients and in African American and Caucasian patients. Its efficacy was not explained by differences in baseline urinary protein excretion or follow-up mean arterial blood pressure. Importantly, patients receiving ACE inhibitors had a risk reduction of 50% in the combined clinical outcome of either death or ESRD. Again, this effect of ACE inhibitors was independent of any effect on systemic blood pressure. There were few adverse effects reported, with no ARF and only 6 hyperkalemic events. Thus, this study convincingly demonstrated that ACE inhibition is renoprotective in both normo- and hypertensive patients with Type I DM and clinically evident proteinuria.

Treatment in patients with early diabetic nephropathy characterized by microalbuminuria has also been demonstrated to have a beneficial effect [14]. Studies in patients with both Type I and Type II DM demonstrated that the use of ACE inhibitors leads to a decrease in the urinary albumin excretion with far fewer patients progressing to overt proteinuria. The consistent finding of a beneficial effect of ACE inhibitors in patients with microalbuminuria strongly suggests that these patients should be considered for such therapy to preserve their remaining renal function. Added benefits of ACE inhibitors are improved insulin sensitivity, and plasma lipid profile.

Far fewer studies have been performed examining the efficacy of calcium channel blockers in patients with diabetic nephropathy [15]. These studies were performed in small numbers of patients, most of whom had Type II DM. Recently, it has been suggested that a combination of ACE inhibitors and calcium channel blockers may be of additional benefit. Further investigation is needed to clarify the role of calcium channel blockers in the treatment of patients with DM and diabetic nephropathy.

Improved Blood Sugar Control

Intensive blood sugar control prevents the development of diabetic nephropathy and ameliorates established diabetic nephropathy in animal studies. In humans, the Stockholm Diabetes Intervention Study and the Diabetes Control and Complications Trial have now conclusively demonstrated that intensive blood sugar control in Type I diabetics can delay the development or slow the progression of diabetic nephropathy [16]. Patients in these trials achieved intensive blood sugar control ($HgbA_1C$ ~7.0%) with insulin deliv-

ered either by an insulin pump or by 3 or more injections daily. These patients had a dramatic decrease in the risk of developing microalbuminuria or progressing from microalbuminuria to proteinuria compared to the patients in the conventional therapy group who achieved hemoglobin A_1Cs of approximately 9%. Intensive blood sugar control in these studies not only dramatically reduced the risk of nephropathy, but also the risk of retinopathy and neuropathy. The chief adverse event associated with intensive therapy was a 2 – 3-fold increase in severe hypoglycemic episodes requiring assistance. These hypoglycemic episodes occurred in the intensive therapy group despite careful study management and support measures beyond what most clinics could provide. Secondary analysis of these studies demonstrated reduced nephropathy risk for any reduction in hemoglobin A_1C levels [17]. This reflects the absence of a threshold effect, indicating that any improvement in blood sugar control achievable in the routine clinical setting would reduce the risk of developing diabetic nephropathy. Thus, all patients with Type I DM should achieve the tightest blood sugar control that can be safely achieved in their clinical setting. In Type II diabetics, however, it has not yet been conclusively demonstrated that glycemic control confers a similar advantage. One relatively small study done in Japan has indicated a beneficial effect of tighter blood sugar control in the Type II population. Tight blood sugar control in this population is very difficult to achieve and may have more associated risks.

Prevention of the Formation of AGEs

It has been demonstrated that AGEs accumulate in tissues of diabetic patients and may, at least in part, be responsible for the end-organ complications of DM [5]. Aminoguanidine is a nucleophilic hydrazine compound that prevents the formation of AGEs and glucose-derived collagen crosslinks in vitro and in vivo. Its use in diabetic rats decreases albuminuria and glomerulosclerosis. Clinical trials using aminoguanidine in patients with Type I and Type II DM and established nephropathy are ongoing. This drug is currently available only in research settings.

Dietary Protein Restriction

In many experimental animal models of renal disease, including DM, high dietary protein intake accelerates the deterioration of renal function. Low-protein diets improve glomerular hemodynamics in animal models by vasoconstriction of the afferent arteriole, resulting in decreased glomerular intracapillary pressures. In humans with DM, low protein diets have been demonstrated to reduce glomerular hyperfiltration, decrease urinary albumin excretion, and slow the rate of decline of renal function. Although, individual studies in patients with DM have enrolled small numbers of patients, a recent meta-analysis supported the efficacy of low protein diets in patients with diabetic nephropathy [18].

Lipid-lowering Agents

Dyslipidemia is common in the diabetic state and worsened by coexistent diabetic nephropathy. Patients with poor glycemic control usually have hypertriglyceridemia. The presence of diabetic nephropathy is associated with higher levels of plasma low-density lipoprotein (LDL) cholesterol and lipoprotein B (Lp(b)), and lower levels of high-density lipoprotein (HDL) cholesterol. In

many animal models of kidney disease, dyslipidemia is implicated in causing direct renal injury and hastening the progression of established renal diseases. Treatment of dyslipidemia in these animals leads to reduced glomerular injury. In humans with diabetic nephropathy, hyperlipidemia has been identified as a risk factor for a more rapid rate of decline in GFR and increased mortality. Recently, several small uncontrolled preliminary studies in diabetic patients with proteinuric renal disease showed that treatment with β-hydroxy-β-methyl glutaryl-COA (HMG-CoA) reductase inhibitors can lead to a stabilization and improvement of renal function [19]. Because dyslipidemia is closely related to the progression of cardiovascular disease, and highly prevalent in diabetics, lipid-lowering agents are recommended, irrespective of their potential effect on diabetic nephropathy.

Miscellaneous Interventions

Smoking is an important risk factor for the development and progression of both diabetic nephropathy and atherosclerotic disease. Smoking cessation is an important part of the management of all diabetics.

A variety of other pharmaceutical interventions have been applied to a small number of patients in preliminary studies or in animal models. Pentoxifyline decreased microalbuminuria and proteinuria in Type I patients in a placebo-controlled trial. This drug induces membrane changes that increase erythrocyte deformability, reducing blood viscosity. Similarly, dipyramadole has been shown to decrease urinary albumin excretions in Type I patients with microalbuminuria. Octreotide, a somatostatin analogue, reduced GFR and kidney size in 11 patients with Type I DM and glomerular hyperfiltration. It has also been shown to decrease urinary albumin excretion and renal hypertrophy in rats with streptozotocin-induced DM. Although the potential mechanism of the beneficial effect is unknown, it may be mediated by inhibition of insulin-like growth factor-1.

Lastly, DM has been characterized by an increase in plasma levels of thromboxane B_2. Thromboxane synthetase inhibitors significantly lower urinary protein excretion in diabetic rats. In a recent randomized, double-masked, placebo-controlled trial in 30 patients with DM and microalbuminuria, picotamide (a dual antithromboxane ag-coent that inhibits thromboxane synthetase and blocks the thromboxane receptor) significantly lowered urinary albumin excretion compared to placebo.

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This clinical trial is a conclusive demonstration that intensive glycemic control decreases the risk of developing diabetic nephropathy in patients with Type I DM

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The clinical trial reported in this paper demonstrates the dramatic efficacy of ACE inhibitors in slowing the progression of renal insufficiency in patients with Type I DM and diabetic nephropathy.