A REVIEW OF THE CURRENT TREATMENT MODALITIES FOR DIABETIC NEPHROPATHY

Interview with Ralph Rabkin, MD

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A senior clinical editor for Advanced Studies in Medicine (ASiM) interviewed Dr Rabkin to discuss the importance of early screening and the current treatment modalities for diabetic nephropathy.

ASiM: Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD), thus early detection and institution of treatment would seem important. What is the earliest manifestation of diabetic renal involvement that can be detected in clinical practice?

Dr Rabkin: The most sensitive clinical marker of renal involvement in diabetes is an increase in excretion of albumin in the urine. Keeping in mind the fact that healthy humans excrete at least 10 to 20 mg of albumin a day, an increase in albumin excretion to between 30 to 300 mg/day signifies incipient nephropathy and is referred to as microalbuminuria. This amount of protein is undetectable with urine dipsticks and requires more sensitive laboratory tests. When the urine albumin excretion exceeds 300 mg a day, it becomes dipstick detectable in concentrated urine and signifies clinical nephropathy and is referred to as macroalbuminuria.

The most reliable way to quantify albumin excretion is the use of timed urine collection over 24 hours. A more practical and preferred way is to screen patients with diabetes by collecting a random urine sample to measure the concentration of albumin and creatinine, then express the values as the amount of albumin excreted per gram of creatinine. When the excretion ratio exceeds 30 mg albumin per gram creatinine, it suggests that total 24-hour albumin excretion is above 30 mg and microalbuminuria is present. Clinicians should remember that there are normal variations in urine albumin excretion, thus before accepting this as a marker of incipient nephropathy, a urine collection must be repeated on at least 2 or 3 occasions over several months. For example, after exercise, albumin excretion tends to increase in healthy subjects and, when fever is present, albuminuria may increase.

Another consideration when calculating the albumin creatinine excretion ratio is the patient’s muscle mass because the amount of creatinine generated for excretion is dependent on muscle mass. Therefore, if you are treating an elderly patient whose health is deteriorating, the albumin excretion may be overestimated because of reduced creatinine generation and excretion. The converse also applies; in a muscular young man, albumin excretion may be underestimated.
because of the normally large amounts of creatinine excreted in this type of individual.

In addition to being a general marker of glomerular damage or dysfunction, there is evidence of an association between microalbuminuria and cardiovascular disease, even in apparently healthy subjects. The risk of cardiovascular events increases with the absolute level of microalbuminuria. Therefore, if microalbuminuria is detected in a patient with diabetes, it may also reflect an increased risk for vascular disease. Accordingly, it is prudent to screen these patients when first seen, not only for renal disease but also for vascular disease.

Microalbuminuria can be stabilized or abolished with tight glycemic and blood pressure control because it may not actually reflect structural damage but may instead be caused by reversible functional changes. The most effective agents are the inhibitors of the renin-angiotensin system, and these agents should be prescribed for patients with microalbuminuria, even if they are normotensive.

AS\textsuperscript{1}M: Because the key to the development of diabetic nephropathy is the hyperglycemic state, what effect does glycemic control have on the development and progression of the nephropathy?

Dr Rabkin: It is well established that therapy using strict glycemic control in patients with diabetes who don't have diabetic nephropathy reduces the risk of developing this disease. This was first established in 2 major studies: the Diabetes Control and Complications Trial (DCCT) in the United States, and the UK Prospective Diabetes Study (UKPDS) in the United Kingdom. In the DCCT study, patients were observed for a mean of 6.5 years, and tight glycemic control reduced the appearance of microalbuminuria by 39% and overt proteinuria by 54%. Recently, a DCCT follow-up study of 8 years was published, comparing patients who had intensive therapy with patients who did not. The investigators found that although the glycemic control had been relaxed over the course of 8 years (to the level of conventional therapy), the beneficial effects of intensive therapy on the kidneys persisted. In addition, fewer of these patients developed hypertension. The reason for this salutary outcome is as yet unknown, but it may be that these patients were protected during the period of intensive insulin therapy and the progression to nephropathy was merely delayed by that period of time. If this is the case, then with relaxation of glycemic control the manifestations of nephropathy would be expected to eventually appear. I should point out that there is some evidence that euglycemia can lead to amelioration of the glomerular lesions over time, as shown in a study of a small group of patients with type 1 diabetes mellitus who received pancreatic transplants.

AS\textsuperscript{1}M: What are the general goals of pharmacologic treatment in diabetic nephropathy and when should treatment be initiated?

Dr Rabkin: The overall goal of pharmacologic therapy in diabetes is to prevent the development and progression of renal injury and to avoid the adverse effects of renal failure and the complications of diabetes, such as cardiovascular disease. The mainstay of early treatment is aggressive control of the glycemic state because this may prevent or delay the onset of microalbuminuria, reverse or reduce this condition when present, and possibly even slow the progression of established renal disease.

Another important goal of pharmacotherapy is aggressive control of blood pressure, and the reason is quite obvious: high blood pressure leads to more rapid progression of diabetic nephropathy, apart from its deleterious effect on the cardiovascular system. Hypertension is common in kidney disease caused by diabetes mellitus: among patients with type 1 diabetes, it is present in up to 50% of patients with microalbuminuria and in 90% of those patients with macroalbuminuria. Among patients with type 2 diabetes mellitus, the percentages are even greater.

The good news for patients with diabetes with hypertension is that in addition to reducing the risk for cardiovascular disease and retinopathy, aggressive treatment of hypertension can modify the progression of kidney disease caused by diabetes mellitus. Therefore, the blood pressure must be monitored in patients with diabetes whenever they come for an office visit, including patients who do not have any renal manifestations in addition to those patients who do.

Antihypertensive therapy must be especially aggressive in patients with diabetes because they have a high rate of cardiovascular complications and because of the established benefit of controlling blood pressure on the progression of renal disease caused by diabetes mellitus. The recommended blood pressure goal is 130/80 mm Hg; however, in those patients who have proteinuria, blood pressure level should be lower to reduce proteinuria to less than 1 gm/day. However, I wouldn't recommend that blood pressure level be below approx-
imately 100 mm Hg systolic. The clinical guidelines formulated by the National Kidney Foundation, which are available on the Internet, are especially helpful in this respect.

All patients with diabetes who have a systolic blood pressure above 140 mm Hg require an antihypertensive agent. Usually more than one agent is required, and an agent that blocks the renin-angiotensin system should be included. For patients with a systolic blood pressure reading between 130 to 140 mm Hg or diastolic pressure between 80 to 90 mm Hg, the initial recommendation could be a lifestyle modification for a few months, but if the target blood pressure of 130/80 mm Hg is not achieved, then initiating antihypertensive therapy with pharmacologic agents is indicated. When microalbuminuria or macroalbuminuria is detected, agents that block the renin-angiotensin system should be prescribed, even if the patient is not hypertensive.

Another therapeutic goal is reducing proteinuria because there is increasing evidence indicating that apart from being a marker of glomerular injury, exposure to high concentrations of filtered proteins produces a tubulointerstitial inflammatory response that can lead to interstitial fibrosis and progression of the nephropathy. This response has been demonstrated in animal models; epidemiologic studies in humans seem to confirm this suspicion. Proteinuria can be reduced with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB). These drugs are effective in reducing proteinuria in hypertensive and normotensive patients with diabetes. Therefore, the benefit of these agents may be more than is achieved from simply lowering blood pressure. With ACE inhibitors, the tighter the blood pressure control, the greater the decrease in proteinuria.

Other agents, such as the nondihydropyridine calcium channel blockers (non-DCCB), have also been effective in reducing proteinuria in patients with type 2 diabetes mellitus. Although the medical community generally assumes that a reduction in proteinuria predicts long-term improvement in the renal outcome of diabetic nephropathy, this still remains to be established.

Another important goal of pharmacotherapy is to control the hyperlipidemia that is common in the diabetic population and is worsened by the development of renal failure, especially if proteinuria is heavy and features of the nephrotic syndrome are present. Unfortunately, this aspect of treatment is often neglected. Apart from the adverse cardiovascular effects of hyperlipidemia, there are several animal studies indicating that hyperlipidemia can lead to the development of glomerulosclerosis in the nondiabetic state. In patients with diabetes, high serum cholesterol levels are associated with a more rapid decline in renal function. Therefore, aggressive management of hyperlipidemia, including the administration of statins and other antihyperlipidemia agents, is indicated.

AS/M: Please discuss the existing antihypertensive renoprotective therapies that are available in terms of their effectiveness, safety, and tolerability and the limitations or drawbacks of these agents.

Dr Rabkin: There are many antihypertensive agents that are effective in controlling the blood pressure of patients with diabetes, including the ACE inhibitors, ARBs, diuretics, β blockers, α blockers, and the non-DCCB agents.

There are few studies directly comparing the renoprotective effects of different antihypertensive agents, but what has been established is that the ACE inhibitors and the ARBs can actually delay the onset and slow the progression of renal injury. Furthermore, in addition to their renoprotective effect, the ACEs and ARBs offer some protection against the other microvascular and vascular complications of diabetes mellitus. Therefore, the use of ACE inhibitors or ARBs as first-line agents in most patients with diabetes is widely recommended.

The seminal study of an ACE inhibitor (ie, captopril) was carried out more than a decade ago and demonstrated the effectiveness of ACE inhibition in slowing the progression of diabetic nephropathy in type 1 diabetes mellitus. Proteinuria was lessened and the endpoints of doubling the serum creatinine level, the mortality rate, or need for dialysis were all reduced by 50%. Subsequently, there have been several other studies that have confirmed this advantage in patients with type 1 diabetes mellitus.

For patients with type 2 diabetes mellitus, there are no comparable large studies involving ACE inhibitors, but there have been recent trials with ARBs (ie, losartan and irbesartan) that established the value of this class of agents.1 In patients with microalbuminuria, irbesartan attenuated the progression from microalbuminuria to macroalbuminuria. In patients with established diabetic nephropathy, the relative risk of time to doubling the creatinine level was reduced by 25% and development of ESRD was reduced by 28% by using...
losartan; creatinine level was reduced by 33% and ESRD by 37% by using irbesartan. Both agents were effective in lowering proteinuria values.

Based on the data available, an ACE inhibitor is the preferred agent for patients with type 1 diabetes mellitus, and an ARB is preferred for patients with type 2 diabetes mellitus, even in normotensive patients. However, either agent can be prescribed as an alternative if the preferred agent cannot be used. There are several other hypertensive agents, including diuretics and β blockers, that may also modify the course of diabetic nephropathy, but their true value has not been evaluated in large-scale studies.

Because the natural history of diabetic nephropathy can be significantly modified by antihypertensive therapy, treatment should be especially aggressive in the hypertensive patient with diabetes when microalbuminuria or macroalbuminuria is present. If the target blood pressure of less than 130/80 mm Hg cannot be achieved with an ACE inhibitor or an ARB, a diuretic should be added to the patient’s treatment regimen. If necessary, a β blocker or non-DCCB also should be added (a non-DCCB is preferred because there is still some question regarding the safety of DCCBs). If proteinuria doesn’t fall below 1 gram albumin per gram creatinine, then the blood pressure should be lowered even further by increasing the ACE inhibitor or ARB dose or by using an ACE inhibitor and an ARB in combination. Alternatively, in patients with type 2 diabetes mellitus, a non-DCCB such as diltiazem can be added because this agent can reduce proteinuria in these patients.

ASiM: Please comment on the potential renoprotective effects that combining existing therapies that interrupt the renin-angiotensin system may have on improving outcomes in the treatment of diabetic nephropathy.

Dr Rabkin: There is sufficient evidence from studies of patients with chronic renal disease who do not have diabetes that combining an ACE inhibitor with an ARB affords better renoprotection than either agent alone. The data pertaining to diabetic renal disease are somewhat limited, but they do suggest that dual blockade is more effective than either agent alone. However, until the true value of combination therapy is established, the current recommendation for renoprotection, as measured by a reduction in proteinuria, is to use one of these agents alone at the maximum dose; the other agent should be added only if proteinuria fails to decrease to below 1 g/g creatinine level.

ASiM: Each of the agents discussed is an antihypertensive drug designed to lower blood pressure and diminish effects on the kidneys. Is there a place for the use of any of these agents in the management of diabetic nephropathy in the absence of hypertension?

Dr Rabkin: Yes. The aim of using an ACE inhibitor or an ARB is to reduce protein excretion, regardless of whether the patient is hypertensive or normotensive. The dose of the ACE inhibitor or the ARB may be increased to the highest level the patient can tolerate. Clinicians must remember that in blocking the renin-angiotensin system, there is a predisposition to hyperkalemia and a falling glomerular filtration rate (GFR). The patient must be monitored closely, especially when treatment is initiated.

ASiM: What role, if any, does diet and exercise have in the management of diabetic nephropathy?

Dr Rabkin: In addition to pharmacotherapy, the management of patients with diabetes with kidney disease should include attention to lifestyle modification, including weight loss, protein and sodium restriction, moderate exercise, reduction of alcohol consumption, and smoking. Exercise improves insulin sensitivity, lowers blood pressure, and improves the lipid profile. Sodium restriction is important for blood pressure control and to maximize the antiproteinuria effect of the ACE inhibitor. Smoking, apart from its primary cardiovascular effect, has a direct adverse effect on the kidneys. Clear benefits of dietary restriction have not been established, but there are some small clinical studies suggesting that protein intake reduction may reduce the proteinuria and slow the progression of the disease. Accordingly, it would be prudent to restrict protein intake in patients with diabetes and nephropathy. Of course, there are dietary limitations of fat and carbohydrates already imposed on the patient, thus a moderate restriction to approximately 1 g protein/kg/day would be reasonable. If there is progression of renal disease, protein intake could be reduced modestly to approximately 0.8 g/kg/day. Therefore, in addition to pharmacotherapy, optimal management of diabetic nephropathy includes an approach that is directed at several lesser factors contributing to the development and progression of the disease.
ASiM: Is there a need for a different and more effective treatment for diabetic nephropathy?

Dr Rabkin: Yes, definitely. Although considerable progress has been achieved in the management of diabetic nephropathy, once the nephropathy is established, current therapy at best only delays or slows the progression of the disease, and many patients will eventually develop end-stage kidney failure.

Diabetic nephropathy remains by far the predominant cause of ESRD. Therefore, we still have a long way to go to prevent or to completely arrest this disease.

Several agents that inhibit different pathologic processes in the kidneys of patients with diabetes are under intense preclinical or early clinical study, including agents that inhibit protein kinase C (PKC), transforming growth factor-β, cyclooxygenase-2 (COX-2), the growth hormone receptor, formation of advanced glycation end-products, and fibrosis. This long list of agents, albeit incomplete, reflects the anticipation that no single agent will be effective therapy alone. A combination of agents directed at different processes are required for truly effective therapy.

ASiM: Please discuss the emerging therapeutic class (ie, PKC-β inhibitors) and their role in filling the treatment gap.

Dr Rabkin: This is an interesting and promising class of therapeutic agents. The PKCs are a family of multifunctional enzymes that play a key role in signal transduction and intercellular communication. Increased activation of the isoform PKC-β has been implicated in the pathogenesis of diabetic nephropathy. Several diabetic rodent studies have shown that the PKC-β inhibitor ruboxistaurin mesylate, even with persistent hyperglycemia and hypertension present, normalizes glomerular hyperfiltration, reduces albuminuria, and attenuates the structural damage to the kidney while reducing loss of kidney function. Apart from its role in the development of diabetic nephropathy, PKC has also been implicated in other diabetic microvascular complications. Encouraged by animal studies and small clinical studies, large-scale clinical studies of PKC-β for the treatment of diabetic nephropathy, diabetic neuropathy, and diabetic retinopathy are in progress. The results of these studies are eagerly awaited.

ASiM: Are there any special considerations in the management of the patient with diabetes with impaired kidney function?

Dr Rabkin: Yes, there are certain considerations the clinician must keep in mind. When intensive antihypertensive therapy is initiated, lowering of the patient’s blood pressure may often lead to a hemodynamic decline in GFR during the early months of treatment. However, treatment should only be modified if the serum creatinine level rises more than 30% over baseline because this initial fall in renal function reflects a lowering of intraglomerular pressure that may actually be renoprotective and is reversible.

Careful monitoring of the serum K+ is important in the patients with diabetes in whom the renin-angiotensin-aldosterone system is interrupted with pharmacologic agents, especially in those patients with impaired renal function and hyporeninemic-hypoaldosteronism. Nonsteroidal anti-inflammatory drugs, COX-2 inhibitors, K supplements, and K-sparing diuretics should be avoided. Diuretics should be used with special care to avoid dehydration. Hyperkalemia should be treated by discontinuation of any of the K-elevating agents discussed in this clinician interview, by reducing dietary K intake and, after correcting any volume depletion that may have reduced renal function, by the careful use of diuretics. The ACE/ARB inhibitor should be discontinued and, when the serum K is normalized, the drug may be cautiously reintroduced at a lower dose with careful monitoring of the serum K and creatinine levels.

Because drug pharmacokinetics may alter as renal function falls, the clinician must review whether drug dosage must be modified. For example, the half-life of insulin is prolonged in renal failure and insulin requirements may fall as kidney function declines, necessitating a reduction in dosage. Metformin is another example of a drug often prescribed for the patient with diabetes that accumulates in renal failure. As drug accumulation increases the risk of lactic acidosis, metformin should be discontinued when the patient’s serum creatinine is elevated above 1.5 mg/dL in males, above 1.4 mg/dL in females, or when a GFR is less than 60 to 70 mL/min.

Renal failure in patients with diabetes may also arise from nondiabetic kidney disease, and nondiabetic kidney disease may be superimposed on diabetic nephropathy. This consideration often arises in the patient with recent-onset type 2 diabetes mellitus and
with evidence of renal disease. An example is the older man with diabetes mellitus in whom a decline in renal function may reflect an obstructive uropathy caused by prostatic hypertrophy; an ultrasound examination to exclude obstruction may be required. An examination of the retina can alert the physician of this condition because retinopathy eventually develops in most patients with diabetes with long-standing advanced diabetic nephropathy. The absence of retinopathy in patients with diabetes with overt renal disease raises the question as to whether the disease is caused by diabetes, and a more extensive workup may be indicated.

REFERENCES

