

Facilitating Diabetic Care:

Linking Endocrinology and Nephrology

Endocrinologists and diabetologists should focus on disease development much earlier on.

BY MARK E. MOLITCH, MD

As endocrinologists and diabetologists, we are used to treating diabetic patients early in their disease progression. We screen patients for microalbuminuria, and we know that we also have to screen for serum creatinine. We are efficient at controlling blood pressure by instituting treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs).

But what about when the development of the disease progresses in between our comfort level and when the nephrologist sees the patient? These patients still have a fairly well maintained glomerular filtration rate (GFR), however they may develop secondary hyperparathyroidism and anemia. I think we can help our patients by focusing on these areas of disease development much earlier.

PREVIOUS TRIALS

In the United Kingdom Prospective Diabetes Study (UKPDS), patients with no sign of nephropathy had about a 2% annual risk of developing microalbuminuria and a 1.4% annual risk of mortality. As patients begin to develop kidney disease, it becomes equal in terms of those who will die and those who will progress to albuminuria. As GFR falls, patients die at a greatly increased rate compared to patients progressing to end stage renal disease (ESRD). This accounts for the fact that many patients die before they reach the dialysis unit.

We need to delay the progression of diabetic nephropathy once it begins. This can be achieved through glycemic and BP control, blockade of the renin angiotensin aldosterone system, protein restriction and perhaps anemia therapy.

Data from the UKPDS, the Diabetes Control and Complications Trial (DCCT) and the Kumamoto study have shown marked improvement in the progression and development of diabetic complications with glycemic control.

A number of studies have also shown that the rate GFR falls becomes much more shallow as antihypertensive treatment is instituted. With a goal blood pressure of 130/80 mm Hg, the rate of fall of GFR is quite low, and perhaps if we can blood pressure down to 125/75 mm Hg it may be very slow indeed.

Including ACE inhibitors and ARBs in diabetes treatment has a substantial additional benefit to lowering blood pressure. They have been shown to decrease the rate of progression of diabetic kidney disease as well reduce heart disease in these patients who are at such high risk for both.

The ATP guidelines (Adult Treatment Panel III) stated that LDL cholesterol should be <70 mg/dL for those who are at high risk for coronary artery disease. I can't think of any group at higher risk for coronary artery disease than a diabetic patient with progressive chronic kidney disease (CKD).

Anemia is prevalent in patients with CKD. Many patients we see in the office have serum creatinines of 2, 2.5 or 3 mg/dL. In the past, some of us may not have been overly concerned about creatinine levels in this range, as it was understood that anemia is most likely attributable to CKD.

Anemia is, however, a real problem for patients. When tissues are deprived of oxygen, complications may occur. A hemoglobin reduction by one-third causes a compensatory increase in cardiac output that results in an increase of left ventricular hypertrophy. Progressive cardiac damage as well as progressive kidney damage may result from anemia.

One study looked at nondiabetic patients with modest CKD (serum creatinine 2.4 mg/dL) who also had heart failure (average NYHA class 3.8) and anemia (hemoglobin 10.3 g/dL). These patients were treated with an erythropoietin agent to increase hemoglobin levels to 13.1 g/dL. While creatinine levels did not change, GFR improved slightly in the rate of fall, and there was a very significant improvement in heart failure and quality of life.

TABLE 1. ENDOCRINOLOGIST GOALS FOR TREATING CKD PATIENTS

- Lower blood pressure to <130/80 mm Hg
- Use drugs that are active in the renin angiotensin aldosterone system
- Reduce proteinuria
- Improve glycemia control to <7%
- Lower LDL to < 70 mg/dL
- Treat anemia
- Treat elevated parathyroid hormone levels
- Patients at risk for CHD should use aspirin

The RENAAL trial (Reduction of Endpoints in Non-Insulin Dependent Diabetes Mellitus with Angiotensin II Antagonist Losartan) studied losartan in the treatment of progressive kidney disease in patients with type 2 diabetes. Patients were stratified according to hemoglobin, and researchers found that the rate of progression to ESRD was higher in the group that had the lowest hemoglobin levels.

There is a push to be aggressive in anemia treatment. From a nutritional point of view, we have to make sure that these patients are getting enough iron and that they are not folate or B12 deficient. We may consider erythropoietin therapy for these patients, which may give us the ability to reverse the development of LVH, improve cardiovascular symptoms, and reduce mortality and morbidity.

INCREASING HEMOGLOBIN

We aim for a target hemoglobin of 11 to 12 g/dL with our therapy, increasing the hemoglobin by about 1 g/dL per month. Iron and folic acid deficiency may occur over the course of treatment so we have to look for it. Hypertension is usually not a major problem.

Another issue we have ignored as endocrinologists and should not be ignoring is problems with calcium, vitamin D and bones. Vitamin D has to be hydroxylated in the liver into 25-hydroxy vitamin D and that gets further hydroxylated at the 1 position to 1,25-Dihydroxy vitamin D in the kidney.

As patients develop progressive kidney disease they develop secondary hyperparathyroidism due to changes in 1,25 Dihydroxy vitamin D, calcium and phosphorus. While hypocalcemia and the increase in serum phosphate occur later in disease development, the decrease in 1,25-Dihydroxy vitamin D occurs early.

We often see patients who already have low 25-hydroxy vitamin D levels. This is a subclinical vitamin D deficiency that is quite common in the diabetic population and in the older general US population. We have to look for this in patients who are developing kidney disease.

As glomerular filtration rates (GFRs) drop down to the 40 to 60 mL/min/1.73 m² range, 1,25-dihydroxy vitamin D levels fall, and about 30% to 50% of patients will develop secondary hyperparathyroidism. The fall in activated vitamin D occurs long before phosphate retention and hypocalcemia. The secondary hyperparathyroidism along with vitamin D deficiency causes a decrease in bone mineral density (BMD) that translates to an increase in fractures. There is a fourfold increased fracture risk among patients on dialysis.

We have to start much earlier to check parathyroid hormone levels and treat secondary hyperparathyroidism in our diabetic patients.

We can treat these patients with a 1-hydroxylated activated form of vitamin D. Calcitriol has been around for over 25 years and there are others that may be used. Paracalcitol has been used to treat ESRD patients on dialysis. Recently, it was approved to treat patients with stage 3 or 4 CKD. Activated vitamin D analogs are also effective for increasing BMD.

Vitamin D may also have an effect on mortality. A very large retrospective analysis of vitamin D treatment in patients on dialysis found that those getting vitamin D had an improved mortality rate compared to those who were not getting vitamin D. This is something we currently do not fully understand, but there may be more to vitamin D than just effects on calcium and bone.

Treatment goals for secondary hyperparathyroidism are to correct 25-hydroxy vitamin D deficiency and control serum phosphate levels when they start to increase. We want to treat patients with vitamin D to reduce the elevated parathyroid levels, which prevent bone loss and improve survival.

When should diabetologists and endocrinologists refer patients to nephrologists? When we make the diagnosis of diabetic nephropathy we ought to know what we are dealing with. If there is something out of the ordinary with a patient, then we should consider referral.

If a complication presides in a patient that we are not comfortable in dealing with, no matter what it is, then it is time for a referral. It is important to remember to continue to be active in the management of the patient once they come under the care of a nephrologist. We must continue to manage the other diabetic complications as well. ■

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Practical implementation - facilitating medical care: Linking endocrinology and nephrology. Presented