

Diabetic Nephropathy - Misreading the Tea Leaves?



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One of the most feared complications of diabetes is kidney disease, also called diabetic nephropathy (DN). DN is the leading cause of end-stage renal disease in the U.S., and the incidence of DN is poised to double over the next ten years due to the rapid rise in the number of cases of diabetes, particularly type 2 diabetes. The expected cost of this problem is expected to top \$28 billion. Keep in mind that this is not the cost of treating diabetes per se, but only this single complication. This is a BIG issue.

Most of what we know about DN comes from observations made in patients with type 1 diabetes, and we have tended to extrapolate what we have learned from that condition to type 2 diabetes. As we will see, this may not have been a completely valid approach. At any rate, the course of DN is believed to begin with the spillage of small amounts of a blood protein called albumin into the urine. The kidney contains millions of structures called glomeruli; you can think of each glomerulus as a filter, similar to the fuel or air filters in your car. Water, salt, and other small molecules can pass freely into the urine, but larger things, like red blood cells and proteins, are kept in the bloodstream. In diabetes, the filtering function of the glomeruli fails, and albumin begins to show up in the urine. At this stage, the problem is called microalbuminuria. Over time (usually years), if things go untreated, progressively more protein will get through the filters until a level is reached called macroalbuminuria, or overt nephropathy.

Despite the leaky filters, up to this point the kidneys are still functioning fine, in that they are clearing the blood of toxins that build up during metabolism. Once you reach a state of overt nephropathy, however, things tend to go south, and many folks (but not all) will experience a progressive loss of kidney function until end-stage renal disease occurs. From that point on, patients will require dialysis or kidney transplantation to survive.

In the clinic, we screen for the appearance of DN and monitor its progression by measuring albumin levels in the urine, using either "spot" urines (collected in a cup at the time of the visit), or more accurately, timed collections that range from 4 to 24 hours. We do this because (a) monitoring the course of DN can help patients and physicians prepare for the possibility of end-stage renal disease, (b) cardiovascular complications of diabetes are more common and more severe in patients with DN, and (c) there are things you can do to prevent DN from showing up, or, if already present, from getting any worse. For example, it has been shown that tight blood glucose control can prevent the onset of DN or delay its progression. Similarly, careful attention to blood pressure control is also important, as are two specific classes of antihypertensive agents called ACE inhibitors (ACE-I) and angiotensin receptor blockers (ARBs). Interestingly, these drugs appear to be useful in DN even if the patient does not

have high blood pressure. Finally, there is some evidence that eating a protein-restricted diet can reduce the progression of DN, although this is less well supported than the other strategies.

In the last few weeks, two new studies have appeared that question some of the most basic assumptions that we have had about DN. There is good news and bad news, and because I prefer getting bad news out of the way first, we'll start with a study just published in the *Journal of the American Medical Association (JAMA)*. This report looked at a little over a thousand adults with type 2 diabetes, and asked what percentage of them had a serious loss of kidney function without showing the telltale signs of protein in the urine that define DN. Thirteen percent of these folks had a serious reduction of kidney function. What was amazing, however, was that roughly a third of those unlucky 13% had no evidence of albumin in their urine, which means that they would have been missed by our current screening approaches. Furthermore, in type 1 diabetes, the presence of DN is almost invariably associated with diabetic retinopathy, or eye disease. In these patients with type 2 diabetes, however, that was not the case, with only 28% of the patients with kidney damage showing signs of retinopathy. The authors interpret these results to indicate that the classic pathological mechanisms that cause DN in type 1 diabetes may not explain what's going on in type 2 diabetes. Other insults that might be contributing to the loss of kidney function in type 2 diabetes could include age-related changes, atherosclerosis of the arteries leading to kidneys, or possibly cholesterol emboli. This latter condition occurs when little fragments of cholesterol-laden plaques inside blood vessels break off and clog small arteries in the kidney (or elsewhere), leading to lack of proper blood flow and the death of large parts of the affected kidney. Regardless of what's going on, the suggestion here is that physicians should not rely solely on urine protein levels and the presence of diabetic eye disease to diagnose kidney disease in people with diabetes. Instead, a blood test and subsequent calculation that allows physicians to estimate the creatinine clearance, a measure of renal function, should also be used.

Now for the good news. A study in the *New England Journal of Medicine* shows that close to 60% of type 1 diabetes patients who have been given the diagnosis of microalbuminuria can display regression of the levels of protein in their urine. This is in sharp contrast to what has traditionally been felt to be the strictly progressive nature of DN. As mentioned earlier, we knew that interventions like good glucose and blood pressure control could prevent the onset or delay the progression of DN, but it was widely believed that once you have it, the horse is out of the barn, and not much could be done to make it go away. The people who were the most likely to see regression of their albuminuria were those who had not had DN for very long, and who had hemoglobin A1c levels less than 8% and good blood pressure and cholesterol levels.

These two papers show us that we have lots to learn still about even the most basic and timeworn questions in diabetes care. DN has been studied extensively for years, yet we can still find out remarkable things that will definitely change

the way we treat people with this condition. We will need to include measures of renal function outside of simple urine protein determinations in our screening tests, for one thing. The thought that we may have been missing up to a third of all cases of poor renal function in our diabetic patients is mortifying, and we simply must do better on that front. But we have also learned that, in type 1 patients at least, there are things that can push back the clock on DN, and patients can still heed the clarion call for better glucose and blood pressure control even after the diagnosis is made.

References:

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