

Diabetic Kidney Disease: A Review of the Science

Diabetes amplifies both chronic kidney disease and the cardiovascular disease paradigms.

BY KATHERINE R. TUTTLE, MD

Diabetic kidney disease is an important clinical problem. From a diabetes perspective, it is one of the most common microvascular complications, affecting about 30% of patients with type 1 diabetes and 40% of those with type 2. From a nephrology standpoint, diabetic kidney disease is the most common cause of end stage renal disease (ESRD), and is responsible for 43% of incident patients and 55% of prevalent patients. In other words, more than half of all patients on dialysis or who have had a kidney transplant have diabetes – and almost all of them have type 2 diabetes.

Kidney disease also progressively amplifies cardiovascular disease (CVD) risk. In fact, in diabetes, much of the excess CVD risk occurs in the subset of patients with chronic kidney disease (CKD). I believe this has been a widely underappreciated phenomenon.

The Kidney Disease Outcomes Quality Initiative (K/DOQI) staging system for CKD is used no matter what the underlying cause of kidney disease. It is also important to recognize that staging is done by glomerular filtration rate (GFR).

PREVALENCE, CKD AND CVD

The prevalence of CKD, where half of all cases are caused by diabetes, totals some 20 million people. This is an extremely common – though largely under recognized – problem. The prevalence drops off dramatically between stages 3 and 4, from 7.6 million patients to 400,000. Why? Most of these patients die from CVD and never reach ESRD.

In type 2 diabetes, survival curves drop off progressively when levels of proteinuria increase. This is accounted for by increasing rates of both stroke and cardiovascular (mostly coronary) events. When we think about diabetes and CKD and the progression to ESRD, we also have to be concerned about CVD and high rates of death. Diabetes amplifies the CKD and CVD paradigm. Stages of CKD parallel stages of CVD; so that when GFR is falling there is a very high rate of CVD events. If we have more CVD survivors, we are going to have more people at ESRD unless treatments for CKD are implemented earlier.

At the onset of hyperglycemia, there is a seeming paradox of high GFR. This is maladaptive, largely caused by increased pressure in the glomerulus which drives filtration at this time. This condition leads to structural damage to cells, progressing to glomerular sclerosis. As this damage is occurring, many patients will have high or normal GFR, but we are concerned about people when high GFR begins to drop into the normal range. This may indicate disease progression, especially if blood pressure is rising and albuminuria begins to appear in the urine. Note that this rise in blood pressure does not mean overt hypertension, especially in type 1 patients. Rising blood pressures often herald the onset of CKD.

The glomerulus is where much of the action in diabetic kidney disease takes place. It's a corollary circulation that is quite unique in its anatomic structure, in that it has an artery on both afferent and efferent ends.

As such, you can view it as arterialized circulation; the mean arterial pressure in these capillaries is 50 to 60 mm Hg, where as in most capillary circulation it would be 10 to 15 mm Hg. Therefore, the glomerulus is very susceptible to pressure-related injury.

HYPERFILTRATION HYPOTHESIS

The so-called hyperfiltration hypothesis has been around for a long time. While it does not explain all of the disease, it is a very important mechanism in the progression of kidney disease.

Hyperfiltration leads me to what I think is the most important nutritional issue related to diabetes and kidney disease, the effect of dietary protein. It has been known for some 50 years that high-protein diets cause glomerular hyperfiltration. We know this is a major mechanism of injury because hyperfiltration is driven by hypertension in the glomerular capillaries, even in the presence of normal systemic pressure. Diabetic kidneys are particularly sensitive to hemodynamic disturbances. High-protein diets activate the renin-angiotensin system with increased angiotensin 2 levels.

In a study our group did years ago, we looked at the sensitivity of the diabetic kidney to increased amino acids that

TABLE 1: STAGES OF CKD

Stage	Description	GFR (mL/min/1.73m ²)
1	kidney damage with normal or rising GFR	≥90
2	kidney damage with mild falling GFR	60-89
3	moderate falling GFR	30-59
4	severe falling GFR	15-29
5	kidney failure	<15 or dialysis

basically replicate a protein meal. In this study, when amino acids were infused, GFR rose predictably in normal patients by about 30% but the diabetic patients had a double response (60% GFR). We have replicated this data over and over through the years, its true in type 1 and type 2 patients.

FEEDING HORMONE

We and others have studied whether there is a hormone released in protein feeding that causes the hemodynamic changes. There was a lot of experimentation done, for example with octreotide and indomethacin. The bottom line is we still do not know the cause of hyperfiltration in response to this, and none of these hormonal mediators have been shown to block the response.

In recent years, our group and others have focused on the cellular basis of kidney injury. In diabetes the mesangium is greatly expanded and there is proliferation of cells and excess matrix production. The basement membrane is thickened and the filtration surface is eroded by this expanding mesangium. Also, there are fewer podocytes and the podocyte glomerular basement membrane abnormalities are believed to largely be responsible for proteinuria. The expansion of the mesangium and loss of filtration surface is largely felt to be responsible for reduction in GFR.

We have also examined a model of dietary protein on mesangial cells. We have shown that that amino acids induce at least as much proliferation as high glucose, and the combination produces an even greater effect. This shows there are some cellular mechanisms responsible for this enhanced sensitivity, in addition to hemodynamic changes.

Data from the National Health and Nutrition Examination Survey (NHANES) database shows the relationship between the development of microalbuminuria and protein intake. Patients in the highest quintile of protein intake, >20% of their daily calories, versus those in the lowest quintile, ≤12%, had threefold higher risk of developing microalbuminuria if they had diabetes and hypertension.

Data from the Nurse's Health Study is not limited to diabetic patients. Among women with early CKD stages 1 and 2, those who ate more protein (90 grams versus 60 grams,

within the range of the general population), had a 3.5 fold risk of losing ≥15% of the kidney function over 15 years. The other thing of interest here is types of protein. It appears that in these women with early CKD, animal protein is more harmful than dairy or vegetable.

Is there evidence that low-protein diets are protective? In kidney disease there is. A meta-analysis looking at nondiabetic CKD, stages 3 to 4, showed a 30% reduction of progression to ESRD independent of other traditional treatments. The numbers were smaller for diabetic patients in the same meta-analysis, however the effect size was at least as great.

A more recent Scandinavian trial looked at type 1 patients with stage 2 CKD. Even with a relatively modest limitation of dietary protein, going from about 1 gram per kilo per day to 0.89 there was a 70% reduction in ESRD or death. More than half of the adverse events were death, and all were cardiovascular related.

STAY INVOLVED

As clinicians and specialists, we need to be involved with these patients. In the earlier stages, the care is up to the primary care practitioners and the diabetologists. In later stages, kidney specialists need to be involved.

Patients need to be screened for CKD to identify high-risk patients for intervention. Type 1 patients should be screened after 5 years and then annually. Screening in type 2 patients should occur at diagnosis and then annually. The first thing we want to do in the screening process is look at the urinary albumin-to-creatinine ratio in a spot (untimed) collection. But also, remember to get a urinalysis because sometimes these patients have other forms of kidney disease or they have a urinary tract infection that may influence the measurements. This should be confirmed on at least two positive samples within 3 months.

Part of the screening should be estimating GFR from the serum creatinine, or eGFR. We recommend using the modified MDRD (Modification of Diet in Renal Disease) formula (using age, race, gender, and serum creatinine). It is available for download from the National Kidney Foundation Web site (www.kidney.org). Generally this is used in the outpatient

TABLE 2. THE DASH EATING PLAN BASED ON 2,000 CALORIES PER DAY

Food Group	Daily servings	Serving sizes	Examples and notes	Significance of each food group
Grains and grain products	7-8	1 slice bread 1 oz dry cereal*, 1/2 c cooked rice, pasta or cereal	whole wheat bread, English muffin, bagel, cereals, grits, oatmeal, crackers, unsalted pretzels and popcorn	major sources of energy and fiber
Vegetables	4-5	1 c raw leafy vegetable, 1/2 c cooked vegetable, 6 oz vegetable juice	tomatoes, potatoes, carrots, green peas, squash broccoli, turnip greens, collards, kale, spinach, artichokes, green beans, lima beans, sweet potatoes	rich sources of potassium, magnesium and fiber
Fruits	4-5	6 oz fruit juice, 1 medium fruit, 1/4 c dried fruit, 1/2 c fresh, frozen or canned fruit	apricots, bananas, dates, grapes, oranges, orange juice, grapefruit, grapefruit juice, mangoes, melons, peaches, pineapples, prunes, raisins, strawberries, tangerines	important sources of potassium, magnesium and fiber
Low-fat or fat-free dairy foods	2-3	8 oz milk, 1 c yogurt, 1 1/2 oz cheese	fat-free, skim or low-fat 1% milk, fat-free or lowfat buttermilk, fat-free or low-fat regular or frozen yogurt, low-fat and fat-free cheese	major sources of calcium and protein
Meats, poultry, fish	2 or less	3 oz cooked meats, poultry or fish	select only lean, trim away visible fats, broil, roast or boil instead of frying, remove skin from poultry	rich sources of protein and magnesium
Nuts seeds and dry beans	4-5 per week	1/2 c or 1 1/2 oz nuts, 2 TBSP or 1/2 oz seeds, 1/2 c cooked dry beans or peas	almonds, filberts, mixed nuts, walnuts, peanuts, sunflower seeds, kidney beans, lentils	rich sources of energy, magnesium, potassium, protein and fiber
Fats and oils**	2-3	1 tsp soft margarine 1TBSP light mayonnaise, 2TBSP light salad dressing, 1 tsp vegetable oil	soft margarine, low-fat mayonnaise, light salad dressing, vegetable oil such as olive oil, corn, canola or safflower	DASH has 27% of calories as fat including fat in or added to foods
Sweets	5 per week	1 TBSP sugar, 1TBSP jelly or jam, 1/2 oz jelly beans, 8 oz lemonade	maple syrup, sugar, jelly, jam, fruit-flavored gelatin, jelly beans, hard candy, fruit punch, sorbets, ices	sweets should be low in fat

** fat content changes serving counts for fats and oils. For example, 1 TBSP of regular salad dressing equals 1 serving, 1 TBSP of a lowfat dressing equals 1/2 serving; 1 TBSP of a fat-free dressing equals 0 servings.

Source: www.nhlbi.nih.gov/health/public/heart/hbp/dash/

clinic. The diagnosis of diabetic kidney disease is confirmed with macroalbuminuria and without evidence of other disease for example on urinalysis. With microalbuminuria, the diagnosis is confirmed if retinopathy is present and in type 1 diabetes duration ≥ 10 years.

As a practical matter, consider referral to a nephrologist or further work up for the following specific indications:

- a rapid decline in GFR;
- sudden onset of nephrotic syndrome. Remember that proteinuria can be nephrotic in diabetes, but its usually a gradual, progressive process. The sudden explosive onset of nephrotic syndrome would imply another disease;
- refractory hypertension;
- an active urinary sediment, particularly hematuria;
- signs or symptoms of systemic disease: if the patient has lupus and diabetes, for example, then probably additional evaluation should be done; and
- $>30\%$ reduction in renal function after starting an angiotensin converting enzyme or angiotensin 2 receptor antagonist, in which case we might think about renal vascular disease. The staging system is shown in Table 1.

RISK FACTOR TREATMENT

Blood pressure. Lifestyle should be part of the treatment of every risk factor. With regard to blood pressure, all of the major professional societies that have reviewed the evidence and commented on this recommend a blood pressure $\leq 130/80$ mm Hg for patients with diabetes. Renin angiotensin system inhibition should be part of this treatment: ACE inhibitors are recommended in type 1 and angiotensin II receptor antagonists in type 2. There is nothing wrong with either type of drug in either type of diabetes.

A sodium restriction is also recommended, as most people with diabetes have salt-sensitive hypertension. The DASH-style diet (Dietary Approaches to Stop Hypertension) has been shown to be quite effective. Its emphasis is on fresh fruits, vegetables, whole grains and exercise (Table 2).

Hyperglycemia. No matter what CKD stage a patient is in, we should always be striving to achieve the American Diabetic Association goals for HbA1c. The emphasis here may be the prevention of nephropathy (micro- and macroalbuminuria) and other complications like retinopathy. However, the data on slowing loss of GFR is not very strong, especially at lower levels of GFR, but there are many other reasons we should control glucose.

The full armamentarium of drugs can be used to control hyperglycemia in CKD, although insulin and the sulfonylureas need to be adjusted as GFR falls. Thiazolidinedione doses need not be adjusted, but they carry a higher risk of edema. Avoid metformin for serum creatinine levels >1.5 mg/dL in men or >1.4 mg/dL in women. Unfortunately, the Food and Drug Administration labeling for use of metformin

has not converted to an estimated GFR.

Lifestyle aspects are familiar here with regard to carbohydrate intake, and we would also add that patients should avoid high-protein diets as a way to control glycemia, and of course include exercise in daily life.

Lipids. LDL cholesterol should be <100 mg/dL for patients in CKD stages 1 to 4 because of extremely high CVD risk. We should consider levels <70 based on ATP III (Adult Treatment Panel) guidelines and the risk status.

The drugs of choice are statins in CKD stages 1 to 4. In ESRD, those diabetic patients with an LDL >190 mg/dL should not initiate statin therapy, based on a negative statin trial. Patients should reduce fat, saturated fat, cholesterol and incorporate daily exercise.

Diet. Finally, what is probably unique to diabetes and CKD is the issue of dietary protein. Our recommendation is that it should not exceed the Recommended Dietary Allowances which is 0.8 g per kilogram per day or 10% of calories. This is worth emphasizing, however because most Americans overeat protein and because of the fad diets that have been promoted. Salt, fat and carbohydrate intake are not necessarily adjusted based on level of CKD, but dietary protein should be. At CKD stages 3 and 4 more restriction is probably beneficial.

CONTROVERSIES

Why not high-protein diets for weight loss and glycemic control? If patients lose weight and blood sugar is controlled won't that do them enough good that we do not have to worry about their kidneys? There is really no evidence to support that. Weight loss is not sustained in these diets, and rebound gain is common, particularly after 6 months. The improvements in glycemia are probably most related to weight change, although I understand that may be arguable. There are absolutely no outcomes data on benefit, and epidemiologic studies show potential harm to the kidney.

The source of protein does matter; animal is worse than vegetable or dairy, and there may be some differences in types of vegetable. Some have promoted soy and flaxseed, but those have been rather challenging studies, however these are healthy nutrients for a number of reasons. ■

Katherine R. Tuttle, MD, is Medical and Scientific Director of Research at the Heart Institute and Providence Medical Research Center of Spokane, Washington. She is also co-chair of the Work Group for the National Kidney Foundation, Diabetes and Chronic Kidney Disease Clinical Practice Guidelines. She can be reached at KTuttle@this.org.



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