

Diabetic Kidney Disease: A Call to Action

Katherine R. Tuttle, Guest Editor

As guest editor for this *Diabetes Spectrum* From Research to Practice section, I am pleased to introduce a *tour de force* on the theme topic of diabetic kidney disease (DKD).

My journey in diabetes began as an observer. In youth, during the early 1970s, I watched my tennis partner, Cindy, struggle with the complexities of her blood glucose control, while still striving to play competitively. Her episodes of hypoglycemia were scary, and urine glucose testing just did not cut it. The era of self-monitoring of blood glucose was still years away, but eventually we got there.

Fast forward to medical school days in the late 1970s. I remember what a breakthrough it was to have “chemsticks” to check blood glucose at the bedside of hospitalized patients. Diabetes educators appeared on the wards and taught the patients (and us) just how to do it. A new age in diabetes care had surely arrived.

Throughout medical school, and then a residency in internal medicine, I was captivated by the physiology of metabolic disorders and the application of science to medicine. During this formative time, Dr. Mark E. Molitch was one of my inspirational mentors. I admired his commitment to advancing care for people with diabetes that has endured over the many years that followed our time together in the early 1980s. With his great wisdom and perception, he has penned a compelling editorial for the

current issue titled, “Diabetic Kidney Disease: Much Progress, but Still More to Do” (p. 154).

After residency, my next stop was fellowship training in endocrinology and metabolism. I was thrust into a world of insulin-glucose clamp studies with concurrent physiological assessments related to glucose counterregulation. And, we did these studies in real people with diabetes. I was amazed that they actually volunteered for such intensive, time-consuming, and sometimes risky studies. The “artificial pancreas” we used almost filled an entire room.

Back in the day, we fellows learned by first piloting clamp studies on each other. I was a “normal control” subject for a study utilizing a hyperglycemic-hyperinsulinemic clamp. My blood glucose plummeted from 300 to 30 mg/dL within minutes when the novice fellow conducting the study simultaneously turned off both dextrose and insulin infusions. Severe hypoglycemia feels terrible. Now, no longer an observer, I had a real diabetes-like experience that was unforgettable.

A young woman with type 1 diabetes, named Kathy (like me), volunteered for one of my clamp studies. She was committed, stoic, and determined to complete a series of three sequential clamps. We spent a lot of time together during those long (8- to 12-hour) ordeals. We were both in our mid- to late 20s and shared about our hopes, dreams, and aspirations. Although she was well-educated and

Providence Health Care and University of Washington, Spokane, WA

Corresponding author: Katherine R. Tuttle, Katherine.Tuttle@providence.org

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experienced with diabetes, she still had fears. She confided that kidney failure was one of them. At that time, in the mid-1980s, screening for early DKD was not really on the radar. Patients with DKD commonly presented with severely symptomatic uremia. At least by then, dialysis and kidney transplant were offered to people with diabetes, which was not the case in the early period of “renal replacement” therapy in the 1970s. Later in that same year of the clamp studies, Kathy presented to a hospital emergency department with severe dyspnea, life-threatening hyperkalemia, and overt kidney failure. Hemodialysis was started emergently, and she never recovered kidney function. She died less than a year later, at the age of 29 years.

And so, it was these people who called me into the DKD field. I subsequently pursued fellowship training in nephrology in the mid-to late 1980s and have since focused my professional efforts on what is now termed “translational research” in DKD.

It has been 30 years since I began the research with those clamp studies, and certainly progress has been made, but the needs in DKD are more urgent than ever because of the worldwide pandemic of diabetes (1,2). Modest reductions in incidence rates of end-stage renal disease (ESRD) attributed to diabetes have been observed over the past decade, but the overall prevalence of DKD has risen steadily as more people are living with diabetes (3–5). Diabetes dwarfs all other causes of ESRD and accounts for about half of all cases (5). Moreover, we now recognize the fatality risks, particularly cardiovascular diseases and infections, associated with DKD (5–8). Just one in 10 of those with DKD will survive to ESRD.

The mainstays of DKD prevention (glycemic control) and treatment (antihypertensive therapy with a renin-angiotensin-aldosterone system inhibitor) are only moderately

effective at reducing risk of loss of glomerular filtration rate and ESRD (9–14). Importantly, these treatment approaches have not been shown to decrease risk of death in DKD. Compared to other diabetes complications, improvement in rates of ESRD has been much less than for macrovascular complications such as myocardial infarction and stroke (4). In those with DKD, risks of retinopathy and limb loss are also greatly amplified by the presence of kidney disease (15–17).

To address these urgent needs, the American Diabetes Association (ADA) convened a consensus conference chaired by Dr. Molitch and me, which culminated in a summary report that was jointly published in both *Diabetes Care* and the *American Journal of Kidney Diseases* in October 2014 (18). ADA also stepped up to support research in DKD by issuing a request for applications to fund cutting-edge research. The consensus conference participants and other specially selected authors share their expertise and deep insights about DKD in this issue of *Diabetes Spectrum*.

In the From Research to Practice section, a distinguished panel of experts discusses state-of-the-art issues at the forefront of DKD research and clinical care. Drs. Andrew S. Narva and Rudolf W. Bilous provide a review titled, “Laboratory Assessment of Diabetic Kidney Disease” (p. 162), which describes current recommendations for screening and assessment, along with their strengths, limitations, and research recommendations. Drs. Brad P. Dieter, Radica Z. Alicic, Rick L. Meek and I, along with our laboratory colleagues Robert J. Anderberg and Sheryl K. Cooney, wrote an update focused on translational research in DKD therapeutics titled, “Novel Therapies for Diabetic Kidney Disease: Storied Past and Forward Paths” (p. 167). Drs. Vikram Patney, Adam Whaley-Connell, and George Bakris inform about the cur-

rent understanding and approach to hypertension, including an in-depth discussion of controversies such as use of dual renin-angiotensin system blockade and mineralocorticoid inhibition in their contribution titled, “Hypertension Management in Diabetic Kidney Disease” (p. 175). Drs. Jordi Goldstein-Fuchs and Kamyar Kalantar-Zadeh have written an authoritative review about nutritional therapies for an extremely challenging clinical situation: management of patients with diabetes and substantially impaired kidney function. Their article (p. 181) is titled “Nutrition Intervention for Advanced Stages of Diabetes Kidney Disease.” In their article titled, “Comprehensive Care for People with Diabetic Kidney Disease” (p. 187), Drs. Koyal Jain and Amy K. Mottl offer a wide-ranging discussion of care of the whole patient by addressing the multiple chronic conditions related to DKD that must be co-managed.

In additional articles elsewhere in this issue, Drs. Josh J. Neumiller (Editor-in-Chief of *Diabetes Spectrum*) and Irl B. Hirsch impart expert guidance concerning assessment of glycemia in the setting of kidney disease and appropriate drug-dosing strategies for those with diabetes and reduced kidney function in an article titled, “Management of Hyperglycemia in Diabetic Kidney Disease” (p. 214). Finally, Dr. Jane Chiang, a pediatrician and specialist in diabetes, rings the alarm and provides direction about the consequences of youth-onset diabetes and risks of major complications, particularly hypertension and DKD, early in life in her far-reaching article titled, “Hypertension and Diabetic Kidney Disease in Children and Adolescents” (p. 220).

We seem to be at a tipping point in the field of DKD. Although the needs are great, the future is bright. Advances in the science and understanding of the disease process have been absolutely transformative. Novel biomarkers for diagnosis

and prognostication are quickly emerging to inform identification of risk, as well as the underlying disease mechanisms that allow for targeted therapies and monitoring of individual patients with DKD. Kidney-specific drug treatments are within sight. Promising drugs have a range of actions, including inhibition of inflammation and fibrosis via targeting signal transduction and transporters in kidney cells, as well as aberrant metabolic products and mediators in the circulation, among others. And, we must think even further outside the box. For example, drug combinations and drug “holidays” may be effective approaches to maximize efficacy and reduce risks of treatment.

At the end of the day, however, these advances will only have meaningful impact when they reach people in need. We must always keep the patients in view and concurrently develop strategies for awareness, detection, and implementation that turn these hopes and dreams into reality for improving the true outcomes: how people with DKD feel, function, and survive. This is the reason I stepped a bit out of my comfort zone as a physician-scientist to share some of my stories about people who have inspired and driven this journey for me. The time is now for a call to action. We must join the cause by standing beside our patients with advocacy and a strong voice for recognition, funding support, and health policies that lead to advances

in research and clinical care and ultimately deliver on a promise to make life better for people with DKD.

Duality of Interest

Dr. Tuttle is a consultant in the area of novel therapies for DKD for Amgen, Eli Lilly and Company, and Noxxon Pharmaceuticals. No other potential conflicts of interest relevant to this article were reported.

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