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Kidney Disease in People with Diabetes: the *Expanding* Epidemic

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Chronic kidney disease (CKD) is highly prevalent in the US and associated with substantial morbidity, mortality and health care costs. Diabetes, a growing epidemic in the U.S., is identified as a leading cause of all stages of CKD and the cause of kidney failure in approximately half of all dialysis patients. With this in mind, de Boer et al examine the prevalence of diabetic kidney disease in the U.S.(1).

What does this important study show?

de Boer et al analyzed data from the Third National Health and Nutrition Examination Survey (NHANES III) conducted in 1988-1994 and the continuous NHANES (1999-2008) to investigate trends in CKD in people with diabetes. This study found that the prevalence of CKD among people with diabetes has increased over the past two decades and it has done so in proportion to the increasing prevalence of diabetes. This is in contrast to the recent plateau in rates of diabetic end stage renal disease (ESRD).

The authors compared estimates from the 1988-1994, 1999-2004, and 2005-08 survey periods. They defined diabetes as the use of glucose-lowering medications, HbA1c $\geq 6.5\%$, or both. To maximize the use of objective criteria, persons who were diagnosed but were treated by only diet or lifestyle modifications would have been classified as nondiabetic if their HbA1c value was $< 6.5\%$. Glomerular filtration rate (GFR) was estimated from calibrated serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (2) and categorized based on the classification system established by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (3). Kidney disease was defined as an estimated GFR < 60 mL/min/1.73 m², albuminuria (albumin-to-creatinine ratio > 30 mg/g), or both, and kidney disease in a person classified as having diabetes was classified as diabetic kidney disease.

The proportion of the adult population with diabetic kidney disease increased from 2.2% to 3.3% over this 20-year period. The largest increases were observed among persons aged 65 or older (7.1% to 10.7%). Among persons with diabetes, the prevalence of kidney disease remained relatively constant over time at $\sim 35\%$. Among diabetic adults 65 or older, the

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prevalence of kidney disease was approximately 50%; this was also constant over the study period. By contrast, the prevalence of albuminuria (with or without low GFR) in persons with diabetes decreased over the study period: from 27.3% in 1988-94 to 24.9% in 1999-2004 to 23.7% in 2005-08. This trend was largely explained by demographic factors, and the temporal differences were not statistically significant after adjustment. By contrast, the prevalence of estimated GFR <60 mL/min/1.73 m² in persons with diabetes increased over the study period, rising from 14.9% in 1988-94 to 16.7% in 1999-2004 to 17.7% in 2005-08.

Accompanying the observed trends in diabetic kidney disease were significant increases in body mass index and duration of diabetes and significant decreases in mean HbA1c, blood pressure, and serum lipids. As has been shown in other studies (4-6), the use of glucose-lowering medications, cholesterol-lowering medications, and renin-angiotensin-aldosterone system (RAAS) inhibitors increased dramatically during this period. The authors show that among persons with diabetes, the proportion taking glucose-lowering medication increased from 56.2% to 74.2%; the proportion taking lipid-lowering medications increased from 8.9% to 50.2%; and the proportion taking RAAS inhibitors increased from 11.2% to 40.6%.

The authors comment that the observed changes in medication use have not translated into a decreased prevalence of diabetic kidney disease. However, trends in obesity and changes in the diagnostic criteria for diabetes are difficult to take fully into account. The decreases in mean HbA1c and increases in average duration of diabetes over time suggest that the case-mix of diabetic adults has changed substantially. The definition of diabetes used in the study does not entirely overcome bias resulting from temporal changes since prescribing practices will reflect both changes in diabetes diagnostic criteria and availability of diabetes drugs over the 20-year period.

Limitations of this study to be considered in the interpretation of the results include the inherent limitations of the cross-sectional (prevalence study) design, which is optimal for estimating prevalence trends, but cannot establish temporality or evaluate the risk of diabetic kidney disease. The lack of information on ESRD—a critical clinical and economic consequence of diabetic kidney disease—is also a weakness. Data from the United States Renal Data System suggest that ESRD incidence rates have reached a plateau in the past decade despite more prevalent comorbid conditions like diabetes (7). The study is also limited by the availability of only single measurements of albumin and creatinine to characterize CKD. The authors estimate persistence of albuminuria but the subsample of diabetic individuals with repeat albuminuria assessments is small. Serum creatinine-based GFR estimating equations such as the CKD-EPI equation are known to be affected by muscle mass and dietary intake. Decreased muscle mass is associated with certain pathologic changes, including glucose intolerance (8); thus, the lowered serum creatinine and associated higher estimated GFR may lead to lower estimates of the burden of diabetic kidney disease than might be obtained with another filtration marker. Finally, while this study describes the burden of kidney disease in people with diabetes, it is not clear how much of the burden is due to classic diabetic kidney disease (9).

The study benefited from a large sample size, multiple survey periods, and rigorous data collection procedures in NHANES that have remained relatively consistent over time. These data represent some of the most comprehensive data on the prevalence of diabetic kidney disease in the general U.S. population. However, the trends in diabetic kidney disease presented in this study ultimately reflect a complex interplay of changes in diabetes screening, diagnosis, and treatment along with changes in the burden of kidney disease.

How does this study compare with prior studies?

These results extend previous studies, which also have demonstrated an increasing burden of CKD in the U.S. (10-12). Diabetes is a leading cause of CKD and the prevalence of diagnosed diabetes has increased from 5.1% (2) to 11.9% to in the past 20 years in the U.S. (13). However, the prevalence of undiagnosed diabetes has remained relatively constant over this period (14). Trends in diabetes prevalence reflect the lowering of the diagnostic threshold for fasting glucose from 140 mg/dL to 125 mg/dL in 1997 and changes in screening and diagnostic practices. More recently, in 2010, the American Diabetes Association recommended for the first time that an HbA1c value $\geq 6.5\%$ be considered diagnostic for diabetes (15). Trends in glucose-lowering medication use have also changed dramatically over time; the number of patients with diabetes currently using oral glucose-lowering medications has increased, while the proportion who are using insulin has decreased (4). Furthermore, RAAS inhibitors have been increasingly used to manage hypertension and prevent diabetic nephropathy (5, 6). The study by de Boer et al should be interpreted in the context of these trends.

The trends demonstrated here using the CKD-EPI equation parallel the overall increase in CKD from NHANES 1988-1994 to 1999-2002 with low GFR defined by the Modified Diet in Renal Disease (MDRD) Study equation (10). Previously, the decline in estimated GFR was still significant after adjusting for sex, race, body mass index, hypertension, and diabetes. The observed increase in albuminuria, however, was no longer significant after adjustment. De Boer et al report similar findings after adjusting for age, sex, and race and extending the period of observation to 2008.

Another NHANES study examined GFR using a cystatin C-based equation to compare prevalent CKD in 1988-94 with 1999-2002 (16). These authors concluded that estimated GFR declined with the MDRD Study equation, but there was no downward trend when GFR was estimated with cystatin C. It should be noted that cystatin C measurements are only now being standardized, limiting comparison of prevalence between survey periods. Thus, more work needs to be done on comparisons of CKD prevalence across different markers of kidney function.

What should clinicians and researchers do?

The major message from this study is the absolute increase in burden of diabetic kidney disease - which mirrors the increase in diabetes prevalence. These data raise the concern that the plateau in rate of ESRD in people with diabetes may be temporary and may increase as the dual epidemics of obesity and diabetes mature, as the lag time from onset of diabetes to ESRD is typically two decades or more. Clinicians should optimize treatment of diabetes to prevent the onset of diabetic nephropathy (17) and slow its progression. de Boer et al show important improvements in use of glucose-lowering medication, lipid-lowering medication, and RAAS inhibitor use, but rates of compliance with guidelines should also be examined. Indeed, increasing evidence suggests that high normal albuminuria (albumin creatinine ratio of 10-29 mg/g) is associated with elevated risk (18), but long-term trials have not examined the benefits of RAAS inhibitor use in populations with high normal albuminuria or chronic kidney disease. Researchers should continue to monitor CKD trends in the US and worldwide. In particular, future studies should compare estimates across markers of kidney function and damage, define the full range of complications, and, most importantly, develop and rigorously test strategies to prevent and treat CKD in persons with and without diabetes.

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