Prediabetes, Prehypertension . . . Is It Time for Pre-CKD?

Gary C. Curhan

Channing Laboratory and Renal Division, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts; and Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts

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There is no doubt that chronic kidney disease (CKD) is common in the United States (1) and is associated with important adverse outcomes, such as cardiovascular disease and mortality (2). Factors that are associated with higher risk for CKD include hypertension, diabetes, obesity, and African ancestry.

The currently accepted definitions of hypertension and diabetes are somewhat arbitrary; in fact, previous definitions of hypertension and diabetes were revised on the basis of the recognition that values lower than the prevailing acceptable thresholds for BP or blood glucose were associated with higher risk for adverse outcomes. The new designations "prediabetes" (also known as impaired glucose tolerance or impaired fasting glucose) and "prehypertension" were recently introduced, yet these terms are somewhat awkward because the risks associated with blood glucose and BP are continuous rather than dichotomous. Nonetheless, individuals with prediabetes are at high risk for the development of diabetes and at increased risk for cardiovascular disease (3).

As we continue to refine our understanding of the relations between risk factors and adverse outcomes, we must also evaluate the criteria we use to assess disease and revise our definitions accordingly. Considerations such as whether individuals in the "predisease" phase are at higher risk for relevant outcomes and the availability of effective interventions that can reduce the likelihood of developing the adverse outcome will inform the establishment of guidelines for screening and treatment.

Guidelines for screening for diabetes already exist (4). High-risk individuals should be screened regardless of age. For others, screening is recommended beginning at age 45. Effective interventions are available for individuals who meet the criteria for prediabetes to reduce the risk for progression to diabetes and the associated morbidities.

Screening for albuminuria and measurement of serum creatinine (and calculation of estimated GFR [eGFR]) are currently recommended by the American Diabetes Association upon diagnosis of either prediabetes or diabetes and annually thereafter (4). The preferred screening method for albuminuria is measurement of the albumin-to-creatinine ratio (ACR) in a spot (random) urine sample. Although the measurement of albumin excretion rate on the basis of a 24-h urine collection is likely more precise, this procedure does not provide sufficient improvement in prediction or accuracy and is not supported in the National Kidney Foundation position statement (5).

What are our definitions for CKD?

1. The most commonly used staging system is based on the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines; however, there continues to be active and important discussion regarding the limitations of this approach. This staging system considers albuminuria and eGFR for stages 1 and 2 but only eGFR for stages 3 through 5.
2. Albuminuria and glomerular filtration each reflect distinct processes. A recently published landmark study examined several adverse outcomes and demonstrated the independent contributions and the importance of distinguishing GFR from albuminuria, even for stages 3 through 5 (6).
3. To be consistent with previous reports, many recent studies used the original Modification of Diet in Renal Disease (MDRD) equation; however, given the demonstrated improved accuracy of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, this should become the new standard.
4. The definition of "abnormal" albuminuria remains unsettled and controversial. Although the previous reports based on National Health and Nutrition Examination Survey (NHANES) data on CKD prevalence used a single definition (ACR $\geq$30 mg/g), gender-specific thresholds would be more appropriate (7). Of note, the use of gender-specific thresholds would lead to an even higher overall prevalence of CKD. Although dichotomous categories are used for albuminuria, the risk for adverse outcomes with albuminuria is continuous, as it is for BP and glucose.

In this issue of *CJASN*, Plantinga *et al.* (8) used the 1999 through 2006 NHANES data to examine the prevalence of CKD in four groups: Self-reported diagnosed diabetes, undiagnosed diabetes (fasting plasma glucose [FPG] $\geq$126 mg/dl), prediabetes (FPG $\geq$100 and $<$126 mg/dl), and no diabetes (FPG $<$100). CKD was defined as having either ACR $\geq$30 mg/g or eGFR 15 to 59 ml/min per 1.73 m^2.

Their findings are striking and have major public health implications. For example, whereas $>$10% of those without diabetes had CKD, nearly 40% of individuals with diabetes had

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Correspondence: Dr. Gary C. Curhan, Channing Laboratory, Brigham and Women's Hospital, 181 Longwood Avenue, Boston, MA 02115. Phone: 617-525-2683; Fax: 617-525-2008; E-mail: gcurhan@partners.org

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CKD and the percentage was just as high in those with undiagnosed diabetes. Notably, 18% of those with prediabetes also had CKD. Given the known influence of age on prevalence of diabetes and CKD, the adjusted values were attenuated but still impressive, particularly for undiagnosed diabetes. More than half of the CKD cases were identified by ACR ≥30 mg/g.

Interpretation of these findings should be made with some caution in light of a few caveats. The presentation of the actual rather than the weighted samples sizes from NHANES can be somewhat misleading because of oversampling of certain subgroups. The findings presented are in fact weighted percentages; therefore, they are representative of the US population. It is notable that more women than men with prediabetes or no diabetes met the criteria for CKD. This is likely because of higher ACR values in women than in men because of lower creatinine excretion, thereby raising the ACR (7). Individuals who were pregnant, were younger than 20 years, or had eGFR <15 ml/min per 1.73 m^2 were excluded; therefore, the generalizability is somewhat reduced.

What are the implications of these important findings? First, we should examine our current definition for prediabetes. The prevalence of CKD in those with prediabetes is 70% higher than in those without diabetes; however, the higher prevalence may be the result of one or more shared risk factors for prediabetes and CKD. For example, obesity both increases albuminuria and is strongly associated with prediabetes. The authors did not present prevalence values adjusted for body mass index (BMI), but simple adjustment for BMI alone may not remove its potential influence. Higher BMI is associated with albuminuria in overweight and obese adults with type 2 diabetes (9). Likewise, thiazide use both increases the risk for development of diabetes (10) and can raise the serum creatinine level. Age is clearly associated with diabetes and CKD, yet this should not be interpreted to mean that the development of CKD is an inevitable part of normal aging. Recent reports from large cohort studies, such as the Cardiovascular Health Study (11) and the Nurses' Health Study (12), demonstrated that in a substantial proportion of individuals, renal function did not change meaningfully during a 6- to 11-year period. Given that CKD is not inevitable, we should continue to focus on prevention as a priority.

The findings from the Diabetes Prevention Program Trial highlight that multiple factors contribute to the development of albuminuria. For example, no improvement in the median ACR was seen despite a marked reduction in progression to diabetes in the intensive lifestyle intervention and metformin groups (13); therefore, it is essential to focus on the prevention of the development of chronic conditions that have an impact on the risk for CKD, including obesity, diabetes, and hypertension. The majority of cases of diabetes (14) and hypertension (15) in the United States are preventable.

As we consider modifying definitions for diabetes and hypertension to include "pregroups," I propose that we consider the introduction of the term "pre-CKD." Low levels of albuminuria, well below the widely used definition of microalbuminuria, are associated with the development of important adverse outcomes such as hypertension (16), cardiovascular disease, and death (17). As with diabetes and hypertension, is there a stage at which CKD is reversible? An analysis from the Prevention of Renal and Vascular Endstage Disease (PREVEND) study demonstrated that weight loss can reduce albuminuria in the general population (18). The National Kidney Disease Education Program is working toward the creation of an international standard for the measurement of albuminuria that will lead to increased confidence and improved assessment of low levels of albuminuria and will assist with research in this area.

The important clinical and public policy implications of this study deserve consideration. Screening for CKD should focus on those at higher risk, and individuals with prediabetes should now be included; however, screening alone is not sufficient. Pharmacologic intervention with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers should be used to slow progression. The low rates of use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers reported by Plantinga *et al.* (8) would be expected among those with undiagnosed diabetes and prediabetes, but use was only marginally higher among individuals with diagnosed diabetes and CKD.

Future research studies should focus on determination of optimal cut points for defining diabetes (FPG, glycosylated hemoglobin), hypertension (systolic BP, diastolic BP), and CKD (albuminuria, GFR). Although the risks are continuous, cut points are required for clinical utility. These studies would enable us to create a protocol for serial albuminuria and creatinine measurements to follow the change in albuminuria and renal function over time. As recently demonstrated for eGFR (19), change in albuminuria will likely provide useful prognostic information that can guide treatment decisions. Furthermore, it is essential to determine whether other factors that have been shown to be associated with CKD and adverse outcomes, such as serum phosphate and left ventricular hypertrophy, should be included in the screening. These data could lead to the development of risk scores, which would be particularly helpful in the clinical setting. Finally, the importance of prevention cannot be overstated. To make a substantial impact on this growing problem, we as a community need to focus on helping individuals avoid these preventable conditions.

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Disclosures

None.

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See related article, "Prevalence of Chronic Kidney Disease in US Adults with Undiagnosed Diabetes or Prediabetes," on pages 673–682.

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KIDNEY DISEASE HIDES IN PEOPLE WITH UNDIAGNOSED DIABETES

Up to 13 Million Americans May Have Unsuspected Kidney Damage

Washington, DC (March 22, 2010) — Millions of Americans may have chronic kidney disease (CKD) and not know it, according to a study appearing in an upcoming issue of the *Clinical Journal of the American Society Nephrology* (CJASN).

"Our research indicates that much of the CKD burden in the United States is in persons with prediabetes and undiagnosed diabetes, who are not being screened for CKD," comments Laura C. Plantinga, ScM (University of California, San Francisco). The researchers believe that broader screening may be needed to detect patients with these two "relatively silent yet harmful diseases."

In a study funded by the Centers for Disease Control and Prevention, Plantinga and colleagues analyzed a nationally representative sample of about 8,200 Americans from the National Health and Nutrition Examination Survey. Standard laboratory tests were used to assess the rate of CKD, focusing on people with undiagnosed diabetes or prediabetes (sometimes called "borderline" diabetes).

Based on lab tests, 42 percent of subjects with undiagnosed diabetes had CKD—similar to the 40 percent rate in those with diagnosed diabetes. "Only a small percentage of participants were aware of the diagnosis of CKD," says Plantinga.

In addition, CKD was present in nearly 18 percent of subjects with prediabetes. Among participants without diabetes or prediabetes, the rate of CKD was about 11 percent.

"Based on these results, there may be a substantial number of individuals in the United States—up to 13 million—who have undiagnosed diabetes or prediabetes and who already have signs of kidney damage and/or reduced kidney function," says Plantinga. Such patients would be at high risk for worsening kidney disease and diabetes, and for the poor outcomes associated with both conditions—including cardiovascular disease and death.

Diabetes is the most important risk factor for kidney disease, but the new results suggest that harmful effects on the kidneys may be occurring even before diabetes is diagnosed. "Persons at risk for diabetes and their health care providers should be aware that earlier screening for both diabetes and kidney disease may be warranted," says

Plantinga. "Earlier screening would allow for appropriate, timely medical care to prevent further progression and poor outcomes."

In an accompanying editorial, Gary C. Curhan, MD, ScD (Brigham and Women's Hospital, Boston, MA) calls for CKD screening to be extended to patients with prediabetes. Curhan also suggests that it may be time to consider the concept of "pre-CKD"—identifying patients at a very early stage of CKD when the disease may still be preventable or reversible.

Although the study shows an association, it cannot determine whether the development of CKD followed the development of diabetes, or whether CKD was actually caused by diabetes. There is also likely some misclassification of both diseases, although the association remained significant when tested under a range of different assumptions.

Study co-authors include Deidra C. Crews, Josef Coresh, Edgar R. Miller III (Johns Hopkins University, Baltimore, MD), Rajiv Saran, Elizabeth Hedgeman (University of Michigan, Ann Arbor), Jerry Yee (Henry Ford Hospital, Detroit, MI), Meda Pavkov, Mark S. Eberhardt, Desmond E. Williams (Centers for Disease Control and Prevention, Atlanta, GA), and Neil R. Powe (University of California, San Francisco) on behalf of the Centers for Disease Control and Prevention Chronic Kidney Disease Surveillance Team. Disclosures: The authors reported no financial disclosures.

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