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Epidemiology of chronic kidney disease among normotensives— But what is CKD?

Rajiv Agarwal, M.D.

Indiana University School of Medicine and Richard L. Roudebush Veterans Administration Medical Center, Indianapolis, IN

Among adults in the United States one in four has hypertension and one in eight has chronic kidney disease (CKD). Although the relationship between hypertension and CKD has been recognized for several hundred years, the prevalence of CKD among patients with normal blood pressure has not been assessed in randomly sampled populations. Crews and colleagues in this issue of *Hypertension* are the first to report such estimates¹: 13.4% of people who have normal blood pressure have CKD. Among those with pre-hypertension the prevalence is 17.3%, among those with undiagnosed hypertension 22% and among those with diagnosed hypertension 27.4%. The magnitude of these CKD prevalence estimates is astounding and may even be misleading unless placed in appropriate context. The awareness of CKD diagnosis was dismal: <10% of people were aware of CKD regardless of hypertension category. A thorough analysis of the definition of CKD is necessary in order to understand how the varying definitions of CKD may have influenced both the prevalence and awareness estimates.

Effect of CKD Definition on Prevalence Estimates

The prevalence estimates may be inflated because of CKD that is so mild that it may not be considered a disease at all. For example, examination of Figure (derived from Table 3 of the paper) shows that if one considers the prevalence of more severe CKD defined as macroalbuminuria or estimated GFR <45 mL/min/1.73m², then the prevalence estimates fall dramatically. These stricter definitions of CKD yield the following prevalence estimates of CKD: normal blood pressure 0.5%; pre-hypertension 1%; undiagnosed hypertension 2%; and less than 5% prevalence of CKD among those with diagnosed hypertension. These prevalence estimates are much lower than those obtained with the more sensitive definition that is typically used to define CKD. Thus, the prevalence estimates of CKD may be driven up by people in the GFR range of 45–60 ml/min/1.73m² and people with microalbuminuria. So what is wrong with these definitions?

These definitions are too sensitive and sometimes not appropriate. For example, a single recording of microalbuminuria is not sufficient to diagnose CKD; microalbuminuria has a high degree of day to day variability² and requires reconfirmation at a later date in order to be of diagnostic importance. The day-to-day variability is not unique to microalbuminuria. This variability is shared by other analytes such as glucose. In fact, the prevalence estimates of diabetes mellitus fall by 25% when confirmation of the diagnosis of diabetes is required by a second measurement³. GFR in the 45–60 ml/min/1.73m² range may be of little clinical consequence especially when the GFR is stable over years, when it is solely a manifestation of age, gender, and race (as may occur in elderly non-Black women), and when it is

Correspondence: Rajiv Agarwal M.D., Professor of Medicine, Indiana University and VAMC, 1481 West 10th Street, Indianapolis, IN 46202, Phone 317-988 2241, Fax 317-988 2171, ragarwal@iupui.edu.

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unaccompanied by other manifestations of kidney disease such as albuminuria. The good news is that we do not have so many patients with more severe CKD; the bad news is that there are plenty with mild chronic kidney “disease”.

Additionally, there is another caveat in assessing the viability of the definition of hypertension. Blood pressure among patients with CKD is considered hypertensive at 130/80 mmHg or more. Although the non-CKD definitions of hypertension may have diluted prevalence estimates of CKD in the hypertension groups, this was probably of minor importance. Examination of the Figure will reveal that using more specific definitions (eGFR<45 mL/min/1.73 m² or macroalbuminuria) may increase the prevalence of CKD by only a slight amount, at most by a few tenths of one percent.

Effect of CKD Definitions on Awareness Estimates

Although patients with CKD are uniformly (nearly 99%) aware of their diagnosis of hypertension⁴, this study suggests that those patients with hypertension, in fact, had poor awareness of CKD. The awareness of CKD among those with normal BP was 2%, among those with pre-hypertension 2.2%, and among those with undiagnosed hypertension was 3.5%. Even among patients with diagnosed hypertension, the awareness of CKD diagnosis was only 9.1%. Again, the more sensitive definition of CKD may paint a gloomier picture about CKD awareness than a more specific definition. There are several reasons for this. *First*, physicians may not want to diagnose their patients based on single measurements of estimated GFR or microalbuminuria. Epidemiological studies ignore this fact. As examples: 1) a patient will be classified as having CKD even with a GFR of 59 mL/min on one occasion; 2) even in the absence of diabetes, a patient will be diagnosed with CKD when urine albumin/urine creatinine ratio is 40 mg/g on a single test. *Second*, there may be little reason to screen patients for CKD when risk factors such as hypertension or diabetes mellitus are absent. It is now well established that testing for microalbuminuria among normotensives is not cost effective and not recommended. Although cost effective, testing all patients with uncomplicated hypertension for microalbuminuria is not routine and even if microalbuminuria is detected on a single occasion it may not represent CKD. *Third*, minimally impaired estimated GFR may not warrant a diagnosis of CKD. Since patients with low eGFR in this study on average were 72.4 years of age, it is possible that physicians appropriately and wisely avoided labeling their patients with a diagnosis of chronic kidney “disease” especially when they were elderly. Since, the prevalence of kidney disease of greater severity (defined as eGFR<45 mL/min/1.73 m² or macroalbuminuria) was about 0.5% among normotensives, 1% among prehypertensives, 2% among undiagnosed hypertensives, and <5% among diagnosed hypertensives, the awareness of CKD diagnosis for more severe impairment in kidney function may have been substantially higher. In fact, analyses from NHANES indicate that even among patients with stage 3 CKD, awareness was increased 3 fold when they had proteinuria and 2 fold when they had diabetes⁵.

Trade-offs with CKD Definitions

The use of sensitive or specific definitions when assessing the awareness and prevalence of CKD has its advantages and its pitfalls. A more specific definition would identify those individuals with CKD who are at increased absolute risk. In such patients, the absolute risk for cardiovascular morbidity and mortality and the risk for ESRD would be increased. Given the heightened absolute risk, number of people needing treatment to prevent one event would be lower. Lower numbers needed to treat may translate to more cost effective therapies and allow us to target our resources to those individuals who are most in need of care. However, if more sensitive definition is used, then we may be able to identify CKD at an earlier stage and intervene before it progresses to a later stage. Identification of microalbuminuria or milder

degrees of clinical reductions in GFR may be of enormous prognostic importance to patients who have the appropriate clinical context or disease trajectories that suggest progression. Population based studies suggest that the joint consideration of both parameters of kidney function—albuminuria and estimated GFR—may be most effective in assessing prognosis ⁶. Thus, sensitive and specific definitions both have a role at the bedside and for clinical epidemiologists. Which definition to use to define CKD depends on the context.

The link between hypertension and CKD: estimated GFR versus albuminuria

An important finding of this report was that hypertension was more strongly related to albuminuria rather than the estimated GFR. These results confirm earlier observations made through ambulatory blood pressure monitoring which disclose that proteinuria was the most important correlate of systolic hypertension among patients with CKD; proteinuria trumps estimated GFR ⁷. Analysis of NHANES data also suggests that albuminuria is an important correlate of hypertension control ⁸. In the more recently reported hypertension prevalence and control from the chronic renal insufficiency study cohort assessed by clinic BP measurement confirms that albuminuria is an important correlate of poor hypertension control ⁴. Whereas only increasing severity of albuminuria is related with the mean level of ambulatory blood pressure any CKD whether detected by the presence of albuminuria or an impairment in estimated GFR is associated with marked impairment in circadian rhythm of blood pressure including dipping ⁹. These data point out the important relationships between albuminuria and hypertension above and beyond estimated GFR.

Conclusions

Taken together, the results of the study indicate that the prevalence estimates of CKD are strongly dependent upon the definitions that we use to define this disorder. More specific definitions yield low estimates, more sensitive definitions yield up to 26 fold higher estimates especially among normotensive and pre-hypertensive individuals. The study provides strong evidence that hypertension is not *sine qua non* of CKD. Since pre-hypertensive state can identify patients who have mild impairments of kidney function or microalbuminuria, physicians must not rely solely on the presence of hypertension to screen for CKD among patients who are at high risk such as those with diabetes mellitus. Finally, given the higher prevalence of white coat and masked hypertension among patient with CKD ¹⁰, the assessment of cardiovascular and renal risk by measurement of BP in the clinic can be enhanced by home blood pressure monitoring ¹¹.

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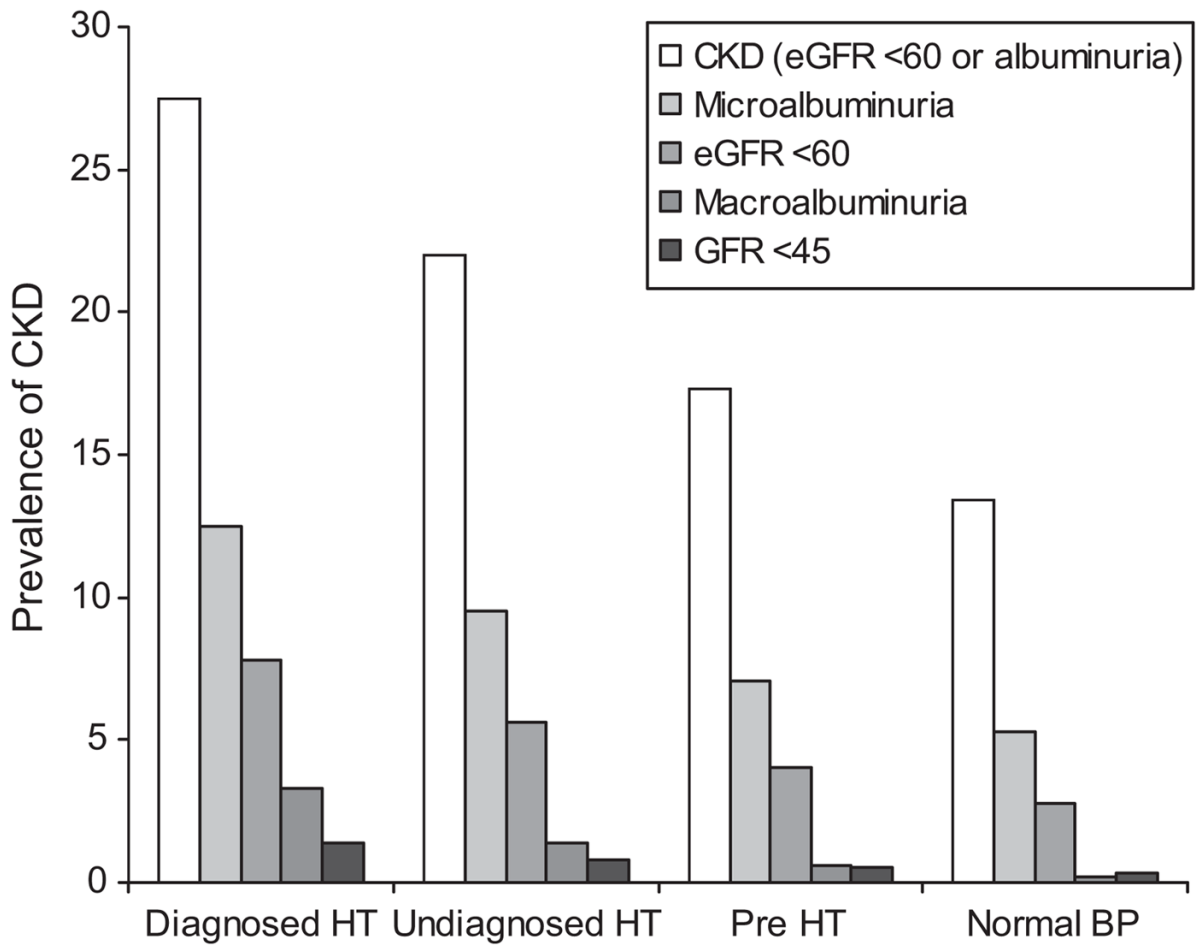


Figure. Prevalence of chronic kidney disease in the US depends on the definition of kidney disease. Prevalence estimates are in percent.