

## World Kidney Day 2009: Problems and Challenges in the Emerging Epidemic of Kidney Disease

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World Kidney Day is an occasion to mark growing concerns over the impact of kidney disease on global public health. Although the distribution of causes of kidney disease and access to dialysis and transplantation may vary among regions of the world, arguably, one point is universal. An expanding proportion of people in every nation in the world are affected by chronic kidney disease (CKD). In the United States, the most recent data suggest that 27 million individuals have CKD, representing nearly one in every seven adults and a 30% increase over the past decade.<sup>1</sup> Population sampling studies from around the globe now indicate similar prevalence rates, usually ranging between 10 and 13%. Because the prevalence of CKD rises dramatically with age and is also associated with obesity and diabetes, kidney disease will be a public health concern for the foreseeable future.

Kidney disease is linked with major adverse health outcomes, including premature cardiovascular disease, with a graded increase in risk as kidney function is lost.<sup>2,3</sup> This is now clear from epidemiologic studies, community-based studies, and reanalysis of clinical trials of patients with kidney disease. The rising rate in the number of patients who do

reach end-stage kidney disease and are treated with dialysis or renal transplantation also continues to be of concern. There is significant risk that the growing economic burden will render treatment costs unsustainable even in resource-rich environments. An overall decline in physical performance and cognitive function is also linked to kidney disease, markedly affecting quality of life. As a global community, we need to ask ourselves whether we have in place the strategy to address fully the universal health problems arising from kidney disease, given the biologic and culture heterogeneity of populations, diverse environments, and varying capabilities of health care delivery systems around the world.

Several subpopulations deserve specific consideration. The prevalence of CKD rises dramatically with age, yet many elderly individuals are less likely than their younger counterparts with similar levels of kidney function to progress to ESRD and may not be at higher risk for adverse outcomes than age peers with kidney function in the normal range.<sup>4</sup> Nevertheless, a subset of older patients with CKD do account for a growing proportion of the ESRD population. We have only a limited understanding of the mechanisms underlying age-related risks in CKD, and we know even less about treatment of kidney disease–related morbidities in the elderly.

Obesity is also a matter of worldwide concern. Overweight is the sixth most important risk factor contributing to the overall burden of disease worldwide.<sup>5</sup> The epidemic of obesity includes emerging and developed countries. Unfortunately, even a large proportion of children are overweight or obese, along with more than 1 billion adults worldwide. Obesity is a potent predictor of albuminuria, and a recent meta-analysis demonstrated that obesity is a risk factor for the development and progression of CKD, particularly in the setting of metabolic syndrome.<sup>6</sup>

The development of guidelines for care is an essential foundation for attacking any global crisis. Guidelines as developed by the National Kidney Foundation and more recently through the Kidney Disease: Improving Global Outcomes (KDIGO) have helped raise awareness of the magnitude of the public health burden imposed by kidney disease; however, despite widespread dissemination, guidelines frequently do not have the full desired effect of changing clinical practice and improving care.<sup>7–10</sup>

Although standardization is a critical tool to optimize quality of care, physicians and other health care workers must relinquish some autonomy to implement practice guidelines.<sup>11</sup> Empirical data demonstrate that standardized care guidelines are most effective when the evidence supporting protocols and processes by which guidelines are created is transparent and when there is trust in the organization that creates standards. Guideline acceptance by physicians and other caregivers also requires a sound scientific basis and a

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high standard of available evidence. There is a large literature addressing potential barriers to the implementation of guidelines across many subspecialties,<sup>12</sup> recognizing that specific barriers vary significantly on the basis of practice setting. Given this, the focus should be local and point at the needs of specific communities, taking advantage of local health care system resources.

Physicians need to treat individual patients with chronic diseases “within the larger context of family, community and society, as well as to treat the community itself.”<sup>13</sup> Key questions for each nephrologist to ask are, “Have we adequately disseminated information on the importance of kidney disease as a public health problem in our local area?” and, “Have we educated the colleagues we interact with on a daily basis on the availability of practice guidelines and patient-centered educational materials about kidney disease?” Although national campaigns for education have been successful and under way, this is a battle that needs to be fought in the trenches.

In 2006, more than 40% of incident dialysis patients in the United States had not previously seen a nephrologist.<sup>14</sup> Even more disturbing, the majority of these individuals seem not to have had a plasma creatinine measured within the previous year or been treated with inhibitors of the renin-angiotensin system to slow progression of kidney disease. Although the barrier of dissemination of the importance of screening for and optimally treating CKD is one that can be attacked locally, there are also many additional barriers that we as a community need to assess and discuss and for which to advocate for solutions. Access to health care, including overcoming currently existing racial and ethnic disparities, is crucial for progress to be made.<sup>15</sup> Efforts to increase screening and early identification of kidney disease require knocking down barriers based on inability to pay or on lack of insurance. Research is needed to facilitate the optimal translation of guideline recommendations into actual health care improvements in diverse populations.

A gap in the public’s awareness of the risk for kidney disease has been well documented.<sup>16</sup> Although not surprising those with the most advanced disease are most likely to be aware, still less than half of patients with stage 4 CKD were aware of having reduced kidney function in the National Health and Nutrition Examination Survey. In earlier stages of CKD, when interventions arguably might have an even more significant impact, awareness is reported to be as low as 3 to 8%. Previous campaigns that can be emulated include promoting awareness of cardiovascular risk factors such as “hypertension—the silent killer” and the association between good and bad cholesterol in the development of heart disease. The National Kidney Disease Education Program sponsored by the National Institutes of Health provides templates and educational materials to support this effort.

Nationally, progress toward awareness and improvement in care is on the horizon with the Medicare Improvements for Patients and Providers Act (MIPPA) of 2008 passed into law this past summer. In MIPPA, the Kidney Disease Education and Awareness Provisions authorized Centers for Medicare

and Medicaid Services, beginning January 2009, to conduct pilot initiatives in three states to promote awareness of CKD, focusing on prevention. In addition, the Agency for Healthcare Research and Quality recently hosted an open meeting to gather information and opinions on existing educational resources and programs on kidney disease. Thus, momentum that should lead to tangible progress over time is being established.

There are also many examples of local successes that demonstrate the renal community recognizes the importance of more local tailored efforts and how essential it is to act now. In addition to many successful screening programs such as the Kidney Early Evaluation Program (KEEP), a number of states have recently begun grassroots campaigns on public awareness and screening. For example, North Carolina has successfully initiated the Kidney Education Outreach Program (KEOP). The objective of this program is to screen and provide education about CKD using a mobile unit equipped with a fully functional examination room, restrooms, and a common area. In the state of Washington, the nonprofit Northwest Kidney Center’s Living Well with CKD program is addressing CKD through education, health screening, and collaboration with community organizations and health care providers, with specific outreach to the black community. The Centers for Disease Control and Prevention is also pilot-testing a new kidney disease screening program in California, Florida, New York, and Minnesota in collaboration with the National Kidney Foundation and the Chronic Diseases Research Group. This effort is targeting those who are older than 50 yr or those who have diabetes or hypertension.

Clearly, efforts to recognize CKD as a public health problem are moving forward. We need to recognize that fundamental aspects of kidney disease will likely translate to unique features of a public education/screening and prevention plan. The often-asymptomatic nature of kidney disease in early stages is a major hurdle toward effective disease recognition. We need to learn from what has worked in the past to get patients to doctors, doctors to screen, and insurance to cover. We need never to stop asking “why” when we uncover a barrier to improved care.

## DISCLOSURES

None.

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## Albuminuria, Wherefore Art Thou?

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No concept in kidney physiology raises as much interest and debate as proteinuria. All agree that the glomerular capillary wall is a highly selective barrier that restricts the passage of plasma proteins—thus its moniker the “glomerular filtration barrier” (GFB). Albumin is the most abundant plasma protein, and significant albuminuria is considered “selective glomerular proteinuria,” in contrast to the low molecular weight proteinuria that is classically linked to tubular abnormalities. Although most attention has been focused on GFB abnormalities as being responsible for albuminuria, Comper *et al.*<sup>1</sup> continue to present evidence for a tubular origin, with the latest appearing in this issue of *JASN*.<sup>2</sup> The view they advocate is in stark disagreement with long-accepted dogma of kidney physiology and pathophysiology, but if these investigators are correct, then there would be a major shift in the way proteinuric kidney diseases are viewed and, most important, treated.

Inherent in the hypothesis of a tubular origin for proteinuria is the claim that albumin's glomerular sieving coefficient (GSC) is high, at 0.02 to 0.04. This means that 2 to 4% of the albumin molecules subjected to the GFB cross into the glomerular filtrate. This estimate is approximately 50 times higher than the widely accepted GSC of approximately 0.0006.<sup>3</sup> The difference between these values is staggering; if the higher value is correct, then it means that in normal rats (GFR of 2 ml/min), 2 to 4 g/d albumin would be filtered, as opposed to only approximately 66 mg/d with the historically accepted GSC. When scaled to humans (GFR of 120 ml/min), 150 to 300 g/d albumin would be filtered; this level of albumin (essentially all of the albumin in the bloodstream) would obviously have to be reclaimed by a very efficient mechanism in the tubules to explain the lack of nephrotic-range albuminuria and negative nitrogen balance in healthy individuals. Indeed, Comper and colleagues<sup>4</sup> hypothesize that such a mechanism exists, and that albuminuria is caused primarily by defects in tubular uptake of intact albumin rather than by increased leakiness of the GFB. A corollary of the hypothesis is that albumin is not tubulotoxic, at least under normal conditions.

In this issue of *JASN*, Russo *et al.*<sup>2</sup> use two-photon microscopy in living rats to study the early diabetic kidney's handling of fluorescent Alexa568-conjugated rat albumin. Their data are in agreement with their previous results and support their hypothesis. By comparing the fluorescence signals in Bowman's space with those inside the glomerular capillary, they calculate the GSC of Alexa568-albumin to be 0.034, which is not changed in proteinuric diabetic animals. Filtered fluorescent albumin is rapidly taken up by proximal tubule cells (PTCs) in the normal kidney, but, in proteinuric animals, the retrieval pathway is impaired, resulting first in increased peptiduria and eventually in frank albuminuria. Glycemic control in diabetic animals prevents albuminuria by protecting the retrieval pathway in PTCs. Furthermore, the GSC of a 69-kD fluorescent dextran tracer, calculated to be 0.025, was comparable to that of the fluorescent albumin. The half-life of albumin, however, was longer, and only al-