

World Kidney Day 2011: Protect your kidneys, save your heart

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The sixth World Kidney Day, an annual event jointly sponsored by the International Society of Nephrology and the International Federation of Kidney Foundations, will be celebrated on 10 March 2011. Since its inception in 2006, World Kidney Day has grown dramatically to become the most widely celebrated event associated with kidney disease in the world and the most successful effort to raise awareness among both the general public and government health officials about the dangers of kidney disease, especially chronic kidney disease (CKD).

In 2011, World Kidney Day will call attention to the large, and often unappreciated, role played by kidney dysfunction in increasing premature cardiovascular disease (CVD), the most common cause of morbidity and mortality worldwide.

Can a focus on early detection and prevention of kidney disease really improve long-term cardiovascular health? In this Editorial, we hope to convey the message that increased attention to the kidneys will indeed improve long-term health outcomes by reducing both kidney and cardiovascular disease and should therefore be a central component of any global health strategy intended to reduce the enormous and growing burden of chronic non-communicable disease (NCD).

Cardiovascular disease and the kidney

CVD is the most common of the chronic NCDs that impact global mortality. About 30% of all deaths worldwide and 10% of all healthy life lost to disease are accounted for by CVD alone. Although there has been some decline in mortality from CVD in developed countries, no such decline has occurred in developing countries, in ethnic and socially disadvantaged minority populations, or in people with accompanying CKD.

The presence of CKD significantly increases the risk of a cardiovascular (CV) event in both diabetes and hypertension. However, less well appreciated is that CKD alone is a strong risk factor for CVD, independent of diabetes, hypertension, or any other conventional CVD risk factor. This is especially true when an increase in proteinuria, a major target of any CKD screening program, is present.

The 20- to 30-fold increase in CVD in patients with end-stage renal disease has long been recognized, but the increased risk for CVD associated with lesser degrees of renal-functional impairment was definitively demonstrated only in 2004, when an independent and graded association between glomerular filtration rate (GFR) and risk of death, CV events, and hospitalizations was reported in a community-based study of over 1000 individuals.

Is this dramatic increase in CVD risk associated with CKD really due to CKD, or does it just reflect the coexistent diabetes or hypertension that is present in a majority of these patients? The independent effect of CKD alone has now been well documented in many studies. The risk of cardiac death is increased by 46% in people with a GFR between 30 and 60 ml/min (stage III CKD) independent of traditional CV risk factors, including diabetes and hypertension. The increased risk of CV events and mortality in people over 55 with CKD alone is equivalent to, or even higher than, that seen in patients with diabetes or previous myocardial infarcts. Both general and high-risk populations exhibit an increased risk of CVD with CKD. This increased risk of CVD is not confined to the elderly; in volunteers with an average age of 45, the risk of myocardial infarct, stroke, and all-cause mortality was doubled in those with CKD.

Proteinuria and cardiovascular risk

In considering the value of recommending screening for CKD along with conventional CVD risk factors in selected individuals, data showing that the risk of CVD is better correlated with proteinuria (albuminuria) than with GFR alone are particularly relevant, because proteinuria is virtually always a marker of kidney disease and is not a conventional CVD risk factor.

With regard to proteinuria as a predictor of later CVD, the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study showed a direct linear relationship between albuminuria and risk of CV death in the general population even at levels of albumin excretion generally considered within the normal range (15–29 mg/d) and the risk of CV death was increased more than sixfold when albumin excretion exceeded 300 mg/d.

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Recent data from the US National Health and Nutrition Examination Survey (NHANES) database as well as from Japan also document an independent effect of albuminuria on risk of both CVD and all-cause mortality at all levels of GFR. In patients with congestive heart failure but without diabetes, hypertension, or reduced GFR, increased urinary albumin predicts both CV and all-cause mortality. Similar results are obtained in patients with coronary disease or previous myocardial infarcts, in whom proteinuria confers a greater risk of mortality than reduced GFR, although both adversely impacted outcomes.

Interestingly, not only the likelihood but also the time to development of a CV event is accelerated significantly by the presence of proteinuria at all levels of GFR. Of nondiabetic subjects with normal serum creatinine levels undergoing percutaneous coronary interventions, about 78% have demonstrable CKD when screened more stringently for renal function (estimated GFR, urine protein). Not only is the presence of CKD a likely factor in accelerating development of coronary disease in these patients, but it has also been associated with an increase in other risks, including hemorrhagic complications, contrast nephropathy, restenosis, and death. Thus multiple studies now confirm that proteinuria is a graded risk factor for CVD independent of GFR, hypertension, and diabetes and that this risk extends down into ranges of albumin excretion generally considered normal. Moreover, this increased CV risk has been well demonstrated in several studies in which only dipsticks were used to screen for increased protein excretion.

Although there has been concern that CKD diagnosed by reduced GFR alone identifies predominantly older adults at increased risk because of age alone, the establishment of proteinuria as an independent risk factor for CV mortality has been confirmed by meta-analysis of 22 separate, general-population, cohort studies and in both older (>65) and younger people of several nationalities and ethnic groups.

Can treatment of chronic kidney disease reduce cardiovascular disease?

Finally, and most importantly from a clinical perspective, there are provocative data to suggest that renal-targeted interventions designed to reduce proteinuria and slow progression of CKD can reduce CVD risk as well. Angiotensin-converting enzyme inhibitors (ACEIs) and/or angiotensin receptor blockers are of documented benefit in slowing progression of established diabetic and nondiabetic CKD. It is interesting, with regard to

slowing progression, that the incidence of CVD in CKD is significantly higher with more rapid loss of GFR independent of other risk factors, suggesting that interventions that slow progression may also reduce CVD. A 44% reduction in CV mortality over 4 years has been reported in patients screened from a general population with no risk factors except increased albumin in the urine and treated with renal-targeted ACEI therapy. This effect was seen primarily in people with albumin excretion rates higher than 50 mg/d in a pilot study, and the intervention was shown to be cost effective in that population. CV end points were significantly reduced in direct proportion to the reduction of albuminuria with ACEI therapy, and albuminuria proved to be the only predictor of CV outcome. Other studies have also demonstrated that changes in proteinuria (in diabetics) better predict outcomes than changes in blood pressure achieved with ACEI therapy. The potential benefit of renal-targeted therapies has recently been highlighted by observations that higher doses of renin-angiotensin system blockers than are required for blood pressure control alone can further reduce proteinuria independently of effects on blood pressure or GFR, and that addition of salt restriction or diuretics, both very inexpensive interventions, can further enhance the proteinuria-reducing effect of renin-angiotensin system blockade. Data are not yet available to establish that screening for CKD and subsequent interventions will reduce CV mortality and be cost effective in younger people (<55). However, it is now known that albuminuria is a better predictor of renal and cardiovascular events than blood pressure alone, that reducing proteinuria is more renal protective and cardioprotective than lowering blood pressure alone, and that identification of CKD can improve CV outcomes.

Conclusion

As celebrations of the sixth World Kidney Day on 10 March 2011 approach, it is worth noting that before the past decade, kidney disease was seen by most government and public-health authorities as being largely confined to patients with end-stage renal disease—thankfully a rare condition, because the enormous cost of renal replacement therapy disproportionately consumes scarce health-care resources and is well beyond the means of countries inhabited by more than 80% of the world's population. Much has changed. We now appreciate that kidney disease is not rare—some 10% of the population has evidence of renal dysfunction. And we know that these individuals are of concern not just because a few will progress

to end-stage renal disease, but more because they carry a greatly enhanced risk of premature death from CVD, the single largest and most expensive health-care threat we confront at a global level. Just as progress is being made in treating most of the traditional CV risk factors, CKD has emerged as yet another one that causes substantial vascular toxicity independently. Fortunately, there is good news as well. Biomarkers of CKD (proteinuria, estimated GFR) are easy and relatively inexpensive to detect, and one of these, proteinuria, emerges early in the evolution of generalized vascular disease. Thus kidney-targeted detection and prevention programs seem to offer a valuable opportunity to institute early preventive measures that go beyond traditional cardioprotective approaches. There is now compelling evidence that including selective screening for CKD in global health programs designed primarily

to reduce CVD will significantly improve the outcomes of not only renal disease, but especially the NCDs such as diabetes and CVD that dominate future health-care strategies. Road maps for accomplishing this have already been presented for both developed and emerging countries. However, effective implementation of such strategies will come only when both the general public and the renal community work together to convince health authorities it is in the public interest to do this. It is our sincere hope that worldwide celebration of World Kidney Day 2011 will provide an opportunity to reinforce the message that kidney disease is indeed common, harmful, and treatable and that protecting your kidneys is an important health strategy that may save your heart.

DISCLOSURE

The authors declared no competing interests.