The Importance of Early Identification of Chronic Kidney Disease

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Detection and intervention in early stage chronic kidney disease is more effective in delaying the progression of CKD-related morbidity and mortality.

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Abstract

Chronic kidney disease (CKD) is increasingly common and there is increasing recognition that early identification and management is critical in delaying progression of CKD as well as related complications. However, CKD is silent, awareness is low, and usually undetected until advanced stages. Herein, we will review screening and detection strategies for CKD as well as the importance of intervention in early stages to reduce progression and the burden of CKD.

Introduction

Chronic kidney disease (CKD) is increasingly common and affects approximately 24-28 million in the U.S. with an approximate 20 million more unidentified or at risk.[1,2] With the exponential growth of type 2 diabetes mellitus and other risk factors for CKD in developed and developing countries, it has become evident that CKD is now a global public health problem. Indeed, CKD progression to renal replacement therapy (RRT) is increasing both in incidence and prevalence worldwide in addition to an increasing recognition that management of CKD is critical in delaying progression to RRT as well as related complications.[3,4]

In this context, cardiovascular disease (CVD) is the leading cause of morbidity and mortality associated with CKD and improving individual cardiovascular risk is a major objective in the management of this population.[4,5] There are currently several interventions to delay progressive loss of renal function and/or reduce development of CVD. However, CKD is usually silent, awareness is low, and usually undetected until advanced stages; thereby many CKD patients are detected only shortly before or, in some cases, after the onset of symptomatic uremia, when opportunities to prevent adverse outcomes are few.[6-8] Intervention in early stage CKD is likely to be more effective in delaying the progression of disease as evidence support that early and regular nephrology specialist care is associated with reductions in CKD-related morbidity and mortality.[6]

Importance of Screening for Early Stage CKD

There are approximately 400,000 persons in the United States that receive renal replacement therapy (dialysis or transplantation) for treatment of ESRD in 2000, and by 2030 this number may increase to more than 2 million with a marked impact on health care expenditures.[3] The estimated prevalence for earlier CKD stages (stages 1-4) in U.S. adults

has increased from previous estimates from 20 million to 24 to 28 million, a number much higher than the RRT population with many millions more at risk based on the National Health and Nutrition Examination Survey (NHANES) 1999-2004.[1,2]

With the recognition that incident and prevalent CKD is increasing, the primary focus of current practice guidelines is to promote screening and detection of CKD in early stages in order that appropriate interventions to prevent progression of kidney disease can be undertaken. Several initiatives like the NKF sponsored Kidney Early Evaluation Program (KEEP)[9], National Institutes of Health (NIH) Healthy People 2010, and the Kidney Disease Education Program (KDEP), have taken the lead in educating patients as well as health care professionals about CKD and its implications, and the positive impact of early screening and treatment. Given the increasing number of people with CKD, and those at-risk, a concerted team effort by the primary care physician and sub-specialist communities are necessary to tackle this public health problem.

The KDOQI, KDIGO, as well as the American Diabetes Association clinical practice guidelines recommend screening/stratifying at-risk individuals for CKD using blood pressure, GFR estimation (eGFR) based on serum creatinine and other variables, urine albumin-to-creatinine ratio, examination of the urine sediment for red blood cells, white blood cells and casts, and imaging studies of the kidneys (in select individuals at increased risk of developing CKD). Those identified as being at highest risk are those with diabetes, hypertension, autoimmune diseases, patients recovering from an episode of acute renal failure, or those with a family history of CKD.

Detection of Early Stage CKD

The most common markers used in clinical practice for detection of CKD are serum creatinine (sCr), eGFR, and proteinuria. Although serum creatinine is a readily available test used in clinical practice to assess renal function, it varies with race, age, sex, muscle mass and diet and can be influenced by certain medications as well. Furthermore, with the recent introduction of standardized Cr assays that measure only true Cr levels as opposed to other "non-Cr chromogens," the range of normal has had to be adjusted by those using it and there are other medical centers that still report non-standardized creatinine levels. As a result, the use of sCr may not provide an accurate estimate of the kidney function. However, when used to calculate eGFR, sCr is considered one of the best overall measures of renal function and can be used as a screening tool for the diagnosis and monitoring of CKD. The traditional method of eGFR by calculating creatinine clearance from a timed (usually 24 hour) urine collection, is cumbersome and sometimes inaccurate due to lack of understanding the procedure. To overcome this, eGFR values can now be calculated from prediction equations that take into account sCr as well as other variables like age, gender, race, and body size. The equations most commonly used for eGFR in adults are the Cockcroft-Gault (10), MDRD (U.S. Modification of Diet in Renal Disease) [11], and the recent CKD-EPI equations (Chronic Kidney Disease Epidemiology Collaboration equation).[12]

In the U.S., diagnosis and classification of CKD is based on a set of established clinical practice guidelines through the National Kidney Foundation (NKF) Dialysis Outcome Quality Initiative (DOQI) in 2002 and the Kidney Disease: Improving Global Outcomes (KDIGO) in 2005.[7,8] CKD is defined as either (a) kidney damage ≥ 3 months, as confirmed by kidney biopsy or markers of kidney damage (presence of structural or functional abnormalities as evidenced by abnormal blood, urine or imaging studies) with or without a decrease in glomerular filtration rate (GFR) or (b) GFR < 60 mL/min/1.73 m^2 for ≥ 3 months with or without kidney damage. CKD is then stratified by risk into stages 1 through 4 based on the level of GFR with declining GFR being associated with worsening CKD. GFR < 15 mL/min/1.73 m^2 is considered stage 5 CKD/ ESRD.

In the context of diagnosis and detection of CKD at earlier stages with an eGFR > 60 mL/min/1.73 m^2, assessing for the presence of proteinuria is required to diagnose CKD. The KDOQI and KDIGO work groups advocate under most circumstances untimed ("spot"), first morning void urine samples to detect and monitor proteinuria in children and adults.[13] Although random sampling and even dipsticks are acceptable, individuals that test positive should undergo confirmation. Monitoring should then be performed using quantitative measurements of protein (or albumin)-to-creatinine ratio in spot urine samples and in general are stratified based on risk; 30-300 mg/g to diagnose microalbuminuria and > 300 to diagnose macroalbuminuria or overt proteinuria.[7,8]

Proteinuria is considered a marker for kidney injury and has been shown over time to be a strong marker/ predictor of cardiovascular outcomes as well as kidney disease progression[3,4,7,14]. Accordingly the KDIGO international work group readdressed this important point in 2009 in a conference dedicated to the controversies in definition, classification and prognosis of CKD. Central

to the discussion is a strong understanding from recent data that CKD and other high risk populations (e.g hypertension and diabetic) are increasing and, accordingly, so is cardiovascular morbidity and mortality associated with CKD. The work group recently reached a consensus on CKD staging based on the need for improvements in prediction of prognosis for CKD that could be improved by including proteinuria and estimated GFR along with cause of disease (e.g. diabetes and hypertension) in the classification scheme. It should be noted the work group did not advocate changing the definition rather to modify and include proteinuria and cause of disease. It is anticipated the NKF KDOQI will readdress with a new set of guidelines in the near future.

Early Stage CKD as a Risk factor for CVD

The most common risk factors for incident and prevalent CKD include type 2 diabetes mellitus and hypertension. In the context of early stage CKD (e.g. eGFR >60 and the presence of proteinuria), diabetes and hypertension related kidney disease often accompanies other co-morbid conditions, particularly the other traditional Framingham cardiovascular disease (CVD) risk factors: dyslipidemia, tobacco use, and increasing age. In addition, the presence of CKD can be associated with non-traditional CVD risk factors such as mineral metabolism disorders, anemia, uremia, oxidative stress and inflammation. However, these co-morbid conditions largely manifest at more advanced stages, especially as GFR diminishes <60 ml/min/BSA. The collective weight of these co-morbid conditions contribute to overall high morbidity and mortality associated with CKD. Thereby, it is widely considered that therapeutic interventions, both pharmacologic and lifestyle modifications are imperative to reducing cardiovascular risk as well as kidney disease progression in early stage CKD.

The traditional measured outcomes of CKD include progression of CKD (doubling of serum creatinine); progression to ESRD (requirement of RRT), CVD morbidity and mortality, and development of complications of impaired kidney function (e.g. eGFR < 60) such as anemia, disorders of mineral metabolism, and secondary hyperparathyroidism. The correlation between raised serum creatinine (sCr) levels and CVD mortality was first observed by Shulmar *et al.*, in 1989 in the Hypertension Detection and Follow up Program (HDvFP) study [15]. This concept received wide attention in 2003 after the scientific statement from the American Heart Association (AHA) endorsed the fact that increased CVD mortality is noted in patients with CKD when compared to the general population.[16] There is a strong, continuous correlation between increased risk for CVD events and impaired renal function, which begin at the earliest stages of renal impairment and rise continuously to 20 to 30 times above the general population as the renal damage progresses to ESRD.[17] While the risk for CVD morbidity and mortality is modestly evident at eGFR < 60, which increases sharply when eGFR < 45, it is important to note that this relationship starts with an eGFR < 90[18] and is strongest at early stages of CKD when weighted with proteinuria.[19]

The Importance of Diabetes on Early Stage CKD and CVD

Type 2 diabetes mellitus is a growing, worldwide epidemic of at least 171 million people[20]. As a result, diabetic complications such as CKD and CVD represent grave public health threats. At least 80 percent of deaths in the U.S. in patients with type 2 diabetes mellitus are attributable to CVD, and their age-adjusted relative risk of fatal CVD has been calculated to be three times higher than for the non-diabetic population. Numerous studies have described a similar relationship in those with early stage CKD; the presence of type 2 diabetes mellitus augments prevalent CVD compared to non-diabetics [19,21].

The role of diabetes in early stage CKD, especially in the context of CVD morbidity and mortality, is highlighted when considering that proteinuria at an eGFR > 60 strengthens predictors of kidney disease progression and CVD event[4,5,13]. Numerous studies have demonstrated a continuous, graded relationship between increasing levels of proteinuria and prevalent risk factors for CVD event including; insulin resistance, hypertension, obesity, dyslipidemia,[22, 23, 24, 25] findings that are especially pronounced in the presence of lower level proteinuria or microalbuminuria, a finding characteristic of early stage CKD. Thereby, the presence of one or more of the traditional cardiovascular risk factors with microalbuminuria such as insulin resistance, hypertension, obesity, dyslipidemia, tobacco use, and advanced age convey significantly higher risk for CVD mortality in diabetic individuals with early stage CKD.

Given the enormous CVD risk burden observed in patients with CKD, especially in those with diabetes, multiple work groups have convened to address CVD in CKD. Current practice should dictate that patients with CKD, even early stage, be considered in the "highest risk group" for subsequent CVD events as recommended by the AHA[23] as well as complementary statements from the

JNC-VII[26] and NKF. As a result, early stage CKD, those with eGFR > 60 and demonstrated proteinuria, should be treated as a coronary artery disease equivalent for purposes of risk stratification.

Conclusion

It is well recognized that incident and prevalent CKD is increasing along with the growth of diabetes and other risk factors for CKD in developed and developing countries. In this context, the burden of CKD morbidity and mortality is high, an observation that extends into the earliest stages of CKD and that is augmented by the presence of diabetes. Management of early stage CKD is critical in delaying progression to RRT as well as CKD related complications and there are currently several interventions now available. However, awareness of CKD is low and CKD is usually silent and not usually detected until advanced stages; thereby many patients are detected only shortly before onset of symptomatic uremia, when opportunities to prevent adverse outcomes are few. Ultimately, detection and intervention in early stage CKD is more effective in delaying the progression of CKD-related morbidity and mortality.

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Disclosure

None reported.