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Original Paper

A Case for Early Screening for Diabetic Kidney Disease

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Abstract
Chronic kidney disease (CKD) is a public health dilemma contributing to increasing global morbidity and mortality. There is increasing recognition that early detection and management of CKD is critical in delaying disease progression as well as improving mortality rates. However, kidney disease is a silent process and usually goes undetected until more advanced stages, wherein the opportunity to intervene and improve kidney-related outcome is diminished, since awareness of CKD is low in earlier stages. Herein, we will review the screening and detection strategies for CKD as well as the importance of intervention in early stages to reduce progression and also the burden of CKD.

Introduction

Chronic kidney disease (CKD) is increasingly common and affects approximately 24–28 million people in the United States, with an approximate 20 million more unidentified or at risk [1, 2]. With the exponential growth of type 2 diabetes mellitus, the leading cause of incident CKD and end-stage renal disease (ESRD), it has become evident that CKD is now a global public health problem [3]. Indeed, CKD progression to ESRD is increasing in inci-

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dence and prevalence worldwide in addition to an increasing recognition that management of diabetic-related complications is critical in improving survival and delaying progression to ESRD [4, 5].

In this context, the presence of kidney disease in patients with diabetes augments the risk for cardiovascular disease (CVD)-related outcomes, the leading cause of morbidity and mortality associated with diabetes [5, 6]. Thereby, improving individual CVD risk is the foremost concern in the management of the CKD population [3]. There are several interventions to delay progressive loss of renal function and/or improve CVD-related morbidity and mortality. However, awareness of CKD is low in early stages and disease progression is asymptomatic, hence the majority of patients either do not survive to require renal replacement therapy or CKD is detected only shortly before the onset of symptomatic uremia, when opportunities to prevent adverse CVD outcomes are few [7–9]. Therefore, intervention in early-stage CKD is likely to be more effective in delaying disease progression and improving morbidity and mortality [3, 7].

Screening in Early Stages for CKD

With the recognition that incident and prevalent CKD is increasing [1–4, 10], the primary focus of current practice guidelines is to promote screening and detection of CKD in early stages so that appropriate interventions to prevent progression of kidney disease can be undertaken. Several initiatives – such as KEEP, the National Kidney Foundation (NKF)-sponsored Kidney Early Evaluation Program [11], the National Institutes of Health Healthy People 2010 [12], and NKDEP, the National Kidney Disease Education Program [13] – have taken the lead in educating patients as well as healthcare professionals about CKD and diabetic kidney disease (DKD), the implications of CKD and DKD, and the positive impact of early screening and treatment.

However, conventional wisdom may dictate screening for CKD in early stages, and it is not known whether population-based screening is cost-effective. A recent population-based study screening for CKD with assessment of estimated glomerular filtration rate (eGFR) was found to be not cost-effective in subgroups with hypertension or older people. However, targeted screening of patients with diabetes was associated with cost-effectiveness [14]. At this point, a concerted effort by primary care physicians and subspecialists targeting those identified as being at highest risk, i.e., patients with diabetes, hypertension, and/or autoimmune diseases, patients recovering from an episode of acute renal failure, or those with a family history of CKD, is necessary to tackle this public health dilemma [15].

The Kidney Disease Outcomes Quality Initiative (KDOQI) [15], Kidney Disease: Improving Global Outcomes (KDIGO) [16], and the American Diabetes Association [17] clinical practice guidelines recommend screening and stratifying at-risk individuals for CKD using blood pressure, eGFR based on serum creatinine (sCr) 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 [15–17]).

Detection of CKD in Early Stages

The most common markers used in clinical practice for the detection of CKD are sCr, eGFR, and proteinuria [15]. Although sCr is a readily available test used to assess renal function in clinical practice, its results vary with age, sex, muscle mass, and diet. As a result, the

use of sCr may not give an accurate estimate of the kidney function. However, when sCr is used to calculate eGFR, it is considered one of the best overall measures of renal function and can be used as a screening tool for the diagnosis, staging, and monitoring of CKD.

The traditional method of estimating GFR values by calculating creatinine clearance from a timed (usually 24 h) urine collection is cumbersome. To overcome this, eGFR values can now be calculated from prediction equations that take sCr as well as other variables, such as age, gender, race, and body size, into account [15, 18, 19]. The equations most often used for eGFR in adults are the Cockcroft-Gault [18], the US Modification of Diet in Renal Disease (MDRD) [19], and the recent CKD Epidemiology Collaboration (CKD-EPI) equations [20].

In the United States, diagnosis and classification of CKD are based on a set of established clinical practice guidelines – the 2002 NKF-KDOQI and the 2005 KDIGO guidelines [7, 8]. Based on these guidelines, CKD is defined as one of two options [15]:

(1) Kidney damage ≥3 months, as confirmed by kidney biopsy or by markers of kidney damage (i.e., presence of structural or functional abnormalities as evidenced by abnormal blood, urine, or imaging studies) with or without a decrease in GFR, or
(2) GFR <60 ml/min/1.73 m^2 for ≥3 months, with or without kidney damage. CKD is then stratified by risk into stages 1–4 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.

When using eGFR >60 ml/min/1.73 m^2 for the diagnosis and detection of CKD at earlier stages, the presence of proteinuria is one marker to meet the diagnosis [15, 16]. 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. Although random sampling and even dipsticks are acceptable, individuals that test positive should undergo confirmation. Monitoring should then be performed using quantitative measurements of the protein (or albumin)-to-creatinine ratio in spot urine samples and in general are stratified based on risk: >30 mg/g normoalbuminuric, 30–300 mg/g to diagnose microalbuminuria and >300 mg/g to diagnose macroalbuminuria or overt proteinuria.

Proteinuria is considered a marker for kidney injury and has been shown over time to be a strong marker/predictor of cardiovascular outcome, as well as kidney disease progression [4, 5, 15, 21]. The KDIGO international work group readdressed this important point in 2009 at a conference dedicated to the controversies in definition, classification, and prognosis of CKD [16, 22]. Central to the discussion is a strong understanding from recent data that CKD and other high-risk conditions (e.g., hypertension and diabetes) are increasing and, accordingly, so is CVD morbidity and mortality associated with CKD [23]. The KDIGO work group recently reached a consensus on CKD staging based on the need for improvements in the prediction of prognosis for CKD that could be improved by including proteinuria and eGFR measures, along with the cause of disease (e.g., diabetes and hypertension) in the classification scheme [22]. The work group, however, did not advocate a change in the definition but rather opted to modify and include proteinuria and the cause of disease. It is anticipated that the NKF-KDOQI will address this issue in a new set of guidelines in the near future [22].

Even though sCr is the most commonly used test in clinical practice to assess renal function, sCR may not be the most accurate in early stages of kidney disease when screening and detection are critical. There are multiple reasons including biologic, pharmacologic, and estimation misclassification. In this context, rises in sCr appear only after significant loss of functioning nephrons. Moreover, the generation of Cr is based on muscle mass and diet, and the excretion or secretion of sCr is influenced by drugs such as cephalosporins, aminoglycosides, cisplatin, cimetidine, and trimethoprim.

Table 1. Recent studies utilizing CKD-EPI

Study	Participants n	Demographics	Study aim	Outcomes	Comments
Kurella Tamura et al. [26]	26,231	United States community screening program	CKD awareness comparison of MDRD and EPI equations	9.5 vs. 10% patients were aware of CKD using MDRD versus EPI equations, respectively	using EPI-based GFR led to a modest increase in overall awareness rates, primarily due to reclassification of low-risk unaware participants
White et al. [27]	11,247	Australia baseline screening for the AusDiab study survey of adults >25 years	comparison of prevalence and mortality risk of CKD in adults >25 years	prevalence of CKD was 13.4 vs. 11.5% using MDRD and EPI equations, respectively	lower rates using EPI versus MDRD were seen, most predominantly in women with low CVD risk
López-Suárez et al. [28]	858	Spain population aged 50–75 years	assessing prevalence of CKD by MDRD and EPI equations in older adults	prevalence rates using MDRD were 35% in men and 68% in women vs. 25 and 45% in men and women using EPI, respectively	compared to MDRD, the EPI equation generated a substantial reduction in all patients, most notably in non-albuminuric women
Horio et al. [29]	763 patients	Japan based on estimates of 574,024 participants for health check	comparison of Japanese coefficient-modified CKD-MDRD and CKD-EPI equations	modified CKD-EPI equation yielded a lower prevalence (7.9%) than using CKD-MDRD (10%)	most study participants had CKD and few patients had GFR >90 ml/min

However, estimating GFR may be the best available index for kidney function. The NKDEP, NKF, and the American Diabetes Association recommend estimation of GFR from sCr using either the MDRD study equation or the Cockcroft-Gault equation [13, 15, 17]. Both equations take sCr along with age, sex, and weight variables into account, thus minimizing the limitations using sCr alone. However, there are limitations of the MDRD equation for eGFR due to imprecision and systematic underestimation of GFR at higher levels (e.g. eGFR >60 ml/min/1.73 m^2) [24]. The MDRD study equation was developed using data from 1,628 CKD patients with a mean measured GFR of 40 ml/min/1.73 m^2 [25]. It has been shown to be valid in similar populations but may underestimate measured GFR at the higher range leading to misclassification to a lower category and thus over diagnosis of CKD. Thereby, in 2009 a recent adaption for estimating GFR, the CKD-EPI equation, may overcome the limitations of MDRD in earlier stages for screening, detection, and classification of CKD (table 1) [26–29]. The CKD-EPI equation was developed using data from 8,254 people and validated in a separate data set of 3,896. Both the development and validation data sets included people with and without kidney disease and a wide range of GFRs, with a mean measured GFR of 68 ml/min/1.73 m^2. The CKD-EPI equation has been shown to be a better estimate of measured GFR than the MDRD study equation, particularly at higher levels.

CVD in Early Stages of CKD

The most common risk factors for incident and prevalent CKD include type 2 diabetes and hypertension [1–3, 15]. In the context of early-stage CKD (e.g., eGFR >60 ml/min/1.73 m^2 and the presence of proteinuria), diabetes- and hypertension-related kidney disease often accompany other comorbid conditions, particularly the other traditional Framingham CVD risk factors – dyslipidemia, tobacco use, and increasing age. In addition, the presence of CKD

can be associated with nontraditional CVD risk factors, such as mineral metabolism disorders, anemia, uremia, oxidative stress, and inflammation [15, 30–32]. However, these comorbid conditions largely occur at more advanced stages, especially as GFR diminishes to <60 ml/min/body surface area. The collective weight of these comorbid conditions contributes to the overall high morbidity and mortality associated with CKD [5, 6]. It is therefore considered that therapeutic interventions, both pharmacologic and lifestyle interventions, 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 sCr); progression to ESRD; CVD morbidity and mortality, and development of complications of impaired kidney function (e.g. eGFR <60 ml/min/1.73 m^2), such as anemia and disorders of mineral metabolism. The correlation between raised sCr levels and CVD mortality was first observed in 1989 by Shulman et al. [21] in the Hypertension Detection and Follow-Up Program study. This concept received wide attention in 2003 after the scientific statement from the American Heart Association endorsed the finding that increased CVD mortality is noted in patients with CKD compared with the general population [30]. There is a strong, continuous correlation between increased risk for CVD events and impaired renal function, which begins at the earliest stages of renal impairment and rises continuously to 20–30 times above the risk in the general population as renal damage progresses to ESRD [32]. Although the risk for CVD morbidity and mortality is evident at eGFR <60 ml/min/1.73 m^2, increasing sharply when eGFR <45 ml/min/1.73 m^2, the evidence for this begins with an eGFR <90 ml/min/1.73 m^2, and is strongest at early stages of CKD when weighted with proteinuria [31].

The Importance of Diabetes in Early-Stage CKD and CVD

Type 2 diabetes mellitus is a growing worldwide epidemic affecting at least 171 million people [33]. As a result, diabetic complications, such as CKD and CVD, represent a critical public health threat. Numerous studies suggest the presence of type 2 diabetes augments prevalent CVD in those with CKD [31, 34]. Many studies further demonstrate a continuous, graded relationship between increasing levels of proteinuria and prevalent risk factors for the CVD event, such as the presence of insulin resistance, hypertension, obesity, and dyslipidemia [5, 6, 30]. CVD risk factors are especially pronounced in the presence of lower-level proteinuria or microalbuminuria, a finding characteristic of early-stage CKD. In this context, it should be noted that the risk for CVD extends into the earliest stages of CKD (e.g. >60 ml/min/1.73 m^2) and the presence of albuminuria strengthens predictors of kidney disease progression and CVD event [5, 6, 10, 21, 31, 33].

Given the high CVD risk that CKD conveys, there is little information on CVD risk reduction strategies in the context of CKD detection in early stages. There are two programs that screen for CKD: the US KEEP [10, 11] and the Dutch Prevention of Renal and Vascular End-Stage Disease (PREVEND). NKF-KEEP utilizes personal and family medical history in the detection of CKD while PREVEND uses the presence of microalbuminuria and has an intervention trial (PREVEND IT). In PREVEND IT, investigators randomize participants to angiotensin-converting enzyme inhibition or lipid-lowering therapy with an HMG-CoA reductase inhibitor (e.g. statin), and participants were followed over time to determine risk reduction for cardiovascular morbidity and mortality outcomes. Recent data from PREVEND IT would suggest that during the 9.5-year follow-up incorporation of an angiotensin-converting enzyme inhibitor only improved CVD mortality at the higher quartiles of proteinuria (e.g. urine albumin excretion >50 mg/day) and not at lower quartiles or with

statin use [35] suggesting the presence of proteinuria may strengthen this association. However, previous work on targeting proteinuria for CVD risk reduction in CKD has centered around clinical hypertension trials utilizing angiotensin-converting enzyme inhibitors or angiotensin type 1 receptor blockers in CKD [36, 37]. However, the bulk of these trials have concentrated on heavier proteinuric burden and not focused on the detection in early stages as the KEEP and PREVEND, suggesting further work is needed.

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 at early stage, be considered in the 'highest risk group' for subsequent CVD events, as recommended by the American Heart Association [30], as well as by complementary statements from the JNC 7 (Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) [34] and the NKF [15]. As a result, those with early-stage CKD (eGFR > 60 ml/min/1.73 m^2) and demonstrated proteinuria should be treated as a coronary artery disease equivalent for purposes of risk stratification [36].

Conclusions

It is well recognized that incident and prevalent CKD is increasing, along with the growth of diabetes. 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/DKD is critical in delaying progression, as well as CKD-related complications, and several interventions are now available. However, awareness and identification of CKD remains low. Managed care organizations and healthcare professionals can and should work together to increase awareness of CKD and ensure that screening programs are effectively implemented in at-risk populations. Ultimately, aggressive screening programs will prevent or delay further development of CKD to more advanced stages, which will help decrease overall healthcare expenditures related to CKD/DKD and improve the quality of life of this patient population as well as decrease the burden on their caregivers.

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