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Review

Diagnosis

Importance of urine albumin-creatinine ratio in the diagnosis and prognosis of chronic kidney disease

CH Fox[1]*, K Neuhaus[2], JA Vassalotti[3]

Abstract

Introduction

New Kidney Disease Improving Global Outcomes guidelines represent a significant change from the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative, which indicate that the urinary albumin/creatinine ratio is now integral to the classification of chronic kidney disease. The urinary albumin/creatinine ratio has been found to be fundamentally important for both the diagnosis and the prognosis of chronic kidney disease. It is now recommended that all patients with diabetes or hypertension be screened annually with this test. The presence of albuminuria helps decide the medications for the treatment of hypertension. This review discusses the importance of urine albumin–creatinine ratio in chronic kidney disease.

Conclusion

More research is needed to determine definitively whether or not the treatment of albuminuria delays the progression of chronic kidney disease and reduces mortality.

Introduction

The 2012 Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines[1] represent a significant update from the 2002 National Kidney Foundations Kidney Disease Outcomes Quality Initiative (KDOQI)[2], which indicates that the urinary albumin–creatinine ratio (UACR) is now integral to the classification of chronic kidney disease (CKD). The UACR is found to be fundamentally important for both the diagnosis and the prognosis of CKD. It is now recommended that all patients with diabetes and/or hypertension be screened annually with this test.

Worldwide, the incidence of CKD is on the rise, and it generally remains asymptomatic until advanced stage. Only 10% of CKD patients are recognised by primary care clinicians[3]. A study conducted in 2011 found that approximately 39% of US citizens with end-stage renal disease (ESRD) had never consulted a nephrologist prior to initiation of dialysis[4]. Kidney disease is very costly in the Medicare population[5]. Major risk factors for CKD are diabetes, hypertension, age (60 years or greater), and a family history of CKD. Current population detected with CKD may be significantly under-represented because proteinuria/albuminuria test is underutilised[4]. In USA, the lifetime risk estimate of CKD surpasses that of other common conditions, including coronary disease, diabetes and invasive cancer[6]. Importantly, CKD is a major cardiovascular risk, which is equivalent to that of either having diabetes before a heart attack incidence[2]. The level of kidney function predicts the risk of myocardial infarction and mortality rate[7]. The aim of this review was to discuss the importance of UACR in the diagnosis and prognosis of CKD.

Discussion

The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

Diagnosis and staging of CKD

The most significant change in the new KDIGO guidelines[8] (versus the original KDOQI guidelines)[2] is the new classification that makes the UACR as important as estimated glomerular filtration rate (eGFR) in evaluating the severity of the disease[9]. The recommendations call for characterising CKD based on underlying cause, GFR category and albuminuria category, as all these influence clinical management, outcomes and mortality[8]. (Figure 1) demonstrates (reprint of KDIGO, Figure 4) rapid increase in mortality once the eGFR drops below 60 ml/min/1.72 m^2 and/or once the UACR rises above 3.0 mg albumin/mmol creatinine[10]. Effects of both eGFR and UACR are additive in causing mortality in patients with both CKD and acute kidney injury (AKI) (Figure 2)[9]. Opportunities to delay progression of the disease and prevent cardiovascular events are lost if the clinician relies only on changes in eGFR and serum creatinine to diagnose and follow the progression of disease.

CKD is diagnosed based on low eGFR, which is <60 ml/min/1.73 m^2, and/or UACR of >30 mg albumin/g creatinine. The UACR is also known as the microalbumin test. There must be two consecutive abnormal values for eGFR and/or UACR of at least 90 days apart to confirm the diagnosis of CKD[11]. The

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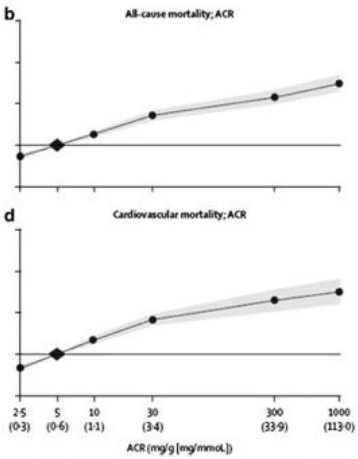


Relationship of albuminuria with mortality. HRs and % CIs for all-cause (**b**) and cardiovascular mortality (**d**) ording to ACR. HRs and 95% CIs (shaded areas) are adjusted for e, sex, ethnic origin, history of CVD, systolic BP, diabetes, oking, and total cholesterol and spline eGFR. The reference mond) was ACR 5 mg/g (0.6 mg/mmol) and eGFR 95 ml/min/ 3 m^2, respectively. Circles represent statistically significant and ngles represent not significant. ACR plotted in mg/g. To vert ACR in mg/g to mg/mmol multiply by 0.113. Approximate versions to mg/mmol are shown in parentheses. ACR, umin-to-creatinine ratio; BP, blood pressure; CI, confidence erval; CVD, cardiovascular disease; eGFR, estimated glomerular ation rate; HR, hazard ratio. Reprinted from The Lancet, vol i, Matshushita K, van de Velde M, Astor BC, et al.[4] Association of imated glomerular filtration rate and albuminuria with all-cause d cardiovascular mortality in general population cohorts: a laborative meta-analysis, p. 2073-2081, 2010, with permission m Elsevier; accessed http://download.thelancet.com/pdfs/ rnals/lancet/PIIS0140673610606745.pdf

Figure 1: UACR and eGFR both affect mortality.

eGFR is widely accepted as the best assessment mean of kidney function because eGFR is usually reduced only following widespread structural damage and also because most of other kidney functions decline in parallel with the GFR[8]. As eGFR declines, patients experience higher rates of drug toxicity, AKI, CKD complications, CVD, and all-cause mortality. Direct measurement method of GFR is not routinely available to clinicians; therefore, estimated, or eGFR, is derived from serum creatinine and biometric variables of age, gender, race, and serum creatinine. It is reported as part of a standard metabolic profile by most of the laboratories. Currently preferred formula is CKD-EPI[12], as it is more accurate for estimating GFR above 60 ml/min/1.73 m^2.

Albuminuria is currently the primary laboratory indicator for ongoing kidney structural damage, and is the principle urine protein in most of the renal diseases[13,14]. It is the earliest marker of glomerular disease, and often appears before any reduction in eGFR. Physiologically, albuminuria is related to endothelial damage, and correlates with both cardiovascular disease and retinopathy. Despite recent emphasis on the importance of assessing urine microalbumin levels regularly in diabetes patients, there is widespread inconsistent use of and misapplication of the term in clinical settings to include everything from dipstick assessment of total protein to the intended quantitative measurement of UACR. Too low levels of "microalbuminuria", which is referred to as urine albumin, are to be detected by a routine urine dipstick test. KDIGO recommends discontinuing the use of micro- and macroalbuminuria levels in favour of the terms "moderate" and "severe" albuminuria.

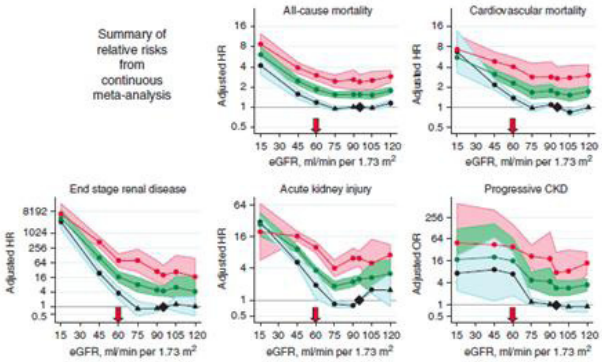
For each GFR stage, the degree of albuminuria is an independent risk modifier (Figure 3). Recent studies have suggested that urinary albumin may play a causative role in renal damage[15]. Renin–angiotensin–aldosterone system (RAAS) blockade has been demonstrated to reduce albuminuria and reduce the rate of eGFR decline[16]. For simplicity and clinical relevance, current recommendations suggest recognition of three categories of albuminuria (Figure 4).

Stage A1: UACR <3 mg albumin/mmol creatinine level is currently considered to be physiologic level

Stage A2: UACR 3–29.9 mg albumin/mmol creatinine, formerly microalbuminuria, now referred to as moderate albuminuria

Stage 3: UACR =>3 mg albumin/mmol creatinine, formerly macroalbuminuria, now referred to as moderate-to-severe albuminuria

Risk related to the level of albuminuria is continuous, that is, it is graded across the spectrum, and current categories may be revised, based on the results of ongoing studies. Levels of 15–30 mg/ml (15–30 mg albumin/mmol creatinine) may prove to be clinically significant, as it has been demonstrated recently that even as little as 1.5 mg albumin/mmol creatinine is associated with an increased risk of adverse events[10]. Some researchers have referred to those with <3 mg albumin/mmol creatinine as normoalbuminuric (or similar terms) to distinguish these patients from those with undetectable urine albumin. Prevention of Renal and End Stage vascular Disease (PREVEND) a



Summary of continuous meta-analysis (adjusted RRs) for general population cohorts with ACR. Mortality is reported for general population cohorts assessing albuminuria as urine ACR. Kidney outcomes are reported for general population cohorts assessing albuminuria as either urine ACR or reagent strip. eGFR is expressed as a continuous variable. The three lines represent urine ACR of <30, 30-299 and ≥300 mg/g (<3, 3-29, and ≥30 mg/mmol, respectively) or reagent strip negative and trace, 1+ positive, ≥2+ positive. All results are adjusted for covariates and compared to reference point of eGFR of 95 ml/min/1.73 m^2 and ACR of <30 mg/g (<3 mg/mmol) or reagent strip negative (diamond). Each point represents the pooled RR from a meta-analysis. Solid circles indicate statistical significance compared to the reference point ($P < 0.05$); triangles indicate non-significance. Red arrows indicate eGFR of 60 ml/min/1.73 m^2, threshold value of eGFR for the current definition of CKD. ACR, albumin-to-creatinine ratio; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; OR, odds ratio, RR, relative risk. Reprinted with permission from Macmillan Publishers Ltd: *Kidney International*. Levey AS, de Jong PE, Coresh J, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO controversies conference report. Kidney Int 2011; 80: 17-28[30]; accessed http://www.nature.com/ki/journal/v80/n1/full/ki2010483a.html

Figure 2: UACR and eGFR are synergistic in their effects on mortality[8].

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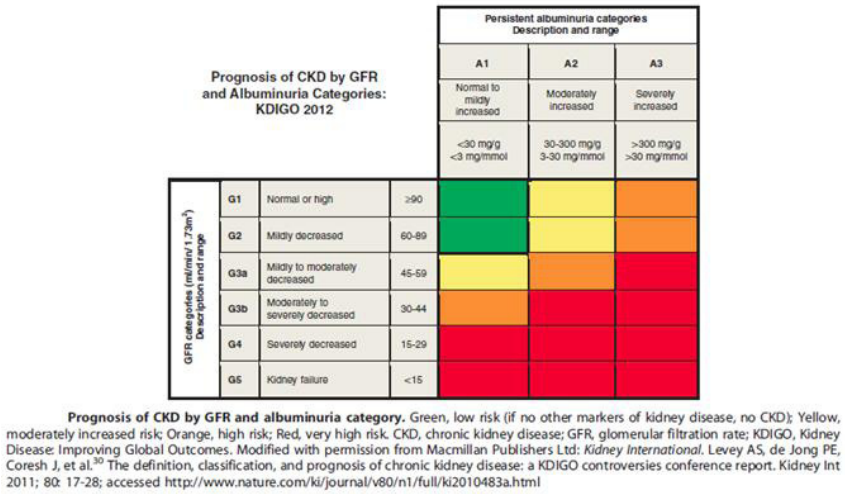

Prognosis of CKD by GFR and albuminuria category. Green, low risk (if no other markers of kidney disease, no CKD); Yellow, moderately increased risk; Orange, high risk; Red, very high risk. CKD, chronic kidney disease; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes. Modified with permission from Macmillan Publishers Ltd: *Kidney International*. Levey AS, de Jong PE, Coresh J, et al.[30] The definition, classification, and prognosis of chronic kidney disease: a KDIGO controversies conference report. Kidney Int 2011; 80: 17-28; accessed http://www.nature.com/ki/journal/v80/n1/full/ki2010483a.html

Figure 3: Classification and risk of CKD based on eGFR and UACR.

other recent population-based studies have suggested that albuminuria of <3.0 mg/mmol is associated with increased risk factors for CVD and mortality, and is a potential early indicator of glomerular hyperperfusion and elevated GFR in the early stages of diabetic glomerulonephropathy[17]. Levels above 30 mg albumin/mmol creatinine are already recognised by specialty centres, such as levels in excess of 220 mg albumin/mmol creatinine in nephrotic syndrome.

Screening and monitoring with UACR

Although a recently published article indicated a 60% lifetime risk of Stage 3 CKD or worse in US population[6], which may foretell trends in other developed nations, routine screening of all adults is not recommended by the US Preventive Services Task Force[18] and is unlikely to be cost-effective, according to the Belgian PREVEND study[17]. KDOQI and KDIGO guidelines recommend[2,8] obtaining urine protein or albumin–creatinine ratio annually during the routine physical examination for adults with risk factors for CKD, including hypertension, diabetes, family history of CKD, and age >60 years.

The prevalence of CKD increases with age, prompting the US National Kidney Foundation to recommend screening of all adults aged 60 years and older, in response to a recent finding that 6 of 10 US adults will develop CKD[18]. Owing to the widespread availability of non-prescription nonsteroidal anti-inflammatory drugs (NSAIDs) in many countries, coupled with general public unawareness of the potential renal risk[19], routine screening of older adults can help identify and monitor individuals at a higher risk.

Additional risk groups may benefit from routine checking of UACR, though the evidence supporting its efficacy is lacking. Those with impaired glucose tolerance/metabolic syndrome, atherosclerosis, a history of AKI, certain autoimmune disorders and smokers are also at a higher risk, and recent evidence indicates that obesity is an independent risk factor for CKD, even in the absence of other known predictors. African-Americans tend to develop kidney disease 10–15 years earlier than the general population; therefore, earlier screening may be warranted for this group[20].

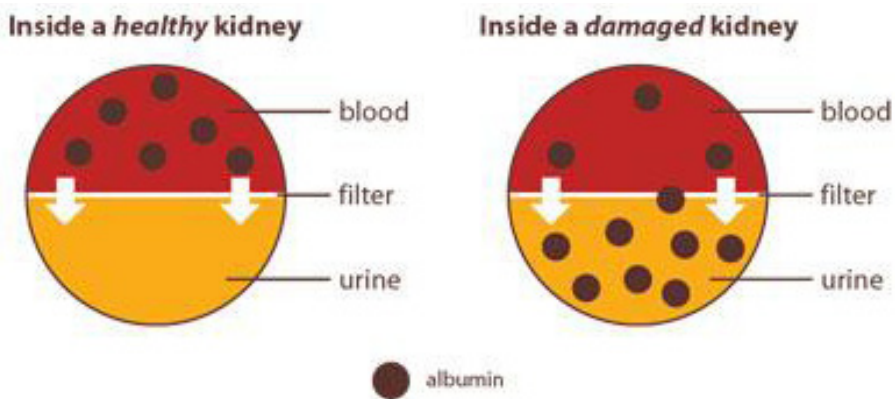

Figure 4: Albuminuria represents kidney damage.

Management of albuminuria

Measurement of albuminuria is an indication for the treatment of hypertension with an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker[21]. Dual RAAS blockade with spironolactone has also been found to be helpful. This, of course, comes with the caveat that potassium has to be carefully monitored in such circumstance[22]. However, safety signals of AKI and hyperkalaemia in the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) and Nephron D trials suggest that dual RAAS blockade with an ACE inhibitor and ARB should be avoided. Intensifying monotherapy with ACE inhibitor or ARB may be a better strategy[23–25].

Conclusion

Diagnosis and classification of CKD require assessment of both eGFR and UACR. Urine albumin–creatinine screening should be incorporated

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into routine assessments for all at-risk adults. This screening can be integrated into other chronic care processes. This will enhance the ability of primary care providers to detect and manage kidney functional change, and to refer to the nephrologist when appropriate. The most effective treatment is RAAS blockade and avoidance of NSAIDs. More research is needed to know if delay of progression of albuminuria results in improved clinical outcomes and whether the rate of increase of albuminuria is a poor prognostic indicator.

Abbreviations list

AKI, acute kidney injury; CGA, GFR category, and albuminuria category; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; KDIGO, Kidney Disease: Improving Global Outcomes; KDOQI, Kidney Disease Outcomes Quality Initiative; RAAS, renin–angiotensin–aldosterone system; UACR, urinary albumin/creatinine ratio.

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