

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

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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 guidelines¹ 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 clinicians³. 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 dialysis⁴. Kidney disease is very costly in the Medicare population⁵. 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 underutilised⁴. In USA, the lifetime risk estimate of CKD surpasses that of other common conditions, including coronary disease, diabetes and invasive cancer⁶. Importantly, CKD is a major cardiovascular risk, which is equivalent to that of either having diabetes before a heart attack incidence². The level of kidney function predicts the risk of myocardial infarction and mortality rate⁷. 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 guidelines⁸ (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 disease⁹. The recommendations call for characterising CKD based on underlying cause, GFR category and albuminuria category, as all these influence clinical management, outcomes and mortality⁸. (Figure 1) demonstrates (reprint of KDIGO, Figure 4) rapid increase in mortality once the eGFR drops below 60 ml/min/1.72 m² and/or once the UACR rises above 3.0 mg albumin/mmol creatinine¹⁰. 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 m², 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 CKD¹¹. The

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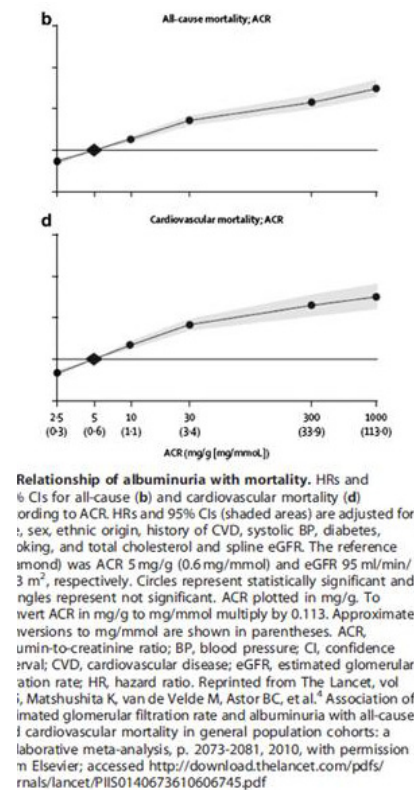


Figure 1: UACR and eGFR both affect mortality.

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 GFR⁸. 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-EPI¹², as it is more accurate for estimating GFR above 60 ml/min/1.73 m².

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 damage¹⁵. Renin-angiotensin-aldosterone system (RAAS) blockade has been demonstrated to reduce albuminuria and reduce the rate of eGFR decline¹⁶. 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 =>30 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 events¹⁰. 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

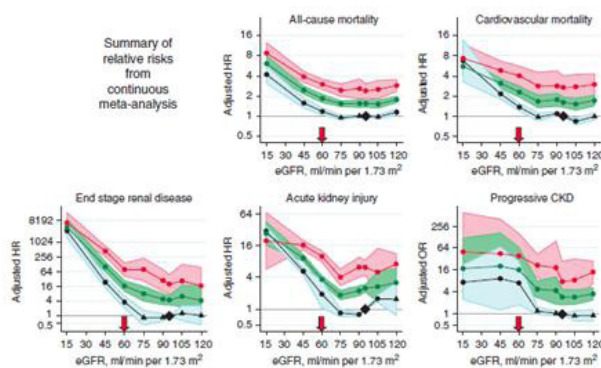


Figure 2: UACR and eGFR are synergistic in their effects on mortality⁸.

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Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012			Persistent albuminuria categories			
			A1	A2	A3	
			Normal to mildly increased	Moderately increased	Severely increased	
			<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol	
GFR categories (ml/min/1.73m ²) Description and range	G1	Normal or high	>90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

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.²⁰ 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 glomerulonephropathy¹⁷. 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 population⁶,

which may foretell trends in other developed nations, routine screening of all adults is not recommended by the US Preventive Services Task Force¹⁸ and is unlikely to be cost-effective, according to the Belgian PREVEND study¹⁷. 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 CKD¹⁸. 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 risk¹⁹, 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 group²⁰.

Management of albuminuria

Measurement of albuminuria is an indication for the treatment of hypertension with an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker²¹. 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 circumstance²². 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

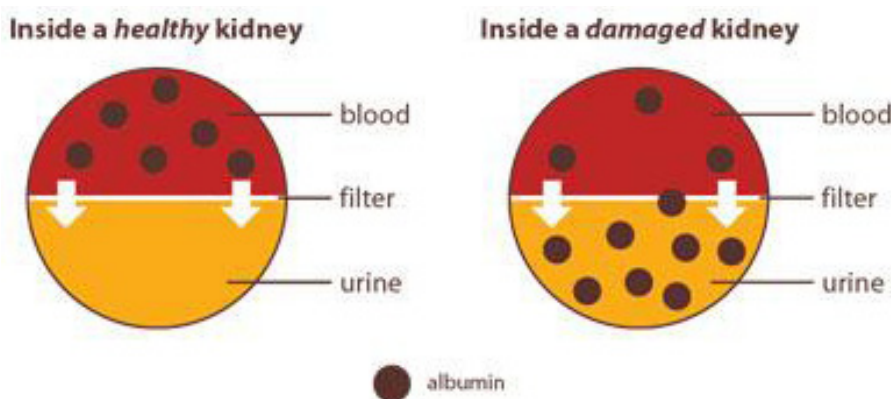


Figure 4: Albuminuria represents kidney damage.

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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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