Mini-Review

Global Proteinuria Guidelines: Are We Nearly There Yet?

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Abstract
Assessment of albumin and/or protein excretion in the urine is a key step in the early detection and appropriate management of chronic kidney disease. The approach to testing for albuminuria/proteinuria in the community is variable and often suboptimal. It is hampered by: variation in laboratory measurement; lack of standard reference materials and testing procedures; variable definitions and units of reporting; conflicting recommendations and practices regarding who to test; and uncertainty over when and how testing is most appropriately done. This review discusses the current status of proteinuria guidelines around the world and the key clinical issues that need to be addressed before a unifying global guideline can be developed.

Background
Chronic kidney disease (CKD), defined as reduced kidney function (glomerular filtration rate (GFR) <60 mL/min/ 1.73m^2) and/or evidence of kidney damage (usually albuminuria/proteinuria) for a period of at least three months,[1] is a major public health problem in Australia and throughout the world. Based on data from the AusDiab study,[2] it is estimated that approximately six million Australian individuals (about 30% of the population) have one or more of the major CKD risk factors and that about two million Australian adults have CKD. Of those with CKD, approximately 320,000 have proteinuria, 800,000 have microalbuminuria and 80,000 have macroalbuminuria. As CKD is usually silent until its late stages, many patients with CKD are detected only shortly before the onset of symptomatic kidney failure when there are few opportunities to prevent adverse outcomes.[3] Early identification and management of CKD through the detection of albuminuria/proteinuria is highly cost-effective and can reduce the risk of kidney failure progression and cardiovascular disease by up to 50%.[4]

In spite of its demonstrated importance, the approach to testing for albuminuria/proteinuria in the community is variable and often suboptimal. For example, an audit of primary care records of patients aged 50–75 years who had either hypertension or diabetes demonstrated that only 29% contained a test for proteinuria within the preceding 12 months.[5] Similarly, a recent audit of incident CKD patients referred to two south-east Queensland Renal Units found that only 43% had undergone urine protein testing prior to their referral.[6] The measurement of albuminuria/proteinuria is also considerably hampered by laboratory measurement variation, lack of standard reference materials and testing procedures, variable definitions, variable units of reporting, and conflicting recommendations and practices regarding who to test and how it is most appropriately done (*viz*. dipstick versus laboratory measurements, timed versus spot versus first morning void collections, albumin versus protein measurement, and concentration versus excretion versus creatinine ratio).

The aim of this paper is to review the current status of proteinuria guidelines around the world and the key clinical issues that need to be addressed before a standard global guideline can be developed.

Albuminuria/Proteinuria Testing: Key Clinical Issues

1. Who Should be Screened for Albuminuria/Proteinuria?
The available evidence does not support screening the entire Australian population for albuminuria/proteinuria.[7] Instead, current recommendations strongly advocate targeted opportunistic screening in the primary care setting (Table 1). An Australian cost-effectiveness study by Howard *et al*. reported that for every 1000 people screened, proteinuria testing would prevent 2 cases of end-stage kidney disease (ESKD) and 14 cardiovascular deaths.[8] The cost of a CKD targeted-screening program was reported to be as (or more) cost-effective than

Table 1. Current guidelines pertaining to evaluation of albuminuria/proteinuria in different countries around the world.

Aspect of Proteinuria Evaluation	Guideline	Recommendation
Who should be screened for proteinuria?	KCAT[14]	At-risk individuals (diabetic, hypertensive, obese, smoker, Indigenous, family history of CKD, age >50 years).
	CARI[15]	At-risk individuals (diabetic, hypertensive, Indigenous, family history of CKD, known vascular disease).
	RACGP[13]	At-risk individuals (diabetic, hypertensive, obese, smoker, Indigenous, family history of CKD, age >50 years).
	KDOQI[1]	At-risk individuals.
	NICE[16]	At-risk individuals (diabetes, hypertension, cardiovascular disease, structural renal tract disease, renal calculi, prostatic hypertrophy, multisystem diseases e.g. systemic lupus erythematosus, family history of stage 5 CKD or hereditary kidney disease, opportunistic detection of haematuria).
	SIGN[17]	At-risk individuals (diabetics or non-diabetics with a high prevalence of proteinuria).
	CSN[29]	At-risk individuals (diabetes, hypertension, vascular disease, autoimmune disease, estimated glomerular filtration rate <60 mL/min/1.73m^2 or oedema).
	ERBP[30]	No recommendations.
	KDIGO[19]	At-risk individuals (hypertension, diabetes, cardiovascular disease, family history of CKD, hyperlipidaemia, obesity, metabolic syndrome, smokers, treatment with potentially nephrotoxic drugs, some chronic infectious diseases and cancers, age >60 years).
How often should proteinuria screening be performed?	KCAT[14]	Annually.
	CARI[15]	Not specified.
	RACGP[13]	Annually (diabetic) or every 5 years (age >50 years or smoker) or every 3 years (hypertension, obesity, family history of kidney disease, or Indigenous).
	KDOQI[1]	Not specified.
	NICE[16]	At least annually.
	SIGN[17]	Not specified.
	CSN[29]	Not specified.
	ERBP[30]	According to available guidelines and the target group to be tested. In absence of specific recommendations, testing need not be more frequent than once per year.
Dipstick versus laboratory?	KCAT[14]	Initial dipstick proteinuria testing for non-diabetics, followed by UPCR if dipstick protein ≥1+. Initial UACR for diabetics.
	CARI[15]	Do not use dipstick.
	RACGP[13]	Initial dipstick proteinuria testing for non-diabetics, followed by laboratory quantitiation if dipstick protein ≥1+. Initial UACR for diabetics.
	KDOQI[1]	If appropriate, should undergo periodic repeat evaluation.
	NICE[16]	Do not use dipstick.
	SIGN[17]	Dipstick cannot be reliably used in isolation.
	CSN[29]	Do not use dipstick.
	ERBP[30]	Not specified.
	KDIGO[19]	Favour laboratory measurement.
Which specific laboratory test of albuminuria or proteinuria?	KCAT[14]	PCR for non-diabetics. ACR for diabetics.
	CARI[15]	PCR for non-diabetics. ACR for diabetics or high ethnic risk.
	RACGP[13]	Albuminuria for diabetics. No recommendations for non-diabetics.
	KDOQI[1]	Albuminuria preferred to proteinuria, except in non-diabetic children.
	NICE[16]	Use ACR in preference to PCR for all patients.
	SIGN[17]	PCR for non-diabetics. ACR for diabetics.
	CSN[29]	ACR for diabetics. ACR or PCR for non-diabetics.
	ERBP[30]	No recommendations.
	KDIGO[19]	Albuminuria preferred to proteinuria.

Table 1. cont.

Aspect of Proteinuria Evaluation	Guideline	Recommendation
Timed or 'spot' (single void) urine collection?	KCAT[14]	ACR or PCR on first morning void preferred, but random acceptable.
	CARI[15]	ACR or PCR on first morning void preferred, but random acceptable. Timed required for confirmation and monitoring.
	RACGP[13]	No recommendation.
	KDOQI[1]	ACR or PCR. First morning specimens preferred, but random acceptable.
	NICE[16]	ACR, preferably on first morning void.
	SIGN[17]	ACR, preferably on first morning void.
	CSN[29]	ACR or PCR on random urine.
	ERBP[30]	No recommendation.
	KDIGO[19]	ACR on spot urine (no recommendation re first morning void or random).

CARI, Caring for Australasians with Renal Insufficiency; CSN, Canadian Society of Nephrology; ERBP, European Renal Best Practice Guidelines; KCAT, Kidney Check Australia Taskforce; KDIGO, Kidney Disease Improving Global Outcomes; KDOQI, Kidney Disease Outcome Quality Initiative; NICE, National Institute of Health and Clinical Excellence; RACGP, Royal Australian College of General Practitioners; SIGN, Scottish Intercollegiate Guidelines Network; (U)ACR, (urine) albumin/creatinine ratio; (U)PCR, (urine) protein-creatinine ratio.

the estimated efficiency of screening programs (e.g. breast, cervical, bowel cancer) already available in Australia. A US health economic analysis similarly concluded that screening in those with diabetes and hypertension led to a 44% reduction in the cumulative incidence of ESKD.[9] The cost-effectiveness of a CKD screening program in the US has also recently been compared to established screening programs for other conditions estimating that screening for CKD with urinary protein testing on an annual basis in people 50 years or older with diabetes or hypertension was very favourable and similar to screening programs for other conditions such as cervical cancer.[10] Although it is clear that worldwide consensus is building with regards to the need for targeted-screening programs, variation in recommendations reflect both the lack of currently available evidence to guide specific aspects of program implementation and uncertainty regarding cost-quality trade-offs. It is also unclear whether CKD screening should be performed in a stand-alone fashion or in combination with other well-established screening programs (such as the National Heart Foundation and Cardiac Society of Australia and New Zealand cardiovascular risk screening program).

2. How Often Should At-Risk Individuals be Screened for Albuminuria/Proteinuria?

There are currently no published studies available to provide guidance regarding the appropriate frequency of screening for albuminuria/proteinuria in at-risk individuals. Many guidelines therefore make no recommendations regarding testing frequency at all, whilst others recommend repeating albuminuria/proteinuria tests in screen-negative individuals every 1–5 years, depending on their risk factor profile (Table 1). For screen-positive patients, repeat testing on one or two subsequent occasions is often advised, since transient albuminuria/proteinuria is commonly seen in the primary care setting following febrile or other acute medical illnesses (e.g. seizure, heart failure, urinary tract infection and acute kidney injury). It is currently recommended that a diagnosis of kidney damage can only be made if at least two measurements are elevated.

3. Is it Preferable to Screen for Albuminuria or Proteinuria?

The current practices of screening for albuminuria or proteinuria are highly variable, particularly in non-diabetic patients. Albuminuria screening for CKD detection is generally recommended in individuals with diabetes mellitus because the bulk of published evidence linking screening or treatments with clinical outcomes has centred on albuminuria testing.[11] However, it should be noted that screening for albuminuria alone will miss around 20% of patients with diabetes and CKD.[12]

In individuals who do not have diabetes, it is not yet established whether dipstick protein testing or laboratory measurement of either albuminuria or proteinuria is superior for detecting people with CKD at increased risk of progression. Although urine dipstick testing with protein or albumin reagent strips has been long-established in clinical practice and has often been recommended for CKD screening in non-diabetic patients,[13,14] its usefulness as a screening strategy is significantly limited by poor sensitivity and specificity, marked operator dependency and an absence of studies in high risk populations.[7,15,16] Automated devices may perform better, but there is insufficient evidence currently to

recommend them in preference to laboratory measurement of urinary albumin.

With respect to laboratory measurements, the principal arguments favouring assessment of proteinuria in preference to albuminuria for CKD screening in non-diabetic individuals are that the evidence base for CKD intervention strategies based on proteinuria is greater than it is for albuminuria and that tubular proteinuria may be missed in a small number of individuals who are solely screened for albuminuria.[16] On the other hand, testing for albuminuria exhibits greater sensitivity and precision for detecting lower, clinically important proteinuria, is able to be standardised and has been established to be cost-effective as an initial screening strategy compared with protein or albumin reagent strips (followed by laboratory confirmation of albuminuria).[16] While some guidelines favour albuminuria testing in diabetics, others favour proteinuria in non-diabetics and children, and there is no overall consensus for proteinuria or albuminuria testing (Table 1).[1,11,17-19] In the event that global guidelines recommend albuminuria measurement as the preferred initial method for CKD screening, it is likely that testing for proteinuria would still be considered advisable in limited circumstances where patients may have tubular or overflow proteinuria (e.g. children with Fanconi's syndrome or adults with multiple myeloma). In the AusDiab study,[2] using cut-off values of 3.45 mg/mmol for urine albumin/creatinine ratio (UACR) and 22.6 mg/mmol for urine-protein creatinine ratio (UPCR), 68% of patients who screened positive for albuminuria were negative for proteinuria. Conversely, approximately 8% of adults tested positive for proteinuria but negative for albuminuria. It would be preferable from a practical viewpoint for global proteinuria guidelines to recommend one type of measurement only since the relationship of albuminuria to proteinuria is complex and there is no reliable way of estimating urinary protein excretion from urinary albumin measurements or vice versa. In the AusDiab study,[20] the proportions of urinary protein accounted for by albumin progressively increased as total proteinuria increased (21%, 48%, 61% and 73% for measured UPCR of <23 mg/mmol, 23–44 mg/mmol, 45–89 mg/mmol and >89 mg/mmol, respectively). Moreover, a recent study of 6761 urine specimens reported considerable scatter of UACR compared with UPCR values,[21] whilst another study of 579 fresh urine specimens with microscopic haematuria (≥5 red blood cells/high-power field) observed that the urine albumin:protein ratio was significantly higher in patients with glomerular pathology than in those with non-glomerular pathology (0.73±0.11 versus 0.41±0.14 mg/mg, $p<0.001$).[22]

4. How Should Albuminuria/Proteinuria be Defined?

Definitions and units of reporting for normalbuminuria, microalbuminuria, macroalbuminuria and proteinuria vary markedly between different laboratories and different clinical practice guidelines (Table 2). These differences create considerable confusion for patients and clinicians alike, and markedly hamper the diagnosis, staging and monitoring of CKD. Since it is likely that global CKD guidelines will incorporate albuminuria/proteinuria measurements into CKD staging, developing standard definitions for normalbuminuria, microalbuminuria, macroalbuminuria and proteinuria are of paramount importance. The heterogeneity of urinary composition with respect to albumin and protein at different levels of urinary protein excretion needs to be addressed when defining urine protein status in kidney disease.

5. Timed or Spot (Single Void) Urine Collection?

Views regarding this matter are conflicting. Although timed urine collection is considered the gold standard, 24-hour collections in routine clinical practice are inconvenient to patients and are subject to inaccuracies due to incomplete collection of all urine voided, inaccurate timing and appreciable intra-individual variation due to varying activity, hydration and diet. Moreover, measurement in a first morning void provides acceptable accuracy and reliability in most circumstances and a number of studies have demonstrated that 'spot' (random) urine samples are still acceptable if first void samples are impractical.[23,24] When single void urine specimens are examined, results are variously reported as concentrations or creatinine-corrected measurements. A number of studies have demonstrated that correction of urinary albumin measurements for urine creatinine excretion to adjust for variation in urinary concentration results in better correlation with timed urine results.[23,25] However, since creatinine excretion is influenced by muscle mass (which is in turn influenced by gender), gender-specific cut-offs are recommended by some authors.[26] However, there is still no consistent approach taken by laboratories.

Current Status of Global Proteinuria Guidelines

As can be seen from Table 1, there is considerable variation in current best practice recommendations regarding the role, optimal method and classification of albuminuria/proteinuria measurement for CKD diagnosis. Nevertheless, considerable progress is being made in reaching consensus. In 2004, an International Society of Nephrology (ISN) Consensus Workshop on Prevention of Progression of Renal Disease recommended that patients with diabetes and hypertension and relatives of those with kidney disease have regular screening for the development of CKD. More recently in 2006, the Kidney Disease: Improving Global Outcomes (KDIGO) initiative made recommendations that all countries should have a targeted-screening program for CKD, focusing on people known to have diabetes, hypertension and cardiovascular disease.[27] Subsequently, the UK National Institute for Health

Table 2. Definitions of normal, microalbuminuria and proteinuria, according to different guideline recommendations.

Parameter	Guideline	Normal	Microalbuminuria	Proteinuria (Macroalbuminuria)
Albumin/creatinine ratio (ACR)	Diabetes Management in General Practice[11]	0–2.5 mg/mmol (M) 0–3.5 mg/mmol (F)	2.6–25 mg/mmol (M) 3.6–35 mg/mmol (F)	>25 mg/mmol (M) >35 mg/mmol (F)
	KCAT[14]	0–2.6 mg/mmol (M) 0–3.6 mg/mmol (F)	2.6–25 mg/mmol (M) 3.6–35 mg/mmol (F)	>25 mg/mmol (M) >35 mg/mmol (F)
	CARI[15]	≤17 mg/g (≤1.9 mg/mmol) (M) ≤25 mg/g (≤2.8 mg/mmol) (F)	>17–250 mg/g (2.0-28 mg/mmol) (M) >25.1–355 mg/g (2.9-40 mg/mmol) (F)	>250 mg/g (>28 mg/mmol) (M) >355 mg/g (>40 mg/mmol) (F)
	RACGP[13]	<2.5 mg/mmol (M) <3.5 mg/mmol (F)	2.5–25 mg/mmol (M) 3.5–25 mg/mmol (F)	>25 mg/mmol (M) >25 mg/mmol (F)
	National Guide to Preventive Health Assessment in Aboriginal and Torres Strait Islander Peoples[31]	<2.5 mg/mmol (M) <3.5 mg/mmol (F)	2.5–25 mg/mmol (M) 3.5–25 mg/mmol (F)	>25 mg/mmol
	KDOQI[1]	<25 mg/g (F) <17 mg/g (M)	25–355 mg/g (F) 17–250 mg/g (M)	>355 mg/g (F) >250 mg/g (M)
	NICE[16]	≤3.5 mg/mmol (F) ≤2.5 mg/mmol (M)	>3.5–30 mg/mmol (F) >2.5–30 mg/mmol (M)	>30 mg/mmol
Protein/creatinine ratio (PCR)	K/DOQI[1]	≤200 mg/g	NA	>200 mg/g
	NICE[16]	≤45 mg/mmol	NA	>45 mg/mmol
Urinary albumin excretion (UAE)	Diabetes Management in General Practice[11]	<20 µg/min	20–200 µg/min	>200 µg/min
	KDOQI[1]	<30 mg/day	30–300 mg/day	>300 mg/day
Albumin-specific dipstick	CARI[15]	≤3 mg/dL	>3 mg/dL	NA
	KDOQI[1]	≤3 mg/dL	>3 mg/dL	NA
Dipstick protein	CARI[15]	≤30 mg/dL	NA	>30 mg/dL
	KDOQI[1]	≤30 mg/dL	NA	>30 mg/dL
	National Guide to Preventive Health Assessment in Aboriginal and Torres Strait Islander Peoples[31]	≤30 mg/dL	NA	>30 mg/dL or ≥1+protein
24-hour urinary total protein	CARI[15]	<30 mg/day	30–150 mg/day	150 mg/day
	KDOQI[1]	<300 mg/day	NA	>300 mg/day
	National Guide to Preventive Health Assessment in Aboriginal and Torres Strait Islander Peoples[31]	<30 mg/day	30–299 mg/day	≥300 mg/day

CARI, Caring for Australasians with Renal Insufficiency; KCAT, Kidney Check Australia Taskforce; KDOQI, Kidney Disease Outcome Quality Initiative; RACGP, Royal Australian College of General Practitioners; F, female; M, male; NA, not available.

and Clinical Excellence (NICE) Guidelines recommended measuring albumin/creatinine ratio (ACR), preferably on a first void morning specimen, for CKD screening in all at-risk individuals.[16] In October 2009, a Controversies Conference on 'Chronic Kidney Disease: Definition, Classification and Prognosis' sponsored by KDIGO took place in London and reached a consensus on revisions to the classification of CKD based on prognosis, but did not propose to change the definition of CKD.[28] In particular, a key modification was to add albuminuria stages (ACR <30 mg/g, 30–300 mg/g and >300 mg/g) to GFR stages (stage 1 ≥ 90 mL/min/1.73m^2, stage 2 60–89 mL/min/1.73m^2, stage 3 30–59 mL/min/1.73m^2, stage 4 15–29 mL/min/1.73m^2, stage 5 <15 mL/min/1.73m^2). Importantly, no change was made to the level of albuminuria used to define the presence of CKD (urine ACR >30 mg/g). A position statement on behalf of KDIGO will be released in 2011, but it is likely that urine ACR will increasingly be used to define, stage and monitor CKD. The Australasian Proteinuria Consensus Working Party, sponsored by the Australasian Association of Clinical Biochemists (AACB), Australian and New Zealand Society of Nephrology (ANZSN), Kidney Health Australia (KHA), the Royal College of Pathologists of Australasia (RCPA), the Royal Australian College of General Practitioners (RACGP) and the Australian Diabetes Association (ADA) is also developing recommendations for the measurement of urinary albumin and protein in Australia and New Zealand.

Conclusions

Assessment of albumin and/or protein excretion in the urine is a key step in the early detection and appropriate management of CKD. Unfortunately, the approach to testing for albuminuria/proteinuria in the community is variable, often suboptimal and hampered by a paucity of high level clinical evidence to guide who should be screened, when and how often they should be screened, and what test should be employed. These problems are compounded by laboratory measurement variation, lack of standard reference materials and procedures for both protein and albumin measurements, variable definitions of albuminuria/proteinuria and variable units of reporting. Over the last few years, considerable progress has been made towards developing a global position statement on the assessment of albuminuria/proteinuria, which should address many of these issues.

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