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Where now for proteinuria testing in chronic kidney disease?

Good evidence can clarify a potentially confusing message

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INTRODUCTION

Although the value of testing for proteinuria may be undisputed and understood by nephrologists and diabetologists, the lack of clarity about the rationale for testing and the optimal way of doing so in primary care has caused confusion for many practitioners.[1] Issues such as variation in proteinuria definition, laboratory measurement, and reporting methods, along with conflicting messages about who, how, and when to test, have led to uncertainty and under-testing.[1,2] There have been long-standing debates about the use of various dipsticks, the role of proteinuria in urinary tract infection, the use of urinary protein:creatinine ratio (PCR) versus albumin:creatinine ratio (ACR), and the number of tests needed for identification versus quantification of proteinuria. Reporting variations include some laboratories using non-numeric results such as 'ratio too low to calculate' making visualisation of results and accurate audit of ACR testing challenging for busy practitioners. Urinary dipsticks have important limitations in terms of their accuracy in detecting and quantifying albuminuria.[3] In this context, GPs and other clinicians could be forgiven for being uncertain about the clinical utility of its identification.

Chronic kidney disease (CKD) has been included in the Quality and Outcomes Framework (QOF) since 2006–2007, and, from 2009–2010, included a proteinuria indicator ('The percentage of patients on the CKD register whose notes have a record of a urine albumin:creatinine ratio [or protein:creatinine ratio] test in the preceding 12 months'). Currently, several CKD indicators are in the process of being 'retired', including the one relating to proteinuria testing. This increases the potential for uncertainty about the role of proteinuria testing and is likely to lead to a fall in ACR tests in England, particularly in people without diabetes, unless it is seen as valuable in its own right. It may also serve to reinforce the suggestion that labelling people with mild-to-moderate renal dysfunction as having 'disease' is inappropriate.

WHY BOTHER TESTING FOR ALBUMINURIA?

Before we wash our hands completely of ACR testing, it is worth taking a moment to consider albuminuria and why its measurement may be important. Albuminuria prevalence in the English general population (based on the Health Survey for England, a methodologically robust, nationally representative population survey [using a single ACR measure]) is about 8% (23% in people with diabetes, 7% in those without), compared with about 17% (29% in people with diabetes, 13% in those without) among people with mild-to-moderate CKD in primary care (based on up to three samples), suggesting that proteinuria is not uncommon.[4,5] There is also now very strong evidence from international meta-analyses of large-scale general population cohorts of its independent predictive ability for a wide variety of adverse clinical outcomes. These include all-cause and cardiovascular mortality, acute kidney injury (AKI), CKD progression to end-stage renal disease, and heart failure-related hospitalisation (Table 1).[6–10] Recent evidence shows that ACR is a more powerful predictor of cardiovascular mortality and of new heart failure than estimated glomerular filtration rate (eGFR) and traditional cardiovascular risk factors.[11] AKI is a common, serious, and partly preventable condition and its detection and prevention is currently a national programme of NHS England in partnership with the UK Renal Registry (www.thinkkidneys.nhs.uk). As >60% of AKI in hospitals is thought to start in the community, knowledge of albuminuria status can help the early identification of those most at risk of AKI and guide prevention efforts.

Table 1. Risk of various outcomes related to albuminuria status[a]

Outcome	Evidence of independent albuminuria association		HR (95% CI)
All-cause mortality	Compared with ACR 0.6 mg/mmol:[b]	1.1	1.20 (1.15 to 1.26)[9]
		3.4	1.63 (1.50 to 1.77)[9]
		33.9	2.22 (1.97 to 2.51)[9]
Cardiovascular mortality	Compared with ACR 0.6 mg/mmol:[b]	1.1	1.20 (1.15 to 1.26)[9]
		3.4	1.63 (1.50 to 1.77)[9]
		33.9	2.22 (1.97 to 2.51)[9]
Cardiovascular disease	Compared with ACR 0–0.4 mg/mmol:[c]	2.5–25	1.36 (1.12 to 1.64)[10]
		>25	1.59 (1.10 to 2.37)[10]
Incident end-stage renal disease	Compared with ACR <1.1 mg/mmol:[d]	3.4–33.8	12.0 (7.9 to 18.1)[6]
		≥33.9	72.1 (43.0 to 121)[6]
CKD progression	Compared with ACR 0.6 mg/mmol:[d]	3.7	4.87 (2.30 to 10.3)[6]
		33.9	13.4 (5.49 to 32.7)[6]
		113	28.4 (14.9 to 54.2)[6]
Acute kidney injury	Compared with ACR <1.2 mg/mmol:[d]	3.4–33.8	2.5 (1.7 to 3.7)[6]
		≥33.9	6.0 (4.5 to 8.0)[6]
		1.2–3.3	1.9 (1.4 to 2.6)[8]
		3.4–33.8	2.2 (1.6 to 3.0)[8]
		≥33.9	4.8 (3.2 to 7.2)[8]
Heart failure hospitalisation	Compared with ACR <0.22 mg/mmol:[e]	0.22–0.57	1.19 (0.77 to 1.83)[7]
		0.58–1.62	1.95 (1.32 to 2.88)[7]
		>1.62	3.79 (2.65 to 5.41)[7]

[a]Units standardised to mg/mmol to aid comparison. [b]Adjusted for eGFR, age, sex, ethnicity, history of cardiovascular disease (CVD), systolic blood pressure (BP), diabetes, smoking, and total cholesterol. [c]Adjusted for age, sex, smoking, systolic blood pressure, total cholesterol, diabetes mellitus, and body mass index. [d]Adjusted for estimated glomerular filtration rate, age, sex, ethnicity, history of CVD, hypertension, hypercholesterolaemia, diabetes, and smoking. [e]Adjusted for age, sex, systolic, and diastolic blood pressure, waist–hip ratio, diabetes mellitus, or glycated haemoglobin in participants with diabetes. CKD = chronic kidney disease. HR = hazard ratios in general population cohorts. ACR = albumin:creatine ratio.

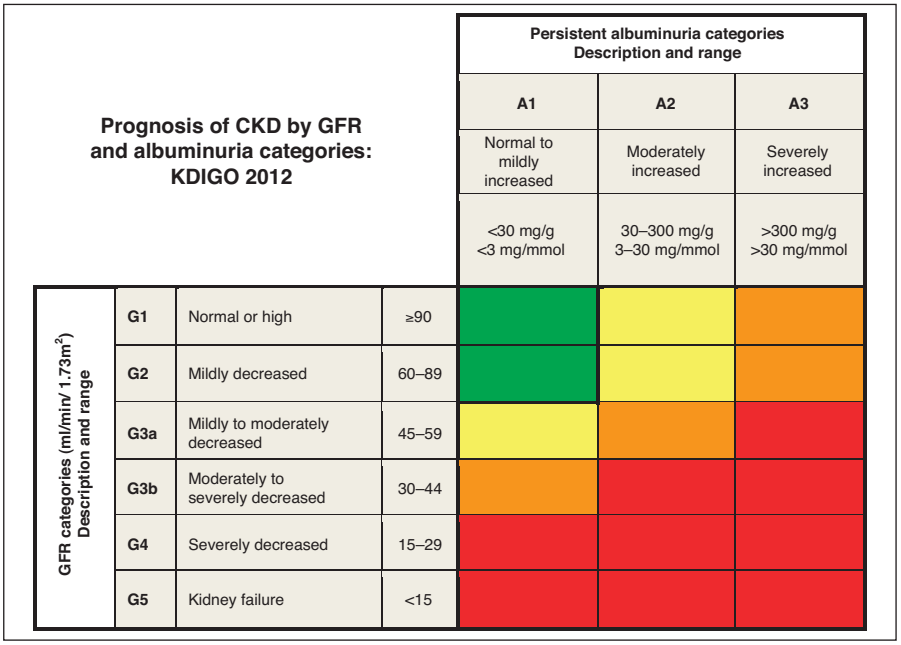

Figure 1. Prognosis of chronic kidney disease (CKD) by glomerular filtration rate and albuminuria category. Green = low risk (if no other markers of kidney disease, no CKD). Yellow = moderately increased risk. Orange = high risk. Red = very high risk. Figure reproduced with permission from: Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney International Supplements 2013; 3: 1–150.[13]

Despite this growing body of evidence, a recent retrospective cohort study of people with incident eGFR-defined CKD, identified from routine data in Hampshire, showed that only about 36% of people with a new, persistently low eGFR had had a ACR test after a median of 3.3 years of follow-up.[2] For people registered as having CKD, the percentage was nearer 80% (consistent with QOF figures). In that study, perhaps unsurprisingly, having diabetes was the single strongest predictor of timely ACR testing, although CKD registration was also a key factor.[2] In terms of people with CKD who do not have diabetes, rarely is such a well-established and strongly evidence-based indicator embraced so inconsistently in practice. The reasons for reluctance to test urine for protein are unclear but may be a reflection of the confusion mentioned above.

WHO SHOULD WE TEST?

The recent (2014) revision to the National Institute for Health and Care Excellence (NICE) CKD guidelines clearly recommends the use of ACR in people with CKD to test for proteinuria (in preference to PCR or dipstick) in order to be able to accurately classify their CKD according to the international Kidney Disease Improving Global Outcomes (KDIGO) guidelines (in which risk is assessed using a combination of both eGFR and ACR, Figure 1).[12,13] In the context of a degree of scepticism in clinical practice about whether to diagnose CKD (and inform patients of that diagnosis), ACR measurement forms a key step in CKD classification and risk stratification, particularly for people with eGFR in the 45–59 ml/min/1.73 m^2 range (KDIGO eGFR category G3a). The NICE CKD guidelines recognise this and clarify the optimal method of assessing proteinuria by advising against the use of reagent strips and recommending ACR in preference to PCR (Box 1).[12] Quantification of albuminuria is recommended in people with diabetes, CKD (defined by eGFR<60 ml/min/1.73 m^2 or where there is strong suspicion of CKD even if eGFR is normal), hypertension, AKI, cardiovascular disease, structural renal tract disease (including recurrent calculi and benign prostatic hyperplasia), multisystem diseases with potential kidney involvement, for example, systemic lupus erythematosus, patients with a family history of end-stage kidney disease, and when haematuria is opportunistically identified.[12]

WHO SHOULD WE REFER?

The NICE guideline advises clinicians to 'regard a confirmed ACR of ≥3 mg/mmol as clinically important

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Box 1. Summary of 2014 NICE guidance on testing for proteinuria[12]

- Do not use reagent strips to identify proteinuria.
- To detect and identify proteinuria, use urine albumine:creatine ratio (ACR) in preference to PCR.
- Classify chronic kidney disease (CKD) using a combination of glomerular filtration rate (GFR) and ACR categories.
- If the initial urine ACR is between 3–70 mg/mmol, this should be confirmed by a subsequent early-morning sample. If the initial urine ACR is ≥70 mg/mmol, a repeat sample need not be tested.
- Regard a confirmed urine ACR of ≥3 mg/mmol as clinically important proteinuria.
- Quantify urinary albumin loss for all people with diabetes and people without diabetes with a GFR of <60 ml/min/1.73 m^2.
- Quantify the urinary albumin loss of people with a GFR of ≥60 ml/min/1.73 m^2 if there is a strong suspicion of CKD.

proteinuria' and recommends referral for specialist assessment for anyone with an ACR of ≥70 mg/mmol (or 30 mg/mmol (KDIGO category A3) with haematuria).[12] This is because people with this magnitude of proteinuria are likely to have a glomerulopathy requiring further investigation (often with a kidney biopsy) and may benefit from disease-specific treatment. Guidelines should of course be applied using clinical judgement. People with diabetes and mild-to-moderate albuminuria may not require referral if optimal care of their diabetes can be provided locally. In frail older patients or others with limited life expectancy, referral with mild albuminuria may also not provide any benefit. Renin-angiotensin system antagonists are recommended for people with CKD who have diabetes and an ACR of ≥3 mg/mmol (A2 or A3), hypertension, and an ACR of ≥30 mg/mmol (A3), or ACR ≥70 mg/mmol irrespective of hypertension or cardiovascular disease status.[12]

Given that the predominant risk in people with CKD is cardiovascular disease, ACR should perhaps be considered as contributing more to cardiovascular than renal risk prediction. Although all people with CKD are at greater cardiovascular risk than the general population, albuminuria is one of the strongest predictors of cardiovascular outcomes in general populations and ACR measurement clearly adds to cardiovascular risk prediction in people with CKD.[11] It should therefore be an important flag that there may be more to be done in terms of blood pressure and lipid control, and consideration of referral for nephrological advice.

CONCLUSION

The fact that albuminuria is present in only a minority of people with CKD means that it provides a simple means to identify the relatively small number of people who require extra attention from the large population with CKD, thereby reducing concerns of overdiagnosis and improving risk stratification. The extent to which we appreciate the clinical importance of proteinuria in CKD (and embrace its testing using ACR) will largely determine whether the 'baby is thrown out with the bath water' of current CKD QOF revisions. Whatever individual clinicians' views may have been on CKD as a diagnosis, the evidence seems to have put beyond doubt the value of albuminuria as an important independent predictor of many outcomes, and we should not abandon testing for it.

Provenance

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Competing interests

The authors have declared no competing interests.

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