Guidelines

Chronic kidney disease and measurement of albuminuria or proteinuria: a position statement

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Large population studies have consistently shown that albuminuria and proteinuria indicate chronic kidney disease (CKD), and strongly and independently predict the risks of CKD progression, cardiovascular disease and all-cause mortality in both diabetic and non-diabetic individuals. Combining albuminuria measurement with eGFR provides synergistic, complementary risk-stratification for both cardiovascular disease and CKD. However, results from recent surveys of pathology laboratories indicated a lack of standardisation in primary care regarding the choice of urine protein test, units of reporting, and age and sex reference ranges. In response, the Australasian Proteinuria Consensus Working Group met throughout 2009 to 2011 to develop recommendations on the measurement of urinary albumin and protein. Seven evidence-based recommendations emanated from this meeting (Box 1).

1 Australasian Proteinuria Consensus Working Group recommendations and levels of evidence*

1 The preferred method for assessment of albuminuria in both diabetic and non-diabetic individuals is urinary albumin-to-creatinine ratio (UACR) measurement in a first-void (first morning) spot specimen. Where a first-void specimen is not possible or practical, a random spot urine specimen for UACR is acceptable. **(1C)**

2 Adults with one or more risk factors for chronic kidney disease (CKD) should be assessed using UACR and estimated glomerular filtration rate every 1–2 years, depending on their risk-factor profile. **(2C)**

3 All pathology laboratories should report cut-points for microalbuminuria and macroalbuminuria according to the standard definitions. Sex-specific cut-points for UACR measurements are recommended. **(1C)**

4 A positive UACR test should be repeated to confirm persistence of albuminuria. CKD is present if two out of three tests (including the initial test) are positive. If the first positive UACR is a random spot (as it may be for opportunistic testing), then repeat tests should ideally be first morning void specimens. **(1C)**

5 There is no reliable way of estimating urinary protein excretion from urinary albumin concentration or vice versa. **(1C)**

6 Use of estimated albumin excretion rate derived from the UACR is not recommended. **(1C)**

7 All pathology laboratories in Australia should implement the relevant recommendations contained in this document as a vital component of an integrated national approach to CKD detection.

* Levels of evidence are defined in the 2006 position statement from Kidney Disease: Improving Global Outcomes (KDIGO), *Kidney Int* 2006; 70: 2058-2065. ◆

Discussion of recommendations

1 Preferred method of testing for albuminuria in the detection of CKD

Albuminuria measurement for CKD detection is already recommended for individuals with diabetes mellitus because the bulk of published evidence linking screening or treatments with clinical outcomes has centred on albuminuria. In individuals who do not have diabetes, it is not yet established whether testing for albuminuria or proteinuria is superior for detection of CKD or for determining risk of progression. However, a retrospective longitudinal cohort study showed that urinary albumin-to-creatinine ratio (UACR) performed as well as urinary protein-to-creatinine ratio (UPCR) and 24-hour urinary albumin and protein measurements in predicting doubling of serum creatinine, commencement of renal replacement therapy and all-cause mortality.

The working group recommended initial laboratory testing for albuminuria rather than proteinuria as the preferred strategy in most individuals at risk of CKD on the basis that the former accurately predicts kidney and cardiovascular risks in population studies and renoprotective benefit in intervention trials; exhibits greater sensitivity for detecting low-grade, but clinically important albuminuria; provides improved analytical precision at low, yet diagnostically important, concentrations; allows assay standardisation; has been established to be cost-effective compared with protein or albumin reagent strips; is favoured by a number of international best-practice guidelines; and provides a simplified initial testing strategy for CKD.

Although dipstick testing of urine with protein or albumin reagent strips has long been established in clinical practice and has often been recommended for detection of CKD in patients who do not have diabetes, its usefulness as an early detection strategy is significantly limited by poor sensitivity, marked operator dependency and limited evidence of its cost-effectiveness in high-risk populations.

While timed urine collection is considered the gold standard for evaluating albuminuria or proteinuria, it has logistical difficulties. Measurement of albuminuria in a first morning void specimen provides acceptable accuracy and reliability in most circumstances. Random urine specimens are acceptable if first-void specimens are impractical. Investigations have also shown that correction of urinary albumin measurements for urinary creatinine excretion accounts for variation in urinary concentration, and results in better correlation with timed urine results.

2 Target population for initial testing for CKD using UACR

Diabetes mellitus, hypertension, obesity, current smoking, established cardiovascular disease, family history of CKD and Aboriginal and Torres Strait Islander origin are risk factors for CKD. The Kidney Check Australia Taskforce and the Royal Australian College of General Practitioners (RACGP) "red book" recommend that patients with one or more of these risk factors should undergo assessment of UACR and eGFR every 1 to 2 years (annually for individuals with diabetes or hypertension).

2 Definitions of microalbuminuria and macroalbuminuria

	Sex	Microalbuminuria	Macroalbuminuria
UACR	Men	2.5–25 mg/mmol	> 25 mg/mmol
	Women	3.5–35 mg/mmol	> 35 mg/mmol
24-h urinary albumin	Either	30–300 mg/day	> 300 mg/day

UACR = urinary albumin-to-creatinine ratio. ◆

3 Standard cut-points for microalbuminuria and macroalbuminuria based on UACR measurement

The mean cut-off for conversion of UACR to albumin excretion rate (AER) at the threshold for microalbuminuria (20 μg/min or 30 mg/day) is greater in women (UACR, 2.8–4.2 mg/mmol) than in men (UACR, 1.8–3.0 mg/mmol). Similar results have been found when using UACR thresholds to predict proteinuria of 0.5 and 1 g/day. As a result, international practice guidelines support adjustment of UACR categories by sex. The definitions and cut-points in Box 2 align with the National Health and Medical Research Council (NHMRC) guidelines for diagnosis, prevention and management of CKD in type 2 diabetes.

There is insufficient evidence to recommend ethnicity-specific or age-specific cut-points for UACR.

4 Number of UACR measurements required to establish the presence of persistent albuminuria

The high intra-individual coefficient of variation of albuminuria (30%–50%) requires that several measurements are undertaken to allow accurate categorisation of albuminuria status. If a UACR is abnormal on at least two occasions over at least 3 months, CKD is present. If the first positive UACR is a random spot, then repeat tests should be first morning void specimens. If an initial UACR test is negative, then repeated testing is not required until the next recommended testing interval.

5 Estimating urinary protein excretion from urinary albumin excretion or vice versa

In the Australian Diabetes, Obesity and Lifestyle (AusDiab) study, the proportion of urinary protein accounted for by albumin was shown to progressively increase as total proteinuria increased. A retrospective, observational cohort study showed that the relationship between UACR and UPCR is non-linear and that 24-hour urinary protein could not be adequately predicted from UACR. Thus, generating an "estimated UPCR" or "estimated" 24-hour urinary total protein from a UACR is likely to result in significant error.

6 Estimating urinary albumin excretion rate (eAER) from UACR

The relationship between UACR and AER is influenced by determinants of muscle mass, including sex, race, age, body surface area and serum creatinine concentration. Studies among patients with diabetes have shown that the use of UACR versus AER provided agreement for the classification of macroalbuminuria, but yielded important differences in the classification of microalbuminuria. The level of agreement with AER for microalbuminuria was not improved by the use of an AER-estimating equation that incorporated sex or other covariates. The working group considered that, until albumin measurements are standardised and the impact of AER-estimating equations on albuminuria classification are assessed in diverse, widely representative populations, the use of eAER cannot be recommended.

7 Role of pathology laboratories

Laboratories should recommend a first morning void specimen for ACR as the preferred test for identification of kidney damage in all settings, although random specimens should be accepted if first morning void specimens are impractical. UACR should be reported in mg/mmol to one decimal place, and the sex-specific ratio ranges (Box 2) should be used as reference intervals. Laboratories should ensure the assays for urine albumin and creatinine are suited for purpose such that assay imprecision, bias and analytic specificity will not adversely affect clinical decision making. Laboratories should develop standardised reporting so that doctors receive the same medical information irrespective of the laboratory used.

Conclusion

Optimal detection and risk stratification in CKD requires consideration of both urinary albumin and eGFR (see recommendations of Australasian Creatinine Consensus Working Group, *page 222*). Standardisation of ACR as the preferred test for albuminuria in the initial assessment of all patients with possible CKD is an important step towards bringing clinical evidence to routine patient care. The testing process requires vital input from clinicians, pathologists, laboratory scientists and researchers, and the involvement of all groups is required to maximise the opportunities for improving kidney and cardiovascular health in Australia.

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