1. Testing for Proteinuria

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Guidelines

No recommendations possible based on Level I or II evidence

Suggestions for clinical care

(Suggestions are based on level III and IV sources)

- High risk populations. Testing for proteinuria is preferred in patients with hypertension, known vascular disease and a family history of renal disease. Recommendation: Initial test – urine PCR.

- Diabetes and Aboriginal and Torres Strait Islanders. Initial testing for albuminuria is preferred to proteinuria as it allows detection of early nephropathy. In patients with established nephropathy there is no evidence that either test is superior. Recommendation: Initial test – urine ACR.
  Subsequent testing:
  initial test negative or microalbuminuria – repeat urine ACR
  initial test macroalbuminuria – urine ACR or PCR.

Background

Proteinuria has been demonstrated to be an independent risk factor for progression of renal disease and is potentially modifiable by available therapy. Routine evaluation of patients at increased risk of renal failure (patients with vascular disease, diabetes, hypertension, immediate relatives of patients with diabetes, hypertension or renal disease, and Aboriginal and Torres Strait Islanders) has been recommended (CARI guideline – Early detection of patients with renal disease). Urine protein assessment is also an important method of assessing progression and response to therapy in patients with known renal disease. The aim of this guideline is to review the different methodologies available for assessing proteinuria and albuminuria. The data available are limited and many fundamental questions such as the relative benefits and harms of screening high risk groups, the comparative usefulness of proteinuria versus albuminuria as a screening tool and frequency of testing have not been sufficiently addressed to form definitive guidelines. Therefore, recommendations based on a review of the current literature have been proposed. It is important to note that the primary message is to improve the rate of screening of high risk individuals and, in the absence of definitive data, the method by which this is done should be tempered by practical considerations such as ease of use, patient acceptability and cost.

Definitions

Proteinuria: Small amounts of protein are normally excreted in the urine (approximately 80 mg/day) and comprise filtered plasma proteins (albumin and low molecular weight immunoglobulin) and secreted tubular proteins (Berggard 2004). There are no official Australian standards for proteinuria and the cut-off for abnormal varies between 150-300 mg/day, depending on the laboratory.

Albuminuria: The normal mean value for urine albumin excretion is 10 mg/day but is increased by many physiological variables including exercise, fever, upright posture and pregnancy. Microalbuminuria is defined as a range from 30-300 mg/day. Macroalbuminuria is defined as above 300 mg/day (see Table 1, Appendices).

Methods of assessment

The guideline will review the performance characteristics of

- dipstick albumin and protein assessment
- 'spot' urine albumin and protein assessment.

Twenty-four hour urine protein excretion has been considered the gold standard for quantitative protein assessment. The recognised difficulty in collecting reliable 24 hr urine samples makes routine use problematic and assessment of random urine samples is an attractive and practical alternative. Urine protein/albumin can be assessed in 'spot' urine samples by assessing urine concentration (UPC, UAC) or as a ratio with creatinine (PCR, ACR). The excretion of creatinine is fairly constant in an individual patient and represents a method of standardising protein excretion in a single-void specimen to correct for variation in hydration.

Search strategy

Databases searched: MeSH terms (when available) and text words for each intervention were combined with text words (no MeSH terms exist) for the comparison. These were further combined with MeSH terms and text words for the outcomes. The search was carried out in Medline (1966 – January Week 1 2003).

Date of search: 21 January 2003.

What is the evidence?

There are no randomised controlled trials on this topic.

Summary of the evidence

Not possible.

Proteinuria

There is an association between proteinuria and progressive renal disease in population studies.

The association between proteinuria and the subsequent development of end stage renal disease (ESRD) has been assessed in Japanese population studies. Iseki et al (1996) demonstrated that proteinuria (detected by random urine dipstick) was more common in men and increased with age. Proteinuria may be transient, particularly in normotensive patients and will resolve in approximately 25% of patients (Yamagata et al 2002). A significant deterioration in renal function (creatinine > 2 mg/dL) occurred in 12% (CI 4.8 - 20.4) of patients with haematuria and proteinuria and in 5.2% (CI 0.5 - 8.2) with proteinuria alone over a 10 year follow-up period. Proteinuria was found to be the strongest risk factor for ESRD (dialysis) in multivariate analysis with adjusted RR 14.9 (10.9 - 20.2). A note of caution in relation to the Japanese population studies is the high rate of ESRD in that population (approximately 8-fold greater than the Australian rate) [ANZDATA 1993].

The severity of proteinuria in population studies is predictive of outcome. In the study by Iseki et al (1996) the relative risk of ESRD increases with increasing proteinuria, from 1+ RR = 1.0; 2 + RR = 7.6; 3 + RR = 16.1 and 4 + RR = 19.5. Yamagata et al (2002) also demonstrated that the degree of proteinuria was significantly higher in patients with progressive rather than non-progressive disease (2.3 +/- 1.5 vs 0.67 +/- 0.06 g/day, $p < 0.0001$). A secondary analysis of the REIN study (Ruggenenti et al 1998) looking at 352 nondiabetic patients found that those with proteinuria 1-1.9 g/day lost GFR at a mean rate of 2 ml/min/year compared with a loss of 10 ml/min/year in those with proteinuria > 3.9 g/day.

Therapeutic intervention can delay progression of renal disease and is most significant in patients with significant proteinuria.

Angiotensin converting enzyme inhibitors (ACEI) and controlling blood pressure have greater benefit in patients with more significant degrees of proteinuria. In a meta-analysis, Jafar et al (2001a, 2001b) demonstrated that anti-hypertensive regimens containing ACEI have a significant benefit in delaying progression of non-diabetic renal disease. The beneficial effect on doubling of serum creatinine or ESRD is not seen until urine protein is > 0.5 g/day. Similar findings were demonstrated in the MDRD study (Hunsicker et al 1997) which showed that the benefit of aggressive blood pressure control on the progression of non-diabetic renal disease was greater in patients with higher urine protein excretion at the onset of therapy. No benefit of aggressive blood pressure reduction was seen in patients with < 1 g/day urine protein.

There are no trials comparing the benefits and harms or best methods of screening in this population. The cost of urine albumin is approximately twice that of urine protein (A$16.00 versus A$8.90) and in the absence of a clear superiority of ACR, it is recommended that PCR be performed.

Albuminuria

Microalbuminuria (MA) is a predictor of progressive renal disease in diabetes.

MA is a marker of early renal disease and has been shown to be an independent predictor of progressive renal impairment in both types of diabetes. Type I diabetics who develop MA in the first 10 years following diagnosis may be more likely to have progressive disease than those who develop MA after 10 years (Warram et al 1996; Forsblom et al 1992). Patients with type II diabetes mellitus (DM) and MA have a 10-fold increase risk of ESRD over 10 years compared with those diabetics without MA (Mogensen 1984, Klein et al 1995). Randomised controlled trials have demonstrated the effectiveness of treatment in all diabetics with MA in delaying renal disease. The treatments of proven benefit are improved glycaemic control and blood pressure lowering through blockade of the renin-angiotensin system (DCCT Research Group 1995, Lewis et al 1993, Lewis et al 2001, UKPDS Study Group 1998). There are no trials to demonstrate a benefit for screening for MA rather than proteinuria, however, it would seem reasonable that earlier diagnosis and institution of therapy will provide better long-term outcomes. In patients with established nephropathy, there is no evidence to suggest that either test is of greater utility.

Albuminuria is a predictor of progressive renal disease in Aboriginal and Torres Strait Islanders (ATSI).

Albuminuria is prevalent in ATSI populations with 36%-50% of adults affected according to different studies (Guest et al 1993, Hoy et al 2001a, Hoy et al 2001b). Renal failure developed in patients with overt albuminuria (mean geometric ACR = 249 g/mol) with a mean follow-up of 5.8 years. Increased age, diabetes, hypertension and body mass index (BMI) were also significant predictors of renal failure but in multivariate analysis were not independent of ACR and GFR. Compared with historical controls, patients with an ACR > 100 g/mol treated with ACEI had a 57% reduction in rate of dialysis (Hoy et al 2000). The follow-up in this study is a relatively short mean of 2.5 yrs and the endpoint is ESRF. There are no data available concerning the rate of decline in function in treated patients with lesser degrees of albuminuria. There is however benefit in identification of patients with lower levels of albuminuria, who have been shown to be at risk for progression of albuminuria and a loss of GFR in a 7 year followup study.

There is increasing evidence that MA is independently associated with an increase in cardiovascular morbidity and mortality (DM, high risk patients, ATSI and post-menopausal women) [Hoy et al 2000, Gerstein et al 2001, Diercks et al 2002, Roest et al 2001, Hillege et al 2001]. In the HOPE study baseline, MA patients had a RR for major CV events of 1.83 (95% CI 1.64 - 2.05, $p < 0.001$), all-cause mortality of 2.09 (95% CI 1.84 - 2.38) and hospitalisation for heart failure of 3.23 (95% CI 2.54 - 4.10) (Gerstein et al 2000). There is a linear relationship between baseline ACR and the risk of both CV outcomes and mortality, which extends into the sub-microalbuminuric range. In the ATSI group, ACR correlates with all-cause death, the risk increasing with the severity of albuminuria. However, there is a clustering of vascular risk factors in patients with MA (hypertension, dyslipidaemia, abnormal glucose and insulin metabolism, hyper-homocysteinaemia, renal dysfunction and abnormal endothelial function) and the role and magnitude of effect of each factor is not known (Rowley et al 2000, Davies et al 2001, Stehouwer et al 2002). There is currently no evidence

that treatment of MA alone as a cardiovascular risk factor improves outcome. The high cardiovascular risk patients in the HOPE study derived benefit regardless of baseline albuminuria (HOPE Study Investigators 2000).

Association between albuminuria and proteinuria in the Australian population

Ausdiab examined a representative cross-section of the Australian adult population for proteinuria (PCR ≥ 0.20 mg/mg) and MA (ACR ≥ 30 mg/g). The key findings of this study were that MA was detected in 6.8% of the population and proteinuria in 2.4%. Patients with either proteinuria or MA were older and more likely to be diabetic or hypertensive. Of those with proteinuria, 0.9% had a PCR > 0.4 mg/mg (roughly equivalent to proteinuria of 400 mg/day).

In the patients with MA in this population, the negative predictive value for proteinuria was 99.8% and the positive predictive value was 32.4%. Of those with proteinuria, 8% had normal ACR, possibly due to increased secretion of tubular proteins. Therefore, if the intention is to screen high risk groups for proteinuria as a marker of significant renal disease, albuminuria at this level (microalbuminuria) performed poorly.

What do the other guidelines say?

Australian Diabetes Society (Professional Group) 1993 position statement:
Testing for microalbuminuria should be performed yearly.

Diabetes Care (American Diabetes Association, Inc.) recommendations for Type 2 Diabetes:
Test urine for protein. If negative, test for albumin. If negative, re-screen annually.

Central Australian Rural Practitioners Association:
Yearly screening from the age of 15 years for all Indigenous populations. To have a urine protein dipstick included in their regular health checks. A reading of 'one +' or more (indicative of macroalbuminuria) needs to be followed by exclusion of other causes and follow up with ACR.

National Heart Foundation:
In the diagnostic evaluation of patients with confirmed hypertension, the urine should be tested by dipstick for blood and protein.

Kidney Disease Outcomes Quality Initiative:
When screening adults at risk for chronic kidney disease, albumin should be measured in a spot urine sample. The guideline also states that although albuminuria is a more sensitive marker than total protein, the literature does not provide substantial information concerning the relative merits of measuring albumin versus total protein to detect and monitor kidney damage.

When screening children without diabetes for chronic kidney disease, total urine protein should be measured.

British Diabetes Association:
Everyone with diabetes aged >11 years should be screened for microalbuminuria annually.

Implementation and audit

The screening of at risk populations largely occurs in general practice. The implementation of these recommendations will require targeted education programmes not only to increase awareness of the need to screen high risk populations but also on the correct management of patients who are screen positive.

Suggestions for future research

Many fundamental questions such as the relative benefits and harms of screening high risk groups, the comparative usefulness of proteinuria versus albuminuria as a screening tool and frequency of testing have not been addressed and would be amenable to study in a randomized controlled trial.

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Appendix

Table 1. Proposed definitions

	Microalbuminuria	**Albuminuria**	**Proteinuria**
Per 24 hours	30-300 mg/d	> 300 mg/d	> 150-300 mg/d
Dipstick	> 3 mg/dL (albumin specific dipstick)	> 20 mg/dL	> 30 mg/dL
Random urine	Males > 17 mg/g (1.9 g/mmol) Females > 25 mg/g (2.8 g/mmol)	Males > 250 mg/g (28 g/mmol) Females > 355 mg/g (40 g/mmol)	Males > 250 mg/g (28 g/mmol) Females > 355 mg/g (40 g/mmol)

Gender specific ranges are from the study by Warram et al (1996) and have been adopted by the K/DOQI guidelines. The American Diabetes Association defines the cut-off for microalbuminuria as ACR > 30 mg/g and albuminuria as ACR > 300 mg/g without gender specific ranges (Bakker 1999).