2. Performance characteristics of tests used in the initial evaluation of patients at risk of renal disease

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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)

- Dipstick protein has been identified to have poor sensitivity and specificity. Dipstick albumin is more reliable but operator (and technique) dependant.

- For initial testing for albuminuria, first morning urine albumin sample is preferred, however, a random urine albumin creatinine ratio (ACR) is acceptable. If abnormal, one or more timed urines are required to confirm microalbuminuria.

- Protein creatinine ratio (PCR) is an accurate test for diagnosis of significant proteinuria (> 1 g/day) but timed urines are required to establish a baseline.

Background

End-stage renal disease (ESRD) develops in about 1500 people each year in Australia, of whom about 1000 are over 50 years of age (a risk of about 200 per million per year). Diabetes, hypertension, impaired renal function and proteinuria are likely independent risk factors for the development of ESRD. About 5% of the general population have proteinuria and these individuals are approximately 15 times more likely to develop ESRD than those without proteinuria. Because of the absence of well done cohort studies, estimating an individual's risk of developing ESRD using values for proteinuria, blood pressure, renal function and diabetes is not possible. The aim of this guideline is to review the different tests available for assessing proteinuria and albuminuria.

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.

Dipstick tests

Dipstick testing for proteinuria

The performance characteristics of dipstick testing have been compared to the reference standard of 24 hour urine protein quantitation. Six relevant studies containing 1558 patients were identified and assessed by meta-analysis by Barratt et al (2003, see Table 1). The studies were of variable quality and carried out in high prevalence populations (mostly renal, rheumatology and obstetric outpatient settings) but use similar tests (mostly Multistix) and similar reference and test thresholds (300 mg and 1+ , respectively). Using this test to detect proteinuria, there was a trade off between sensitivity and specificity:

Sensitivity: 80% Specificity: 85%

Sensitivity: 90% Specificity: 67%

Sensitivity: 60% Specificity: 95%.

The populations used in these studies had high prevalences of proteinuria, mostly over 30% (although the largest had only 7%). It is unlikely that dipstick testing will be employed to screen populations with a prevalence of > 30% beyond the first round of screening. Hence, using dipsticks as a screening tool for proteinuria has marked limitations. These include:

- poor specificity and sensitivity yielding high false positive and false negative rates
- the generally poor quality of studies in this field and absence of studies in suitable at-risk populations, and
- the likely incidence of proteinuria in at-risk populations of < 10%.

Table 1. Studies that compared dipstick to 24 hour urine protein (Barratt et al 2003)

Author, Year	Setting	Reference threshold	Test type	Test threshold	N	Sensitivity (%)	Specificity (%)	Prevalence (%)	PPV	NPV
Ralston, 1988	Rheumatology outpatient department	300mg	Multistix	1+	102	100	36	42	47	100
Harrison, 1989	Renal admissions	300mg	N-Multistix-SG	1+	100	82	77	49	77	82
Allen, 1991	Sequential inpatients & outpatients	250mg	Multistix-10SG	1+	136	47	97	46	93	68
Meyer, 1994	Hypertensive pregnancies	300mg	Multistix	1+	300	67	74	81	92	34
Brown, 1995	Hypertensive pregnant inpatients	300mg	Multistix-10SG	1+	230	86	39	30	38	87
Higby, 1995	Pregnant women	300mg	Micro-buminitest	1+	690	69	98	7	72	98

Dipstick testing for microalbuminuria

Studies found using the search criteria that related to spot urine testing for microalbuminuria and used 24 hour urine collection for albuminuria as gold standard were included. Abstracts of all relevant studies were reviewed and seven articles were identified, with 2 of these being excluded (one due to poor quality and one due to failure to use appropriate reference standard). Of the 5 studies reviewed (see Table 2), the overall standard was poor, with the exception of Gilbert et al (1992). All studies tested the Micral-Test (Boehringer Mannheim, GmbH Mannheim, Germany) test strips and only one used non-diabetic subjects (hypertensive patients, Gerber et al 1998).

Table 2. **Studies that** compared dipstick to 24 hour urine albumin

Author, Year	Reference threshold	Test type	Test threshold	No.	Sensitivity (%)	Specificity (%)	Prevalence (%)	PPV	NPV
Gilbert RE, 1992	20 mg/l	Micral	20mg/l	298	92	92	33	85	96
Gerber LM, 1998	20 mg/l	Micral	20 mg/l	171	81	89	22	68	94
Spooren PF, 1992	20 µg/min	Micral	20 mg/l	132	82?	86?	?		
Marshall SM, 1992	20 mg/l	Micral	20 mg/l	112	100	91	30	83	100
Mogensen CE, 1997	20 mg/l	Micral II	20 mg/l	2228	97	71	52	78	96

Other studies suggest that the Micral-Test is operator dependent with superior results seen in some professional groups and after training in the test technique. The test strips must be immersed in the urine for 5 seconds and read 5 minutes later. Other studies have suggested that test accuracy is very dependent on rigorous adherence to the timing aspects of the test.

It appears that the Micral-Test has better sensitivity and specificity for the detection of microalbuminuria than the dipstick for proteinuria. It has also been studied in appropriate populations, although the quality of these studies still leaves a lot to be desired. The prevalence in the study populations is very high and would not be the case beyond the first round of screening, making the sensitivity and specificity more important.

General comments about dipstick testing

The studies all suggest that using higher cut-offs than 1+ (for proteinuria) and 20 mg/lL (for microalbuminuria) would improve the sensitivity and specificity, at the risk of missing those with very low grade proteinuria or albuminuria. The outcome studies all suggest that those patients with higher levels of proteinuria are at higher risk of renal deterioration and are more likely to benefit from treatment. Therefore, using higher cut-offs for detection may make the urine tests more viable, allowing clinicians to take advantage of the immediacy, ease and cost savings of dipstick testing with a low risk of not treating those patients most likely to benefit from the interventions planned.

Random urine testing for protein and albumin

The performance characteristics of random urine testing have been compared to the reference standard of 24 hour urine collections. The quality of the evidence is marred

by methodological and analytical flaws. Assessment of adequacy of 24 hour collections via determination of the creatinine excretion is variable. In studies where the adequacy of collection is assessed, up 15%-23% of samples were excluded from analysis (Shaw et al 1983), Mitchell et al 1993). The patient populations are mostly taken from specialist hospital clinics and involve both inpatients and outpatients, and may include multiple samples from the same patient.

Random urine testing for protein

Urine protein concentration: protein creatinine ratio

Good correlation between PCR and 24 hour urine total protein (UTP) has been established in a wide range of patient groups (eg. normal, known renal disease, diabetes). A meta-analysis of 7 studies (marked*) containing 873 patients found the sensitivity to be 95% (92%-97%) and specificity 91% (87%-94%) (Barratt et al 2003; see Table 3).

Protein-osmolality ratio has also been used to correct for urine concentration with similar degrees of sensitivity (91%-96%) and specificity (93%-98%) (Wilson and Anderson 1993).

Table 3. Characteristics of Protein Creatinine Ratio compared to 24 hour urine protein

Author	Year	Characteristics	No.	Reference threshold	Test threshold	Sensitivity (%)	Specificity (%)	Correlation
Ginsberg *	1983	Renal outpatient department	46	1g/1.73m^2	1	93	94	0.97
Parag*	1986	Renal outpatient department	34	3000 mg	3000	91	82	0.90
Ralston*	1988	Rheumatology inpatient +outpatient department	102	300 mg	0.04	97	97	0.92
Wilson*	1993	Normal Renal outpatient department	131	156 mg men, 90 mg women	0.05	96	90	0.91
Mitchell*	1993	> 65 yrs, renal outpatient department	52	1000 mg	1000	100	94	0.98
Robert*	1997	Hypertension/ pregnant	71	300 mg	?	93	90	0.94
Ruggenenti*	1998	Trial	98	368 mg		94	92	0.93
Ramos	1999	Pregnant/ hypertensive	47	300 mg	0.5	96	96	0.94
Zelmanovitz	1998	Diabetics	167	541 mg	UPC* PCR†	100 100	92.9 76.2	

Note: Test thresholds are calculated in different ways in different studies; * UPC = urine protein concentration; † PCR = protein creatinine ratio.

Random urine testing for albumin

Review of the literature is made difficult by the various definitions of microalbuminuria, wide variations in test thresholds, and lack of standard comparator. Some studies compared the samples from the same collection, others from samples taken weeks apart. Some studies used overnight urine albumin excretion (which has also been shown to predict development of proteinuria in diabetics). There is some difficulty in comparing overnight samples to random daytime samples as the relationship between daytime and overnight albumin excretion is variable. Overnight albumin excretion is 25% lower than the 24 hour albumin excretion rate (AER) (Ramos et al 1999). The intra-subject day-to-day variability in albumin excretion in a daytime sample is also greater than in an overnight sample (presumably due to the effect of variable exercise). Therefore, studies using 24 hour urine collections are the gold standard but other studies using timed overnight urines are included (see Table 4).

Urine albumin concentration (UAC)

The best correlation with AER is found with a first morning sample with a sensitivity from 86%-97% and specificity from 74%-97%. Random urine albumin concentration correlates poorly with AER in a timed specimen and lacks sensitivity (56%-96%) and specificity (81%-80%).

Albumin: creatinine ratio (ACR)

Correction for urine flow rate increases the sensitivity and specificity with best results seen with early morning samples. However, almost all of the studies use the same sample for assessment of ACR and timed urine and this is a serious methodological flaw.

A systematic review of the literature in urine albumin testing in diabetics has been performed by Scheid et al (2001). Ten studies comparing ACR to timed albumin collection and containing 1691 patients were reviewed. Due to the heterogeneity of studies, the trials were not pooled and data is presented as the range (see below).

	No.	Sensitivity	Specificity
First morning ACR	355	70-97	91-94
Morning ACR	240	71-100	95-98
Random ACR	1096	56-97	81-92

Table 4. Characteristics of Urinary Albumin testing compared to 24 hour urine protein

Author, Year	No.	Patient group	Comparator	Reference Threshold	Test Threshold	Sensitivity (%)	Specificity (%)	Correlation
Random UAC					mg/L			
Gatling, 1985	159	Diabetic in GP	Overnight	30 μg/min	25	56	81	0.45
Watts, 1989	160	Type I diabetics	Overnight	15 μg/min	15	96	80	
				30 μg/min	26	100	85	
Zelmanovitz, 1997	95	Diabetic OPD*	24 hour	20 μg/min	16.9	100	79	0.91
Ahn, 1999	105	Diabetic OPD	24 hour	20 μg/min	31	77	82	0.81
Early morning UAC					mg/L			
Gatling, 1985	175	Diabetic in GP	Overnight	30 μg/min	20	86	97	0.9
Hutchison, 1988	261	Diabetic hospital OPD	Overnight	30 μg/min	17	96.8	90.9	0.90
Wiegmann, 1990	135	Diabetics	24 hour	20 μg/min	30	71	23	
Bakker, 1999	2394	Diabetic	Overnight	20 μg/min	15	88.8	90.2	
Random ACR					mg/mmol			
Gatling, 1985	463	Diabetic in GP	Overnight	30 μg/min	3	80	81	0.43
Nathan, 1987	35	Diabetic OPD	24 hour urine	15 μg/min	3.4	94	96	0.82
Zelmanovitz, 1997	95	Diabetic OPD	24 hour	20 μg/min	1.72	100	74	0.92
Wiegmann, 1990	135	Diabetics	24 hour	20 μg/min	3.4	82	81	
Watts, 1989	160	Type I diabetics	Overnight	15 μg/min	2.9	100	80	
				30 μg/min	8	100	96	
Ahn, 1999	105	Diabetic OPD	24 hour	20 μg/min	3.7	77	92	
James, 1995	33	> 55yrs hypertensive OPD non-diabetic	24 hour	30 mg/day	3	92	90	
Early morning ACR								
Hutchison, 1988	261	Diabetic hospital OPD	Overnight		3	96.8	93.9	0.92
Gatling, 1985	171	Diabetic OPD	Overnight	30 μg/min	3.5	100	95	0.9
Marshall, 1986		Diabetics		30 μg/min	3.5	98	69	
Eshoj, 1987	54	Diabetics	24 hour	20 μg/min	3.5	76	97	
Bakker, 1999	2394	Diabetic	Overnight	20 μg/min	2.5	98.5	86.7	

* OPD = outpatient department

Drawing conclusions from these studies is difficult given the variability in methodology and thresholds, but it would appear that ACR (preferably a first morning specimen) can provide a useful semi-quantitative measure which is useful in screening for albuminuria.

Limitations of protein creatinine ratio/albumin creatinine ratio

The use of urine creatinine excretion to correct for variation in urine concentration needs to be applied with an understanding of its limitations. Gender, age and renal function will all affect the creatinine excretion. Unless this is considered, there is a tendency to underestimate proteinuria in men and overestimate its prevalence in the elderly of both genders due to differences in the amount of creatinine excreted with different muscle mass (Verhave et al 2002, Mattix et al 2002). This difference has significance for screening populations. The NHANES III study found a similar prevalence of microalbuminuria (MA), when defined as UAC > 30 mg/L in men and women (10.9% and 11.8%, respectively) but when applying the same reference range in both genders, found that MA (ACR > 30 mg/g) was more common in women (9.7%) compared with men (6.1%) (Jones et al 2002, Garg et al 2002). Gender-specific ranges have been studied in 218 healthy controls and values corresponding to 95% of the respective gender distributions derived. The result is lower in men – 17 mg/mg (1.9 mg/mmol) compared with 25 mg/mg (2.9 mg/mmol) in women. When these different ranges where applied to the NHANES III cohort, the prevalence of MA was the same in the genders (Kramer et al 2002).

The excretion of protein and albumin is not constant over 24 hrs – it is impacted by posture, activity, protein intake and haemodynamic factors. There is evidence that urine protein excretion has a circadian pattern, being highest in the afternoon. There is little corresponding variation in creatinine excretion. Therefore the timing of the sample will markedly influence the predicted proteinuria (mean variation 42%). The best estimates are probably on morning samples (not first void) (Ginsberg et al 1983, Kristal et al 1988, Koopman et al 1989). The variability is less prominent in patients with massive proteinuria. The variability of albumin excretion is similar in magnitude (Stehouwer et al 1991). The average intra-individual daily UAE is 40% and is most marked at low levels of albumin excretion (< 30 mg/day).

There is day-to day variablility of excretion of protein and albumin. Koopman et al (1989) repeated 24 hour urine protein measurements on 3 consecutive days and found that the variablilty, expressed as a coefficient of variation (CV), was 15% and not more reliable when assessed at any particular time point. Cundy et al (1992) measured 24 hour UAE and ACR in 30 diabetics and repeated the test within a month – the CV for 24 hour UAE was 98% and the ACR CV was 90% – with poorer agreement at low levels of albuminuria for both tests. Although the limits of agreement were wide between methods, the correlation was very strong for all comparisons (R = 0.94-0.97). The authors concluded that the variability in albumin excretion was so great that it overcame the poor agreement between tests.

False-negative results for micro-albuminuria may occur in the setting of heavy proteinuria. This results from the prozone or Hook effect, which is an inherent problem with antibody-based immunoassays when the antigen (albumin) is in excess (Price and Newman 1997). It is standard laboratory practice and recommended by the product inserts for the various assay kits, that urine protein be assessed first, usually by dipstick and samples with heavy proteinuria be diluted to achieve appropriate concentration prior to the assay.

Recent studies have demonstrated that urinary albumin is composed of both immunoreactive and immuno-unreactive fractions (Comper et al 2004). When albuminuria is assessed by radio-immuno assay (RIA), as is standard practice, the immuno-unreactive component will be missed. The exact nature of immuno-unreactive albumin is unknown but may involve a conformational change which is not recognized by the antibodies used in the conventional RIA. Total urine albumin can be measured by high performance liquid chromatography (HPLC). No difference is detected in normal controls, however in diabetics, 91% of patients have significantly more albuminuria when assessed by HPLC. The difference is greatest at low level albuminuria, with a two-fold increase in the number of patients in the microalbuminuria range when assessed by HPLC compared with RIA. The HPLC assay also allows earlier detection of patients who progress from normoalbuminuria to microalbuminuria (Comper et al 2004). The assay is not widely available and further studies are required to confirm these findings. In addition, the impact of various interventions such as blockade of the renin-angiotensin system on the immuno-unreactive fraction are unknown.

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative:

Under most circumstances, untimed ("spot") urine samples should be used to detect and monitor proteinuria in adults and children.

It is usually not necessary to obtain a timed urine collection (overnight or 24-hour) for these evaluations in either children or adults.

First morning specimens are preferred, but random specimens are acceptable if first morning specimens are not available.

In most cases, screening with urine dipsticks is acceptable for detecting proteinuria. Standard urine dipsticks are acceptable for detecting increased total urine protein. Albumin-specific dipsticks are acceptable for detecting albuminuria.

Patients with a positive dipstick test (1+ or greater) should undergo confirmation of proteinuria by a quantitative measurement (protein-to-creatinine ratio or albumin-to-creatinine ratio) within three months.

Patients with two or more positive tests temporally spaced by 1 to 2 weeks should be diagnosed as having persistent proteinuria and undergo further evaluation and management for chronic kidney disease.

Specific guidelines for adults:

When screening adults at increased risk for chronic kidney disease, albumin should be measured in a spot urine sample using either:

- Albumin-specific dipstick
- Albumin-to-creatinine ratio.

British Diabetes Association:

Everyone with diabetes aged > 11 years should be screened annually:

- Screen when free of acute intercurrent illness
- Collect an early morning urine sample
- Use a sensitive assay, specific for albumin
- Measure urine albumin concentration or albumin:creatinine ratio and serum creatinine
- Classify as:
  - Lower risk (absence of microalbuminuria and proteinuria and normal serum creatinine)
  - Higher risk (microalbuminuria or proteinuria or elevated serum creatinine)
- If lower risk screen annually
- If higher risk, obtain two further urine tests for confirmation, within three months.

Australian Diabetes Society Position Statement (1993):
Testing for microalbuminuria should be performed at least yearly in all diabetic patients.

The finding of a single albumin excretion rate (AER) value in the rate of 20-200 μg/min is an indication for two additional measurements of AER in the next 6 weeks.

Two of three AER measurements in the range of 20-200 μg/min suggest the presence of incipient diabetic nephropathy in adult patients with type I diabetes > 5 years from diagnosis.

Implementation and audit

Standardisation of methodology and reference ranges between laboratories would be of assistance in decreasing the uncertainty associated with the various definitions of ACR and PCR.

Suggestions for future research

1. Establish the measures of agreement between morning, random urine and 24 hour urine samples.
2. Investigate the variability of morning, random urine and 24 hour urine samples over time.
3. Establish the utility of gender-specific reference ranges for ACR and PCR in predicting progressive renal impairment.

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