Which test to detect micro-albuminuria in diabetic patients?

A systematic review

Ben Ewald, BMed, MMedSci, is a PhD scholar, Centre for Clinical Epidemiology and Biostatistics, University of Newcastle, and a general practitioner, Newcastle, New South Wales.

John Attia, MD, PhD, FRCPC, is Senior Lecturer, Centre for Epidemiology and Biostatistics, University of Newcastle, New South Wales.

BACKGROUND
Current guidelines suggest general practitioners should screen their diabetic patients for microalbuminuria. There is a range of possible tests. We looked for studies that compared a timed urine sample (the gold standard) with a random spot sample.
METHOD
Systematic review and meta analysis of studies comparing albumin to creatinine ratio (ACR) on a random specimen to albumin excretion rate from an overnight or 24 hour timed sample. Studies were identified using Medline and EMBASE to June 2003. Studies were pooled using diagnostic odds ratios and were checked for heterogeneity.
RESULTS
Ten studies covering 1470 patients were included. Use of the ACR in screening 100 diabetic patients would miss only two out of the 20 patients who would be expected to have microalbuminuria, while there would be 13 false positives. A timed specimen would be required to clarify the diagnosis for 31 patients.
DISCUSSION
The marginal benefit of using a timed urine collection over a spot ACR to detect microalbuminuria in the screening of diabetic patients is small, and not worth the cost and inconvenience of collecting a timed sample.

Microalbuminuria reflects early stages of diabetic nephropathy, and is an independent risk factor for cardiovascular disease.[1] Structured care of diabetic patients such as that embodied in the Australian Commonwealth Government's service incentive payment for diabetes includes annual screening of all diabetic patients for microalbuminuria. However, there are differing recommendations about which test should be used. The gold standard for microalbuminuria is the measurement of albumin excretion rate (AER) on a 24 hour timed urine specimen. This may be inconvenient for general practice patients as it requires collection of all urine passed over the specified time in a specialised collection bag and generally two trips to a pathology centre. Timed urine specimens are also prone to recording errors, and incomplete bladder emptying will bias results.[2] A more convenient alternate test is the albumin to creatinine ratio (ACR) done on a single random urine sample that can be collected at the time of a clinic visit.

Excretion of albumin fluctuates widely from day-to-day (and within any day), when standing (rather than lying), and greater with activity (than rest); so any single estimate may not be representative for that patient.

'We suggest routine use of ACR on a random urine sample as the initial test in screening diabetics for microalbuminuria, thereby saving the inconvenience of collecting a timed urine specimen with negligible loss of case detection. One in eight patients will require a timed specimen to clear up false positives'.

The definition of microalbuminuria used in prognostic and interventional research is 'albumin excretion of from 20 to 200 µg per minute demonstrated on two out of three timed urine samples'.[3,4] Various thresholds have been used for interpretation of ACR. Older papers used cut points between 3.0 and 3.7 mg/mmol,[5,6] while more recent papers use a sex specific cut point of 2.5 mg/mmol in men and 3.5 mg/mmol in women.[7,8] Age and sex specific cut points for ACR would increase specificity in the Cardiab study.[8] In the Cardiab study, the prevalence of albumin excretion in Australian diabetic patients seen in general practice was 20% for microalbuminuria and 4% for macroalbuminuria.[9]

The detection of confirmed albuminuria or microalbuminuria changes management in the following ways:[10] the target for blood pressure treatment is lowered to 135/75, angiotensin converting enzyme (ACE) inhibitors should be considered, renal function should be monitored and referral to a renal physician arranged if estimated creatinine clearance falls below 30 mL/minute, although targets for blood sugar levels and cardiovascular risk factors are unchanged efforts to modify them may be increased, and, if the person does not have retinopathy, an alternate cause

for their renal disease should be sought.

We wondered what the marginal benefit was of a timed urine specimen over a spot specimen in the screening of diabetics for micro- or macro-albuminuria in the general practice setting.

Method

We searched Medline and EMBASE databases from 1966 to February 2004 using the MeSH terms 'diabetes mellitus', 'proteinuria', 'albuminuria', 'area under curve', and 'sensitivity and specificity'. Text searches were also conducted for these terms as well as albumin, creatinine, microalbumin, ACR and urine albumin to creatinine (UAC). References of retrieved papers were also searched for eligible studies. Retrieval criteria were developed with regard to the STARD[11] statement of reporting diagnostic research. However, few papers met all the requirements of STARD so it could not be used as inclusion criteria. Papers were of acceptable quality if they set out to compare diagnostic performance of the two tests, all subjects had both tests, cut points were described, and sufficient detail was presented to meet our inclusion criteria as follows. They had to report a series of diabetic patients including adults, compare a random spot urine or first morning UAC ratio with a timed overnight or 24 hour urine albumin estimation, report sensitivity and specificity (or provide sufficient detail so these values could be derived), and include more than 20 subjects.

Several studies reported ACR on urine taken from the 24 hour collection bag. However, as this does not reflect the variation likely to occur with a random specimen, these studies were not included.[3] As these criteria served as a quality filter, no further quality scoring was necessary.

Analysis

The diagnostic odds ratio (DOR) was calculated for each study: it is the product in the 2x2 table of true tests divided by the product of false (a x d/b x c).[12]

True positives (a)	False positives (b)
False negatives (c)	True negatives (d)

Its benefit is that it is not influenced by the choice of cut point used in the various studies. Changes to the cut point will trade off sensitivity against specificity, but the DOR will remain nearly constant making it more suitable when combining studies. The DOR is not clinically applicable, but can be used to derive summary sensitivity and specificity values. Heterogeneity of the DORs was tested using the Breslow-Day Q test, and a summary DOR calculated by the random effects method of DerSimonian and Laird in Stats Direct.[13]

Results

We identified 43 studies, of which 12 fitted the retrieval criteria. Two were excluded: one reported multiple samples per patient,[14] another reported nondiabetic patients,[4] leaving 10 remaining studies (*Table 1*). There was heterogeneity between the 10 studies ($p<0.001$). However, when analysis was restricted to the seven studies that used a 24 hour AER rather than an overnight reference standard, they were found to be homogenous ($p=0.44$) (*Figure 1*). Neither the use of a sex specific cut point for ACR, or the setting (general practice versus hospital clinic) systematically affected the results.

The summary odds ratio estimated with a random effects model was 45.8 (95% CI:

Table 1. Studies comparing random ACR to a timed AER specimen

Study	Setting	Comparison	Sensitivity	Specificity	Prevalence of albuminuria (%)
Zelmanovitz[5]	54, hospital outpatient clinic Brazil	Random ACR vs 24 hour AER	89	89	81
Wiegman[6]	135, USA hospital outpatient clinic 90 with type 1 diabetes	Random ACR vs 24 hour AER	82	81	22
Gatling[15]	311, 40 UK GPs	Random ACR vs timed overnight AER	80	81	6
Jermendy[16]	192, Hungarian diabetes centre	Morning ACR vs timed overnight AER	75	69	68
Claudi[7]	106, Norwegian primary care	Random ACR on near patient analyser vs overnight AER	90	90	NA
Ahn[17]	105, Korean ambulatory patients	Random ACR vs 24 hour AER	77	92	52
Eshoj[18]	54, type 1 Denmark	Morning urine vs 24 hour AER	90	88	46
Ng[19]	65, Singapore outpatients	Morning ACR on desk top DCA2000 vs 24 hour AER	71	98	22
Gyamlani[20]	136, adult diabetics, Olmsted county USA	Early morning ACR vs 24 hour AER	85	85	29
Houlihan[8]	314, Australian hospital outpatients	Spot morning sample vs 24 hour AER	95	81	Male 54% Female 32%

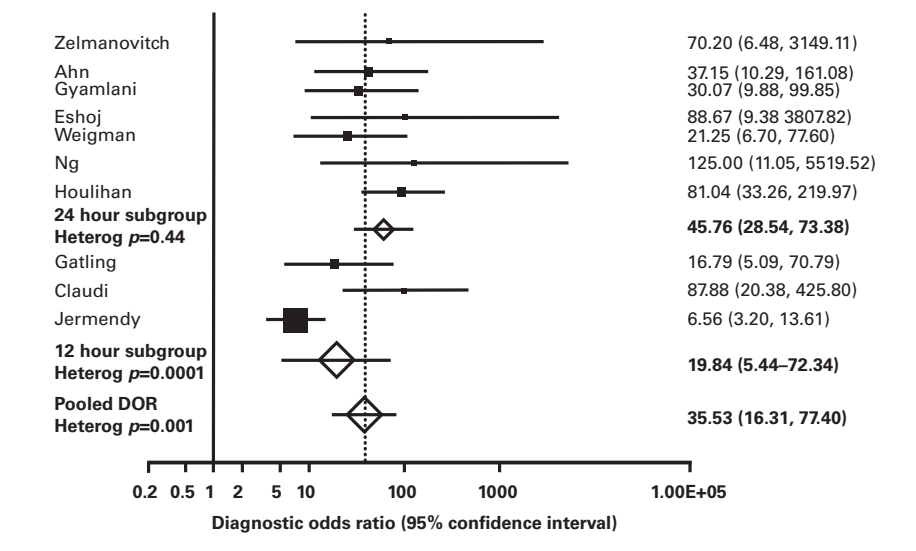

Figure 1. Diagnostic odds ratios of included studies by reference standard and summary estimate

28.5–73.4). The odds ratio can be translated to a pair of sensitivity and specificity values by choosing the sensitivity value from one of the larger studies and calculating the specificity based on the odds ratio by solving simultaneous equations. Sensitivity of 90% as in the study by Claudi,[7] gives specificity of 84% (95% CI: 76–89) or if sensitivity was 80% as in Gatling,[15] specificity would be 92% (95% CI: 88–95).

Discussion

Research into diagnostic processes relies on a gold standard of diagnosis against which other tests are compared. Discordance of test results is interpreted as error in the candidate test and assumes the reference test is always correct. Such research is therefore only as good as the gold standard. The studies we reviewed reported spot urine tests against a single timed specimen, which does not match the 'two out of three' definition of microalbuminuria used in the literature for prognostic and intervention studies.

In one study, both timed albumin excretion and ACR were measured sequentially three times on each subject to categorise them as normal, microalbuminuria, or macroalbuminuria.[16] The timed specimen gave consistent categorisation 80% of the time, while ACR gave consistent categorisation 75% of the time. Unfortunately this paper did not present an analysis of sensitivity and specificity against the 'two out of three' definition.[16]

In another study, the prevalence of microalbuminuria in diabetics was 31% in one of three tests, but only 20% when a 'two out of three' definition was used.[2] The variability of the gold standard means the inaccuracy of the ACR was overestimated.

Two other possible screening tests have not been assessed in this review. The determination of albumin concentration alone on a random specimen does not perform as well as the ACR[3] and uses the same specimen. High sensitivity albumin test strips such as 'Micral' are generally not used in Australian general practice for administrative reasons: the cost of $1.80 per test strip would be borne by the practice while the cost of any laboratory based test is borne by Medicare.

How should we apply these results in practice?

Applying a sensitivity of 90% and specificity of 84% to the screening of 100 diabetic patients, of whom 20 actually had microalbuminuria, the use of a random ACR instead of a timed overnight or 24 hour sample would result in the problem being missed at that screening round in two patients. Based on Australian data, a further four patients would have macroalbuminuria which either test would detect. The use of the simpler test would also incorrectly identify 13 patients as having albuminuria, requiring them to proceed to albumin measurement on a timed urine sample. The use of an ACR followed by a confirmatory timed AER would result in 31 patients requiring a timed urine collection compared to 100 patients undergoing this test if it was used initially.

Insisting on a timed urine collection may reduce adherence to the screening regimen. If the inconvenience of a timed specimen resulted in 10 of the 100 patients not being screened at all, two patients with microalbuminuria would be missed, completely cancelling the benefit of the better test.

As screening for albuminuria is implemented in a practice, the initial round can be expected to find the problem in around 24% of patients. However, subsequent rounds of screening will find only new cases that have developed in the intervening year. If these incident cases of microalbuminuria occur in 2% of diabetics per year, the use of ACR instead of a timed specimen will miss 0.2 of a case per 100 diabetics screened, and 15 patients will need to proceed to a timed specimen to clear up false positives.

We suggest routine use of ACR on a random urine sample as the initial test in screening diabetics for microalbuminuria, thereby saving the inconvenience of collecting a timed urine specimen with negligible loss of case detection. One in eight patients will require a timed specimen to clear up false positives.

Conflict of interest: none declared.

References

1. Dinneen SF, Gerstein HC. The association of microalbuminuria and mortality in noninsulin dependent diabetes mellitus. A systematic overview of the literature. Arch Intern Med 1997;157:1413–1418.
2. Ellis D, Coonrod BA, Dorman JS, et al. Choice of urine sample predictive of microalbuminuria in patients with insulin dependent diabetes mellitus. Am J Kidney Dis 1989;13:321–328.
3. Bakker AJ. Detection of microalbuminuria. Receiver operating characteristic curve analysis favors albumin-to-creatinine ratio over albumin concentration. Diabetes Care 1999;22:307–313.
4. Morgensen C, Vestbo E, Poulsen P, Christiansen C. Microalbuminuria and potential confounders. Diabetes Care 1995;18:572–581.

5. Zelmanovitz T, Gross J, Oliveira J. The receiver operating characteristics curve in the evaluation of a random urine specimen as a screening test for diabetic nephropathy. Diabetes Care 1997;20:516–519.
6. Wiegmann T, Chonko A, Barnard M. Comparison of albumin excretion rate obtained with different times of collection. Diabetes Care 1990;13:864–871.
7. Claudi T, Cooper J. Comparison of urinary albumin excretion in overnight urine and albumin creatinine ratio in spot urine in diabetic patients in general practice. Scand J Primary Health Care 2001;19:247–248.
8. Houlihan C, Tsalamandris C. Albumin to creatinine ratio: a screening test with limitations. Am J Kidney Dis 2002;39:1–10.
9. Carter S, Burns J, Bonney M. CARDIAB. Sydney: Centre for general practice integration studies, University of NSW, 2000.
10. McIntosh A. RCGP Clinical guideline for type 2 diabetes. Diabetic renal disease: prevention and early management. Sheffield: Royal College of General Practitioners, 2002.
11. Bossuyt PRJ. The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. Clin Chem 2003;49:7–18.
12. Deeks JJ. Systematic reviews in health care: systematic reviews of evaluations of diagnostic and screening tests. BMJ 2001;323:157–162.
13. Stats Direct L. Stats Direct. In: 2.2.8 edn. Cheshire UK: Stats Direct, 2003.
14. Nathan DM, Rosenbaum C, Protasowicki VD. Single void urine samples can be used to estimate quantitative microalbuminuria. Diabetes Care. 1987;10:414–418.
15. Gatling W, Knight C, Mullee MA, Hill RD. Microalbuminuria in diabetes: a population study of the prevalence and an assessment of three screening tests. Diabet Med 1988;5:343–347.
16. Jermendy G, Farkas K, Nadas J, Daroczy A, Peterfai E. Practical aspects of measuring microalbuminuria in diabetic patients. Diabetes Nutr Metab Clin Exper 2001;14:195–200.
17. Ahn CW, Song YD, Kim JH, et al. The validity of random urine specimen albumin measurement as a screening test for diabetic nephropathy. Yonsei Medical Journal 1999;40:40–45.
18. Eshoj O, Feldt-Rasmussen B, Larsen ML, Mogensen EF. Comparison of overnight, morning and 24 hour urine collections in the assessment of diabetic microalbuminuria. Diabet Med 1987;4:531–533.
19. Ng WY, Lui KF, Thai AC. Evaluation of a rapid screening test for microalbuminuria with a spot measurement of urine albumin-creatinine ratio. Ann Acad Med Singapore 2000;29:62–65.
20. Gyamlani G, Bergstralh E, Slezak J. Urinary albumin to osmolality ratio predicts 24 hour urine albumin excretion in diabetes mellitus. Am J Kidney Dis 2003;42:685–692.

AFP

Correspondence
Email: ben.ewald@newcastle.edu.au