Urinary albumin excretion: a predictor of glomerular findings in adults with microscopic haematuria

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Summary

Background: Microscopic haematuria without proteinuria is a common clinical finding. When urological causes are excluded, usual findings on renal biopsy are IgA nephropathy (which can progress to end-stage renal failure) or thin basement membrane nephropathy (which has an excellent prognosis). A non-invasive test to discriminate between the two would be useful.

Aim: To examine the value of measurement of urinary albumin excretion in discriminating glomerular causes of microscopic haematuria in patients without proteinuria on urine dipstick tests.

Design: Single-centre retrospective cross-sectional observational study.

Methods: Adult patients who underwent renal biopsy for microscopic haematuria over a 6-year period from January 1994 were identified. Study entry required normal renal function, no proteinuria detected by dipstick, and urinary albumin excretion <300 mg/24 h. Patients with IgA nephropathy had follow-up for a mean of 58 months after biopsy.

Results: Of 169 patients fulfilling study criteria, 119 (70%) had normoalbuminuria (<30 mg/24 h); 52 (30%) had microalbuminuria (30–299 mg/24 h). Of those with normoalbuminuria, 106 (89%) had thin basement membrane nephropathy or no glomerular abnormality. Thirteen (11%) had IgA nephropathy, and of 12 of these followed-up for a mean 64 months, none developed overt, dipstick-positive proteinuria. In contrast, 24 (48%) of those with microalbuminuria had IgA nephropathy, and of 22 followed-up for a mean 55 months, five developed overt proteinuria.

Discussion: Urinary albumin excretion is an indicator of likely glomerular findings in microscopic haematuria, and may influence whether a renal biopsy is necessary.

Introduction

When urological causes of microscopic haematuria have been excluded, the presence of proteinuria detected by dipstick is usually considered an indication for a renal biopsy, as there may be a potentially progressive disorder. In the absence of proteinuria, there is no consensus as to whether a biopsy is necessary. The renal prognosis of such patients is good over the medium term.¹² The long-term prognosis is unclear, particularly as a significant proportion is likely to have IgA nephropathy, which can progress to end-stage renal failure in 20% over 20 years.³⁻⁸ Most of the rest are found to have thin basement membrane nephropathy, which in contrast has an excellent prognosis.⁹,¹⁰ A non-invasive test to discriminate between IgA nephropathy and other conditions would be useful in such patients. We examined the value of measurement of urinary albumin excretion, which has...
been shown to increase early in progressive renal disorders such as diabetic glomerulopathy, and is a more sensitive detector of renal disease than total urinary protein excretion or dipstick test.11

Methods

Patients were identified in the Department of Nephrology, University Hospital Birmingham, who underwent percutaneous renal biopsy for microscopic haematuria between January 1994 and December 2000. At this time, the Department provided the adult renal services for 1.5 million people from Central, South and West regions of Birmingham. Most patients had been referred either directly to the Department by general practitioners or via the Department of Urology, University Hospital Birmingham, after a urological cause of microscopic haematuria had been excluded. At that time, the policy of the Department of Nephrology was to offer a renal biopsy to every patient with microscopic haematuria but without a urological abnormality.

To fulfil the criteria for entry to the study, the patient had to have normal renal function (serum creatinine concentration <126 μmol/l), no proteinuria detected by dipstick, a 24-h urinary albumin excretion measurement within 3 months of the renal biopsy, and an albumin excretion <300 mg/24 h. Normal urinary albumin excretion was <30 mg/24 h; excretion of 30–299 mg/24 h was called microalbuminuria, and excretion of 300 mg/24 h and above corresponded to overt, dipstick-positive proteinuria. These patients had undergone urological investigation before biopsy. For those aged 17–40 years, this included ultrasonography or intravenous urography. Those aged 40 years and over also had cystourethroscopy and urine cytopathology. There was no evidence of diabetes mellitus or inflammatory disorders including vasculitis, nor a family history suggestive of Alport’s syndrome. Renal biopsy specimens were fixed in formal saline and glutaraldehyde. Light microscopic sections were examined in orthodox ways. Immunostaining was done with an immunoperoxidase method for IgG, IgA, IgM and the complement component C9. The piece in glutaraldehyde was embedded in Araldite and sectioned for electron microscopy. IgA nephropathy was diagnosed by the finding of IgA deposition in mesangium on immunoperoxidase study. Thin basement membrane nephropathy was diagnosed by the finding of basement membranes that were thinner than normal on electron microscopy, without irregularities of the external surface, splitting of the lamina densa or inclusions. Many specimens were so unequivocally thin that measurement was not necessary. In cases of doubt, the method of McLay et al. was used to measure the thickness of membranes, with appropriate calibration of the magnification of the microscope.12 A mean thickness <270 nm was considered evidence of thin basement membrane nephropathy. Other diagnoses were made on orthodox criteria.

Most patients found to have thin basement membrane nephropathy were returned to the care of their general practitioners, who were advised to refer a patient back if any new clinical or urinary features appeared. Those found to have IgA nephropathy were offered annual follow-up by the Department of Nephrology. The most recent urine dipstick findings, random urinary albumin/creatinine ratio and serum creatinine concentration were noted. Albumin/creatinine ratio replaced 24-h urinary albumin excretion as the routine means of quantifying proteinuria in the Department of Nephrology in 2001. This is simpler and more convenient because it does not require a 24-h urinary collection, but gives comparable indications of the level of proteinuria.13 It is expressed as the ratio of urinary albumin concentration in mg/l to urinary creatinine concentration in mmol/l. A ratio of 2.5 mg/mmol and under in men, and 3.5 mg/mmol and under in women, is normal. A ratio greater than this, but <30 mg/mmol, corresponds to microalbuminuria, whereas a ratio of 30 mg/mmol and over usually corresponds to dipstick-positive proteinuria.13 A ratio of >100 mg/mmol approximates to a urinary albumin excretion of >1 g/24 h.

Results

Between January 1994 and December 2000, 169 patients who underwent successful percutaneous renal biopsy fulfilled the study criteria (Table 1). Their mean ± SD age was 43 ± 13 years, and their renal function was normal (serum creatinine concentration 93 ± 13 μmol/l). There were 119 patients (70%) with normoalbuminuria, and the other 50 (30%) had microalbuminuria. The patients in the two groups had similar blood pressure prior to biopsy.

Of those with normoalbuminuria, 106 (89%) had thin basement membrane nephropathy or no glomerular abnormality, and 13 (11%) had IgA nephropathy. Of 50 patients with microalbuminuria, 24 (48%) had IgA nephropathy. The two others without thin basement membrane nephropathy or no abnormality had membranous nephropathy and a segmental sclerosing disorder.
Follow-up data were available on 12 of the 13 patients with IgA nephropathy who initially had normoalbuminuria. After a mean period of 64 months (median 64 months), all remained normoalbuminuric as determined by urinary albumin/creatinine ratio. Of 24 patients with IgA nephropathy who initially had microalbuminuria, follow-up was available on 22. Five of these were found after a mean period of 55 months (median 49 months) to have developed overt, dipstick-positive proteinuria and albumin/creatinine ratio >30 mg/mmol. Four had an albumin/creatinine ratio >130 mg/mmol. Of the remaining 17 patients followed up, 12 had remained microalbuminuric, and five had become normoalbuminuric. The reduction in albuminuria in these five patients was not associated with a significant decrease in blood pressure (mean arterial blood pressure at diagnosis 93 mmHg vs. 88 mmHg at follow-up; paired ‘t’ test, \( p = 0.3 \)) or use of antihypertensive medication, including ACE inhibitors. No patients had developed renal impairment (serum creatinine concentration >126 μmol/l).

### Discussion

This is the largest retrospective biopsy series of adult patients with microscopic haematuria but without proteinuria (as detected by dipstick). The glomerular abnormalities are the same as in previous series, but this is the first to define a group with a high prevalence of benign glomerular causes of microscopic haematuria by investigation of urinary albumin excretion. Urinary albumin excretion is a sensitive means of detecting glomerular disease. A five-fold increase in albumin excretion may occur while the total urinary protein excretion remains within the normal range and conventional urine dipstick tests remain negative. This has been shown in diabetes mellitus and systemic lupus erythematosus to be a more sensitive means of detecting patients at risk of developing progressive nephropathy than measurement of total protein excretion. Urinary albumin excretion in the microalbuminuria range was shown in our study to define a group with high prevalence of IgA nephropathy, a potentially progressive glomerulopathy.

There is no consensus whether patients similar to those selected for this study should undergo renal biopsy. A multi-national survey of practice in patients with microscopic haematuria found that many centres only biopsy those patients with urinary protein excretion over 1 g/24 h, if there was no coexisting renal impairment or systemic disease. This policy is supported by studies that identified proteinuria >1 g/24 h as indicative of an underlying progressive nephropathy, while most patients with lesser degrees of proteinuria preserved their renal function. Further, once proteinuria was above >1 g/24 h, it became an independent risk factor for the progression of renal diseases such as IgA nephropathy to end-stage renal failure. Additionally, empirical therapies such as ACE inhibition that reduce blood pressure and proteinuria have a beneficial effect on renal survival in these patients.

However, adopting this biopsy policy may lead to these treatments being initiated late in the disease process. A more proactive strategy that identified patients with microscopic haematuria and progressive IgA nephropathy earlier may be preferable. The natural history of IgA nephropathy is not completely understood; it is difficult to define an optimal time to start these therapies and therefore difficult to define when a histological diagnosis should be sought. Lai et al. have published research addressing this area. These investigators looked for histological predictors of clinical outcomes in 45 patients with IgA nephropathy, who at the time of biopsy...
had normal renal function and a total urinary protein excretion ≤0.4 g/24 h, and were normoten-
vie.22 Over the period of follow-up (median 123
months), eleven (24%) developed hypertension
(>140/90 mmHg), ten (22%) proteinuria (>0.5 mg/
24 h), and five (11%) renal impairment (serum
creatinine concentration ≥1.4 mg/dl), of whom
one reached end-stage renal failure. They con-
cluded that even at this early stage of the disease,
grading the extent of relatively minor glomerular
and tubular damage could differentiate those at
risk of disease progression from those with minimal
risk. This study not only highlighted that clinically
early IgA nephropathy can progress to renal impair-
ment but also that early diagnosis may help identify
those patients at particular risk in whom early
therapeutic interventions could be targeted.

Our study of patients is not only the first to
identify that the non-invasive test of quantifying
urinary albumin excretion defines a group of high
prevalence of IgA nephropathy, but may also help
identify those at greater risk of having the progres-
sive form of the disease, as indicated by increasing
levels of proteinuria. Though early intervention
has been shown to be of benefit in diabetics with
microalbuminuria, it has yet to be demonstrated
by large prospective trials in IgA nephropathy.24

Our finding that an equal number of initially
microalbuminuric patients spontaneously reduced
their urinary albumin excretion to normal levels
highlights the complex natural history of IgA
nephropathy.

Most normoalbuminuric patients in our study
were found to have thin basement membrane
nephropathy. This, unlike Alport’s syndrome,
is rarely associated with extrarenal abnormalities
such as deafness, and does not lead to overt
proteinuria and renal impairment.25,10 Alport’s syn-
drome is usually X-linked and leads to renal failure
in the second or third decade of life. By adulthood,
therefore, Alport’s syndrome is unlikely in a male
presenting with haematuria in the absence of
proteinuria, deafness, or renal impairment.25 Simi-
larly, the 5% of female carriers of the X-linked
disorder who progress to renal failure will have
developed overt signs of disease by adulthood, and
the majority will have a family history of Alport’s
syndrome.26 Our study did not detect any patients
with previously unsuspected Alport’s syndrome.
Less frequently, Alport’s syndrome is inherited as
an autosomal recessive disorder. Carriers of this
disorder can present with microscopic haematuria
and are found to have glomerular basement
membranes identical to those found in thin base-
ment membrane nephropathy.26 Evidence from
 genetic studies has identified causative genes for
autosomal recessive Alport’s syndrome in 40% of
patients with thin basement membrane nephrop-
athy.26–28 Thus thin basement membrane nephrop-
athy in some of our patients represents the carrier
state of autosomal recessive Alport’s syndrome.

Retrospective studies have identified that there
are more males than females with IgA nephropathy,
whereas thin basement membrane nephropathy is
more common in women. The amount of haema-
turia is higher in those with IgA nephropathy, and
they are more likely to have total proteinuria
≥500 mg/24 h at the time of biopsy. Episodes of
macroscopic haematuria or co-existing hypertension
are not discriminatory.10,29 About two-thirds of
patients with thin basement membrane nephrop-
athy have another family member with microscopic
haematuria, but those with IgA nephropathy do not.26,29 We did not screen family members
for microscopic haematuria as part of our patient
assessment. Had we done so, this information
combined with the patients’ urinary albumin
excretion would probably have been able to
discriminate with greater accuracy those with IgA
nephropathy.

Microscopic haematuria in the absence of pro-
teinuria is a common clinical finding, and consti-
tutes a significant part of a nephrologist’s workload.
After appropriate urological investigations, a renal
biopsy may be considered. A policy of biopsying
all such patients would establish the cause in the
majority and help plan appropriate follow-up
arrangements. However, this leads to a large
number of patients with a non-progressive glomer-
ular disorder undergoing an invasive procedure,
and is labour-intensive. Conversely, a policy of
following all patients until more overt signs of a
progressive nephropathy develop may delay the
appropriate management of progressive diseases.
Although in this study urinary albumin excretion
did not identify IgA nephropathy with complete
accuracy, the prevalence of IgA nephropathy was
four times higher in those with urinary albumin
excretion 30–299 mg/24 h (48%) than in those
<30 mg/24 h (11%). Further, a significant proportion
of those patients with microalbuminuria and IgA
nephropathy developed signs of disease progression
within 5 years of follow-up, unlike normoalbumi-
uric patients. Patients now referred to our Depart-
ment with microscopic haematuria but without
proteinuria on urine dipstick testing, and without
evidence of an inflammatory or hereditary disorder,
rarely undergo renal biopsy if normoalbuminuric.
The findings of our study may help other nephrol-
ogists in their decision whether to offer a renal
biopsy.
References
