

Time to abandon testing for microscopic haematuria in adults?

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Although there is no doubt that macroscopic haematuria is serious, the clinical significance of asymptomatic microscopic haematuria is controversial. Should it still be tested for?

Macroscopic haematuria has always been considered to be serious. Hippocrates stated, "If a patient passes blood, pus, and scales, in the urine, and if it has a heavy smell, ulceration of the bladder is indicated." The clinical significance of "microhaematuria" (microscopic haematuria), on the other hand, is more controversial. No consensus exists on the role of asymptomatic microhaematuria in the diagnosis of diseases, and guidelines are contradictory.¹⁻³ Thus, this finding, which has been brought to the fore by the wide use of dipstick testing, presents a dilemma for doctors and even for patients.⁴ Recently the clinical importance of symptomatic microhaematuria has also been questioned.⁵ This article looks at the evidence base for the diagnostic value of microhaematuria.

Methods

I was one of a panel of Swedish general practitioners and urologists set up by National Board of Health and Welfare in Sweden 1999 to formulate evidence based policy statements and recommendations for evaluating microhaematuria in adults. The panel recommended that testing for microhaematuria should be abandoned. This article continues that work and is based on an updated computer aided literature search up to May 2002 aimed at addressing four key questions:

- What is the significance of asymptomatic microhaematuria (compared with a control group with a negative test)?
- What diseases do we want to diagnose with this test?
- What is the efficacy of testing for microhaematuria in populations at high risk?
- What is the diagnostic significance of microhaematuria in patients with pain in the loin or lower urinary tract symptoms?

Clinical significance of asymptomatic microhaematuria

Most relevant studies report the results of investigating a cohort of patients with asymptomatic microhaematuria. For ethical and other reasons, comparison with a control group without haematuria is seldom possible, but in three studies a cohort of people with asymptomatic microhaematuria (cases) were examined

Summary points

Microhaematuria is poorly predictive of cancers of the urinary tract

Haemoglobin dipstick testing is not a reliable way of detecting early bladder cancer in patients at high risk

Microhaematuria is not reliable evidence of a stone in the ureter and may be misleading, as it is often present in other serious conditions that cause acute loin pain

Testing for microhaematuria is not helpful in evaluating men with lower urinary tract symptoms

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BMJ 2003;326:813-5

retrospectively and compared with a matched group of controls.⁶⁻⁸ The group was followed up for from 3-13 years by review of their medical records.

Mohr et al grouped the diseases considered to be potential causes of microhaematuria into minor, moderate, and severe categories, and graded the degree of microhaematuria for patients in the severe category.⁶ Patients were classified by age, sex, and any drugs being taken. Markedly more diseases were found among elderly women in the minor category and middle aged



Diseases commonly associated with microhaematuria**Non-malignant renal disease**Thin glomerular basement membrane nephropathy
IgA nephropathy**Urogenital tract disease**Inflammatory conditions of the urethra, bladder, and prostate
Benign prostatic hypertrophy
Calculi
Malignancies

men were under-represented in the moderate category. Serious disease was no more common in cases than controls. Hiatt et al found that the relative risk for urogenital cancer was not significantly greater in cases than in controls,⁷ and Choi et al did not find a higher cumulative incidence of urinary tract diseases in cases than in controls, even after adjusting for age and smoking.⁸ In summary, these controlled studies did not find more urinary cancers in patients with microhaematuria than in those without it. The exception was that prostatic carcinoma was commoner in cases than in controls in one study.⁶ However, now that we can test for prostate specific antigen, the value of an additional method of detecting prostatic cancer is questionable. With respect to non-malignant disease, renal calculi and various causes of raised serum creatinine were significantly more common in patients with a positive test for microhaematuria.⁶

Diagnostic value for diseases of the kidney and lower urinary tract

When considering the diagnostic value of microhaematuria we have to decide which diseases we want to find at an asymptomatic stage (box). Non-malignant diseases of the kidney are diagnosed mainly by renal biopsy, a procedure difficult to justify in patients who have only microhaematuria.⁹ Otherwise the main focus is on tumours of the urogenital tract, of which the commonest are tumours of the bladder, kidney, and prostate, and we need to establish how often these malignancies present with only microhaematuria.

The most common symptom in series of newly diagnosed cancers of the bladder is painless macroscopic haematuria. Theoretically, microhaematuria should precede visible blood in the urine, but nothing is known about the time intervals involved. In a Swedish population based study of patients with newly diagnosed bladder cancer only 4% had been referred solely on account of microhaematuria¹⁰; in a similar American study the rate was 6%.¹¹ The literature provides no evidence that cancers causing only microhaematuria are

less advanced at diagnosis than those causing macroscopic haematuria.¹² In patients reported to the American tumour registry, those detected by screening for microhaematuria did not differ from unscreened patients in tumour stage or grade,¹³ nor in the proportions of low grade superficial cancer as opposed to high grade or invasive bladder cancer.¹⁴

How early does microhaematuria occur in the evolution of urinary bladder carcinoma? Data from a screening study showed that a screening interval of nine months was too long, and from this it was assumed that bladder cancer has a brief preclinical duration.¹⁴ A recent report on a study of a cohort of Chinese workers exposed to benzidine is informative.¹⁵ They were prospectively tested with biomarkers (DNA 5CER, G-actin, p300) and conventional methods (cytology and testing for microhaematuria). Two of the biomarkers were good markers of individual risk and predicted disease 15-33 months before the cancers were diagnosed. The corresponding lead times for positive cytology and a positive microhaematuria test were eight and three months respectively. The authors concluded that the sensitivities of cytology and of testing for microhaematuria as primary screening methods for detecting bladder cancer are poor.

With the increased use of abdominal imaging, renal cancer has since the 1980s commonly been an incidental finding.¹⁶ Renal tumours seldom give rise to microhaematuria and in one series only 8% were diagnosed by discovery of microhaematuria.¹⁷ In this series the prevalence of microhaematuria was significantly lower in patients with tumours found incidentally (39%) than in those presenting with classic symptoms (69%). In large ultrasound screening studies, no abnormalities were found by urine analyses of patients with tumours.¹⁸ In summary, only tumours of the bladder present with microhaematuria to an extent that it can be considered to be an early sign of the disease.

Efficacy of microhaematuria testing in populations at high risk

If urologists consider that microhaematuria is a good indicator for bladder cancer it should be used in the highest risk population: those who have been treated for bladder cancer and are under observation for recurrence. The risk of recurrence is reported to be 26-70%.¹⁹⁻²¹ Studies in which no other test was used as a control found that microhaematuria testing is highly sensitive, but in spite of this it is not generally used.²²⁻²³ Recent studies evaluating new screening tests for patients at high risk for bladder cancer compared the performance of the haemoglobin dipstick test in three groups of patients (table).²⁴⁻²⁶ Sensitivity was 41-69%, but it was probably over-rated because microhaematuria was sometimes the indication for the investigation in these studies. Specificity was 68-87%. One of the studies correlated the result of the test with the stage of the disease.²⁴ The microhaematuria test had a sensitivity of only 31% in superficial malignant bladder disease, and it is in this group that early detection would be most valuable. All the new tumour markers evaluated in these studies performed better than testing for microhaematuria. Overall, only half of the patients with bladder cancer in these series had microhaematuria.

Sensitivity and specificity of testing for microscopic haematuria in different patient groups at high risk of bladder cancer

| Criteria for including patients | No (%) with bladder cancer | Sensitivity (%) | Specificity (%) |
|--|----------------------------|-----------------|-----------------|
| Follow up after bladder cancer ²⁴ | 192 (41) | 41 | 87 |
| Presenting to urology clinic ²⁵ | 130 (46) | 69 | 68 |
| Undergoing cystoscopy ²⁶ | 196 (29) | 47 | 84 |

Microhaematuria in patients with urinary tract symptoms

Symptoms arising from the urinary tract fall into two main groups: flank pain, and the various symptoms of disorders of the lower urinary tract. In both these groups examination for microhaematuria is usually a primary diagnostic investigation.

More than 80% of patients with acute flank pain due to a stone in the ureter have microhaematuria.²⁷ Recent data show that more than half of patients without calculi, as assessed by computed tomography, also have microscopic haematuria.⁵ One group of authors has concluded that testing for microhaematuria has insufficient positive predictive value for diagnosing stones in the ureter, and also that it could be misleading as other serious conditions resulting in acute loin pain, such as an inflammatory process near the ureter, can yield a positive test result.⁵

In patients with lower urinary tract symptoms due to benign prostatic hyperplasia, one third had microhaematuria, but this was not positively correlated with any clinical feature.²⁸ Thus the test does not seem to be helpful when assessing patients with urological symptoms.

Conclusion

Extrapolating the clinical importance of macroscopic haematuria to microscopic haematuria has not been rewarding. As with dipstick testing for bacteriuria, which has questionable value for screening adults, so the usefulness of testing for microhaematuria is now doubted. Even so, urine is an excellent medium for non-invasive diagnosis of diverse diseases and with the advent of molecular markers such as tumour antigens, nuclear matrix proteins, adhesion molecules, cytoskeletal proteins, and growth factors, examining the urine will remain an important part of routine clinical investigation.

Competing interests: None declared.

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(Accepted 21 January 2003)

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