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URINARY LACTOFERRIN AS A PROMISING, NEW, IMPROVED SURROGATE MARKER FOR URINARY TRACT INFECTION.

Hypothesis / aims of study

There is growing evidence to incriminate chronic cystitis as an important aetiological factor in the development of lower urinary tract symptoms (LUTS), particularly storage (OAB), voiding and painful LUTS.

There is a fundamental problem that stems from the original 1957 Kass criteria [(1)] for diagnosing urinary tract infection using culture of a midstream urine sample (MSU). The threshold stipulates 10^5 colony forming units (cfu) ml^{-1}, of a single species of a known urinary pathogen. Kass based his case on data from 74 pregnant women with acute pyelonephritis, and 337 asymptomatic controls. There was never any justification for applying such a threshold to other symptomatic groups. This quandary is further complicated by the popularity of urinary dipsticks analysis. The validation of urinary leucocyte esterase and nitrite tests was not only extremely deficient, but used the Kass criteria as the gold standard. Recently dipstick analysis and routine culture have attracted harsh criticisms for being extremely misleading [(2)].

All available data confirm that the best surrogate marker of urinary infection is the microscopy of a fresh unspun specimen of urine in a haemocytometer in order to count the white cells. The test is not perfect but remains the optimum with 66 to 70% sensitivity [(2)]. The facilities for effecting the microscopy are not routinely available in the ordinary clinics and delayed analysis results in an underestimate.

We thus need a reliable alternative to the dipstick test that can reflect the true pyuria levels whilst avoiding complex manipulation by the clinician. Anti-microbial molecules and cytokines present very attractive options because of modern advances in proteomics.

Lactoferrin is an iron binding glycoprotein expressed in the distal collecting tubules and can be found associated with the luminal surface. It is released in response to mucosal pathogenic invasion and prevents bacterial access to iron, essential for bacterial growth and development. Lactoferrin damages microbes both by chelation of iron and by affecting membrane integrity and has been detected in abundance in patients with acute UTI [(3)]. Hence urinary lactoferrin has potential as a promising surrogate marker for UTI and this experiment explored this hypothesis.

Study design, materials and methods

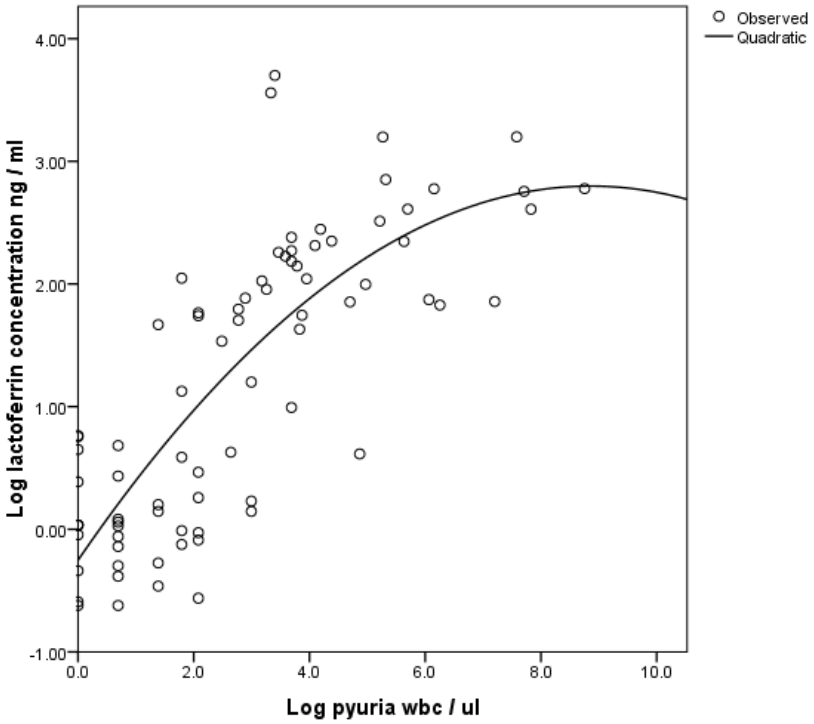
Patients presenting with LUTS were recruited from incontinence clinics and clean-catch midstream urine samples obtained. Healthy control volunteers were recruited from hospital staff. Storage, voiding, and pain symptoms were collected using a fixed protocol and recorded into a bespoke database. Light microscopy was performed on fresh urine for leucocytes and urothelial cell counts. The urine was cultured on selective chromogenic agar media and aliquots of spun urine frozen at -80°C. These were then analysed for urinary lactoferrin using a sandwich ELISA.

Results

There were 65 patients (90% female and 10% male) with a mean age 62.3 yrs; sd 16.99. The control group consisted of 14 healthy control volunteers (60% female, 40% male) with a mean age 53.6 yrs; sd 16.98. Symptom analysis showed that mean 24 hour frequency within the patient group was 11.4 and less than 7 in the control group. Total 24 hour incontinence episodes were 1.22 in the patient group and 0 in the control group. 81% of patients had urgency symptoms, 31% complained of stress symptoms, 17.2% complained of voiding symptoms and 36.2% complained of pain symptoms.

A Q-Q plot was used to confirm a normal distribution for log lactoferrin and parametric tests were used for analysis. A quadratic regression model was fitted to the log pyuria data, with log lactoferrin as the dependent variable; R was calculated at 0.8 ($p<0.001$; df = 2 and 76) – see figure.

The log lactoferrin was raised in patients compared to controls ($t=4.8$, df=77, mean diff = 1.5, 95% CI 2.0 to 0.9, $p<0.001$). The regression model implied that this difference related to the presence of inflammation. It was noted that 72% of patients had negative routine urine cultures.



Interpretation of results

These data demonstrated that urinary lactoferrin levels discriminate successfully between patients with LUTS and controls. There is evidence that the lactoferrin reflects the pyuria status quantitatively with a high effect size of R = 0.8.

Concluding message

Lactoferrin appears to be a remarkably strong candidate for replacing urine dipstick analysis and point-of-contact urinary microscopy with a potential for promoting a considerable improvement in patient diagnosis and management.

References

1. Arch.Intern.Med., 1957, 100; 709, 714.
2. J.Urol., 17-3-2010, 183; 1843, 1847.
3. Eur.J Clin.Invest, 2008, 38 Suppl 2; 29, 38.

Disclosures

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