ORIGINAL ARTICLE

Urinalysis for interleukin-8 in the non-invasive diagnosis of acute and chronic inflammatory diseases

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Background and aims: Given its role in mediating inflammation, the use of urinary interleukin-8 (IL-8) was assessed in the non-invasive diagnosis of acute and chronic inflammatory diseases.
Methods: IL-8 was measured by an enzyme linked immunosorbent assay in random urine samples (1 ml each) carrying code numbers and taken from 208 patients: 177 adults and 31 children presenting with a range of active or inactive inflammatory conditions.
Results: In the appropriate controls and in patients with inactive inflammation, the median urinary IL-8 levels ranged from 7–12 pg/ml, compared with 104 pg/ml in active ulcerative colitis ($p = 0.002$), 54 in active Crohn's disease ($p = 0.025$), 93 in active rheumatoid arthritis ($p = 0.001$), 107 in acute cholecystitis ($p<0.0001$), 127 in acute appendicitis ($p = 0.0001$), and 548 pg/ml in urinary tract infection ($p<0.0001$). Children with non-viral inflammation/infection also had higher IL-8 values (median, 199 pg/ml; $p = 0.0001$) than those with viral infection (median, 7 pg/ml) or non-specific conditions (median, 10 pg/ml). In the study group as a whole urinary IL-8 values correlated positively with peripheral blood white cell count ($r = 0.32$; $p < 0.001$), erythrocyte sedimentation rate ($r = 0.41$; $p<0.001$), and C-reactive protein ($r = 0.33$; $p<0.001$).
Conclusion: Taking the appropriate clinical situation into account, urinary IL-8 measurement helps in the non-invasive assessment of active inflammation in at least a number of common acute and chronic conditions.

Inflammation is one of the commonest disease entities, and the diagnosis of its activity is frequently needed for the initiation or the amendment of the relevant therapy. Diagnostic approaches have ranged from blood tests to faecal, radiological, endoscopic, or histological assessments.[1 2] Sometimes, surgical intervention is required to verify cases suspected of having inflammatory conditions such as appendicitis or cholecystitis. These tests can be unpleasant, invasive, and might be complicated by pain, irradiation, bleeding, and perforation. Less invasive approaches are, therefore, still needed for the assessment of inflammatory conditions.

Interleukin-8 (IL-8) is a potent chemoattractant and activator of neutrophils. It is produced by a wide variety of cell types, including macrophages, neutrophils, endothelial cells, fibroblasts, chondrocytes, and osteoclasts.[3 4] Immunohistological and in vitro studies have shown that IL-8 levels are raised in various diseases including the serum of patients with septic shock,[5] rheumatoid arthritis,[6 7] and colonic mucosa of patients with inflammatory bowel disease.[8–10]

It is not clear whether IL-8 levels are changed when measured in the urine of patients with active inflammatory conditions, and the clinical significance of such urinalysis remains to be clarified. Over the years, traditional bedside urinalysis for blood and protein has been a convenient and non-invasive procedure in the screening for simple conditions such as urinary tract infection; however, it is of limited value in assessing the activity of other inflammatory conditions such as inflammatory bowel disease, etc. We, therefore, aimed at assessing urinary IL-8 levels in patients with a variety of acute and chronic inflammatory diseases, given the importance of IL-8 as an inflammatory mediator.[5–10]

METHODS

Patients

Patients were recruited from the departments of internal medicine, rheumatology, surgery, and paediatrics regardless of their age or gender. Patients were included if they had inflammatory bowel disease, ulcerative colitis or Crohn's disease, irritable bowel syndrome, or rheumatoid arthritis. Patients with acute inflammatory conditions were also studied including those presenting with cholecystitis, appendicitis, diverticulitis, gastroenteritis, urinary tract infection, and constipation. Paediatric patients suspected of having infection or inflammation were also included. Patients were excluded if they had acute or chronic renal failure, malignancy, or if they took excess alcohol, diuretics, or high dose steroids (the equivalent of 7.5 mg prednisolone or more daily).

The Ethics Committee of Ayrshire and Arran Health Board approved the study protocol. Informed consent was obtained from study subjects or their guardians. Apart from 1 ml urine samples for IL-8 measurement, taken from routine specimens, the inclusion of paediatric patients did not involve any extra activity or procedure on top of the standard care routinely delivered to them.

Control groups

The controls for patients with active chronic inflammatory bowel disease included patients known to have irritable bowel syndrome, and also those with inactive ulcerative colitis or Crohn's disease. Patients with inactive rheumatoid arthritis were the controls for those having active arthritis. Patients presenting with non-specific abdominal pain or constipation acted as controls for those admitted with acute abdominal inflammatory conditions, including appendicitis, cholecystitis, urinary tract infection, diverticulitis, and gastroenteritis. In the paediatric group, patients diagnosed as having viral infection or non-specific conditions were the controls for those presenting with non-viral inflammation/infection.

Abbreviations: ELISA, enzyme linked immunosorbent assay; ESR, erythrocyte sedimentation rate; IL-8, interleukin-8

Table 1 Demographic details of study subjects

	Median (IQR) age	Male/female (ratio)	No (%) smoking	No (%) using alcohol
Chronic conditions				
Ulcerative colitis				
Active (n=15)	35 (26–62)	6/9 (0.66)	2 (13)	8 (53)
Inactive (n=19)	40 (30–64)	12/7 (1.7)	6 (32)	8 (42)
Crohn's disease				
Active (n=10)	32 (19–42)	3/7 (0.43)	4 (40)	5 (50)
Inactive (n=9)	34 (26–37)	5/4 (1.3)	3 (33)	3 (33)
Controls (n=14)	40 (28–52)	6/8 (0.75)	5 (36)	6 (43)
Rheumatoid arthritis				
Active (n=21)	62 (53–68)	4/17 (0.24)	7 (33)	1 (5)
Inactive (n=22)	56 (48–59)	9/13 (0.7)	3 (14)	11 (50)
Acute conditions				
Cholecystitis (n=15)	44 (30–80)	3/12 (0.25)	4 (27)	7 (47)
Appendicitis (n=8)	29 (22–42)	2/6 (0.33)	2 (25)	4 (50)
Urine infection (n=12)	33 (20–40)	4/8 (0.5)	4 (33)	5 (42)
Others* (n=12)	64 (32–72)	2/10 (0.2)	2 (17)	7 (58)
Controls† (n=20)	48 (43–80)	6/14 (0.43)	5 (25)	8 (40)
Inflammation in children				
Viral (n=9)	8 (3–10)	5/4 (1.3)	–	–
Non-viral (n=12)	6 (4–8)	5/7 (0.7)	–	–
Controls (n=10)	9 (8–12)	1/9 (0.11)	–	–

*Patients with other acute inflammatory conditions, including eight with diverticulitis and four with gastroenteritis.
†Patients acting as controls for acute surgical inflammatory conditions, including 11 with non-specific abdominal pain and nine with constipation.
IQR, interquartile range.

Assessment of inflammation

Inflammation and its activity were diagnosed depending on clinical history, physical examination, peripheral blood white cell count, erythrocyte sedimentation rate (ESR), C-reactive protein, and the appropriate imaging, endoscopic, or histological techniques. Patients with active chronic inflammatory bowel disease presented with a rise in the frequency of their liquid or soft stools, urgency to defecate, rectal bleeding or excess mucus, and with abdominal pain. They also had radiological, and/or endoscopic and histological evidence of active mucosal inflammation, with or without a rise in the ESR, C-reactive protein, and white cell count. These features are consistent with the Disease Activity Index for the Assessment of Ulcerative Colitis Activity,[11] and with Crohn's Disease Activity Index.[12] Patients scoring ⩾3 on the ulcerative colitis index, or ⩾150 on the Crohn's disease index were considered to have active inflammatory bowel disease. Patients with active rheumatoid arthritis were diagnosed according to the criteria of the American Rheumatism Association,[13] including the presence of painful and tender joints, early morning stiffness, limitation of joint function, and raised ESR and/or C-reactive protein. The diagnosis of acute inflammatory conditions (cholecystitis, appendicitis, diverticulitis, etc) relied on the relevant clinical, laboratory, imaging, and, where appropriate, surgical procedures, conducted by senior clinicians.

Interleukin-8 measurement

A random urine sample was taken from each patient for routine bedside analysis for blood, protein, glucose, microscopy, and culture. A portion of the same sample, 1 ml, was given a code number, and kept frozen at −20° C for IL-8 measurement. The latter was carried out using an in-house enzyme linked immunosorbent assay (ELISA). The assay plates were passively coated with capture antibody overnight at 4°C, then biotinylated detection antibody was used to detect the bound standard. This was quantified by introducing streptavidin peroxidase, and measuring the peroxidase by a colour reaction. Standards and samples were added to the wells in a total of 100 µl. Toray (Japan) standard, 2000 pg/ml/well, was used for the IL-8 assay. The plates were sealed using adhesive sealers and incubated at 4°C overnight. After the first incubation, the plates were washed four times with washing buffer. The ELISA/wash buffer was prepared using the following reagents: 100 mM Tris pH 7.2; 150 mg/l 2-methylisothizolone; 150 mg/l bromonitrodioxane; 2 mg/ml bovine serum albumin; phenol red 300 µl 0.5% solution/l; sodium chloride 9 g/l; EDTA 2 mM 4 ml/l of 0.5 molar stock; and Tween 20 0.05% (5 ml/l of 10% stock). The final pH was 7.2. Stock detection antibody was made up to 1 ml (50 µg/ ml); 5 µl of stock was added to 6.5 ml assay buffer and used at 60 µl/well. Again the plate was covered with a sealer and incubated for 45 minutes, with shaking, at room temperature. The plate was then washed four times with wash buffer. An aliquot of 100 µl of diluted (1:1000) streptavidin-peroxidase was added to each well at a concentration of 0.125 units/ml, and incubated for 20–30 minutes, with shaking, at room temperature. The plate was again washed four times with wash buffer, then 200 µl of substrate was added to each well. The substrate, tetramethyl benzidine, was prepared from stable solutions consisting of: (A) urea-hydrogen peroxide 0.3 g/50 ml of 50 mM sodium acetate buffer pH 6.0; (B) tetramethyl benzidine 2 mg/ml in dimethyl formamide; 2 ml of solution (A) and 2 ml of solution (B) were added to 20 ml of 100 mM sodium acetate buffer, pH 6.0. The plates were left for approximately 20 minutes until the colour developed, and then 50 µl of 2N sulphuric acid was added to quench colour development. The plate was read at 450 nM within 30 minutes of quenching.

The assay had a detection limit of 4 pg/ml, with an interassay variation of 11% and an intra-assay variation of 9.1% relative standard deviations. IL-8 measurements were conducted under completely blind conditions, and without the knowledge of any of the patients' details.

Statistical analysis

This was performed with the SPSS statistical package, SPSS Inc, Chicago, USA. The Kruskal-Wallis test was used to compare IL-8 levels of multiple groups, including controls. The Mann-Whitney U test and 95% confidence intervals were used to compare IL-8 results of two groups. The possible correlation between IL-8 levels and the values of ESR, C-reactive protein, and white cell count was tested using Spearman's correlation coefficient. Multivariate analysis was used to test the possible

Table 2 Urine interleukin-8 (IL-8), median (interquartile range)

	IL-8 (pg/ml)	95% Confidence interval	p Values	Comparison
Chronic conditions				
Ulcerative colitis				
(A) Active (n=15)	104 (16–196)	38 to 128	0.002	A *v* B
(B) Inactive (n=19)	12 (6–26)			
Crohn's disease				
(C) Active (n=10)	54 (26–247)	7 to 222	0.025	C *v* D
(D) Inactive (n=9)	12 (9–37)			
(E) Controls (n=14)	9 (8–21)	16 to 127	0.001	E *v* A+C
Rheumatoid arthritis				
(F) Active (n=21)	93 (30–183)	13 to 99	0.001	F *v* G
(G) Inactive (n=22)	11 (6–41)			
Acute conditions				
(H) Cholecystitis (n=15)	107 (67–231)	64 to 174	<0.0001	H *v* L
(I) Appendicitis (n=8)	127 (46–296)	41 to 269	0.0001	H *v* L
(J) Urine infection (n=12)	548 (288–1354)	328 to 1108	<0.0001	J *v* L
(K) Others (n=12)	191 (63–324)	54 to 304	0.0001	K *v* L
(L) Controls (n=20)	8 (3–19)			
Inflammation in children				
(M) Viral (n=9)	7 (3–36)	–12 to 9	0.7	M *v* O
(N) Non-viral (n=12)	199 (68–334)	58 to 380	0.0001	N *v* O
(O) Controls (n=10)	10 (5–19)			

influence of the demographic details, age, gender, alcohol, and smoking, as well as disease activity on IL-8 levels.

RESULTS

A total of 208 patients were studied. These included 177 adults with chronic and acute inflammatory conditions, and 31 children (table 1). The paediatric group included nine patients with viral upper respiratory tract infection, and 12 patients with non-viral active inflammation and infection. The latter consisted of seven patients with urinary tract infection, two with bacterial meningitis, one with tonsillitis, one with gastroenteritis, and one with an appendicular mass. The paediatric controls (n=10) included seven with non-specific abdominal pain, two with diabetes, and one with simple headache.

Interleukin-8 levels

These are shown in figs 1–3 and in table 2. In chronic conditions, fig 1, urinary IL-8 levels were higher in patients with active inflammatory bowel disease than in the control group or those with inactive inflammation. The same was observed when patients were subgrouped according to the basic diagnosis of ulcerative colitis or Crohn's disease. Also, patients with active rheumatoid arthritis had higher levels of IL-8 compared with patients having inactive arthritis.

Likewise, patients presenting with acute abdominal inflammatory conditions, fig 2, had greater IL-8 values than the controls. The highest levels of IL-8 were observed in patients with urinary tract infection ($p = 0.002$, Kruskal-Wallis test). These patients were also found to have blood and protein on their bedside routine urinalysis, unlike patients with other conditions.

In the paediatric group, subjects with viral upper respiratory tract infections had IL-8 values similar to those of the control group. However, non-viral inflammatory conditions were associated with a significant increase of IL-8 levels.

Correlation between urinary IL-8 and blood inflammatory parameters

Taking the study subjects as one group, there was positive correlation between urinary levels of IL-8 and peripheral blood white cell count ($r = 0.32$; $p<0.001$), ESR ($r = 0.41$; $p<0.001$), and C-reactive protein ($r = 0.33$; $p<0.001$). Despite the correlation between them, each of these inflammatory parameters predicted the activity of the relevant inflammatory process in an independent manner. Also, there was positive correlation between ESR and C-reactive protein ($r = 0.73$; $p<0.001$), C-reactive protein and white cell count ($r = 0.28$; $p<0.001$), ESR and white cell count ($r = 0.23$; $p = 0.02$), and between the white cell count and neutrophil count ($r = 0.92$; $p<0.001$).

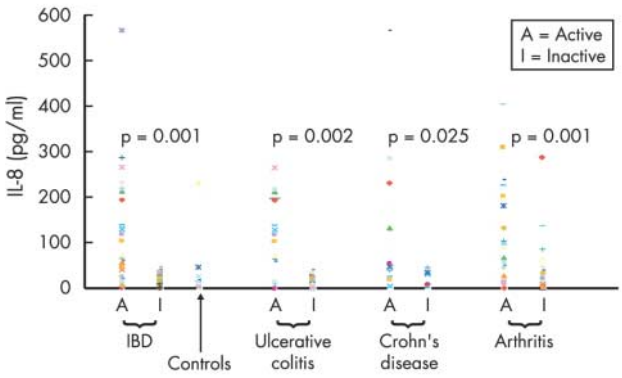

Figure 1 Urine IL-8 levels in chronic inflammatory conditions. Patients with active inflammatory bowel disease (IBD) had higher IL-8 values than those with inactive disease or other controls (patients known to have irritable bowel syndrome). Likewise, patients with active ulcerative colitis, Crohn's disease, or rheumatoid arthritis, had higher IL-8 levels than the respective group with inactive chronic disease.

Factors influencing IL-8 levels (multivariate analysis)

In both adults and children in the study group as a whole, but excluding adults with urinary tract infection, females had higher IL-8 levels than males. In the inflammatory bowel disease subgroups and their controls, the log values of IL-8 were assessed using the analysis of variance to improve the distribution of data. The influence of age, gender, smoking, and alcohol was tested in addition to disease activity. IL-8 levels were higher in females than males ($p = 0.001$), in active ulcerative colitis than controls ($p = 0.00006$), and in active Crohn's disease than controls ($p = 0.0001$) while correcting for age and gender. IL-8 values also increased with advancing age ($p = 0.001$). There was no significant influence of smoking or alcohol on IL-8 levels.

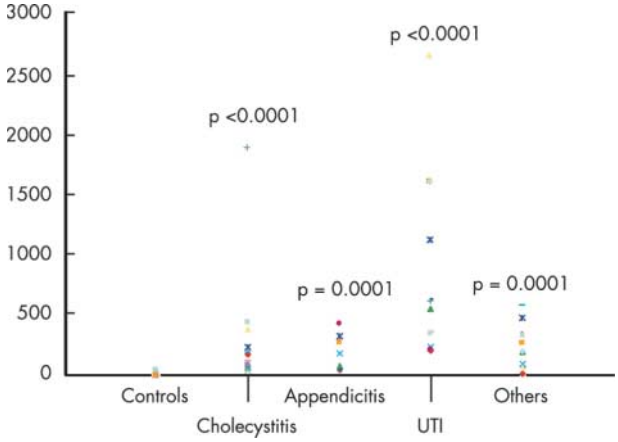

Figure 2 Urine IL-8 levels in acute inflammatory conditions. Patients with acute cholecystitis, appendicitis, urinary tract infection (UTI) or other acute inflammatory conditions had higher IL-8 values than controls.

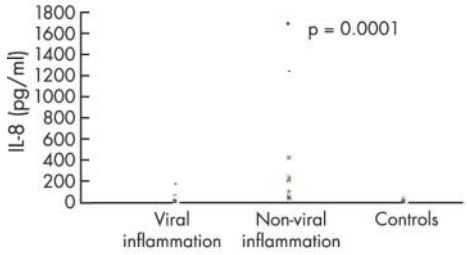

Figure 3 Urine IL-8 levels in the paediatric groups. Children with non-viral inflammatory conditions had higher IL-8 values than controls. No significant differences were found in IL-8 levels between children with viral infection and controls.

Sensitivity and specificity of urinary IL-8 measurement

In diagnosing active inflammation in the study group as a whole, there were 114 positive and 94 negative urinary IL-8 results, at an arbitrary cut off point of 40 pg/ml guessed to produce a reasonable test performance. These included 92 true positive, 22 false positive, 80 true negative, and 14 false negative results. These give a sensitivity of 87% and specificity of 78%.

DISCUSSION

This study shows that urinary IL-8 levels are higher in subjects with active chronic and in acute inflammatory conditions compared with the respective inactive conditions or controls. In addition, urinary IL-8 levels correlate positively with blood inflammatory parameters, including white cell count, ESR, and C-reactive protein.

Inflammation is associated with the production of a number of cytokines such as interleukins, interferons, and tumour necrosis factor. We studied IL-8 because it is relatively stable, which facilitates its handling and measurement, and because it is produced in large quantities in active inflammation.[3–10 14 15] We also included several control groups for comparison with the relevant conditions studied. However, it is worth noting that IL-8 levels were similar in all the control groups, and no statistically significant differences were detected between them.

The diagnosis of flare-ups of chronic inflammatory bowel disease leads to intensification of therapy, and frequently relies on sigmoidoscopic and histological assessments as well as measurement of ESR and C-reactive protein. Likewise, the diagnosis of active disease in patients with chronic rheumatoid arthritis involves clinical, blood and, sometimes, radiological tests. Our finding of raised urine IL-8 in these active episodes, and its positive correlation with ESR and C-reactive protein would help a significant number of these patients avoid the discomfort and the risks of the above invasive tests. Urine IL-8 measurement also has the potential to be used by patients as an objective method for self monitoring of the activity of their chronic diseases, which in turn might help them decide the best time to seek specialist advice for the treatment of their conditions. Urinary tract infection, gastroenteritis, and possibly other infections can increase IL-8 production. Early identification of this by means of self monitoring is also relevant to the management of patients with chronic diseases, especially if they are taking immunosuppressive therapy.

The rise in urine IL-8 in acute surgical conditions, demonstrated in our study, can be used to support the clinical impression and narrow the differential diagnosis of these diseases. For example, it is often difficult to decide the extent to which gallstones, seen on abdominal ultrasound scans or other imaging techniques, contribute to acute right upper abdominal complaints. Raised IL-8 levels in such patients would point to the presence of cholecystitis. Also, the combination of acute right lower abdominal pain and high IL-8 values would suggest the presence of an inflammatory process such as appendicitis. It is interesting to find that urinary IL-8 is not raised in children with viral respiratory tract infection, which can sometimes mimic appendicitis.

Patients with urinary tract infection have the highest levels of IL-8. These can be distinguished from patients with other acute conditions by the relevant symptoms such as dysuria and frequency, and by simple bedside urinalysis for blood and protein.

Children with non-viral inflammation or infection have higher urine IL-8 levels than those with viral infections or controls. This is not unlike the pattern with serum C-reactive protein, which also fails to rise with viral infection.[2] It also suggests that urine IL-8 is more likely to rise in inflammation or infection mainly mediated by the neutrophils, known for their considerable contribution to IL-8 production.[3] In the study group as a whole, urine IL-8 rose with advancing age, and females had higher levels than males. The reason for this is not clear, but it might be related to differences in renal threshold between the sexes and between young and older subjects. In a previous study, smoking in subjects with dyspepsia was associated with lower IL-8 excretion.[16] In the present larger study, smoking had no significant effect on urinary IL-8 levels as shown by the multivariate analysis. In addition to the types and numbers of patients, the two studies also differ in the types of assays used. The intake of bismuth compounds could also have influenced IL-8 excretion in patients with dyspepsia.[16]

Urinary IL-8 has been studied in a number of renal, urological, and obstetric conditions including haemolytic uraemic syndrome, glomerulonephritis, bladder cancer, and intra-amniotic infection.[17–20] We have excluded patients with malignancy or intrinsic renal disease, apart from urinary tract infection, and the conditions included in our present study have not been investigated before.

In conclusion, urine IL-8 level is raised in both acute and active chronic inflammatory conditions, and correlates positively with ESR, C-reactive protein, and white cell count. This would be helpful, pending further studies, in the non-invasive assessment of active inflammation in a number of common intra-abdominal and extra-abdominal diseases. As in any other test, the relevant clinical situation has to be considered to facilitate the appropriate interpretation.

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