Is low proteinuria an early predictor of severity of acute pancreatitis?

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SUMMARY Serial six hourly urine collections were made for seven days on 20 patients with acute pancreatitis. Quantitative immunoassay of urinary albumin and IgG on the first urine sample after admission showed increased excretion rates in 14 and 13 patients, respectively. Urinary protein excretion rates remained normal or approached normal by seven days in 17 patients who made uneventful recoveries. The maximum urinary excretion rates of both albumin and IgG within the first 36 hours correlated with the serum C-reactive protein concentration 72 hours after admission. The highest IgG excretion rates were found in three patients who later developed severe complications. These preliminary data suggest that low proteinuria is a very early response in acute pancreatitis, and that it may reflect the severity of inflammation.

Eighty per cent of patients with acute pancreatitis make a rapid recovery with conservative treatment; in the remaining 20%, however, attacks are more severe and associated with a 50% mortality.¹ It is important to identify at an early stage patients likely to develop severe pancreatitis as they will require more vigorous resuscitation and close monitoring in an intensive care unit. Such patients may also be candidates for early surgery, peritoneal lavage, or endoscopic sphincterotomy.²

Prognostic scoring systems based on factors such as age, measurement of blood glucose, serum calcium, albumin, urea, transaminase activity, and white cell count or arterial oxygen saturation have been used.¹ Such methods suffer the disadvantage that they are cumbersome to determine and may have a delayed response time, thus reducing their clinical usefulness. Measurement of C-reactive protein (CRP) has been used as an aid in the early assessment of the severity of inflammation in acute pancreatitis but differentiation between mild and severe attacks can only be made 48 to 72 hours after the onset of the condition.³ There still remains a need for a simple predictor of disease severity which can be practically applied during the first 12 to 24 hours after admission.

Within hours of burn injury, trauma, ischaemia and surgery there is an increase in renal permeability leading to low proteinuria.⁴⁻⁷ The degree of proteinuria correlates with severity of the insult, and because all these conditions provoke a systemically mediated

inflammatory response, we have proposed that changes in renal permeability to plasma proteins reflect overall vascular permeability rather than isolated renal disease.⁸ The purpose of this study was to determine if similar changes in renal permeability occur in patients with acute pancreatitis.

Patients and methods

Studies were carried out on 20 consecutive patients admitted with a clinical diagnosis of acute pancreatitis and a serum amylase activity of > 1000 U/l (normal 300 U/l). Patients had had severe symptoms for not more than 24 hours before admission, and no patient had a history of renal disease (table). Serum creatinine at admission was normal (< 120 μ mol/l) in 19 patients and 164 μ mol/l in one patient who subsequently developed renal failure. One patient was a type 2 diabetic. All patients were initially managed conventionally with nasogastric suction, analgesics, antibiotics (cefuroxime) and intravenous fluids. Seventeen patients made an uneventful recovery, although in one patient an asymptomatic pseudocyst was discovered six weeks after discharge from hospital. Three patients with gallstone pancreatitis, who developed severe complications within 48 hours of admission, two of which were fatal, are detailed below.

A 35 year old man developed severe respiratory distress (pO₂ 3.7 kPa on room air) and required mechanical ventilation 48 hours after admission. The patient subsequently died from overwhelming sepsis

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Table Summary of patients studied

Sex	Age	Aetiology of pancreatitis	Serum amylase (IU/l) on admission	Complications	Outcome
M	34	Gallstones	9100	Respiratory failure/sepsis	Death
F	61	Gallstones	5886	Multiple organ failure	Death
M	45	Gallstones	6420	Respiratory failure	Recovery
F	29	Unknown	3195	None	Recovery
F	79	Gallstones	1014	None	Recovery
M	71	Unknown	3865	None	Recovery
M	33	Unknown	3660	None	Recovery
M	82	Unknown	29,500	Pseudocyst	Recovery
F	63	Unknown	9920	None	Recovery
F	65	Gallstones	7800	None	Recovery
F	73	Gallstones	1735	None	Recovery
M	22	Alcohol	2485	None	Recovery
M	60	Unknown	3195	None	Recovery
F	46	Unknown	3080	None	Recovery
F	71	Unknown	6080	None	Recovery
F	62	Gallstones	4060	None	Recovery
M	37	Hyperlipidaemia	1450	None	Recovery
M	62	Gallstones	6885	None	Recovery
F	79	Unknown	2628	None	Recovery
F	72	Unknown	4596	None	Recovery

on day 5. The second patient, a 61 year old woman, became hypotensive despite adequate fluid replacement and ionotrope support, and died seven days after admission from multiple organ failure. Finally, a 45 year old man became hypoxic (pO_2 6.7 kPa) 17 hours after admission. The patient was treated with oxygen and monitored on an intensive care unit but did not require mechanically assisted ventilation. He recovered and was discharged four weeks later.

All urine passed after admission was saved in six hourly collections for seven days. Where clinically indicated, patients were catheterised ($n = 10$); otherwise all voided urine was saved in six hour collections. Urine volume was measured and an aliquot was stored at 4°C for measurement of protein. Urinary albumin and IgG were estimated by automated immunoturbidimetry⁹ using rabbit anti-human antisera (Dako Ltd, High Wycombe, England, A001 and A090, respectively) and a Cobas Mira analyser (Hoffman-La Roche, Basle, Switzerland). Median (range) values for urinary albumin and IgG excretion rates in normal subjects were 3.4 (0.2–22.9) and 1.4 (0.2–4.5) $\mu\text{g}/\text{minute}$, respectively. Polyacrylamide gel electrophoresis of selected urines was performed in sodium dodecyl sulphate buffer using a vertical slab discontinuous system (LKB Instruments Ltd, Croydon, England).¹⁰ Where necessary, urine samples were concentrated using the Minicon concentration system (Amicon Ltd, Gloucester, England). Gels were stained with PAGE Blue G 90 (BDH Ltd, Poole, England). Blood samples taken for routine investigations on admission and subsequently every day were also used for serum CRP measurements by latex-enhanced immunoturbidimetry using the Cobas Mira, reference range of <15 mg/l. Serum amylase activity was measured by the Phadebas technique (Pharmacia

Diagnostics AB, Uppsala Sweden), reference range <300 U/l.

Results

Fourteen patients (70%) showed increased urinary albumin and 13 (65%) increased their IgG excretion during the first 36 hours after admission. The mean serum amylase, CRP, urinary albumin and urinary IgG excretion rates for all patients are summarised in fig 1. Electrophoresis of urine showed both small and large molecular weight proteins including IgG, transferrin, and albumin.

In the patients who made uneventful recoveries urinary proteins remained normal or gradually fell towards normal by day 7. In those patients with complications the mean (SD) peak albumin and IgG excretion rates within the first 36 hours after admission of 297.9 (61.2) and 106.5 (23.8) $\mu\text{g}/\text{minute}$, respectively, seemed to be higher than in those patients who made uncomplicated recoveries of 101.4 (98.4) and 22.0 (29.3) $\mu\text{g}/\text{minute}$, respectively ($p \leq 0.05$, Wilcoxon rank sum test (fig 2). There was a significant correlation between serum CRP concentrations three days after admission and both maximum albumin and IgG excretion rates ($r = 0.621$, $p \leq 0.025$, and $r = 0.640$, $p \leq 0.02$, respectively) within the first 36 hours.

Discussion

Although low level proteinuria, including albumin, has been described in acute pancreatitis,^{11–13} samples of urine taken shortly after admission have not been studied, and as only 24 hour collections were made the rapid changes in renal permeability identified in the

Fig 1 Mean (SEM) values for serum amylase, CRP, and urinary albumin and IgG excretion rates for 20 patients admitted with acute pancreatitis. The upper limit of normal is indicated thus — — — — —.

present study were not detected. Our results accord with those of Karlsson and Jacobson¹¹ in that although low molecular weight proteins were present, the pattern was not typical of simple tubular proteinuria as large molecular weight proteins including

IgG were also found in urine passed immediately following admission. This is consistent with the finding of glomerular lesions¹⁴ and increased amylase clearance¹⁵ in acute pancreatitis. During the first 36 hours after admission urinary IgG and albumin

Fig 2 Maximum albumin and IgG excretion rates for 20 patients with acute pancreatitis during the first 36 hours after admission. Patients who developed severe complications are indicated by closed circles and the upper limit of the reference range thus — — — — —.

excretion were higher in the three patients who developed major complications compared with patients who made uneventful recoveries, suggesting that the initial increase in renal permeability might be an early reflection of the severity of inflammation. This is supported by the positive correlation found between urine protein excretion during the first 36 hours and the serum CRP concentration three days after admission.

The mechanisms producing a rapid and reversible change in renal permeability to plasma proteins in acute pancreatitis are not clear, but catheterisation does not cause proteinuria.⁷ The phenomenon may be related to systemic changes as release of pancreatic enzymes has been implicated in complement activation and release of the anaphylatoxin C5a in granulocyte activation, leading to increased vascular permeability.¹⁶ Mediators of the microcirculatory response in acute pancreatitis are complex, but the same mechanisms which increase vascular permeability may also increase renal permeability.

Several prognostic systems using multiple analyses have been proposed to predict the severity of acute pancreatitis.¹ Serial measurement of CRP and phospholipase A2 differentiate between mild and haemorrhagic pancreatitis,¹⁷ but serum CRP does not dis-

tinguish mild from severe pancreatitis until 48 to 72 hours after admission.³ It remains to be seen whether determination of individual urinary proteins immediately after admission predicts disease severity, and if so which protein might give the greatest sensitivity.

We thank the consultant surgeons at Selly Oak Hospital for allowing their patients to be studied, and the nursing staff who helped collect the specimens.

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