

Pancreatic Involvement in Salmonella Infection

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ABSTRACT

Context *Salmonella* has been identified as a causative agent of acute pancreatitis.

Objective We prospectively evaluated the frequency of acute pancreatitis, pancreatic enzyme elevation and morphological pancreatic abnormalities in patients with *Salmonella* infection.

Subjects Thirty consecutive patients with salmonellosis (*Salmonella enterica* serovar Enteritidis: n=25; *Salmonella enterica* serovar Typhimurium: n=5) and 30 sex- and age-matched healthy subjects were studied.

Main outcome measures All subjects underwent serum amylase and lipase determination and ultrasonography.

Results None of the subjects developed acute pancreatitis. Two patients (6.7%) and two controls showed serum amylase activity above the upper reference limit whereas, in five patients (16.7%) and one control subject (3.3%), the serum lipase activity appeared above the upper reference limit. *Salmonella* infection significantly increased serum activity of lipase ($P<0.001$) while it did not significantly affect serum amylase levels ($P=0.204$). Serum lipase activity was significantly higher in patients infected by *Salmonella enterica* serovar Typhimurium than in those infected by *Salmonella enterica* serovar Enteritidis ($P=0.012$). Ultrasono-

graphy did not show pancreatic abnormalities in any of the subjects.

Conclusions Our data demonstrated an elevation of serum lipase activity in gastroenteritis due to *Salmonella* infection, but this elevation does not seem to have clinical significance. The elevation of serum lipase seems to be particularly related to infection from *Salmonella enterica* serovar Typhimurium.

INTRODUCTION

Many case reports [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11] have identified *Salmonella* as a causative agent of acute pancreatitis. Furthermore, two retrospective studies [12, 13] have reported a frequency of hyperamylasemia of 50% and a frequency of clinical pancreatitis ranging from 28 to 62% in patients with *Salmonella* infection. On the basis of these results, the authors of the two studies concluded that clinical pancreatitis should be considered a frequent complication of salmonellosis. However, up to now, there has been a lack of prospective studies on pancreatic involvement during the course of acute pancreatitis due to *Salmonella* infection. For this reason, we sought to prospectively evaluate the frequency of acute pancreatitis, serum pancreatic enzyme elevation and morphological pancreatic abnormalities in patients with acute gastroenteritis due to *Salmonella* infection.

METHODS

Subjects

Thirty consecutive patients (16 males, 14 females; mean age 27.3 years, range 4-82 years) admitted to the Emergency Room for acute *Salmonella*-related gastroenteritis were enrolled from October 1994 to September 2001. The mean interval between onset of the symptoms and hospital admission was 1.6 days (range: 1-3 days). None of them had a previous history of pancreatic, renal, liver or salivary gland disease. Thirteen patients (43.3%) were under 14 years of age. One patient had asymptomatic gallstones, one had coronary heart disease and one had type 2 diabetes mellitus; none of these patients was under chronic pharmacological treatment. Fourteen patients (46.7%) were drinkers (less than 40 g of pure alcohol per day) and eight (26.7%) were smokers. Upon admission, the number of evacuations per day was 7.8 ± 3.0 (mean \pm SD; range 5-18). Fecal specimens collected after natural evacuation at admission, and again after 24 and 36 hours, were cultured and analyzed for the presence of blood, leukocytes and parasites. *Salmonella enterica* serovar Enteritidis serotype D1 was isolated in the fecal specimens of 25 patients (83.3%), whereas *Salmonella enterica* serovar Typhimurium was found in five patients (16.7%). The time of hospitalization was 5.9 ± 1.8 days (mean \pm SD; range 3-9). Thirty healthy subjects recruited from blood donors, the medical staff and subjects

undergoing routine medical check-ups and matched for sex and age (± 3 years) and time of enrollment, were studied as controls. None of them was drinker ($P < 0.001$ vs. patients), eight (26.7%) were smokers ($P = 1.000$ vs. patients), and all of them had normal bowel habits (number of evacuations per day: 1.2 ± 0.4 mean \pm SD; range 1-2; $P < 0.001$ vs. patients). All these subjects were in good general health, none was taking drugs and none had any signs of the disease.

Biochemical and Imaging Evaluations

All subjects underwent routine blood and biochemistry tests: leucocyte count (reference values 4,800-8,500 μL^{-1}), serum determination of AST (upper reference value 40 IU/L), ALT (upper reference value 37 IU/L), blood urea nitrogen (upper reference value 0.45 g/L), creatinine (upper reference value 1.2 mg/dL), glucose (upper reference value 120 g/L), potassium (reference values 4.0-5.5 mEq/L) and sodium (reference values 131-145 mEq/L). The results of these biochemical parameters are reported in Table 1; no statistically significant differences were found between patients with acute gastroenteritis and healthy subjects.

Serum amylase (AMY Amylase, Dade Behring S.p.A., Milan, Italy, upper reference value 220 IU/L) and lipase (LIP Lipase, Dade Behring S.p.A., Milan, Italy, upper reference value 270 IU/L) activity was determined within 24 hrs from admission in patients and after an overnight fasting in healthy subjects.

Table 1. Laboratory parameters in the 30 patients with acute gastroenteritis due to *Salmonella* infection and in the 30 healthy subjects. (Mean \pm SD values and ranges are reported).

	<i>Salmonella</i> infection	Healthy subjects	P value
White blood cell count (μL^{-1})	8,033 \pm 3,647 (2,810-18,890)	6,895 \pm 1,646 (4,123-9,856)	0.185
AST (IU/L)	25.7 \pm 12.9 (12-85)	20.5 \pm 7.9 (12-36)	0.071
ALT (IU/L)	20.4 \pm 11.2 (10-56)	20.6 \pm 8.0 (12-33)	0.484
Blood urea nitrogen (g/L)	0.34 \pm 0.22 (0.06-1.21)	0.25 \pm 0.10 (0.12-0.50)	0.130
Creatinine (mg/dL)	0.90 \pm 0.40 (0.1-2.2)	0.89 \pm 0.28 (0.2-1.3)	0.681
Glucose (mg/dL)	1.05 \pm 0.35 (0.66-2.21)	0.94 \pm 0.13 (0.67-1.23)	0.247
Potassium (mEq/L)	3.92 \pm 0.56 (2.7-5.0)	3.99 \pm 0.38 (3.3-4.7)	0.531
Sodium (mEq/L)	136.2 \pm 4.6 (126-145)	137.6 \pm 4.3 (129-145)	0.488

Ultrasonographic examination was carried out in all subjects to detect pancreatic abnormalities.

Definition of Acute Pancreatitis

According to the current criteria [14, 15], acute pancreatitis was considered to be present if serum activity of amylase and lipase was at least five times greater than the upper reference limits in association with pancreatic pain and the findings of the imaging techniques.

ETHICS

The study was approved by the Clinical Committee of the Emergency Department. All subjects, and when necessary their relatives, gave informed consent to participate in the study. All the patients were managed according to the practical guidelines suggested by the World Health Organization [16].

STATISTICS

Means, standard deviations (SD), ranges, and frequencies were used as descriptive statistics. Laboratory parameters, length of hospitalization, number of evacuations per day, time interval between onset of symptom and hospital admission, and frequencies of abnormal serum pancreatic enzyme activity were analyzed by means of the Mann-Whitney, Spearman rank correlation, McNemar and Fisher's exact tests.

The normal distribution of the serum pancreatic enzymes was tested by means of the Kolmogorov-Smirnov test and by evaluating a standardized score of the skewness. The log-transformed amylase and lipase values showed a normal distribution. In order to take into account the paired experimental protocol, the repeated measure one-way ANOVA design was used to estimate the global effects of the *Salmonella* infection and to compare the effects of the two different serotypes. The anti-log transformation of the parameter estimates,

together with their 95% confidence intervals (95% CI), were used to measure the fractional effects of the factors taken into account.

All statistical evaluations were performed by running the SPSS statistical package (version 8) by using a personal computer. Two-tailed P values less than 0.05 were considered statistically significant.

RESULTS

None of the patients studied had pain or other clinical signs compatible with acute pancreatitis.

Individual serum activity of amylase and lipase in the patients with *Salmonella* infection and in healthy subjects is shown in Figure 1. Two patients (6.7%) and two controls had serum amylase activity above the upper reference limit (patients: 229 and 272 IU/L; controls: 266 and 333 IU/L), whereas, in five patients (16.7%) and one control subject (3.3%), serum lipase activity appeared above the upper reference limit (patients: range 273-471 IU/L; control subject: 293 IU/L). A simultaneous increase in serum amylase and lipase was found in two patients affected by *Salmonella enterica* serovar Typhimurium. The elevation of amylase and

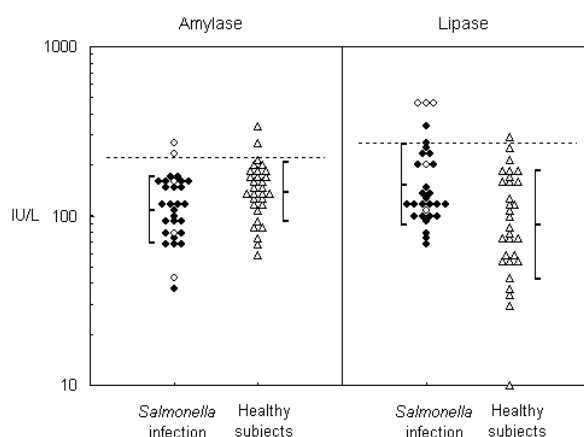


Figure 1. Individual serum activity of amylase and lipase in the 30 patients with acute *Salmonella*-related gastroenteritis (circles) and in the 30 healthy subjects (triangles). Open circles indicate patients with acute gastroenteritis due to *Salmonella enterica* serovar Typhimurium; filled circles indicate the patients with *Salmonella enterica* serovar Enteritidis infection. Horizontal dashed lines indicate the upper reference limits. Mean±SD values are also reported.

Table 2. Effects of *Salmonella* infection and its different serotypes on serum pancreatic enzyme activity.

	F value	P value	Effect (95% CI)
AMYLASE			
<i>Salmonella</i> infection	1.69	0.204	0.94 (0.86-1.03)
Serotype	0.90	0.351	1.09 (0.91-1.29)
Interaction: Typhimurium vs. Enteritidis infection	0.13	0.717	1.04 (0.86-1.25)
LIPASE			
<i>Salmonella</i> infection	21.03	<0.001	1.32 (1.17-1.48)
Serotype	1.00	0.325	1.16 (0.87-1.53)
Interaction: Typhimurium vs. Enteritidis infection	7.17	0.012	1.38 (1.09-1.75)

CI: confidence interval

lipase serum activity in all subjects was always less than two times the upper reference limit. The results of statistical analysis are reported in Table 2. Serum amylase activity did not show any significant difference while *Salmonella* infection significantly increased serum activity of lipase ($P<0.001$); in particular, this increase was estimated to be 32%. In addition, the analysis of the interaction showed that the serum lipase activity was significantly higher in patients infected by *Salmonella enterica* serovar Typhimurium than in those infected by *Salmonella enterica* serovar Enteritidis ($P=0.012$) and this increase was estimated to be 38%. No significant relationship was found between the time interval from onset of symptoms to hospital admission and serum pancreatic amylase ($P=0.066$) and lipase ($P=0.466$) activity.

No significant differences were found in the frequency of abnormal amylase ($P=1.000$) and lipase ($P=0.219$) values between patients and healthy subjects. The frequencies of hyperamylasemia and hyperlipasemia were significantly higher ($P=0.023$ and $P=0.022$, respectively) in patients with *Salmonella enterica* serovar Typhimurium (40.0% and 60.0%, respectively) than in those infected by *Salmonella enterica* serovar Enteritidis (0% and 8.0%, respectively). The five patients with elevated serum amylase and/or lipase activity had a period of hospitalization (5.2 ± 1.8 days) not significantly different ($P=0.331$) from those with normal serum activity of amylase and lipase (6.0 ± 1.8 days).

In patients with *Salmonella* infection, no significant relationship was found between the number of evacuations per day and serum activity of amylase ($P=0.462$) and lipase ($P=0.658$).

Ultrasonography did not show morphological abnormalities of the pancreatic gland in either patients or healthy subjects.

DISCUSSION

In this study, we prospectively evaluated the behavior of serum amylase and lipase in patients with acute gastroenteritis due to *Salmonella* infection. Nevertheless, we found an elevation of serum lipase activity in *Salmonella* infected patients; hyperamylasemia and hyperlipasemia were recorded only in 6.7% and 16.7% of patients, respectively. However, none of the patients in the present study had clinical, biochemical or morphological alterations compatible with an acute inflammation of the pancreas, thus suggesting a low risk of acute pancreatitis in patients with *Salmonella* infection. Even if ultrasonography have a sensitivity lower than that of other imaging techniques, such as computed tomography or magnetic resonance, to detect fine alterations of the pancreatic gland, it was proved to be able to routinely visualize edema and necrosis of the pancreas [17]. In our study it was a logical approach to choose such a technique since its non-invasiveness, low costs and ethical aspects. In fact: i) in our practice, ultrasonography is the first line imaging technique performed to

detect pancreatic alterations in acute pancreatitis patients [15]; ii) the presence of healthy control subjects was taken into account. The difference between our results and those previously reported [12, 13] may be due to the fact that, in our study, the definition of pancreatitis was stricter than that applied in the other above-mentioned studies.

We also found a positive association between *Salmonella enterica* serovar Typhimurium gastroenteritis and serum lipase activity. Despite the small number of cases studied, pancreatic hyperenzymemia seems to be of some clinical relevance only in these patients (hyperamylasemia: 40%; hyperlipasemia: 60%).

Even if the elevation of serum pancreatic enzymes in our patients was lower than that reported by others [12, 13, 18, 19], our data confirm, in a prospective manner, that hyperamylasemia and hyperlipasemia can be found in patients infected by *Salmonella*. As in the study of Ben-Horin *et al.* [19], who studied patients with acute gastroenteritis due to various infective agents, in our series the elevation of serum amylase and lipase activity was slight and did not exceed a two-fold elevation of the respective upper reference limit. For this reason, the elevation of amylase and lipase serum activity should be interpreted cautiously. The reason why there is an elevation of serum pancreatic enzymes during the course of acute gastroenteritis due to *Salmonella* infection could be explained in several ways. Intestinal inflammation could lead to an increased permeability which allows the reabsorption of macromolecules such as amylase as suggested by Gnadinger *et al.* [20]. These authors demonstrated an increased intestinal permeability for oral ⁵¹Cr-EDTA in two patients with elevated amylase serum levels in the course of entero-invasive salmonellosis. We did not test the intestinal permeability for ethical reasons; however, in our series, only a low percentage of patients had an increase in serum amylase and lipase activity, so this mechanism may be excluded.

Hyperamylasemia and hyperlipasemia could also be the result of a reduced excretion due to either impaired renal or liver function [21,

22]; however, none of our patients had abnormal serum concentrations of blood nitrogen urea and creatinine; serum levels of transaminases were also not compatible with liver involvement.

Furthermore, hyperamylasemia could represent the effect of direct pancreatic localization of bacteria through a haematogenous route during acute gastroenteritis as suggested by Schmid *et al.* [23]. This hypothesis was not confirmed; in fact, Tositti *et al.* [18] found that, in those patients in whom *Salmonella spp.* was isolated from blood cultures, hyperamylasemia was not detected. Finally, there is also some evidence that *Salmonella enterica* serovar Enteritidis and *Salmonella enterica* serovar Typhimurium are present in bile fluid and gallstone cultures [24, 25]; in this way, bacteria may directly infect the pancreas via the biliary duct system [26]. This may explain, at least in part, the presence of hyperamylasemia and hyperlipasemia in our patients infected by *Salmonella spp.*, but the reason why our patients infected by *Salmonella enterica* serovar Typhimurium had a frequency of hyperenzymemia higher than those infected by *Salmonella enterica* serovar Enteritidis requires further investigation.

Our study also revealed that the length of hospitalization was not significantly different between patients with pancreatic hyperenzymemia and those not having this alteration; this finding is in contrast with previous data reported by Ben-Horin *et al.* [19].

In conclusion, our study demonstrated an elevation of serum lipase activity in gastroenteritis due to *Salmonella* infection, but this elevation does not seem to have clinical significance, at least in the experimental conditions of our study. Most important, the elevation of serum lipase seems to be particularly related to the infection due to *Salmonella enterica* serovar Typhimurium.

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