



Serum Levels of Cytokines in Alcoholic Liver Cirrhosis and Pancreatitis

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Abstract: Although altered cytokine homeostasis has been implicated in the pathogenesis of both alcoholic liver and pancreas diseases, the serum cytokine pattern characteristic of concomitant alcoholic liver cirrhosis and pancreatitis has not been examined. In this paper we examine the serum levels of proinflammatory cytokines, such as IL-6, IL-8, TNF- α , and also antiinflammatory ones, such as IL-10 and TGF- β , in 22 patients with alcoholic liver cirrhosis and 28 patients with chronic pancreatitis and compare them with those detected in the sera of 14 patients with concomitant alcoholic cirrhosis and pancreatitis. All patients were heavy alcohol drinkers, consuming more than 70 g of pure alcohol per day for at least 5 years. The control group consisted of 33 age- and sex-matched healthy subjects receiving an annual health examination. They were not addicted to alcohol and confirmed to be free of major cardiopulmonary, gastrointestinal and hepatobiliary-pancreatic diseases. The results indicated that the cytokine pattern in the sera of patients with concomitant liver cirrhosis and pancreatitis was characterized by increased levels of two proinflammatory cytokines: TNF- α , the concentration of which seemed to be influenced by both liver and pancreas injury, and IL-6, which seemed to be rather connected with pancreas injury. Increased levels of IL-8, which were detected in the sera of patients with cirrhosis, pancreatitis and concomitant cirrhosis and pancreatitis, were rather connected with exacerbation of the disease processes which occurred only in some of the patients. No significant changes in the levels of IL-10 or TGF- β were detected in the sera of patients with chronic pancreatitis and concomitant cirrhosis and pancreatitis, while in patients with cirrhosis significantly decreased levels of IL-10 were found. A significant imbalance between proinflammatory/antiinflammatory signals was especially characteristic of alcoholic cirrhosis and concomitant cirrhosis with pancreatitis.

Key words: alcohol; compensated cirrhosis; chronic pancreatitis; interleukin 6, 8, 10; tumor necrosis factor α ; transforming growth factor β .

Introduction

Alcohol abuse is the main cause of acute or chronic pancreatitis and also alcoholic liver disease (ALD), ranging in severity from a fatty liver to hepatitis and

alcoholic cirrhosis^{2, 28, 40}. In ALD activation of the inflammatory response system has been described which is characterized by increased concentrations and activities of plasma cytokines produced by monocytes, macrophages and hepatocytes, including interleukin 1

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(IL-1), IL-6, IL-8 and tumor necrosis factor α (TNF- α). In alcoholic liver cirrhosis, especially, the role of TNF- α , IL-6 and IL-8 and TGF- β overproduction but decreased IL-10 production in progressing liver injury is considered^{3, 5, 7, 11–13, 16, 20–27, 29–31, 43, 44, 46, 48}. In alcoholic acute pancreatitis, increased serum levels of TNF- α , IL-1, IL-6 and IL-8, but decreased IL-2 concentrations were detected, while in chronic pancreatitis the role of TGF- β in remodelling of pancreatic tissue is considered^{1, 6, 8–10, 17–19, 32–39, 41, 42, 45, 47}. Although altered cytokine homeostasis has been implicated in the pathogenesis of both alcoholic liver and pancreas diseases, the serum cytokine patterns characteristic of concomitant alcoholic cirrhosis and pancreatitis has not been examined. In this study we examined the serum levels of proinflammatory cytokines such as IL-6, IL-8, TNF- α and also antiinflammatory ones such as IL-10 and TGF- β 1 in patients with either alcoholic liver cirrhosis or chronic pancreatitis and compared them with those detected in the sera of patients with concomitant alcoholic cirrhosis and pancreatitis.

Materials and Methods

Patients. In all, 64 patients (58 men, 6 women) admitted to the Medical University Hospital in Lublin were included in the study. All of them were heavy alcohol drinkers, consuming more than 70 g of pure alcohol per day for at least 5 years. The patients were selected because they had either chronic alcoholic pancreatitis (28 patients), alcoholic compensated cirrhosis (22 patients) or concomitant alcoholic pancreatitis with cirrhosis (14 patients). The diagnosis was based on clinical history, clinical examinations, laboratory findings, gastroscopy and ultrasonography. Some of the pa-

tients were diagnosed by retrograde cholangiopancreatography (EPC) or liver biopsy. None of the patients examined had chronic B or C viral hepatitis or HIV infections and none had received blood transfusion or was under treatment with steroids or immunosuppressive therapy. Blood tests included complete blood pictures, electrolytes, urea, creatinine, glucose, cholesterol, albumin, gamma globulins and prothrombin time. Plasma amylase, lipase, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity were measured on admission to hospital and several times if deemed necessary. A blood sample for measuring the cytokine level was obtained from each patient on admission to hospital.

The control group consisted of 33 age- and sex-matched healthy subjects, University workers receiving their annual health examination. They were not alcohol abusers and were confirmed to be free of major cardiopulmonary, gastrointestinal and hepatobiliary-pancreatic diseases. None of them had drunk alcohol for at least 3 weeks. Blood samples were obtained and serum cytokine levels were measured to provide local reference material for this study. The characteristics of the subjects from each group are described in Table 1. Agreement for this study was granted by the Clinical Ethics Committee of the University Medical School in Lublin.

Cytokine concentration assay. Serum concentrations of IL-6, IL-8, IL-10, TNF- α and TGF- β 1 were measured by the enzyme-linked immunosorbent assay-Predicta ELISA kits (Genzyme Diagnostics, Cambridge, MA, USA). The sensitivity of the assay was IL-6 18 pg/ml, IL-8 1 pg/ml, IL-10 5 pg/ml, TNF- α 3 pg/ml and TGF- β 1 0.05 ng/ml.

Data analysis. Data were expressed as mean $\pm$ SD. Statistical analysis was performed using the two-tailed

Table 1. Clinical characteristics of patients with alcoholic liver and pancreas disease

Parameter	Controls n=33	Cirrhosis n=22	Pancreatitis n=28	Cirrhosis + pancreatitis n=14
Age	43 $\pm$ 13	49 $\pm$ 15	44 $\pm$ 10	43 $\pm$ 11
Sex M/F	30/3	20/2	26/2	12/2
AST U/ml	<50	99.3 $\pm$ 50.3	48.0 $\pm$ 39.1	173.0 $\pm$ 137.5
ALT U/ml	<50	66.5 $\pm$ 41.1	31.8 $\pm$ 25.6	66.0 $\pm$ 42.1
Lipase U/ml	<3	5.2 $\pm$ 3.3	12.0 $\pm$ 16.4	20.8 $\pm$ 20.7
α -amylase U/ml	<32	87.0 $\pm$ 83.2	157.6 $\pm$ 194.7	235.4 $\pm$ 233.6
GGT U/ml	10–100	52.7 $\pm$ 42.7	53.1 $\pm$ 141.2	62.9 $\pm$ 59.8
T-bilirubin mg/dl	<1	3.5 $\pm$ 4.8	1.1 $\pm$ 0.9	6.8 $\pm$ 10.3
Albumin % of total plasma proteins	54–60	54.0 $\pm$ 7.9	60.8 $\pm$ 8.5	46.5 $\pm$ 3.2
Cholesterol mg/dl	200–250	162.8 $\pm$ 44.6	205.2 $\pm$ 84.2	128 $\pm$ 47.9
Leukocytes $\times 10^9/l$	4.5–10.0	9.9 $\pm$ 6.0	11.3 $\pm$ 4.9	12.5 $\pm$ 5.9
Neutrophils % of leukocyte total number	45–65	74 $\pm$ 11.1	70.1 $\pm$ 17.5	76.3 $\pm$ 7.4

Mann-Whitney U test. Statistical significance was set at $p < 0.05$.

Results

The patients with concomitant cirrhosis and pancreatitis had significantly higher levels of TNF- α and IL-6 than those who had either alcoholic compensated cirrhosis or chronic pancreatitis (Fig. 1). It seems likely that both types of the diseases contributed to the final

serum level of TNF- α , but the IL-6 level resulted largely from pancreatitis. In contrast to the above findings, the serum level of IL-8 was the highest in the sera of patients with cirrhosis and lower in the sera of those with pancreatitis and concomitant cirrhosis and pancreatitis (Fig. 1). However, it should be noted that the differences were not statistically significant because of large variations among the subjects. When TGF- β 1 serum levels were examined, no differences between control and both groups of patients were seen. When the serum level of IL-10 was estimated, patients with

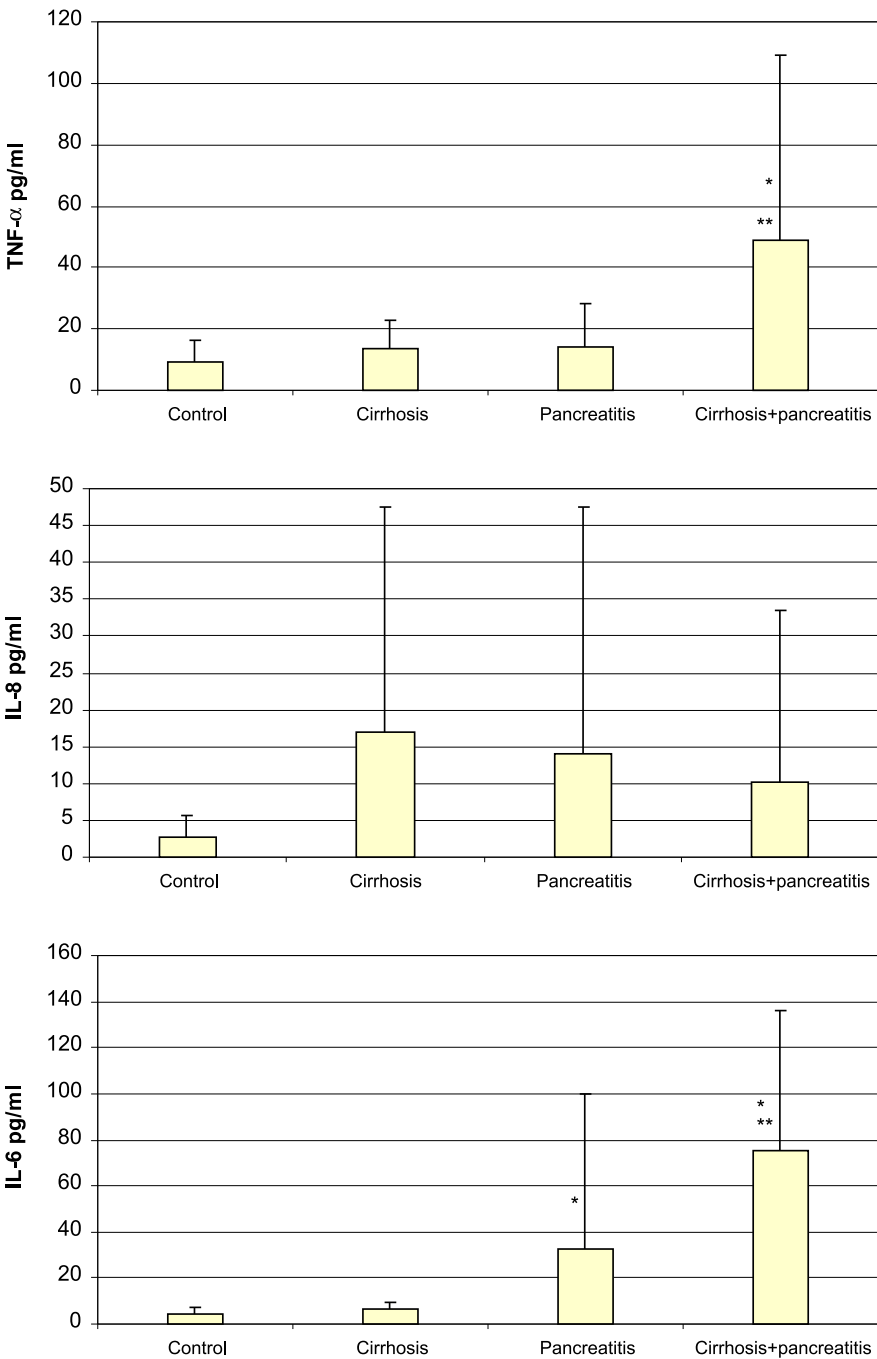


Fig. 1. Levels of TNF- α , IL-8 and IL-6 in the sera of patients with alcoholic compensated cirrhosis, chronic pancreatitis and concomitant cirrhosis and pancreatitis. *Statistically significant difference in comparison to control at $p < 0.05$. **Statistically significant difference in comparison to the group with cirrhosis at $p < 0.05$

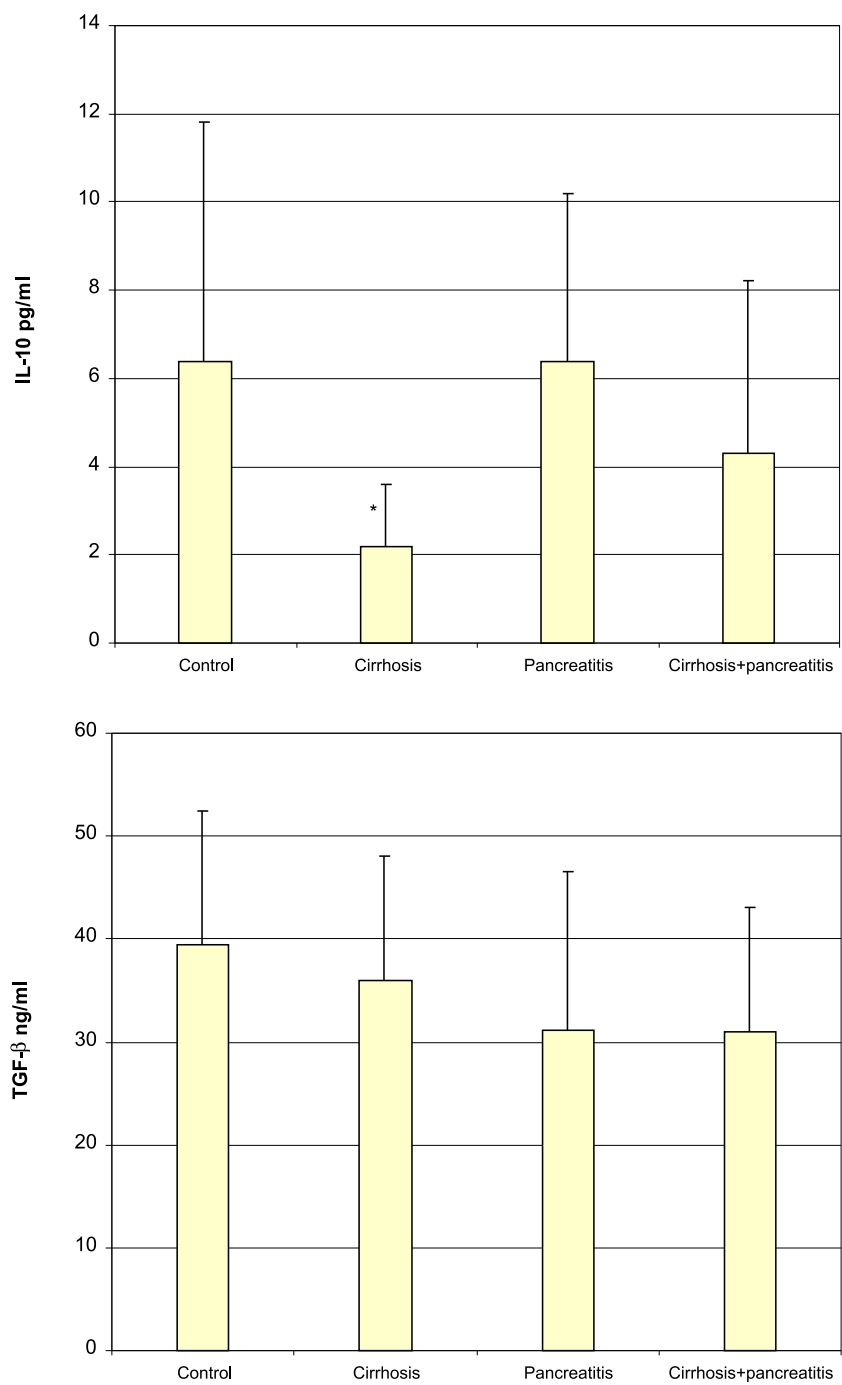


Fig. 2. Levels of IL-10 and TGF-β in the sera of patients with alcoholic compensated cirrhosis, chronic pancreatitis and concomitant cirrhosis and pancreatitis. *Statistically significant difference in comparison to control at $p<0.05$

alcoholic liver cirrhosis had in their blood significantly lower levels of IL-10 in comparison with control and patients with pancreatitis or concomitant cirrhosis and pancreatitis (Fig. 2).

Discussion

Several studies have indicated a correlation between circulating levels of proinflammatory cytokines and ALD progression during chronic ethanol consumption^{11–13, 20–27, 29–31}. The exact mechanism of liver injury

in ALD has not been defined, but much evidence suggests that acute and chronic ethanol consumption can increase gut permeability to endotoxin and impair the reticuloendothelial function of the liver⁴. These changes may increase plasma endotoxin concentrations. Since endotoxin is a major stimulus for the production of cytokines, increased serum levels of TNF-α and IL-6 are the consequence of the phenomena mentioned above^{3, 11–13, 16, 20, 25, 26, 46}. Moreover, the association of ALD with increased TNF-α levels in plasma indicates that this cytokine is a major mediator of the deleterious effect of ethanol on the liver. The cytokine acts directly

on hepatocytes or indirectly by induction of adhesion molecules and increases infiltration of neutrophils into the liver^{25, 46}. The highest levels of TNF- α were detected in patients with alcoholic hepatitis. In cirrhosis the levels of TNF- α were described to be lower²⁴, and some authors²² stated that increased TNF- α serum concentrations are connected with infections superimposed on cirrhosis. In our study none of the patients examined had such infections and we agree with the data of HIRSCH et al.²², because the TNF- α serum levels of our patients with alcoholic compensated cirrhosis were not significantly higher than those in the control group.

In alcoholic pancreatitis, increased TNF- α levels were detected in the acute but not the chronic form of the disease^{8, 10, 32, 36}. Our results also confirmed the fact that chronic alcoholic pancreatitis was not characterized by significantly increased TNF- α serum levels. However, we can extend these findings that patients with concomitant alcoholic cirrhosis and pancreatitis had significantly increased TNF- α levels.

Patients with chronic pancreatitis had significantly higher levels of IL-6 in comparison to controls and patients with alcoholic cirrhosis. IL-6 was detected as an excellent severity marker of acute pancreatitis 48 h after the onset of the disease, but later in the course of pancreatitis its role as disease severity marker disappears^{19, 38}. The results of our study indicate that in the sera of patients with chronic pancreatitis and, especially, in the sera of patients with concomitant liver cirrhosis and pancreatitis, the level of IL-6 was high. The increased IL-6 levels were rather connected with pancreas injury and not liver dysfunction.

In our study we also examined the serum level of IL-8 and found it in increased levels in patients with alcoholic cirrhosis, alcoholic pancreatitis and in the sera of patients with concomitant cirrhosis and pancreatitis, but the differences compared to the control were not statistically significant because of large individual differences. It seems likely that the IL-8 level is rather linked to an acute inflammatory process and its level is especially high in alcoholic hepatitis and acute pancreatitis^{7, 18, 21, 23, 39, 44}. In cirrhosis and chronic pancreatitis, increased IL-8 level can be rather connected with exacerbation of the diseases, which can occur in some patients and which resulted in large differences within the group examined.

As overproduction of proinflammatory cytokines can be connected with a defect in the production of inhibitory cytokines such as IL-10 and TGF- β ^{14, 15}, we also examined the serum levels of these cytokines in patients with alcoholic liver and pancreas disease. The results showed that there were no differences in the

levels of TGF- β 1 measured in the sera of patients with chronic pancreatitis, compensated alcoholic liver cirrhosis and with concomitant injury of both organs. However, IL-10 production was significantly decreased in patients with alcoholic cirrhosis and comparable to the control group in other groups of patients. As the balance between proinflammatory and antiinflammatory cytokines is very important for the function of the immune system, we can speculate that even in patients with cirrhosis, in whom no significant increase in proinflammatory cytokines was detected, a disturbance of the immune system occurs. Also patients with concomitant cirrhosis and pancreatitis, who had a normal level of IL-10 as antiinflammatory cytokine, had increased levels of IL-6 and TNF- α . An imbalance between proinflammatory/antiinflammatory signals in the organism causes dysregulation of the immune response and injury to organs in which the inflammatory processes take place. Similar observations were reported by other authors²⁷, who found that blood monocytes of patients with alcoholic cirrhosis exhibited a defect in LPS-stimulated IL-10 production. They concluded that this defect was responsible for TNF- α overproduction in LPS-stimulated monocytes.

Normal TGF- β levels found in our study did not confirm the results of other authors, who detected overproduction of this cytokine in pancreas^{1, 17, 42, 45} and in liver^{5, 29, 30} tissue. One possible explanation for this phenomenon is that TGF- β produced locally is rapidly bound by stellate and other cells in the liver or pancreas, so its overproduction is not reflected by an increased level of this cytokine in the blood.

In summary, the results of the present study indicate that the cytokine pattern in the sera of patients with concomitant liver cirrhosis and pancreatitis is characterized by increased levels of two proinflammatory cytokines: TNF- α , whose concentration seems to be influenced by both liver and pancreas injury, and IL-6, which seems to be rather connected with pancreas injury. Increased levels of IL-8, which were detected in the sera of patients with cirrhosis, pancreatitis and concomitant cirrhosis and pancreatitis, were rather associated with exacerbation of the disease process, which occurred only in some of the patients. No significant changes in the levels of IL-10 or TGF- β were detected in the sera of patients with chronic pancreatitis and concomitant cirrhosis and pancreatitis, while in those with cirrhosis, significantly decreased levels of IL-10 were found. This means that a significant imbalance between proinflammatory/antiinflammatory signals is particularly characteristic of alcoholic liver cirrhosis and concomitant cirrhosis with pancreatitis.

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