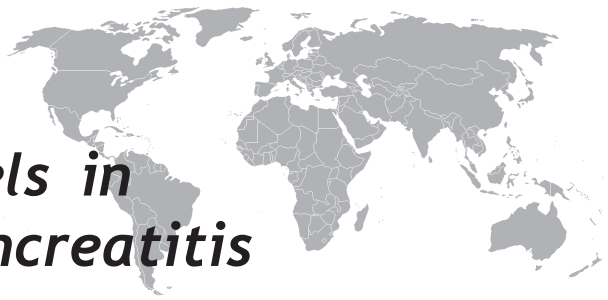

Serum TNF-Alpha Levels in Acute and Chronic Pancreatitis

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ABSTRACT

Aim: *Acute and chronic pancreatitis are inflammations of pancreatic tissue which have systemic effects and clinical presentations such as bacteremia and septic shock. Inflammatory markers have growing importance in diagnosis and identification of the severity of the pancreatitis. We aimed to determine TNF-alpha levels in acute and chronic pancreatitis and evaluate the relation between TNF-alpha levels and the pancreatic enzyme concentrations in two forms of the disease.*

Methods: *13 patients with acute pancreatitis, 36 patients with chronic pancreatitis and 14 healthy controls were included to our study. TNF-alpha determinations were performed with ELISA method.*

Results: *TNF-alpha concentrations were 13.30±4.42 (7.04-21.35) pg/ml and 9.88±4.68 (3.99-27.73) pg/ml 10.09±1.01 (8.69-14.96) pg/ml in patients with acute and chronic pancreatitis and healthy controls respectively. TNF-alpha concentrations were significantly higher in patients with acute pancreatitis than the patients with chronic pancreatitis. But there was no significant difference between healthy controls and patients with either acute or chronic pancreatitis for TNF-alpha levels. There was no significant correlation between TNF-alpha concentrations and pancreatic enzyme levels.*

Conclusion: *We concluded that in acute pancreatitis TNF-alpha levels were higher than the chronic form of the disease. But its concentrations did not correlate with the severity of the disease. By investigation of the other inflammatory markers and acute phase reactants with TNF-alpha, this process will be more clarified.*

Key Words: *TNF-alpha, acute pancreatitis, chronic pancreatitis.*

INTRODUCTION

Acute pancreatitis is an acute inflammatory process and besides the improvements in critical care applications, it still has high mortality rates. Most common causes of acute pancreatitis are alcoholism and biliary stones (1, 2). Multi-organ dysfunction syndrome, the extent of pancreatic necrosis, infection and sepsis are the major determinants of mortality in acute pancreatitis. Pancreatic necrosis is considered as a potential risk for infection, which represents the primary cause of late mortality. Occurrence of failures in respiratory, cardiovascular and excretory systems can predict the fetal outcome in severe acute pancreatitis. A wide range of mortality (20%-60%) has been reported in severe acute pancreatitis. Early diagnosis and prognostic evaluation are extremely important and may reduce the morbidity and mortality associated with severe acute pancreatitis (3-6). Pancreatic tissue damage is induced mostly with the inappropriate intracellular activation of trypsinogen to trypsin. Then a cascade of enzymatic activation process begins including the activation of phospholipases and elastases. Neutrophil migration to the pancreas and secretion of the inflammatory mediators join the process. Many inflammatory cytokines including interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), platelets activating factor (PAF) and tumor necrosis factor (TNF) play important roles in either pathogenesis or systemic complications of acute pancreatitis (7-9).

Chronic pancreatitis is a clinical outcome in which permanent and progressive parenchyme damage and functional disturbances are involved. It is defined as an irreversible damage which develops as a result of chronic inflammation and fibrosis of panreatic tissue and a cause of exocrine and endocrine insufficiency of pancreas. It is characterised with chronic abdominal pain and symptoms of pancreatic insufficiency (10). Recent in vitro and in vivo studies have shown objectively the role of activated pancreatic stellate cells in fibrogenesis in chronic pancreatitis (11, 12). A number of factors like inflammatory mediators, oxidative stress and toxins activate these cells. These pro-inflammatory mediators include IL-1, IL-6 and TNF-alpha. One of the major toxins that cause chronic pancreatitis is ethanol. In vitro studies have shown that ethanol can produce chronic pancreatitis through a number of mechanisms (13). Besides generating oxidant stress, ethanol can also predispose the pancreas to auto-digestion and necroinflammation. Production of pro-inflammatory cytokines including TNF-alpha, IL-1 and IL-6 is observed as a result of these; and they contribute and progress the pancreatic inflammation and activate pancreatic stellate cells (14, 15).

In recent years, growing interest was focused on use of inflammatory markers with pancreatic enzymes in diagnosis and prognostic evaluation of acute and chronic pancreatitis. Inflammatory markers or acute phase reactants like high sensitive CRP, interleukines and TNF-alpha were used in diagnosis and follow up of two forms of the disease and different results were obtained. The researchers investigated TNF-alpha levels in either acute or chronic form of the disease and compared with healthy controls. But there is no report which gives information about TNF-alpha levels in both forms of the disease. So we aimed to determine TNF-alpha levels in acute and chronic pancreatitis and evaluate the relation between TNF-alpha levels and the disease severity in two forms of the disease.

METHODS

13 patients with acute pancreatitis, 36 patients with chronic pancreatitis and 14 healthy controls were included to our study. Patients in acute pancreatitis group had signs and symptoms of pancreatitis accompanied by elevations in biochemical tests such as pancreatic enzymes (amylase, lipase). Diagnosis of chronic pancreatitis was confirmed with one or usually a combination of radiological tools (i.e.ultrasonography, computerized tomography, endoscopic ultrasonography).

Blood samples taken for routine biochemical analysis during their hospitalisation were aliquoted in eppendorf tubes after enzyme analysis and stored at -70ºC. TNF alpha analysis was performed with a commercially available ELISA kit (BioSource).

SPSS for Windows statistical program (version13.0) was used for statistical evaluation. Kruskal Wallis Variance analysis was performed for comparison of TNF-alpha levels of the all groups and post hoc Mann Whitney-U test was used. Spearman Correlation analysis was performed for correlations. $p< 0.05$ was assumed as statistically significant.

RESULTS

The mean ages of patients with acute pancreatitis, chronic pancreatitis and control groups were 47±16.27 (13-73), 45.82±17.93 (11-76) and 39.78±10.59 (29-55) years respectively. Biochemical measurements were

Table 1. Demographic characteristics and laboratory findings of control and pancreatitis groups.

Parameter	Acute pancreatitis (n= 13)	Chronic pancreatitis (n= 36)	Control (n= 14)
Amylase (U/L)	1664 ± 1085	81.25 ± 40.28	
Lipase (U/L)	1058 ± 720	37.64 ± 22.01	
TNF-alpha (pg/mL)	13.30 ± 4.42	9.88 ± 4.68	10.09 ± 1.61
	(p= 0.01, p= 0.08)	(p= 0.133, p= 0.01)	(p= 0.08,p= 0,133)

summarized in (Table 1). TNF-alpha concentrations were 13.30±4.42 (7.04-21.35) pg/ml and 9.88±4.68 (3.99-27.73) pg/ml and 10.09±1.01 (8.69-14.96) pg/ml in acute and chronic pancreatitis and control groups respectively (Table 1). TNF-alpha concentrations were significantly higher in patients with acute pancreatitis than the ones with chronic form of the disease ($p< 0.05$). But there was no significant difference between healthy controls and patients with either acute or chronic pancreatitis for TNF-alpha concentrations. We performed Spearman correlation analysis but there was no significant correlation between TNF-alpha levels and pancreatic enzyme concentrations.

DISCUSSION

In our study we aimed to determine TNF-alpha levels in acute and chronic pancreatitis and evaluate the relation between TNF-alpha levels and pancreatic enzyme concentrations in two forms of the disease. Our results showed that TNF-alpha levels were significantly higher in acute pancreatitis than chronic pancreatitis. But no significant increase was observed in TNF-alpha production in either form of the disease compared to healthy individuals. Correlation analysis was performed between pancreatic enzymes (amylase and lipase) and TNF-alpha levels but we did not find any significant correlation.

TNF-alpha is a cytokine that causes unwanted effects in many different autoimmune and inflammatory diseases. It is a key regulator of other proinflammatory cytokines and of leukocyte adhesion molecules and it is a priming activator of immune cells (16). In recent years, several studies suggested that TNF alpha plays a pivotal role in the pathogenesis of acute pancreatitis. Use of TNF-alpha in acute pancreatitis was assumed to predict disease severity and development of complications such as multiple organ failure and septic shock (16). Brivet et al concluded that during acute severe pancreatitis, pro- and anti-inflammatory cytokine response occured early and persisted in the systemic circulation for several days. They also observed an association with the disease severity at onset and outcome. But cytokine plasma concentrations were considered to be unable to predict death accurately in individual patients (17).

Different results were reported about TNF-alpha levels in chronic pancreatitis. Szuster-Ciesielska et al observed increased TNF-alpha and IL-6 levels in alcoholic liver cirrhosis and chronic pancreatitis (18). To clarify the pathophysiological significance of cytokines in chronic pancreatitis, Xie et al analyzed tissue expressions of various cytokines in the onset and progression in rats with chronic pancreatitis and their results suggested that tissue expressions of TNF-alpha and IL-6 were involved in the onset of pancreatitis and that IFN-gamma expression was related to the progression of chronic pancreatitis (19).

In order to clarify whether there was a difference in the dynamics of cytokine levels at chronic pancreatitis with different etiologic factors Zhukov et al investigated the production of TNF in chronic alcoholic and chronic relapsing pancreatitis and showed that it could be a reliable marker of the severity of aggravation irrespective of the etiologic factor of the disease and also as a prognostic factor (20). High cytokine levels were found to be correlated with exacerbation severity. However in transition to remission, the levels of cytokines and acute phase proteins decreased. It was demonstrated that TNF-alpha rose in remission most frequently in patients with biliary-pancreatic reflux (21).

In this study we have investigated TNF-alpha concentrations in both acute and chronic forms of pancreatitis. TNF-alpha levels were significantly higher in patients with acute pancreatitis than patients with the chronic form of the disease. But there was no significant difference between healthy controls and patients with either acute or chronic pancreatitis for TNF-alpha concentrations. According to our findings we suggest that TNF-alpha increases in acute form of the disease but not in the chronic form. Although acute pancreatitis group had higher TNF-alpha levels than the healthy controls this difference was not statistically significant. And this might be as a result of the factor that our study included small number of cases in acute pancreatitis and control groups.

Our findings agree with the previous results in acute pancreatitis but disagree with the results in chronic form of the disease. In most of the studies performed on patients with chronic pancreatitis, higher TNF-alpha levels were observed (18-21) and thought to be correlated with the exacerbation severity (20,21). But we found similar TNF-alpha levels in healthy controls and patients with chronic pancreatitis. In a previous report the researchers claimed that reduced capacity of TNF production was claimed to be responsible for the induction of chronic pancreatitis and low TNF-alpha secreting genetic variant was found to be predominant in this form of the disease (22), although some others concluded that there was no relation between TNF-alpha gene polymorphisms and chronic pancreatitis (23-25).

We did not find any correlation between the pancreatic enzyme activities and TNF-alpha levels. Although TNF-alpha levels were accepted to reflect disease severity and development of complications in acute pancreatitis in previous reports we did not observe this relation in our study. Limited number in acute pancreatitis group might be the cause of this incompatible finding.

We concluded that in acute pancreatitis TNF-alpha levels were higher than the chronic form of the disease. But its concentrations did not correlate with the severity of the disease. By investigation of the other inflammatory markers and acute phase reactants with TNF-alpha, this process will be more clarified. Researches on secretion characteristics of TNF-alpha in experimental pancreatitis models in animals will be more helpfull in clarifying the relation between TNF-alpha and pathogenetic process of the disease.

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