Evaluation of hypertriglyceridemia-induced acute pancreatitis: A single tertiary care unit experience from Turkey

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ABSTRACT

Background/Aims: *This study aimed to determine the frequency of hypertriglyceridemia (HTG)-induced acute pancreatitis (AP) and assess different clinical and prognostic features in these patients.*

Materials and Methods: *The patients who were hospitalized with AP due to HTG (HTG-AP) between January 2005 and December 2014 were retrospectively evaluated in the clinic. The patients with AP due to non-HTG (non-HTG-AP) were also investigated during the same period.*

Results: *Of 635 patients with AP admitted to the clinic, 33 (5.2%) had HTG-related AP. Mean triglyceride levels were 2653 mg/dL (range: 439-13700 mg/dL). Mean Ranson score at the time of admission was 1.5, and the APACHE II score was 4.63. The mean duration of hospitalization was 4.4 days (range: 2-14 days). One of these patients died on the sixth day of hospitalization due to multiple-organ failure. Patients with a triglyceride level of >1000 mg/dL were younger, had a longer hospital stay, and had a higher recurrence rate. Compared with non-HTG-AP, HTG-AP was observed at a younger age (57.4±17.3 vs. 37.6±14.8, p<0.05, respectively) and more frequently in males (45.2% vs. 57.6%, p<0.05, respectively). The frequency of multiple AP in patients with HTG-AP was higher than non-HTG-AP (63.4% vs. 7.6%, respectively).*

Conclusion: *HTG-AP was observed at a younger age and was responsible for most cases of recurrent pancreatitis. The duration of hospitalization was long, and the risk of recurrence and mortality were high in patients with HTG-AP having a triglyceride level >1000 mg/dL.*

Keywords: *Acute pancreatitis, hypertriglyceridemia, recurrence*

INTRODUCTION

Acute pancreatitis (AP) due to hypertriglyceridemia (HTG; HTG-AP) is a rare condition responsible for approximately 3%-4% of all AP cases. Gallstones and alcohol abuse are the most common causes of AP. Cases considered as idiopathic pancreatitis constitute 15%-25% of total cases (1-3). HTG is responsible for >50% of AP cases in pregnancy. HTG is defined as an increase in the fasting serum triglyceride level to >150 mg/dL. It is considered a risk factor for pancreatitis, particularly when the serum triglyceride levels are >1000 mg/dL (4). However, evidence shows that pancreatitis may develop at lower triglyceride levels; therefore, HTG may be missed in patients with pancreatitis because of blood sampling after long-term fasting. Moreover, AP diagnosis can be bypassed because serum amylase levels may be within the normal range in HTG-AP attacks. When the serum triglyceride level is >500 mg/dL, the serum amylase level can be measured normally, but if serial dilutions are made, the serum amylase level can be detected as high (5). Therefore, it is difficult to diagnose HTG-AP.

The present study investigated demographic and clinical characteristics, serum triglyceride levels, clinical outcomes, and treatment difficulties of patients with HTG-AP. It also analyzed whether these patients differed from patients with AP due to non-HTG causes (non-HTG-AP).

MATERIALS AND METHODS

A total of 763 patients hospitalized with AP in the clinic between January 2005 and December 2014 were examined. Of these, 128 patients were excluded because of deficiencies. Finally, a total of 635 patients were included in the study. The etiology was HTG in 33 (5.2%) of these patients. At the time of admission, clinical course notes, laboratory results, and images were retrospectively reviewed. At the time of hospitalization, the serum amylase and lipase levels; liver function test results; leukocyte counts; fasting blood glucose, C-reactive protein (CRP), triglyceride, and lactate dehydrogenase (LDH) levels; the number of total pancreatitis episodes; gender; reasons for recourse; and accompanying diseases were recorded.

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Additionally, Ranson and Apache II scores were calculated. Antibiotic necessity, local and/or systemic complications, intensive care unit requirement, and the length of hospital stay in days were recorded during the follow-up. In addition to the standard treatment of AP, 6 of these patients underwent lipid apheresis and 27 received 5% dextrose infusion, 0.05-0.1 unit/kg/day) insulin infusion, and 20,000 unit/day heparin infusion. Additionally, all patients received gemfibrozil 2×600 mg/day orally.

At least two of the three criteria of abdominal pain, elevated serum amylase/lipase levels, and ultrasonographic findings of pancreatitis (pancreatic edema, peripancreatic fluid collection, and decreased pancreatic parenchyma echogenicity and heterogeneity) should be met for the diagnosis of pancreatitis (6,7). A total of 32 patients with HTG-AP, who were still alive, were contacted by phone. The patients and their close relatives were asked whether or how many times they were previously hospitalized due to pancreatitis. Additionally, the results of the other 602 patients diagnosed with AP due to other causes during the same period (main findings, age, sex, clinical, imaging and laboratory findings, hospital stay, and so forth) were evaluated.

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences 13.0 version (SPSS Inc.; Chicago, IL, USA) program. The Mann-Whitney U test, Spearman correlation analysis, and Fisher exact test were used to evaluate the data. $p<0.05$ was considered statistically significant.

RESULTS

In the present study, 19 (57%) of the patients with HTG-AP were males, and 14 (43%) were females. The average age of patients at the time of admission was 37 years. One patient had a fever of 38.3°C in addition to abdominal pain, whereas 32 (97%) patients had only abdominal pain. Type 2 diabetes mellitus was found in 12 patients, impaired glucose tolerance in 5 patients, hypertension in 6 patients, and fatty liver in 8 patients (Table 1); 2 of the patients reported regular alcohol consumption. At the time of admission, the average levels were 416.81 U/L for amylase, 1045.09 U/L for lipase, 305 U/L for LDH, 171 mg/dL for fasting blood sugar, 63.4 mg/L for CRP, 13.9×10^3/mL for leukocytes, and 2653 mg/dL for triglyceride (range: 439-13700 mg/dL). Mean Ranson score at the time of admission was 1.5, and the APACHE II score was 4.63 (Table 2).

Table 1. Accompanying diseases in patients with acute pancreatitis due to hypertriglyceridemia

	Number	%
Type II diabetes mellitus	12	36
Impaired fasting glucose	5	15
Hypertension	6	18
Fatty liver	8	24
Hypothyroidism	0	0

Owing to recurrent pancreatitis, eight patients were hospitalized twice, five patients thrice, four patients four times, and three patients more than four times (Table 3). Broad-spectrum antibiotics were added to the treatments of eight patients (24%) on the third day of admission. Two patients (6%) required intensive care. One of these patients (3%) died on the sixth day following admission due to multiple-organ failure. The mean duration of hospitalization was 4.4 days (range: 2-14 days).

Because of repayment problems, only six patients were able to undergo lipid apheresis (Table 3). Triglyceride levels of patients treated with lipid apheresis were in the range of 4115-13750 mg/dL (mean, 7432±3612 mg/dL). Mean triglyceride level before discharge was 820±241 mg/dL. Mean triglyceride level at the time of admission was 1590±1096 mg/dL (439-5003 mg/dL) in 27 patients who received insulin plus heparin infusion and gemfibrozil treatment, and mean triglyceride level before discharge was 531±221 mg/dL (Table 4).

A total of 10 patients had a triglyceride level <1000 mg/dL. Their mean age was 54.3 years, and male-to-female ratio was 7/3. All of these patients had only one pancreatitis episode during their follow-up. Mean length of hospital stay was 3.4 days. Mean age of patients with triglycerides >1000 mg/dL was 30.3 years, whereas the male-to-female ratio was 12/11 (Table 5). The mean number of recurrent pancreatitis episodes during the follow-up period of these patients was 2.86, whereas the mean hospital stay was 4.8 days. The differences were observed between the two groups in terms of the mean age, female-to-male ratio, number of attacks, and average length of hospital stay, but only mean age and number of attacks were statistically significant ($p<0.05$) (Table 5).

The number of patients with non-HTG-AP was 602, and 272 (45.2%) were males. The most common cause of AP in these patients was gallstones (420 patients or 69.8%). The number of patients with AP due to alcohol was 54 (9%), whereas the number of patients with AP due to other causes (fibrosis, drug, tumor, idiopathic, etc.) was

Table 2. Characteristics of acute pancreatitis due to hyperlipidemia (HTG-AP) and other causes of acute pancreatitis (non-HTG-AP)

	HTG-AP (N=33)	Non-HTG-AP (N=602)	p
Average age (year)	37.6±14.8	57.4±17.3	0.000
Female/Male	14/19 (42.4%)	330/272 (54.8%)	0.193
Alcohol use	2 (6%)	61 (10.1 %)	0.097
Average number of attacks	2.1±0.85	1.16±0.66	0.017
Number of patients with more than one attack	21 (63.4%)	46 (7.6%)	0.000
Average length of stay (day)	4.4±2.5	4.82±3.1	0.549
Number of deaths	1 (3%)	15 (2.5 %)	0.478
Leucocytes (/mL)	13946.1±4145.3	12.713±5641	0.169
Fasting blood glucose (mg/dL)	171.2±91.7	136.3±60.9	0.002
AST (U/L)	48.9±46.3	222.9±238.8	0.000
LDH (U/L)	305.5±182.6	399.1±261.9	0.013
Triglyceride (mg/dL)	2652.9±2872.4	123.7±71.8	0.000
Platelet (/mL)	272636.4±91094.3	254260±99101.5	0.635
CRP (mg/L)	63.4±81.1	44.6±68.7	0.247
Amylase (U/L)	416.8±482.7	1167±1874	0.000
Lipase (U/L)	1045.1±1198.2	2209±2042	0.000
ALP (U/L)	78.2±32.4	176.8±151.6	0.017
GGT (U/L)	32.7±41.9	152.3± 134.9	0.000
Total bilirubin (mg/dL)	1.4±2.1	1.9±1.4	0.047
Direct bilirubin (mg/dL)	0.2±0.7	1.1±0.9	0.038
Ranson	1.5±1.5	2.2±1.6	0.043
Apache	4.6±2.8	4.93±3.33	0.659

AST: aspartate aminotransferase; LDH: lactate dehydrogenase; CRP: C-reactive protein; ALP: alkaline phosphatase; GGT: gamma-glutamyl transferase

Table 3. Features of patients with acute pancreatitis due to hypertriglyceridemia

		Number	%
Sex	Female	14	43
	Male	19	57
Total number of attacks	1	13	36
	2	8	24
	3	5	15
	4	4	12
	≥5	3	9
Chronic alcohol use		2	6
Antibiotic need		8	24
Intensive care requirement		2	6
Lipid apheresis		6	18
Exitus		1	3

128 (21.2%). The mean age of patients with non-HTG-AP was 57.4±17.3 years (age range: 17-97). Further, 99.8% of the patients had abdominal pain; one patient had no abdominal pain accompanied by nausea and vomiting. Owing to recurrent pancreatitis, eight patients were hospitalized twice, five patients thrice, four patients four times, and three patients more than four times; 556 patients (92.4%) had recourse once. Antibiotics were started in 202 patients (34%) during the treatment period. Also, 22 patients (3.6%) required intensive care, and 15 patients (2.5%) died due to various reasons (Table 2).

Compared with patients with non-HTG-AP, those with HT-AP were younger in age (57.4±17.3 vs. 37.6±14.8, $p<0.05$, respectively) and the disease mostly affected men (45.2% vs. 57.6%, $p<0.05$, respectively). The prevalence of more than one recurrence was higher in patients with HTG-AP (63.4%, 7.6%, $p<0.05$, respectively). The AST, LDH, ALP, GGT, and total and direct bilirubin levels

were higher in patients with non-HTG-AP, whereas the blood sugar levels were higher in patients with HTG-AP (Table 2). Because of HTG, the amylase and lipase levels were significantly lower in these patients compared with the non-HTG-AP group (Table 2). Local complications, such as abscess, pseudocyst, and necrosis, were not observed in patients with HTG-AP, but 38 (6%) of patients with non-HTG-AP had these complications. Systemic complications affecting the kidney, circulation, and respiration were higher in patients with HTG-AP but not statistically significant (9.1% vs. 7.6%, p>0.05, respectively). No differences in the hospitalization time and mortality were found (Table 2).

Table 4. Lipid-lowering therapy

Treatment Protocol	Hospitalization Value (mg/dL)	Before Discharge (mg/dL)	p
Lipid apheresis+ gemfibrozil (n=6)	7432±3612	820±241	0.000
Heparin+insulin+ gemfibrozil (n=27)	1590±1096	531±221	0.000

DISCUSSION

Chylomicrons are triglyceride-rich lipid particles that cause ischemia, leading to the occlusion of the pancreatic capillaries. This process further induces the release of pancreatic lipase, causing structural changes in the acini. An increased concentration of lipase results in increased levels of cytotoxic free fatty acids in circulation. These fatty acids cause vascular endothelial cell damage, aggregation of erythrocytes, and pancreatic ischemic damage by causing AP and activating Toll-like receptor-2 (TLR2) and TLR4 (8,9). Active neutrophils further exacerbate the situation by releasing superoxide radicals and several proteolytic enzymes (cathepsins B, D, G, collagenase, and elastase). Finally, macrophages secrete cytokines, leading to systemic complications, particularly in severe cases. The primary mediators are tumor necrosis factor alpha, interleukin (IL)-1, IL-4, IL-8, and platelet-activating factor (10). These inflammatory mediators increase pancreatic vascular permeability, thereby causing hemorrhage, edema, and eventually, pancreatic necrosis.

Table 5. Demographic and laboratory values of patients according to triglyceride level

	Triglyceride <1000 mg/dL (N=10)	Triglyceride ≥1000 mg/dL (N=23)	p
Average age (years)	54.3±12.7	30.3±8.37	0.000
Female/Male	3/7	11/12	0.357
Alcohol use	1	1	0.101
Average number of attacks	1±0.0	2.86±1.36	0.000
Average length of stay (day)	3.4±1.27	4.8±2.92	0.067
Number of deaths	0	1	-
Leucocytes (/mL)	13900.9±4279.8	14050.1±4038.1	0.926
Fasting blood glucose (mg/dL)	185.3±103.6	139±45.2	0.084
AST (U/L)	47.7±50.9	51.9±35.5	0.351
LDH (U/L)	298.9±163.1	320.7±230.6	0.223
Triglyceride (mg/dL)	3512.6±3072.2	675.6±172.2	0.000
Platelet (/mL)	281478.3±92744.9	252300±88425	0.402
CRP (mg/L)	57.9±91.1	75.9±53.3	0.486
Amylase (U/L)	398.7± 521.6	458.4±393.3	0.811
Lipase (U/L)	976.4±1315.4	1203.1±930.2	0.335
ALP (U/L)	75.7±34.6	83.9±27.4	0.185
GGT (U/L)	31.8±44.1	34.8±36.9	0.652
Total bilirubin (mg/dL)	1.5±2.2	1.2±1.9	0.485
Direct bilirubin (mg/dL)	0.2±0.8	0.2±0.5	0.912
Ranson	1.4±1.2	1.8±2.1	0.485
Apache II	4.8±3	4±2.5	0.420

AST: aspartate aminotransferase; LDH: lactate dehydrogenase; CRP: C-reactive protein; ALP: alkaline phosphatase; GGT: gamma-glutamyl transferase

Hypertriglyceridemia occurs due to primary (familial dyslipidemia types 1, 4, and 5) or secondary causes (alcohol use, diabetes, hypothyroidism, and kidney and liver diseases). Severe HTG with triglyceride levels >1000 mg/dL occurs usually due to primary causes. It is present in approximately 1.7% of the adult population (11). Approximately 15%-20% of this group develops AP (12). HTG-AP constitutes 1%-10% of all pancreatitis cases in different studies published worldwide (1,2,4,8). In the present study, HTG-AP cases accounted for 5.2% of all cases.

In the present study, 23 patients had a serum triglyceride level of >1000 mg/dL, whereas 10 patients had a serum triglyceride level of <1000 mg/dL. Pancreatitis etiology was screened in these 10 patients (medication history, USG, MRCP, EUS, CT, serum IgG4 levels, etc.). HTG-AP was considered because no etiology factors were determined except HTG. In the literature, HTG-AP cases are typically associated with high serum triglyceride levels (≥1000 mg/dL). However, cases with HTG-AP at lower serum triglyceride levels have also been reported in the literature (13-16). The threshold value of 1000 mg/dL should be questioned. If the serum triglyceride levels were considered as a threshold value of 1000 mg/dL, HTG-AP cases would account for 3.6% of all cases. Serum lipid levels of patients with HTG-AP in the emergency center can be evaluated after hospitalization. Occasionally, hospitalization may last up to 36 hours. During this time, the patient receives nonspecific fluid therapy. Consequently, the serum triglyceride levels may be <1000 mg/dL. One of the limitations is that the serum triglyceride levels at the time of first admission cannot be measured in some patients.

The etiology cannot be detected with anamnesis, laboratory tests, and hepatobiliary USG in approximately 30% of patients with HTG-AP. In certain cases of recurrent pancreatitis, no etiology can be detected even after comprehensive investigations such as the MRI, MRCP, EUS, ERCP, microlithiasis analysis, and Oddi sphincter manometry. Such cases are considered idiopathic pancreatitis, and they constitute 15%-25% of all patients with AP. Patients whose serum triglyceride levels are <1000 mg/dL were diagnosed with idiopathic pancreatitis in several studies. Hence, some of the cases diagnosed as idiopathic pancreatitis may actually be HTG-AP.

When the patients were divided into two groups based on the serum triglyceride levels (Table 4), a statistically significant difference was observed between the two groups in terms of mean age and number of attacks. On the contrary, average length of stay in hospital and male-to-female ratio was different but not statistically significant. In a study on HTG-AP in China, patients were divided into two groups: those with a triglyceride level between 500 and 1000 mg/dL and those with a level >1000 mg/dL (16). Mean age of onset, sex, development rate of local and systemic complications, and recurrence rate were found to be similar. Moreover, the amylase and lipase levels were higher in the AP group with the low triglyceride level, similar to that in the present study. Only a few studies on this issue have been reported in the literature. Hence, studies with more cases based on serum triglyceride levels are needed to validate the findings.

The patients with HTG-AP and non-HTG-AP were compared in the present study. The patients in the HTG-AP group were mostly males, were younger in age and had a higher likelihood of recurrent AP. No statistically significant difference was found between the groups in terms of local and systemic complications, hospitalization time, and mortality rate. The above-mentioned Chinese study found that patients with HTG-AP had a higher risk of developing local and systemic complications compared with patients with biliary and alcohol-induced pancreatitis (16). In a multicenter study from Hungary, the incidence of HTG-AP was higher in males, with no difference between the mortality rates in both groups (non-HTG-AP and HTG-AP) (17). The overall mortality rate (2.83%) was similar to that observed in the present study. Ranson 0-h score was marginally higher in patients with HTG-AP than in non-HTG-AP patients in the present study, but no difference was found between the APACHE II scores. Clinical trials evaluating the effect of HTG on the AP severity have yielded contradictory results (18). The increase in amylase and lipase levels was lower in patients with non-HT-AP than in those with HTG-AP. Similar results on amylase and lipase levels were obtained in previous studies (16-21).

The treatment of HTG-AP is still not well established; no published guidelines exist in this regard. However, because the clinical appearance of HTG-AP does not differ from that of non-HTG-AP, it is considered that the clinical treatment approach does not differ. However, it is important in this patient group that HTG is normalized or reduced to at least 500 mg/dL. For this purpose, protocols combining insulin plus heparin based on increasing lipoprotein lipase activity in the acute phase can be applied (22) or lipid apheresis that removes triglycerides can be attempted (23-24). Antilipidemic medication should also be administered to support the treatment.

The first choice in this regard is the fibrates. In resistant cases, nicotinic acid and omega-3 fatty acids may be added to the treatment. Treatment of HTG-AP in pregnancy is similar to the treatment for others; however, fibrates are not used (25). Both insulin plus heparin infusion and lipid apheresis effectively reduced the triglyceride levels of the patients in this study. However, only six patients with lipid apheresis could be treated as a result of changes in the refund policy. Because of the small number of patients, no statistical evaluation was performed to determine which treatment protocol was more effective. The efficacious results in treatment protocols to reduce HTG support the results found in previous studies (22,24,26,27).

In conclusion, diagnosis of HTG-AP is difficult because, sometimes, the serum amylase values are normal or the serum triglyceride levels are low for various reasons. The generally accepted serum triglyceride threshold value of 1000 mg/dL should be questioned, and serum triglyceride levels higher than normal should be kept in mind as a cause of pancreatitis. HTG-AP is seen at a younger age compared with non-HTG-AP, affects men more frequently, and tends to recur. When the triglyceride level is >1000 mg/dL, the risk is slightly increased.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of the Mersin University School of Medicine (Decision Date: June 05, 2014; Decision No: 2014/117).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

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