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Association of elevated serum triglyceride levels with a more severe course of acute pancreatitis: Cohort analysis of 1457 patients

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ABSTRACT

Background: Previous publications have reported an association between hypertriglyceridemia (HTG) and severity of acute pancreatitis, but this relationship remains somewhat controversial.
Objective: To evaluate the outcome of acute pancreatitis according to serum triglyceride levels on admission.
Methods: Retrospective analysis of prospectively collected data, which included all consecutive cases of acute pancreatitis admitted to a tertiary hospital (January 2002–December 2014). Acute pancreatitis patients were classified into 3 groups based on serum triglyceride levels (mg/dl) measured within 48 h from admission: normal triglycerides-mild HTG (<200); moderate HTG (200–749); severe HTG (≥750). Primary outcomes were the difference in organ failure, pancreatic necrosis, acute peripancreatic collections and mortality among the three groups.
Results: A total of 1,457 cases were included: 1,335 with normal-mild HTG, 77 with moderate HTG and 45 with severe HTG. The rates of organ failure (11.2% in normal-mild HTG group, 15.6% in moderate HTG and 20.0% in severe HTG), persistent multiple organ failure (2.5% vs. 5.2% vs. 6.7%), pancreatic necrosis (9.2% vs. 14.3% vs. 26.7%) and acute collections (21.6% vs. 40.3% vs. 55.6%) increased significantly with hypertriglyceridemia severity grades. On multivariate analysis, triglycerides as a quantitative variable, evaluated in increments of 100 mg/dl, was independently associated with organ failure, pancreatic necrosis, acute collections and mortality ($p < 0.05$).
Conclusions: Elevated serum triglyceride levels are independently associated with a more severe course of pancreatitis. It must be highlighted the elevated frequency of local complications in patients with HTG that increases proportionally and significantly with HTG severity grades.

Introduction

Acute pancreatitis (AP) is one of the main causes of hospital admission for gastrointestinal disorders in many countries, with increasing incidence over the last few decades [1,2]. AP has a variable clinical course; the majority of patients have a mild disease with early recovery. However, in 15–20% of patients it progresses to a severe course with high morbidity and significant mortality [3].

Hypertriglyceridemia (HTG) is considered the third most frequent cause of acute pancreatitis, after gallstones and alcohol [4], accounting for 2–7% of all cases of AP [4–6]. There is no clear threshold of triglycerides (TG) which triggers AP, but it seems that "the higher the level of TG, the higher the risk of AP" [7,8]. Hypertriglyceridemic acute pancreatitis (HTG-AP) is most commonly defined as the presence of serum TG levels > 1000 mg/dl in absence of other etiologic factors for AP [9]. The exact process by which HTG causes AP is not well understood. Moreover, according to some series, a mild to moderate increase in triglyceride levels can be present in up to one third of patients with AP and has been proposed as an epiphenomenon secondary to the AP itself [10–12].

HTG can be of primary origin, due to a genetic abnormality of lipid metabolism, or, more commonly, because of secondary factors like diabetes mellitus, alcohol abuse, obesity, dietary factors, pregnancy and drugs. Severe HTG usually occurs due to the presence of secondary factors in a subject with an underlying genetic TG metabolism abnormality [13]. Determining the exact etiology of

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pancreatitis in a patient with severe HTG and alcohol abuse is a challenge. Some authors consider that it is controversial to ascribe the cause of AP to HTG when a high alcohol intake coexists, because heavy alcohol consumption is associated with higher plasma triglycerides levels and both are associated with an increased risk for pancreatitis. However, in most patients with very high TG levels and heavy alcohol intake, alcohol is a trigger for severe HTG in a patient with an underlying lipid metabolism disorder [14].

Although clinical presentation of HTG-AP is similar to other etiologies, some available data have shown that HTG-induced AP has a worse outcome with higher rates of organ failure. Furthermore, various studies have reported that elevated TG levels on admission are associated with aggravation of AP [9,15–19]. However, other studies have not shown any significant relationship between the level of serum TG and the clinical course of AP [4,11,12,20]. Results published on the association between triglyceride serum levels on admission and outcome of AP are diverse and heterogeneous, probably due to the diversity of severity measures used, the cut-off values chosen for HTG and the small sample size in some studies [9].

The aim of our study is to assess the differences in clinical features and outcome in patients with acute pancreatitis according to serum triglyceride levels on admission (within the first 48 h of admittance).

Patients and methods

A retrospective analysis was performed on all consecutive cases of acute pancreatitis admitted at the Hospital Clinic University of Valencia, a tertiary and academic center, over 2 time periods (the first from January 2002 to December 2011 and the second from January 2013 until March 2014). All patient data had been prospectively recorded in a database.

AP diagnosis was based on the presence of 2 of the following 3 criteria: 1) suggestive clinical symptoms, 2) increased blood amylase and/or lipase >3 times the upper normal level and 3) radiological alterations consistent with AP. Patients whose serum TG levels within the first 48 h of admittance were not available or those with a diagnosis of chronic pancreatitis were excluded from the study. All patients included were adults (≥18 years).

Etiology of AP was classified into: biliary, alcoholic, HTG-induced, mixed etiology (alcohol + HTG) and miscellaneous. A patient was diagnosed with HTG-induced AP when TG levels exceeded ≥1000 mg/dl and/or when latescent serum was detected in the emergency blood test, if no other obvious cause of AP was apparent. Patients with severe hypertriglyceridemia (≥1000 mg/dl) and alcohol abuse ≥ 60 g/day were identified as having mixed etiology (HTG + alcohol) as the cause of pancreatitis.

Patients were categorized into three groups based on serum TG levels measured within the first 48 h of admission (definition of severe HTG based on an intermediate cut-off point among the different criteria used to define severe HTG) [13,21,22]. 1) TG < 200 mg/dl (normal TG/mild HTG), 2) TG 200–749 mg/dl (moderate HTG), 3) TG ≥ 750 mg/dl (severe HTG).

Patients' demographic and clinical characteristics including age, sex, body mass index (BMI), alcohol consumption, presence of diabetes mellitus (DM) and comorbidities were collected. Comorbidity was calculated according to the Charlson index [23] by assigning a score of 1, 2, 3 or 6 to each disease depending on severity and risk of mortality. A patient was considered to have comorbidity if Charlson Index was ≥1 point. Alcohol consumption was quantified in grams of alcohol ingested per day (g/d) and divided into four categories: 1) none, when the patient never or occasionally drinks alcohol (no daily intake of alcohol); 2) light, for a daily or almost daily alcohol intake of <20 g/d; 3) moderate (20–60 g/d); 4) heavy (≥60 g/d).

The severity of AP was predicted by Ranson score [24], C-reactive protein (CRP) at 48–72 h of admission and Computed Tomography (CT) severity index [25], based on Balthazar grade (0–4 points) plus the extent of pancreatic necrosis (0–6 points) on a 10-point severity scale.

Pancreatic necrosis was defined as non-enhanced areas of the pancreas on an intravenous contrast CT performed at 72–96 h from admission. The degree of necrosis was quantified as comprising <30%, 30–50% or >50% of the total pancreatic parenchyma [24]. Acute pancreatic and/or peripancreatic collections (APC) were considered as the presence of Grades D or E in the Balthazar CT score [26].

Organ failure (OF) was defined according to the Atlanta classification [27]: respiratory insufficiency ($PaO2 \leq 60$ mm Hg), renal failure (creatinine of ≥2 mg/dl after rehydration) and shock (systolic blood pressure of less than 90 mm Hg). 'Multiple organ failure (MOF)' was defined as the presence of two or more organ failures. Duration of organ failure was measured and described according to the Revision of the Atlanta Classification as: 'transient organ failure' if the organ failure resolved within 48 h or as 'persistent organ failure' if it persisted for more than 48 h [28]. 'Any organ failure' included any type of.

Primary outcomes were measured by the differences in organ failure, pancreatic necrosis, acute collections, need for intensive care unit (ICU), length of hospital stay and in-hospital mortality, according to the TG level category within the first 48 h of admission. Demographic and clinical characteristics, comorbidity, severity indexes and the etiology of the AP were also analyzed according to TG levels, in order to assess differences between the groups and to identify confounding factors.

The hospital's institutional review board approved the study protocol, which conforms to the Declaration of Helsinki (6th revision, 2008). The study was approved by the hospital's medical ethic committee.

Statistical analysis

Results are presented as percentages or median and interquartile range (IR) in case of quantitative variables, because none of them followed a normal distribution pattern.

Categorical data were analyzed by χ^2 test and 2-tailed Fisher's exact probability test when more than 20% of expected values were less than 5. For continuous variables, non-parametric tests such as Kruskal-Wallis test were used, because normal distribution could not be assumed. Trend tests were performed to determine if there was a statistically significant trend between TG levels and AP outcome; linear-by linear association for categorical variables and the Jonckheere-Terpstra rank-based test for continuous variables.

Multivariate binary logistic regressions (Wald's test) were performed to evaluate the association between TG level and severity of AP. All variables considered were categorical with the exception of TG, which was analyzed as a quantitative variable evaluated in increments of 100 mg/dl for a more intuitive understanding. The models were adjusted for relevant risk factors for AP severity. *P*-value <0.05 was considered statistically significant. The strength of association was reported as odds ratios (OR) with 95% confidence interval (95% CI). The linear relationship between continuous predictor variables and the logit of the outcomes was verified by correlation analysis.

Results

Demographics and clinical features

During the study period, 1,565 cases of acute pancreatitis in

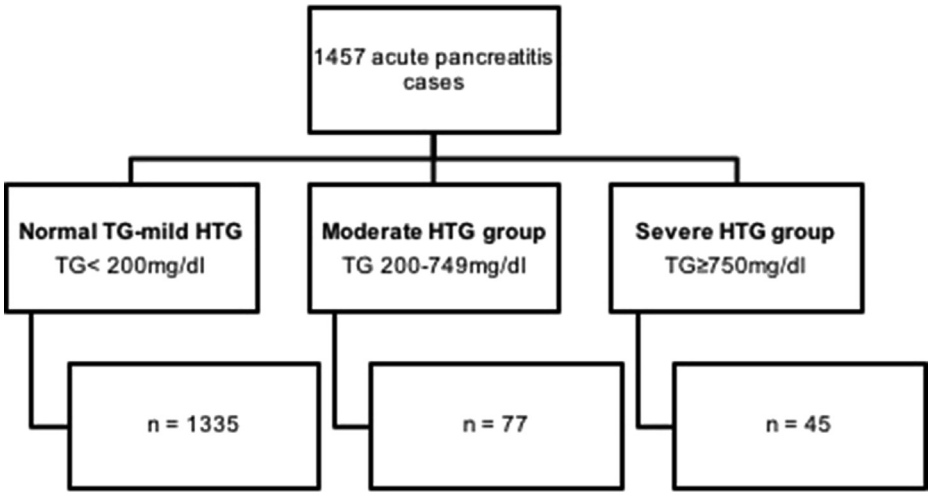

Fig. 1. Distribution of Acute pancreatitis patients in hypertriglyceridemia severity grades within 48 h of admission.

1,316 patients were admitted at the Hospital Clinic University of Valencia. One hundred and eight patients (6.9%) did not have serum TG levels measured within first 48 h of admission and were excluded. Of the 1,457 AP cases included, 1,335 (91.6%) were classified according to TG levels into normal TG-mild HTG group (TG < 200 mg/dl), 77 (5.28%) into the moderate HTG group (TG 200–749 mg/dl), and 45 (3.09%) into the severe HTG group (TG ≥ 750 mg/dl) (Fig. 1). Only 122 (8.37%) patients with AP had associated hypertriglyceridemia on admission (TG ≥ 200 mg/dl).

Study population characteristics are shown in Table 1. Male rates were higher as TG levels increased (47.2% vs. 66.2% vs. 82.2%, $p < 0.01$). A linear relationship between age and TG levels was observed: age decreased as TG increased, and patients were significantly younger in the severe HTG group ($p < 0.01$). Obesity (BMI ≥ 30) was more common in the groups with higher TG levels (29.3% vs. 37.5% vs. 37.2%), although there were not significant differences ($p = 0.093$). BMI data were unavailable for 265 patients (18.19%). The frequency of DM was greater in the moderate and severe HTG groups (28.6% and 20.0%) (p (trend) < 0.05). At baseline, there were no differences regarding comorbidities between the 3 groups (54.5% vs. 59.7% vs. 40.0%, $p = 0.26$). Furthermore, the frequency of moderate and severe alcohol intake increased linearly in relation to TG levels.

The distribution of acute pancreatitis etiologies was different in the three groups. In the group with TG < 200 mg/dl, the most common cause was gallstone-related (73.6%). In the group with TG 200–749 mg/dl, the frequency of alcoholic etiology (37.7%) was greater and biliary etiology was lower (41.6%) than in the previous group. Logically, HTG was the most frequent cause (93.3%) in the TG ≥ 750 mg/dl group, but alcohol intake is an associated etiological factor in almost half of the patients (46.6%). The overall prevalence of HTG-AP as a cause of AP was 2.95%, including patients with mixed etiology (alcohol + HTG) (Table 2).

Prognostic factors such as CRP and CT severity index were higher in moderate and severe HTG groups. Conversely, there were no differences in the Ranson score among the three groups (Table 2).

Outcomes

The evaluation of primary outcomes is shown in Table 3. While there was no significant trend between HTG groups and the frequency of persistent renal failure, a linear relationship and significantly higher percentages of any organ failure (11.2% vs.15.6% vs. 20.0%), persistent respiratory insufficiency (4.4% vs. 7.8% vs. 11.1%), persistent shock (2.1% vs. 3.9% vs. 6.7%) and persistent MOF (2.5% vs. 5.2% vs. 6.7%) were observed as TG levels at admission increased.

Local complications were assessed by contrast-enhanced CT performed on 1,223 (83.9%) patients. TG levels were positively associated with necrosis (9.2% vs. 14.3% vs. 26.7%), development of acute pancreatic or peripancreatic collections (21.6% vs. 40.3% vs. 55.6%) and need for ICU (3.6% vs. 6.5% vs. 15.6%). There were no significant differences between the three groups regarding mortality.

An analysis comparing patients with normal/mild HTG (<200 mg/dl) and patients with moderate/severe HTG (≥200 mg/

Table 1
Demographic and clinical data of acute pancreatitis patients according to the level of serum triglycerides within first 48 h of admission.

Variable	Normal/mild HTG[a] (TG < 200 mg/dl) n = 1335	Moderate HTG (TG 200–749 mg/dl) n = 77	Severe HTG (TG ≥ 750 mg/dl) n = 45	p
Sex (male)	630 (47.2%)	51 (66.2%)	37 (82.2%)	p < 0.01
Age in years (median and range)	68.0 (17–98)	49.9 (30–92)	41.9 (28–72)	p < 0.01
BMI[b] ≥ 30	320 (29.3%)	27 (37.5%)	16 (37.2%)	NS
Diabetes	203 (15.2%)	22 (28.6%)	9 (20.0%)	p < 0.05
Comorbidity	727 (54.5%)	46 (59.7%)	18 (40.0%)	NS
Alcohol consumption				p < 0.01
- None	1133 (84.9%)	40 (51,9%)	18 (40%)	
- Light (<20 g/d)	3 (0.2%)	0 (0%)	0 (0%)	
- Moderate (20–60 g/d)	62 (4.6%)	8 (10.4%)	6 (13.3%)	
- Heavy (≥60 g/d)	137 (10.3%)	29 (37.7%)	21 (46.7%)	

[a] HTG: hypertriglyceridemia.
[b] BMI: Body Mass Index.

Table 2
Etiology and prediction factors of severity in the series of patients with acute pancreatitis according to the level of serum triglycerides within first 48 h of admission.

Variable	Normal/mild HTG[a] (TG < 200 mg/dl) n = 1335	Moderate HTG (TG 200–749 mg/dl) n = 77	Severe HTG (TG ≥ 750 mg/dl) n = 45	p
Etiology				
- Biliary	983 (73.6%)	32 (41.6%)	1 (2.2%)	p < 0.01
- Alcohol	145 (10.9%)	29 (37.7%)	2 (4.4%)	
- HTG	0 (0%)	1 (1.3%)	23 (51.1%)	
- Alcohol + HTG	0 (0%)	0 (0%)	19 (42.2%)	
- Miscellaneous	207 (15.5%)	15 (19.5%)	0 (0%)	
CRP[b] 48 h (mg/L) (median and range)	83.4 (0–528)	159 (3.4–550)	155.7 (3.9–529.9)	p < 0.01
CT[c] severity index (median and range)	1 (0–10)	2 (0–10)	3 (0–10)	p < 0.01
Ranson score (median and range)	2 (0–8)	1 (0–8)	2 (0–6)	p > 0.05

[a] HTG: hypertriglyceridemia.
[b] CRP: C- Reactive Protein.
[c] CT: Computed Tomography.

Table 3
Outcome measures in acute pancreatitis patients according to the hypertriglyceridemia severity grades within first 48 h of admission.

Variable	Normal/mild HTG[a] (TG < 200 mg/dl) n = 1335	Moderate HTG (TG 200–749 mg/dl) n = 77	Severe HTG (TG ≥ 750 mg/dl) n = 45	p
Any Organ failure	150 (11.2%)	12 (15.6%)	9 (20.0%)	p < 0.05
Persistent renal failure	53 (4.0%)	7 (9.1%)	3 (6.7%)	NS
Persistent respiratory insufficiency	59 (4.4%)	6 (7.8%)	5 (11.1%)	p < 0.05
Persistent shock	28 (2.1%)	3 (3.9%)	3 (6.7%)	p < 0.05
Persistent MOF[b]	33 (2.5%)	4 (5.2%)	3 (6.7%)	p < 0.05
Necrosis	113 (9.1%)	11 (14.3%)	11 (24.4%)	p < 0.01
- <33%	70 (5.8%)	7 (9.1%)	6 (14.0%)	p < 0.01
- 33–50%	23 (1.8%)	3 (3.9%)	2 (4.7%)	
- >50%	20 (1.7%)	1 (1.3%)	3 (7%)	
Acute peripancreatic collections	239 (21.6%)	27 (40.3%)	25 (55.6%)	p < 0.01
ICU[c] admission	48 (3.6%)	5 (6.5%)	7 (15.6%)	p < 0.01
Mortality	32 (2.4%)	2 (2.6%)	3 (6.7%)	NS
Hospital stay in days (median and range)	5 (1–290)	5 (2–103)	7 (2–90)	p < 0.01

[a] HTG: hypertriglyceridemia.
[b] MOF: Multiple Organ failure.
[c] ICU: Intensive Care Unit.

dl) was performed. Results regarding demographic, clinical data, etiology, prediction factors of severity and outcomes were similar to those achieved when patients were categorized in three HTG groups (Table 4).

Multivariate analysis, adjusting for variables which could determine the severity of the acute pancreatitis such as advanced age (≥70 years), body mass index ≥30 (class I obesity), diabetic status, comorbidity and alcohol etiology, showed that TG as a quantitative variable, evaluated in increments of 100 mg/dl, was independently associated with any organ failure (OR: 1.05, 95%CI: 1.01–1.09), persistent renal failure (OR: 1.06, 95%CI: 1.01–1.12), persistent shock (OR: 1.07, 95%CI: 1.01–1.13), persistent MOF (OR: 1.06, 95%CI: 1.00–1.12), necrosis (OR: 1.04, 95%CI: 1.01–1.08), development of acute peripancreatic collections (OR: 1.05, 95%CI: 1.02–1.10), ICU admission (OR: 1.06, 95%CI: 1.02–1.11), and mortality (OR: 1.11, 95% CI:1.04–1.18) (Table 5).

Discussion

Several experimental and clinical studies support the concept that HTG can cause AP. However, existing data on the association between HTG and the severity of acute pancreatitis are heterogeneous, due to the different cut-off values used and small sample size in some studies. While some series [15–19,29–32] report that HTG-AP has a more severe disease course, there are others that have not shown any significant relationship between the level of serum TG and the clinical course of AP [4,11,12,20].

In this report, we study a large series of all cases of acute pancreatitis consecutively admitted in a tertiary center during a 11 year 3 month period, with the main goal of determining the effect of serum TG levels on the clinical features and outcomes of AP. Patients were classified into 3 different groups based on serum TG levels within the first 48 h from admission. For the multivariate regression analysis, TG was analyzed as a quantitative variable evaluated in increments of 100 mg/dl.

We found it striking that in our series the patients with severe HTG were predominantly male and younger. Diabetes, a secondary factor for HTG, was more frequent in moderate and severe HTG groups (p trend <0.05). Obesity was more frequent in moderate and severe HTG groups, but this difference did not reach statistical significance. In a study conducted in the United States [17], the authors also reported higher percentages of obesity in AP patients with HTG than in normal TGs ones; however, the percentage of subjects with BMI ≥ 30 (43.8%) was higher than in our series (30%); in contrast, in a Japanese study [29], the rate of obesity was much lower (4.8%). Patient characteristics differed between our study and other studies, probably due to differences in the population and the study design. It is noteworthy in our series that the frequency of heavy alcohol intake increased with greater TG levels, as also reported by Hamada el al [29]. In our study, 46.7% of patients with severe HTG had heavy alcohol consumption; therefore, alcohol is the main secondary etiologic factor for HTG in our patients.

Moreover, the prevalence of HTG-AP in our series as a cause of AP was 2.95%, including patients with mixed etiology

Table 4
Demographic, clinical data, etiology, prediction factors of severity and outcomes in acute pancreatitis, comparing patients with normal/mild HTG and patients with moderate/severe HTG within first 48 h of admission.

Variable	Normal/mild HTG [a] (TG < 200 mg/dl) n = 1335	Moderate/severe HTG[a] (TG ≥ 200 mg/dl) n = 122	OR[b]	95% CI[c]	p
Sex (male)	630 (47.2%)	88 (72.1%)	2.90	1.92 −4.37	p < 0.01
Age in years (median and range)	68.0 (17–98)	47 (28–92)	0.96	0.95 −0.97	p < 0.01
BMI[d] ≥ 30	320 (29.3%)	43 (37.4%)	1.44	0.97 −2.15	NS
Comorbidity	727 (54.5%)	64 (52.5%)	0.92	0.64 −1.34	NS
Moderate-heavy alcohol consumption (≥20 g/d)	199 (14.9%)	64 (52.5%)	6.33	4.28 −9.23	p < 0.01
Etiology					p < 0.01
- Biliary	938 (73.6%)	33 (27%)			
- Alcohol	145 (10.9%)	31 (25.4%)			
- HTG	0 (0%)	24 (19.7%)			
- Alcohol + HTG	0 (0%)	19 (15.6%)			
- Miscellaneous	207 (15.5%)	15 (12.3%)			
CRP[e] 48 h (mg/L) (median and range)	83.4 (0–528)	157.35 (3.4–550)	1.01	1.00 −1.01	p < 0.01
Persistent renal failure	53 (4.0%)	10 (8.2%)	2.16	1.07 −4.36	p < 0.05
Persistent respiratory insufficiency	59 (4.4%)	11 (9.0%)	2.14	1.09 −4.18	p < 0.05
Persistent shock	28 (2.1%)	6 (4.9%)	2.41	0.98 −5.94	p < 0.05
Necrosis	113 (9.1%)	22 (18.0%)	2.19	1.32 −3.62	p < 0.01
Acute peripancreatic collections	239 (21.6%)	52 (46.4%)	2.13	1.39 −3.25	p < 0.01
ICU[f] admission	48 (3.6%)	12 (9.8%)	2.93	1.51 −5.67	p < 0.01
Mortality	32 (2.4%)	5 (4.1%)	1.74	0.67 −4.55	NS

[a] HTG: hypertriglyceridemia.
[b] OR: odds ratio.
[c] 95% CI: 95% confidence interval.
[d] BMI: Body Mass Index.
[e] CRP: C- Reactive Protein.
[f] ICU: Intensive Care Unit.

Table 5
Multivariate binary regressions in acute pancreatitis patients showing association between TG levels on admission (evaluated in increments of 100 mg/dl) and necrosis, acute peripancreatic collections, organ failure and mortality.

Necrosis			**Acute peripancreatic collections**		
Variables	**OR (95%CI)**	**p**	**Variables**	**OR (95%CI)**	**p**
Age > 70 years	0.79 (0.49, 1.26)	0.32	Age > 70 years	0.81 (0.56, 1.17)	0.81
BMI [a] > 30	0.71 (0.44, 1.14)	0.15	BMI[a] > 30	0.91 (0.64, 1.28)	0.58
Comorbidity	1.11 (0.70, 1.74)	1.11	Comorbidity	0.78 (0.55, 1.12)	0.18
TG [b]	1.04 (1.01, 1.08)	0.02	TG [b]	1.05 (1.02, 1.10)	0.00
Alcohol etiology	1.77 (1.07, 2.93)	0.03	Alcohol etiology	3.11 (2.11, 4.58)	0.00
Diabetes	0.99 (0.55, 1.82)	1.00	Diabetes	0.91 (0.56, 1.50)	0.71
		p 0.00[c] [aa]cp0.00			*p 0.00*[c]
Any organ failure			**Mortality**		
Variables	**OR (95%CI)**	**p**	**Variables**	**OR (95%CI)**	**p**
Age > 70 years	3.60 (2.27, 5.68)	0.00	Age > 70 years	14.56 (3.07, 69.03)	0.00
BMI [a] > 30	1.22 (0.81, 1.83)	0.34	BMI[a] > 30	3.02 (1.17, 7.84)	0.02
Comorbidity	1.54 (0.98, 2.41)	0.06	Comorbidity	1.38 (0.47, 4.10)	0.56
TG [b]	1.05 (1.01, 1.09)	0.01	TG [b]	1.11 (1.04, 1.18)	0.00
Alcohol etiology	2.29 (1.25, 4.20)	0.01	Alcohol etiology	6.93 (1.44, 33.37)	0.02
Diabetes	1.03 (0.63, 1.69)	0.91	Diabetes	0.83 (0.25, 2.75)	0.76
		p 0.00[c]			*p 0.00*[c]

[a] BMI: Body Mass Index.
[b] TG levels evaluated in increments of 100 mg/dl.
[c] p value of correlation analysis to verify logit linearity.

(alcohol + HTG). This figure is similar to the prevalence of HTG-AP in other reports (2–4%) [14], although in other studies it ranges from 2 to 26%, reflecting diversity among published reports [9–11,17,19,33].

According to some series [11,12,33] a mild to moderate increase in triglyceride levels can be present in up to one third of all cases of AP, which have lent credence to the concept that HTG can be secondary to AP. The prevalence of HTG (TG ≥ 200 mg/dl) among all AP cases in our series was 8.37%. This is much lower than the frequency in the above-cited studies; nevertheless, we must take into account the high prevalence of alcoholic pancreatitis in these series, which could justify the greater prevalence of HTG. The frequency of mild to moderate HTG in our study is no greater than HTG prevalence in the general population (8%–31%) [34,35]. Therefore, according to our results, it seems unlikely that HTG could be secondary to AP.

Although data from some studies support that HTG has no significant correlation with severity of AP [4,11,20], others report that HTG is associated with systemic complications [15–19,29,32,36,37]. The results of the current study show that HTG is independently associated with any organ failure with a 5% increased risk for each 100 mg/dl rise in TG levels, persistent renal failure (6% increased risk for each 100 mg/dl), persistent shock (7% increased risk), and persistent multiorgan failure (6% increased risk).

Nawaz et al. reported that the frequency of persistent organ failure was higher in patients with greater TG levels [17]. The rate of persistent organ failure (40%/17% of patients with HTG/normal TG) was greater than in our study (11.48%/7.1%); it must be taken into account that the population in the study of Nawaz et al. was different, with around half of the enrolled patients transferred from other centers. Cheng et al. [33] also reported that TG elevation at the early stage of acute biliary pancreatitis was associated to higher risk of respiratory failure. Hamada et al. [29] showed that subjects with HTG ≥ 200 mg/dl were at significantly higher risk for renal failure, but did not find significant differences for persistent organ failure, shock and respiratory insufficiency. A recent Hungarian meta-analysis [32] investigated the effect of different TG levels on AP outcome. The authors found that HTG increased the risk of systemic and local complications, but an increase in serum TG up to 5.6 mM was not significantly associated with severity of AP.

Controversial results have been reported on the relationship between HTG and local complications in AP. The study of Nawaz et al. [17] did not show any significant association between HTG and pancreatic necrosis. Zhang et al. [18] did not find differences in local complications between HTG-AP and other etiologies. However, significantly higher incidence of local complications in HTG groups has been shown in other reports [15,32]. Nevertheless, the existing data are diverse and heterogeneous, and in some studies CT scores were not applied. The strength of the present study lies in the long series of consecutive AP cases included, with CT performed in most patients. In our study, it seems clear that the rate of pancreatic necrosis (9.1% in normal-mild HTG/14.3% in moderate HTG/24.4% in severe HTG) and acute pancreatic or peripancreatic collections (21.6%/40.3%/55.6%) increases proportionally and significantly with HTG severity grades.

The exact pathophysiological function of HTG in the development of AP and its influence on AP outcomes are not clearly defined. However, the most accepted hypothesis is that the excess TG is hydrolyzed by pancreatic lipase causing accumulation of high amounts of free fatty acids. According to some experimental studies [38–40], lipotoxicity mediated by free fatty acids in acute pancreatitis could explain the worse outcomes in patients with severe HTG and/or visceral obesity.

This study has several potential limitations. First, this is a single-center study, with a long data collection period (eleven years and three months). During this time, some changes in AP management have been introduced, such as a more conservative approach to infected pancreatic necrosis. Furthermore, there has been a change in the definition of local complications; the Revision of the Atlanta Classification of AP (2012) makes an important distinction between collections composed of fluid alone and ones with a solid component arising from necrosis. Likewise, computed tomography technology and images have improved over the years. We have defined the presence of acute peripancreatic collections when classified as Grade D or E in the Balthazar CT score, without differentiating if they were liquid or necrotic, because of the great difficulty of re-evaluating CTs performed over the 11 years (less accurate images in the first years of the series). Second, TG levels were determined within first 48 h of admission and these levels can decrease considerably after a few hours of fasting.

Summarizing, this paper studies a large series of AP cases and confirms that elevated TG levels are independently associated with a more severe course of acute pancreatitis. TG levels are positively associated with any organ failure, persistent renal failure, persistent shock, persistent MOF, necrosis, development of acute collections, ICU admission and mortality. It must be highlighted the elevated frequency of local complications in patients with HTG that increases proportionally and significantly with HTG severity grades. Further studies are needed to confirm the action mechanism of TG in AP, with the aim of developing new therapies for the severe forms of AP associated with HTG.

Disclosures

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