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Association of serum triglyceride levels with severity in acute pancreatitis: results from an international, multicenter cohort study

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Short Title: Hypertriglyceridemia and severity of acute pancreatitis

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Abstract

Background: Hypertriglyceridemia (HTG) is considered within the top 5 etiologies in acute pancreatitis (AP), but the association of serum triglyceride (TG) levels with the clinical course of AP remains controversial.
Objectives: This study aims to examine the effect of triglyceride levels on severity of AP.
Methods: Patients were enrolled prospectively through APPRENTICE. High triglyceride levels were defined based on the Endocrine Society Clinical Practice Guidelines. Hypertriglyceridemia (HTG) was categorized as mild (serum TG levels 150-199 mg/dl), moderate (200-999 mg/dl), severe (1,000-1,999 mg/dl), and very severe (≥2,000 mg/dl). Severity of AP was based on the Revised Atlanta Classification criteria.
Results: TG levels were measured in 764 subjects and found elevated in 342 (120 with mild, 176 moderate, 46 severe/very severe HTG). Patients with increased TG levels were younger (age ≥60, 16.7% vs. 30.3%), more likely to be male (66.1% vs. 51.2%), with more frequent alcohol use (62.8% vs. 50.7%), and diabetes mellitus (30.2% vs. 12.3%; all $p \leq 0.005$). Severe AP (24.9% vs. 10.0%), ICU admission (32.5% vs. 19.7%), and mortality (5.3% vs 1.7%; all $p \leq 0.005$) were more frequently seen in patients with elevated TG levels. Based on multivariable analysis, elevated TG levels were independently associated with severe AP ($p < 0.05$) with the association being proportional.
Conclusion: This large multicenter study confirms that elevated TG levels are associated with severe disease regardless of AP etiology.

Introduction

Hypertriglyceridemia (HTG) is a common cause of acute pancreatitis (AP), accounting for 1-10% of all cases (1). Elevated triglyceride (TG) levels can be found in different etiologies, showing that they can either be a risk for or an epiphenomenon of AP. Conflicting findings have been reported regarding the association of TG levels and severity of AP. Some studies reported similar clinical outcomes (2), while others showed a more severe clinical course of AP in patients with high TG levels (3). Most studies, though, reported retrospective data, deriving from a single-center health care setting. We aim to evaluate the effect of triglyceride levels on severity of AP in a large, prospective, multicenter cohort.

Methodology

Acute pancreatitis patient registry to examine novel therapies in clinical experience (APPRENTICE) is an international, multicenter consortium focusing on prospective enrollment of acute pancreatitis (AP) patients (4). We collected the data on AP patients at 22 international centers, 8 from the US, 6 from Europe, 5 from Latin America, and 3 from India. Subjects were enrolled between October 2015 and January 2018. The study protocol was approved by the Institutional Review Board or Ethics Committee at each participating study site of APPRENTICE. University of Pittsburgh's IRB approved the study and acted as an umbrella IRB for all centers (IRB# PRO15040389/Approval date: 07/14/2015). A written, informed consent was obtained from all enrolled subjects.

High triglyceride levels were defined based on the Endocrine Society Clinical Practice Guidelines (5). Hypertriglyceridemia (HTG) was categorized as mild (serum TG levels 150-199 mg/dl), moderate (200-999 mg/dl), severe (1,000-1,999 mg/dl), and very severe (≥2,000 mg/dl). TG levels were measured within 48 hours of admission. Revised Atlanta Classification was used to define severity, distributing AP patients in 3 categories: mild, moderately severe, and severe (6). The etiology of AP was assigned by the treating physician at each participating site. Biliary etiology was defined by the presence of cholelithiasis (stones/sludge in gallbladder) and/or choledocholithiasis (stones/sludge in common bile duct) on imaging (right upper quadrant ultrasound, computerized tomography scan or magnetic resonance imaging) and/or elevated hepatic injury tests (and/or bilirubin). Alcoholic etiology was based on the assessment of the treating physician and required history

of heavy alcohol consumption. Active alcohol use was based on active consumption within past 6 months before hospitalization. This included any alcohol use within this time period and did not take into consideration the amount of alcohol consumed. Thus, active alcohol use was not equivalent to alcoholic etiology. Active alcohol use was divided into 2 subgroups, one was termed as 'mild alcohol use', and the other one was termed as 'moderate/heavy alcohol use' (7). Subjects with ≤ 1 average drink per day were included in the 'mild alcohol use' subgroup, while subjects with >1 average drink per day were included in the 'moderate/heavy alcohol use subgroup'.

Pearson chi-square test was used for categorical variables, while t-test or rank sum test were used for continuous variables as appropriate. P-value was considered statistically significant when < 0.05.

Results

Out of 1,347 AP patients enrolled, early TG levels within 48 hours were measured in 764 subjects. Of those, 342 subjects had HTG: 120 mild, 176 moderate, and 46 patients with severe/critical HTG. Patients with HTG (**table 1**) were more likely to be younger (age ≥60, 16.7% vs. 30.3%), male (66.1% vs. 51.2%), and have a non-biliary etiology of AP (69.6% vs. 46.7%; all p<0.001), or alcoholic etiology of AP (34.5% vs. 24.8%; p=0.038). Also, subjects with elevated TG levels were more likely to be diabetic (30.2% vs. 12.3%), have active alcohol use (62.8% vs. 50.7%), and be enrolled during a recurrent episode of AP (26.9% vs. 20.4%; all p≤0.03). HTG subjects did not have a significant difference in terms of mild vs. moderate/heavy alcohol use (58.3% vs. 66.1%; p=0.175). In terms of clinical outcomes, there was a positive correlation between HTG and severe AP (24.9% vs. 10.0%). ICU admission (32.5% vs. 19.7%) and mortality (5.3% vs. 1.7%; all p≤0.005) were seen more frequently in HTG patients. The median hours from pain onset to admission were 15 hours for subjects with normal triglyceride levels, and 10 hours for subjects with high triglyceride levels.

A proportional correlation was noted between TG levels and younger age, alcohol use, diabetes, recurrent AP, and non-biliary etiology of AP (all p≤0.002; **table 2**).
A multivariable logistic regression analysis with severe AP as the outcome, adjusting for age, gender, race, BMI, alcohol use, diabetes and etiology showed that TG levels defined according to the Endocrine Society Clinical Practice Guidelines were independently correlated with severe AP (**table 3**).

Subjects with early triglyceride measurement were more likely to develop severe AP (16.6% vs 5%; p<0.001) and require ICU admission (25.4% vs 7.6%; p<0.001) compared to the subjects with no early triglyceride measurement. On the other hand, mortality was not significantly different between the 2 groups (3.3% vs 1.7%; p=0.075).

Discussion

This study confirms that elevated TG levels are independently and proportionally associated with severe AP. High TG levels measured early in the course of AP are associated with worse clinical outcomes regardless of disease etiology, and this effect appears to be dose dependent (the higher the TG levels, the higher the risk of organ failure). Excess amount of free fatty acids, produced by the breakdown of TG from lipase, leads to damage of the pancreatic gland through multiple mechanisms, including direct injury (lipotoxicity), inflammatory response, and ischemia (8). However, these differences in clinical outcomes, including mortality, should be interpreted with caution, given that treatment of AP may vary among different centers.

Interestingly, a recent study conducted from our consortium that focused on HTG as the primary etiology of AP, rather than the effect of TG levels on all causes of AP, did not show a significant association with AP severity compared to other etiologies (9). This finding supports the notion of assessing elevated TG levels as a dose-dependent risk factor rather than a primary AP etiology using a certain cut-off of 500 or 1000 mg/dl.

It must be noted that TG levels were measured only in a subgroup of AP patients, based on the clinical judgement of treating physicians, which likely limits the generalizability of our results. TG levels are not routinely measured in all patients with AP around the world. The decision for measuring TG levels in this study was based on the clinical judgement of the treating physicians. TG levels were more likely to be measured in subjects without a clear AP etiology identified during the initial evaluation. Our findings suggest that AP patients with measured TG levels had a more complicated clinical course compared to those without available TG levels.

Nonetheless, our analysis includes a large number of patients derived from different sites around the world. HTG patients were also found to have distinct baseline characteristics, including younger age, male gender, diabetes, and active alcohol use. TG levels were found to be independently and proportionally related to severe AP. Additional research work is

needed on the pathogenic role of high triglycerides and free fatty acids in AP progression, as well as designing clinical trials on the effect of lowering high TG levels in AP patients.

Acknowledgement

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Statement of Ethics

The study protocol conforms to the ethical guidelines of the World Medical Association Declaration of Helsinki. The study protocol was approved by the Institutional Review Board or Ethics Committee at each participating study site of APPRENTICE. University of Pittsburgh's IRB approved the study and acted as an umbrella IRB for all centers (IRB# PRO15040389/Approval date: 07/14/2015). A written, informed consent was obtained from all enrolled subjects.

Disclosure Statement

No conflicts of interest to declare.

No funding was required for this study.

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