

HYPERTRIGLYCERIDEMIA AND ACUTE PANCREATITIS

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Abstract

Background: Acute pancreatitis (AP) is an acute inflammatory process of the pancreas characterized by severe abdominal pain and elevated pancreatic enzymes. Acute pancreatitis is a common disease with significant associated morbidity and mortality. Patients with Hypertriglyceridemia are prone for recurrent episodes of pancreatitis. This study aims to assess the effect of elevated serum triglyceride (TG) levels on serum amylase and lipase levels. **Objectives:** 1. Establish correlation between triglyceride levels and amylase and lipase levels in all patients. 2. To find the association between mild to moderate elevation in triglyceride levels with acute pancreatitis. **Materials and Methods:** This study included 419 patients over a period of three months. Estimation of Fasting lipid profile, amylase and lipase was done in both groups. The patients were divided into 2 groups depending on their triglyceride levels. Group 1 containing patients with normal triglyceride level (<150mg/dl) and group 2 containing patients with hypertriglyceridemia (> 150mg/dl). **Results:** Mann Whitney U statistical test was applied which showed significant difference between 2 groups for Amylase (p value < 0.001) and lipase (p value < 0.001) levels. In patients with triglyceride levels between 151mg/dl to 500mg/dl, 22.5% of patients showed raised amylase levels, 26% patients showed raised lipase levels. Therefore, mild to moderate levels of hypertriglyceridemia can be considered as risk factor for development of pancreatitis. **Conclusion:** Even mild to moderate level of hypertriglyceridemia can lead to acute pancreatitis. Serum Triglyceride estimation is an easily available and affordable parameter. Early recognition of hypertriglyceridemia and its prompt treatment is essential in both the initial and long-term management of pancreatitis and are essential to prevent recurrent acute pancreatitis.

INTRODUCTION

Acute pancreatitis (AP) is an acute inflammatory process of the pancreas characterized by severe abdominal pain and elevated pancreatic enzymes. Recent U.S. estimates from the Nationwide Inpatient Sample report that acute pancreatitis is the most common inpatient principal gastrointestinal diagnosis(1). The incidence of acute pancreatitis also varies in different countries and depends on cause (e.g., alcohol, gallstones, metabolic factors like Hypertriglyceridemia, hypercalcemia; Endoscopic retrograde cholangiopancreatography (ERCP); drugs like azathioprine, 6-mercaptopurine, sulfonamides, estrogens, tetracycline, valproic acid, anti-HIV medications, 5-aminosalicylic acid; Trauma (especially blunt abdominal trauma); Postoperative (abdominal and nonabdominal operations)). The annual incidence ranges from 13 to 45 cases per

100,000 persons(1). Acute pancreatitis results in >250,000 hospitalizations per year(1).

Despite the exponential growth of medical knowledge and more effective treatments, pancreatic diseases remain poorly understood, costly, and difficult to manage(2). Acute pancreatitis is a common disease with significant associated morbidity and mortality. There is now an increasing evidence that suggests patients with just one episode of acute pancreatitis have a high risk of developing diabetes mellitus and chronic pancreatitis(3)(4).

Gallstones and alcohol are main two causes of acute pancreatitis. Hypertriglyceridemia is third common cause of acute pancreatitis(1). Hypertriglyceridemia (HTG) is defined as fasting serum triglyceride levels above 150 mg/dL. Patients with HTG are prone for recurrent episodes of pancreatitis(1). Any factor (e.g., drugs or alcohol) that causes an abrupt increase in serum triglycerides can precipitate a bout of acute pancreatitis(1).

This study aims to assess the effect of elevated serum triglyceride (TG) levels on serum amylase and lipase levels. As many studies show association between HTG and AP, objective of my study was to find the association between mild to moderate elevation in triglyceride levels with acute pancreatitis.

MATERIALS AND METHODS

This cross-sectional study included total 429 Adult male and female patients were enrolled over span of 3 months after taking informed consent. Blood collection was done after 12 hours of fasting and were analyzed for serum fasting lipid profile, serum amylase and lipase levels analyzed with fully automated clinical chemistry analyzer - Beckman coulter Au5800.

The patients were divided into 2 groups depending on their serum triglyceride levels.

Group 1 with serum triglyceride levels < 150mg/dl included 228 patients.

Group 2 with serum triglyceride levels > 150mg/dl included 191 patients.

Serum Amylase and Lipase levels were compared in both groups.

RESULTS

Kolmogorov-Smirnov Test was applied which showed non parametric distribution.

Mann Whitney U statistical test was applied which showed significant difference between both groups for Amylase and lipase levels. Therefore, hypertriglyceridemia can be considered as risk factor for development of acute pancreatitis.

Table 1: Showing Mean ± SD Value of Group 1 And 2 And P Value

	GROUP 1 (TG < 150mg/dl) (MEAN ± SD)	GROUP 2 (TG > 150mg/dl) (MEAN ± SD)	P VALUE
AMYLASE	54.13 ± 20.65 U/L	95.39 ± 116.94 U/L	< 0.001
LIPASE	27.37 ± 18.19 U/L	121.49 ± 356.66 U/L	< 0.001
SAMPLE SIZE	228	191	

Group 2 is further divided into 4 subgroups depending on their triglyceride levels according to NCEP ATP III guidelines:

Group 2(a) with TG level 150-199 mg/dL had 81 patients

Group 2(b) with TG level 200-499 mg/dL included 97 patients.

Group 2(c) with TG level 500-1000 mg/dl included 9 patients.

Group 2(d) with TG level >1000 mg/dl included 4 patients

Table 2: Showing Percentage of Patients in Each Subgroup with High Amylase (>103U/L) and Lipase (>82U/L) Levels

GROUP	TRIGLYCERIDE	AMYLASE	LIPASE
2a	150-199 mg/dl (81 patients)	23%	28%
2b	200- 499 mg/dl (97 patients)	22%	24%
2c	500-1000 mg/dl (9 patients)	11%	11%
2d	>1000 mg/dl (4 patients)	25%	25%

DISCUSSION

Hypertriglyceridemia (HTG) is third common cause of acute pancreatitis.^[1] The cause of hypertriglyceridemia can be underlying disorder of lipoprotein metabolism or the presence of a secondary condition such as uncontrolled diabetes, alcohol abuse, or medication use. HTG is defined as triglyceride levels > 150mg/dl (NCEP ATP III). Genetic causes include syndromes that present primarily with HTG (common) or chylomicronemia (rare). Familial hypertriglyceridemia (excess Very Low-Density Lipoprotein but normal cholesterol) and Familial combined hyperlipidemia (polymorphisms of apolipoprotein C-II (apoC-II), apolipoprotein C-III (apoC-III), etc.) present predominantly with HTG.^[5] Lipoprotein lipase deficiency, Apolipoprotein C-II deficiency, Apolipoprotein AV deficiency, and dysbetalipoproteinemia are examples of genetic syndromes that present with chylomicronemia.^[5] According to National Cholesterol Education

Program Adult Treatment Panel III (NCEP ATP III) guidelines, HTG is classified into mild: TG level 150-199 mg/dL, high: TG 200-499 mg/dL and very high: TG > 500 mg/dl.^[5]

Secondary causes of HTG include certain medical conditions, drugs, and dietary causes. Obesity, metabolic syndrome, Diabetes mellitus type 2, hypothyroidism, Cushing's syndrome, chronic kidney disease, Human Immunodeficiency virus, pregnancy, and some autoimmune conditions such as systemic lupus erythematosus have been associated with HTG.^[5] Medications that cause HTG include thiazides, beta-blockers, oral estrogens, tamoxifen, OCPs, anti-retroviral protease inhibitors, atypical antipsychotics, isotretinoin, corticosteroids, bile acid-binding resins, and immunosuppressive agents such as sirolimus.^[5] Dietary causes of HTG include excessive alcohol intake and foods rich in saturated fat or with a high glycemic index.^[5]

The pancreas secretes 1500–3000 mL of isosmotic alkaline (pH >8) fluid per day containing about 20 enzymes. The acinar cell is highly

compartmentalized and is concerned with the secretion of pancreatic enzymes. The pancreas secretes amylolytic, lipolytic, and proteolytic enzymes into the duct lumen.^[1]

Autodigestion of the pancreas is prevented by i) the packaging of pancreatic proteases in precursor (proenzyme) form, ii) intracellular calcium homeostasis (low intracellular calcium in the cytosol of the acinar cell promotes the destruction of spontaneously activated trypsin), iii) acid-base balance, and iv) the synthesis of protective protease inhibitors (pancreatic secretory trypsin inhibitor [PSTI] or SPINK1), which can bind and inactivate about 20% of intracellular trypsin activity. Chymotrypsin C can also lyse and inactivate trypsin. These protease inhibitors are found in the acinar cell, the pancreatic secretions, and the $\alpha 1$ - and $\alpha 2$ - globulin fractions of plasma. Loss of any of these four protective mechanisms leads to premature enzyme activation, autodigestion, and acute pancreatitis.^[1]

Acute pancreatitis (AP) is a potentially life threatening acute inflammatory condition of the pancreas with a worldwide rising incidence.^[6] Though most cases are rather mild, there is a subset of patients with severe pancreatitis where mortality may reach up to 30%.^[7] To determine the etiology of acute pancreatitis is crucial to the management of this potentially fatal condition.

The most common etiology of acute pancreatitis is gallstone disease and alcohol.^[8] However, hypertriglyceridemia (HTG) is a well-known cause of AP and hypertriglyceridemia-induced acute pancreatitis (HTG-AP) is not a rare condition. In series of cases with AP, HTG was considered causative of the attack ranging from 1% up to 10% (8–14). Some studies on gestational pancreatitis even report HTG as the underlying cause in more than half of all cases.^[15]

The pathophysiology of HTGP is associated with accumulation of free fatty acids (FFA) and activation of the inflammatory response. Triglycerides are not inherently toxic to the pancreas, but it is the breakdown of triglycerides into FFAs by pancreatic lipase that causes lipotoxicity.^[16] The severity of pancreatitis is dependent on the severity of the inflammatory response and the injury caused by lipotoxicity.^[16]

Excess triglycerides are hydrolyzed by lipase from pancreatic acinar cells to produce FFAs. These high concentrations of FFAs trigger an inflammatory reaction, releasing intracellular calcium and causing acinar necrosis. High levels of FFAs aggregate into micelles with detergent-like properties, causing ischemia, triggering acidosis, activating trypsinogen to form active trypsin resulting in pancreatic autodigestion.^[17] FFAs have a direct cytotoxic effect on acinar and vascular endothelial cells.^[16]

FFAs also increase inflammatory mediators such as TNF-alpha, interleukin-6, and interleukin-10 and these inflammatory cytokines play an important role in HTGP. Plasmapheresis used in the treatment of

HTGP has been shown to reduce the levels of these proinflammatory factors.^[16]

Disturbances of pancreatic microcirculation also factor in the pathogenesis of HTGP. HTG leads to the release of a large number of vasoconstrictor thromboxane A2 and reduced secretion of the vasodilator prostaglandin 2. This imbalance results in excess contraction of capillary beds and aggravation of pancreatic microcirculation.^[16]

Additionally, there may be specific genes associated with HTGP. Chang et al performed genetic analysis of 126 patients with HTG in whom 46 had HTGP. They found that the CFTR gene mutation rate was 26.1% in those with HTGP, and only 1.3% in those without HTGP. This suggests that there may be a polygenic component to the development of HTGP.^[18]

Even modest elevations in baseline triglyceride levels were associated with an increased risk of AP. My study correlated with these findings. In my study, patients with group 2a and 2b with serum triglyceride level < 500mg/dl (151 - 500mg/dl), 22.5% of patients showed raised amylase levels, 26% patients showed raised lipase levels. Wu et al showed in 151 patients with a first baseline outpatient serum triglyceride level \geq 500 mg/dL that 29.8% had at least 1 recurrence and 16.6% of patients had multiple episodes of recurrent acute pancreatitis. This association held at both moderately elevated triglyceride levels (201 – 500 mg/dL) and highly elevated levels (> 500 mg/dL), with a 5-fold and 8-fold increase of readmission for AP, respectively.^[19] In my study, in group 2c i.e. patients with triglyceride levels between 500 – 1000 mg/dl, only 11% patients showed raised amylase and lipase levels, this does not correlate with above study may be due to less number of patients in the group. In group 2d i.e. patients with triglyceride level above 1000mg/dl, 25% showed raise in serum amylase and lipase which correlates with this study.

A French cohort study showed that the severity of HTG-AP was higher than that of AP induced by gallstones or alcohol. Severe pancreatitis (defined as: need for intensive care, C - reactive protein > 150 mg/L, or Balthazar score > C) was observed in 71.5% of the HTG-AP study collective.^[20]

The natural history of HTGP has also been shown to lead to chronic pancreatitis. In a cohort study of 121 patients with HTGP, Vippera et al showed that chronic pancreatitis was noted in 16.5% of patients with new onset of chronic pancreatitis in 9%.^[21]

Once the HTG-AP attack has been resolved, prevention of a next episode is compulsory. Lifestyle changes and dietary modifications are the key features in long-term management of HTG.^[17]

The results of systematic review and meta-analysis done by Sankaran et al have indicated that 10% of patients with their first episode of AP and 36% with RAP transition to CP. The risk of transition to CP is greater in patients who smoke, have a high alcohol intake, and are male.^[4]

A systematic review and meta-analysis done by Stephanie L M Das et al.^[3] A total of 24 prospective clinical studies, involving 1102 patients with first episode of AP, met all the eligibility criteria. Prediabetes and/or DM was observed in 37% (95% CI 30% to 45%) individuals after AP. The pooled prevalence of prediabetes, DM and treatment with insulin after AP was 16% (95% CI 9% to 24%), 23% (95% CI 16% to 31%), and 15% (95% CI 9% to 21%), respectively. Newly diagnosed DM developed in 15% of individuals within 12 months after first episode of AP and the risk increased significantly at 5 years (relative risk 2.7 (95% CI 1.9 to 3.8)). A similar trend was observed regarding treatment with insulin. The severity of AP, its etiology, individuals' age and gender had minimal effect on the studied outcomes.

Generally, serum triglyceride levels >1000 mg/dL are considered responsible for acute pancreatitis.^[1] But, in my study it is evident that even with mild to moderate levels of hypertriglyceridemia, there is a chance of developing acute pancreatitis. Therefore, hypertriglyceridemia should be detected and treated promptly to decrease the incidence and recurrence of acute pancreatitis which may ultimately lead to chronic pancreatitis and diabetes mellitus.

CONCLUSION

Acute pancreatitis is an acute emergency. Hypertriglyceridemia is third common cause of acute pancreatitis. Even mild to moderate level of hypertriglyceridemia can lead to acute pancreatitis. Recurrent episodes of acute pancreatitis may lead to development of chronic pancreatitis, ultimately leading to development of insulin resistance and diabetes mellitus. Serum Triglyceride estimation is an easily available and affordable parameter. Hypertriglyceridemia can be easily managed with lifestyle changes like regular exercise, dietary management, avoiding sugar and refined carbohydrates, etc. Early recognition of hypertriglyceridemia and its prompt treatment is essential in both the initial and long-term management of pancreatitis and are essential to prevent recurrent acute pancreatitis.

As my study was cross-sectional, follow up of patients was not done which is limitation of my study. Further studies can be done to study correlation of HBA1C, triglyceride levels and pancreatic enzymes.

Conflicts of Interest Statement

There was no conflict of interest while conducting the study.

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