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ACUTE PANCREATITIS IN PATIENTS WITH SEVERE HYPERTRIGLYCERIDEMIA IN A MULTIETHNIC MINORITY POPULATION

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ABSTRACT

Objective: To investigate the prevalence and predictors of hypertriglycerdemic acute pancreatitis (HTG-AP) in a multiethnic minority population.

Methods: A retrospective cross-sectional study from 2003 to 2013 of 1157 adults with serum triglyceride (TG) level ≥ 1000 mg/dL comparing baseline characteristics and risk factors between those with and without HTG-AP.

Results: Mean study population age was 49.2±11.5 years; 75.6% males; 31.6% African Americans, 38.4% Hispanics, 22.7% Caucasians, 5.7% Asians and 1.6 % Pacific Islanders.

Prevalence of HTG-AP was 9.2%. Patients with HTG-AP were significantly younger (41.3 vs 50.0 years, p<0.001) than those without HTG-AP. Excessive alcohol intake [Odds Ratio (OR), 3.9; 95% Confidence Interval (CI), 2.5-6.0; *P<.001*], gallstone disease (OR, 3.9; 95% CI, 1.4-10.8; *P=.008*) and TG>2000 (OR, 4.8; 95% CI, 3.1-7.4; *P<.001*) remained significant independent risk factors. TG for patients with HTG-AP were higher [median TG 2394 mg/dL; Interquartile range (IQR), 1152-4339 mg/dL vs median TG 1406 mg/dL; IQR, 1180.7-1876.5 mg/dL]. TG levels > 2000 mg/dL were

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associated with higher incidence of AP (22% vs 5%). Patients with TG levels of < 2000 mg/dL and no risk factors had prevalence of 2% compared to 33.6% with one risk factor and TG > 2000 mg/dL. Patients with HTG-AP had higher incidence of diabetic ketoacidosis at admission (7.5% vs 2.5%; *P=.004*).

Conclusion: TG level ≥2000 mg/dL was associated with higher HTG-AP prevalence in ethnic minorities. Presence of excessive alcohol intake and/or gallstones further accentuated risk.

Key words: Acute pancreatitis, diabetes mellitus, hypertriglyceridemia

Abbreviations:

AP = acute pancreatitis, **DM =** diabetes mellitus, **HbA1c =** hemoglobin A1c, **HIV =** human immunodeficiency virus, **HTG =** hypertriglyceridemia, **HTG-AP =** hypertriglyceridemic acute pancreatitis**, ROC =** receiver operating characteristic**.**

INTRODUCTION

Acute pancreatitis (AP) is an inflammatory condition of the pancreas, accounting for more than 220,000 annual hospital admissions (1) and associated with a mortality ranging from 3-30% (1-3). Hypertriglyceridemia (HTG) as an underlying etiology is present in 1.3-3.8% of patients with AP, making it one of the most common etiologies for AP after gallstone disease and excessive alcohol intake (4). Several pathophysiological

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mechanisms have been suggested for acute pancreatitis in the presence of hypertriglyceridemia (HTG-AP) with the most commonly accepted theory being that excess TG is hydrolyzed by pancreatic lipase resulting in free fatty acids (FFAs). These excess FFAs consequently overwhelm the binding capacity of albumin and cause acinar and pancreatic capillary injury. In addition, hyperviscosity resulting from chylomicronemia causes impaired pancreatic blood flow leading to ischemia and acidosis, ultimately resulting in further pancreatic injury (5-7).

The Endocrine Society Clinical Practice Guidelines (2012) define severe HTG as TG levels between 1000 to 1999 mg/dL and very severe HTG as TG levels ≥ 2000 mg/dL (8). While a threshold TG value of ≥ 1000 mg/dL is often cited as the cut-off for developing pancreatitis, not all patients with severe HTG develop AP (8). At present, there is little information about the risk of AP in relation to TG levels. Some studies have reported cut-off TG values as high as 1772 mg/dL, while other studies stratified patients based on TG levels > 500 mg/dL (9-12). Not only is there ambiguity in the level of HTG causative of pancreatitis, literature is also lacking on the correlation of increased TG levels and the risk of developing AP. Furthermore, the existing literature on HTG-AP has limited data on the prevalence in ethnic minority populations (10, 12-14). Given the above-mentioned gaps in literature, we conducted a retrospective study in a large medical center with high rates of ethnic minorities with the aim of determining the prevalence of HTG-AP in patients with severe HTG (TG ≥1000 mg/dL) and to study other risk factors of HTG-AP.

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METHODS

Patients

In this retrospective study, patients found to have severe hypertriglyceridemia in Cook County Health & Hospitals System, an urban safety-net hospital system in Chicago, Illinois, catering to a diverse racial community were analyzed. The patient population of this system is approximately 53% African American and 29% Hispanic. Inclusion criteria for this study were adult patients (≥ 18 years) who were found to have a fasting TG ≥ 1000 mg/dL whether in inpatient or outpatient settings at any point of time during the collection period from 2003 to 2013. Exclusion criteria included the age < 18 years or TG < 1000 mg/dL. A diagnosis of HTG-AP was made when any two of the following three criteria were present: abdominal pain characteristic of pancreatitis, computed tomography (CT) evidence of pancreatitis, or serum lipase levels three times the upper level of normal (15) and documented TG > 1,000 mg/dL at time of presentation. In cases where multiple episodes of pancreatitis occurred in the same patient, the first episode of AP was included in the analysis.

Based on detailed chart review, spanning from January 2003 to March 2013, we obtained demographic data including self-identified race or ethnicity, presenting symptoms and presence of risk factors such as excessive alcohol intake, family history of pancreatitis, smoking, recent trauma, preceding endoscopic retrograde cholagiopancreatography (ERCP), infections and human immunodeficiency virus (HIV). Gallstone disease was considered present if documented in admission history or in previous or current imaging investigations (ultrasound or CT). Excessive alcohol intake was defined using the Centers

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for Disease Control (CDC) definition stating that it includes binge and heavy drinking (16).

Laboratory values collected included TG levels, lipase levels, calcium, parathyroid hormone (PTH) levels, hemoglobin A1c (HbA1c), thyroid stimulating hormone (TSH), and free tetra-iodothyronine (FT4). Our lab utilized *Olympus Beckman*® assay for lipase, triglycerides, and calcium. *The Access Immunoassay System*® was used for TSH and FT4.

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Statistical analysis

Descriptive statistics are reported as percentages for binary and categorical variables as mean ± standard deviation if normally distributed and as median (IQR) if non-normally distributed for variables measured on continuous scale. The significance of association between categorical variables are measured by the χ^2 test. Variables measured on continuous scale are compared between two groups by the independent-samples *t* test, or alternatively, by the non-parametric Mann-Whitney test.

Univariate analysis was used to test the association of age, race, excessive alcohol use, gallstone disease, smoking, TG levels, and DM with acute pancreatitis (Table 1). We included all risk factors with $p<0.1$ in the univariate model into our multivariable risk-adjusted model (Table 2).

Receiver operating characteristic (ROC) curves were used to describe the best predictors for AP development. Based on multivariable analysis, a predictive model for HTG-AP was developed (17) based on variables which were significantly associated with acute pancreatitis. We used 3-fold cross-validation for internal validation of our model in which the patients were divided into three groups of equal sizes; two of the groups were used as training sets based on which probability of AP development was predicted for the remaining validation group. This process was repeated three times. These cross-validated predictions were plotted against the actual data of AP occurrence in a cross-validated ROC curve. A two-tailed $P < 0.05$ was considered statistically significant. SPSS version

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24 software (IBM) was used for all statistical analyses. The study was approved by the Institutional Review Board of Cook County Health & Hospitals System.

RESULTS

Based on the inclusion criteria, a total of 1157 patients with TG ≥1000 mg/dL were included in the study, 871 patients had TG 1000-1999 and 286 patients had TG ≥2000. The clinical and laboratory characteristics are shown in Table 1. Mean age was 49.2±11.5 years and males accounted for 75.6%. The majority (77.3%) consisted of ethnic minority populations: African Americans (31.6%), Hispanics (38.4%), Asians (5.7%) and Pacific Islanders (1.6%). Excessive alcohol intake and history of smoking were found in 30% and 32.4% respectively. A previous diagnosis of DM and HIV were found in 70.9% and 8.9% respectively. Only 2% (24 patients) had history of gallstones.

The prevalence of AP in patients with severe HTG in this study was 9.2% (107 patients). Among patients who had acute pancreatitis, abdominal pain as the presenting symptom was found in 97.1%, 84.5% had a lipase level three times above the upper limit of normal, and 94.5% had CT evidence of AP. Acute pancreatitis complicated by phlegmon formation occurred only in 2 patients, both were HIV positive. The rate of AP was significantly less in HIV patients compared to patients without HIV (1.8% vs 10.0%, P=.004).

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Patients with AP were significantly younger than those without AP (41.3 vs 50.0 years; P<.001). AP was present in 13.7% in patients younger than 50 years compared to 4.8% for those above 50 years of age (P<.001). Although men clearly out-numbered women in both groups, there was no significant difference in prevalence of AP between male and female patients (9.0% vs 9.9%).

A history of excessive alcohol intake was found in 57.9% (90.3% males) of patients with AP compared with 27.2% (86.7% males) in patients without AP (P<.001). In the AP group, excessive alcohol intake was found in 78.9% of Caucasians, 66.7% of African Americans, 42.9% of Asians, 48.9% of Hispanics, and 0.0% of Pacific Islanders. Excessive alcohol intake was significantly associated with HTG-AP in univariate analyses for all racial subgroups except Asians and Pacific Islanders.

History of gallstones was present in 6.5% of patients with AP and 1.62% without AP (P=.004). Women were more likely to have gallstone disease than men (62.5% vs 37.5%; P<.001). Smoking was equally prevalent in patients with and without AP (37.4% vs 31.9%; P=.249). The DM prevalence and mean HbA1c values were comparable in both patients with and without AP. Nine percent of the group had a diagnosis of HIV at the time of presentation. HIV patients were older than those without (54.5±2.1 vs 41.1±9.8 years; P=.05). The two patients with HIV and AP were African American males with a TG levels of 1785 and 2265 mg/dL. Both HIV positive patients had pseudocyst formation seen on imaging.

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Patients with HTG-AP had higher incidence of diabetic ketoacidosis at admission (7.5% vs 2.5%; P=.004), 88% were men and 12% were women in both cohorts. No one in our cohort had history of trauma, ERCP, pancreas divisum, autoimmune pancreatitis, or pregnancy.

In multivariable logistic regression analysis (Table 2), younger age, excessive alcohol intake, gallstone disease and TG > 2000 mg/dL remained significant independent risk factors for the development of HTG-AP.

The median TG level for patients with AP was higher than in those without AP (2394 vs 1406 mg/dL; P<.001). When TG was divided in two groups based on Endocrine Society guidelines for the classification of HTG (group 1: TG between 1000 to 1999 mg/dL; group 2: TG $\geq$ 2000 mg/dL), the prevalence of AP was significantly higher in group 2 with 5.1% in group 1 and 22% in group 2 (Figure 1A). When TG levels were divided into four equal progressive range groups, there was a significant and incremental increase in prevalence of AP from 6.6% in the lowest group to 66.6% in the highest TG group (Figure 1B).

TG levels association with AP were further stratified by the presence or absence of excessive alcohol intake and/or gallstones. Presence of one or two risk factors in each TG range group increased further the association with AP (Figure 1C and D). It showed that patients in lower TG range groups (both in two or four ranges groups analyses) and without any other risk factors have low association with AP (prevalence of 2.2% and

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3.0% respectively) and addition of even one risk factor raises the association significantly.

ROC Curve Analysis and Predictive Model

The ROC curve, using predicted values from a model with the four independent risk factors of age, triglycerides, presence or absence of excessive alcohol intake, and gallstones, yielded an area under the curve of 0.834 (95% CI, 0.80-0.87; P<.001) (Figure 2). The cross-validated ROC curve, using 3-fold cross-validated predictions, yielded a comparable area under the curve of 0.813 (95% CI, 0.77-0.85; P<.001).

A predictive model using the four independent risk factors was developed to calculate the probability of developing AP (Supplemental Table 1). Based on this model, we calculated several different scenarios of risk for two hypothetical patients: a younger 30 years old and an older 60 years old (Figure 3). The risk in the younger patient ranged from 1.7% and progressed as high as 57.0% as the number of the risk factors increased. In the older patient, the risk range for AP was much lower (0.2% to 14.1%) as the same risk factors was accumulating.

Based on our ROC curve, we suggest three cut-offs to determine the probability of developing acute pancreatitis (%): low risk as < 4.4%, intermediate risk as 4.4% to < 12.0%, and high risk as ≥ 12.0%. The sensitivity and specificity for the ≥ 4.4% cut-off were 94.4% and 52.9% respectively while for the ≥ 12.0% cut-off they were 71.0% and 81.7% respectively.

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DISCUSSION

The prevalence of HTG-AP in our cohort was 9.2%, which is slightly lower than the weighted mean prevalence of 14.0% with a wide range of prevalence estimates (8-31%) reported by a recent systematic review of observational studies (13). However, the size of our cohort is larger than the entire pooled patient population from that review. Plus, this is the first HTG-AP report in a multiethnic minority population.

This study clearly shows that the AP risk increases with higher levels of TG values, especially >2000 mg/dL. This study validates the Endocrine Society's suggested cut-off of TG >2000 mg/dL as a risk factor to develop HTG-AP and shows a 4.3-fold increase in the prevalence of AP at this level compared to the group with TG 1000-1999 mg/dL (22.0% vs 5.1%). This trend was further noted when the TG values were divided into 4 incremental groups with the risk of AP increasing 11-fold in the highest group.

Alcohol is a well-known independent risk factor for acute pancreatitis (15, 18, 19). Our study shows that patients with a history of alcohol intake have 4 times the odds of developing AP. These results are concordant with previous literature on HTG-AP (20). It is well known that alcohol leads to markedly higher TG levels through inhibition of lipolysis, especially in patients with pre-exiting LPL deficiency (9). Several additional mechanisms have been suggested for the causative role of alcohol intake in AP, including sphincter of Oddi dysfunction, plugging of the pancreatic ductules resulting in acinar injury, stimulation of pancreatic enzyme secretion predisposing to endotoxin-induced

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damage, direct toxic effect mediated by metabolites such as fatty acid ethyl esters, and, finally, through localized hypoxia produced by increased oxygen requirements during ethanol metabolism (21-25).

Although smoking was not significantly associated with development of HTG-AP, we observed that approximately 50% of patients with a history of alcohol intake were also smokers, and amongst those with a history of smoking, 82.5% had a history of alcohol intake. Therefore, it is evident that these two modifiable risk factors often co-exist. In previous studies, smoking has been shown to increase progression of chronic alcoholic pancreatitis and also potentiate pancreatic ischemia and damage in acute alcoholic pancreatitis (26, 27).

Gallstone disease is also a known independent risk factor for acute pancreatitis (15, 18, 19). Our analysis revealed that gallstone disease was an independent risk factor for HTG-AP development. We also found that in patients with AP, prevalence of gallstone disease was significantly higher in women compared to men, which has been well described in the past (15, 18, 19).

In addition to the degree of hypertriglyceridemia, excessive alcohol intake and presence of gallstones, other factors were associated with AP. Patients who developed AP were younger and younger age showed to be an independent risk factor associated with HTG-AP. It is not clear why older patients with similar risk factors were less susceptible to developing AP. A recent retrospective comparison of HTG-AP, biliary AP, and alcoholic

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AP highlighted this fact by reporting that patients with HTG-AP are significantly younger as compared to patients with biliary AP or alcoholic AP (10). We also observed that men clearly outnumbered women in both the overall cohort and the AP subgroup. This finding is similar to a study by Sandhu *et al* (12), who reported that 70% of the patients in their large cohort of HTG patients were men. Interestingly, despite the lower overall prevalence of women with HTG in our study, there was an equal prevalence of AP in male and female patients (9.1% vs 9.9%).

We found that a large number of patients in our cohort had a previous diagnosis of DM (70.9%) with an average A1c of 9.6%, indicating poor glycemic control especially in men (10.1% vs. 8.1% in women). Uncontrolled DM has been previously reported in studies on HTG-AP at varying prevalence ranging from 43-72% (4, 28). Our data reveals that there is no difference in either prevalence of DM or in mean HbA1c values between patients with and without HTG-AP. These findings are concordant with two studies, one retrospective and one prospective (12, 20).

Our study is retrospective and, therefore, has limitations inherent to this type of study. However, we subjected our data to rigorous checks, including periodically choosing random patients and by sorting each continuous variable in ascending order to evaluate accuracy and look for outliers. In addition, the large size of our cohort makes the statistical analysis robust and the results credible. Since our study group is unique in racial composition, it cannot be fully generalized to the general population. Also, when stratifying the patients by TG levels, the number of patients in the highest two quartiles

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were small. Therefore, caution needs to be observed in interpreting data from these two subgroups. Our data also lacked details of medication usage and BMI values. These could possibly contribute to unmeasured confounding variables in our regression model.

In this study, the prevalence of AP increased within each TG group with the concomitant presence of excessive alcohol intake and gallstones. In absence of these risk factors, the prevalence of AP was very low (2-3%) in the lower TGs groups. These risk predications are further corroborated by the ROC analyses and the predictive model developed. In addition, the predictive model shows the importance of young age as additional important risk factor (in Figure 3). Using this model, younger patients had a much higher risk, as much as four-fold to develop pancreatitis than their older counterpart with similar risk factors. However, this model will need further validation. The findings of the study might help risk stratify patients with severe hypertriglyceridemia in the outpatient setting to assess their risk for developing acute pancreatitis. It may also have therapeutic implications and help the clinician to decide on the urgency and intensity of management of severe hypertriglyceridemia based on the patient's risk.

CONCLUSION

This large retrospective study is the first report on HTG-AP in a US multiethnic minority population. Early detection and counseling on behavioral risk factors in patients with severe hypertriglyceridemia may help in reduction of pancreatitis risk. The predictive modelling suggested in this study, if externally validated, may be a useful tool for individualizing therapy in such patients.

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Table 1: Baseline characteristics for all patients with severe HTG and in patients with and without pancreatitis

Variable	Total study population with TG ≥ 1000 mg/dL	Patients who developed acute pancreatitis	Patients who did not develop acute pancreatitis	P-value (with AP vs without AP)
Demographics				
Patients (No.)	1157	107	1050	
Age (y), mean ± SD	49.2 (11.5)	41.3 (9.9)	50.0 (11.3)	<.001
Male sex (No. [%])	875 (76)	79 (74)	796 (76)	.65
Race (No. [%])				
African American	366 (32)	30 (28)	336 (32)	
Hispanic	444 (39)	47 (44)	397 (38)	.401
Caucasian	242 (21)	19 (18)	223 (21)	
Asian	66 (6)	7 (7)	59 (6)	
Pacific Islander	18 (2)	2 (2)	16 (2)	
Unknown	21 (2)	2 (2)	19 (2)	
Clinical Presentation (%)				
Abdominal pain	-	97	4	<0.001
Positive CT findings	-	94.5	0	
Lipase > 3ULN	-	84.5	0	
Risk factors and comorbid conditions (No. [%])				
Alcohol use	348 (30)	62 (58)	286 (27)	<0.001
Smoking	375 (32)	40 (37)	335 (32)	.249
Family history of pancreatitis	4 (0)	1 (1)	3 (1)	.276
Pregnancy	1 (0)	0 (0)	1 (0)	1
Recent trauma	15 (1)	0 (0)	15 (1)	.213
Endoscopic retrograde cholangio-pancreatography (ERCP)	2 (0)	0 (0)	2 (0)	.651
Gallstone disease (either history or imaging evidence)	24 (2)	7 (7)	17 (2)	.001
HIV	103 (9)	2 (2)	101 (10)	.004
Diabetes	820 (71)	76 (71)	744 (71)	.53
Hypothyroidism	15 (1)	1 (1)	14 (1)	.953
Laboratory (normal values)				
HbA_{1C} (4.4-6.7 %), mean ± SD	9.6 (2.8)	9.6 (3.2)	9.5 (2.8)	.954
TG (30-150 mg/dL), median (IQR)	1444 (1196.5-1991.5)	2394 (1552-4339)	1406 (1180.7-1876.5)	<0.001
Lipase (5-55 IU/L), median (IQR)	151 (55-440.2)	413 (218.5-1224.7)	56.5 (38-98.2)	<0.001
Ca (8.5-10.5mg/dL), mean ± SD	9.2 (0.8)	8.48 (1.2)	9.31 (0.7)	<0.001

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TSH (0.34-5.6 uIU/L), median (IQR)	1.8 (1.1-2.7)	1.3 (0.9-2.1)	1.8 (1.2-2.7)	.833

Comparisons between groups were made using t-tests and for non-parametric data, the Mann-Whitney test was used. Chi-square was used for analysis of categorical variables.

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Table 2: Risk-adjusted multivariable model for factors associated with acute pancreatitis in patients with severe hypertriglyceridemia

	Patients with pancreatitis	Patients without pancreatitis	Unadjusted OR (95% CI)*	Unadjusted p-value	Final model Adjusted OR (95% CI)**	Adjusted p-value∞
Gallstone disease	7%	2%	4.3 (1.7-10.5)	.002	3.9 (1.4-10.8)	.008
Excessive alcohol use	58%	27%	3.7 (2.5-5.5)	<.001	3.9 (2.5-6.0)	<.001
Age in years [mean (SD)]	41.3 (9.9)	50.0 (11.3)	0.93 (0.92-0.95)	<.001	0.93 (0.91-0.95)	<.001
Triglycerides >2000 mg/dL	59%	21%	5.3 (3.5-8.0)	<.001	4.8 (3.1-7.4)	<.001

*Abbreviations: OR=odds ratio, CI=confidence interval

** Only variables with P-value <0.1 in the univariate analysis were entered into the multivariable model.

∞ Model adjusted for gallstone disease, excessive alcohol use, age (year) and triglycerides >2000 mg/dL

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