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ORIGINAL ARTICLE

Necrotizing Pancreatitis from Hypertriglyceridemia: More Severe Disease?

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Abstract

Background Necrotizing pancreatitis (NP) is caused by hypertriglyceridemia (HTG) in up to 10% of patients. Clinical experience suggests that HTG-NP is associated with increased clinical severity; objective evidence is limited and has not been specifically studied in NP.

Aim The aim of this study was to critically evaluate outcomes in HTG-NP. We hypothesized that patients with HTG-NP had significantly increased severity, morbidity, and mortality compared to patients with NP from other etiologies.

Methods A case–control study of all NP patients treated at a single institution between 2005 and 2018 was performed. Diagnostic criteria of HTG-NP included a serum triglyceride level > 1000 mg/dL and the absence of another specific pancreatitis etiology. To control for differences in age, sex, and comorbidities, non-HTG and HTG patients were matched at a 4:1 ratio using propensity scores. Outcomes were compared between non-HTG and HTG patients.

Results A total of 676 NP patients were treated during the study period. The incidence of HTG-NP was 5.8% ($n = 39$). The mean peak triglyceride level at diagnosis was 2923 mg/dL (SEM, 417 mg/dL). After propensity matching, no differences were found between non-HTG and HTG patients in CT severity index, degree of glandular necrosis, organ failure, infected necrosis, necrosis intervention, index admission LOS, readmission, total hospital LOS, or disease duration ($P = $ NS). Mortality was similar in non-HTG-NP (7.1%) and HTG-NP (7.7%), $P = 1.0$.

Conclusion In this large, single-institution series, necrotizing pancreatitis caused by hypertriglyceridemia had similar disease severity, morbidity, and mortality as necrotizing pancreatitis caused by other etiologies.

Keywords Triglycerides · Case–control studies · Propensity score · Morbidity · Disease severity

Introduction

Acute pancreatitis (AP) is the leading gastrointestinal cause for inpatient hospitalization accounting for nearly 300,000 hospital admissions each year in the USA [1]. The majority of AP cases are mild and self-limiting, though necrotizing pancreatitis (NP) develops in up to 20% of AP patients and is characterized by a more severe clinical course [2–4]. The most common etiologies of NP are gallstones and alcohol, together accounting for about 70% of patients [5, 6]; however, hypertriglyceridemia (HTG) is responsible for about 10% of cases [7]. Clinical experience suggests that HTG-NP is associated with increased clinical severity compared to NP from other etiologies, but this association remains under considerable debate.

Patients with elevated triglycerides develop AP with a remarkably high prevalence of about 14% [7].

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Hypertriglyceridemia may be primary (inherited) or secondary to another pathology, and in both scenarios, pancreatic lipolysis of elevated serum triglycerides results in generation of free fatty acids leading to acinar injury and activation of the inflammatory cascade [8, 9]. Patients with HTG-AP are frequently younger in age than non-HTG-AP patients, but often several HTG-related comorbidities coexist including obesity, hypertension, and diabetes [9]. It is unknown if the mechanism of HTG-NP results in a more severe clinical course or if observed differences in patient's clinical course are due to preexisting medical conditions. Existing literature evaluating the severity of HTG-AP is mixed; small case series report a wide variety of severity metrics making comparison among studies difficult [10–14]. In contemporary literature, for example, a recent systematic review as well as several large institutional series found no significant difference in outcomes between HTG and other etiologies of AP [7, 15–17]. No study to date has specifically evaluated the effect of HTG etiology on outcomes in NP.

In our high-volume pancreas practice, an anecdotal clinical observation has been that among NP patients, those with HTG etiology seem to have a more severe and protracted disease course. Therefore, the aim of this study was to systematically and critically evaluate outcomes of a large series of consecutive HTG-NP patients. We hypothesized that patients with HTG-NP had significantly increased disease severity, morbidity, and mortality compared to patients with NP from other etiologies.

Materials and Methods

Study Population

Patients treated at Indiana University Health University Hospital (IU-UH) between 2005 and 2018 were considered for this study. The IU-UH NP database is a prospective, Institutional Review Board (IRB)-approved database cataloging all NP patients regardless of age, etiology, or treatment strategy and includes informed consent. All data are stored in compliance with the Health Insurance Portability and Accountability Act (HIPAA). The Indiana University IRB granted approval for this specific analysis which was performed in compliance with the Declaration of Helsinki.

Definitions

Acute pancreatitis, necrotizing pancreatitis, and infected necrosis were defined according to the revised Atlanta classification [18]. Infected necrosis was diagnosed on organ failure which was defined according to the modified Marshall scoring system for organ dysfunction [18]. Onset of pancreatitis was defined as the date of first symptom onset [18]. Consistent with previous literature, diagnosis of HTG-NP required a serum triglyceride > 1000 mg/dL and the exclusion of another possible etiology of NP [7]. Hyperlipidemia as a comorbidity was defined as patients receiving medication for elevated serum low-density lipoproteins (LDL) or triglycerides prior to the onset of pancreatitis.

Severity of NP was evaluated using the computed tomography severity index (CTSI) [19], degree of pancreatic gland necrosis, organ failure, infected necrosis, index hospital admission length of stay (LOS), unplanned hospital readmission, total hospital LOS prior to disease resolution, disease duration, and mortality. Infected necrosis was suspected in the presence of gas within the (peri-)pancreatic collection on cross-sectional imaging and confirmed by microbiology culture of aseptically obtained specimens [18]. Only unplanned readmissions were included in this study and were defined as any unanticipated readmission from home, clinic, or the emergency room for any indication. Planned readmissions for scheduled intervention were excluded [5]. Additional outcomes of interest included the presence of disconnected pancreatic duct syndrome and pancreatic necrosis intervention. Disconnected pancreatic duct syndrome was diagnosed when parenchymal necrosis involved ≥ two centimeters of pancreas resulting in viable upstream pancreatic tissue and extravasation of contrast or total cutoff of the main pancreatic duct on endoscopic retrograde pancreatography (ERP) or magnetic resonance pancreatography (MRP) [20].

Management of Necrotizing Pancreatitis

Institutional management of NP begins with medical supportive care tailored to the individual patient. Infected pancreatic necrosis is initially treated with antibiotics. When indicated, necrosis intervention is delayed at least 4 weeks from NP onset, as able, and begins with percutaneous drainage or endoscopic transgastric drainage—the initial treatment approach is determined by consensus agreement among pancreatic surgeons, interventional radiologists, and advanced endoscopists experienced in the management of NP patients [6, 21]. Necrosis refractory to minimally invasive approaches is managed with a combination of percutaneous and endoscopic techniques or escalated to surgical management. In patients with biliary etiology of pancreatitis, surgical management is considered earlier in the treatment strategy.

Statistics

To control for differences in age, sex, and comorbidities, non-HTG and HTG patients were matched at a 4:1 ratio using propensity scores. R version 3.5.0 (R Core Team 2018) and the R *MatchIt* package (Ho, Imai, King, Stuart 2011) were used for both propensity score generation and

matching. Variables used for propensity score generation included age, gender, and comorbidities including any history of alcohol abuse, cerebrovascular accident (CVA), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), coronary artery disease (CAD), diabetes mellitus (DM), hyperlipidemia, hypertension, obesity (body mass index ≥ 30 kg/m^2), obstructive sleep apnea (OSA), peripheral vascular disease (PVD), and tobacco use. For propensity matching, a greedy nearest neighbor algorithm (without replacement) was used. All variables achieved balance in the matched dataset.

After case–control propensity matching, outcomes were compared between non-HTG-NP and HTG-NP groups. Continuous variables are reported as mean with standard error of the mean (SEM) or median with interquartile range (IQR). Categorical variables are reported as number with percentage. Where applicable, independent groups *t* test, Mann–Whitney *U* test, or Pearson's Chi-squared test were used to detect differences between non-HTG and HTG patients. *P* values < 0.05 were accepted as statistically significant.

Results

Between 2005 and 2018, a total of 676 NP patients were treated. The etiology of NP was attributed to HTG in 39 (6%) patients. The mean peak triglyceride level at diagnosis was 2923 mg/dL (SEM, 417 mg/dL). Treatment for elevated triglycerides included supportive care only in 23 (59%) patients, insulin infusion in 13 (33%) patients, and plasmapheresis in three (8%) patients. Prior to propensity matching, the differences in baseline demographics and comorbidities between the non-HTG-NP and HTG-NP groups are shown in Table 1. Notably, patients with HTG-NP were younger and more frequently had coexisting obesity, diabetes mellitus, and hyperlipidemia compared to non-HTG-NP patients. Non-HTG-NP patients had a higher incidence of alcohol abuse as a comorbidity.

After propensity matching, a total of 195 NP patients were included in the analysis: 156 patients with non-HTG-NP and 39 patients with HTG-NP. Table 2 shows baseline demographics after propensity matching. Overall, disease severity was similar between groups. The rate of organ failure in non-HTG-NP patients was 35% and in HTG-NP patients was 44%; $P = 0.3$. Individual organ failure rates, including respiratory failure, renal failure, and cardiovascular failure, and CTSI were also similar (Table 3). No difference in the volume of pancreatic gland necrosis was seen between groups (Fig. 1).

Clinical outcomes were similar between groups including infected necrosis, DPDS, index admission LOS, unplanned readmission, and total hospital LOS (Fig. 2). The intervention to achieve disease resolution was similar between groups (Fig. 3). Overall disease duration was similar between non-HTG-NP patients (median, 5.4 [3.4-8.8] months) and HTG-NP patients (median, 4.7 [3.2–6.4] months), $P = 0.2$. Eleven (7%) patients died in the non-HTG-NP group, and three (8%) patients died in the HTG-NP group ($P = 1.0$).

Table 1 Differences in demographics and comorbidities prior to propensity matching between non-HTG-NP and HTG-NP patients

Variable	Non-HTG-NP, *n* (%)	HTG-NP, *n* (%)	*P*
Number of patients	637	39	
Age, years*	53.2 (0.6)	41.5 (1.9)	< 0.0001
Male sex	411 (65)	30 (77)	0.1
Hypertension	381 (60)	28 (72)	0.2
Obesity (BMI > 30 kg/m^2)	322 (51)	31 (79)	0.0004
Tobacco	256 (40)	15 (38)	0.9
Hyperlipidemia	215 (34)	23 (59)	0.002
Diabetes mellitus	146 (23)	24 (64)	< 0.0001
Alcohol abuse	98 (18)	1 (3)	0.03
Chronic obstructive pulmonary disease	81 (13)	1 (3)	0.07
Coronary artery disease	77 (12)	2 (5)	0.3
Congestive heart failure	29 (5)	1 (3)	1.0
Obstructive sleep apnea	26 (4)	4 (10)	0.09
Cerebrovascular accident	25 (4)	0 (0)	0.4
Chronic kidney disease	22 (3)	2 (5)	0.6
Peripheral vascular disease	16 (3)	1 (3)	1.0

HTG hypertriglyceridemia, *NP* necrotizing pancreatitis, *BMI* body mass index, *kg* kilograms, m^2 square meters

*Continuous variable reported as the mean value (with standard error of the mean)

Table 2 Comparison of demographics and comorbidities between non-HTG-NP and HTG-NP patients after 4:1 propensity matching

Variable	Non-HTG-NP, N (%)	HTG-NP, N (%)	*P*
Number of patients	156	39	
Age, years*	43.7 (0.6)	41.5 (1.9)	0.3
Male sex	109 (70)	30 (77)	0.4
Hypertension	101 (65)	28 (72)	0.5
Obesity (BMI > 30 kg/m^2)	109 (70)	31 (79)	0.3
Tobacco	52 (33)	15 (38)	0.6
Hyperlipidemia	66 (42)	23 (59)	0.07
Diabetes mellitus	75 (48)	24 (64)	0.1
Alcohol abuse	5 (3)	1 (3)	1.0
Chronic obstructive pulmonary disease	6 (4)	1 (3)	0.7
Coronary artery disease	11 (7)	2 (5)	0.7
Congestive heart failure	5 (3)	1 (3)	1.0
Obstructive sleep apnea	11 (7)	4 (10)	0.7
Cerebrovascular accident	0 (0)	0 (0)	–
Chronic kidney disease	6 (4)	2 (5)	1.0
Peripheral vascular disease	3 (2)	1 (3)	1.0

HTG hypertriglyceridemia, *NP* necrotizing pancreatitis, *BMI* body mass index, *kg* kilograms, m^2 square meters

*Continuous variable reported as the mean value (with standard error of the mean)

Table 3 Comparison of computed tomography severity index (CTSI) and organ failure between non-HTG-NP and HTG-NP patients after 4:1 propensity matching

Variable	Non-HTG-NP, N (%)	HTG-NP, N (%)	*P*
Number of patients	156	39	
Computed tomography severity index*	7.4 (0.6)	6.8 (0.3)	0.6
Organ failure	54 (35)	17 (44)	0.3
Respiratory	48 (31)	11 (28)	0.08
Renal	37 (24)	14 (36)	0.1
Cardiovascular	20 (13)	5 (13)	1.0

Continuous variable reported as the mean value (with standard error of the mean)

Length of stay reported as mean with standard error of the mean represented by the error bars

HTG hypertriglyceridemia, *NP* necrotizing pancreatitis

Discussion

In this series of 676 NP patients treated over a 13-year period, the incidence of HTG-NP was 6%. Compared to other etiologies, HTG-NP patients were younger with obesity, diabetes mellitus, and hyperlipidemia more often present as medical comorbidities. Propensity matching is the most statistically rigorous method to control for these baseline differences and was used to evaluate the impact of HTG etiology on outcomes in NP. After propensity matching, 39 patients with HTG-NP were found to have a similar disease course compared to the 156 matched patients with non-HTG-NP. No differences were observed in disease severity, clinical course, or outcomes. In fact, the overall clinical course in patients with HTG-NP was remarkably similar to NP patients from other etiologies, disproving the study's original hypothesis.

Severe acute pancreatitis and associated organ failure develop in NP when the inflammatory reaction to pancreatic acinar cell injury results in overactivation of proinflammatory mediators relative to the typically balanced anti-inflammatory response [22–26]. In patients with HTG etiology of NP, the inciting event is lipolysis of serum triglycerides that results in free fatty acid formation and acinar cell injury. Free fatty acids result in additional proinflammatory oxidative stress and endothelial dysfunction. Understanding this biology, it is logical to speculate that HTG etiology of NP is associated with more profound inflammation resulting in more local and systemic complications compared to NP of other etiology. In the current series, the local and systemic complications in HTG-NP patients and non-HTG-NP patients were not different.

Hypertriglyceridemia as an etiology of acute pancreatitis has previously been associated with a more severe clinical course, including an increased likelihood of pancreatic necrosis and organ failure [10, 11]. Additionally, increased rates of mortality have been associated with HTG-AP in a few studies; however, this association is not replicated in all studies [12–14, 27]. The severity of NP can be assessed by a number of local and systemic complications as well

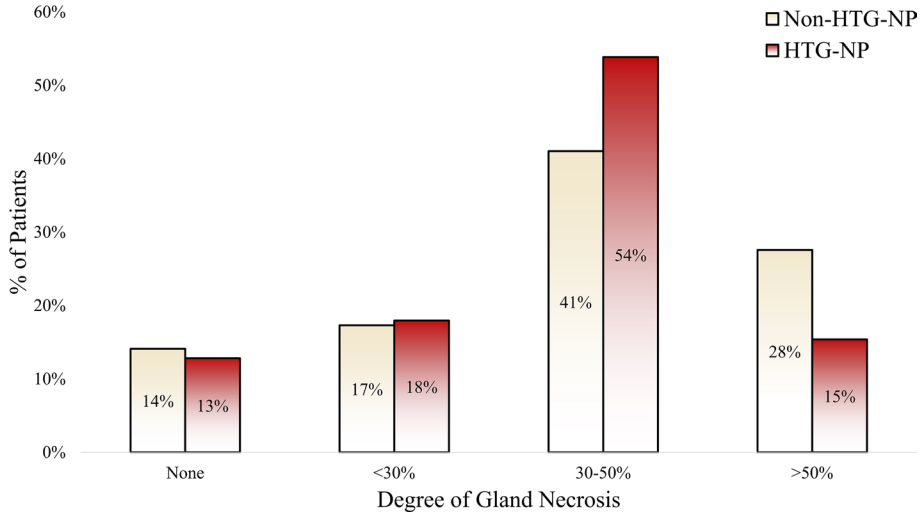

Fig. 1 The degree of gland necrosis was similar between patients with non-HTG-NP compared to patients with HTG-NP ($P = 0.4$). *HTG* hypertriglyceridemia, *NP* necrotizing pancreatitis

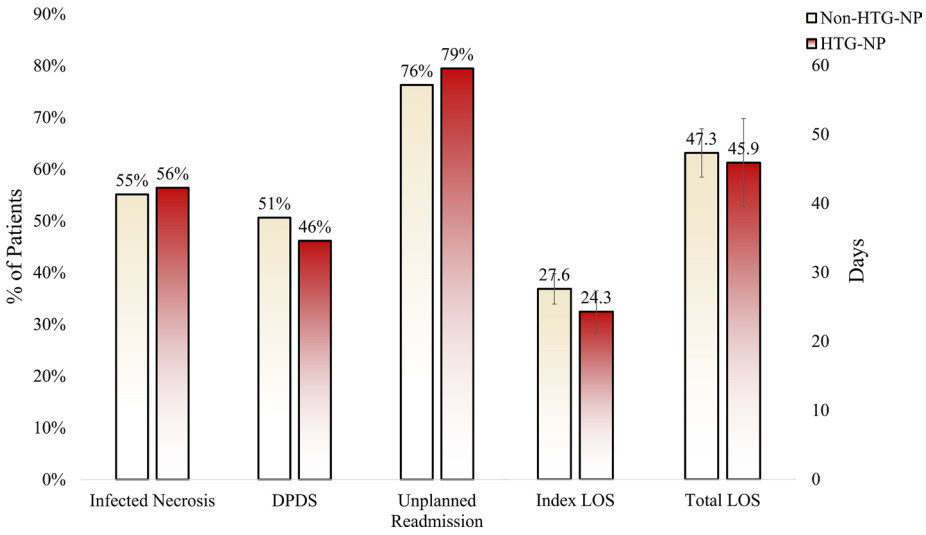

Fig. 2 Clinical outcomes in patients with non-HTG-NP and HTG-NP. No differences were observed in infected necrosis, DPDS, unplanned readmission, index LOS, or total LOS ($P = $ NS). *HTG* hypertriglyceridemia, *NP* necrotizing pancreatitis, *DPDS* disconnected pancreatic duct syndrome, *LOS* length of stay

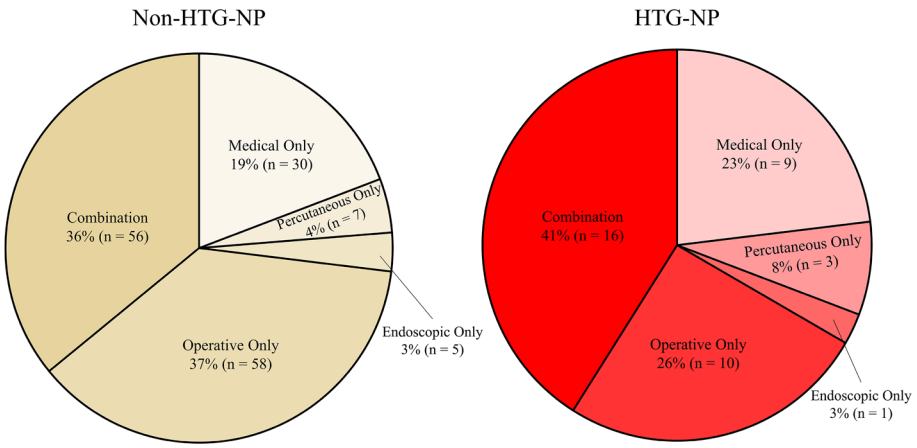

Fig. 3 Necrosis intervention to achieve disease resolution in patients with non-HTG-NP and HTG-NP. No differences were observed in necrosis intervention ($P = 0.6$). *HTG,* hypertriglyceridemia, *NP* necrotizing pancreatitis

as overall disease duration and mortality rates. Local complications assessed in this study included the volume of gland necrosis, DPDS, infected necrosis, and the need for necrosis intervention. No differences were observed in any of these severity metrics when comparing HTG-NP patients to propensity score matched non-HTG-NP

patients. Systemic complications and clinical course were compared and included organ failure, admission LOS, unplanned readmission, and total hospital LOS—no differences were observed between groups in these metrics of disease severity. Mortality rates were no different between HTG-NP patients and non-HTG-NP patients. Once pancreatic necrosis develops, the severity and clinical course of NP do not appear to be impacted by the etiology of pancreatitis.

Any perceived increase in NP disease severity noted clinically may potentially be explained by coexisting medical conditions present at the time of NP onset. Supporting this concept is a recently published propensity matched study evaluating the impact of HTG etiology in AP patients. This study found that, after controlling for baseline differences between groups, overall severity and prognosis of HTG-AP were not different than non-HTG-AP [15]. Two large contemporary cross-sectional series reached similar conclusions [16, 17]. In the current series, prior to propensity score matching HTG-NP patients had higher rates of obesity, diabetes mellitus, and, not surprisingly, hyperlipidemia when compared to non-HTG-NP patients. Obesity has previously been identified as an independent predictor of severity, organ failure, and degree of necrosis in AP [28–38]. Select studies have even linked obesity to increased mortality in AP; however, a recent meta-analysis of five studies found no association between mortality and obesity or body mass index [28, 33–35, 38]. Diabetes mellitus (DM) is a chronic disease with systemic implications involving every organ system; therefore, it is not surprising that DM in some studies has been associated with worse outcomes in AP [39–41]. Mortality does not appear to be affected by DM.

Hypertriglyceridemia as an etiology of NP is a relatively uncommon pathology, and this study included 39 HTG-NP patients. This represents a significant strength of this study, as the number of HTG-NP patients evaluated is two-to-four times as large as the largest previously published reports, which are limited to less than 20 HTG-NP patients [11, 15]. Future investigation will aim to confirm the results of this report in a multi-institutional collaborative effort. Additionally, this single-institution database allows for granular data often not available in large, multicentric databases. Acute pancreatitis, and the associated inflammatory response, is known to cause transient elevations in serum lipid concentrations, and it is therefore possible for patients with elevated triglycerides resulting from NP from any etiology to be incorrectly categorized as HTG-NP [42, 43]. To overcome this potential limitation, the serum TG concentration to meet diagnostic criteria for HTG-NP was purposely set at the higher end of the diagnostic range reported in the literature [7].

Conclusion

In this large, single-institution series, necrotizing pancreatitis caused by hypertriglyceridemia had similar disease severity, morbidity, and mortality as necrotizing pancreatitis caused by other etiologies.

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Author's contribution TK Maatman and JA Westfall-Snyder were involved in the acquisition, analysis, and interpretation of data in addition to drafting and revising the work. TK Maatman, EP Ceppa, MG House, A Nakeeb, CM Schmidt, TK Nguyen, and NJ Zyromski were involved in the conception of the project, interpretation of the data, and revision of work. All authors were involved in the final approval. NJ Zyromski serves as the mentor and corresponding author and agrees to be accountable for the work.

Compliance with Ethical Standards

Conflict of interest The authors declare no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Review Board and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent This study was approved by the Indiana University Institutional Review Board. Informed consent was obtained in all patients prior to data collection.

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