Hypertriglyceridemia associated with acute pancreatitis, case series

Abstract

Hyperglyceridemia (HTG) is a rare cause of Acute Pancreatitis (AP) however, in many studies it was reported the third most common following gallstones and alcoholic etiologies. HTG could be familial in type I and IV hyperlipidemia or secondary to Type 2 Diabetes Mellitus (T2DM), excessive alcohol intake, drugs, hypothyroidism, and obesity. Therefore, metabolic conditions causing pancreatitis are less common, representing 10%-15% of AP. We reported four patients presented with AP secondary to HTG following reviewed hospital medical records of twenty-three patients admitted with the same confirmed according to Atlanta criteria. The patient's age was range 35-41 years, two patients from each gender and three patients had T2DM. All patients had high Triglyceride (TG) on the day of admission to the Intensive Care Unit (ICU) and had responded to treatment of infusion intravenous insulin combined with Dextrose. We conclude patients with DM presented with AP, the HTG should be highly considered as a cause in this group of patients however, TG is an essential blood test in all patients with AP.

Introduction

Acute pancreatitis is an inflammatory condition of the pancreas and over the last 20 years, the incidence of AP increased 10-folds [1]. There are many causes of AP, which can be easily identified in 75%-85% of patients. Gallstones and alcohol are the most common causes contributing to 38% and 36% of cases, respectively [2]. HTG increases the risk of AP, accounting for a minor but a significant proportion of patients (2%-7%) [3] whereas in other studies up to 10% of all cases [4], 0.7%-20% [5] and it may account up to 56% of all cases of gestational pancreatitis [6].

The tendency of pancreatitis increases significantly when TG level above 1000 mg/d or 11.3 mmol/L [7] and several treatment modalities have been described in the literature, including insulin, heparin, plasmapheresis, and pharmacologic therapy.

The mechanism of AP in HTG is unclear however there are several potential or proposed mechanisms in this aspect. The hyperviscosity of the largest lipid-protein transporting, the lipoprotein can form a thrombus and obstruct the pancreatic flow causing ischemia and acidosis [8,9]. Further ischemia induced by excessive hydrolysis of TG by pancreatic lipase to free fatty acids exceeding the plasma albumin-binding capacity. Excess FFAs self-aggregate to form micellar structures that act as detergents within an acidic microenvironment; these micelles compromise the integrity of pancreatic acinar cells and pancreatic capillaries, causing inflammation and ischemia [10]. In addition, the acidic environment triggers activation of trypsinogen leading to autodigestion [9].

The genetic factors may play a role in AP induced by HTG; a Spanish study finds the apolipoprotein E e4 allele of the APOE gene is more common in patients with HTG induced AP [11] and a Chinese study found a CFTR mutation/variant/haplotype and a TNF promoter polymorphism were independent risk factors for HTG causing AP. The CFTR gene mutation rates in HTG with and without AP are 26.1% (12 out of 46) and 1.3% (one out of 80), respectively [12].

Methods

Series of cases identified in this retrospective study from our hospital records following reviewing admissions of patients to the ICU of Mediclinic Parkview hospital between September 2018 to March 2021 with AP. Out of

Fuad AlSaraj[1], Sarah Alkabbani[2], Montaser AlSmady[2], Rasha Awawdeh[3*], Apoorva Bushan Singhal[4], Paula Medhat Ibrahim[4], Hossam Elshekhali[4], and Seemin Shiraz[4]

[1]Department of Endocrinology of Mediclinic Parkview Hospital, UAE

[2]Mohammed Bin Rashid University of Medicine and Health Sciences, UAE

[3]Department of Internal Medicine of Mediclinic Parkview Hospital, UAE

[4]Department of Intensive Care Unit of Mediclinic Parkview Hospital, UAE

**Author for correspondence:*

Rasha.Awawdeh@mediclinic.ae

TABLE 1. Demography and laboratory results of the patients.

Cases	Case 1	Case 2	Case 3	Case 4
Age (years)	41	38	40	35
Gender	M	F	M	F
Smoking	No	No	20/day.	No
Alcohol	No	No	Rare	No
Biliary disease	No	No	No	No
BMI (kg/m^2)	33	29.6	29.2	23.4
H/of DM	T2DM	T2DM	No	T2DM On admission
Duration of stay (days)	6	7	7	7
Complications and mortality	No	No	No	No
Amylase 25-125 (U/L)	152	139	93	1418
Lipase 8-78 (U/L)	704	142	98.6	1544
HbA1c (%)	11.5	8.4	5.4	11.8
Glucose (mmol/L)	23.9	12.3	4.8	14.7
triglycerides (mmol/L)	8.69	7.6	7.65	13.48
TG	8.69	7.6	7.65	13.48
Calcium	2.14	2.52	2.15	2.43

twenty-three patients, four patients confirmed AP associated with HTG. Atlanta criteria were applied for diagnosis of AP, which required the presence of at least two of the following: 1) new onset of upper abdominal pain or tenderness, 2) elevation in serum levels of pancreatic enzymes of three or more folds, 3) radiological changes suggestive of AP [13]. The diagnosis of HTG induced pancreatitis was based on patients with TG levels (normal levels <150 mg/d, 1.7 mmol/L) above 1000 mg/dL, and other causes of the same were excluded.

Results

Four patients (17.4%) confirmed HTG induced pancreatitis identified out of 23 admissions of AP to the ICU. Two patients of each gender with an age range of all (35-41) years with a mean age of 38+0.5 SD but in males the range of age was slightly higher than female age (40-41) and (35-38) years respectively **(TABLE 1)**. The diagnosis was confirmed with presenting symptoms, laboratory tests and all had CT scan confirmed inflamed pancreas.

The history of smoking was only in one patient and alcohol intake was not of clinical importance. Biliary diseases excluded in all patients. One of the three patients with poorly controlled DM was newly diagnosed with HbA1c of 11.8%. The fourth patient has normal glucose throughout his admission.

Overweight and obesity were in three patients and one patient with normal BMI. The duration of stay in the ICU was 48 hours-72 hours in all patients admitted with AP. But for patients with HTG associated AP was 6.77 days slightly higher than other patients with AP related to other causes was 6.25 days. Mortality was neither reported nor serious complications. The protocol of management applied the fasting and insulin with dextrose infusion was successful in lowering TG level.

A ll patients had high TG and lipase serum levels on the day of admission whereas amylase initially was normal in one patient and high in the others. Hypercalcemia and hypothyroidism were excluded.

Discussion

Acute pancreatitis is a life-threatening inflammatory condition of the pancreas, which has a yearly incidence in the USA estimated to be about 40 cases per 100,000 adults [14] and HTG, is the third most common cause after gallstones and alcohol [15-17]. The etiology of AP is multifactorial [18] however, per NICE guidelines gallstones cause around 50% of cases, 25% by alcohol, and 25% by other factors [19]. In our cohort, AP was confirmed with classical symptoms of upper abdominal pain, supported by high TG serum level and CT scan inflammatory changes of the pancreases.

The two above common causes in addition to other metabolic including hypothyroid and hypercalcemia excluded. None of the patients was on regular medications such as estrogen, estradiol, glucocorticoids, thiazide diuretics; beta-blockers, sertraline, protease inhibitors, valproate, and related drugs, and isotretinoin can cause severe HTG and the chylomicronemia syndrome in patients with inherited lipid metabolic syndromes [20]. These drugs reduce Lipoprotein Lipase (LPL) and hepatic triglyceride lipase activity [21]. Oddly, fenofibrate, which decreases TG levels, causes an increased risk of pancreatitis among patients with T2DM [22]. The incidence of HTG associated AP managed in the ICU in our cohort was 17.4% is higher than a study by Tan et al reported 4% of the same with an increased rate of ICU admission in this group [23]. In our study, all patients with AP were admitted to the ICU and had the same duration of ICU admission of 48 hours-72 hours but the total duration of hospitalization was slightly higher in patients with HTG associated AP than other causes of the same.

However, the risk of AP increases significantly when TG level above 1000 mg/d or 11.3 mmol/L [7], the serum TG level in our patient was less than this level. While in children HTG is considered on fasting plasma TG level above the 95th percentile for age and sex [22,24]. Common cofactors in patients with HTG induced AP are T2DM, obesity, alcohol misuse, and gallstones with more ICU admission in patients with higher serum levels of TG compared with AP patients without HTG [23]. Confirmed increase in severity of AP with rising levels of TG as compared to normal levels specifically with TG level ≥ 11.2 mmol/L associated with significantly increased risk of persistent organ failure and ICU admission, but without a significant increase in mortality compared to those with normal TG levels [25]. Other studies, however, have not demonstrated a correlation between absolute TG levels and disease severity [26]. None of our patients had serious sequences or complications and all survived.

Hyperglycemia itself is known to stimulate chylomicron secretion, thereby potentiating the risk of HTG [27]. Poorly controlled T2DM has been found as the predominant clinical risk factor, irrespective of geographical location; 53% in Denmark, 74% in the United States, and 30% in Japan [28-30]. Similar was observed in three out of four patients in our study.

Our patients had high lipase and amylase except one patient had a false normal serum amylase level. The latter may appear in patients with AP whereas, serum TG levels ranging from 500 mg/100mL to 6000 mg/100mL. initially, was first thought to be due to interference of light transmission in the colorimetric reaction caused by lactescent serum specimens [31]. However, Warshaw, et al. suggested the presence of circulating amylase inhibitors in the serum and urine in patients with HTG induced AP [32]. True amylase levels can be determined after correcting the lactescent serum with serial dilutions with normal saline [31,32].

The management of this group of patients in our hospital protocol was with fasting and IV insulin infusion with dextrose. The response of low TG was observed within 48 hours-72 hours of initiating this regime.

Insulin activates LPL that degrade chylomicrons into glycerol and Free Fatty Acids (FFA) resulting in a rapid reduction of TG levels [33,34]. This protocol appears safe and efficacious for acutely lowering TG levels in this metabolic cause of AP [23] and more efficacious than subcutaneous insulin for treating HTG induced AP [35]. It is an effective management option as it has been shown to reduce TG levels by 87% in 24 h, as compared to a 40% TG reduction with IV insulin alone or 23% with subcutaneous insulin alone [36]. The use of insulin promotes intracellular TG generation within adipocytes and the FFA metabolism in insulin-sensitive cells, which reverts the stress associated with the release of FFA acid from adipocytes [37].

The use of heparin in the management of HTG induced AP remains controversial. Heparin can stimulate the release of endothelial LPL into circulation; however, it may only result in a transient rise in LPL followed by increased degradation of plasma stores causing LPL deficiency [38]. Concerns have been raised about this form of management in this group because of increased bleeding risk, for example, in patients with pancreatic necrosis, and the observed temporary depletion of LPL, if the hepatic degradation of LPL exceeds its production and release, resulting in rebound HTG [39].

Another form of therapy is plasma apheresis; in selected cases, plasmapheresis reduces serum TG levels rapidly and can be used in symptomatic

patients with severe HTG associated with AP [40]. Apheresis is capable of rapidly lowering markedly elevated TG levels, clear pancreatic enzymes, and provides symptoms relief from pancreatitis within 2.5 hours [41,42]. Several studies have shown that apheresis can significantly decrease serum TG and cause both clinical and laboratory improvement when conservative treatment with diet and pharmaceutical drugs fail. [43-46] because lipid apheresis rapidly reduces TG by 50%-80% [27].

TG level is mandatory in all patients presented with AP with or without a history of DM or family history of dyslipidemia however we have a small cohort. Early recognition and initiation therapy will reduce further sequences and improve overall outcomes.

Conclusion

The prevalence of metabolic causes of AP is under-reported in this region and it is imperative to address these potential causes during the medical assessment and investigations phase to establish an appropriately timed diagnosis. Thus, improving the patient's prognosis and ensuring adequate intervention. More studies must be conducted regarding the epidemiology of metabolic etiologies of this emergency condition in the Middle East.

Fund

Any company, agency, or employer did not fund this work.

Data availability

Data will be available upon request and the permission of the Ethics Committee of the Mediclinic Middle East to release the data.

References

Kingsnorth A, O'Reilly D. Acute pancreatitis. *Br Med J*. 332, 1072-1076 (2006).

Wang GJ, Gao CF, Wei D, et al. Acute pancreatitis: Etiology and common pathogenesis. *World J Gastroenterol*. 15, 1427-1430 (2009).

Yoon YK, Ji JH, Mun BS. Hypertriglyceridemia-induced pancreatitis. *Korean Gastroenterol*. 51, 309-313 (2008).

Anderson F, Thomson SR, Clarke DL, et al. Dyslipidaemic pancreatitis clinical assessment and analysis of disease severity and outcomes. *Pancreatology*. 9, 252-257 (2009).

Valdivielso P, Ramirez-Bueno A, Ewald N. Current knowledge of hypertriglyceridemic pancreatitis. *Eur J Intern Med*. 25, 689-694 (2014).

Chang CC, Hsieh YY, Tsai HD, et al. Acute pancreatitis in pregnancy. *Zhonghua Yi Xue Za Zhi (Taipei)*. 61, 85-92 (1998).

Dominguez-Munoz JE, Malfertheiner P, Ditschuneit HH, et al. Hyperlipidemia in acute pancreatitis. Relationship with etiology, onset, and severity of the disease. *Int J Pancreatol*. 10, 261-267 (1991).

Vonlaufen A, Wilson JS, Apte MV. Molecular mechanisms of pancreatitis: current opinion. *J Gastroenterol Hepatol*. 23, 1339-1348 (2008).

Saharia P, Margolis S, Zuidema GD, et al. Acute pancreatitis with hyperlipemia: studies with an isolated perfused canine pancreas. *Surgery*. 82, 60-67 (1977).

Havel RJ. Pathogenesis, differentiation, and management of hypertriglyceridemia. *Adv Intern Med*. 15, 117- 154 (1969).

Ivanova R, Puerta S, Garrido A, et al. Triglyceride levels and apolipoprotein E polymorphism in patients with acute pancreatitis. *Hepatobiliary Pancreat Dis Int*. 11, 96-101 (2012).

Chang YT, Chang MC, Su TC, et al. Association of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) mutation/variant/haplotype and Tumor Necrosis Factor (TNF) promoter polymorphism in hyperlipidemic pancreatitis. *Clin Chem*. 54, 131-138 (2008).

Banks PA, Bollen TL, Dervenis C et al. Classification of acute pancreatitis-2012: revision of the Atlanta classification and definitions by international consensus. *Gut*. 62, 102-111 (2013).

Granger J, Remick D. Acute pancreatitis: models, markers, and mediators. *Shock*. 24, 45-51 (2005).

Fortson MR, Freedman SN, Webster PD 3rd. Clinical assessment of hyperlipidemic pancreatitis. *Am J Gastroenterol*. 90, 2134-2139 (1995).

Toskes PP. Hyperlipidemic pancreatitis. *Gastroenterol Clin North Am*. 19, 783-791 (1990).

Sunil K, Siva K, Sruti J, et al. Hypertriglyceridemia-induced recurrent acute pancreatitis: A case-based review. *Indian J Endocrinol Metab*. 16, 141-143 (2012).

Simon PY, Jonathan PT. Severe acute pancreatitis. *Continuing Edu Anesth, Critical Care Pain*. 8, 125-28 (2008).

Pancreatitis. NICE guideline September 2018. (2018).

Van de Wiel A. The effect of alcohol on postprandial and fasting triglycerides. *Int J Vasc Med*. 862504 (2012).

Schneider J, Liesenfeld A, Mordasini R, et al. Lipoprotein fractions, lipoprotein lipase and hepatic triglyceride lipase during short-term and long-term uptake of ethanol in healthy subjects. *Atherosclerosis*. 57, 281-291 (1985).

Brunzell JD. Clinical practice. Hypertriglyceridemia. *N Engl J Med*. 357, 1009-1017 (2007).

Tan HLE, McDonald G, Payne A, et al. Incidence and management of hypertriglyceridemia-associated acute pancreatitis: A prospective case series in a single Australian tertiary centre. *J Clin Med*. 9, 3954 (2020).

Schaefer E, Leung A, Kravarusic J, et al. Management of severe hypertriglyceridemia in the hospital: A review. *J Hosp Med*. 7, 431-438 (2007).

Kiss L, Fur G, Matrai P, et al. The effect of serum triglyceride concentration on the outcome of acute pancreatitis: Systematic review and meta-analysis. *Sci Rep*. 8, 14096 (2018).

Lloret Linares C, Pelletier AL, Czernichow S, et al. Acute pancreatitis in a cohort of 129 patients referred for severe hypertriglyceridemia. *Pancreas*. 37, 13-22 (2008).

Laufs U, Parhofer KG, Ginsberg HN, et al. Clinical review on triglycerides. *Eur Heart J*. 41, 99-109 (2020).

Pedersen SB, Varbo A, Langsted A, et al. Chylomicronemia risk factors ranked by importance for the individual and community in 108 711 women and men. *J Intern Med*. 283, 392-404 (2018).

Tada H, Kawashiri MA, Nakahashi T, et al. Clinical characteristics of Japanese patients with severe hypertriglyceridemia. *J Clin Lipidol*. 9, 519-524 (2015).

Esparza MI, Li X, Adams-Huet B, et al. Very severe hypertriglyceridemia in a large US county health care system: Associated conditions and management. *J Endocr Soc*. 3, 1595-1607 (2019).

Fallat RW, Vester JW, Glueck CJ. Suppression of amylase activity by hypertriglyceridemia. *JAMA*. 225, 1331-1334 (1973).

Warshaw AL, Bellini CA, Lesser PB. Inhibition of serum and urine amylase activity in pancreatitis with hyperlipemia. *Ann Surg*. 182, 72-75 (1975).

Jain P, Rai RR, Udawat H, et al. Insulin and heparin in treatment of hypertriglyceridemia-induced pancreatitis. *World J Gastroenterol*. 13, 2642-2643 (2007).

Bota VM. Urgent apheresis combined with insulin infusion in hypertriglyceridemia-induced acute pancreatitis. *Am J Emerg Med*. 31, 1-2 (2013).

Roy Y Lu ML, Agito MD. Triglyceride-induced pancreatitis: Diagnostic and therapeutic approach.

Gastroenteral Hepatol Endosc. 1, 1-5 (2016).

Thuzar M, Shenoy VV, Malabu UH, et al. Extreme hypertriglyceridemia managed with insulin. *J Clin Lipidol*. 8, 630-634 (2014).

Gelrud A, Whitcomb DC. Hypertriglyceridemia-induced acute pancreatitis. UpToDate Waltham, USA (2019).

Ewald N, Kloer HU. Treatment options for severe hypertriglyceridemia (SHTG): the role of apheresis. *Clin Res Cardiol Suppl*. 7, 31-35 (2012).

Whayne TF Jr. Concerns about heparin therapy for hypertriglyceridemia.

Arch Intern Med. 170, 108-109 (2010).

Valaiyapathi B, Sunil B, Ashraf A. Approach to Hypertriglyceridemia in the Pediatric Population. *Pediatr Rev.* 38, 424-434 (2017).

Weintraub M, Rassin T, Eisenberg S, et al. Continuous intravenous heparin administration in humans causes a decrease in serum lipolytic activity and accumulation of chylomicrons in circulation. *J Lipid Res*. 35, 229-238 (1994).

Asstrom B, Stegmayr B, Gupta J, et al. A single bolus of a low molecular weight heparin to patients on haemodialysis depletes lipoprotein lipase stores and retards triglyceride clearing. *Nephrol Dial Transplant*. 20, 1172-1179 (2005).

Piolot A, Nadler F, Cavallero E, et al. Prevention of recurrent acute pancreatitis in patients with severe hypertriglyceridemia: value of regular plasmapheresis. *Pancreas*. 13, 96-99 (1996).

Kadikoylu G, Yavasoglu I, Bolaman Z. Plasma exchange in severe hypertriglyceridemia a clinical study. *Transfus Apher Sci*. 34, 253-257 (2006).

Stefanutti C, Di Giacomo S, Vivenzio A. Therapeutic plasma exchange in patients with severe hypertriglyceridemia: a multicenter study. *Artif Organs*. 33, 1096-1102 (2009).

Schneider J, Liesenfeld A, Mordasini R, et al. Lipoprotein fractions, lipoprotein lipase and hepatic triglyceride lipase during short-term and long-term uptake of ethanol in healthy subjects. *Atherosclerosis*. 57, 281-291 (1985).