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Hypertriglyceridemia-induced Acute Pancreatitis in Diabetic Population

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Abstract
Hypertriglyceridemia induced acute pancreatitis has become the third major cause of acute pancreatitis resulting in high morbidity and mortality. Currently, specific mechanism behind association between hypertriglyceridemia in diabetic population and the correlation of causing acute pancreatitis are still not well identified. This literature review summarizes recent understanding of the pathogenesis of hypertriglyceridemia in diabetic populations and its correlation with acute pancreatitis along with clinical management of this disease.
Keywords: Hypertriglyceridemia, Pancreatitis, Diabetic Population

Introduction

Acute pancreatitis is an acute inflammatory process of the pancreas characterized by severe abdominal pain, elevated pancreatic enzymes, and pancreatic changes on abdominal imaging. The disease is the leading cause of gastrointestinal-related hospitalization and a potentially lethal disease. The incidence continues to rise worldwide, and the severity varies ranging from mild to severe with complicated disease resulting in high morbidity and mortality.[1] The most common causes of acute pancreatitis are gallstones, chronic alcohol abuse, and hypertriglyceridemia consecutively. Hypertriglyceridemia (HTG) and low high-density lipoprotein (HDL-C) are commonly seen in diabetic populations and associated with insulin deficiency or insulin resistance. One study revealed from the National Health and Nutrition Examination Survey (NHANES) that 40 % US adults with diabetes receiving statin therapy had triglyceride levels >150 mg/dl. The prevalence of hypertriglyceridemia-induced pancreatitis (HTGP) has been reported to be as high as 22% in severe hypertriglyceridemia cases.[2,3] The risk and severity of acute pancreatitis increase with the increasing levels of serum triglyceride. Early recognition of hypertriglyceridemia in the setting of acute pancreatitis is vital for appropriate management and prevent future recurrence. [4] The purpose of this review is to assess current treatment options for management of HTGP.

Hypertriglyceridemia-induced Pancreatitis (HTGP) Overview

Hypertriglyceridemia (HTG) is a disorder where fasting plasma triacylglycerols (triglycerides, TG) is greater than 150 mg/dL. There is no clear threshold which HTG is known to trigger acute pancreatitis but serum level >1000 mg/dl has been strongly associated with acute pancreatitis.[5] One study assess retrospectively revealed the incidence of acute pancreatitis was 20% in patients with severe HTG (triglycerides >1000 mg/dL). In another retrospective cohort study, the incidence of acute pancreatitis was higher in patients with HTG (15,8%) than other patients with lower triglyceride lvels. [6,7] The etiology of hypertriglyceridemia is multifactorial and divided

into primary and secondary causes. Primary hypertriglyceridemia is due to genetic predispositions and some rare congenital disorders include syndromes that present primarily with hypertriglyceridemia (common) or chylomicronemia (rare). Primary HTG is most often associated with familial hyperlipidemia syndromes (specifically Fredrickson Type I, IV, and V), which usually presents in infancy and early adulthood. Acquired or secondary hypertriglyceridemia is more common, usually due to dietary causes or underlying medical conditions such as diabetes mellitus, metabolic syndrome, central obesity, hypothyroidism, and chronic kidney disease, as well as medication-induced dyslipidemia (with high TG level).[8,9] Both primary (genetic) and secondary HTG are associated with hypertriglyceridemia-induced pancreatitis (HTGP). Secondary HTG does not become the sole risk factor for acute pancreatitis (AP) but the interaction of several conditions in secondary factors or a combination of both primary and secondary factors might result in severe HTG levels. [9] The clinical course of HTGP is often similar to that of acute pancreatitis with presence 2 of 3 conditions: abdominal pain, elevated pancreatic enzymes 3 times over the upper limit of normal, and radiologic evidence of acute pancreatitis. The initial symptoms may not be typical, pain pattern and severity can be in very hard to characterize. The only distinguishing clinical presentation observed is the presence of HTG as well as patients with HTGP are more likely to have severe disease courses and have a higher likelihood of persistent organ failure. Amylase level at presentation could be normal and should be interpreted with caution due to calorimetric interference of lipemic serum, it's advisable to repeat measure of amylase levels with dilutions. [10]

Pathophysiology of Hypetriglyceridemia-induced Acute Pancreatitis in Diabetic Population

Hypertriglyceridemia is the most common lipid abnormality in diabetic populations. Serum triglyceride levels are not simply elevated along with the degree of hyperglycemia, but hyperinsulinemia compensated by insulin resistance is closely related with triglyceride levels. It is postulated that the defect in patients with impaired glucose tolerance is to be the loss of normal insulin sensitivity, leading to compensatory hyperinsulinemia which increased VLDL-TG secretion. Patients with type 2 diabetes have relative insulin deficiency and elevated FFA levels increase hepatic VLDL-TG secretion. In type 1 diabetes which has absolute insulin deficiency, increased FFA levels do not stimulate the secretion of hepatic VLDL-TG because the liver cannot respond to the increased FFA flux due to insulin deficiency. Hence, HTG in type 1 diabetes is primarily due to defect in the removal of VLDL-TG. [11,12]

Specific pathophysiology behind hypertriglyceridemia triggered pancreatic injury is still unknown. Recent studies suggest that the pathogenesis of HTG-AP is associated with the accumulation of free FA, the activation of the inflammatory response, and gene polymorphism. It is postulated that other factors such as the pancreatic lipase activity, the efficiency of clearing fatty acid (FA) from the serum, and the severity of the underlying pancreatic injury are likely to influence the severity of acute pancreatitis. In normal state, triglycerides are packed and transported via VLDLs and chylomicrons. Breakdown of excess triglycerides by pancreatic lipase results in the generation of FFA which has pro-inflammatory and cytotoxic characteristics. Hence, the degree of triglyceride elevation is associated with the severity of acute pancreatitis. Excess FFA is a major cause of ischemia in pancreas where FFA molecules aggregate into micelles with detergent-like properties. This condition is a major cause of ischemia in the pancreas which triggers acidosis, activates lysosomal cathepsin-B and activates and convert acinar cell trypsinogen into trypsin, leading to pancreatic self-digestion and injury. FFA also has a direct cytotoxic effect on pancreatic acinar and vascular endothelial cells,

causing FFA-induced vascular damages such as endothelial dysregulation, vascular leakage, and coagulation activation. Hence, FFA is widely recognized as one of the critical factors to initiate the pathogenesis of HTG-AP [10,13] Another mechanism proposed was non-esterified triglycerides can act as pro-inflammatory substrates, leading to an increase in pro-inflammatory cytokines such as interleukin (IL) 1, IL-16, IL-10, and Tumor Necrosis Factor-α (TNF- α). Furthermore, increase plasma viscosity by hyperchylomicronemia leads to decreased capillary blood flow causing local pancreatic ischemia and necrosis.[14]

Current Management of Hypetriglyceridemia-induced Acute Pancreatitis

Thus far, neither consensus recommendations nor guidelines has been well established for the management of hypertriglyceridemia-induced acute pancreatitis. Management of patients with HTG-AP is to treat acute pancreatitis and lowering serum triglyceride levels with the aim of preventing local - systemic complications therefore reducing mortality. Conservative treatment includes supportive care with intravenous hydration, initial bowel rest, pain control, and nutritional support should be initiated as soon as diagnosis is suspected. Patients should be risk-stratified based on the severity of acute pancreatitis to guide appropriate management. APACHE II and Balthazar score has high sensitivity for predicting complicated acute pancreatitis. Patients with Balthazar grade E and/or APACHE II score ≥ 8 should be considered as severe pancreatitis with high mortality and should managed in intensive care unit. [15,16]

Numerous treatment options for lowering triglycerides levels are insulin drip, heparin, and plasmapheresis. Insulin and heparin therapy have been studied as concomitant and monotherapy options to induce lipoprotein lipase to degrade triglycerides or as an alternative approach for patients who could not tolerate apheresis. Insulin is a recommended treatment for the disease and the use of heparin, however, is still controversial. [16–18] Insulin lowers the level of serum triglycerides by triggering the enzymatic activity of lipoprotein lipase and inhibition of hormone-sensitive lipase. Lipoprotein lipase metabolizes chylomicrons and VLDLs into the free fatty acids and glycerol. Therefore, it ultimately decreases the serum triglyceride levels. The insulin dosage used for therapy is given at a rate of 0,1 – 0,3 Units/Kg/Hour intravenously. It is mandatory to perform glucose test every 30 minutes to every hour. An adjuvant 5% dextrose infusion can be added when the blood glucose level fell below 200 mg/dL. Serum triglyceride levels should be monitored every 12 hours. [16,19] Heparin initially stimulates a rise in lipoprotein lipase which lowers triglyceride levels by converting them to free fatty acids. The decreasing levels of triglycerides is transient, and the degradation of lipoprotein lipase contributes to the depletion of plasma storage of lipoprotein lipase. The depletion leads to an increase of chylomicrons from the endothelium into the circulation may have potential risk of lipotoxicity. Heparin also increase the risk of bleeding in the pancreatic tissues in the setting of acute pancreatitis.[17] In summary, both insulin and heparin can be used in lowering therapy but due to concern of rebound hypertriglyceridemia and risk of bleeding, heparin preferably should be avoided.

The American Society of Apheresis guidelines have approved the use of therapeutic apheresis (plasmapheresis) for severe HTGP in the setting of worsening organ dysfunction or multi-organ failure, worsening systemic inflammation, or lactic acidosis. Plasmapheresis removes triglycerides and chylomicrons from the circulation hence, significantly decrease triglyceride levels and reduce inflammatory cytokines.[4] Plasmapheresis has a major advantage over insulin in treating HTG in terms of reducing triglycerides levels instantly but the treatment costs a lot of money. Patients at a higher risk of problems or showing evidence of organ failure or necrosis may benefit from this treatment. A

systematic review and meta-analysis revealed that the effect of plasmapheresis in HTG-induced AP is not superior to that of conventional treatment, even resulting in a greater economic burden to patients and health care system. [20,21] More comparative, prospective randomized high-quality studies are still needed in the treatment of hypertriglyceridemia induced acute pancreatitis.

Apart from potentially serious mortality caused by acute pancreatitis secondary to hypertriglyceridemia, the overall prognosis is not as terrifying. One nationwide retrospective comparing the prognosis of biliary pancreatitis and HTG-induced AP revealed that patients with HTG-induced AP has less odds of developing comorbid sepsis, septic shock, and less odds of requiring transfusion of blood products compared to those with biliary pancreatitis. In terms of hospital stay and charges, it is stated that it is better in patients with HTG-induced AP than the latter.[22] Intensive insulin therapy can be used as a salvage therapy in patients with severe HTGP, resulting in a remarkable recovery.[19] Long term management is needed to maintain triglycerides level at normal range and to prevent recurrent episodes of HTG-induced AP. The optimal goal triglyceride level is not clearly approved but it is recommended to maintain triglyceride levels below 500 mg/dL. It is advisable for the patients to undergo lifestyle changes with dietary fat and sugar restriction, aerobic exercises, weight loss, and blood sugar control. Triglycerides lowering drugs such as fibrates and omega-3 fatty acids remains to be the drug of choice and can be used to lower serum triglyceride levels and reduce the recurrence risk of HTG-induced AP.[23]

Conclusions

HTG-induced pancreatitis is the third most common cause of acute pancreatitis with complicated pathophysiology. Currently, there is no approved treatment guideline for the management of HTG-induced pancreatitis is available. Initial management including bowel rest, intravenous fluids, and symptomatic treatment is crucial in preventing morbidity and mortality. Following the initial management of HTGP, appropriate measures to decrease serum TG levels are necessary to reduce the risk of relapse. Various treatment modalities such as insulin, heparin, apheresis (plasmapheresis) has found to be effective in reducing triglycerides levels, but each usage needs to be taken into consideration to provide the best for the patients. Lifestyle modification and controlling of secondary triggering factors are necessary to prevent the relapse of HTG-induced pancreatitis. Further investigations on pathological mechanism and the safety of other treatment modalities are needed to guide future therapies and established standardized guidelines of this important clinical entity.

References

1. Li C li, Jiang M, Pan C qiu, Li J, Xu L gang. The global, regional, and national burden of acute pancreatitis in 204 countries and territories, 1990–2019. BMC Gastroenterol. 2021 Aug 25;21(1):332.
2. Roberts SE, Morrison-Rees S, John A, Williams JG, Brown TH, Samuel DG. The incidence and aetiology of acute pancreatitis across Europe. Pancreatology. 2017 Mar 1;17(2):155–65.
3. Barrera Echegoyen FX, Szeto A, Mendez AJ, Garg R, Goldberg RB. The nature and characteristics of hypertriglyceridemia in a large cohort with type 2 diabetes. J Diabetes Complications. 2023 Feb 1;37(2):108387.
4. Yang AL, McNabb-Baltar J. Hypertriglyceridemia and acute pancreatitis. Pancreatol Off J Int Assoc Pancreatol IAP Al. 2020 Jul;20(5):795–800.
5. Kalra SS, Innabi A, Runnstrom M, Lascano J, Patel DC. Severe hypertriglyceridemia, acute pancreatitis and chyloptysis. QJM Int J Med. 2020 Jan 1;113(1):47–8.
6. Sandhu S, Al-Sarraf A, Taraboanta C, Frohlich J, Francis GA. Incidence of pancreatitis, secondary causes, and treatment of patients referred to a specialty lipid clinic with severe

hypertriglyceridemia: a retrospective cohort study. Lipids Health Dis. 2011 Sep 11;10:157.
7. Lloret Linares C, Pelletier AL, Czernichow S, Vergnaud AC, Bonnefont-Rousselot D, Levy P, et al. Acute Pancreatitis in a Cohort of 129 Patients Referred for Severe Hypertriglyceridemia. Pancreas. 2008 Jul;37(1):13.
8. Rygiel K. Hypertriglyceridemia - Common Causes, Prevention and treatment Strategies. Curr Cardiol Rev. 2018 Feb;14(1):67–76.
9. Mitchell-Brown F. Hypertriglyceridemia-induced acute pancreatitis. Nursing2020 Crit Care. 2020 Jul;15(4):18.
10. Guo YY, Li HX, Zhang Y, He WH. Hypertriglyceridemia-induced Acute Pancreatitis: Progress on Disease Mechanisms and Treatment Modalities. Discov Med. 2019 Feb 28;27(147):101–9.
11. Lewis GF, Carpentier A, Adeli K, Giacca A. Disordered fat storage and mobilization in the pathogenesis of insulin resistance and type 2 diabetes. Endocr Rev. 2002 Apr;23(2):201–29.
12. Hirano T. Pathophysiology of Diabetic Dyslipidemia. J Atheroscler Thromb. 2018 Sep 1;25(9):771–82.
13. Kumar BGV, Prasad K, Singh D, Sethy PC. Hypertriglyceridemia induced acute pancreatitis: 4 years' experience from a tertiary care institute and quick literature review. J Fam Med Prim Care. 2022 Jun;11(6):3360.
14. Scherer J, Singh V, Pitchumoni CS, Yadav D. Issues in Hypertriglyceridemic Pancreatitis - An Update. J Clin Gastroenterol. 2014 Mar;48(3):195–203.
15. Cofaru FA, Nica S, FierbinȚeanu-Braticevici C. Assessment of severity of acute pancreatitis over time. Rom J Intern Med. 2020 Jun 1;58(2):47–54.
16. Singh R, Singh RJ, Kakar S, Kaur J. Hypertriglyceridemia Induced Acute Pancreatitis: A Learn from New Cases. Sci Pharm. 2023 Jan 5;2(1):1–13.
17. Garg R, Rustagi T. Management of Hypertriglyceridemia Induced Acute Pancreatitis. BioMed Res Int. 2018 Jul 26;2018:e4721357.
18. Reed JM, Hogan BM, Nasser-Ghodsi N, Loftus CG. Management of Hypertriglyceridemia-Induced Acute Pancreatitis in a Nondiabetic Patient. Mayo Clin Proc Innov Qual Outcomes. 2021 Feb;5(1):230–5.
19. Inayat F, Zafar F, Baig AS, Chaudhry NA, Aslam A, Khan ZH, et al. Hypertriglyceridemic Pancreatitis Treated with Insulin Therapy: A Comparative Review of 34 Cases. Cureus. 2018 Oct 27;10(10):e3501.
20. Yan LH, Hu XH, Chen RX, Pan MM, Han YC, Gao M, et al. Plasmapheresis compared with conventional treatment for hypertriglyceridemia-induced acute pancreatitis: A systematic review and meta-analysis. J Clin Apheresis. Available from: https://onlinelibrary.wiley.com /doi/abs/10.1002/jca.22018
21. Munoz MA, Sathyakumar K, Babu BA. Acute pancreatitis secondary to hypertriglyceridemia. Cleve Clin J Med. 2020 Nov 23;87(12):742–50.
22. Shaka H, Asotibe JC, Achebe I, Pudasaini G, Shaka H, Asotibe JC, et al. Higher Inpatient Morbidity and Mortality in Biliary Pancreatitis Compared to Hypertriglyceridemia-Induced Pancreatitis: A Nationwide Retrospective Study. Cureus J Med Sci;12(9). Available from: https://www.cureus.com/articles/39881-higher-inpatient-morbidity-and-mortality-in-biliary-pancreatitis-compared-to-hypertriglyceridemia-induced-pancreatitis-a-nationwide-retrospective-study Simha V. Management of hypertriglyceridemia. BMJ. 2020 Oct 12;m3109.