

Management of Severe Hypertriglyceridemia

Herni Basir¹, Andi Makbul Aman^{1*}

¹ Department of Internal Medicine, Subdivision of Endocrine Metabolism and Diabetes, Faculty of Medicine Hasanuddin University, Makassar, Indonesia

***Corresponding Author:**

Andi Makbul Aman, MD. Department of Internal Medicine, Subdivision of Endocrine Metabolism and Diabetes Faculty of Medicine Hasanuddin University, Makassar, Indonesia.
Email: makbul_aman@yahoo.com

INTRODUCTION

Hypertriglyceridemia is a condition characterized by increased fasting plasma triglyceride levels with or without other lipoprotein disturbances. Based on The Endocrine Society (ESC) 2010 levels of triglyceride levels are divided into five, namely: normal (<150 mg/dL), mild (150–199 mg/dL), moderate (200–999 mg/dL), severe (1000–1999 mg/dL), and very severe (≥ 2000 mg/dL).¹

Acute pancreatitis is one of the complications of hypertriglyceridemia, along with cardiovascular complications. After gallstones and alcohol, Hypertriglyceridemia is the third most common cause of acute pancreatitis, with an incidence of 4–10%. The incidence of acute pancreatitis increases by up to 4% for each 100 mg/dL increase in triglycerides.² A large-scale study reported that the incidence of acute pancreatitis was 3.2 times greater in the group with triglyceride levels >500 mg/dL compared to those with triglyceride levels <150 mg/dL.²

The prevalence of hypertriglyceridemia is higher in men than in women, with a ratio of 28.7% for men and 21.5% for women, with the highest age in men between 40 and 59 years of age and in women over 60 years of age.³

This paper discusses the management of severe hypertriglyceridemia, especially in special conditions such as pregnancy and acute pancreatitis complications.

ETIOLOGY AND DIAGNOSTIC CRITERIA

Hypertriglyceridemia can be caused by excessive triglyceride production in the liver, decreased hepatic clearance of chylomicrons and VLDL, inefficient lipolysis, or a combination of these three. Triglyceride levels are affected by environmental and genetic factors. Persistent hypertriglyceridemia is typically caused by monogenic, polygenic, or genetic factors with unknown causes. Secondary hypertriglyceridemia is caused by a specific disease condition or the influence of drugs.³

Based on etiology, hypertriglyceridemia is divided into primary and secondary. Primary Hypertriglyceridemia caused by genetic disorders, by Fredrickson, is divided into five types, namely: familial chylomicronemia (type 1), familial combined hyperlipoproteinemia (type 2 B), familial dysbetalipoproteinemia (type 3), familial Hypertriglyceridemia (type 4), and primary mixed hyperlipidemia (type 5), while secondary Hypertriglyceridemia is caused by several conditions such as nephrotic syndrome, type 2 diabetes mellitus, hypothyroidism, chronic kidney disease, alcoholism, pregnancy, and consumption of certain drugs, namely corticosteroids, oral contraceptives, protease inhibitors (for people with HIV), antihypertensive drugs (thiazides and beta blockers).⁴

Diagnostic criteria for hypertriglyceridemia based on the National Cholesterol Education Program Adult Panel

Treatment (NCEP-ATP III) are divided into four levels, namely: normal (<150 mg/dL), borderline (150–199 mg/dL), high (200–499 mg/dL), very high (>500 mg/dL). Meanwhile, based on ESC 2010, triglyceride levels are divided into five,

namely: normal (<150 mg/dL), mild (150–199 mg/dL), moderate (200–999 mg/dL), severe (1000–1999 mg/dL), and very severe (≥ 2000 mg/dL).⁵

Table 1. Diagnostic Criteria for Hypertriglyceridemia Based on NCEP-ATP III and The ESC 2010⁵

NCEP ATP III (3)			The Endocrine Society 2010 ^a		
Normal	<150 mg/dl	<1.7 mmol/liter	Normal	<150 mg/dl	<1.7 mmol/liter
Borderline-high triglycerides	150–199 mg/dl	1.7–2.3 mmol/liter	Mild hypertriglyceridemia	150–199 mg/dl	1.7–2.3 mmol/liter
High triglycerides	200–499 mg/dl	2.3–5.6 mmol/liter	Moderate hypertriglyceridemia	200–999 mg/dl	2.3–11.2 mmol/liter
Very high triglycerides	≥ 500 mg/dl	≥ 5.6 mmol/liter	Severe hypertriglyceridemia	1000–1999 mg/dl	11.2–22.4 mmol/liter
			Very severe hypertriglyceridemia	≥ 2000 mg/dl	≥ 22.4 mmol/liter

CLINICAL OVERVIEW

Until triglyceride levels reach >1000 mg/dL, the clinical manifestations of Hypertriglyceridemia are typically asymptomatic. A portion of the clinical picture that emerges can have an impact on various systems. In the central nervous system as mood and neurocognitive disorders, lipemia retinalis; in the gastrointestinal system as nausea, vomiting, and hepatosplenomegaly; and in the musculoskeletal system as eruptive xanthoma and xanthoma striata palmaris. (Figure 1).⁶

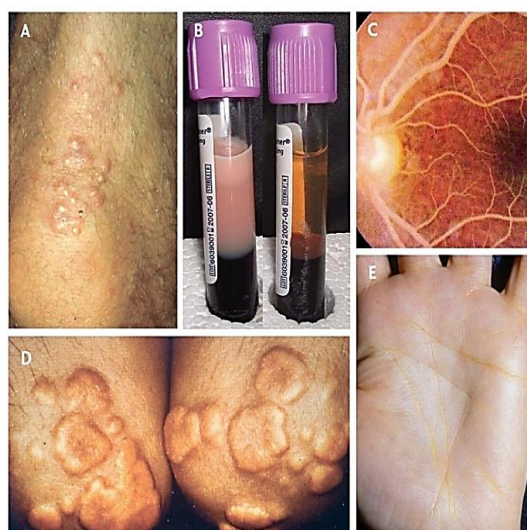


Figure 1. Clinical manifestations of hypertriglyceridemia ⁶

Triglyceride Metabolism

There are two primary pathways for triglyceride metabolism in the body: exogenous and endogenous. The exogenous pathway begins in the small intestine and concludes in the liver, where chylomicrons containing triglycerides derived from food in the small intestine are formed. Chylomicrons then enter the bloodstream through the thoracic duct. Triglycerides and chylomicrons in fat tissue are hydrolyzed by lipoprotein lipase to produce free fatty acids (FFA) and glycerol, which then enter peripheral tissues and are stored as adipocytes and energy sources.⁷

The endogenous pathway is the next step in the synthesis of triglycerides. In this pathway, the liver synthesizes triglycerides from glycerol and FFA derived from three main sources: adipocytes, remnant chylomicrons, and fat derived from food absorbed directly from the small intestine through the portal vein. 10% of healthy individuals undergo *de novo* lipogenesis, whereas 22% of patients with insulin resistance and nonalcoholic fatty liver disease (NAFLD) do. The liver then releases triglycerides and VLDL into the plasma, where VLDL undergoes lipolysis, produces remnant particles, as with chylomicrons, or complete lipolysis, and is converted into LDL. Extra LDL will accumulate in the blood vessels and cause atherosclerosis. Lipoprotein lipase plays an important role in the lipolysis of triglycerides and VLDL.^{7,8}

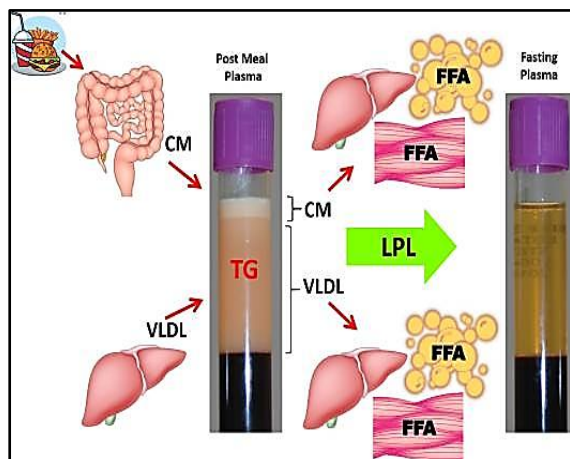


Figure 2. Triglyceride metabolism: exogenous pathway and endogenous pathway⁷

Management of Hypertriglyceridemia

Hypertriglyceridemia management aims to reduce the incidence of acute pancreatitis and cardiovascular complications. Two hypotheses explain the occurrence of hypertriglyceridemia-related acute pancreatitis. The first theory is that high triglycerides cause an increase in chylomicrons, which are then hydrolyzed into free fatty acids (FFA). FFA aggregates micellar structures that cause damage to platelets, vascular endothelium, and acinar cells, which then trigger ischemia and acidosis, then activate trypsinogen, which causes pancreatitis. The second theory posits that increased chylomicrons will increase plasma viscosity, resulting in capillary damage, tissue ischemia, and acidosis, all of which will initiate pancreatitis.⁹

In conditions of severe hypertriglyceridemia, triglycerides must be lowered immediately to prevent further complications. Management in the form of nutritional intervention, anti-hyperlipidemic drugs, and plasmapheresis can be performed in emergency conditions such as acute pancreatitis due to hypertriglyceridemia.¹⁰ The following is the management of hypertriglyceridemia in certain conditions.

Management of Hypertriglyceridemia in Pregnancy

Hypertriglyceridemia is associated with elevated levels of estrogen and human placenta lactogen (HPL) during pregnancy. Estrogen causes an increase in VLDL, while HPL increases the hydrolysis of adipose tissue, resulting in an increase in FFA levels; consequently, triglyceride synthesis increases in the liver. Acute pancreatitis caused by hypertriglyceridemia is more prevalent in the third trimester of pregnancy since triglyceride levels increase with gestational age, increasing two to fourfold and reaching a peak in the third trimester.^{11,12}

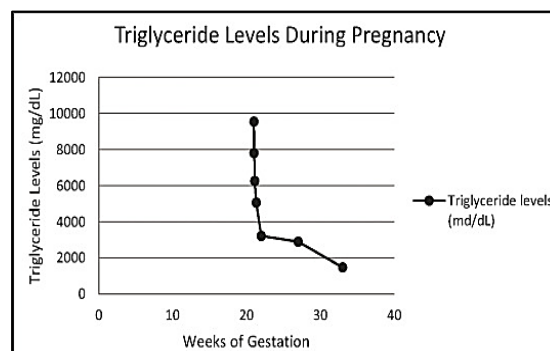


Figure 3. Triglyceride levels during pregnancy¹³

Multidisciplinary disciplines, including nutrition, obstetrics, gynecology, and endocrine metabolism, should be involved in managing acute pancreatitis caused by Hypertriglyceridemia during pregnancy to prevent complications for both the mother and the fetus.

a. Diet and nutrition therapy

To reduce chylomicron levels, the diet must be isocaloric, low in fat, and the total calorie requirement from fat must be <20%. Parenteral nutrition (NP) may be used to optimize the nutrition of pregnant women. It is believed that NPs are effective due to the delivery of systemic lipids through the portal system, which permits peripheral metabolism and transplacental fat release. The diet must contain at least 300 mg of EPA and DHA because a deficiency increases the risk of brain disorders and visual

development in the fetus by <2%. Since omega-3 fatty acids contain EPA and DHA, which decrease liver lipogenesis and increase fatty acid oxidation in the liver and skeletal muscle, they are the nutritional therapy of choice. Several studies have found that nutritional therapy can reduce triglyceride levels by 25 to 30 percent.^{12,13}

b. Pharmacological therapy

b.1. Niacin

Niacin is also known as nicotinic acid or vitamin B3. Niacin inhibits diacylglycerol acyl transferase 2, which is involved in the enzymatic esterification of triglyceride production in hepatocytes. Niacin inhibits hepatocyte HDL catabolism receptors, thereby preventing damage to HDL apo A I due to a decrease in triglyceride synthesis-induced intracellular apo B degradation. The recommended daily intake of niacin during pregnancy is 18 mg/day, but a pharmacological dose of niacin is required to achieve lipid reduction (2 to 3 g/day), and there are no studies on the effects of pharmacological doses of niacin during pregnancy. Niacin is a pregnancy category C drug.^{12,13}

b.2. Heparin

Heparin administered intravenously can decrease triglyceride levels by releasing LPL from endothelial cells into the plasma. Intravenous administration of heparin is still controversial because the increase in LPL is only temporary and rebound Hypertriglyceridemia will occur shortly after therapy is discontinued. Furthermore, the risk of pancreatic bleeding is very high, meaning heparin is not recommended for the treatment of acute pancreatitis in pregnancy.¹²

b.3. Insulin

Insulin therapy administered intravenously can reduce triglyceride levels by accelerating chylomicron degradation, activating LPL enzymes, and inhibiting hormone-sensitive lipase (HSL). Reduced HPL activation will decrease the breakdown of adipocytes and

triglycerides, decreasing circulating FFA and reducing the pancreas' toxic and inflammatory effects. Insulin is administered at a 0.1–0.3 U/kg/hour dose, while blood sugar, electrolytes, and triglycerides are monitored every hour and 12 hours, respectively. Insulin can reduce triglycerides by 50% to 75% in two to three days.^{14,15}

b.4. Plasmapheresis

Plasmapheresis as a therapy for severe Hypertriglyceridemia was first introduced by Betteridge et al. in 1978, indicated in emergency conditions such as pancreatitis due to hypertriglyceridemia in pregnancy with triglyceride levels > 1000 mg/dL. Plasmapheresis can reduce triglyceride levels by 50–80% in the first 24 hours.^{10,16} In addition to rapidly reducing triglyceride levels, plasmapheresis can also inhibit proinflammatory cytokines and adhesion molecules, which play a significant role in the pathogenesis of pancreatitis. This action is extremely safe and effective for treating hypertriglyceridemia-related pancreatitis during pregnancy. Possible adverse effects include urticaria, hypotension, headache, and chills.^{17,18}

Management of Acute Pancreatitis Due to Hypertriglyceridemia

The third cause of acute pancreatitis, after gallstones and alcohol, is Hypertriglyceridemia. The clinical manifestations are identical: nausea, vomiting, and heartburn; however, the resulting complications and organ damage are significantly more severe. There are currently no standard guidelines for the treatment of acute pancreatitis caused by hypertriglyceridemia.^{10,16}

Management of acute pancreatitis generally consists of stopping oral intake, adequate fluid hydration, correction of electrolyte imbalance, administration of adequate analgesia, administration of antibiotics if needed, and specific therapy depending on the cause.¹⁷ Plasmapheresis is the primary treatment option for hypertriglyceridemia related

acute pancreatitis. Plasmapheresis can reduce triglycerides more rapidly than other conservative therapies, such as intravenous insulin and heparin, as well as reduce morbidity and mortality. One plasmapheresis session usually reduces triglycerides by 50-80%. Plasmapheresis removes triglyceride-rich plasma through filtration or centrifugation and replaces it with colloidal fluid components (albumin, plasma, or crystalloids).^{19, 20}

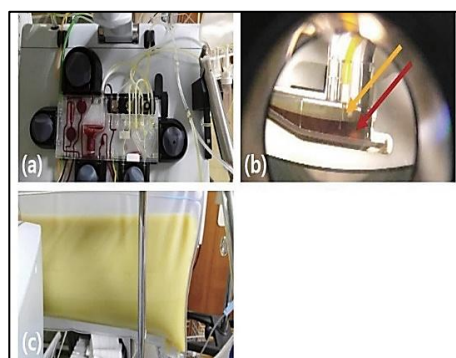


Figure 4. Plasmapheresis: a. Plasmapheresis process b. The patient's blood is separated into two parts c. The bag contains triglyceride-rich plasma after plasmapheresis²²

Other conservative treatment options are intravenous insulin or heparin. Intravenous insulin therapy is considered more minimally invasive and easy to do with a dose of 0.1-0.3 U/kg/hour while monitoring blood sugar every hour and triglycerides every 12 hours, given 5% dextrose if the blood sugar level is <200 mg/dL. For the heparin used is unfractionated heparin (UFH) at a dose of 60 U/kg bw, or low molecular weight heparin (LMWH) at a dose of 1 mg/kg of weight in several studies showing the same effect on both UFH and LMWH in the treatment of acute pancreatitis due to Hypertriglyceridemia.²¹ Insulin is preferred even in non-diabetic patients due to the risk of pancreatic bleeding and rebound Hypertriglyceridemia associated with administering heparin.¹⁶ The following is an algorithm for the management of acute pancreatitis due to Hypertriglyceridemia.

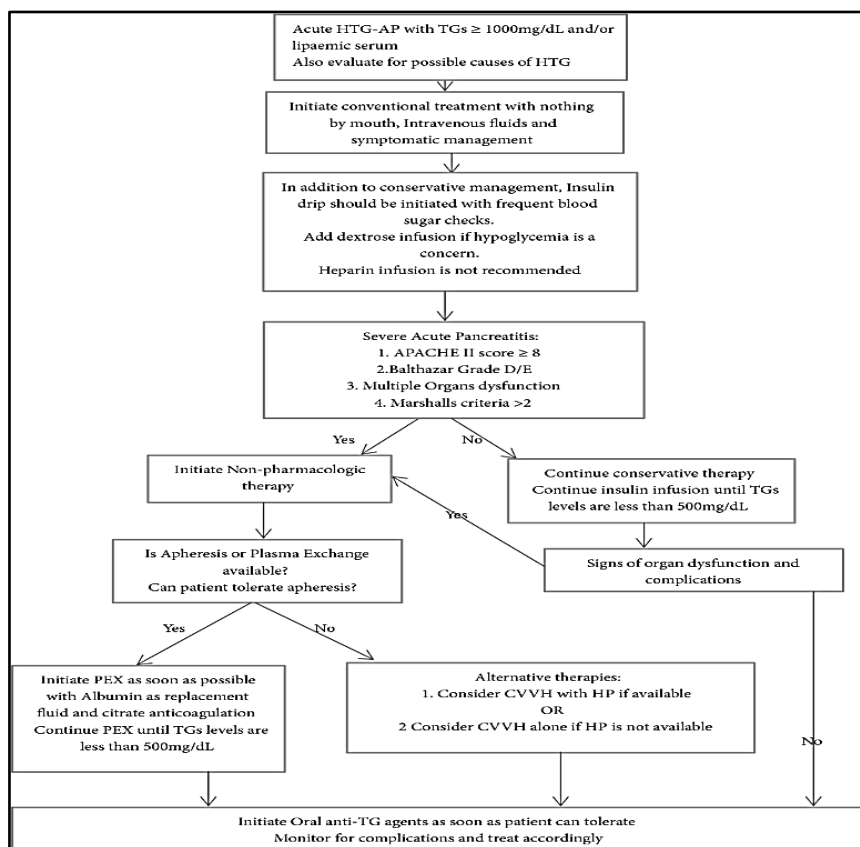


Figure 5. Algorithm for the management of acute pancreatitis due to hypertriglyceridemia¹⁶

SUMMARY

Hypertriglyceridemia is characterized by elevated fasting plasma triglyceride levels with or without other lipoprotein abnormalities. Acute pancreatitis is one of the complications of hypertriglyceridemia, along with cardiovascular complications. After gallstones and alcohol, hypertriglyceridemia is the third most common cause of acute pancreatitis.

In general, the treatment of acute pancreatitis includes cessation of oral intake, adequate hydration, correction of electrolyte imbalance, administration of adequate analgesia, administration of antibiotics if necessary, and specific therapy based on the underlying cause.

Plasmapheresis is the primary treatment option for hypertriglyceridemia-related acute pancreatitis. Plasmapheresis can reduce triglycerides more rapidly than other conservative therapies, such as intravenous insulin and heparin, as well as reduce morbidity and mortality.

REFERENCES

- Berglund L, Brunzell JD, Goldberg AC, Goldberg IJ, Sacks F, Murad MH, et al. Evaluation and treatment of hypertriglyceridemia: An endocrine society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism*. 2012;97(9):2969-89.
- Garg R. Management of Hypertriglyceridemia Induced Acute Pancreatitis. 2018;2018(iv).
- Hernandez P, Passi N, Modarressi T, Kulkarni V, Soni M, Burke F, et al. Clinical Management of Hypertriglyceridemia in the Prevention of Cardiovascular Disease and Pancreatitis. *Curr Atheroscler Rep*. 2021;23(11).
- Dron JS, Hegele RA. Genetics of Hypertriglyceridemia. *Front Endocrinol (Lausanne)*. 2020. 24;11:455.
- European Association for Cardiovascular Prevention & Rehabilitation. ESC Committee for Practice Guidelines (CPG) 2008-2010 and 2010-2012 Committees. *Eur Heart J*. 2011. 32(14):1769-818.
- Zhang X. Hypertriglyceridemia: Its etiology, effects and treatment. *CMAJ*. 2007;176(8):1113-20.
- Wolska A, Yang ZH, Remaley AT. Hypertriglyceridemia: New approaches in management and treatment. *Curr Opin Lipidol*. 2020;31(6):331-9.
- Alves-Bezerra M, Cohen DE. Triglyceride metabolism in the liver. *Compr Physiol*. 2018;8(1):1-22.
- de Pretis N, Amodio A, Frulloni L. Hypertriglyceridemic pancreatitis: Epidemiology, pathophysiology and clinical management. *United European Gastroenterol J*. 2018;6(5):649-55.
- Ewald N, Kloer HU. Treatment options for severe hypertriglyceridemia (SHTG): The role of apheresis. *Clin Res Cardiol Suppl*. 2012;7(SUPPL.1):31-5.
- Kleess LE, Janicic N. Case report severe hypertriglyceridemia in pregnancy: A case report and review of the literature. *AACE Clin Case Rep*. 2019;5(2):e99-103. Available from: <https://doi.org/10.4158/ACCR-2018-0168>
- Goldberg AS, Hegele RA. Severe hypertriglyceridemia in pregnancy. *J Clin Endocrinol Metab*. 2012;97(8):2589-96.
- Kleess LE, Janicic N. Severe Hypertriglyceridemia in Pregnancy: A Case Report and Review of the Literature. *AACE Clin Case Rep*. 2019;5(2):e99-103. Available from: <https://doi.org/10.4158/ACCR-2018-0168>
- 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;10(10).
- Masson W, Rossi E, Siniawski D, Damonte J, Halsband A, Barolo R, et al. Severe hypertriglyceridemia. *Clin e Invest en Arteri*. 2018;30(5):217-23.

16. Garg R, Rustagi T. Management of Hypertriglyceridemia Induced Acute Pancreatitis. *Biomed Res Int*. 2018;2018(IV).
17. Uyar S, Harmandar F, Kök M, Taş Z, Dolu S, Tokuç A, et al. Management of hypertriglyceridemia induced acute pancreatitis and therapeutic plasmapheresis: Report of nine cases and review of literature. *Acta Gastroenterol Belg*. 2017;80(1):71-4.
18. Gubensek J, Buturovic-Ponikvar J, Romozi K, Ponikvar R. Factors affecting outcome in acute hypertriglyceridemic pancreatitis treated with plasma exchange: An observational cohort study. *PLoS One*. 2014;9(7).
19. Gubensek J, Andonova M, Jerman A, Persic V, Vajdic-Trampuz B, Zupunski-Cede A, et al. Comparable Triglyceride Reduction With Plasma Exchange and Insulin in Acute Pancreatitis - A Randomized Trial. *Front Med (Lausanne)*. 2022;9(April):1-7.
20. Chen Z, Huang X, Zhang M, Han N, Ning Y. Rapid reduction in triglyceride levels by therapeutic plasma exchange in patients with hypertriglyceridemic pancreatitis. *J Clin Apher*. 2022;37(1):82-90.
21. Kuchay MS, Farooqui KJ, Bano T, Khandelwal M, Gill H, Mithal A. Heparin and insulin in the management of hypertriglyceridemia-associated pancreatitis: Case series and literature review. *Arch Endocrinol Metab*. 2017;61(2):198-201.
22. Choi J, Kim H, Jun J, Ryu J, Lee HY. Recurrent Pancreatitis in a Pregnant Woman with Severe Hypertriglyceridemia Successfully Managed by Multiple Plasmapheresis. *J Atheroscler Thromb*. 2022;29(7):1108-16.



InaJEMD
 Indonesian Journal of Endocrinology
 Metabolism and Diabetes