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A CASE OF SEVERE HYPERTRIGLYCERIDEMIA WITH LIPAEMIA RETINALIS IN TYPE 2 DIABETES

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ABSTRACT

We present a rare case of a 39-year-old male type 2 diabetes with very severe hypertriglyceridemia (HTG) having a total triglyceride (TG) of > 6,000 mg/dL in the absence of pancreatitis. Informed consent was taken. He was not an alcoholic. Based on literature review, this is one of the highest recorded TG counts in an adult without evidence of pancreatitis. HTG is a common occurrence in clinical practice, but rarely do numbers exceed 2000 mg/dl. It is crucial to evaluate and rapidly lower TG levels to prevent potentially life-threatening complications such as severe pancreatitis. Removal of potential predisposing medications, control of underlying diseases known to cause HTG, and maintenance therapies are essential to prevent reoccurrence.

On 2-9-2021
Male
39 years
Duration of diabetes-11 years.
BMI -27 kg/sqmt.
Waist circumference-95 cms
Blood pressure – 130/80 mm.
FPG-221 mg/dl
PPPG-280 mg/dl
HBA1c-11.6%
TSH- normal.
Triglycerides more than 6117 mg/dl
Treated with combination of rosuvastatin 10 mg + fenofibrate 160 mg for 21 days
On 23-9-2021
FPG- 137 mg/dl
PPPG – 239 mg/dl
Total cholesterol-338 mg/dl
HDL- 22.1 mg/dl
LDL- 80 mg/dl
Triglycerides- 1631 mg/dl
VLDL- 306 mg/dl

Serum of this patient which is white and opaque. (Fig 1)

ATP III Classification of Serum Triglycerides (mg/dL) (Table 1)

<150	Normal
150-199	Borderline high
200-499	High
> 500	Very high

Endocrine society classification of hypertriglyceridemia (Table 2)

The classification of hypertriglyceridemia	**Serum triglyceride (mg/dl)**
Mild and moderate hypertriglyceridemia	150 -999
Severe hypertriglyceridemia	1000 -1999
Verysevere hypertriglyceridemia	>2000

Fredrickson classification of primary hypertriglyceridemia (Table 3)

Type	Elevated lipoprotein	Lipid profile	Clinical manifestations	Relative frequency
I – familial chylomicronemia	Chylomicron	TC + TG +++	Presents in infancy, eruptive xanthomas, recurrent pancreatitis, failure to thrive	<1%
II b – familial combined hyperlipidemia	LDL, VLDL, Apo-B	TC ++ TG ++	Xanthomas less common. Risk of premature cvd	40%
III – familial dysbetalipoproteinemia	IDL	TC ++ TG ++	Palmar xanthomas, risk of premature cvd	<1%
IV – familial hypertriglyceridemia	VLDL	TC + TG ++	Associated w/ dm, insulin resistance, obesity, htn	45%
V – primary mixed hyperlipidemia	Chylomicron, VLDL	TC +++ TG +++	Similar to type 1 but develops in adulthood	5%

TC = total cholesterol; TG = triglycerides; DM = Diabetes Mellitus; HTN = Hypertension; CVD = cardiovascular disease; LDL = low-density lipoprotein; VLDL = very low-density lipoprotein; IDL = intermediate density lipoprotein; Apo-B = apolipoprotein B

DISCUSSION

Hypertriglyceridemia (HTG) is one of the most common lipid abnormalities and has been known to be associated with other metabolic derangements. It is estimated that the number of patients with HTG who have levels exceeding 500 mg/dL has risen to >4 million Americans and that this is more common in the Hispanic-American population.[1,2] The presence of very severe HTG (TG levels greater than 2000 mg/dL) is estimated to be 1.8 cases per 10,000 white adults.[3] Hypertriglyceridemia is defined as TGs >150 mg/dL. The Endocrine Society 2010 guidelines further classify HTG into mild (150–199 mg/dL), moderate (200–999 mg/dL), severe (1000–1999 mg/dL), and very severe (greater than or equal to 2000 mg/dL).[4] Severe and very severe HTG have been shown to increase the risk for acute pancreatitis and cardiovascular disease. When levels are > 1,000 mg/dL, the risk of pancreatitis rises to approximately 5%, and, when levels are >2000 mg/dl, the risk significantly rises to 10-20%.[5]

The prevalence rates of various fasting dyslipidemia in the first phase of ICMR INDIAB study by Joshi S.R. et al restricted to urban and rural populations in 4 states in India was hypercholesterolemia in 13.9%, high triglycerides in 29.5%, low HDL cholesterol in 72.3% and high LDL cholesterol in 11.8%. 79% men and women had abnormalities in at least one of the lipid parameters.

The etiologies of HTG can be further classified into primary and secondary. The Fredrickson classification scheme is commonly used to organize various primary hypertriglyceridemias into different categories (Table 3). In the United States, the most common primary HTGs include familial combined hyperlipidemia (Fredrickson type IIb) and familial hypertriglyceridemia (Type IV).[6] Secondary causes frequently include medical conditions such as obesity, untreated diabetes mellitus, excessive alcohol intake, hypothyroidism, nephrotic syndrome, liver disease, and pregnancy.[4] Certain medications are also well known to cause elevations of TG levels such as estrogens, glucocorticoids, thiazides, beta-blockers, antipsychotics (Olanzapine), immunosuppressants, protease inhibitors, isotretinoin, and bile acid resins.[4,6]

There is a broad spectrum of clinical manifestations of HTG, the most common of which being patients who are asymptomatic. Other symptoms may include mid-epigastric abdominal pain, nausea, and vomiting in relation to acute pancreatitis. Cutaneous manifestations are usually associated with elevations of LDL levels and include eruptive cutaneous xanthomas, palmar crease xanthomas, tendinous xanthomas, tuberous xanthomas, and eyelid xanthelasmas.[7] Ophthalmologic features can include lipemia retinalis. The risk of pancreatitis increases when TG levels exceed 1000-2000 mg/dL and is the third leading cause of pancreatitis after alcohol and gallstones. There are also moderate to highly significant associations between triglyceride values and the risk of coronary heart disease. Diagnosis of specific HTG disorders requires extensive and costly workup. Therefore, the most critical initial step is to exclude secondary causes. This includes medication review, evaluation of body mass index (BMI), hemoglobin A1c, TSH, and renal and liver function testing.[6] When potential secondary causes have been ruled out, patients should be evaluated for various primary HTG.

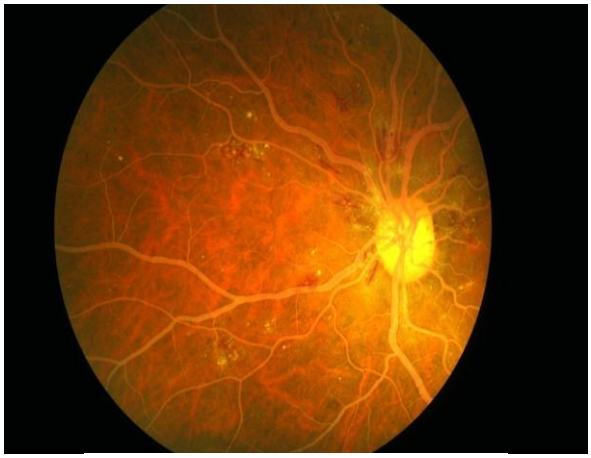
Severe and very severe hypertriglyceridemia can be caused by several genetic defects that impair metabolism by lipoprotein lipase of triglycerides in chylomicrons and very low density lipoproteins (VLDL). This is also called familial chylomicronemia (type 1 dyslipidemia).[8]

Our patient was asymptomatic and he came for evaluation of his diabetes. his triglycrides were more than 6000 mg/dl and fundus was examined by the

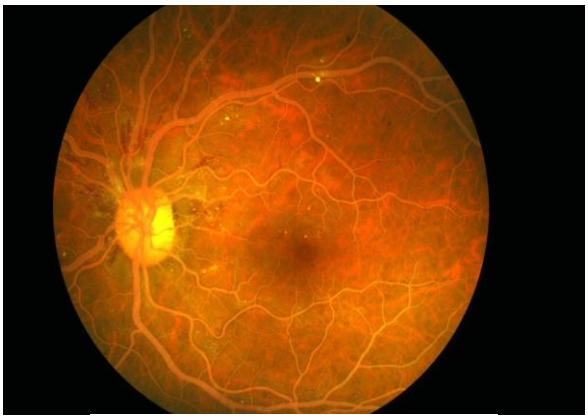
ophthalmologist. Lipaemia retinalis was detected in this patient.

Lipaemia retinalis (Fig 2 and 3) - Lipemia retinalis is an ocular finding associated with elevated plasma levels of triglycerides. It serves as a vital clinical sign of hypertriglyceridemia because acute triglyceride elevations may be asymptomatic at first, delaying treatment of a potentially lethal metabolic disorder. The ocular findings result from light scatter induced by the triglyceride-laden chylomicrons in the plasma.

The early signs of lipemia retinalis occur in the peripheral retina, and as triglyceride levels increase, they spread to the posterior pole. At triglyceride levels of 2500–3499 mg/dL, the peripheral vessels appear creamy and thin; at levels of 3500–5000 mg/dL, the vessels in the posterior pole assume a creamy color; and at levels exceeding 5000 mg/dL, the fundus becomes salmon-colored, with creamy arteries and veins that can be distinguished by caliber only. The clinical appearance is graded accordingly as early, moderate, or marked (Stages I-III, respectively).



Lipaemia retinalis – Right eye (Fig 2)



Lipaemia retinalis – Left eye (Fig 3)

Hypertriglyceridemia is an uncommon but well-recognized cause of acute pancreatitis and has been found to be the underlying etiology in 2%-4% of the patients. A triglyceride level of more than 1,000 mg/dL is typically associated with the development of acute pancreatitis; however, the exact level above which acute pancreatitis may occur is unknown and may vary among the patients.[9] The exact mechanism by which hypertriglyceridemia causes acute pancreatitis is not yet fully understood; however, two theories have been put forward to explain the pathophysiology. According to one of these theories, the metabolism of excess triglycerides, transported as triglyceride-rich lipoprotein particles, known as chylomicrons, occurs in the vascular bed of the pancreas. This results in the release of high levels of free fatty acids (FFAs), which exceed the binding capacity of plasma albumin. The unbound, cytotoxic free fatty acids self-aggregate into micellar structures and can cause damage to the acinar cells, vascular endothelium of pancreatic capillaries, and platelets. The resultant ischemia subsequently produces an acidic environment, which further increases free fatty acid toxicity by causing activation of trypsinogen, and this, in turn, triggers acute pancreatitis.[10,11] The second hypothesis suggests that the elevated levels of chylomicrons cause plasma hyperviscosity. The increase in plasma viscosity leads to the plugging of pancreatic capillaries and ischemia. This enhances acidosis and eventually triggers acute pancreatitis. It may be likely that both these proposed mechanisms play a contributory role in the development of hypertriglyceridemia-induced acute pancreatitis.[10]

AHA-ACC guideline recommendations

The class I recommendation first identifies a population 20 years of age or older who have moderate hypertriglyceridemia defined as fasting or nonfasting triglycerides (TG) 175-499 mg/dL (1.9-5.6 mmol/L) and advises searching for and treating secondary factors (see Table 4).

Table 4

Lifestyle	Obesity	Metabolic syndrome	
Secondary disorders	Diabetes mellitus or hypothyroidism	Chronic liver disease	Chronic kidney disease and/or nephrotic syndrome
Medications	Hormone related: oral estrogens tamoxifen raloxifene retinoids glucocorticoids	Immune related: cyclosporine tacrolimus sirolimus cyclophosphamide interferon	Other: beta blockers thiazides atypical antipsychotics rosiglitazone bile acid sequestrants l-asparaginase

Use of statin therapy in moderate hypertriglyceridemia

The second recommendation (class IIa) is targeted at adults age 40-75 with moderate or severe hypertriglyceridemia >500mg/dL (5.6mmol/L) with an ASCVD risk of 7.5% or higher for whom the above factors have been addressed. It identifies persistently elevated TG as a risk enhancer which favors initiation or intensification of statin therapy to reduce ASCVD risk.

Use of statin therapy in severe hypertriglyceridemia

The third recommendation (class IIa) endorses the initiation of statins in those with severe hypertriglyceridemia with ASCVD equal to or greater than 7.5% in concert with addressing secondary factors.

Other therapies in severe hypertriglyceridemia

The fourth recommendation (class IIa) is directed towards those with severe hypertriglyceridemia and especially those with triglycerides ≥1,000 mg/dL (11.3mmol/L). It is more complex and addresses many of the factors traditionally discussed in the management of hypertriglyceridemia. Although most cases of severe hypertriglyceridemia have a genetic component, secondary conditions often contribute and addressing secondary factors is again recommended.

The Categories of Hypertriglyceridemia, Lipoproteins Involved, Goals and Therapies (Table 5)

Category of hypertriglyceridemia	Elevated lipoprotein(s)	Goal	Treatment
Moderate htg - fasting or nonfasting triglycerides 150-499 mg/dl	Vldl (atherogenic similar to ldl)	Reduce vldl and ascvd risk	-Address secondary factors -Statin
Severe htg - fasting triglycerides ≥500 mg/dl	Elevated vldl *and* chylomicrons	Reduce ascvd risk *and* risk of acute pancreatitis	-Address secondary factors -Statin *and* -Very low fat diet -Avoid refined carbohydrates and alcohol -Omega-3 fatty acids -Fibrates

Treatment of hypertriglyceridemia Optimizing lifestyle (fat free diet, cessation of alcohol consumption, weight loss, exercise), control of diabetes and hypothyroidism are important measures in the tratment of very severe hypertriglyceridemia. Conventional pharmacological therapy of hypertriglyceridemia includes: fibrates, niacin, statins, ezetimibe, omega-3-fatty acid. Fibrate therapy can reduce plasma triglycerides levels by modulation of the activity of peroxisome proliferator–activated receptor-α in the liver, with a decrease of hepatic secretion of very-lowdensity lipoprotein (VLDL) and increased lipolysis of plasma triglycerides.[12] Barter PJ and Rye KA state in an article published in 2006 in Circulation that fibrates significantly reduce plasma triglycerides levels and raise the HDLcholesterol levels.[13] Nicotinic acid inhibits the lipolysis in adipose tissue and reduced plasma fatty acids. Daily administration of 3 gram of nicotinic acid may lead to reduction of plasma triglyceride levels by 45% and increase plasma HDL-cholesterol.[14] Statins reduce

levels of the cholesterol and may reduce triglycerides levels by inhibiting hydroxymethylglutaryl coenzyme A reductase.[12] Ezetimibe is a cholesterol absorption inhibitor that significantly reduce LDL-cholesterol, triglycerides levels and increase the HDL-cholesterol levels.[12,15] Omega-3 fats may decrease triglycerides levels by 20% when administered with other triglyceride-lowering therapies.[12,16] The proposed mechanism by which omega-3-fatty acid decrease triglycerides levels are decline in hepatic production of VLDL and the increase clearance of VLDL.[17]

Insulin will reduce triglyceride levels, by reducing the synthesis of triglycerides and also by accelerating their metabolism. Insulin works via a variety of pathways to reduce levels of both triglycerides and free fatty acids. Insulin may rapidly reduce free fatty acid levels, via mechanisms that are *independent* of triglyceride levels (Chow 2011, Afari 2015). Thus, it is possible that insulin could rapidly reduce free fatty acid levels, *before* the total level of triglycerides was reduced. This could explain how insulin is more effective than plasmapheresis clinically, despite causing a slower clearance of triglycerides.

The insulin infusion should generally be infused between 0.1-0.3 units/kg/hr depending on the patient's degree of insulin resistance. Higher insulin infusion rates will achieve more rapid decline in triglyceride levels. An infusion of dextrose (usually 10% dextrose in water) is often needed to avoid hypoglycemia, with titration of the dextrose infusion based on the serum glucose to target glucose of ~150-200 mg/dL. This is fairly easy to do within an ICU, with attention to avoid the following complications:

- Hypoglycemia
- Hypokalemia, hypophosphatemia (Cycle electrolytes and replete as needed).
- Hypervolemia (Follow volume status and consider furosemide if the patient is retaining lots of volume from the dextrose infusion)

It's unclear exactly when to stop the insulin infusion. It might be ideal to continue the infusion until the triglyceride level is <500 mg/dL. However, this can take a while. For patients with mild pancreatitis who are already clinically improving, targeting a triglyceride level <1,000 mg/dL may be reasonable.[21]

Many patients with hypertriglyceridemic pancreatitis have underlying diabetes. These patients may be bridged from an insulin infusion to subcutaneous long-acting insulin. The dose of subcutaneous insulin varies, with some type II diabetic patients requiring surprisingly high doses of long-acting insulin.

Other triglyceride-lowering therapies include plasmapheresis and lipoprotein lipase gene therapy.

Indications of plasmapheresis

1. Patient with triglyceride levels above– 1000 mg/dl that do not respond to conventional therapy,
2. Values of serum lipase that exceed three– times reference values,
3. Severe hypocalcemia,
4. Lactic acidosis.[18]

The beneficial effect of plasmapheresis is generated by a rapid decrease in triglyceride levels. A multicenter study in which 17 patients with very severe hypertriglyceridemia were included, revealed that plasmapheresis significantly reduces mean plasma triglycerides (from 1929 mg/dl to 510 mg/dl) and total cholesterol levels (from 762 mg/dl to 227 mg/dl).[19] Plasmapheresis performed in 18 patients that did not respond to conventional therapy reduced levels of triglycerides from 1977.1 mg/dl to 692.6 mg/dl and levels of cholesterol from 436.7 mg/dl to 222 mg/dl.[20]

Plasmapheresis has a number of drawbacks compared to insulin infusion:

- More invasive (Requiring hemodialysis catheter).
- More expensive plasmapheresis *doubled* the total hospitalization cost.
- Requires anticoagulation, which causes complications (citrate may cause hypocalcemia, whereas heparin may cause bleeding and possibly increased mortality; Gubensek 2014).
- If fresh frozen plasma is used for replacement, this may cause allergic or infectious complications.
- Extracorporeal blood circuits can cause leukocyte activation, increasing inflammation.
- Plasmapheresis requires buy-in from hematology consultants and the assistance of specialized nurses (who may be unavailable during off hours). Most hospitals lack plasmapheresis capabilities. These factors may lead to considerable delays before therapy can be initiated.

Available evidence suggests that insulin is equivalent or superior to plasmapheresis. This data is admittedly quite limited. However, when combined with the drawbacks of plasmapheresis, this suggests that insulin may be a first-line therapy for hypertriglyceridemic pancreatitis.[21]

Lipoprotein lipase deficiency is an autosomal recessive condition characterized by reduced chylomicron triglyceride lipolysis and persistently elevated triglyceride levels. An adeno-associated virus vector (AAV)1-lipoprotein lipase Ser447X gene therapy, variant of the human lipoprotein lipase gene that administered intramuscularly to patients with lipoprotein lipase deficiency can reduce significant the levels of plasma triglycerides.[22,23,24]

Our patient was prescribed combination of roosuvastatin 10 mg and fenofibrate 160 mg and treatment was given for controlling blood glucose. He responded well with triglycerides reducing from 6000 mg/dl to 1631 mg/dl. In

the second visit rosuvastatin was increased to 20 mg and fenofibrate was continued.

CONCLUSIONS

Hypertriglyceridemia is frequently encountered in clinical practice. Very severe hypertriglyceridemia above 1000-2000 mg/dL should be evaluated for primary and secondary causes. Rapidly lowering of triglyceride levels is essential to prevent serious complications such as acute pancreatitis. Long term effects of elevated TG count have also been associated with coronary artery disease. Rapid lowering can be achieved with intravenous insulin drip, even in nondiabetic patients. Maintenance therapy with dietary changes and medications such as fibrates is highly recommended.

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