MALAYSIAN JOURNAL OF BIOCHEMISTRY & MOLECULAR BIOLOGY

The Official Publication of The Malaysian Society For Biochemistry & Molecular Biology (MSBMB)
http://mjbmb.org

INSULIN THERAPY FOR TREATING HYPERTRIGLYCERIDEMIA – A CASE REPORT FROM A TERTIARY CARE HOSPITAL IN COASTAL KARNATAKA, INDIA

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History
Received: 12th March 2020
Accepted: 3rd June 2020

Keywords:

Hypertriglyceridemia; dyslipidemia; insulin; fenofibrates

Abstract

Severe hypertriglyceridemia (HTG), being one of the most common causes of dyslipidemia is hazardous and predisposing factor leading to increased risk of atherosclerosis and acute pancreatitis. Various genetic disorders leading to disordered metabolism of triglycerides result into primary HTG. We are reporting a case of a 49-year-old non-diabetic male with severe HTG with triglyceride levels of 1032 mg/dl. He was treated with insulin infusion therapy along with fenofibrates and saroglitazar for 3 days as a result of which, TG levels came down to 331 mg/dl. During his follow up visit after 6 months, normal triglyceride level of 105 mg/dl was found. This implies that aggressive treatment and monitoring are required in such patients to ensure an appropriate and optimal therapeutic response and to prevent the development of atherosclerosis and coronary heart disease in future.

INTRODUCTION

Elevated levels of triglyceride in the blood stream > 150 mg/dl is termed as hypertriglyceridemia (HTG). TG levels > 800 mg/dl is a major risk factor for acute pancreatitis and secondary risk factor for atherosclerosis. The National Cholesterol Education Program has stratified TG levels into 4 groups i.e < 150 mg/dl considered to be normal, range between 150-199 mg/dl is considered as borderline high, 240-499 mg/dl of high range and a very high range is considered to be above 500mg/dl [1].Ischemic stroke can be caused due to very high levels of triglyceride resulting in atherogenicity and thrombosis. Patients suffering from HTG should be treated with reduction in weight, modification of diet and regular exercise. Diet especially rich in refined carbohydrates and high glycemic index are preferred [2]. Consumption of alcohol should be strictly restricted. A meta-analysis study which was performed on several patients on follow up for greater than 10 years depicted increased triglyceride levels by 88mg/dl leading to increased cardiovascular risk by 76% in women and 32% in men independent of HDL cholesterol levels [2]. Hypertriglyceridemia is divided into 2 categories primary and secondary. Various genetic disorders leading to disordered metabolism of triglycerides result in primary HTG. High dietary fat, obesity, uncontrolled diabetes mellitus, alcohol abuse, renal disease which is of end stage nature, hypothyroidism, chronic and acute kidney diseases, infectious disease such as human immunodeficiency virus (HIV) and many drugs which are used as anti-HIV agents are the secondary causes for HTG [3].

The evidence gathered from anecdotes states that heparin and insulin combination can be fruitful in treating severe hypertriglyceridemia associated pancreatitis, but the usefulness of this treatment is yet to be established. Mikhail et al reported a case of a 38-year-old female with TG levels of 10,560 mg/dl being brought down to 712 mg/dl by treating with subcutaneous insulin lispro for 3 days [4]. Twilla et al reported a case of 39-year-old male with TG levels of 5366 mg/dl being brought down to 717 mg/dl after administration of insulin continuously and subcutaneous heparin for 5 days [5]. Studies done in European population showed a prevalence of 10-19% patients developing acute pancreatitis due to high TG levels > 1000mg/dl [6]. In an Indian study

conducted by the ICMR the prevalence of HTG was found to be 29.5 % which was restricted to the population of both urban and rural population in the four states of the country [7]. The success rate of treating HTG patients with insulin is yet to be known and further prevalence studies are required in order to confirm this.

Mechanism of Insulin Therapy for Treating HTG Patients

Insulin diminishes the serum triglyceride levels by stimulating the activity of enzyme lipoprotein lipase and by inhibiting lipase which is a hormone sensitive enzyme. The metabolism of chylomicrons and very low-density lipoprotein (VLDL) take place by the enzyme lipoprotein lipase by transforming them into free fatty acids and glycerol, as a result of which it diminishes the levels of serum triglyceride. The diminished activity of hormone sensitive lipase results in decline in breakdown of adipocyte-triglyceride which further results in diminished release of free fatty acids in the blood circulation controlling the venomous effects on the pancreas thereby bringing down the rate of inflammatory process [8]. Insulin also rests the tissue of pancreas and may improve the total paralysis state of the immune system via increasing the regulation of human leukocyte antigen expression on monocytes and thereby leading to decline in death of cells [9]. On administration of insulin intravenously the levels of TG are found to decrease by 50-75% within 2-3 days [10].

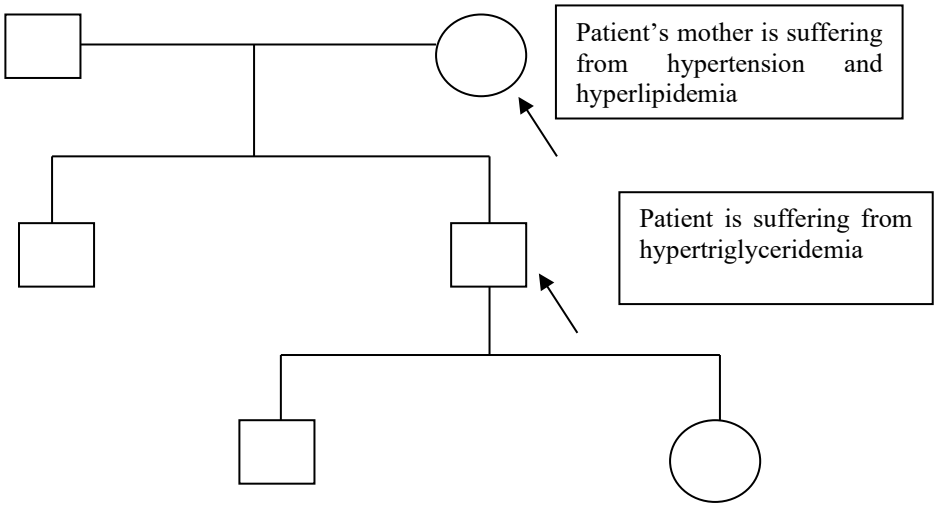
In India the magnitude of dyslipidemia is too high which demands a modification in the lifestyle. Thus, the evaluation and management of this disorder should be more often looked into for better prognosis of the disease and to prevent further risk of atherosclerosis and CAD. Here, we present a case of middle-aged male with severe familial HTG presenting with fatigue and was successfully treated with insulin infusion, fenofibrate and saroglitazar.

Case Presentation

Our patient is a 49-year old average-built man who was admitted to ICU at a hospital in coastal Karnataka for HTG. The patient presented with a history of general weakness in the last one month which was progressive and as a result could not perform his daily activities smoothly. On examination his vitals were found to be stable and systemic examination was unremarkable. Lipemia retinalis, xanthomas and xanthalesma were not present. On examination normal blood pressure of 130/80, body-mass index of 28.2, pulse rate of 86/minute and respiratory rate of 18/minute were found. On inquisition, he was found to be a non-smoker, non- alcoholic, non-vegetarian without any physical exercise. He was not taking any lipid lowering medications before. He had constipation since past one week and was under stool softeners. The patient didn't have any history of hypertension, heart complications and diabetes mellitus in the past.

The patient was found to be afebrile, conscious, coherent and co-operative. Respiratory and cardiovascular examinations were found to be un-remarkable. 2D Echo showed normal biventricular systolic function, no abnormality in wall motion, mitral valve prolapse and mild mitral regurgitation. US abdomen showed grade 1 fatty liver and 4.5 mm renal calculus. On inquisition his mother was found to have hyperlipidemia and hypertension since many years.

FAMILY TREE



Fasting serum sample was sent to Biochemistry lab for the lipid profile analysis. 2 ml of blood sample was collected from the patient and was sent to biochemistry lab for centrifugation and analysis. The clear sample was utilized for lipid profile analysis after centrifuging the sample for 10 minutes at 3000r.p.m. The total cholesterol, triglyceride and high-density lipoprotein were analyzed by Cobas 6000 autoanalyzer from Roche Diagnostics. Plasma LDL cholesterol could not be evaluated by Friedewald's formula as triglyceride levels were abnormally high[11].Several other biochemical tests such as liver function test, renal function test, thyroid panel test, complete blood count test, all blood glucose parameters, HIV test, amylase, lipase, creatinine phosphokinase (CPK), calcium, vitamin B12 and complete urine analysis with microscopy were done.

On analysis the following results were obtained: Total cholesterol: 245 mg/dl, Triglycerides:1032 mg/dL, High-density cholesterol: 37 mg/dl and Total Cholesterol/HDL-Cholesterol ratio: 6.6, Vitamin B12- 242.5 pg/ml. LDL cholesterol levels could not be determined by Friedewald's formula (LDL CHOLESTEROL=TC –TG/5- HDL CHOLESTEROL) due to very high triglyceride levels. As the biochemical reports showed high triglyceride levels of 1032 mg/dl the patient was admitted at ICU and was given insulin infusion at the rate of 1ml/hour to treat HTG. Sugar levels were monitored from time to time. He was started on saroglitazar 4mg/day, fenofibrate 160 mg/day, and ω3 fatty acids after which his triglyceride levels showed improvement. Proper monitoring of blood sugars was performed and repeated triglyceride levels were checked until it came down to normal levels.

TREATMENT AT THE HOSPITAL

The patient was given insulin infusion for 3 days at the ICU and fenofibrates to treat HTG. The preferred drugs used for patients having triglyceride levels above 1000 mg/dl are fibrates and niacin. Insulin infusion, use of fenofibrate along with saroglitazar brought down the triglyceride levels.

DISCUSSION

HTG patients are more prone to develop acute pancreatitis and atherosclerosis which is of premature nature. Insulin infusion, long term use of pharmacological agents like fibrates and niacin, use of fish oil are used to treat HTG patients having TG levels >1000 mg/dl [12].

Based on the guidelines by ATP 3, fibrates are considered as the vital drug for treating patients with severe HTG > 500 mg/dl along with niacin as supporting therapy. Statins, niacin, ω3 fatty acids and fibrates are considered to diminish levels of TG by 10%, 18%, 20% and 36.3% respectively. Among those fibrates have been considered as the most effective drug among all the anti-hyperlipidemia drugs. If fibrates are administered in a patient along with statins there is an elevated risk of rhabdomyolysis which is nearly two times in comparison with fibrate myopathy but the overall risk is very less. The most common unfavorable effects which are found in association with fibrates are cholelithiasis, myopathy and elevation in creatinine levels in a reversible manner [8]. The levels of serum TG are brought down by 25-50 % by fibrates and the levels of HDL-cholesterol are elevated by 5-20%. Fibrates assist in diminishing the levels of apolipoprotein B, non-HDL cholesterol, LDL cholesterol particles. There may also be a possibility of shifting of small LDL cholesterol particles towards the LDL particles which are larger in size. However, it does not show any noted effects in lipoprotein A. Cardiovascular events in patients with high levels of TG and low levels of HDL cholesterol are found to decline if the patients are treated only with a single drug i.e fibrates [13].

Past studies suggest that atherosclerosis develops from HTG through several mechanisms. Atherosclerosis promotion, abnormality in the function of endothelial tissues, oxidative stress resulting from lipid derived free radicals, vasodilatation leading to impairment of endothelial tissues, thrombogenicity promotion, elevated plasma viscosity, elevated levels of plasma fibrinogen levels, decreased activity of fibrinogen, elevated clotting factor levels when compared to normolipidemic control and association of increased markers of atherosclerosis such as CRP, fibrinogen and circulating adhesion molecules are the possible mechanisms [14]. The patient in this case was treated with insulin infusion to bring down the abnormal TG levels.TG is converted to glycerol and fatty acids which is hydrolyzed by an enzyme known as lipoprotein lipase (LPL) which is produced by adipose tissues and capillary endothelial cells of muscles. This enzyme also helps in removal of TG from plasma and plays an essential role in decreasing serum TG levels [15]. The synthesis of LPL is promoted by insulin which helps in reducing levels of TG [16]. The translocation and release of tissue bound LPL which is termed as a heparin binding protein with high affinity in the capillary endothelium is promoted by heparin, an anticoagulant. Injecting heparin intravenously leads to release of LPL into the stream of blood in humans and animals' population. Intravenous insulin and anticoagulant heparin were used in various subjects to bring down the TG levels abruptly so as to elevate the LPL activity and increase the damage of chylomicrons. The LPL activity which prevents the transformation of enzyme into units that are monomeric, and which are not active in nature is maintained by binding of heparin via the region of carboxyl terminal end. For localization of LPL to cell membranes rich in proteoglycan optimal LPL binding to heparin is required for directing of fatty acids which are created newly to tissues in an efficient manner [17-18]. 5 cases were reported by Berger et al where serum TG levels were found to be diminished to <500 mg/dl within a span of 3 days in each of the cases [19]. Other two cases with similar findings were reported by Jain et al with insulin and heparin [20].

In this patient repeated triglyceride levels were monitored thereafter, and the triglyceride levels finally came down to 331 mg/dl after treatment before discharge. The patient was discharged with Vitamin E, statin, acidity reliever and Vitamin B12 medications. When the patient came back for follow up after 6 months normal triglyceride level of 105 mg/dl was found. Hence, aggressive treatment and monitoring are required in such patients to ensure an appropriate and optimal therapeutic response and to prevent the development of atherosclerosis and coronary heart disease in future.

INFORMED CONSENT

Informed consent was taken from the patient.

ACKNOWLEDGMENT

We would like to thank the Medical Record Department of the hospital for allowing us to take the details of the patient.

CONFLICT OF INTEREST

The authors state that the study is without any conflict of interest.

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