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Treatment of Very Severe Hypertriglyceridemia ： A Case Report

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Abstract

Hypertriglyceridemia is common in diabetic patients and patients with severe hypertriglyceridemia refractory to conventional treatment are occasionally identified. This report describes a diabetic patient with triglyceride levels as high as 18150 mg/dL and concurrent acute pancreatitis. Multiple antilipidemic drugs were prescribed including statin, fibrate, ezetimibe and fish oil in addition to insulin treatments. In the one year follow up period since the time of his initial diagnosis and hospitalization, the patient's triglyceride levels fluctuated from 1000 to 4000 mg/dL, but no further signs and symptoms of acute pancreatitis were experienced. This case serves to relay the various treatment modalities available to diabetic patients with severe hypertriglyceridemia. (J Intern Med Taiwan 2008; 19: 164- 169)

Key Words ： Severe hypertriglyceridemia, Diabetes mellitus, Acute pancreatitis

Introduction

The most common pattern of dyslipidemia in type 2 diabetic patients is elevated triglycerides and low high density-lipoprotein (HDL) cholesterol levels. Diabetic patients with genetic lipoprotein disorders may suffer from severe hypertriglyceridemia. An alteration in lipid profiles places these patients at an increased risk for developing acute pancreatitis.

In this report, we describe a case of male patient with type 2 diabetes with triglyceride levels measured as high as 18150 mg/dL. In addition, the various treatment modalities employed to manage this patient's hypertriglyceridemia are also described.

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Case Report

A 44-year-old Chinese man was admitted to the Far Eastern Memorial Hospital on January 2006 complaining of abdominal pain. A diagnosis of type 2 diabetes mellitus, severe hypertriglyceridemia and acute pancreatitis was rapidly made. At the time of admission, the patient's body weight was 79 kg and height was 1.7 m (body mass index was 27.3 kg/m^2) with a waist circumference of 86 cm. His blood pressure was 130/70 mmHg. No other abnormalities were noted on physical examination, except for epigastric tenderness. In particular, no evidence of lipemia retinalis was observed. The laboratory investigations included marked hypertriglyceridemia of 18150 mg/dL (normal: <200 mg/dL) and hyperamylasemia of 526 IU/L (normal: 30-110 IU/L). Other abnormal laboratory results included total cholesterol 1550 mg/dL (normal: <200 mg/dL), HDL cholesterol 234 mg/dL(normal: >35 mg/dL), fasting blood glucose 196 mg/dL (normal: 70-110 mg/dL), glycosylated hemoglobin 11.4%(normal: 4.3%-6.6%), uric acid 9.9 mg/dL (normal: <7 mg/dL) and white blood count 13.2x10^3/ μ L (normal:3.8-10.4x10^3/ μ L).

The patient's past history was generally unremarkable. The patient used to smoke one pack of cigarette per day for the past 20 years and consumed two to three cans of beer per night. The patient's father and brother both were diagnosed with hyperlipidemia. His father's low density lipoprotein (LDL) cholesterol level and triglyceride levels were 120 mg/dL and 325 mg/dL, respectively and his brother's were 162 mg/dL and 1200 mg/dL. Both the father and brother were receiving anti-hyperlipidemic therapy at another medical facility. Other noteworthy items include the fact that the patient's father suffered from cerebrovascular disease and his brother had been diagnosed with several episodes of acute pancreatitis.

The patient was permitted nothing *per os* for his first 3 days of hospitalization. Glucose, electrolytes fluids and a continuous infusion of regular insulin were administered. At the time of discharge, the patient was prescribed twice daily premixed insulin injections: 35 units before breakfast and 25 units before dinner. This patient was also prescribed a combination of atorvastatin 10 mg and fenofibrate supra 160 mg.

Two months following his discharge from the hospital, the patient's triglyceride level was still elevated at 4080 mg/dL and the LDL cholesterol levels was 300 mg/dL. As a result, the antihyperlipidemic drugs were increased to atorvastatin 40mg and fenofibrate supra 320 mg. In addition, he was educated regarding the risk and symptoms of rhabdomyolysis. At his 5 month evaluation, the patient's triglyceride level was 2960 mg/dL, LDL cholesterol was 210 mg/dL, and creatinine kinase (CK) level was 61 IU/L(normal:20-170 IU/L). In light of the persistently unsatisfactory lipid profile, ezetimibe 10 mg daily was added to the patient's drug regimen. Poor lipid control persisted over the next several months despite aggressive monitoring and the prescription of various combinations of anti-hyperlipidemic agents including statin, fibrate and ezetimibe. Over this time, the patient's triglyceride levels fluctuated between 1000 to 4000 mg/dL.

At the time of this last evaluation on May 2007, the triglyceride level was 1404 mg/dL, LDL cholesterol was 152 mg/dL, apolipoprotein B was 150 mg/dL, HbA1c was 6.8%, uric acid was 5.3 mg/dL and free T4 and TSH were 1.34 ng/dL and 2.20 μU/mL respectively. The current list of medications included atorvastatin 40 mg, fenofibrate supra 320 mg, ezetimibe 10 mg, and aspirin 100 mg daily. In addition, the patient administered premixed insulin 30 units in the morning and 20 units before dinner. While orlistat was suggested for control of body weight, the patient refused. Instead, it was recommended that the patient include fish oil as part of his treatment.

This patient did not suffer from any further episodes of pancreatitis following discharge from the hospital, and lifestyle modifications included cessa-

Table 1.Average effects of different classes of lipid lowering drugs on serum lipids

Drug Class	Serum LDL Cholesterol	Serum HDL Cholesterol	Serum Triglycerides
Bile acid sequestrants	↓ 15 to 30%	No to slight increase	No Change*
Nicotinic acid	↓ 10 to 25%	↑ 15 to 35%	↓ 25 to 30%
HMG CoA reductase inhibitors	↓ 20 to 60%	↑ 5 to 10%	↓ 10 to 33%
Gemfibrozil	↓ 10 to 15%	↑ 15 to 25%	↓ 35 to 50%
Fenofibrate (micronized form)	↓ 6 to 20%	↑ 18 to 33%	↓ 41 to 53%
Ezetimibe	↓ 17%	No change	No change

↑ : Increase ; ↓ : Decrease.

* Serum triglyceride levels may increase in patients with preexisting hypertriglyceridemia.

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tion of smoking and consumption of alcohol. Regular exercise was recommended, but compliance was poor on the patient's part.

Discussion

The National Cholesterol Education Program Adult Treatment Panel III designated that plasma triglyceride levels greater than 500 mg/dL were deemed very high[1]. Further, Capell et al. divided hypertriglyceridemia (HTG) into three categories: moderate HTG (150-400 mg/dL), impending severe HTG (400-1000 mg/dL) and severe HTG (> 1000 mg/dL) [2]. Triglyceride levels above 400 mg/dL were considered the cut off between the moderate and impending severe categories because it is the level when chylomicrons begin to persist in fasting serum. In addition, HTG levels above 1000 mg/dL were considered the threshold for predisposition to acute pancreatitis[3]. Severe HTG usually occurs in a patient with genetic predisposition and can be exacerbated by secondary factors.

In the report described herein, the patient represents a case of familial combined hyperlipidemia (FCH) phenotype IIb. This autosomal dominant disorder is the most common heritable dyslipidemia (1-2% of the general population) and it is associated with insulin resistance and carries an increased risk of premature cardiovascular disease. FCH is characterized by mixed dyslipidemia with hepatic overproduction of very low density lipoprotein (VLDL) particles leading to elevated triglyceride and LDL cholesterol levels[3]. An elevated plasma apoB level in our patient also supported the above diagnosis. Secondary factors contributing to the development of hyperlipidemia in this patient included concurrent type 2 diabetes mellitus, a sedentary life style, obesity, and alcohol consumption.

The pathogenesis of HTG is due to excessive entry or defective clearance of triglyceride-rich lipoproteins. Management of HTG includes identifying and eliminating secondary contributors. One aspect of case management includes recommending an initial dietary fat intake of less than 10% of total daily caloric intake in patients with a fasting triglyceride level above 1000 mg/dL. If triglyceride levels are between 400 and 1000 mg/dL, then dietary fat of approximately 20% of caloric intake is permitted, but restrictions in consumption of simple sugars should be emphasised [3].

While the patient described above was able to quit smoking and stopped consuming alcoholic beverages, his physical activity continued at inadequate levels. As a result, no significant loss of body weight was achieved.

Although dietary and lifestyle modifications are key in managing this condition, medications are typically required to assist patients reach their target lipid levels. Fibrates such as gemfibrozil or fenofibrates are first-line agents for controlling triglycerides. Fibrates decrease hepatic VLDL secretion and in-

crease lipoprotein lipase level[5]. The patient in this report had elevated LDL cholesterol in addition to the observed severe hypertriglyceridemia. Thus, a combination of statin and fibrate were prescribed[6]. It has been reported that about 1% of patients treated with this combination of statin and fibrate experienced significant elevations in CK levels of more than three times the upper limit of normal[7]. Thus, patients should be informed of this possible consequence and encouraged to report muscle aches, weakness or brown urine to their physicians. If patient exhibit increases in CK levels up to 10 times the normal limit, then the drug should be discontinued. For patients with elevated CK, thyroid function should also be tested because thyroid disease may also result in elevated CK levels.

While a potential concern, elevated CK levels remain uncommon. For example, a meta-analysis of controlled trials reported that after a 5 year follow-up, only 0.01% more patients using the statin and fibrate combination developed rhabdomyolysis compared to the control group[8].

In light of the the fact that the patient described above was unable to attain his treatment goals, ezetimibe was added to the statin and fibrate combination. Ezetimibe binds to the Niemann-Pick C1-like protein complex located on the luminal side of the enterocyte and produces about 50% reduction of cholesterol absorption[10] The combination of ezetimibe and low dose statin may effectively lower cholesterol levels while avoiding the adverse drug reactions noted at higher doses of statin. Indeed, it has been reported that the combination of ezetimibe 10 mg and atorvastatin 10 mg can achieve similar result to atorvastatin 80mg[9].

Ezetimibe reduces cholesterol absorption, but has no effect on hypertriglyceridemia. In fact, ezetimibe was shown to potentially increase the synthesis of VLDL in the liver[10]. Ezetimibe-induced hypertriglyceridemia was described in a case report of a woman with a rare genetic variant of the Niemann-Pick C like protein 1 transporter[10]. In this case, ezetimibe did not reduce cholesterol absorption, but instead induced a large increase in VLDL production resulting in a 770% increase in triglycerides[10]. Ezetimibe should therefore be employed cautiously in patients with predominantly hypertriglyceridemia.

As illustrated in this case, patients with triglyceride levels above 1000 mg/dl are at an increased risk of developing acute pancreatitis. Plasmapheresis is efficacious for hypertriglyceridemic necrotizing pancreatitis. Moreover, Furuya et al. suggested that plasmapheresis should be applied as soon as possible for acute pancreatitis and triglyceride level above 2000 mg/dL[11]. In their report, the authors used fresh-frozen plasma for the supplementation of deficit substances such as protease inhibitors in patients with severe necrotizing pancreatitis, as well as the removal of the humoral mediators which cannot be removed by continuous hemofiltration[11]. In the case report of Furuya et al., triglyceride levels, which were initially 1420 mg/dL, decreased to 718 mg/dL after one hour and to 507 mg/dL after only four hours of the plasma exchange session[11]. Intensive, long term plasma exchange therapy for refractory hypertriglyceridemia was performed in acquired generalized lipoatrophy[11].

In addition to plasmapheresis, insulin and heparin infusion have been used in the treatment of severe hypertriglyceridemia-induced pancreatitis in non-diabetic patients[12]. The rationale for using insulin and heparin in the management of severe hypertriglyceridemia is based on the fact that they are both rapid and potent activators of lipoprotein lipase. Lipoprotein lipase is a hydrolytic enzyme essential for the removal of triglycerides from plasma. Intravenous glucose is generally administered concomitantly with the insulin infusion to prevent hypoglycemia. The advantages of administering an insulin infusion in acute pancreatitis is that patients may not be able to tolerate oral medications due to abdominal pain and because oral medications may take several weeks to be effective.

In our case, the patient received a continuous insulin infusion for the management of the acute pancreatitis. His blood glucose control was satisfactory with insulin treatment and we advised him not to shift to oral anti-diabetic agent following discharge in light of the beneficial effect of injectable insulin on the hypertriglyceridemia.

In addition to these above-mentioned first line drugs, second line pharmacotherapeutic agents that be beneficial in the management of severe HTG include omega-3 fatty acid supplements, orlistat and a high-dose antioxidant regimen[13]. The effects of these different anti-lipidemic agents are summarized in table 1[5]. For patients with triglycerides over 1000 mg/dL, fibrates and niacin are the drug of choice. If LDL cholesterol levels remain high after triglycerides are lowered, combination therapy can be considered[5].

In summary, this case report describes a man with severe hypertriglyceridemia whose triglyceride levels improved following lifestyle modification, combinations of anti-hyperlipidemic drugs and insulin treatment. In order to obtain a treatment goal of maintaining triglyceride levels below 400 mg/dL, such patient require aggressive treatment and monitoring to ensure an appropriate and optimal therapeutic response and to prevent the development of acute pancreatitis.

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嚴重高三酸甘油血症的治療：一病例報告

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摘　要

高三酸甘油血症於糖尿病患是常見的。偶而我們會遇到嚴重而且難以治療的高三酸甘油血症病例。我們報告一例44歲男性，其三酸甘油值高達18150 mg/dL並併發了急性胰臟炎。患者於一年前的住院被診斷出患有糖尿病。我們以多種藥物包括statin, fibrate, ezetimibe和魚油爲患者治療，並建議他在血糖控制良好後仍繼續施打胰島素。在過去一年中患者的三酸甘油值在1000 mg/dL至4000 mg/dL之間，並未再發生胰臟炎。本文敘述了這病例的治療過程並探討了高三酸甘油血症的不同治療方式。