

## Rapid Reduction of Severely Elevated Serum Triglycerides with Insulin Infusion, Gemfibrozil and Niacin

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The conventional methods of treatment of severe hypertriglyceridemia are dietary restriction and lipid lowering medications, mainly fibric acid derivatives. In the medical literature, use of insulin infusion to treat hypertriglyceridemia has not been highlighted sufficiently. We report a 53-year-old male who presented with a four-day history of epigastric pain. The patient's clinical history was significant for hypertriglyceridemia, type-2 diabetes mellitus with medication noncompliance, obesity, status post-gastric bypass surgery, and alcohol abuse with prior admissions for detoxification. Physical examination revealed mild epigastric tenderness. Laboratory studies revealed severely elevated serum triglyceride (TG) level (8116 mg/dL). Computed tomography (CT) scan of the abdomen exhibited no evidence of pancreatitis. Regular insulin infusion was started at 3 U/h and gradually increased to 7-10 U/h. Dextrose infusion was titrated to avoid hypoglycemia and maintain blood glucose levels below 150 mg/dL. Gemfibrozil and niacin were also started. After 24 hours, his TG levels were decreased to 2501 mg/dL. Insulin infusion was continued for about 48 hours. A low carbohydrate diet excluding simple carbohydrates was given. The patient's serum TG levels normalized over a period of one month. Thus insulin infusion can be considered a safe modality of treatment for rapid reduction of serum TG in addition to fibrates and niacin.

**Keywords:** Acute pancreatitis; Hypertriglyceridemia; Insulin

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In patients with severe hypertriglyceridemia (HTG), the risks for development of acute pancreatitis and premature atherosclerosis are elevated. Insulin is a potent triglyceride (TG)-lowering agent that acts by promoting the synthesis of lipoprotein lipase which is the crucial enzyme for the hydrolysis of TG.<sup>1</sup> In patients with severe HTG, immediate lowering of the TG level to below 1000 mg/dL is possible with insulin infusion, while long-term maintenance therapy can be provided with utilization of other pharmacological agents, such as fibrates, niacin and fish oil.

### Clinical Presentation

A 53-year-old male presented with epigastric pain of four-day duration. The patient's medical history included HTG, coronary artery disease, type-2 diabetes mellitus, obesity, status post-gastric bypass surgery 15 years ago, alcohol abuse (12 cans of beer/day) with prior admissions for detoxification, obstructive sleep apnea and leg cramps secondary to statin use. He was on ezetimibe 10 mg daily, gemfibrozil 600 mg twice daily, metoprolol 100 mg daily, and clopidogrel 75 mg once daily. A family history of premature coronary artery disease in his father and brothers was present. He denied alcohol consumption recently. On examination, the patient weighed 93 kg (body mass index of 32 kg/m<sup>2</sup>) and exhibited central

**Table 1.** Summary of laboratory test results.

Laboratory Test	Reference Range	Day 1	Day 2	Day 3
Pancreatic amylase	12-50 U/L	20 U/L	18 U/L	15 U/L
Lipase	91 U/L	91 U/L	58 U/L	52 U/L
Total Cholesterol	100-200 mg/dL	1244 mg/dL	1033 mg/dL	747 mg/dL
High Density Lipoprotein	40-59 mg/dL	25 mg/dL	74 mg/dL	38 mg/dL
Serum Triglycerides	20-150 mg/dL	8116 mg/dL	2501 mg/dL	1765 mg/dL
Aspartate aminotransferase	15-46 U/L	91 U/L	65 U/L	39 U/L
Alanine aminotransferase	10-61 U/L	45 U/L	36 U/L	27 U/L
Total alkaline phosphatase	40 to 125 U/L	137 U/L	123 U/L	107 U/L
Random blood glucose		122 mg/dL	127 U/L	117 U/L
Creatinine	0.7-1.3 mg/dL	0.9mg/dL	1.0 mg/dL	0.9 mg/dL
Thyroid Stimulating Hormone	0.46-4.48 µU/mL	1.78 µU/mL		
Hemoglobin A1C	4.0-6.0 %	6.9 %		
Blood alcohol		negative		

obesity. He was afebrile; blood pressure was 130/74 mmHg and pulse was 84 beats per minute. Abdominal examination revealed mild epigastric tenderness with no rigidity or guarding. Eruptive cutaneous xanthomas, or lipemia retinalis were absent. Lipemic plasma with serum TG 8116 mg/dL was remarkable. Laboratory results are summarized in table 1.

Computed tomography scan of the abdomen was negative for pancreatitis. The patient was admitted and kept fasting. Regular insulin infusion was started at 3 U/h and gradually increased to 7 to 10 U/h. Dextrose infusion was titrated to avoid hypoglycemia and maintain blood glucose levels below 150 mg/dL. Insulin infusion was continued for about 48 hours. He did not have any significant hypoglycemia during this treatment. Gemfibrozil (600 mg twice a day) and niacin (250 mg/day) were started at the same time. Within 24 hours, epigastric pain resolved. The patient's TG and lipase levels decreased to 2501 mg/dL and 52 U/L, respectively. His diet was advanced slowly. A low carbohydrate diet excluding simple carbohydrates was given. On the third day, the triglyceride levels showed further reduction to 1765 mg/dL, and the patient was discharged on request. He refused insulin injections. At one month post-discharge, serum triglycerides levels were 180 mg/dL.

### Discussion

Hypertriglyceridemia is diagnosed when the serum TG level exceeds 150 mg/dL. The Adult Treatment Panel III of the National Cholesterol Education Program has suggested four TG strata: normal, <150 mg/dL; borderline high; 150-199 mg/dL; high, 200- 499 mg/dL; and very high, ≥ 500mg/dL.<sup>2</sup> The percentage of adults in the United States with TG levels above 150 mg/dL, 200 mg/dL 500 mg/dL and 1000 mg/dL is 33, 18, 1.7, and 0.4 percent, respectively.<sup>3</sup> Hypertriglyceridemia can be inherited as a primary familial trait in combination with dyslipidemia or can occur secondary to uncontrolled diabetes mellitus, obesity, alcohol consumption or estrogen therapy. More complex forms of secondary HTG develop with hypothyroidism, end-stage renal disease, nephrotic

syndrome, human immunodeficiency virus (HIV) infection and many anti-HIV drugs.<sup>4</sup> Patients with TG levels above 2000 mg/dL almost always have both a secondary and a genetic form of HTG.<sup>4</sup>

It is estimated that HTG accounts for 1% to 7% of all cases of acute pancreatitis.<sup>5</sup> Exact mechanisms involved in acute pancreatitis arising from elevations in TG levels are not clearly understood. Currently, the most accepted mechanism, proposed by Havel,<sup>6</sup> suggests that hydrolysis of TG by pancreatic lipase, in and around the pancreas, promotes the accumulation of free fatty acids in the pancreatic capillary beds. Free fatty acid accumulation results in capillary plugging, leading to ischemia and acidosis. It is postulated that the acidic environment results in trypsinogen activation and initiation of acute pancreatitis.<sup>6</sup>

Triglyceride levels greater than 1000 mg/dL to 1500 mg/dL require urgent treatment to reduce the risk of pancreatitis.<sup>7,8</sup> The benefit of treating mild-to-moderate elevations in TG levels for prevention of acute pancreatitis is less clear.<sup>8</sup> The duration of persistent elevation necessary to cause pancreatitis is unknown.<sup>5,9</sup> Identification and elimination of secondary contributors is critical in alleviating ongoing TG-rich lipoprotein accumulation. Patients with TG levels above 2000 mg/dL secondary to alcohol use benefit from alcohol abstinence.<sup>10,11</sup> Avoidance of simple sugars, which have been associated with postprandial HTG, is also advised.<sup>12</sup>

Case reports have documented substantial decreases in serum TG following administration of heparin or insulin. Lipoprotein lipase is a crucial enzyme that is needed for removal of TG from plasma. It is produced by adipocytes and myocytes and is transported to the surface of endothelial cells where it becomes bound. Insulin promotes the synthesis of lipoprotein lipase, which hydrolyzes TG into fatty acids and glycerol and facilitates storage of the fatty acids in adipocytes.<sup>1</sup> In a non-diabetic adolescent patient with severe HTG, a bolus dose of regular insulin (0.1 U/kg) given subcutaneously decreased

serum TG from 1893 mg/dL to 1015 mg/dL after only 4 hours.<sup>13</sup> Heparin promotes the release and translocation of tissue bound lipoprotein lipase in the capillary endothelium. Lipoprotein lipase hydrolyzes circulating TG into free fatty acids while it is bound to the luminal surface of the endothelial cell. Lipoprotein lipase is a high affinity heparin binding protein. It is released into the blood stream of humans and animals by intravenous injection of heparin. Heparin binding via the carboxyl terminal region is required to maintain lipoprotein lipase activity and probably prevents the conversion of enzyme into inactive monomeric units. Optimal lipoprotein lipase binding to heparin is required to localize lipoprotein lipase to proteoglycan-rich cell membranes leading to efficient targeting of newly created fatty acids to tissues.<sup>14</sup> Berger et al<sup>15</sup> reported five cases where serum TG levels decreased to <500 mg/dL in less than three days in all five cases. Jain et al<sup>16,17</sup> also reported similar results in two other cases with insulin and heparin.

Use of plasmapheresis for removal of TG and chylomicrons from circulation has been reported. This intervention involved replacement of TG-rich plasma with salt-free human albumin or fresh-frozen plasma, thereby substantially reducing TG levels. Plasmapheresis was shown to decrease TG levels by as much as 70% within several hours.<sup>18</sup> Low fat diet, supplements of omega-3 fatty acids (fish oil) and fibrates are recommended for long-term maintenance therapy. Drug therapy can effectively reduce TG levels by 20% to 60%.<sup>19</sup> In a study performed in 12 male patients with elevated TG, administration of nicotinic acid caused reduction of plasma TG by 52% in one month.<sup>20</sup> Pooled meta-analysis of randomized placebo-controlled clinical trials demonstrated a reduction of TG by 30% in a mean duration of about five years.<sup>21</sup> We demonstrated a 68% decrease in TG in 24 hours and believe that insulin infusion contributed significantly to this rapid decline. Moderate weight loss may be associated with reductions in TG levels.<sup>22</sup>

Our patient had several secondary risk factors for HTG including obesity, severe alcohol abuse, uncontrolled diabetes mellitus, and a sedentary life style. During his hospital stay, he was prescribed a low fat diet which excluded simple sugars, and he was counseled to abstain from alcohol consumption, this likely being the most influential of his secondary contributors. Administration of intravenous insulin was likely the major contributor in the rapid reduction of serum TG by 68% within a span of 24 hours. Insulin infusion presented in the context of this case report achieved outcomes comparable to those reported with plasmapheresis, at relatively lower cost and in a minimally-invasive manner. The patient continued on niacin (500 mg/day) and gemfibrozil (600 mg twice daily) for one month. He abstained from alcohol consumption and followed a low carbohydrate diet. After one month, his TG decreased to 180 mg/dL, and he had no recurrence of abdominal pain.

## Conclusion

Although HTG is a common form of dyslipidemia, very high elevation of serum TG can be associated with significant morbidity and mortality. Treatment with insulin infusion is an effective and minimally-invasive form of rapidly treating severe HTG in addition to other pharmacological agents.

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