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# A Case Series of Tirzepatide Treatment in Patients with Type 2 Diabetes, Chylomicronemia and Genetic Variants Affecting Lipoprotein Lipase

**Stephan Babirak PhD, MD[1] and Mark Henschke Pharm D, DO[1]**

[1]Metabolic Leader, LLC, PA Scarborough, Maine, USA

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## ABSTRACT

**Background/Aim:** Tirzepatide has been shown to improve glycemic control, improve insulin sensitivity, increase adipocyte lipoprotein lipase (LPL) activity and decrease apolipoprotein C3 levels. We previously reported that a patient who had type 2 diabetes (T2DM), persistent chylomicronemia and heterozygosity for LPL deficiency had resolution of his chronic chylomicronemia and near normalization of serum triglycerides in response to tirzepatide therapy. Therefore, the aim of this study was to perform a case series using tirzepatide treatment in a group of patients with T2DM or metabolic syndrome, chylomicronemia and multiple genetic variants affecting LPL to verify similar results in a larger group of patients with Metabolic Chylomicronemia Syndrome.

**Method:** 61 patients with chylomicronemia who were referred to our lipid clinic were screened. Fiftyeight out of 61 patients had identifiable genetic variations in one of the 7 genes associated with chylomicronemia and 57/61 had T2DM. Twenty of these chylomicronemic patients (19 with T2DM and 1 with prediabetes) were able to be treated with tirzepatide and 17/20 had a genetic variant associated with a decrease in LPL: 5 having heterozygosity for LPL deficiency, 10 having variants of apolipoprotein A5, 1 with a variant of the LMF-1 gene and one patient with prediabetes who was a compound heterozygote having LPL heterozygosity plus an apolipoprotein A5 variant. Three patients had no identifiable genetic variation associated with chylomicronemia and all were treated with tirzepatide given to maximum tolerated dose.

**Results:** In all patients, there was a resolution of their chylomicronemia. In patients who had a history of chylomicronemia induced pancreatitis or abdominal pain, there were no episodes of pancreatitis or abdominal pain while on tirzepatide. Pre-/post lipid profile averages as follows: total triglyceride decreased from 9.25 to 3.19 mmol/L (-65%, P value < 0.006), total cholesterol decreased from 5.12 to 3.72 mmol/L (-27%, P < 0.0013), LDL cholesterol decreased from 2.14 to 1.72 mmol/L (-20%, P<0.40), non-HDL cholesterol decreased from 4.09 to 2.97 mmol/L (-27%, P <0.002). HDL cholesterol increased from 0.74 to 0.84 mmol/L (+13%, P <0.023). In addition, the average A1c decreased from 7.6% to 6.0% (-15%, P <0.0001) and body weight decreased from 98.0 to 91.8 kg (-6.5%, P <0.0001).

**Conclusion:** In this case series of patients with a history of chylomicronemia, T2DM/ metabolic syndrome and multiple gene variants affecting LPL, tirzepatide caused a resolution of chylomicronemia with a significant decrease in total triglyceride, total cholesterol and non-HDL cholesterol levels as well as an increase of HDL cholesterol. Tirzepatide resulted in a significant improvement of A1C as well as a decrease in body weight. The mechanism(s) underlying these effects is(are) not completely understood but warrants further investigation. The results of this case series suggest that tirzepatide may be an agent useful for the treatment of patients with T2DM and chylomicronemia who have genetic variants affecting LPL.

## Introduction

Chylomicronemia syndrome was first described in 1981 as a clinical syndrome associated with severely elevated chylomicron and very low density lipoprotein (VLDL) triglyceride with total triglyceride levels > 10 mmol/L or 885 mg/dl, caused by a deficiency in lipoprotein lipase (LPL) activity.[1-3]. LPL is the rate limiting enzyme responsible for the clearance of triglyceride from the circulation and LPL deficiency can be monogenic or polygenic. The clinical syndrome is characterized by recurrent abdominal pain, pancreatitis, eruptive xanthomas, lipemia retinalis, hepatosplenomegaly and neurologic disorders. Acute pancreatitis caused by chylomiconemia is the most serious complication which can be fatal. There are 2 major syndromes associated w the Chylomicronemia Syndrome.

Familial chylomicronemia syndrome (FCS) is a rare genetic disease affecting approximately 1/1,000,000 people and caused by inactivating mutations in both alleles of the LPL gene or by other variants in genes including proteins that are required for LPL activity (see below)[3-13]. Patients who are heterozygotes for LPL deficiency (HeLPL) have an approximate 50% decrease in LPL activity/mass[14] and may also develop chylomicronemia or cardiovascular disease but usually in polygenic fashion or associated with secondary factors[3,15,16]. Other variants in genes encoding proteins that are required for LPL activity such as apolipoprotein C2 or A5 (ApoC2 and ApoA5), glycosylphosphatidylinositol anchored high density lipoprotein binding protein (GPIHBP1), lipase maturation factor 1 (LMF-1) as well as other variants have also been described which may or may not be associated with chylomicronemia[6-13]. An inhibitor of LPL activity, apolipoprotein C3 (ApoC3), is another key regulatory protein which can decrease LPL activity directly or indirectly by lipoprotein triglyceride removal unrelated to LPL (17).

Metabolic Chylomicronemia Syndrome (MCS) is a far more common cause of chylomicronemia with and estimated frequency of 1.4% in the United States population which is associated with multiple genetic variants affecting LPL and/or other secondary factors which can reduce LPL activity such as Diabetes Mellitus, hypothyroidism and drugs which can cause hyperlipidemia[1,2]. In approximately 70% of MCS patients, chylomicronemia is associated with hyperglycemia in uncontrolled Type 2 diabetes (T2DM) and genetic variants, drugs or other factors affecting lipoprotein metabolism[3]. Uncontrolled hyperglycemia and/or insulin resistance contribute to an increase of VLDL formation in the liver due to the elevated glucose and free fatty acids which are substrate for triglyceride formation. Since insulin is required for LPL synthesis, the LPL activity is reduced in T2DM with insulin deficiency or patients with metabolic syndrome, leading to a decrease in removal of triglyceride rich lipoproteins. In patients with T2DM and/or metabolic syndrome, mild to moderate hypertriglyceridemia is common and may worsen to develop chylomicronemia if coexistent genetic variants of LPL are present in the same patient which may progress to the clinical sequela of chylomicronemia as well as cardiovascular disease. For the T2DM patients who have persistent chylomicronemia and/or chylomicronemia induced pancreatitis, there has not been a very effective treatment to prevent their severe hypertriglyceridemia despite the use of multiple drug regimens[3], however there are new agents on the horizon as recently reported in apolipoprotein C3 inhibition[18-20]. We previously reported that a patient who had T2DM, persistent chylomicronemia and heterozygosity for LPL deficiency had resolution of his chronic chylomicronemia and near normalization of triglyceride levels in response to tirzepatide therapy[21]. Since tirzepatide has been shown to improve glycemic control as well as improve insulin resistance, decrease free fatty acids, increase adipocyte LPL activity and decrease apolipoprotein C3 levels[22], we studied a larger group of patients with T2DM or metabolic syndrome who presented to our lipid clinic with chylomicronemia to verify similar results.

## Methods

61 patients with chylomicronemia were referred to Metabolic Leader lipid clinic for evaluation/

management and screened using the Prevention Genetics lab (part of Exact Sciences, Marshfield, Wisconsin, USA ) for 7 genes associated with chylomicronemia (LPL heterozygosity, apolipoprotein A5/C2/C3, LMF-1, CREB3L3, GDP1, GPIHBP1 variants). Of the 61 patients screened, 58 patients (95%) had an identifiable genetic variant in 1 or more chylomicronemic genes, 57/61 patients had T2DM with 1 patient having prediabetes/metabolic syndrome and 3 patients had no identifiable variant of the 7 genes that were tested. Patients were referred to a Registered Dietician and instructed on a 20% low-fat diet by a physician at each visit. Exercise was recommended with walking 30 minutes daily and alcohol consumption prohibited. All patients were treated with full dose fenofibrate and maximal combination lipid-lowering therapy tolerated/ available to the patient through their insurance (18/ 20 treated with statin, 5 with a PCSK9 inhibitor, 10 with ezetimibe and 3 were treated w icosopent ethyl acid). Patients receive the most aggressive diabetes regimen tolerated/available to the patient possible in our Diabetes Center of Excellence, using combination of antiglycemic regimens that were tolerated and available in order to get to the best A1C possible for each patient. Fifteen patients had baseline treatment with semaglutide (glucagon-like peptide 1 receptor agonist) prior to changing over to tirzepatide (glucagon-like peptide 1 receptor agonist and gastric inhibitory polypeptide). In this group of 61 patients, 20/61 had a clinical indication as well as the financial ability to stop semaglutide and switch to tirzepatide which was titrated to the maximum tolerated dose. In the 15 patients who previously were on semaglutide, patients were started on tirzepatide 5 mg subcutaneously every week and patients who were not on semaglutide were started on tirzepatide 2.5 mg subcutaneously every week. Each patient had monthly phone contact and the tirzepatide was increased monthly to the maximum tolerated dose and followed up in the clinic every 3 to 6 months for assessment. None of the patients who were started on tirzepatide needed to discontinue tirzepatide therapy due to side effects. The mean length of tirzepatide treatment was 57 weeks, ranging from 8 to108 weeks. There were 4 patients with a history of chylomicronemia induced pancreatitis prior to tirzepatide initiation and 4 other patients had a history of chylomicronemia induced abdominal pain prior to tirzepatide (see table 1). All laboratories were done in the patients' local hospital labs. A1c levels were performed with the office based analyzer (Afinion AS100) or in their local hospital lab. Statistical analysis was performed using the student paired t Test.

## Results

In the 20 patients who presented with chylomicronemia 17 had genetic variants associated with chylomicronemia and 19/20 patients had T2DM. The patient without T2DM had Metabolic Syndrome and also benefited from tirzepatide therapy. The most common gene variant observed was Apo5 variants (10 patients), heterozygosity for LPL deficiency in 5 patients and one patient with the LMF-1 variant. 15 patients were heterozygote for a single gene variant and 5 patients were compound heterozygotes (Table 1). All patients who presented with chylomicronemia had a durable resolution of their chylomicronemia and 19/20 patients had a decrease in their triglyceride levels after treatment with tirzepatide, even in the 3 patients who did not have an identifiable genetic variant. One patient (patient #11) had an increase of triglyceride levels while on tirzepatide and did not have any obvious clinical explanation for the increase. Table 2 shows pre and post tirzepatide lipid profiles which revealed an average decrease in total triglyceride from 9.25 to 3.19 mmol/L (-65%, $P < 0.006$), total cholesterol decreased from 5.12 to 3.72 mmol/L (-27%, $P < 0.0013$), LDL cholesterol decreased from 5.12 to 3.72 mmol/L ( -20%, $P<0.40$), non-HDL cholesterol decreased from 4.09 to 2.97 mmol/L (-27% , $P <0.002$). HDL cholesterol increased from 0.74 to 0.84 mmol/L (+11%, $P <0.023$). In addition, the average A1c decreased from 7.6% to 6.0% ( -15 %, $P <0.0001$) and body weight decreased from 98 to 91.8 kg (-6.5%, $P <0.0001$). There were no documented episodes of chylomicronemia or pancreatitis in any patient during tirzepatide therapy. In the patients

who did have a history of abdominal pain before tirzepatide, the abdominal pain resolved during tirzepatide therapy.

# Table 1

## Clinical Characteristics

| Patient | Age (Years) | Sex (M/F) | History$_1$ (Years) | Highest $TG_2$ (mmol/L) | Pancreatitis | $CVD_3$ | DNA $ID_4$ |
|---|---|---|---|---|---|---|---|
| LPL Heterozygote | | | | | | | |
| 1 | 51 | M | 20 | >67.73 | x 4 | No | c.775G>A |
| 2 | 69 | M | 30 | 26.93 | x 3 | Yes | c.644G>A |
| 3 | 61 | M | 43 | 15.80 | No | Yes | c.953A>G |
| 4 | 52 | M | 12 | 13.86 | Pain | No | c.953A>G |
| 5 | 54 | M | 7 | >71.80 | Pain | No | c.953A>G |
| Apolipoprotein A5 Variants | | | | | | | |
| 6 | 40 | M | 4 | 37.25 | No | No | c.-3A>G<br>c.56C>G |
| 7 | 69 | F | 17 | 12.64 | No | No | c.-3A>G |
| 8 | 58 | M | 13 | 23.05 | No | No | c.-3A>G |
| 9 | 53 | F | 7 | 99.91 | No | Yes | c.-3A>G |
| 10 | 53 | M | 7 | 24.84 | x 1 | No | c.-3A>G<br>c.56C>G |
| 11 | 63 | M | 17 | 15.31 | No | No | c.-3A>G<br>c.56C>G |
| 12 | 48 | F | 24 | >67.73 | x 5 | No | c.56C>G |
| 13 | 61 | M | 7 | 9.71 | No | Yes | c.56C>G |
| 14 | 50 | F | 3 | 37.22 | Pain | No | c.-3A>G |
| 15 | 42 | M | <1 | 68.04 | No | No | c.-3A>G<br>c.56C>G |
| Other Genetic variants | | | | | | | |
| 16 | 55 | M | 11 | 9.63 | No | No | LMF-1<br>c.115+1G>A |
| 17 | 68 | F | 20 | >67.73 | No | No | A5 c.56C>G<br>LPL c.881G>C |
| No Gene Variants | | | | | | | |
| 18 | 32 | M | 3 | 20.57 | Pain | No | No Gene |
| 19 | 76 | M | 49 | >56.55 | No | Yes | No Gene |
| 20 | 46 | F | 2 | 98.08 | No | No | No Gene |

### Header Definitions

(1)Years of known Chylomicronemia

(2)Highest known Triglyceride Level

(3)Documented Cardiovascular Disease

(4)DNA Identification of Genetic Variance

# Table 2

## Pre and Post Tirzepatide

| Patient | Tirzepatide Duration[1] (weeks) | Final Dose (mg/week) | | A1C[2] (%) | TC[3] (mmol/L) | TG[4] (mmol/L) | LDL[5] (mmol/L) | HDL[6] (mmol/L) | NHDL[7] (mmol/L) | BW[8] (kg) | BMI[9] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| LPL Heterozygote | | | | | | | | | | | |
| 1 | 83 | 15 | Pre | 7.4 | 9.43 | 33.85 | - | - | - | 104.8 | 32.7 |
| | | | Post | 5.7 | 3.28 | 1.78 | 1.71 | 0.75 | 2.53 | 96.1 | |
| 2 | 76 | 15 | Pre | 5.9 | 2.43 | 5.68 | - | 0.34 | 2.09 | 75.3 | 23.1 |
| | | | Post | 5.3 | 3.26 | 3.35 | 1.19 | 0.54 | 3.13 | 69.4 | |
| 3 | 105.3 | 15 | Pre | 6.9 | 4.13 | 15.85 | - | - | - | 85.3 | 27 |
| | | | Post | 5.7 | 2.64 | 3.62 | 1.21 | 0.54 | 2.09 | 79.4 | |
| 4 | 14.6 | 10 | Pre | 7.4 | 4.13 | 3.34 | 1.50 | 1.11 | 3.02 | 81.2 | 25.7 |
| | | | Post | 6.2 | 3.05 | 1.63 | 1.24 | 1.06 | 1.99 | 77.1 | |
| 5 | 65.6 | 15 | Pre | 6.8 | 6.87 | 3.61 | 4.34 | 0.88 | 5.99 | 132.4 | 39.2 |
| | | | Post | 6.3 | 5.50 | 2.90 | 3.28 | 0.90 | 4.55 | 122.0 | |
| Apolipoprotein A5 Variants | | | | | | | | | | | |
| 6 | 28.5 | 12.5 | Pre | 9.0 | 4.16 | 3.45 | 1.81 | 0.78 | 3.38 | 106.6 | 33.7 |
| | | | Post | 4.9 | 3.33 | 1.33 | 1.68 | 1.03 | 2.30 | 99.3 | |
| 7 | 94.6 | 15 | Pre | 6.5 | 4.52 | 9.39 | 0.70 | 0.67 | 3.85 | 114.3 | 41.3 |
| | | | Post | 5.5 | 3.93 | 4.02 | 1.99 | 0.83 | 3.10 | 102.5 | |
| 8 | 25.6 | 15 | Pre | 5.3 | 2.87 | 9.99 | 0.98 | 0.36 | 2.51 | 91.2 | 28.8 |
| | | | Post | 4.9 | 2.79 | 6.36 | 1.14 | 0.41 | 2.38 | 88.4 | |
| 9 | 74.2 | 15 | Pre | 7.2 | 3.93 | 6.41 | 1.60 | 0.93 | 3.00 | 91.6 | 36.9 |
| | | | Post | 7.6 | 3.26 | 5.76 | 1.14 | 0.93 | 2.33 | 89.8 | |
| 10 | 76.6 | 15 | Pre | 9.0 | 3.59 | 3.68 | 1.03 | 0.88 | 2.71 | 109.3 | 31.8 |
| | | | Post | 6.0 | 4.29 | 2.64 | 2.12 | 0.96 | 3.33 | 102.0 | |
| 11 | 108 | 15 | Pre | 8.4 | 4.57 | 3.85 | 2.38 | 0.62 | 3.95 | 85.3 | 29.9 |
| | | | Post | 7.1 | 4.93 | 5.55 | 2.53 | 0.78 | 4.16 | 79.8 | |
| 12 | 21 | 5 | Pre | 7.8 | 5.94 | 20.14 | 2.07 | 0.54 | 5.40 | 69.4 | 25.5 |
| | | | Post | 5.0 | 2.56 | 1.93 | 1.06 | 0.62 | 1.94 | 59.4 | |
| 13 | 34 | 12.5 | Pre | 7.8 | 5.92 | 4.82 | 3.10 | 1.03 | 4.88 | 83.0 | 31.4 |
| | | | Post | 6.0 | 4.00 | 3.86 | 1.27 | 0.98 | 3.02 | 82.1 | |
| 14 | 62 | 10 | Pre | 10.6 | 6.23 | 25.31 | - | - | - | 87.5 | 32 |
| | | | Post | 5.5 | 3.10 | 2.51 | 0.93 | 1.03 | 4.70 | 90.7 | |
| 15 | 31 | 15 | Pre | 5.5 | 7.49 | 8.23 | 2.51 | 0.90 | 6.59 | 164.6 | 53.6 |
| | | | Post | 4.8 | 5.17 | 3.13 | 3.10 | 1.06 | 4.11 | 139.7 | |
| Other Genetic variants | | | | | | | | | | | |
| 16 | 56.2 | 10 | Pre | 8.9 | 6.07 | 6.65 | 2.25 | 0.67 | 5.40 | 108.4 | 39.8 |
| | | | Post | 7.6 | 4.06 | 4.28 | 2.12 | 0.75 | 3.31 | 102.9 | |
| 17 | 22 | 7.5 | Pre | FBG=101 | 6.07 | 5.18 | 3.33 | 0.88 | 5.19 | 69.8 | 26.4 |
| | | | Post | FBG=85 | 3.69 | 2.56 | 1.63 | 0.90 | 2.79 | 66.7 | |
| No Gene Variants | | | | | | | | | | | |
| 18 | 8 | 5 | Pre | 9.3 | 5.74 | 6.22 | 2.71 | 0.93 | 4.81 | 115.2 | 33.5 |
| | | | Post | 8.5 | 4.34 | 3.09 | 2.02 | 0.90 | 3.44 | 111.1 | |
| 19 | 70.3 | 10 | Pre | 7.8 | 2.79 | 4.78 | 0.44 | 0.49 | 2.30 | 110.7 | 30.5 |
| | | | Post | 7.6 | 3.18 | 2.54 | 1.40 | 0.62 | 2.56 | 111.6 | |
| 20 | 92.4 | 15 | Pre | 7.8 | 5.19 | 3.77 | 2.95 | 0.93 | 4.26 | 63.9 | 27.5 |
| | | | Post | 4.5 | 3.80 | 1.08 | 1.86 | 1.45 | 2.09 | 59.9 | |

### Header Definitions

(1)Duration of Tirzepatide therapy in weeks

(2)Hemaglobin A1C

(3)Total Cholestorol

(4)Total Triglycerides

(5)Low Density Lipoprotein

(6)High Density Lipoprotein
(7)Nonhigh Density Lipoprotein
(8)Body Weight
(9)Body Mass Index

## Discussion

There were 3 genetic variants associated with chylomicronemia in this MCS patient population-10 had apolipoprotein A5 variants, 5 were LPL deficient heterozygotes and 1 patient had the LMF-1 variant. In these patients with MCS who presented with chylomicronemia, the chylomicronemia is likely multifactorial and likely related to their genetic variants which affect LPL activity. Although no studies have been reported using tirzepatide in chylomicronemic patients, tirzepatide has been shown in multiple trials to significantly lower serum triglyceride levels in T2DM patients in a dose dependent average from 27-41%[21-23] as well as lower non-HDL cholesterol. In this study, tirzepatide had an average triglyceride reduction of 65% which is consistent with the literature. T2DM patients have hyperglycemia, increased plasma fatty acids and insulin deficiency/resistance which result in an increase in VLDL synthesis and a decrease in triglyceride clearance via LPL. Tirzepatide improves glycemic control by several mechanisms including a decrease in hyperglycemia and free fatty acids as well as an improvement in insulin sensitivity[22], resulting in better glycemic control. However, the improvement in hypertriglyceridemia was also seen in patients with a normal A1c (patient #2,8,15) as well as the patient who did not have diabetes (patient #17), suggesting other reasons for triglyceride lowering are also possible. The switch from semaglutide (glucagon-like peptide 1 receptor agonist) to tirzepatide which has both glucagon-like peptide 1 and gastric inhibitory polypeptide (GIP) receptor agonist activities may be related to the addition of the GIP hormone[21]. It has been reported that the GIP receptor moiety increases LPL by increasing gene upregulation in adipocytes and the additional GIP receptor agonism provided by tirzepatide may have contributed to further lowering of hypertriglyceridemia via LPL[24,25]. Another proposed mechanism is that tirzepatide has been reported to cause a dose-dependent decrease in ApoC3, an inhibitor of LPL, resulting in an increase in LPL activity but not LPL mass[22]. In addition, ApoC3 inhibition has also been associated with an LPL independent triglyceride clearance reported in FCS and MCS patients which may add to additional triglceride lowering[18-20]. Whatever the mechanism(s) of the triglyceride lowering in these MCS patients with T2DM and a genetic variant causing chylomicronemia, tirzepatide therapy resulted in a resolution of their chylomicronemia with a significant reduction in triglycerides.

Diabetic patients have multiple potential causes of pancreatitis and the incidence of pancreatitis in diabetes patients is fourfold higher than the general population, certainly chylomicronemia is one possible cause. Chylomicronemia is considered to be a reversible cause of pancreatitis in MCS patients[3]. It has been reported that when serum triglycerides are less than 5.65 mmol/L (500 mg/dL), the odds of chylomicronemia induced pancreatitis are similar to the general population[3]. However, lowering triglycerides in the MCS population has proven to be difficult with the currently available drugs utilized in lipid-lowering. In this study, we observed a resolution of chylomicronemia without any recurrent pancreatitis and a resolution of recurrent abdominal pain, however, the numbers of patients in this study were not adequate to assess this complication of chylomicronemia. Whether or not tirzepatide therapy can prevent pancreatitis in these patients with chylomicronemia, T2DM or metabolic syndrome who have a genetic variant of LPL remains to be determined.

## Conclusions

In this case series of patients with a history of chylomicronemia, T2DM/metabolic syndrome and multiple gene variants affecting LPL, tirzepatide caused a resolution of chylomicronemia with a

significant decrease in total triglyceride, total cholesterol and non-HDL cholesterol levels as well as an increase of HDL cholesterol. Tirzepatide therapy resulted in a significant improvement of A1C as well as body weight. The mechanisms underlying this effect is not completely understood but warrants further investigation.

## Conflict of interest:

Stephan Babirak is a speaker for Abbvie, Boehringer-Ingelheim and Novo Nordisk.
Mark Henschke is a speaker for Abbvie.

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