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Case Report

Tirzepatide Therapy in a Patient with Type 2 Diabetes Mellitus, Chylomicronemia, and Heterozygosity for Lipoprotein Lipase Deficiency

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ABSTRACT

Background/Objective: A patient with well-controlled type 2 diabetes mellitus (T2DM) and a heterozygote for lipoprotein lipase deficiency (HeLPL) presented with chronic chylomicrons (CMs). Some patients with T2DM can develop CMs due to poor glycemic control or genetic defects that result in a decrease in the lipoprotein lipase (LPL) activity. This study aimed to describe a patient with HeLPL with T2DM and persistent CM on maximal standard lipid-lowering therapy who then used tirzepatide as a novel way to treat CM.

Case Report: A patient with well-controlled T2DM with persistent CM and HeLPL was treated with tirzepatide and titrated to 15 mg/week, resulting in resolution of his CM (triglyceride [TG] level, <850 mg/dL) with a 58% reduction in the serum TG level after 2 months and then an 86% reduction after 5 months of therapy. His A1C level and body weight decreased from 6.9% to 6.3% and by 12 lbs in 2 months and then to 5.6% and by 20 lbs after 5 months, respectively.

Discussion: The resolution of CM and reduction in the TG level by tirzepatide cannot be solely explained by an improvement in glycemic control or a decrease in body weight but may also be related to other effects of tirzepatide.

Conclusion: Tirzepatide caused a significant decrease in the TG level in a patient with CM, T2DM, and HeLPL. The mechanism(s) underlying this effect is not completely understood but warrants further study.

Introduction

Chylomicrons (CMs) are more common in patients with type 2 diabetes mellitus (T2DM) who have uncontrolled hyperglycemia or have genetic defects in lipoprotein metabolism.[1] Lipoprotein lipase (LPL) is the rate-limiting enzyme for the clearance of CMs/triglycerides (TGs), and patients with a decreased LPL activity commonly have hypertriglyceridemia (HTG) and mixed hyperlipidemia or develop CM.[2] Patients who are heterozygotes for LPL deficiency (HeLPL) have an approximately 50% decrease in the LPL activity, which predisposes them to HTG, CM, pancreatitis, or cardiovascular disease.[2,3] Patients with T2DM may also have HeLPL with effective treatment for glycemic control but have persistent HTG because there has been no effective treatment for HeLPL. It has been reported that tirzepatide can increase the LPL activity by several potential mechanisms.[4-6] This case study aimed to treat a patient with CM with well-controlled T2DM and HeLPL to determine whether tirzepatide could reduce CM/HTG.

Case Report

A 60-year-old White man was identified with long-standing T2DM and stable glycemic control with a chief complaint of CM (HTG, with varying TG levels between 1100 and 4000 mg/dL) while adherent to lipid-lowering therapy. His alcohol consumption was <1 drink/week, on consistent 20% low fat diet and exercise with 30 minutes of daily walking. He did not have a history of pancreatitis; however, examination revealed moderate

Abbreviations: CM, chylomicron; GIP, gastric inhibitory polypeptide; HeLPL, heterozygote for lipoprotein lipase deficiency; HTG, hypertriglyceridemia; LPL, lipoprotein lipase; TG, triglyceride; T2DM, type 2 diabetes mellitus.

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hepatomegaly but no eruptive xanthomata. His glycemic control was stable with the A1C level consistently between 6.0% and 7.0% for at least 2 years before intervention, as determined by an office-based analyzer (Afinion AS100), and lipid profiles were performed by local hospital laboratories. He was diagnosed with HeLPL with the variant p.Asn291Ser in LPL by PreventionGenetics.

At baseline, the patient's lipid-lowering therapy was fenofibrate 145 mg daily, icosapent ethyl 2 g twice daily, ezetimibe 10 mg daily, and atorvastatin 40 mg daily. His T2DM was treated with semaglutide 1.0 mg subcutaneously weekly, empagliflozin 10 mg/day, and metformin 1000 mg twice daily. He was stable for several months on both lipid and diabetes therapies as described earlier with his baseline values listed in the Table.

Semaglutide was discontinued, and the patient was switched to tirzepatide, titrated up to 15 mg subcutaneously weekly, and stable for 2 months without any major side effects. His lipid-lowering therapy remained consistent and adherent. No other changes were made in his clinical care, medications, exercise, or diet. His repeat laboratory examinations after the switch from semaglutide to tirzepatide are labeled as tirzepatide therapy in the Table.

After the switch from semaglutide to tirzepatide, the TG level decreased approximately 58% from 1404 to 583 mg/dL with resolution of CM (TG level, <880 mg/dL or 10 mmol/L) after 2 months of tirzepatide 15 mg/week. His A1C level decreased from 6.9% to 6.3% and his body weight decreased by 12 lbs after the switch to tirzepatide. After 6 months of tirzepatide, his TG level continued to decrease to 202 mg/dL, which was the lowest TG level ever reported in this patient's medical history, even lower than before the diagnosis of T2DM.

Discussion

This case report demonstrates that tirzepatide therapy resulted in a 58% reduction in HTG and resolution of CM after 2 months of maximal tirzepatide therapy in this patient with T2DM, CM, and HeLPL with near normalization of HTG after 6 months. Glycemic control improved after the switch from semaglutide to tirzepatide, and his body weight decreased, which partially explains the improvement in CM/HTG. The resolution of CM and improvement in HTG may also be partly related to 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. It has been reported that the GIP receptor moiety may increase the LPL activity by increasing gene upregulation in adipocytes[5]; therefore, the additional GIP receptor agonism provided by tirzepatide may have contributed to the improvement in CM/HTG in this patient with HeLPL. Another potential mechanism for TG lowering could be that tirzepatide has been reported to cause a dose-dependent decrease in apolipoprotein CIII, which is an LPL inhibitor, resulting in an increase in the LPL activity.[6]

Whatever the mechanism of TG lowering in this patient, patients with CM/HTG are extremely difficult to treat using standard TG-lowering therapies, as illustrated in this patient before switch to tirzepatide. Patients with HeLPL are particularly difficult to treat because there has been no effective therapy to ameliorate the genetically mediated decrease in the LPL activity. Because other genetic deficiencies and metabolic causes result in a decreased LPL activity, tirzepatide may be a potential option to treat severe HTG/CM and decrease the cardiovascular risk in these patients. The use of tirzepatide is associated with a risk of pancreatitis; however, patients with CM are at high risk of pancreatitis, and tirzepatide may decrease such risk in these patients. In the future, a case series may help us better understand tirzepatide as a possible option for TG lowering in these difficult-to-treat patients.

Highlights

- Chylomicronemia is common in people with diabetes and difficult to treat
- Lipoprotein lipase (LPL) deficiency predisposes to chylomicronemia, which is also difficult to treat
- Tirzepatide resolved chylomicronemia in a patient with LPL deficiency and diabetes
- Tirzepatide at 15 mg/week decreased the serum triglyceride level by 58%
- An increased gastric inhibitory polypeptide activity may increase the LPL activity in LPL deficiency

Clinical Relevance

Chylomicronemia in patients with diabetes is clinically dangerous because it predisposes them to pancreatitis, which is sometimes fatal. This case demonstrates the new finding that tirzepatide resolved chylomicronemia in a patient with diabetes and partial lipoprotein lipase deficiency, possibly by an increase in the gastric inhibitory polypeptide activity.

Conclusion

Tirzepatide therapy resulted in resolution of CM with a significant decrease in the TG level in a patient with CM, T2DM, and HeLPL. The mechanism(s) underlying this TG-lowering effect is not completely understood, and these results warrant further study.

Disclosure

S.P.B. is Speaker for both Lilly and Novo Nordisk Pharmaceuticals.

Table
Baseline Characteristics Before and After Switching From Semaglutide to Tirzepatide

Therapy	Height (inch)	Weight (pounds)	BMI	A1C(%)	TC (mg/dL)	TG (mg/dL)	LDL (mg/dL)	HDL (mg/dL)	Non-HDL (mg/dL)
Baseline	70	188	27.0	6.9	160	1404	35	Unable	Unable
Tirzepatide 15 mg after 2 mo	70	176	25.3	6.3	111	583	33	18	93
Tirzepatide 15 mg after 6 mo	70	168	24.1	5.3	106	202	42	24	82

Abbreviations: BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein; non-HDL = total cholesterol−high-density lipoprotein; TC = total cholesterol; TG = triglyceride.

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