Case Report

Acta Medica
Okayama

Marked Hypertriglyceridemia in a Patient with type 2 Diabetes Receiving SGLT2 Inhibitors

Mayumi Senoo, Atsuhito Tone*, Yusuke Imai, Satoko Watanabe,
Mitsuhiro Kaneto, Yasuyuki Shimomura, Sanae Teshigawara and Tatsuaki Nakatou

Department of Internal Medicine, Diabetes Center, Okayama Saiseikai General Hospital, Okayama 700-8511, Japan

A 43-year-old male with type 2 diabetes, under treatment with 5 mg/day of dapagliflozin, was referred to our hospital with upper left abdominal pain and marked hypertriglyceridemia (triglycerides [TGs], 5,960 mg/dl). He was also on a low-carbohydrate diet that promoted ketosis under sodium glucose cotransporter 2 (SGLT2) inhibitor administration. Polyacrylamide gel electrophoresis revealed a remarkable increase in very-low-density lipoprotein, a TG-rich lipoprotein particle synthesized in the liver using free fatty acids derived from adipose tissue. Although SGLT2 inhibitors generally improve the lipid profile, under certain conditions such as a low-carbohydrate diet, they may adversely exacerbate the lipid profile via ketosis.

Key words: sodium glucose cotransporter 2 inhibitor, dyslipidemia, hypertriglyceridemia, type 2 diabetes mellitus

Sodium-glucose cotransporter 2 (SGLT2) inhibitors suppress glucose reabsorption in the renal proximal tubule and improve glycemic control. Recent studies have reported the evidence that SGLT2 inhibitors reduce the risk of cardiovascular and renal events [1-4]. Based on the results of these large-scale clinical trials showing organ-protective effects, the algorithm described by the American Diabetes Association (ADA) in its *Standards of Medical Care in Diabetes-2020* recommends SGLT2 inhibitors as a second-line therapy option following metformin, especially in patients with atherosclerotic cardiovascular disease (ASCVD), heart failure (HF) or chronic kidney disease (CKD) [5]. Furthermore, the 2019 European Society of Cardiology/European Association for the Study of Diabetes (ESC/EASD) Guidelines on diabetes regard SGLT2 inhibitors as a first-line therapy for diabetic patients with heart disease [6]. This is a significant turning point in the US and Europe, where biguanides have long been the first-line strategy for diabetes.

SGLT2 inhibitors are also recognized for their weight loss effect and favorable effects on the lipid metabolism. Therefore, they are expected to constitute a "comprehensive" therapeutic strategy for type 2 diabetes with metabolic syndrome. With regard to the lipid metabolism in particular, it has been reported that SGLT2 inhibitors improve the overall lipid profile by decreasing triglycerides (TGs) and increasing high-density lipoprotein cholesterol (HDL-C) [7].

Here, we report the case of a type 2 diabetic patient with significant worsening of the lipid profile including marked TG elevation during the administration of SGLT2 inhibitors. Although SGLT2 inhibitors are now widely used and play a central role in the treatment of diabetes, their proper use requires attention.

Case Presentation

A 43-year-old male with type 2 diabetes presented with upper left abdominal pain lasting for two weeks and marked TG elevation (5,960 mg/dl). His primary care doctor suspected acute pancreatitis and referred him to our hospital. The patient had been diagnosed with type 2 diabetes at the age of 41 ((hemoglobin A1c [HbA1c], 12.1%; fasting blood glucose [FBG], 243 mg/dl) and administration of the dipeptidyl peptidase-4 (DPP-4) inhibitor teneligliptin was started. Two months before the patient's first visit to our hospital, his therapy for diabetes was switched from 20 mg/day of teneligliptin to 5 mg/day of dapagliflozin, an SGLT2 inhibitor, because of poor glycemic control (HbA1c, 11.6%; BG, 291 mg/dl). He was also on a low-carbohydrate diet, restricted to 90-120 grams per day with the aim of losing weight over a period of one month. According to an interview with a registered dietitian, his lipid intake was normal and he was on a protein-based diet.

In addition, the patient had dyslipidemia and was being treated with 2 mg/day of pitavastatin calcium. Under pitavastatin administration, his levels of TG, low-density lipoprotein cholesterol (LDL-C) and HDL-C were 500-800 mg/dl, 100-140 mg/dl and 40-45 mg/dl, respectively. He had no family history of dyslipidemia, stroke or coronary artery disease, but his mother has type 2 diabetes. The patient neither drinks nor smokes, and does not frequently drink sugar-sweetened beverages.

At his first visit to our hospital, the patient's body mass index was 30.1 kg/m² (height, 160 cm; body weight, 77.0 kg) and his weight was approximately 5 kg less than it had been 3 months earlier. Time-course changes in his examination findings are shown in Table 1. His blood test results at his first visit (Day 1) revealed marked TG, total cholesterol (TC) and free fatty acid (FFA) elevation (fasting TG, 4,632 mg/dl; TC, 594 mg/dl; FFA, 5.66 mEq/l) and decreased HDL-C (17 mg/dl). Urinary ketone measured by dipstick was strongly positive, but no metabolic acidosis was detected by arterial blood gas analysis (pH, 7.415; pO_2, 94.0 mmHg; pCO_2, 35.0 mmHg; HCO_3-, 22.0 mmol/l; base excess, -1.3 mmol/l). Regarding exocrine pancreatic enzymes, the patient's elastase-1 level had increased to 1,160 ng/dl, though his amylase, lipase, SPan-1 and DU-PAN-2 levels were within normal range. With respect to liver function, his transaminase levels were elevated. Abdominal plain computed tomography (CT) showed only marked fatty liver, but no evidence of the suspected acute pancreatitis such as swelling in the pancreas or increased adipose tissue density around the pancreas.

Considering the possibility that a low-carbohydrate diet combined with the SGLT2 inhibitor might cause ketosis, the administration of dapagliflozin was discontinued and the patient was instructed to eat at least 150 g of rice per meal as a staple food. Teneligliptin was resumed at a dosage of 20 mg/day and insulin therapy with insulin degludec was initiated at a dosage of 4 units per day.

At his return visit 3 days after the initial visit (Day 4), the patient's gastrointestinal symptoms had disappeared and his TG level had decreased to 2,968 mg/dl. His urinary ketone excretion had also decreased, although it had not disappeared completely. His venous ketone body levels were mildly elevated (total ketone bodies, 175 µmol/l; acetoacetate, 77.0 µmol/l; 3-hydroxybutyrate, 97.5 µmol/l). After confirming that his endogenous insulin-secreting capacity was maintained (serum C-peptide reactivity [CPR], 4.11 ng/ml), we discontinued insulin degludec and asked the patient's primary care doctor to administer 500 mg/day of metformin. On Day 39, the patient's TG level decreased to 452 mg/dl and urinary ketone bodies were negative (Table 1).

Lipoproteins were analyzed by polyacrylamide gel electrophoresis (PAGE). On Day 1, PAGE revealed a remarkable increase in very low-density lipoprotein (VLDL) and the almost complete disappearance of LDL fraction (Fig. 1A). On Day 39, on the other hand, PAGE detected a significant rise in HDL and LDL, and a relative decrease in VLDL (Fig. 1B).

After these results, the patient's treatment for dyslipidemia was changed from 2 mg/day of pitavastatin calcium to 0.2 mg/day of pemafibrate, and his postprandial TG levels were found to be 190-350 mg/dl.
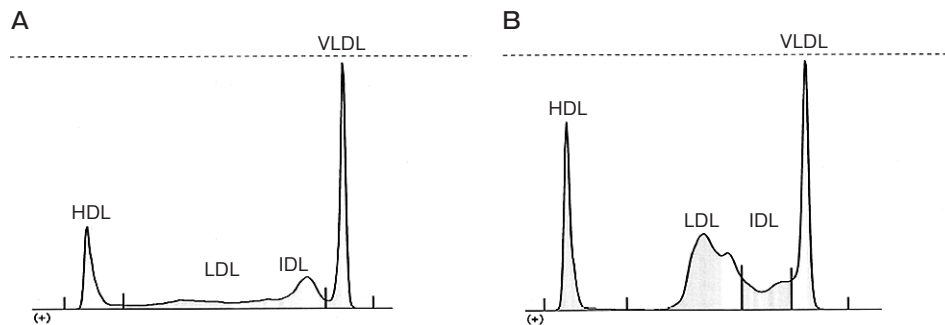
Discussion

SGLT2 inhibitors selectively inhibit SGLT2 in the renal proximal tubules and suppress glucose reabsorption, resulting in the promotion of urine glucose excretion. In addition to the positive effects on diabetes through urine glucose excretion, SGLT2 inhibitors have been reported to improve insulin resistance, hypertension and obesity [8]. They have also been reported to have favorable effects on the lipid profile, such as increased HDL-C and decreased TG associated with hepatic glu-

Table 1   Time-course changes in examination findings and medication

	Day 1	Day 4	Day 39
HbA1c (%)	13.0	–	10.0
BG (mg/dl)	184 (fasting)	333 (PPG 2H)	154 (fasting)
IRI (μU/ml)	8.6	–	14.5
TC (mg/dl)	594	478	222
HDL-C (mg/dl)	17	23	46
TG (mg/dl)	4632	2968	452
LDL-C (mg/dl) (direct measurement)	62	88	130
non HDL-C (mg/dl)	577	455	176
FFA (mEq/l)	5.66	–	1.01
AST (U/l)	82	–	34
ALT (U/l)	52	–	52
γ-GTP (U/l)	156	–	84
T-Bil (mg/dl)	0.6	–	–
ChE (U/l)	438	–	–
Alb (g/dl)	4.4	–	–
PLT ($\times 10^3/\mu$l)	341	–	–
FIB-4 Index	1.43	–	–
U-Ketone	(3+)	(1+)	(−)
Body weight (kg)	77.0	78.0	81.4

Medication

dapaglifrozin 5 mg   →×
teneligliptin 20 mg   →
insulin degludec 4u   →×
metformin 500 mg   →
pitavastatin calcium 2 mg   →×
pemafibrate 0.2 mg   →

Fig. 1   Polyacrylamide gel electrophoresis (PAGE) of serum lipoproteins.
A: Day 1.
B: Day 39.

coneogenesis enhancement, although the detailed mechanisms remain unknown [7].

In the present case, the administration of SGLT2 inhibitors was initially expected to improve the patient's obesity and lipid profile, but conversely, it eventually caused marked hypertriglyceridemia. Dyslipidemia in diabetes is often associated with elevated LDL-C and TG and decreased HDL-C, based on insulin resistance. Impaired insulin action, which is often observed in type 2 diabetes, causes the activation of hormone-sensitive lipase (HSL) in adipocytes and the degradation of adipose tissue triglycerides, resulting in elevated FFA release into

the blood. The blood-borne FFAs flow into the liver, where they play roles in increased VLDL production and secretion as a substrate for TG synthesis. In addition, the decreased activity of insulin also impairs lipoprotein lipase (LPL) activity and VLDL-TG catabolism, resulting in hypertriglyceridemia.

The following mechanism was considered to be the cause of the marked hypertriglyceridemia following SGLT2 inhibitor administration in the present case. A strict low-carbohydrate diet in combination with the SGLT2 inhibitor impaired hepatic glycolysis and promoted lipolysis in adipose tissue and the release of FFAs into the blood [9]. An oversupply of FFAs to the liver enhanced β-oxidation in the mitochondria, resulting in increased VLDL synthesis and secretion [10]. On the other hand, since LPL activity was decreased due to insulin resistance, it appeared that the catabolism of VLDL and intermediate-density lipoprotein (IDL) did not proceed, resulting in elevated TG-rich lipoproteins and marked hypertriglyceridemia (Fig. 2) [11-16]. The upper left abdominal pain that led the patient to be referred to our hospital with suspected pancreatitis was considered to be associated with ketosis mediated by increased β-oxidation. In addition, at his first visit to our hospital, a weight loss of 5 kg over 3 months was observed and eventually ascribed to ketosis. However, it may have been difficult for the patient to recognize this weight loss, as it had been masked by the SGLT2 inhibitors and the low-carbohydrate diet.

In this case, only elastase-1, an exocrine pancreatic enzyme, was elevated. Elastase-1 has a long half-life, and once it increases, it takes 2-4 weeks to normalize. Therefore, high elastase-1 levels may persist even after other pancreatic enzymes are reduced and normalized. Although the possibility of acute pancreatitis occurring a few weeks before the patient's first visit to our hospital cannot be completely ruled out, we diagnosed his abdominal symptoms as being due to ketosis, comprehensively considering the levels of other pancreatic enzymes, CT findings, medical history and the presence of ketosis. During the patient's clinical course, his abdominal symptoms rapidly disappeared as the ketosis improved.

SGLT2 inhibitors are currently a central therapeutic strategy for diabetes worldwide due to their beneficial effects on HF, CKD, body weight and lipid profiles, as well as on glycemic control. On the other hand, there are some points to be noted regarding the safety of SGLT2 inhibitors, such as the potential for genital and urinary tract infections, hypoglycemia when combined with sulfonylureas or insulin, and an increased risk of keto-acidosis. Ketoacidosis under SGLT2 inhibitor administration in particular is often accompanied by only moderately increased blood glucose levels and is known as
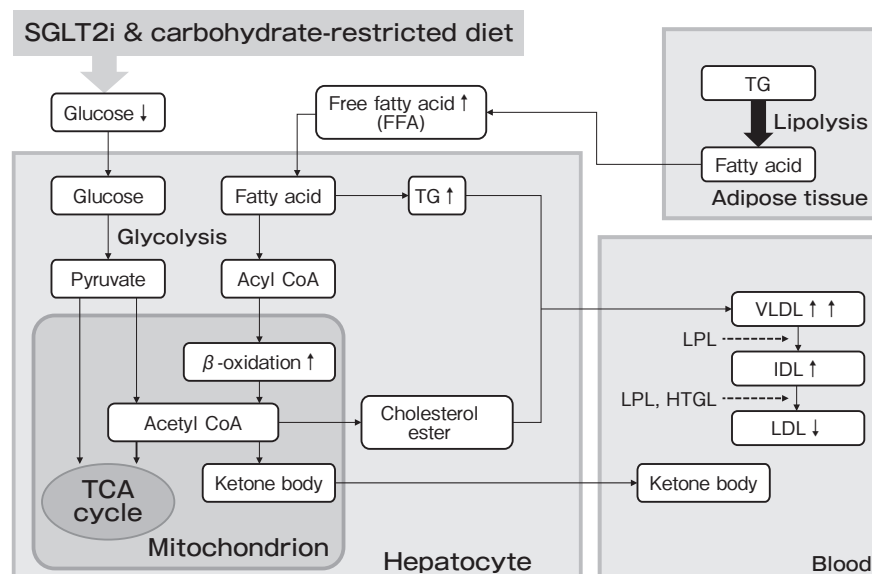

Fig. 2   Assumed mechanism: regulation of glucose and lipid metabolism during dietary carbohydrate restriction with SGLT2 inhibitors. TG, triglyceride; VLDL, very low-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LPL, lipoprotein lipase; HTGL, hepatic triglyceride lipase.

euglycemic diabetic ketoacidosis (DKA) [17]. The U.S. Food and Drug Administration (FDA) warns about and identifies potential DKA-triggering factors such as acute illness, reduced caloric or fluid intake, reduced insulin dose and a history of alcohol intake (http://www.fda.gov/downloads/Drugs/DrugSafety/UCM446954.pdf).

The present study has the limitation that the chylomicrons identified by agarose gel electrophoresis, LPL activity and ApoE phenotype have not yet been evaluated.

In recent years, dietary habits have diversified, and patients with a strict carbohydrate-restricted diet or an imbalanced diet may have an increased risk of DKA when such a diet is combined with SGLT2 inhibitors. In conclusion, although SGLT2 inhibitors generally improve the lipid profile, under certain conditions such as a low-carbohydrate diet, they may adversely exacerbate the lipid profile via ketosis.

References

1. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC and Inzucchi SE: Empagliflosin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med (2015) 373: 2117–2128.

2. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M and Matthews DR; CANVAS Program Collaborative Group: Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med (2017) 377: 644–657.

3. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Ruff CT, Gause-Nilsson IAM, Fredriksson M, Johansson PA, Langkilde AM and Sabatine MS: Dapagliflozin and Cardiovascular outcomes in Type 2 Diabetes. N Engl J Med (2019) 380: 347–357.

4. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, Cannon CP, Capuano G, Chu PL, de Zeeuw D, Greene T, Levin A, Pollock C, Wheeler DC, Yavin Y, Zhang H, Zinman B, Meininger G, Brenner BM and Mahaffey KW: Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med (2019) 380: 2295–2306.

5. American Diabetes Association: Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes-2020*. Diabetes Care (2020) 43: S98–S110.

6. Cosentino F, Grant PJ, Aboyans V, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Filippatos G, Grobbee DE, Hansen TB, Huikuri HV, Johansson I, Jǔni P, Lettino M, Marx N, Mellbin LG, Östgren CJ, Rocca B, Roffi M, Sattar N, Seferovic̀ PM, Sousa-Uva M, Valensi P and Wheeler DC; ESC Scientific Document Group: 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J (2020) 41: 255–323.

7. Kaku K, Inoue S, Matsuoka O, Kiyosue A, Azuma H, Hayashi N, Tokudome T, Langkilde AM and Parikh S: Efficacy and safety of dapagliflozin as a monotherapy for type 2 diabetes mellitus in Japanese patients with inadequate glycemic control: a phase a multicenter, randomized, double-blind, placebo-controlled trial. Diabetes Obes Metab (2013) 15: 432–440.

8. Maliha G and Townsend RR: SGLT2 inhibitors: their potential reduction in blood pressure. J Am Soc Hypertens (2015) 9: 48–53.

9. Sengenes C, Stich V, Berlan M, Hejnova J, Lafontan M, Pariskova Z and Galitzky J. Increased lipolysis in adipose tissue and lipid mobilization to natriuretic peptides during low-calorie diet in obese women. Int J Obes Relat Metab Disord (2002) 26: 24–32.

10. Julius U. Influence of plasma free fatty acids on lipoprotein synthesis and diabetic dyslipidemia. Exp Clin Endocrinol Diabetes (2003) 111: 246–250.

11. Panarotto D, Rémillard P, Bouffard L and Maheux P: Insulin resistance affects the regulation of lipoprotein lipase in the postprandial period and in an adipose tissue-specific manner. Eur J Clin Invest (2002) 32: 84–92.

12. Bjornstad P and Eckel RH: Pathogenesis of Lipid Disorders in Insulin Resistance: a Brief Review. Curr Diab Rep (2018) 18: 127.

13. Frayn KN: Adipose tissue and the insulin resistance syndrome. Proc Nutr Soc (2001) 60: 375–380.

14. Lewis GF, Uffelman KD, Szeto LW, Weller B and Steiner G: nteraction between free fatty acids and insulin in the acute control of very low density lipoprotein production in humans. J Clin Invest (1995) 95: 158–166.

15. Avramoglu RK, Basciano H and Adeli K: Lipid and lipoprotein dysregulation in insulin resistant states. Clin Chim Acta (2006) 368: 1–19.

16. Ginsberg HN, Zhang YL and Hernandez-Ono A: Regulation of plasma triglycerides in insulin resistance and diabetes. Arch Med Res (2005) 36: 232–240.

17. Rosenstock J and Ferrannini E: Euglycemic Diabetic Ketoacidosis: A Predictable, Detectable, and Preventable Safety Concern With SGLT2 Inhibitors. Dibetes Care (2015) 38: 1638–1642.