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Body Weight Gain and Hyperphagia After Administration of SGLT-2 Inhibitor: A Case Report

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Male, 44
Final Diagnosis: Type 2 diabetes
Symptoms: Hunger • increased appetite
Medication: GLP-1 receptor agonist • SGLT-2 inhibitor
Clinical Procedure: —
Specialty: Internal Medicine/Diabetology

Objective: Unusual or unexpected effect of treatment

Background: A detailed description is given of a case we encountered in which unexpectedly marked weight gain occurred following a treatment switch from a GLP-1 receptor agonist to an SGLT-2 inhibitor.

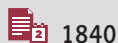
Case Report: The patient, a 44-year-old man with type 2 diabetes mellitus, had gained about 10 kg in weight in the previous year. Therefore, metformin was replaced with liraglutide to obtain reduction of body weight. Although the patient lost about 8 kg (7%), during the 18-month period on the medication, the weight loss stabilized; therefore, the treatment was again switched to tofogliflozin to obtain further reduction of body weight. However, the patient reported increasing hunger and an exaggerated appetite from week 3 onward after the start of tofogliflozin, and gained about 9 kg in weight within 2 weeks, associated with a tendency towards increased HbA1c; therefore, tofogliflozin was discontinued. Immediate reinstitution of liraglutide resulted in reduction of the increased appetite, weight, and HbA1c level.

Conclusions: Caution should be exercised against hyperphagia and weight gain due to hunger that may occur following discontinuation of a GLP-1 receptor agonist and/or initiation of an SGLT-2 inhibitor.

MeSH Keywords: Body Weight Changes • Diabetes Mellitus, Type 2 • Glucagon-Like Peptide 1 • Sodium-Glucose Transporter 2

Abbreviations: GLP-1 – glucagon-like peptide-1; SGLT-2 – sodium glucose cotransporter-2; HbA1c – glycated hemoglobin; BMI – Body mass index

Full-text PDF: <http://www.amjcaserep.com/abstract/index/idArt/896233>



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Background

Glucagon-like peptide-1 (GLP-1) receptor agonists are ideal as hypoglycemic agents for patients with obesity and type 2 diabetes mellitus, as they exert both an appetite-suppressing and weight-reducing effect via their actions on the central nervous system (CNS) and stomach [1,2], but their weight-reducing effect appears to diminish within 6 months.

Another new class of hypoglycemic agents with a promising weight-reducing effect is the class of sodium glucose cotransporter-2 (SGLT-2) inhibitors. These drugs act through a novel mechanism: they promote urinary glucose excretion by inhibiting glucose reabsorption in the uriniferous tubules [3]. Tofogliflozin is the most highly selective for SGLT-2 among the inhibitors. However, we recently encountered a case in which conspicuous weight gain occurred within a short period, after the therapy was switched from liraglutide to a tofogliflozin because of stabilized weight loss.

Case Report

The patient was a 44-year-old man, with an unremarkable family medical history and no history of habitual drinking or smoking. He had a history of having been diagnosed with fatty liver, gout, and hypertension. He was already obese, weighing 85 kg (body mass index [BMI] 25.4) even at age 20, and his weight

reached a peak of 116 kg (BMI, 34.6; height 183 cm) when he was 38 years old. In 2011, at age 40, the patient visited our hospital with the complaints of tinnitus and dizziness, and was diagnosed as having sudden deafness; at the same time, he was detected for the first time as having abnormal glucose tolerance. Initial examination revealed a high HbA1c value of 10.0% and a high postprandial blood glucose level of 265 mg/dL, with evidence of insulin hypersecretion. Because he was found to be negative for diabetes-related autoantibodies, a diagnosis of type 2 diabetes mellitus was made. There was no evidence of diabetic retinopathy or nephropathy. During hospitalization for the treatment of hearing loss, the patient was administered short-term insulin treatment for the control of blood glucose, and by the time of discharge, he had lost about 7 kg. His subsequent clinical course is illustrated in Figure 1. With oral metformin administered at the dose of 500 mg/d, the HbA1c was maintained at about 6%; however, his weight rebounded by 10 kg within 1 year. The biguanide as the hypoglycemic agent was therefore switched to a GLP-1 receptor agonist (Liraglutide; Novo Nordisk Pharma Ltd.) starting November 2012, to obtain weight reduction.

Liraglutide therapy was initiated at the dose of 0.3 mg/d, with the dose raised weekly thereafter to 0.9 mg/d, which yielded a favorably smooth body weight loss of a little less than 5 kg (4%) from 115 kg during the first 6 months of treatment. However, the body weight decrease then became slower and fluctuated slightly due, at least in part, to a lack of physical

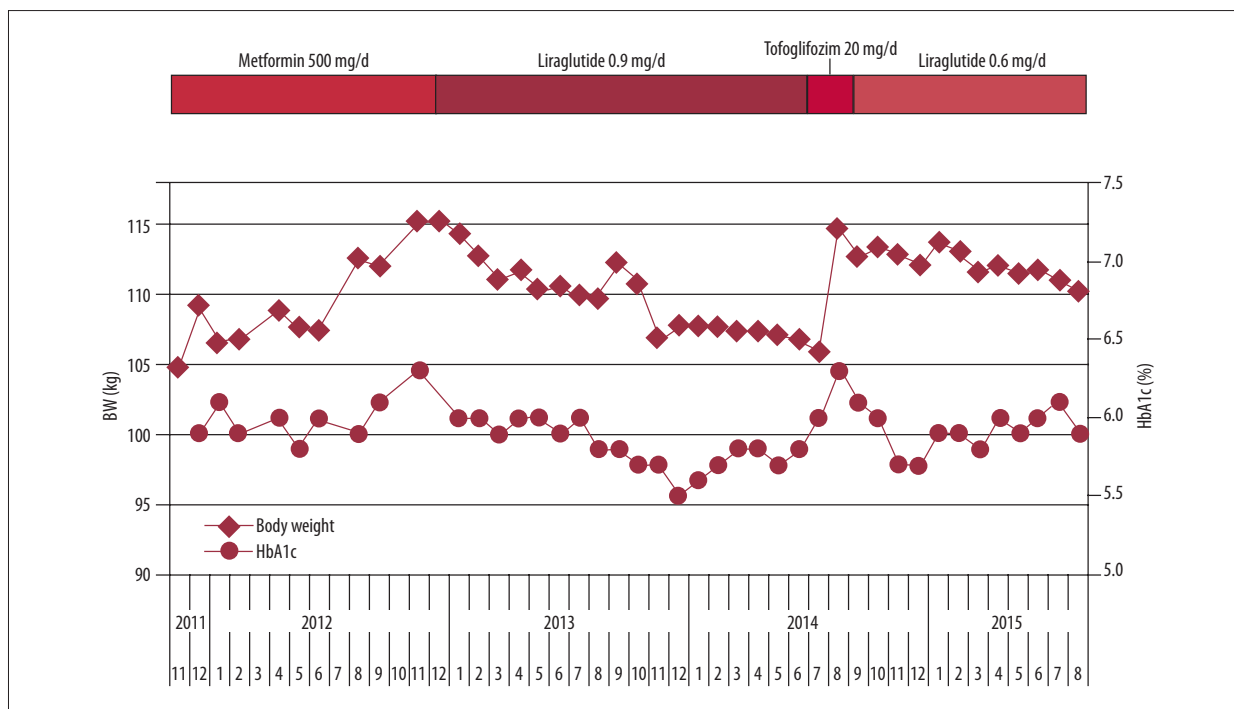


Figure 1. Clinical course. Changes in body weight (◆) and HbA1c (●) over time and doses and durations of the drugs administered from 2011 to 2015.

exercise from pressing work and dizziness. A weight loss of 8 kg (7%) was finally achieved over an 18-month period, but the weight failed to reach the baseline. The HbA1c value remained at around 6%, notwithstanding a slight tendency towards increase. With apprehensions about a possible exacerbation of insulin resistance and worsening of glucose tolerance with the persistent overweight state, the therapy was again switched to 20 mg/day of tofogliflozin (Kowa Pharmaceutical Co. Ltd.) from July 2014, in anticipation of further weight reduction. The hematologic/blood chemical and urinalysis findings at this time are summarized in Table 1. There were no significant abnormalities, except for an elevated serum triglyceride level, which was attributed to the postprandial blood sampling.

The patient had no significant subjective symptoms and lost 1 kg during the first 2 weeks of tofogliflozin therapy; however, from week 3 onwards of treatment, he began to experience increased urinary frequency and hunger, with an uncontrollably exaggerated appetite. Because he rapidly gained about 9 kg of weight during the next 2 weeks, the tofogliflozin was discontinued at the end of week 4. At the time of discontinuation of tofogliflozin after a month of treatment, the HbA1c level was higher by 0.3% from the baseline. Tests for ketonuria were negative, and blood assays for fractionated ketones were not performed.

Liraglutide treatment was then immediately reinstated at the dose level of 0.9 mg/day. The excessive appetite began subsiding from week 3 onward after the resumption of liraglutide, along with rapid improvement of the HbA1c value. The patient complained of symptoms indicative of hypoglycemia at 4 months after the resumption of liraglutide, necessitating a dose reduction of the drug to 0.6 mg/d. During the first year after the resumption of liraglutide, the body weight gradually decreased by 4 kg (corresponding to nearly half of the gain).

Discussion

In regard to the weight-reducing effect of liraglutide, it was reported that weight was reduced by a little less than 10% (a difference by about 6% from the placebo group) within a short period of 6 months with 0.3 to 0.9 mg/d of liraglutide in obese type 2 Japanese diabetes patients [4]. As to the long-term effect, weight-reducing effect was noted in about 80% of patients for 1 year and a weight loss of $\geq 4\%$ was maintained until the end of 2 years of treatment [5]. However, a close review of the changes in the body weight over time has revealed that the weight loss was conspicuous until the first 6 months of treatment, following which it stabilized. According to data from a subanalysis of the LEAD-3 study, in which white people made up about 80% of the study population, weight was reduced by 2.1 kg and 2.7 kg after 2-years of treatment with liraglutide at the dose of 1.2 mg/d or 1.8 mg/d, respectively.

Table 1. Laboratory findings at the time of initiation of treatment with tofogliflozin.

Blood chemistry	
AST (GOT)	40 IU/L
ALT (GPT)	65 IU/L
LDH	273 IU/L
Alp	201 IU/L
γ -GTP	73 IU/L
BUN	14.7 mg/dl
Cr	0.87 mg/dl
UA	6.1 mg/dl
Na	143 mEq/L
K	3.6 mEq/L
Cl	106 mEq/L
Tch	169 mg/dl
HDL-c	41 mg/dl
TG	186 mg/dl
LDL-c	105 mg/dl
NonHDL-c	128 mg/dl
eGFR	76.7 ml/min/1.73 m ²
Hematology	
WBC	78 *100/ μ l
RBC	489 *10 ⁴ / μ l
Hb	14.7 g/dl
Ht	41.7 %
Plt	23.9 *10 ⁴ / μ l
Urinalysis	
Protein	–
Glucose	–
Ketone	–
Urinary Pro/Cr ratio	0.03
Urinary micro-Alb/Cr ratio	3.4
Data related diabetes mellitus	
HbA1c	6.0 %
Plasma glucose	106 mg/dl
Immunoreactive insulin	61.9 μ U/m
C-peptide	5.72 ng/ml

As found in other studies, in this analysis body weight curve leveled off from 6 months onwards of treatment [6].

There are 2 types of GLP-1 receptor agonists in terms of the duration of action – short-acting and long-acting – and the liraglutide preparation referred to in this report belongs to the latter type. Short-acting GLP-1 receptor agonists (e.g., exenatide and lixisenatide) frequently produce gastrointestinal symptoms, while having a profound postprandial hypoglycemic effect owing to their potent action of delaying gastric emptying. Liraglutide, on the other hand, is a long-acting agonist causing only a modest delay in gastric emptying. In an animal experimental study, the activity of this drug of delaying gastric emptying diminished rapidly by day 14 after the start of treatment [7]. In humans, such diminution of the effect, tachyphylaxis, is also observed for this receptor agonist. It causes a lesser degree of gastrointestinal adverse effects because of tachyphylaxis 1-2 months after starting the medication [8]. We inferred that the slowing of weight loss that was observed after 6 months of treatment with liraglutide in this patient was due to this tachyphylaxis phenomenon.

We initially thought that the appetite-suppressing effect of liraglutide was diminished. However, it would be reasonable to assume that the effect was sustained beyond 6 months of treatment according to the patient's clinical course, which revealed that the patient developed exaggerated appetite after the discontinuation of liraglutide and then the appetite subsided again after reinstatement of the drug. It has been demonstrated in an experimental study in rats that the centrally-mediated appetite-suppressing effect of long-acting GLP-1 receptor agonists is sustained for longer than their effect of delaying gastric emptying [7]. It was therefore expected that the centrally-mediated effect would persist in the present case as well.

SGLT-2 inhibitors promote urinary glucose excretion with a consequent loss of calories and reduction of body weight. A weight loss of nearly 2 kg occurred by 6 months after the start of treatment [9], and a mean weight loss of about 3 kg was observed following long-term treatment with this agent alone for 52 weeks. When this agent was administered as an add-on drug to other hypoglycemic drugs, a 1.6 to 3.8 kg weight loss was observed after 52 weeks of treatment [10]. These results compare favorably with those of trials of GLP-1 receptor agonists, indicating that tofogliflozin is a promising new drug. However, it was reported that tofogliflozin increased appetite in animal experiments by approximately 10% [11]. As for the time of onset of the appetite enhancement, experimental studies in rats treated with dapagliflozin have demonstrated that the total food intake increased from day 7 onward in animals treated with a high dose and from day 18 onward in those treated with a low dose; hence, the time of onset tended to be delayed in a dose-dependent fashion [12,13]. A 2-fold difference in the

weight-reducing effect was also observed between a rat group on restricted diet and a rat group on *ad libitum* diet, indicating that the hyperphagia attenuates the weight-reducing effect.

The hyperphagia is not thought to be a direct action of the SGLT-2 inhibitor itself, since no SGLT-2 expression has been detected in the brain. Furthermore, it is assumed that the hyperphagia may represent an adaptive or compensatory response to involuntary glucose excretion, inasmuch as it occurs not immediately after the initiation of treatment with an SGLT-2 inhibitor, but after a delay [13]. In recent years, there have been an increasing number of papers reporting that hypothalamic neurons have the capacity to sense fluctuations in local nutrient concentrations and to modify the activity in response to that sensation [14]. When these findings are taken into account, it may be said that the hyperphagia is a consequence of physiological and adequate hypophyseal accommodations to changes in the energy sources, such as ketones and glucose, which vary according to the fasting state.

It is unclear as yet as to how the appetite is altered in response to administration of a SGLT-2 inhibitor in humans. It is also unknown whether the present patient became predisposed to the development of ketosis due to the administration of the SGLT-2 inhibitor, since the case was not assessed in detail in this respect. However, the timing of onset of the appetite enhancement bore close resemblance to the animal experimental data, which strongly suggests that not only the discontinuation of the GLP-1 receptor agonist, but also treatment with the SGLT-2 inhibitor had a causal bearing on the conspicuous weight gain.

Based on the above findings, GLP-1 receptor agonist is better than the SGLT-2 inhibitor to reduce weight. However, SGLT-2 inhibitor increased glucagon levels [15] and GLP-1 receptor agonist decreased these levels [16] and will act symbiotically with the SGLT-2 inhibitor to reduce glucose levels. Saroka also reported that an SGLT-2 inhibitor (canagliflozin) significantly further reduced mean HbA1C levels and body weight in patients with type 2 diabetes mellitus when added to a regimen of GLP-1 therapy [17]. Therefore, it would be more desirable to use the SGLT-2 inhibitor in conjunction with the GLP-1 receptor agonist to achieve further weight reduction without evoking hyperphagia, as in the present case.

Conclusions

The CNS-mediated appetite-suppressing effect of long-acting GLP-1 receptor agonists is likely to be long-sustained; therefore, caution needs to be exercised against possible enhancement of appetite when the agonist medication is discontinued. It should also be noted that an appetite-enhancing effect may be evoked by hunger that emerges about 2 weeks after the start of treatment with an SGLT-2 inhibitor.

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