Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Increased sugar intake as a form of compensatory hyperphagia in patients with type 2 diabetes under dapagliflozin treatment

Ichiro Horie [a,*], *Norio Abiru* [a], *Ryoko Hongo* [b], *Takeshi Nakamura* [a], *Ayako Ito* [a], *Ai Haraguchi* [a], *Shoko Natsuda* [a], *Ikuko Sagara* [a], *Takao Ando* [a], *Atsushi Kawakami* [a]

[a] *Department of Endocrinology and Metabolism, Nagasaki University Hospital, Nagasaki, Japan*
[b] *Division of Dietary Service, Nagasaki University Hospital, Nagasaki, Japan*

ARTICLE INFO

Article history:
Received 30 May 2017
Received in revised form
18 October 2017
Accepted 10 November 2017
Available online 21 November 2017

Keywords:
SGLT2
Dapagliflozin
Hyperphagia
BDHQ
Diet history
Sugar

ABSTRACT

Aims: Sodium-glucose cotransporter 2 inhibitors (SGLT2i) cause substantially less weight loss than would be expected based on their caloric deficits, probably due to enhanced appetite regulation known as "compensatory hyperphagia," which occurs to offset the negative energy balance caused by increased glycosuria. We examined whether any specific nutrients contributed to the compensatory hyperphagia in diabetic patients taking SGLT2i.
Methods: Sixteen patients with type 2 diabetes were newly administered dapagliflozin 5 mg daily as the experimental SGLT2i group. Sixteen age-, sex- and BMI-matched type 2 diabetes patients not receiving dapagliflozin served as controls. A brief-type self-administered diet history questionnaire (BDHQ) was undertaken just before and 3 months after study initiation to evaluate changes of energy and nutrient intakes in each group.
Results: At 3 months, daily intakes of total calories and the proportions of the three major nutrients were not significantly increased in either group. However, daily sucrose intake was significantly increased after treatment versus the baseline value in the SGLT2i group ($p = .003$), but not in controls. The calculated intakes of all other nutrients were not significantly changed in either group.
Conclusions: Dapagliflozin treatment specifically increased sucrose intake, which might be an ideal target for nutritional approaches to attenuate compensatory hyperphagia.

1. Introduction

Sodium-glucose cotransporter 2 (SGLT2) is expressed in the brush-borders of cells in the early proximal convoluted tubules of kidney, and is the most important mediator of glucose reabsorption from the glomerular filtrate. Patients with type 2 diabetes are known to express higher levels of SGLT2 than healthy individuals, enhancing their renal glucose

Abbreviations: SGLT2, sodium-glucose cotransporter 2; SGLT2i, SGLT2 inhibitor; BDHQ, brief-type self-administered diet history questionnaire; DHQ, self-administered diet history questionnaire; GLP-1, glucagon-like peptide-1; eGFR, estimated glomerular filtration rate; BMI, body mass index; BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation; 0M, 0 month; 3M, 3 months; P, protein; F, fat; C, carbohydrate

* Corresponding author at: Department of Endocrinology and Metabolism, Nagasaki University Hospital, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan.
E-mail address: holy197741@me.com (I. Horie).
https://doi.org/10.1016/j.diabres.2017.11.016
0168-8227/

uptake [1]. SGLT2 inhibitors are useful anti-diabetic agents that lower the threshold of renal glucose reabsorption and promote urinary glucose excretion, thereby reducing plasma glucose levels and reducing body weight [2].

However, patients with type 2 diabetes under SGLT2 inhibitor (SGLT2i) treatment have been shown to lose less weight than predicted by the caloric deficits related to urinary glucose excretion [3,4]. This might be explained by the increased dietary caloric intake seen in animal models of diabetes [5]. Such increased caloric intake is known as "compensatory hyperphagia" and is assumed to be an adaptive response to calorie loss in glycosuria [5]. Dapagliflozin has been shown to dose-dependently increase food and water intake in rats and the dapagliflozin-treated rats lost more weight when hyperphagia was prohibited [5]. In diabetic patients, SGLT2i treatment was shown to induce compensatory hyperphagia based on energy balance dynamics calculated by a mathematical model [3,4]. However, there has been no report identifying this compensatory increase of energy intake in a clinical setting. Moreover, if compensatory hyperphagia does in fact occur in diabetic patients under SGLT2i treatment, it would be useful to determine whether any specific nutrient contributes unequally to this phenomenon.

The brief-type self-administered diet history questionnaire (BDHQ), a dietary questionnaire developed for assessing dietary habits and nutrition intake in Japanese adults, has been validated and shown to be useful in evaluating the specific nutrient intake based on dietary records [6,7]. Here, we examined calorie intake including specific nutrient intake data using the BDHQ in patients with type 2 diabetes under SGLT2i treatment.

2. Methods

2.1. Patients

Eligible diabetic patients were Japanese adult patients age 18–75 years with HbA1c $\leq$10.0% under treatment with anti-diabetic agents including injections of insulin and/or glucagon-like peptide-1 (GLP-1) receptor agonists. The participants must be under stable control of diabetes for more than 3 months prior to the inclusion without changing of anti-diabetic agents. None of the participants had previously been treated with SGLT2i. Patients with type 1 diabetes, renal disorder with estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2, liver disease, cardiac disease, chronic pancreatitis, history of gastrointestinal surgery, alcoholic abuse, steroid treatment, or pregnancy were excluded.

2.2. Study design

This was a single-center, open-label, prospective cohort study in Japanese patients with type 2 diabetes at Nagasaki University Hospital from December 2015 to February 2017 (UMIN-CTR, UMIN000020157).

Sixteen type 2 diabetic patients who required additional treatment to improve glycemic control in the clinical setting comprised the SGLT2i group. Sixteen age-, sex-, and body mass index (BMI)-matched type 2 diabetic patients whose treatment remained unchanged served as the control group. Baseline characteristics of both groups are shown in Table 1.

The participants in the SGLT2i group orally received dapagliflozin 5 mg once daily after breakfast. Assessments of clinical features and diet histories were studied in the SGLT2i group and in the control subjects before and 3 months after inclusion in the study (Fig. 1). The seasons of the first assessment in the control group were matched with those in SGLT2i group to remove the potential influence of season on dietary behavior. In both groups, changes in the anti-diabetic medications during the study period were permitted only when patients developed hypoglycemia. We discontinued dapagliflozin and excluded the participant from the study if we observed the potential adverse events of dapagliflozin such as severe hypoglycemia (<40 mg/dL), severe dehydration, genital or/and urinary infection that needed a medical treatment, stroke, and myocardial infarction. The study was approved by the ethical committee of Nagasaki University Hospital. Informed consent was obtained from all participants.

2.3. Diet-history questionnaire

The participants undertook the BDHQ [6] to provide data for nutrition intake estimates. The BDHQ was developed recently by shortening the self-administered diet history questionnaire (DHQ) that had been designed to assess dietary habits in Japanese adults [8]. The DHQ has been validated using dietary records [8], 24-h urine [9], serum [10], and doubly labeled water methods [11], and has been widely used in epidemiological studies [12–16]. It should be noted that it takes 45–60 min to complete the DHQ. The BDHQ, on the other hand, requires only 15 min to complete, and is a fixed-portion questionnaire that asks for the consumption frequencies of selected 58 foods, beverages, and seasonings during the preceding month. The food and beverage items listed on the BDHQ were selected to represent foods commonly consumed in Japan, mainly from a food list used in the National Health and Nutrition Survey of Japan [6]. Mean daily intakes of total energy and 99 different nutrients can be estimated by the BDHQ. The food-group intakes and nutrient intakes estimated by the BDHQ have been correlated with an assessment based on 16-day dietary records [6], and the nutrient intakes calculated from the BDHQ have equivalent validity to those from the DHQ regardless of the season or region of Japan [7].

2.4. Study assessments

The primary endpoints were any changes in daily intake of total energy or the amount or energy ratio of any nutrient between baseline and 3 months after starting the study in each group. Other endpoints were any changes of clinical features including body weight, BMI, systolic or diastolic blood pressure, or levels of hematocrit, HbA1c, blood urea nitrogen (BUN), creatinine, eGFR, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (γ-GTP), triglyceride, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, albuminuria, or glycosuria.