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Effect of Tofogliflozin on Cardiac Function: Potential Link Between Ketone Bodies and the Heart

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Abstract

This report describes the effect of tofogliflozin, a sodium-glucose cotransporter 2 inhibitor (SGLT2i), on cardiac function and its related parameters including ketone bodies (acetoacetate and beta-hydroxybutyrate). One case received and two cases discontinued tofogliflozin. Changes of cardiometabolic parameters were compared at 3 months. A 65-year-old patient with decreased heart function received tofogliflozin 20 mg/day. Left ventricular ejection fraction (EF), functional shortening (%FS), or acetoacetate/beta-hydroxybutyrate levels were increased. A 68-year-old patient with normal heart function discontinued tofogliflozin 20 mg/day. EF, %FS or acetoacetate/beta-hydroxybutyrate levels were decreased. A 60-year-old patient with slightly decreased heart function discontinued tofogliflozin. No changes of EF, %FS, or acetoacetate/beta-hydroxybutyrate levels were noted. Taken together, these results suggest that ketone bodies and the heart function appear to be related (concomitant changes by tofogliflozin) and that tofogliflozin might have effects on cardiac function through modulating ketone bodies.

Keywords: Tofogliflozin; SGLT2i; Cardiac function; Ketone bodies; Heart

Introduction

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are novel oral anti-diabetic drugs that exert beneficial effects on metabolic and cardiovascular aspects [1, 2]. The recent result of the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial demonstrated that this SGLT2i was associated with remarkable reductions of the primary composite outcome of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke (three-point major adverse cardiovascular events), hospitalization for heart failure and overall mortality [3]. These effects were observed from the rather early stage (less than 3 months), implicating that they were not caused by ameliorated atherosclerosis, myocardial remodeling or ischemia but rather by other mechanisms. Empagliflozin and other SGLT2i can decrease body weight, blood pressure and serum uric acid [1, 2]. They can also induce natriuresis and/or osmotic diuresis, thereby leading to a decrease of extracellular volume [1, 2]. A small increase in serum high-density lipoprotein cholesterol has been noted with SGLT2i [1, 2]. However, it is unlikely that modest improvements in these cardiometabolic parameters had significantly contributed to the remarkable cardiovascular outcomes observed in EMPA-REG OUTCOME trial within 3 months, since the subjects were already taking a lot of medications that can ameliorate these cardiometabolic parameters (diuretics, statins, anti-hypertensive drugs, etc. [3]).

There are a number of explanations for the surprising results of empagliflozin on heart function. One of them is "ketone hypothesis" [4, 5]. Ketone bodies (mainly acetoacetate and beta-hydroxybutyrate) are the most energy-efficient fuels and yield more ATP per mole of substrate than pyruvate (metabolite of glucose) or fatty acid and increase the free energy released from ATP hydrolysis [6]. Although ketosis is usually regarded as an unfavorable clinical state (e.g., diabetic ketoacidosis), it has been suggested that induction of mild hyperketonemia has certain therapeutic benefits [7]. Heart failure may be caused by reduced energy (ATP) status in the heart tissue and ketone bodies may supply efficient energy to the failing heart. SGLT2i facilitate fat metabolism (lipolysis and fatty acid oxidations), thereby producing ketone bodies [4, 5]. It has been hypothesized that the increased levels of ketone bodies with SGLT2i may offer significant cardioprotection to high risk patients with diabetes [4, 5].

Tofogliflozin is a potent and selective SGLT2i, which is currently available in Japan. In analogies to other SGLT2i, tofogliflozin is associated with body weight reduction, osmotic diuresis and blood pressure lowering [8]. It has also favorable effects on markers of arterial stiffness and vascular resistance, albuminuria and serum uric acid [8]. Here effects of "on and off" of tofogliflozin administration on cardiac function in relation to ketone bodies will be reported. EF and %FS values with heart ultrasonography [9] and some cardiometabolic parameters including acetoacetate/beta-hydroxybutyrate were meas-

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Table 1. Changes of Cardiometabolic Parameters

	Patient A	Patient B	Patient C
Age (years)	65	68	60
Body height (cm)	162	168	165
CTR (%)	58	50	55
Body weight (kg)			
Baseline	64.2	89	76.85
3 months	63.05	90.2	77.45
HbA1c (%)			
Baseline	7.3	8.9	9.8
3 months	7.6	11.4	9
EF			
Baseline	47.8	69.3	47.7
3 months	61.1	66.5	47.7
%FS			
Baseline	24.8	38.9	24.4
3 months	33.1	36.7	24.4
BNP (pg/mL)			
Baseline	71.7	7.2	55.7
3 months	17.1	4.7	53.7
Acetoacetate (µmol/L)			
Baseline	19	63	30
3 months	29	36	30
Beta-hydroxybutyrate (µmol/L)			
Baseline	46	142	75
3 months	53	83	88
Hb (g/dL)			
Baseline	12.9	16.5	14.6
3 months	11.3	15.5	14.5

These parameters are measured at baseline and at 3 months.

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Case Reports

Patient A is a 65-year-old man with T2DM, hyperlipidemia (HL) and hypertension (HTN) since January 2013. He had been receiving metformin 100 mg/day, pravastatin 5 mg/day and furosemide 20 mg/day in the past 6 months. He had a slightly enlarged heart size (cardiothoracic ratio (CTR): 58%; from now on, each value shown below is indicated in Table 1), elevated BNP (71.7 pg/mL) and decreased EF (47.8) levels. However, he had been refusing to treat his heart failure. Since his diabetes control was somewhat not so good, he started tofogliflozin 20 mg/day in November 2016. No adverse events were noted. At 3 months, EF (47.8 - 61.1) and %FS (24.8 - 33.1) levels were effectively increased. Similarly, acetoacetate (19 - 29 µmol/L) and beta-hydroxybutyrate (46 - 53 µmol/L) levels were increased. BNP (71.7 - 17.1 pg/mL) and hemoglobin (Hb; 12.9 - 11.3 g/dL) levels were decreased. This patient was a non-responder to tofogliflozin, since his HbA1c level was increased (7.3-7.6%). Body weight (BW) was decreased (64.2 - 63.05 kg).

Patient B is a 68-year-old man with T2DM, HL and HTN since June 2005. He had been receiving metformin 1,500 mg/day, trelagliptin 100 mg/week, pioglitazone 15 mg/day, atorvastatin 5 mg/day, cilnidipine 10 mg/day and valsartan 40 mg/day in the past 6 months. In January 2016, he started to receive 20 mg/day tofogliflozin. Since he had tolerability problems with tofogliflozin, he discontinued this drug in December 2016. He had normal heart function at baseline (CTR: 50%; BNP: 7.2 pg/mL; EF: 69.3). At 3 months, EF (69.3 - 66.5) and %FS (38.9 - 36.7) levels were decreased. Similarly, acetoacetate (63 - 36 µmol/L) and beta-hydroxybutyrate (142 - 83 µmol/L) levels were decreased. Very slight changes of BNP (7.2 - 4.7 pg/mL) or Hb (16.5 - 15.5 g/dL) levels, though with-

in normal range, were noted. HbA1c (8.9-11.4%) level and BW (89.0 - 90.2 kg) were increased.

Patient C is a 60-year-old man with T2DM since February 2010. He had been receiving metformin 1,000 mg/day in the past 6 months. He had a slightly enlarged heart size (CTR: 55%), moderately elevated BNP (55.7 pg/mL, Table 1) and decreased EF (47.4) levels. He started to receive tofogliflozin 20 mg/day in October 2016. Because he was a non-responder with tofogliflozin, he discontinued this drug in January 2017. Instead, he was administered mitiglinide 30 mg/day + voglibose 0.6 mg/day combination tablet (Glubes, Kissei Pharma). At 3 months, no changes at all were observed with EF (47.7 - 47.7, Table 1) and %FS (24.4 - 24.4) levels. No or little changes were seen in the levels of acetoacetate (30 - 30 μmol/L), beta-hydroxybutyrate (75 - 88 μmol/L), BNP (55.7 - 53.7 pg/mL), or Hb (14.6 - 14.5 g/dL). HbA1c (9.8-9.0%) level was decreased, while BW (76.85 - 77.45 kg) was increased.

Discussion

In this report, it was shown that in patient A with reduced cardiac function, adding tofogliflozin could enhance heart function (see the changes of EF and %FS with ultrasonography and BNP in the blood, Table 1). In this patient, increases of ketone bodies (beta-hydroxybutyrate and acetoacetate) levels were observed (Table 1). This patient A had been receiving furosemide 20 mg/day. It could be possible that furosemide had caused beneficial effects on his heart function. However, this idea is unlikely, since this patient had been taking furosemide before the initiation of tofogliflozin. Further, this small amount of furosemide is unlikely to cause such a dramatic effect on the heart function. By contrast, in patient B with normal cardiac function, withdrawal of tofogliflozin could reduce EF and %FS levels (Table 1). In this patient B, ketone bodies levels were decreased (Table 1). Patient C represented an interesting pattern. This patient had slightly reduced cardiac function (Table 1). Withdrawal of tofogliflozin resulted in no changes in the levels of EF, %FS, ketone bodies, or BNP (Table 1). With this patient C, combination tablet of mitiglinide and voglibose was replaced with tofogliflozin. So far, no effects on heart with this combination tablet were reported.

Although the precise mechanisms of how tofogliflozin could influence heart function remain unclear, these observations presented in this report may implicate that changes of ketone bodies might be linked to those of heart function. Especially increases of ketone bodies with tofogliflozin (patient A) could cooperate with other tofogliflozin-induced changes (reduced blood pressure through diuresis, body weight or uric acid levels) to have beneficial effects on the heart (cardioprotection). This hypothesis may shed light on the pathogenesis and treatment of diabetic (and non-diabetic) cardiovascular disorders. Previous reports indicate that tight glycemic control does not offer benefits on CVD [10]. Indeed, in the case of patient A, he was a non-responder with tofogliflozin (Table 1). Nevertheless, improvements of heart function were observed. In the case of patient C, his glycemic control became better after switching to the combination tablet of mitiglinide and voglibose; however, no changes of heart function were observed (Table1). These observations implicate that glucose control may not affect cardiac function in the short term. Thus, targeting metabolism as a therapeutic strategy (for example, modulating ketone bodies) could be one of the novel, alternative approaches to treat heart failure in patients with or without diabetes. Pharmacological inhibition of fatty acid oxidation or stimulating glucose oxidation may restore energy imbalance and improve cardiac function. Ketone bodies are an efficient fuel that is oxidized by the heart in preference to fatty acids and glucose, and that ketone bodies not only improve cardiac function in the failing heart but also increase mechanical efficiency of the normal heart [11, 12]. Indeed, in the case of patient B with normal heart function, withdrawal of tofogliflozin reduced EF and %FS levels, though within normal range. It remains unclear whether or not SGLT2i can actually regulate ketone oxidations in the heart tissue.

The Hb levels are known to increase with SGLT2i through their diuretic effect [13]. Consequently increased Hb levels enhance oxygen release to the tissues, thereby establishing a powerful synergy with the metabolic substrate shift. This could be another mechanism of why SGLT-2 could have beneficial effects on the heart. However, in patient A, enhancement of heart function was observed, while Hb levels were decreased (Table 1).

There are a number of drawbacks/weak points with this study. It is just observational case series with short study duration. I cannot make any solid conclusions based on this limited information. However, this report may argue that tofogliflozin could affect heart function by modulating ketone bodies. Further randomized, double-blind, placebo-controlled, longer period study with increased number of subjects will be required to strengthen the finding of this study. It would be of interest to study whether or not SGLT2i have beneficial effects on the heart in those without diabetes or with T1DM. At the same time, it remains to be investigated whether or not other SGLT2i (canagliflozin, dapagliflozin, empagliflozin, ipragliflozin, and luseogliflozin) have similar results.

Competing Interests

The author has nothing to declare.

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