Effect of Canagliflozin on Heart Function Involving Ketone Bodies in Patients with Type 2 Diabetes

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ABSTRACT

This report describes the effect of administration (n = 3) or withdrawal (n = 2) of canagliflozin, a sodium-glucose co-transporters 2 (SGLT-2) inhibitor, on cardiac function in relation to ketone bodies. Three cases received and two cases discontinued canagliflozin. Changes of heart function with ultrasonography (EF: ejection fraction and %FS: functional shortening) and cardiometabolic parameters including ketone bodies (acetoacetate/beta-hydroxybutylate) were compared at 3 months. 69, 68 and 60 years old male patients A, B and C, respectively with moderately decreased heart function received canagliflozin 100 mg/day. EF, %FS and acetoacetate/beta-hydroxybutylate levels increased. 60 and 59 years old female patients D and E with normal and borderline heart function, respectively discontinued canagliflozin 50 mg/day. EF, %FS and acetoacetate/beta-hydroxybutylate levels decreased. Taken together, these results suggest that concomitant changes between ketone bodies and heart function were observed with or without canagliflzoin. This drug might have effects on cardiac function through modulating ketone bodies.

Introduction

Sodium-glucose cotransporter 2 (SGLT-2) inhibitors are novel oral hypoglycemic drugs for type 2 diabetes (T2DM) that facilitate glucose excretion into the urine by inhibiting SGLT-2 [1]. Canagliflozin is one of the drugs in this class and is available throughout the world [2]. Recent clinical studies have demonstrated that canagliflozin and empagliflozin, another SGLT-2 inhibitor, could drastically reduce the risk of heart failure in patients with T2DM [3, 4]. The precise underlying mechanisms for this cardioprotection with canagliflozin or empagliflozin are probably multifactorial and remain to be elucidated.

SGLT-2 inhibitors have favorable profiles on cardiometabolic parameters including decreased blood pressure through diuretic effect, triglycerides, uric acid and increased high density lipoprotein cholesterol [1, 2]. However, it is unlikely that modest improvements in these parameters had contributed to the remarkable cardiovascular outcomes observed in CANVAS or EMPA-REG OUTCOME study, since the subjects were already taking a lot of medications that can ameliorate these parameters (diuretics, statins, uric acid lowering agents, beta-blocker, and angiotensin converting enzyme -inhibitors etc, 3, 4). There are a number of explanations for the breaking results of CANVAS or EMPA-REG OUTCOME on heart function. One of them is “ketone hypthesis” which proposes that increased levels of ketone bodies with SGLT-2 inhibitors may offer significant cardioprotection [5, 6]. Ketone bodies could produce more adenosine tri-phosphate (ATP) than glucose or fatty acid per molecule [5, 6]. Heart failure may be due to reduced energy (ATP) status in the heart tissue. Ketone bodies may provide efficient energy to the failing heart.

Previously it was shown that changes in cardiac function were concomitant with those in ketone bodies with one of the SGLT-2 inhibitors, tofogliflozin [7]. In that report, a potential mechanism of SGLT-2 inhibitor-mediated prevention of heart failure is proposed [7]. It is of interest to study whether or not other SGLT-2 inhibitors such as canagliflozin have similar effects. Here effects of "administration and withdrawal" of canagliflozin on cardiac function in relation to ketone bodies will be reported. EF and %FS values with heart ultrasonography and some cardiometabolic parameters including acetoacetate/beta-hydroxybutyrate were measured at baseline and at 3 months.

Case Series

Mr. A is a 69 years old patient with T2DM, hyperlipidemia (HL) and hypertension (HTN) for more than 10 years. He had been taking metformin 1500 mg/day, sitagliptin 50 mg/day, pravastatin 5 mg/day, carvedilol 20 mg/day, insulin lispro 6-8 units before each meal and insulin glargine 14 units before going to bed at least in the past 6 months. He had a slightly enlarged heart size (cardiothoracic ratio: CTR 51 %; from now on, each value shown below is indicated in ▶**Table 1**), elevated brain natriuretic peptide (BNP: 59.7 pg/ml, normal range below 18.4 pg/ml) and borderline EF (60 %; normal range above 61 %) levels. He started canagliflozin 100 mg/day in November 2016. No other drugs were changed. At 3 months, EF (from 60 to 62.1 %) and %FS (32.4 to 33.9 %, normal range above 50 %) levels increased. Similarly, acetocetate (23 to 187 µmol/l) and beta-hydroxybutyrate (60 to 602 µmol/l) levels increased. HbA1c levels decreased (8.1 to 7.5 %). BNP levels (59.5 to 65.5 pg/ml) or body weight (BW; 70.5 to 71 kg) had little, if any, changes. Hematocrit levels (Hct: 45.8 to 47.5 %, normal range between 41 to 48 %) increased. No tolerability problems or adverse events were noted with canagliflozin.

Mr. B is a 68 years old patient of T2DM, HL and HTN for more than 12 years. He has a past medical history of angina and had undertaken PTCA (percutaneous transluminal coronary angioplasty) in 2015. Since then, he had been taking aspirine 100 mg/day, isosorbide mononitrate 20 mg/day, furosemide 20 mg, teneligliptin 20 mg/day, metformin 750 mg/day and rosuvastatin 2.5 mg/day. He had been receiving these medications at least in the past 6 months. He started to receive 100 mg/day canagliflozin in November 2016. No other drugs were changed. He had a slightly decreased heart function at baseline (CTR 53 %, NT-proBNP 359 pg/ml [normal range below 125 pg/ml], EF 59 %). At 3 months, EF (59 to 64.9 %) and %FS (31.4 to 35.3 %) levels increased. Similarly, acetoacetate (18.7 to 30.8 µmol/l) and beta-hydroxybutyrate (18.3 to 36.9 µmol/l) levels increased. Little, if any, reductions of NT-proBNP levels (359 to 348 pg/ml) were seen. HbA1c levels (8.6 to 8 %) and BW (84.1 to 75.6 kg) decreased. Hct levels increased (45 to 47.5 %).

Mr. C is a 60 years old patient of T2DM, HTN, HL, HUA (hyperuricemia) and CKD (chronic kidney disease) for more than 5 years. He had been taking valsartartan 80 mg/day, metformin 500 mg/day, atorvastain 5 mg/day, teneligliptin 40 mg/day, bisoprolol 2.5 mg/day, doxazosin 2 mg/day, allopurinol 100 mg/day, kremezin 2 g/day and acarbose 50 mg before each meal at least in the past 6 months. He had a slightly decreased heat function at baseline (CTR 50 % NT-proBNP: 479 pg/ml, EF 45.7 %). He started to receive canagliflozin 100 mg/day in December, 2016. No other drugs were changed. At 3 months, increases of EF (45.7 to 59.1 %) and % FS (23.1 to 32.1 %) levels were observed. Similarly, modest increases of acetoacetate (22.5 to 25.8 µmol/l) and beta-hydroxybutylate (28.1 to 38.3 µmol/l) levels were seen. BNP levels decreased (479 to 439 pg/ml). This patient was a non-responder with canagliflozin, since his HbA1c levels increased (7.2 to 8.6 %), while no changes of BW were noted (68.6 to 68.6 kg). Hct levels increased (34.7 to 37.9 %).

Mrs. D is a 60 years old patient of T2DM, HL and, HTN for more than 5 years. She had been taking olmesartan 10 mg/day, sitagliptin 100 mg/day, acarbose 100 mg before each meal, metformin 2000 mg/day, atorvastatin 5 mg, insulin glargine 16 units before breakfast and canagliflozin 50 mg/day for at least in the past 6 months. Since she had a urogenital problem with canagliflozin (poliuria, potential mycotic infection), she discontinued this drug in December 2016. She had a normal heart function at baseline (CTR 48 %, BNP 9.2 pg/ml, EF 71.6 %). At 3 months after withdrawing canagliflozin, EF (71.6 to 67.4 %) and %FS (41 to 37.7 %) levels decreased. Similarly, acetoacetate (61 to 24 µmol/l) and beta-hydroxybutylate (208 to 60 µmol/l) levels decreased. BNP (9.2 to 44.5 pg/ml) and HbA1c (7 to 8.2 %) levels increased, while BW (72.5 to 74.1 kg) decreased. Hct levels decreased (40 to 38.2 %).

Mrs. E is a 59 years old patient with T2DM for more than 5 years. She had been taking metformin 1000 mg/day, carvedilol 5 mg/day and canagliflozin 50 mg/day at least in the past 6 months. Since her glycemic control was under adequate range (HbA1c 6.9 %), she requested that she would discontinue canagliflozin in November 2016 due to its high cost. She had a borderline heart function at baseline (CTR 53 %, BNP 58.8 pg/ml, EF 61.5 %). At 3 months after withdrawing canagliflozin, EF (61.5 to 57 %) and %FS (33.1 to 29.1 %) levels decreased. Similarly, acetoacetate (134 to 27 µmol/l) and beta-hydrpxybutylate (319 to 59 µmol/l) levels decreased. Little, if any, decreased of HbA1c levels were noted (6.9 to 6.8 %). BW decreased (72.8 to 71.3 kg), while BNP levels increased (58.8 to 67.4 pg/ml). Hct levels slightly decreased (49 to 48.3 %).

Discussion

In this report, it was shown that in patients with slightly reduced cardiac function (assessed by EF, patients A, B, C), adding canagliflozin could enhance heart function (see the changes of EF and %FS with ultrasonography, ▶**Table 1**). In these patients, increases of the levels of ketone bodies (beta-hydroxybutyrate and acetoacetate), though with varying degrees, were observed (▶**Table 1**). By contrast, in patients D and E with normal and borderline cardiac function, respectively, withdrawal of canagliflozin could down-regulate the levels of ketone bodies and heart function (▶**Table 1**). These results suggest that, in analogy to tofogliflozin [7], concomitant changes were observed between the ketone bodies and heart function with or without canagliflozin, implicating that the changes of ketone bodies were linked to those of heart function. However, the degrees of changes in heart function do not appear to have correlations with those of ketone bodies. For example, patient B or C had small increases of ketone bodies (▶**Table 1**). Nevertheless, efficient increases of EF or %FS levels were observed. By contrast, patient A had dramatic increases of ketone bodies, however, modest, but still effective

▶ **Table 1** Changes of cardiometabolic parameters with administration (patient A, B, C) or withdrawal (patient D, E) of canagliflozin. These parameters are measured at baseline and at 3 months.

	Patient A	Patient B	Patient C	Patient D	Patient E
Age (years)	69	68	60	60	59
CTR (%)	51	53	50	48	53
Body height (cm)	173	161.7	168	146	146
Body weight (kg)					
baseline	70.5	84.1	68.6	72.5	72.8
3 months	71	75.6	68.6	74.1	71.3
HbA1c (%)					
baseline	8.1	8.6	7.2	7	6.9
3 months	7.5	8	8.6	8.2	6.8
FBG (mg/dl)					
baseline	138	175	211	193	175
3 months	103	181	336	211	187
BNP or NT-proBNP (pg/ml)					
baseline	59.7	359 (NT-pro)	479 (NT-pro)	9.2	58.8
3 months	65.5	348 (NT-pro)	430 (NT-pro)	44.5	67.4
Acetoacetate (µmol/L)					
baseline	23	18.7	22.5	61	134
3 months	187	30.8	25.8	24	27
Beta-hydroxybutyrate (µmol/L)					
baseline	60	18.3	28.1	208	319
3 months	602	36.9	38.3	60	59
Hb (g/dL)					
baseline	15.5	15.6	12.8	12.9	15.3
3 months	16	16.1	13.8	12.5	15.9
Hct (%)					
baseline	45.8	45	34.7	40	49
3 months	47.5	47.7	37.9	38.2	48.3
EF (%)					
baseline	60	59	45.7	71.6	61.5
3 months	62.1	64.9	59.7	67.4	57
%FS					
baseline	32.4	31.4	23.1	41	33.1
3 months	33.9	35.3	32.1	37.7	29.2

increases of EF or %FS levels were seen (▶**Table 1**). These backgrounds implicate that factors other than ketone bodies might be involved in the enhancing effect of canagliflozin on heart function.

SGLT-2 inhibitors are known to increase Hct levels via the stimulation of erythropoietin [8]. Increased Hct levels might provide more oxygen to the failing heart tissues, thereby enhancing cardiac function [8]. Indeed these 3 patients (A, B, C) had elevated Hct levels, though in a comparable range (▶**Table 1**). However, it was previously shown that cardioprotective effects of erythropoietin were observed in the absence of increases in Hct levels, eliminating oxygen delivery as an etiologic factor for the enhancement cardiac function [9]. By contrast, ketone bodies have been extensively shown to directly increase heart function [10]. Patients A, B and C were receiving diretics, angiotensin receptor blockers and/or beta-blockers. It could be possible that these drugs had caused enhancement of heart function. However probably this is not the case, since these patients have been taking these drugs long before the initiation of canagliflozin. Further, small amounts of these drugs are unlikely to cause such a dramatic effect on the heart function.

In addition to produce efficient energy (ATP), ketone bodies appears to have other important functions. Beta-hydroxybutylate was recently found to be an endogenous inhibitor of histone deacetylase (HDAC), which is known to regulate gene expression through histone acetylation [11]. Further, beta-hydroxybutyrate has been shown to induce resistance to oxidative stress via HDAC inhibition [11]. Thus, HDAC inhibition by beta-hydroxybutyrate might affect the pathogenesis of clinical disorders such as T2DM in at least two ways: through direct regulation of HDAC-dependent (glucose or other) metabolism, and/or by promoting resistance to oxidative stress. The increased beta-hydroxybutylate with canagliflozin may have beneficial effects with respect to epigenetics and anti-oxidation.

SGLT2 inhibitors are associated with higher incidence of certain adverse events including genital mitotic infections, urinary tract infections, osmotic diuretic related adverse events and volume depletion-related adverse evens [1]. Because of this fact, patients frequently discontinue these drugs like patient D in this report. If the glycemic control is under adequate range, the patients or physicians may discontinue SGLT-2 inhibitors rather than other drugs due to their high cost (occurred in patient E). However, sudden withdrawal of SGLT2 inhibitors might be of concern, since these drugs could change the heart function as presented in this report, especially in those with decreased heart function. Careful follow up process is required in the case of discontinuation of SGLT-2 inhibitors.

To this end, it should be stressed that this report is just an observational case series with short study duration. One cannot make any solid conclusions based on this limited information. This study is merely hypothesis generating. However, one can assume that canagliflozin 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 is expected that the finding in this report will be tested using molecular and cellular approaches to identify the underlying mechanism of canagliflozin on heart function involving ketone bodies. In conclusion, these results implicate that canagliflozin (administration or withdrawal) might influence cardiac function through modulating ketone bodies.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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