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Comparison of Serum Ketone Levels and Cardiometabolic Efficacy of Dapagliflozin versus Sitagliptin among Insulin-Treated Chinese Patients with Type 2 Diabetes Mellitus

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Background: Insulin-treated patients with long duration of type 2 diabetes mellitus (T2DM) are at increased risk of ketoacidosis related to sodium-glucose co-transporter 2 inhibitor (SGLT2i). The extent of circulating ketone elevation in these patients remains unknown. We conducted this study to compare the serum ketone response between dapagliflozin, an SGLT2i, and sitagliptin, a dipeptidyl peptidase-4 inhibitor, among insulin-treated T2DM patients.
Methods: This was a randomized, open-label, active comparator-controlled study involving 60 insulin-treated T2DM patients. Participants were randomized 1:1 for 24-week of dapagliflozin 10 mg daily or sitagliptin 100 mg daily. Serum β-hydroxybutyrate (BHB) levels were measured at baseline, 12 and 24 weeks after intervention. Comprehensive cardiometabolic assessments were performed with measurements of high-density lipoprotein cholesterol (HDL-C) cholesterol efflux capacity (CEC), vibration-controlled transient elastography and echocardiography.
Results: Among these 60 insulin-treated participants (mean age 58.8 years, diabetes duration 18.2 years, glycosylated hemoglobin 8.87%), as compared with sitagliptin, serum BHB levels increased significantly after 24 weeks of dapagliflozin (P=0.045), with a median of 27% increase from baseline. Change in serum BHB levels correlated significantly with change in free fatty acid levels. Despite similar glucose lowering, dapagliflozin led to significant improvements in body weight (P=0.006), waist circumference (P=0.028), HDL-C (P=0.041), CEC (P=0.045), controlled attenuation parameter (P=0.007), and liver stiffness (P=0.022). Average E/e', an echocardiographic index of left ventricular diastolic dysfunction, was also significantly lower at 24 weeks in participants treated with dapagliflozin (P=0.037).
Conclusion: Among insulin-treated T2DM patients with long diabetes duration, compared to sitagliptin, dapagliflozin modestly increased ketone levels and was associated with cardiometabolic benefits.

Keywords: Dapagliflozin; Diabetes mellitus, type 2; Heart disease risk factors; Ketones; Sitagliptin phosphate

INTRODUCTION

sodium-glucose co-transporter 2 inhibitor (SGLT2i) has brought a paradigm shift in the management of type 2 diabetes mellitus (T2DM). Several large-scale randomized controlled trials of SGLT2i have consistently demonstrated cardio-renal benefits with reduced rates of heart failure (HF) hospitalization and adverse renal outcomes [1-8]. More importantly, in pa-

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tients with HF and a preserved ejection fraction (HFpEF), SGLT2i is the first class of agents that has been recently shown to reduce their risks of HF hospitalization and cardiovascular death [9].

Increased serum ketone levels has been reported with the use of SGLT2i, although its significance remains to be elucidated. While an alternative fuel hypothesis has been proposed to explain the cardiovascular benefits brought by SGLT2i [10], the risk of ketoacidosis, albeit small, has also raised considerable concern among patients and clinicians, especially when used in insulin-treated patients. It is well known that patients with insulin deficiency or insulin-treated patients are at an increased risk of SGLT2i-related ketoacidosis [11]. However, since most studies that evaluated serum ketone response after SGLT2i were conducted in insulin-naïve patients with short duration of T2DM [12-17], the extent of increase in serum ketone levels and its clinical relevance among insulin-treated patients, who often have longer duration of diabetes and potentially more insulin deficient, have not been clearly defined. Therefore, we conducted this 24-week randomized, open-label, active comparator-controlled study to evaluate the effects of SGLT2i on serum ketone levels among patients with T2DM who are inadequately controlled with insulin, in comparison with a dipeptidyl peptidase-4 inhibitor (DPP4i), to control for the effects of improvement in glycaemia. In addition, secondary outcomes including the differences between SGLT2i and DPP4i on cardiometabolic parameters including high-density lipoprotein cholesterol (HDL-C) cholesterol efflux capacity (CEC), liver fat and fibrosis, as well as cardiac function were also evaluated.

METHODS

Study design

The DISTINCTION (Metabolic Responses of Dapagliflozin versus Sitagliptin in Type 2 Diabetes Patients Inadequately Controlled with Insulin Therapy) study (http://www.clinicaltrials.gov; Unique identifier: NCT03959501) was an investigator initiated, single-centre, randomized, open-label, active comparator-controlled interventional study that was designed and executed independent of the funder. The study design and protocol were reviewed and approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (Ref: UW 17-166). Written informed consent was obtained from all recruited participants prior to any study-related procedures.

Study participants

A total of 60 participants were recruited from the Diabetes Clinic of Queen Mary Hospital, Hong Kong, where over 3,000 patients with T2DM were being followed up. In this study, Chinese Individuals who had T2DM, aged between 21 and 75 years were eligible if their body mass index (BMI) was between 21 and 40 kg/m^2, and with their glycosylated hemoglobin (HbA1c) between 8% and 10.5% while on single or two doses of insulin therapy (intermediate-acting human insulin, premixed human insulin or insulin analogues) with or without metformin. Participants also had to be on stable insulin doses, which was defined as less than 10% changes in their total daily insulin dose for at least 3 months prior to enrolment. Key exclusion criteria included type 1 diabetes mellitus, history of ketoacidosis, concurrent use of sulphonylurea or loop diuretics, prior use of SGLT2i, DPP4i or glucagon-like peptide-1 receptor agonists in the preceding 3 months, history of intolerance to SGLT2i or DPP4i, an estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2 as calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, history of acute or chronic pancreatitis, benign or malignant pancreatic tumours, bladder cancer, severe liver disease with elevated plasma alanine aminotransferase (ALT) ≥5 times the upper limit of normal, active or history of malignancy in the preceding 5 years, and hospitalization for acute illness in the preceding 3 months before enrolment. Individuals who had severe mental disorder, pregnant or breastfeeding were also excluded.

Randomization and study intervention

Eligible participants were randomly assigned in a 1:1 ratio to receive dapagliflozin 10 mg daily or sitagliptin 100 mg daily for 24 weeks. Randomization was performed in blocks and the sequence was generated using a computer-based allocation method. After randomization, all participants remained on the same insulin dose for 12 weeks unless they had hypoglycaemic events, as defined by the presence of hypoglycaemic symptoms with self-monitored blood glucose concentrations of ≤3.9 mmol/L, or hypoglycaemia judged by the investigators. At 12 weeks, insulin doses were titrated to achieve both fasting and pre-prandial blood glucose concentrations between 4.1 and 7.0 mmol/L according to a titration algorithm (Supplementary Table 1).

Clinical and biochemical assessments

A total of four study visits, including the baseline visit, were arranged over a follow-up period of 6 months. Participants attended all study visits after an overnight fast for at least 8 hours. During the baseline visit, demographic data including age, sex, smoking, and alcohol consumption were obtained. Detailed medical and medication histories were ascertained and verified from the Computer Management System of the Hospital Authority, Hong Kong. In each study visit, anthropometric parameters including body weight (BW), height, BMI, waist circumference (WC), and blood pressure (BP) were measured. Central obesity was defined as WC ≥90 cm in men and ≥80 cm in women [18]. Fasting bloods were drawn for plasma glucose, lipid profile, HbA1c, liver function test, serum creatinine, and C-peptide levels. Chronic kidney disease (CKD) was defined as eGFR <60 mL/min/1.73 m^2 or the presence of albuminuria with urine albumin to creatinine ratio ≥30 mg/g. Serum ketone (β-hydroxybutyrate [BHB]) and free fatty acid (FFA) levels were determined at baseline, 12 and 24 weeks. In both baseline and final visits, HDL-C CEC and serum high sensitivity C-reactive protein (hsCRP) levels were measured. Moreover, all participants were invited for cardiac and hepatic assessments using two-dimensional echocardiography (ECHO) and vibration-controlled transient elastography (VCTE), respectively (Please see below for details).

Measurements of circulating BHB, FFA, and hsCRP levels

Serum BHB (Abcam ab83390, Abcam, Cambridge, MA, USA) and FFA levels (Roche Diagnostics GmbH, Mannheim, Germany) were measured by colorimetric assays. Serum hsCRP levels were measured with a high-sensitivity, particle-enhanced immune-turbidimetric assay (Roche Diagnostics).

HDL-C CEC measurements

In brief, HDL-CEC was measured in apolipoprotein B (apoB)-depleted serum after removing apoB-containing lipoproteins by polyethylene glycol precipitation. RAW264.7 mouse macrophages (ATCC, Manassas, VA, USA) were seeded at (70,000 cells/well) in 24-multi well plates. Cells were maintained in Dulbecco's Modified Eagle Medium (DMEM) plus 10% fetal bovine serum (FBS) and antibiotics in 5% CO_2 for 2 days to reach 70% to 80% confluence. Macrophages were then labelled for 24 hours with 1 μCi/mL of [3H] cholesterol in the presence of 5% FBS. To upregulate ATP-binding cassette transporter A1 (ABCA1) in RAW264.7 cells, 0.3 mM cyclic adenosine monophosphate (Sigma, St. Louis, MO, USA) in 0.2% bovine serum albumin/DMEM medium was added to the cell culture and incubated for another 16 hours. Cells were then washed once with phosphate buffer prior to the addition of 2.5% apoB-depleted serum as HDL fraction for 4 hours incubation. Media were finally removed and cells were lysed in 0.1M NaOH. Samples of both cells and media were counted by liquid scintillation for radioactivity. The efflux of [3H] cholesterol was calculated as the percentage of radiolabel in the media compared with that present in the media plus cells. Background efflux, as measured in the absence of apoB-depleted serum, was subtracted in all experiments.

Echocardiography assessments

Comprehensive transthoracic ECHO examination was performed using commercially available ECHO machines (Vingmed Vivid E9, General Electric Vingmed Ultrasound, Milwaukee, WI, USA) at baseline and follow-up, as previously described [19]. Images were obtained using a 3.5-MHz transducer and digitally stored into three cardiac cycles for analysis by EchoPAC version 112.0 (General Electric Vingmed, Horten, Norway). Inter-ventricular septal dimension and left ventricular (LV) posterior wall thickness at end-diastole (inter-ventricular septal dimension [IVSd] and left ventricular posterior wall thickness at end-diastole [LVPWd], respectively) were measured using a two-dimensional ECHO guided M-mode approach. LV mass was calculated according to the Devereux formula, while LV volumes and ejection fraction (LVEF) were measured using the modified biplane Simpson's method in both apical four- and two-chamber views. Left atrial volume (LAV) was assessed by single-plane disk summation method in apical four-chamber view. LAV index was determined by LAV divided by body surface area of the participants. Pulse-wave and tissue Doppler imaging were applied to assess LV diastolic function in apical four-chamber view. Peak trans-mitral flow velocities in early (E wave) and late diastole (A wave) were measured to calculate the E/A ratio. Deceleration time of the E wave was also determined. Peak velocities of septal and lateral mitral annulus in early diastole (e') was also measured by tissue Doppler imaging to determine the average E/e'.

Vibration-controlled transient elastography assessments

VCTE assessment was performed using Fibroscan (Echosens, Paris, France) as described previously [20]. Controlled attenuation parameter (CAP) and liver stiffness (LS), which reflect

degree of hepatic steatosis and fibrosis, respectively, were measured by two operators with experience in performing over 500 measurements. The inter-observer reliability was satisfactory, as reflected by an intra-class correlation of 0.98 for CAP and 0.97 for LS measurements. Both CAP and LS measurements were represented by the median of 10 reliable measurements, defined when the interquartile range (IQR) was <30%, and with a success rate of >60%. To ensure validity of the results, only CAP values with IQR >40 dB/m were used. All examinations were conducted using the M probe in the first attempt. XL probe was used only when M probe failed to produce valid and reliable measurements, especially in participants with BMI ≥30 kg/m^2. Hepatic steatosis was graded by published CAP cut-offs: 248–267, 268–279, and ≥280 dB/m for mild, moderate and severe hepatic steatosis, respectively [21]. Advanced fibrosis (F3) and cirrhosis (F4) were defined by LS cut-offs: F3 9.6 –11.4 kPa and F4 ≥11.5 kPa (M probe); F3 9.3–10.9 kPa and F4 ≥11.0 kPa (XL probe) [22].

Outcomes of interest

The primary outcome was the change in fasting serum BHB levels before and after treatment with either dapagliflozin or sitagliptin for 24 weeks. Secondary outcomes were changes in cardiometabolic measures including BW, BP, HbA1c, lipid, and FFA levels from baseline to week 24. In *post hoc* analyses, changes in CEC, echocardiographic parameters, CAP and LS measurements from baseline to week 24 were also evaluated.

Statistical analysis

Statistical analysis was performed using IBM SPSS version 26.0 software (IBM Corp., Armonk, New York, USA). All data in the study was analysed based on an intention-to-treat principle, where all participants randomized were included and analysed in the group to which they were originally allocated. Last observation-carried forward method was applied when handling missing data. Data that were not normally distributed as determined by Kolmogorov-Smirnov test, including serum triglyceride, ALT, AST, BHB, and FFA levels, were logarithmically transformed before all analyses. Values were reported as mean±standard deviation (SD), medians with 25th and 75th percentiles (for skewed data), or percentages, as appropriate. Paired *t*-test was performed to compare changes in continuous variables within each intervention group. Chi-square and independent *t*-tests were used for comparisons of categorical and continuous variables, respectively. Sex-adjusted *P* values were presented when comparing changes in variables with significant gender differences, which included serum BHB and FFA levels. Pearson correlation analysis was conducted to determine the associations of changes in BHB levels and echocardiographic parameters with changes in other clinical variables. In all statistical tests, two-sided *P* values <0.05 were considered significant.

RESULTS

A total of 60 participants were recruited and randomized in a 1:1 ratio to receive either dapagliflozin 10 mg daily (*n*=30) or sitagliptin 100 mg daily (*n*=30). All except one participant, who dropped out due to withdrawal of consent, completed the whole study period of 24 weeks. Complete data of serum BHB, biochemical variables and VCTE assessments were available for 29 participants in the dapagliflozin group and 30 partici-

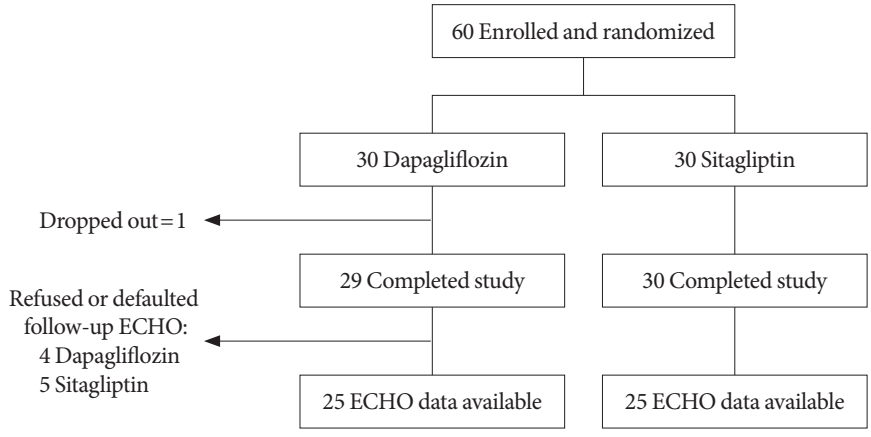

Fig. 1. Flow diagram of the study. ECHO, echocardiography.

pants in the sitagliptin group (Fig. 1). Table 1 summarizes the baseline characteristics of all randomized participants in the study. In both groups, more than 60% of the participants had central obesity and their mean duration of diabetes was more than 17 years. At baseline, over 90% of the participants were on twice daily insulin injections (58% on twice daily premixed hu-

Table 1. Baseline characteristics of the study participants

Baseline variable	Dapagliflozin (n=30)	Sitagliptin (n=30)	P value
Clinical parameters			
Men, %	53.3	66.7	0.292
Age, yr	56.9±10.7	60.6±7.03	0.120
Ever smoker, %	40.0	40.0	1.000
Duration of diabetes, yr	17.1±9.56	19.3±8.50	0.357
BMI, kg/m^2	26.4±3.87	26.9±2.90	0.570
WC, cm	92.7±8.28	92.9±8.19	0.949
Men	94.8±8.96	95.0±6.85	0.952
Women	90.3±6.98	88.6±9.34	0.615
Central obesity, %	83.3	66.7	0.136
Systolic BP, mm Hg	132±13.1	137±14.5	0.143
Diastolic BP, mm Hg	73.1±7.27	75.6±7.99	0.207
Biochemistry parameters			
Fasting glucose, mmol/L	9.35±3.32	9.82±2.89	0.564
HbA1c, %	8.94±0.60	8.79±0.56	0.321
HbA1c, mmol/mol	74.20±6.57	72.60±6.11	0.321
C-peptide, nmol/L	0.29 (0.19–0.39)	0.28 (0.17–0.46)	0.444
HDL-C, mmol/L	1.25±0.34	1.24±0.41	0.945
HDL-CEC, %	22.2±5.24	21.8±6.32	0.792
LDL-C, mmol/L	2.08±0.64	1.86±0.77	0.235
Triglycerides[a], mmol/L	1.15 (0.90–1.63)	1.35 (0.88–2.18)	0.328
ALT[a], U/L	22 (16–37)	23 (19–31)	0.813
AST[a], U/L	20 (18–29)	22 (17–24)	0.447
eGFR, mL/min/1.73 m^2	90.4±19.6	81.2±16.1	0.050
≥60 mL/min/1.73 m^2, %	90.0	93.3	1.000
Albuminuri[a] status			0.865
A1, %	53.3	56.7	
A2, %	33.33	23.3	
A3, %	13.3	20.0	
Fasting FFA, μmol/L	91.5 (63.2–165)	110 (86.6–160)	0.278
Fasting BHB, μmol/L	372 (315–521)	401 (325–514)	0.389
hsCRP[a], mg/L	0.96 (0.51–2.62)	0.89 (0.42–2.49)	0.341
VCTE			
CAP, dB/m	285±48.2	292±56.6	0.625
Minimal <248 dB/m	23.3	20.0	
Mild 248–267 dB/m	16.7	23.3	
Moderate 268–279 dB/m	0.0	3.3	
Severe >279 dB/m	60.0	63.3	
LS[a], kPa	5.75 (4.33–8.95)	6.10 (4.98–8.15)	0.675
F0/1 <5.8 kPa	50.0	46.7	
F2 5.8–9.5 kPa	36.7	43.3	
F3 9.6–11.4 kPa	6.6	3.3	
F4 >11.4 kPa	6.7	6.7	
Medical diseases, %			
Hypertension	80.0	83.3	0.739
Coronary artery disease	13.3	13.3	1.000
Stroke	6.7	6.7	1.000
STDR	6.7	10.0	1.000
Concomitant medications, %			
Metformin	100	100	1.000
Pioglitazone	13.3	16.7	0.718
ACEI	50.0	53.3	0.796
ARB	27.7	26.7	1.000
Statin	63.3	80.0	0.152
Fibrate	0.0	10.0	0.237
Aspirin	26.7	26.7	1.000
Total daily insulin dosage, units	42.0±15.9	45.0±14.1	0.447

Values are presented as percent, mean±standard deviation, or median (interquartile range). Albuminuria status was assessed with a random urine sample, and categorized according to urine albumin to creatinine ratio (A1: <30 mg/g; A2: ≥30–<300 mg/g; A3 ≥300 mg/g).
BMI, body mass index; WC, waist circumference; BP, blood pressure; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; CEC, cholesterol efflux capacity; LDL-C, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; FFA, free fatty acid; BHB, β-hydroxybutyrate; hsCRP, high sensitivity C-reactive protein; VCTE, vibration-controlled transient elastography; CAP, controlled attenuation parameter; LS, liver stiffness; STDR, sight threatening diabetic retinopathy; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blocker.
[a]Log-transformed before analysis.

(*Continued to the next*)

Table 2. Changes in clinical variables before and after study intervention

Baseline variable	Dapagliflozin (n=30)		Sitagliptin (n=30)		Change from baseline		P value (Δchange)
	At baseline	At week 24	At baseline	At week 24	Dapagliflozin	Sitagliptin	
Primary outcome							
BHB[a], μmol/L	372 (315 to 521)	472 (349 to 587)[c]	401 (325 to 514)	403 (326 to 524)	90.5 (–8.10 to 193)	–11.9 (–123 to 79.3)	0.045[b]
Secondary outcomes							
Body weight, kg	70.3±12.8	69.3±12.5[c]	71.5±11.6	72.2±12.8	–0.94±1.89	0.65±2.46	0.006
WC, cm	92.7±8.28	91.6±8.19	92.9±8.19	94.0±9.02[c]	–1.09±4.47	1.11±2.90	0.028
Systolic BP, mm Hg	132±13.1	129±12.9	137±14.5	136±16.4	–2.20±13.2	–1.18±15.8	0.787
Diastolic BP, mm Hg	73.1±7.27	71.7±8.66	75.6±7.99	74.9±9.26	–1.40±6.46	–0.75±6.61	0.701
Total daily insulin dose, units	42.0±15.9	41.4±15.8	45.0±14.1	45.8±14.9	–0.60±3.33	0.80±2.66	0.077
FG, mmol/L	9.35±3.32	7.21±2.11[d]	9.82±2.89	6.79±2.02[e]	–2.14±3.28	–3.03±3.32	0.298
HbA1c, %	8.94±0.60	7.69±0.86[e]	8.79±0.56	7.81±0.93[e]	–1.25±0.78	–0.98±0.80	0.198
HbA1c, mmol/mol	74.20±6.57	60.60±9.38[e]	72.60±6.11	61.80±10.10[e]	–13.60±0.56	–10.70±8.78	0.198
eGFR, mL/min/1.73 m^2	91.9±18.1	90.2±19.8	81.2±16.1	77.7±15.6[c]	–0.21±5.97	–3.43±8.50	0.092
HDL-C, mmol/L	1.25±0.34	1.30±0.37	1.24±0.41	1.20±0.41	0.05±0.15	–0.04±0.18	0.041
LDL-C, mmol/L	2.08±0.64	2.06±0.74	1.86± 0.77	1.76±0.62	–0.02±0.47	–0.11±0.62	0.545
TG[a], mmol/L	1.15 (0.90 to 1.63)	1.15 (0.80 to 1.53)	1.35 (0.88 to 2.18)	1.25 (0.80 to 1.70)[c]	–0.15 (–0.40 to 0.10)	–0.25 (–0.50 to 0.05)	0.611
ALT[a], U/L	21.5 (15.8 to 37.3)	20.0 (15.8 to 27.5)	22.5 (19.0 to 30.5)	27.0 (19.8 to 32.0)	–1.00 (3.00 to –5.50)	2.00 (–2.00 to 5.25)	0.284
AST[a], U/L	20.0 (17.8 to 29.3)	19.0 (16.8 to 25.0)	21.5 (16.8–24.0)	23.0 (20.8 to 27.3)[c]	0.00 (–3.50 to 2.00)	3.00 (–1.00 to 5.25)	0.160
CAP, dB/m	285±48.2	268±50.9[c]	292±56.6	302 ± 58.0	–17.8±40.6	10.0±37.0	0.007
LS, kPa	5.75 (4.33 to 8.95)	5.15 (4.58 to 6.75)[c]	6.10 (4.98 to 8.15)	7.00 (5.10 to 8.58)	–0.50 (–1.25 to 0.15)	0.25 (–0.50 to 1.20)	0.022
HDL-CEC, %	22.2±5.32	24.8±7.60[c]	21.8± 6.32	21.3±6.43	2.66±5.14	–0.50±6.71	0.045
hsCRP[a], mg/L	0.96 (0.51 to 2.62)	0.63 (0.42 to 2.05)	0.89 (0.42 to 2.49)	0.97 (0.42 to 2.22)	–0.19 (–0.95 to 0.002)	–0.10 (–0.60 to 0.63)	0.177
FFA[a], μmol/L	91.6 (64.1 to 164)	119 (69.0 to 164)	110 (86.6 to 160)	106 (56.6 to 174)	9.58 (–41.8 to 45.0)	–6.72 (–43.6 to 26.5)	0.191[b]

Values are presented as median (interquartile range) or mean±standard deviation.
BHB, β-hydroxybutyrate; WC, waist circumference; BP, blood pressure; FG, fasting glucose; HbA1c, glycosylated hemoglobin; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAP, controlled attenuation parameter; LS, liver stiffness; CEC, cholesterol efflux capacity; hsCRP, high sensitivity C-reactive protein; FFA, free fatty acid.
[a]Log-transformed before analysis, [b]Sex-adjusted P value, [c]<0.05, [d]<0.01, [e]<0.001 vs. baseline.

man insulin and 42% on twice daily intermediate-acting human insulin). Their glycaemic control however was suboptimal with mean HbA1c levels ≥8.5% (≥69 mmol/mol) in both groups. Importantly, all clinical parameters, including baseline co-morbidities such as hypertension, cardiovascular disease (CVD), and CKD, as well as concomitant medications were well balanced between groups. Fasting C-peptide levels were low in both groups and there were no significant differences. Notably, the prevalence of fatty liver disease at baseline was more than 70%. In both groups, more than 60% and 10% of the study participants had severe hepatic steatosis and advanced liver fibrosis, respectively. Serum BHB and FFA levels were comparable between both groups at baseline.

Table 2 summarizes the changes in clinical and biochemical variables after 24 weeks of study intervention. Both dapagliflozin and sitagliptin led to significant HbA1c lowering (–1.25% vs. –0.98%, or –13.6 mmol/mol vs. –10.7 mmol/mol; $P=0.198$, respectively) without significant changes in their total insulin doses. With regard to the serum ketone response which is the primary outcome of interest in this study, median fasting serum BHB levels (normal range, 20 to 1,000 μmol/L) increased significantly by 27% from 372 to 472 μmol/L after 24 weeks of dapagliflozin treatment ($P<0.05$), resulting in significant differences in the change of serum BHB levels between the two groups (90.5 μmol/L vs. –11.9 μmol/L, sex-adjusted $P=0.045$ for dapagliflozin and sitagliptin, respectively). Although serum BHB levels started to increase after the use of dapagliflozin, the difference comparing with baseline was only significant at 24 weeks but a trend was observed at 12 weeks. In Pearson correlation analysis, change in serum BHB levels positively correlated with change in FFA levels ($r=0.433$, $P=0.017$) but not with the other clinical and metabolic parameters (Table 3). However, change in FFA levels were comparable between dapagliflozin and sitagliptin groups from baseline to 24 weeks.

Notably, despite similar glycaemic improvement, dapagliflozin led to significant reductions in BW and WC as compared with sitagliptin ($P=0.006$ and $P=0.028$ for BW and WC, respectively). Moreover, these changes were accompanied by significant improvements in hepatic steatosis and fibrosis, as reflected by the reductions in CAP and LS measurements in the dapagliflozin group as compared with sitagliptin ($P=0.007$ and $P=0.022$ for CAP and LS, respectively). These improvements seemed to be more readily observed among those with severe hepatic steatosis (CAP >279 dB/m) and significant liver fibrosis (LS ≥5.8 kPa) at baseline (Supplementary Table 2). Moreover, as compared with sitagliptin, both HDL-C levels and CEC significantly improved after the use of dapagliflozin ($P=0.041$ and $P=0.045$ for HDL-C and HDL-CEC, respectively).

Table 3. Correlations between change in serum BHB levels and changes in other clinical and metabolic variables among participants in the dapagliflozin group ($n=30$)

Change in clinical and metabolic variable	Change in BHB levels, μmol/L	
	Crude *r*	*P* value
Body weight, kg	0.111	0.560
Waist circumference, cm	–0.022	0.910
Systolic BP, mm Hg	0.017	0.929
Diastolic BP, mm Hg	0.239	0.204
Total daily insulin dose, units	0.221	0.241
Fasting glucose, mmol/L	0.068	0.723
HbA1c, %	0.140	0.461
Triglyceride[a], mmol/L	0.188	0.319
LDL-C, mmol/L	–0.344	0.063
HDL-C, mmol/L	–0.052	0.783
HDL-CEC, %	0.107	0.575
ALT[a], U/L	0.088	0.644
AST[a], U/L	0.047	0.804
eGFR, mL/min/1.73 m^2	0.011	0.956
CAP, dB/m	0.239	0.204
LS[a], kPa	–0.208	0.270
FFA[a], μmol/L	0.433	0.017
hsCRP[a]	–0.206	0.274

BHB, β-hydroxybutyrate; BP, blood pressure; HbA1c, glycosylated hemoglobin; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CEC, cholesterol efflux capacity; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; CAP, controlled attenuation parameter; LS, liver stiffness; FFA, free fatty acid; hsCRP, high sensitivity C-reactive protein.
[a]Log-transformed before analysis.

Among the randomized participants, 50 of them had ECHO performed both at baseline and their final visits, and with all echocardiographic measurements available for analysis (Table 4). At baseline, all echocardiographic parameters were comparable between the dapagliflozin and sitagliptin groups. However, at 24 weeks, average E/e' was significantly lower in the group treated with dapagliflozin compared with those on sitagliptin (9.68 vs. 11.3, $P=0.037$, respectively). In Pearson correlation analysis, change in average E/e' levels inversely correlated with change in HDL-CEC levels ($r=–0.405$, $P=0.045$) but

Table 4. Changes in echocardiographic parameters before and after treatment with study intervention

Echocardiographic parameter	Dapagliflozin (n=25)		Sitagliptin (n=25)		Change from baseline		P value (Δchange)
	At baseline	At week 24	At baseline	At week 24	Dapagliflozin	Sitagliptin	
IVSd, mm	11.00±1.42	11.30±1.55	11.50±1.55	11.40±1.76	0.18±1.20	–0.47±1.07	0.374
LVPWd, mm	9.40±1.58	9.26±1.34	9.60±1.79	9.29±1.21	–0.08±1.26	–0.41±1.59	0.680
LV mass, g	92.00±19.60	90.80±16.60	94.70±20.20	95.30±16.70	–1.03±13.50	0.27±11.50	0.615
LVEF, %	62.20±9.90	62.20±6.56	64.30±5.10	64.30±5.37	0.33±9.42	–0.15±5.19	0.970
E/A	0.86±0.20	0.87±0.20	0.98±0.32	0.96±0.31	–0.02±0.18	–0.03±0.21	0.562
DT, ms	208.2±43.3	238.0±28.9[a]	213.6±41.4	238.0±47.5[b]	29.9±45.7	24.4±49.0	0.687
Septal e', m/s	0.0744±0.02	0.0744±0.02	0.0680±0.02	0.0676±0.02	0.0004±0.02	–0.0007±0.01	0.928
Lateral e', m/s	0.094±0.02	0.099±0.02	0.097±0.02	0.094±0.03	0.007±0.01	–0.005±0.02	0.093
Average E/e'	10.20±2.64	9.68±2.77[c]	11.60±2.52	11.30±2.67[c]	–0.55±1.81	–0.22±2.36	0.583
LAVi, mL/m^2	31.50±7.50	30.60±8.27	32.20±8.75	33.60±12.40	–0.46±7.24	1.07±11.50	0.394

Values are presented as mean±standard deviation.
IVSd, inter-ventricular septal dimension; LVPWd, left ventricular posterior wall thickness at end-diastole; LV, left ventricular; LVEF, left ventricular ejection fraction; E wave, peak trans-mitral flow velocities in early diastole; A wave, peak trans-mitral flow velocities in late diastole; DT, deceleration time; e', peak velocities of septal and lateral mitral annulus in early diastole; LAVi, left atrial volume divided by body surface area of the participants.
Paired t-test: [a]P<0.01, [b]P<0.05; [c]P=0.037 for the difference of average E/e' between dapagliflozin and sitagliptin at 24 weeks.

not with that of the other clinical variables including serum BHB levels (Supplementary Table 3, Supplementary Fig. 1).

During the whole study period, both dapagliflozin and sitagliptin were well tolerated and none of the participants developed symptoms suggestive of euglycemic diabetic ketoacidosis (DKA). After 24 weeks of treatment, a significantly higher proportion of these insulin-treated participants on dapagliflozin achieved a composite end-point comprising HbA1c reduction ≥1%, weight loss ≥1 kg and absence of hypoglycaemia, than those randomized to sitagliptin (23.3% vs. 3.3%, P=0.023, respectively).

DISCUSSION

The present study demonstrated that among insulin-treated patients with long duration of T2DM, use of dapagliflozin for 24 weeks led to a modest but significant increase in serum ketone levels. Moreover, as compared with sitagliptin, despite similar degree of HbA1c lowering, use of dapagliflozin as add-on to insulin therapy provided significant metabolic benefits with weight reduction, improvements in hepatic steatosis and fibrosis, as well as HDL-C and its cholesterol efflux function in patients with T2DM. Indices of LV diastolic function was also significantly better at 24 weeks in patients treated with dapagliflozin. Hence, these cardiometabolic benefits are unlikely mediated by improvement in glycaemia.

Several mechanisms have been proposed to explain the increased serum ketone levels after use of SGLT2i [23]. Although reduced renal clearance of ketone bodies has been reported, studies have suggested that overproduction of ketone bodies played a more major role in causing increased ketone levels during SGLT2 inhibition, especially among those with preserved renal function [24]. SGLT2i disrupts insulin-to-glucagon ratio, and shifts substrate utilization from glucose to lipid oxidation, resulting in accelerated lipolysis, enhanced fat oxidation and ketogenesis [14,25]. Insulin deficiency and brisk reduction of exogenous insulin doses are both risk factors of SGLT2i-related ketoacidosis [11]. Indeed, in a recent study involving 1,278 Japanese insulin-naïve patients with T2DM, it was shown that those with the greatest serum ketone excursion after 24 weeks of canagliflozin treatment had significantly longer duration of diabetes, lower BMI, and baseline serum insulin levels [16]. Therefore, in contrast to previous studies which evaluated ketone responses after short-term use of SGLT2i [13,15,26], or in those insulin-naïve patients with relatively shorter duration of diabetes [12,16,17], our study was the first to evaluate the changes in serum ketone levels after chronic use of SGLT2i, in an exclusively insulin-treated population with a long duration of T2DM (mean duration ≥17 years). Interestingly, the elevation of serum BHB levels after dapagliflozin

only became significant at 24 weeks but not at 12 weeks. Moreover, despite the longer duration of diabetes in our participants, their magnitude of elevation in serum ketone levels was modest when compared with the 78% increase reported in a previous study using canagliflozin for a similar duration [16]. These observations are likely due to concomitant insulin treatment in our participants, although intrinsic differences in the pharmacodynamic properties among SGLT2i cannot be ruled out. Further studies are required to validate our findings.

The improvement in HDL-CEC after SGLT2i treatment is another novel finding. ABCA1-related CEC, which has been shown as an independent cardiovascular risk marker in population-based studies [27], is impaired in T2DM [28]. Our findings are in contrast to a previous randomized placebo-controlled trial that failed to demonstrate significant CEC improvement after 12 weeks of dapagliflozin in 31 patients with T2DM [29]. This could be related to differences in the methods of HDL-CEC measurements, as our study utilized the radiolabelled cholesterol method which is more widely used than the fluorescently labelled cholesterol method in their study [30]. Differences in study population could also be another reason. In contrast to their study with only 60% of the participants were on insulin therapy, our study consisted of exclusively insulin-treated patients. Furthermore, it is known that CEC tends to correlate with HDL-C levels [27,30]. However, contrary to ours and most other studies [31], serum HDL-C tended to decrease after dapagliflozin in that study [29]. Therefore, whether this difference in HDL-C responses after SGLT2i could have also contributed to the apparent discordant findings in CEC remains to be confirmed with further studies.

Nonetheless, our observed significant improvement in HDL-C levels with dapagliflozin, as compared with sitagliptin treatment, was in keeping with the overall improvement in metabolic profile after SGLT2i. Indeed, our study showed that dapagliflozin also led to significant attenuation in the severity of fatty liver disease, which is present in more than 70% of patients with T2DM [22]. Previous studies have already demonstrated that dapagliflozin could delay progression of liver fibrosis in patients with T2DM and significant fibrosis on VCTE at baseline [32]. Recently, a pilot study also showed that empagliflozin could alleviate hepatic steatosis, ballooning and fibrosis in patients with biopsy-proven non-alcoholic steatohepatitis and T2DM [33].

To our knowledge, our study is also the first head-to-head prospective study to compare the cardiometabolic efficacy of SGLT2i versus DPP4i as add-on therapy in exclusively insulin-treated patients with T2DM. DPP4i is an appealing option for glycaemic control, owing to its minimal risk of hypoglycaemia, weight-neutral properties and tolerable safety profile. Although previous prospective and real-world retrospective studies with head-to-head comparison between SGLT2i and DPP4i have reported superior cardiovascular benefits of the former, only few participants were on insulin therapy [34,35]. On the other hand, in a recent randomized study involving 44 Japanese patients with short duration of T2DM and without CVD at baseline, no significant difference in cardiac function was observed between participants assigned to empagliflozin and sitagliptin for 12 weeks [36]. Notably, insulin treatment has been associated with adverse cardiac outcomes including diastolic dysfunction in patients with diabetes [37]. Diastolic dysfunction often precedes clinical HF in T2DM [38]. Previous echocardiographic studies have shown that SGLT2i could augment LV diastolic function in patients with T2DM regardless of the presence of clinical HF [39,40]. Recently, empagliflozin was shown to reduce HF hospitalization among patients with HFpEF [9]. In our study, as compared with sitagliptin, significantly lower average E/e' was observed at 24 weeks after dapagliflozin treatment. Our findings have therefore provided further clinical support that SGLT2i as a class is beneficial to LV diastolic function in patients with normal LVEF, including those with long duration of T2DM and on insulin therapy. Our study also observed a correlation between changes in HDL-CEC and average E/e' in the dapagliflozin group. Whether there is a relationship between the improvement in HDL-CEC and LV function warrants investigations in further studies.

Our study has several limitations. First, the sample size is small. Although hyperketonaemia has been suggested as one of the possible mechanisms for improved cardiac function after SGLT2i, our sample size might have inadequate power for further *post hoc* analyses such as the correlations between change in ketones and improvement in LV diastolic function. Secondly, the study period is relatively short, which could have explained the lack of significant changes in other echocardiographic parameters that might take a longer time to improve than the average E/e'. Indeed, a recent echocardiographic study suggested the improvement in LV filling pressure to occur early in the course of SGLT2i treatment, as reflected by the reduction of E/e' brought by empagliflozin could happen as early as one day after treatment [41]. Moreover, since all our partici-

pants had normal LVEF at baseline; thus, rendering it difficult for more in-depth echocardiographic analysis to evaluate for any differential beneficial effects of SGLT2i in patients with preserved and reduced LVEF. Thirdly, this is an open-label study. However, all technicians involved in serum BHB, FFA, and CEC measurements, VCTE operators and the cardiologist were blinded to study treatment allocation of the participants. Moreover, only serum BHB levels, but not the other circulating ketone bodies, were measured in our study. Furthermore, serum glucagon levels were also not assessed in our study participants. Lastly, since our local labelling for eGFR to start SGLT2i was still 45 mL/min/1.73 m^2 at the commencement of our study, whether serum ketone response after SGLT2i differs in patients with worse renal function remains to be addressed in further studies.

In conclusion, our study demonstrated that despite similar HbA1c lowering as sitagliptin, treatment with dapagliflozin for 24 weeks significantly reduced adiposity, attenuated fatty liver disease and improved HDL functionality with slightly better LV diastolic function. More importantly, among these insulin-treated patients with long duration of T2DM, serum ketone levels only rose modestly and none of them had symptoms suggestive of euglycemic DKA. That said, both clinicians and patients should always practice caution with the use of SGLT2i, especially in situations known to precipitate euglycemic DKA such as during the perioperative period and concurrent illness [23]. Nonetheless, SGLT2i represents a safe and effective strategy as add-on therapy to insulin both for HbA1c lowering and optimization of the overall cardiometabolic health in patients with T2DM.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2021.0319.

CONFLICTS OF INTEREST

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

AUTHOR CONTRIBUTIONS

Conception or design: C.H.L., K.C.B.T.
Acquisition, analysis, or interpretation of data: C.H.L., M.Z.W., D.T.W.L., D.S.H.C., C.H.Y.F., S.W.M.S., W.Y., A.C.H.L., J.K.Y.L., Y.C.W., K.K.H.Y.
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