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Original Article

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Dapagliflozin Add-On Therapy Improves Body Composition and Metabolic Parameters in Overweight Type 2 Diabetic Patients: A Pilot Study

Ugo Di Folco[a, b], Alessandra Gatti[a], Maria Rosaria Nardone[a], Claudio Tubili[a]

Abstract

Background: Sodium-glucose cotransporter-2 inhibitors (SGLT2-i) inhibit renal glucose reabsorption in the proximal tubules, and reduce plasma glucose, body weight and cardiovascular risk in patients with type 2 diabetes mellitus (T2DM). The data on the effect of SGLT-2i on body composition are conflicting: in some reports, they reduce fat mass, while in other reports, they determine reduction of extra- and intra-cellular fluids. The aim of our pilot study was to investigate the body compartments changes and the effects on glycemia and plasma lipids of add-on SGLT2-i dapagliflozin therapy in poorly controlled overweight/obese T2DM patients.

Methods: Fifty-six overweight (body mass index (BMI) > 25) uncontrolled (HbA1c > 53 mmol/mol; 7%) T2DM outpatients were recruited. They were treated with metformin and basal insulin (group A) or metformin (group B). Weight, BMI, waist circumference (WC), fasting blood glucose (FPG), HbA1c, plasma lipids, bioelectric parameters and derived body compartments (phase angle (pA), total body water (TBW), fat free mass (FFM) and fat mass (FM)) were assessed at baseline (T0) and after 16 weeks (T1) of dapagliflozin 10 mg add-on treatment. Student's *t*-test and one-way analysis of variance (ANOVA) were used to compare the T0 and T1 data.

Results: After 16 weeks, all the patients had weight loss (-3.0 ± 0.6 kg, P < 0.0001) and reduced WC (-2.5 ± 0.6 cm, P < 0.0001). Weight reduction was significant in both groups separately (group A: -2.5 ± 0.3 kg, P ≤ 0.001; group B: -3.4 ± 0.4 kg, P ≤ 0.001) and was higher in group B. FFM was not impaired in group A (from 60.2 ± 5.2 to 59.5 ± 8.1 kg; ns) and in group B (from 60.4 ± 6.2 to 59.3 ± 6.6 kg; ns). FM decreased in all the patients (29.9 ± 6.84 kg vs. 26.30 ± 7.4 kg, P < 0.000); a higher reduction was found in group B (-3.6 ± 1.2 kg, P < 0.001) vs. group A (-2.3 ± 1.3 kg, P < 0.001). Metabolic control improved in all the patients: FPG 172 ± 49.4 mg/dL vs. 137 ± 36.8 mg/dL at T1, P < 0.0001; HbA1c 69 ± 9.3 mmol/mol (8.5±1.5%) vs. 60 ± 8.7 mmol/mol (7.6±1.4%), P = 0.000. In group A, insulin dose was reduced by 9.3%. Cholesterol and triglycerides (TG) levels decreased in overall population (181.8 ± 48.8 mg/dL vs. 170.7 ± 40.7, P = 0.003; 172 ± 93 mg/dL vs. 143.2 ± 87.8, P = 0.000).

Conclusions: Dapagliflozin add-on therapy induced weight loss and metabolic improvement in overweight and obese T2DM patients. Also insulin-treated patients had weight loss (2.5 kg). Bioelectric impedance analysis (BIA) demonstrated FM loss without FFM impairment and was confirmed to be a simple and effective method to assess body composition in clinical practice.

Keywords: Dapagliflozin; Type 2 diabetes mellitus; Obesity; Body composition; Bioelectric impedance analysis

Introduction

Traditional antidiabetic oral agents (such as sulphonylureas) and insulin induce weight gain in type 2 diabetes mellitus (T2DM) patients [1], impairing insulin sensitivity over the time.

An optimal therapeutic approach to T2DM includes drugs not only effective to get HbA1c targets without inducing hypoglycemia and weight gain, but also capable to reduce cardiovascular risk. Different classes of drugs with original mechanism of action such as sodium-glucose cotransporter-2 inhibitors (SGLT2-i) have been recently introduced. They selectively inhibit glucose reabsorption in the proximal tubules of the kidney, increasing renal excretion and reducing plasma glucose levels. Thus, they promote a negative energy balance leading to body weight loss [2]. Recent studies have demonstrated an improvement in cardiovascular risk profile of T2DM patients with SGLT-2i, such as canagliflozin [3], empagliflozin [4] and dapagliflozin [5, 6]. Few studies at present have evaluated the SGLT-2i-induced weight loss features in terms of body composition changes, and available data are conflicting [7, 8]. Middle long-term observations show body fat reduction: in a 2-year study with dual energy X-rays absorptiometry (DEXA) on T2DM subjects, the association of dapagliflozin to metformin reduced body weight, and this was principally due to fat mass (FM) reduction [9]; other studies in T2DM subjects reported reduction of liver and subcutaneous FM with computed tomography (CT) scan [10, 11].

On the other hand, the short-term weight loss is primar-

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[a]UOSD Diabetology, "S. Camillo-Forlanini" Hospital, Rome, Italy
[b]Corresponding Author: Ugo Di Folco, UOSD Diabetology, "S. Camillo-Forlanini" Hospital, Rome, Italy. Email: difolcougo@gmail.com

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ily due to extra-cellular water (ECW) and to intra-cellular water (ICW) secondly; a report on T2DM subjects treated with tofogliflozin and evaluated with bioelectric impedance put in evidence a rearrangement of body fluids compartments, so that the authors concluded a recommendation to monitor kidney function in the first phases of SGLT2-i treatment [12].

The aim of our pilot study was to investigate the effect on weight and body composition (assessed by bioelectrical impedance analysis (BIA)) of SGLT2-i agent dapagliflozin 10 mg once a day as add-on treatment in overweight/obese T2DM subjects with poor metabolic control. We focused our interest to explore whether the eventual weight loss induced by the therapy was related to body fat mass rather than lean mass decrease or fluid unbalance. BIA is an inexpensive, reproducible, not invasive and sufficiently accurate method to assess body composition in clinical practice [13]. Secondly, we investigated the effects of this therapy on glucose control and plasma lipid profile and the eventual correlation with weight and body fat changes.

Materials and Methods

Fifty-six overweight T2DM outpatients were recruited at the Diabetes Clinic of our hospital.

Inclusion criteria were body mass index (BMI) > 25 kg/m^2 and inadequate glycemic control (HbA1c > 53 mmol/mol; 7%). Acetylsalicylic acid (ASA) and other antiplatelets agents, statins and antihypertensive drugs use were reported. The current therapies were not changed. Exclusion criteria were: renal impairment (estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2), age > 75 years, diuretic therapy, chronic and/or recurrent urinary tract infections and acute illness. Subjects suffering from cancer and diseases affecting nutritional status and body composition (e.g. inflammatory bowel diseases and liver cirrhosis) were also excluded. We divided subjects into two groups: one under metformin and basal insulin (group A, n = 25) and the other under metformin treatment alone (group B, n = 31).

BIA was conducted with a BIA 101 Akern® single frequency (50 kHz) analyzer (Florence); body compartments were calculated according to manufacturer equation.

Weight, BMI, waist circumference (WC), fasting blood glucose (FPG), HbA1c, lipid profile, hematocrit (Hct), eGFR calculated with MDRD formula, albumin excretion rate (AER), blood urea nitrogen (BUN), bioelectrical parameters and body composition derived compartments (phase angle (pA), total body water (TBW), fat free mass (FFM) and FM) were assessed at baseline (T0) and after 16 weeks (T1) of dapagliflozin 10 mg add-on treatment. This second-/third-line option was planned according to the Italian Standard of Care for Diabetes; all the patients underwent a retraining about lifestyle change intervention. A moderate low calorie diet (20 kcal/kg daily; total carbohydrate (CHO) 40%; fat 30%; protein 1.0 - 1.2 g/kcal daily) was prescribed [14].

The number of the visits and the contacts with the team of care was the same of the routine outpatient follow-up.

This study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration and informed consent was provided by participants. All the patients were informed about the research purpose and procedure, benefits and risks, having the freedom to drop out from the study at any time. The study protocol was approved by the Ethical Committee of the San Camillo-Forlanini Hospital in Rome.

The data were reported as average ± standard deviation. Statistical analysis was performed using unpaired Student's *t*-test to compare the two treatment groups, while one-way analysis of variance (ANOVA) was used to compare the T0 and T1 data.

Results

The age of the overall population was 56 ± 10 years, BMI was 31.2 ± 4.5 kg/m^2, HbA1c was 69 ± 6.2 mmol/mol (8.5±1%) and diabetes duration was 16 ± 2 years. Twenty-five patients (group A) were treated with metformin (maximum tolerated dose) plus basal insulin (mean dose 0.64 UI/kg/day), and 31 patients (group B) were treated with metformin alone (maximum tolerated dose). The two groups were comparable for age, diabetes duration, weight, BMI, WC, HbA1c, plasma lipids and body composition at T0. Owing to upgrade of the pharmacological treatment for the poor metabolic control, dapagliflozin (10 mg/day) was added. Table 1 shows the clinical characteristics, anthropometric, and bioelectric and biochemical measurements at T0. T1 data after 16 weeks are presented in Table 2. All the patients presented significant weight loss (-3.0 ± 0.6 kg, P < 0.0001) and WC reduction (-2.5 ± 0.6 cm, P < 0.0001). Weight loss was also significant in both single groups (group A: -2.5 ± 0.3 kg, P ≤ 0.001; group B: -3.4 ± 0.4 kg, P ≤ 0.001), higher in group B. BIA showed that pA, TBW, ICW and FFM did not change at T1 compared to baseline in both groups: FFM decreased slightly in group A from 60.2 ± 5.2 to 59.5 ± 8.1 kg (ns) and in group B from 60.4 ± 6.2 to 59.3 ± 6.6 kg (ns). On the contrary, FM significantly decreased in all the patients (baseline: 29.9 ± 6.84 kg vs. T2: 26.30 ± 7.4 kg, P < 0.000); a higher reduction was found in group B (-3.6 ± 1.2 kg, P < 0.001) vs. insulin-treated group A (-2.3 ± 1.3 kg, P < 0.001).

Metabolic control improved in all the patients: FPG 172 ± 49.4 mg/dL vs. 137 ± 36.8 mg/dL of T1, P < 0.0001; HbA1c 69 ± 9.3 mmol/mol (8.5±1.5%) vs. 60 ± 8.7 mmol/mol (7.6±1.4 %) of T1, P = 0.000. In group A, insulin dose was reduced by 9.3%. Total cholesterol (TC) and triglycerides (TG) levels significantly decreased in overall population (181.8 ± 48.8 mg/dL vs. T1: 170.7 ± 40.7, P = 0.003; 172 ± 93 mg/dL vs. T1: 143.2 ± 87.8, P = 0.000). Finally, there was no significant side effect related to fluid loss: Hct, eGFR, AER and BUN did not change in both groups at T1 compared to baseline; no severe hypoglycaemic event was reported by the patients and no other adverse events were recorded (urinary infections, ketoacidosis and hypotension).

Discussion

Randomized trials [3, 4, 6] and a real-world study [5] demonstrated a reduction of cardiovascular risk in T2DM during

Table 1. Baseline Characteristics of Two Groups

	Group A: metformin+ insulin (n = 25)	Group B: metformin (n = 31)
Age (years)	56 ± 10.8	60 ±11
Diabetes duration (years)	16 ± 3	15 ± 2
Antiplatelets (ASA)	22/25	26/31
Statins	23/25	27/31
Antihypertensive drugs	24/25	28/31
Weight (kg)	90.7 ± 13.1	90.4 ± 12.4
BMI (kg/m^2)	34.4 ± 8.3	31.2 ± 4.5
WC (cm)	111.1 ± 18.5	110.3 ± 13
FPG (mg/dL)	179 ± 65	168 ± 35
HbA1c (mmol/mol)	74 ± 11.8 (8.9±1.9%)	66 ± 6.2 (8.2±1%)
TC (mg/dL)	174.4 ± 35.1	186.7 ± 56.4
HDL (mg/dL)	48.3 ± 19.7	50.0 ± 18
TG (mg/dL)	156.0 ± 123.2	182.7 ± 67.5
Creatinine (mg/dL)	0.8 ± 0.2	0.9 ± 0.2
Hct (%)	41 ± 3.0	40 ± 3.4
eGFR (mL/min/1.73 m^2)	82.4 ± 23.4	83.7 ± 20.3
AER (µg/min)	56 ± 12.2	49.0 ± 11.9
BUN (mg/dL)	31.2 ± 7.1	33.5 ± 12.9
AST (U/L)	23.9 ± 6.1	21.5 ± 3.8
ALT (U/L)	25 ± 8.8	24.2 ± 5.9
FM (kg)	30.5 ± 7.9	30.0 ± 6.2
FFM (kg)	60.2 ± 5.2	60.4 ± 6.2
TBW (L)	42.2 ± 7	43.1 ± 4.4
ECW (L)	39.1 ± 4	39.2 ± 4.1
pA (°)	5.3 ± 0.8	5.2 ± 0.7

The difference was not significant for each variable. ASA: acetylsalicylic acid; BMI: body mass index; WC: waist circumference; FPG: fasting plasma glucose; TC: total cholesterol; HDL: high-density lipoprotein; TG: triglycerides; Hct: hematocrit; eGFR: estimated glomerular filtration rate; AER: albumin excretion rate; BUN: blood urea nitrogen; AST: aspartate transaminase; ALT: alanine transaminase; FM: fat mass; FFM: fat free mass; TBW: total body water; ECW: extra-cellular water; pA: phase angle.

SGLT2-i therapy; in all these studies, weight loss was reported. Obesity is an independent cardiovascular risk factor and is related to all causes mortality [15] and weight loss is related to cardiovascular morbidity and mortality reduction [16]. Our pilot study confirms the favorable dapagliflozin add-on therapy effects on weight reduction and metabolic control improvement in a population of overweight and obese T2DM patients. These effects have been observed for both treatment groups (A: metformin + basal insulin, B: metformin alone). The anabolic effect of insulin and its conflicting role on weight loss are well known; however, patients in group A, despite the lower weight change, have shown benefits in metabolic control and reduced insulin dose. Group A lost 2.5 kg after 16 weeks; this reduction is higher than that reported in a 2-year study on 193 T2DM patients treated with dapagliflozin and insulin vs. placebo and insulin group (1.5 kg at 16 weeks stable at the end of the study) [17].

Metabolic improvement after dapagliflozin introduction is significant, including FPG, HbA1c, TG and cholesterol reduction. It is likely that this result could also be related to weight and visceral fat reduction. We aimed to investigate the body composition changes during dapagliflozin treatment.

Some studies [10, 11] have recently reported a reduction of total FM without affecting skeletal muscle mass or a reduction in liver and abdominal subcutaneous fat assessed by CT scan in T2DM patients. CT is a gold standard method to study body composition and distribution, but it is not feasible in routine settings. Bioelectric analysis is a fast, simple, inexpensive, not invasive and reproducible method, suitable in clinical practice. This method allows calculating body water distribution in intra- and extra-cellular compartments and estimate FFM [18]. Predictive population specific equations are crucial to estimate body compartments. FM is estimated indirectly and the error rate is about 5% everyway. Even if in our study the estimated FM loss is significant, we must underline that the most significant result is the FFM preservation. These results seem to exclude ECW or ICW loss, as previously reported [12].

Table 2. Anthropometric, Biochemical and Bioelectrical Measures of the Two Groups at T0 and T1 After 16 Treatment Weeks

	Group A: metformin + insulin (n = 25)			Group B: metformin (n = 31)		
	T0	T1	P-value	T0	T1	P-value
Age (years)	56 ± 10.8			60 ± 11		
Weight (kg)	90.7 ± 13.1	88.2 ± 16.3	< 0.0001	90.4 ± 12.4	87.0 ± 13.6	< 0.0001
BMI (kg/m^2)	34.4 ± 8.3	33.4 ± 8.2	< 0.0001	31.2 ± 4.5	30 ± 3.4	< 0.0001
WC (cm)	111.1 ± 18.5	108.9 ± 18.7	< 0.0001	110.3 ± 13	107.5 ± 12.9	< 0.0001
FPG (mg/dL)	179 ± 65	136 ± 49	0.007	168 ± 35	139 ± 24	< 0.0001
HbA1c (mmol/mol)	74 ± 11.8 (8.9±1.9%)	64 ± 10.5 (8.0±1.7%)	< 0.0001	66 ± 6.2 (8.2±1%)	56 ± 5.58 (7.3±0.9%)	< 0.0001
TC (mg/dL)	174.4 ± 35.1	161 ± 31.7	ns	186.7 ± 56.4	177 ± 45.3	ns
HDL (mg/dL)	48.3 ± 19.7	49.2 ± 18.1	ns	50.0 ± 18	51.5 ± 18.6	ns
TG (mg/dL)	156.0 ± 123.2	133.3 ± 123.8	0.002	182.7 ± 67.5	149.8 ± 54.9	0.002
Hct (%)	41 ± 3.0	41 ± 2.9	ns	40 ± 3.4	41 ± 3.0	ns
Creatinine (mg/dL)	0.8 ± 0.2	0.8 ± 0.1	ns	0.9 ± 0.2	0.8 ± 0.2	ns
eGFR (mL/min/1.73 m^2)	82.4 ± 23.4	87.8 ± 16.9	ns	83.7 ± 20.3	88.5 ± 22.1	ns
AER (µg/min)	56 ± 12.2	42 ± 11	ns	49.0 ± 11.9	36 ± 11.2	ns
BUN (mg/dL)	31.2 ± 7.1	32.1 ± 9.8	ns	33.5 ± 12.9	33 ± 12.8	ns
AST (U/L)	23.9 ± 6.1	24.1 ± 6.8	ns	21.5 ± 3.8	21.9 ± 3.6	ns
ALT (U/L)	25 ± 8.8	23.2 ± 9.3	ns	24.2 ± 5.9	22.1 ± 6	ns
BIA						
FM (kg)	30.5 ± 7.9	28.2 ± 8.2	< 0.001	30.0 ± 6.2	26.4 ± 7.0	< 0.001
FFM (kg)	60.2 ± 5.2	59.5 ± 8.1	ns	60.4 ± 6.2	59.3 ± 6.6	ns
TBW (L)	42.2 ± 7	40.6 ± 7.9	ns	43.1 ± 4.4	40.9 ± 4.9	ns
ECW (L)	39.1 ± 4	37.3 ± 3	ns	39.2 ± 4.1	35.7 ± 4.2	0.021
pA (°)	5.3 ± 0.8	5.5 ± 0.5	ns	5.2 ± 0.7	5.6 ± 0.6	ns

BMI: body mass index; WC: waist circumference; FPG: fasting plasma glucose; TC: total cholesterol; HDL: high-density lipoprotein; TG: triglycerides; Hct: hematocrit; eGFR: estimated glomerular filtration rate; AER: albumin excretion rate; BUN: blood urea nitrogen; AST: aspartate transaminase; ALT: alanine transaminase; BIA: bioelectrical impedance analysis; FM: fat mass; FFM: fat free mass; TBW: total body water; ECW: extra-cellular water; pA: phase angle.

Furthermore, our data on body composition suggest a specific FM reduction, without hemodynamic and kidney function impairment, and a favorable effect on the metabolic profile.

Recently, it was demonstrated that body fat percentage in bioelectrical measurements is independently associated with the risk of future cardiovascular events and that the calculated percentage with the validated predictive equations can be a more predictive measurement in cardiovascular risk assessment than BMI or WC [19]. Our pilot study provides additional evidence about these results using a BIA. It is a short-term real-world observation and its limitations are the small size of the sample and the lack of a placebo-controlled arm. Furthermore, studies on different groups of patients, in association with other antidiabetic drugs and for longer time, are needed to confirm and better understand the relationship between weight and FM loss and reduction of cardiovascular risk in T2DM.

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Conflict of Interest

The authors have no potential conflict of interest to disclose for this article.

Informed Consent

The authors give informed consent.

Author Contributions

UDF researched data, made statistical analysis and reviewed manuscript. AG wrote the manuscript. MRN edited the manu-

script. CT designed the study, reviewed the manuscript and is the guarantor of the work.

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