



One Year of Dapagliflozin Add-On Therapy Ameliorates Surrogate Indexes of Insulin Resistance and Adiposity in Patients with Type 2 Diabetes Mellitus

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Received: February 7, 2021 / Accepted: March 27, 2021
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ABSTRACT

Introduction: This study investigates the effects of dapagliflozin on the visceral adiposity index (VAI), lipid accumulation product (LAP), product of triglycerides and glucose (TyG) and triglycerides to HDL-cholesterol ratio (TG/HDL-C) in patients with type 2 diabetes mellitus (T2D).

Methods: In this real-life study, dapagliflozin was added to metformin alone (group 1, no. 42) or insulin plus metformin (group 2, no. 58) in 100 T2D patients.

Results: In group 1, after 6 months of dapagliflozin addition, a significant decrease in BMI ($p < 0.001$), waist circumference (WC) ($p < 0.001$), systolic blood pressure (SBP) ($p = 0.009$), diastolic blood pressure (DBP)

($p = 0.012$), mean fasting blood glucose (FBG), post-breakfast glucose (PBG), post-lunch glucose (PLG) and post-dinner glucose (PDG) (all $p < 0.001$), HbA1c ($p < 0.001$), VAI ($p = 0.020$), LAP ($p = 0.028$), Tyg ($p < 0.001$), TG/HDL-C ($p = 0.020$) and glutamate pyruvate transaminase (GPT) ($p < 0.001$) was observed compared to baseline. After 12 months a significant decrease in BMI ($p < 0.001$), WC ($p = 0.006$), SBP ($p = 0.023$), DBP ($p = 0.005$), mean FPG, PBG, PLG and PDG (all $p < 0.001$), HbA1c ($p < 0.001$), total cholesterol ($p = 0.038$), triglycerides ($p = 0.026$), VAI ($p = 0.013$), GPT ($p < 0.001$), LAP index ($p = 0.024$), Tyg index ($p < 0.001$) and TG/HDL-c ratio ($p = 0.016$) was observed compared to baseline. In group 2, after 6 months of dapagliflozin addition, a significant decrease in BMI ($p < 0.001$), WC ($p < 0.001$), SBP ($p = 0.015$), DBP ($p = 0.007$), mean FPG, PBG, PLG and PDG (all $p < 0.001$), HbA1c ($p < 0.001$), VAI ($p = 0.040$), LAP ($p = 0.047$), Tyg ($p < 0.001$), TG/HDL-C ($p = 0.048$) and GPT ($p < 0.001$) was observed compared to baseline. By contrast, after 12 months a significant decrease in BMI ($p < 0.001$), WC ($p < 0.001$), SBP ($p = 0.001$), DBP ($p = 0.002$), mean FPG, PBG, PLG and PDG (all $p < 0.001$), HbA1c ($p < 0.001$), GPT ($p < 0.001$) and Tyg index ($p = 0.003$) was observed compared to baseline. **Conclusions:** Dapagliflozin treatment significantly reduced surrogate indexes of insulin resistance and adiposity in patients with T2D.

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Keywords: LAP; Dapagliflozin; Visceral adiposity index; Cardiometabolic risk; Tyg

Key Summary Points

Sodium-glucose co-transporter type 2 inhibitors (SGLT2i) significantly improve cardiovascular and renal outcomes in patients with type 2 diabetes mellitus (T2DM)

This study aims to investigate the effects of dapagliflozin added to metformin in monotherapy or metformin plus insulin on the metabolic parameters, visceral adiposity index (VAI), lipid accumulation product (LAP), product of triglycerides and glucose (TyG) and triglycerides to HDL-cholesterol ratio (TG/HDL-C) in 100 patients with T2DM

The study confirms the efficacy of dapagliflozin in achieving stable metabolic and glycaemic control and contributing to the improvement in other extraglycaemic targets (BMI, WC, SBP, DBP and TG levels) in a real-life single-centre cohort of patients with T2DM

The study shows that dapagliflozin added to metformin or metformin plus insulin significantly improves surrogate indexes of insulin resistance and adiposity in patients with T2DM

The limitation of the study is the lack of a meaningful control group

INTRODUCTION

Many novel antidiabetic therapies are available for the treatment of type 2 diabetes (T2D) [1] and have a good impact on glycaemic control but also on the distribution of adipose tissue, weight gain and chronic low grade inflammation [2]. Sodium-glucose co-transporter-2 inhibitors (SGLT2i) are novel oral hypoglycaemic drugs that produce glycosuria by blocking the reabsorption of glucose in the renal proximal tubules [3]. As a result, they improve glucose control through direct and indirect mechanisms, with limited risk of hypoglycaemia, and exert other positive effects on body weight, blood pressure, blood uric acid levels and inflammation [4]. In addition, the administration of SGLT-2i decreases abdominal visceral adipose deposits and improves their function [5–9]. Several studies have shown that when added to standard care, SGLT2i reduce the incidence of major cardiovascular events (cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke) in patients with T2D who are at high cardiovascular risk [10–12]. SGLT2i reduce the risk of hospitalization for heart failure and progression to end-stage renal disease in patients with T2D who have high cardiovascular risk, independent from glucose control [13].

The Visceral Adiposity Index (VAI) is an indirect validated gender-specific index, currently one of the best indicators of cardiovascular disease, which positively correlates with visceral adipose distribution and function [14] and adipocytokine levels, and it represents a surrogate index of cardiometabolic risk [15–17]. It can express both the altered endocrine function of adipose tissue and the state of relative leptin resistance and low-grade inflammation, which are all alterations of adipose tissue function. The gold standard to directly measure insulin sensitivity is the euglycaemic hyperinsulinemic clamp [18]. However, many surrogate indexes on insulin sensitivity have been modelled based on clinical and laboratoristic parameters including the lipid accumulation product (LAP), product of triglycerides and glucose (TyG) and the triglycerides to HDL-

DIGITAL FEATURES

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cholesterol ratio (TG/HDL-C) [19]. Therefore, to confirm the role of SGLT2i in determining an improvement of surrogate indexes of insulin resistance and adiposity in patients with T2D, in the current study we aimed to investigate whether dapagliflozin is able to influence the Visceral Adiposity Index (VAI), LAP, TyG and TG/HDL-C ratio indexes before and after 6 and 12 months of dapagliflozin treatment in a real-life cohort of outpatients with T2D.

METHODS

In this real-life study, we evaluated 100 outpatients of white race with T2D (57 men and 43 women; age range, 30–77 years), inadequately controlled with metformin alone (group 1, 42 patients; dual combined treatment; mean metformin dose 2428 ± 367.6 mg) or metformin combined with insulin (group 2, 58 patients; triple combined treatment; mean metformin dose 2297 ± 497.7 mg), who were started on dapagliflozin 10 mg once daily as add-on therapy. Among patients treated with metformin and insulin, 20 were on basal-bolus insulin treatment, while 38 were on long-acting insulin treatment. Patients were followed up for 12 months in a real-world setting. Inclusion criteria were a previous diagnosis of T2D for at least 5 years, HbA1c 6.5–11% (48–97 mmol/mol), age ranging from 30 to 80 years, BMI < 40 kg/m² and stable treatment with metformin alone or metformin and insulin of at least 3 years. We excluded patients with any other concomitant diabetes medications, moderate kidney disease (creatinine clearance < 60 ml/min using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula), high liver enzyme levels such as glutamate pyruvate transaminase (GPT) or glutamate oxaloacetate transaminase (GOT) more than three times above the upper limit of normal or total bilirubin > 2.0 mg/dl, unstable blood pressure and coronary syndrome, symptomatic heart failure or alcohol abuse. Microvascular complications were evaluated as recommended by standard medical care of diabetes [20]. Diabetic retinopathy was evaluated by a comprehensive dilated eye examination

with fundus photography by an expert ophthalmologist. Diabetic nephropathy was assessed by urinary albumin (e.g., spot urinary albumin-to-creatinine ratio) and the estimated glomerular filtration rate (GFR). Normal UACR was defined as < 30 mg/g creatinine and high urinary albumin excretion as ≥ 30 mg/g creatinine. GFR was calculated from serum creatinine using the CKD-EPI formula. Chronic kidney disease (CKD) was defined as stages 1–2 by evidence of high albuminuria with $eGFR \geq 60$ ml/min/1.73 m², while stages 3–5 were defined for lower ranges of GFR. Assessment for distal symmetric polyneuropathy was done by either temperature or pinprick sensation (small fibre function) and vibration sensation using a 128-Hz tuning fork (for large-fibre function). Patients had also 10-g monofilament.

Lipid-lowering drugs were continued during the study. In the dual combined group, 36 out of 42 patients were on statin treatment, while in the triple combined group, 49 out of 58 patients were on lipid-lowering treatment. None was treated with TG lowering drugs.

In all patients, anthropometric and clinical parameters were evaluated at the baseline assessment and after 6 and 12 months of therapy, including BMI, waist circumference (WC), systolic blood pressure (SBP) and diastolic blood pressure (DBP). We also evaluated metabolic and biochemical parameters, self-monitoring blood glucose (SMBG) including mean fasting plasma glucose (FPG) and 2 h post-breakfast, post-lunch and post-dinner glycaemia (PBG, PLG and PDG) by glucometer, HbA1c, fasting total cholesterol, HDL-cholesterol and TG. The VAI was calculated as already described [15] using the gender-specific formulas:

- Male VAI = $[WC/(39.68 + (1.88 \times BMI))] \times (TG/1.03) \times (1.31/HDL)$
- Female VAI = $[WC/(36.58 + (1.89 \times BMI))] \times (TG/0.81) \times (1.52/HDL)$

Additional surrogate indexes of insulin sensitivity and adipose tissue function including the LAP index, TyG index, and TG/HDL-C ratio, which were found to be associated with sub-clinical vascular damage [19], were also calculated. The LAP index was calculated as $(WC - 65) \times (TGs \text{ [mmol/l]})$ in men, and

$(WC - 58) \times (TG \text{ [mmol/l]})$ in women [21]. The TyG index was calculated as the $\text{Ln}[\text{fasting TGs (mg/dl)} \times \text{fasting glucose (mg/dl)}/2]$ [22]. The TG/HDL-C ratio was calculated as the ratio of TG (mg/dl) to HDL-C (mg/dl) [23].

The change from 12 months to baseline (Δ) for the parameters which were statistically significant changed after 6 months of dapagliflozin addition were calculated in both groups of patients. During the 12 months of follow-up, any change in concomitant medications was considered an exclusion criterion.

All procedures were in accordance with the ethical standards of the local committee on human experimentation (institutional and national) and with the Declaration of Helsinki (1964) and its later amendments. Approval was obtained from the Ethics Committee of the Policlinico Paolo Giaccone Hospital, University of Palermo (Ref. 04/2020). At the time of the first visit in our Out-Patient Clinic, all patients provided informed consent to participate in the study and for the publication of the study.

Statistical Analysis

SPSS version 19 (SPSS, Inc., Chicago, IL, USA) was used for data analysis. Data were presented as mean \pm SD or rates and proportions. The normality of distribution of the quantitative variables was assessed using the Kolmogorov-Smirnov test. The differences between the two groups were evaluated with Student's *t*-test for quantitative variables and χ^2 for trend for categorical variables. Changes in parameters from baseline to 6 months and from 6 to 12 months were evaluated using the paired *t*-test. $p < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics and comorbidities of both treatment groups are shown in Table 1. There were no significant differences between groups with regard to sex distribution, age, prevalence of arterial hypertension, cardiovascular disease, ischaemic stroke, peripheral artery disease, diabetic nephropathy and chronic kidney disease, while patients on dual combined

treatment (metformin + dapagliflozin) had lower prevalence of diabetic retinopathy ($p = 0.010$), shorter duration of diabetes ($p = 0.001$), and lower HbA1c ($p = 0.006$), BMI ($p = 0.015$) and WC ($p = 0.004$) than triple combined treatment (metformin + dapagliflozin + insulin). None discontinued the treatment during the 12-month follow-up.

The anthropometric, metabolic and clinical parameters before and after 6 and 12 months of dapagliflozin add-on metformin treatment alone (dual combined treatment) are shown in Table 2. After 6 months of dapagliflozin addition a significant decrease in BMI ($p < 0.001$), WC ($p < 0.001$), SBP ($p = 0.009$), DBP ($p = 0.012$), mean FPG, PBG, PLG and PDG (all $p < 0.001$), HbA1c ($p < 0.001$), VAI ($p = 0.020$) and GPT ($p < 0.001$) was observed compared to baseline (Table 2). No significant differences were found from 12 to 6 months (Table 2). By contrast, after 12 months a significant decrease in BMI ($p < 0.001$), WC ($p = 0.006$), SBP ($p = 0.023$), DBP ($p = 0.005$), mean FPG, PBG, PLG and PDG (all $p < 0.001$), HbA1c ($p < 0.001$), total cholesterol ($p = 0.038$), TG ($p = 0.026$), VAI ($p = 0.013$), GPT ($p < 0.001$), LAP index ($p = 0.024$), Tyg index ($p < 0.001$) and TG/HDL-c ratio ($p = 0.016$) was observed compared to baseline (Table 2).

In the triple combined regimen group, a significant decrease in BMI ($p < 0.001$), WC ($p < 0.001$), SBP ($p = 0.015$), DBP ($p = 0.007$), mean FPG, PBG, PLG and PDG (all $p < 0.001$), HbA1c ($p < 0.001$), VAI ($p = 0.040$), LAP index ($p = 0.047$), Tyg ($p < 0.001$), TG/HDL-C ratio ($p = 0.048$) and GPT ($p < 0.001$) was observed after 6 months of dapagliflozin addition compared to baseline (Table 3). No differences were found comparing 12 and 6 months (Table 3). By contrast, after 12 months a significant decrease in BMI ($p < 0.001$), WC ($p < 0.001$), SBP ($p = 0.001$), DBP ($p = 0.002$), mean FPG, PBG, PLG and PDG (all $p < 0.001$), HbA1c ($p < 0.001$), GPT ($p < 0.001$) and Tyg index ($p = 0.003$) was observed compared to baseline (Table 3).

No differences between dual and triple combined regimens were observed in Δ _BMI, Δ _WC, Δ _SBP, Δ _DBP, Δ _FBG, Δ _PBG, Δ _PLG, Δ _PDG, Δ _HbA1c, Δ _GOT, Δ _GPT, Δ _VAI,

Table 1 Clinical characteristics and comorbidities of patients with type 2 diabetes mellitus before starting dapagliflozin as added dual or triple therapy

	Dual combined therapy <i>N</i> = 42 Subjects (%)	Triple combined therapy <i>N</i> = 58 Subjects (%)	<i>p</i>
Gender			
Male	24 (57.1%)	33 (56.9%)	0.660
Female	18 (42.9%)	25 (43.1%)	
Smoking	13 (31%)	28 (48.3%)	0.336
Cardiovascular disease	3 (7.1%)	6 (10.3%)	0.972
Ischaemic stroke	0	1 (1.7%)	0.256
Peripheral arterial disease	2 (4.8%)	5 (8.6%)	0.393
Arterial hypertension	29 (69%)	45 (77.6%)	0.477
Diabetic retinopathy	4 (9.5%)	17 (29.3%)	0.010
Chronic kidney disease	1 (2.4%)	0	0.373
Diabetic nephropathy	3 (7.1%)	8 (13.8%)	0.236
Diabetic neuropathy	3 (7.1%)	5 (8.6%)	0.587
	Mean ± SD	Mean ± SD	<i>p</i>
Age (years)	57.6 ± 8.21	60.5 ± 8.31	0.089
Duration of diabetes (years)	8.24 ± 5.54	14.1 ± 9.94	0.001
Body mass index (kg/m ²)	30.4 ± 6.31	33.3 ± 4.93	0.015
Waist circumference(cm)	105.7 ± 12.9	113.3 ± 12.6	0.004
HbA1c (%)	8.68 ± 1.49	9.48 ± 1.23	0.006
VAI	3.04 ± 1.87	2.95 ± 2.09	0.812
LAP index	86.1 ± 52.4	93.8 ± 62.8	0.505
Tyg index	9.57 ± 0.62	9.57 ± 0.61	0.966
TG/HDL-C ratio	4.12 ± 2.54	3.97 ± 2.81	0.789

VAI Visceral Adiposity Index, *LAP* lipid accumulation product, *Tyg* product of triglycerides and glucose, *TG/HDL-C* triglycerides to HDL-cholesterol ratio

Δ _LAP, Δ _Tyg, Δ _TG/HDL-C, Δ _total cholesterol, Δ _HDL-cholesterol, Δ _TG and Δ _LDL-c-cholesterol (Fig. 1).

Dapagliflozin was well tolerated, without differences in the occurrence of infections between the groups (data not shown).

DISCUSSION

In the current study, dapagliflozin as add-on therapy to metformin alone or metformin combined to insulin improved glycaemic control in patients with T2D and led to a significant reduction in BMI, WC, SBP, the DBP LAP index,

Table 2 Clinical, anthropometric and metabolic parameters in diabetic patients before and after dual combined therapy of dapagliflozin and metformin

Dual combined treatment (dapagliflozin + metformin)						
	Baseline Mean \pm SD	6 months Mean \pm SD	12 months Mean \pm SD	<i>p</i> *	<i>p</i> **	<i>p</i> ***
Body mass index (kg/m ²)	30.4 \pm 6.31	29.7 \pm 6.29	29.4 \pm 6.32	< 0.001	0.312	< 0.001
Waist circumference (cm)	105.7 \pm 12.9	104.2 \pm 12.4	104.1 \pm 12.2	< 0.001	0.884	0.006
Systolic blood pressure (mmHg)	126.4 \pm 9.61	123.2 \pm 6.46	122.8 \pm 10.1	0.009	0.723	0.023
Diastolic blood pressure (mmHg)	83.1 \pm 11.8	79.3 \pm 9.46	77.5 \pm 7.96	0.012	0.179	0.005
Mean fasting glycaemia (mmol/l)	11.1 \pm 2.66	7.91 \pm 2.24	8.12 \pm 3.62	< 0.001	0.672	< 0.001
Mean 2 h post-breakfast glycaemia (mmol/l)	11.3 \pm 2.21	7.64 \pm 2.16	8.57 \pm 3.54	< 0.001	0.071	< 0.001
Mean 2 h post-lunch glycaemia (mmol/l)	11.1 \pm 2.58	8.29 \pm 2.41	8.63 \pm 3.28	< 0.001	0.381	< 0.001
Mean 2 h post-dinner glycaemia (mmol/l)	11.6 \pm 2.66	8.35 \pm 2.49	8.2 \pm 3.04	< 0.001	0.695	< 0.001
HbA1c (%)	8.68 \pm 1.49	7.31 \pm 0.85	7.53 \pm 1.41	< 0.001	0.124	< 0.001
Total cholesterol (mmol/l)	4.65 \pm 1.12	4.4 \pm 0.97	4.3 \pm 1.06	0.078	0.324	0.038
HDL-cholesterol (mmol/l)	1.15 \pm 0.28	1.2 \pm 0.28	1.22 \pm 0.29	0.218	0.649	0.235
Triglycerides (mmol/l)	1.92 \pm 0.99	1.63 \pm 0.57	1.69 \pm 0.75	0.060	0.541	0.026
LDL-cholesterol (mmol/l)	2.61 \pm 0.93	2.45 \pm 0.85	2.31 \pm 0.92	0.252	0.173	0.067
VAI	3.04 \pm 1.87	2.38 \pm 1.31	2.39 \pm 1.31	0.020	0.984	0.013
GOT (U/l)	20.7 \pm 9.41	21.4 \pm 9.88	21.1 \pm 10.8	0.692	0.799	0.969
GPT (U/l)	26.8 \pm 13.9	18.5 \pm 6.94	17.2 \pm 8.15	< 0.001	0.231	< 0.001
LAP index	86.1 \pm 52.4	71.1 \pm 39.1	72.9 \pm 45.1	0.028	0.707	0.024
Tyg index	9.57 \pm 0.62	9.05 \pm 0.48	9.05 \pm 0.58	< 0.001	0.974	< 0.001
TG/HDL-C ratio	4.12 \pm 2.54	3.14 \pm 1.45	3.23 \pm 1.79	0.020	0.719	0.016

GPT glutamate pyruvate transaminase, *GOT* glutamate oxaloacetate transaminase, *VAI* Visceral Adiposity Index, *LAP* lipid accumulation product, *Tyg* product of triglycerides and glucose, *TG/HDL-C* triglycerides to HDL-cholesterol ratio

*Comparison between baseline and 6 months of treatment

**Comparison between 6 and 12 months of treatment

***Comparison between baseline and 12 months of treatment

Tyg index, TG/HDL-C ratio and VAI after 6 months of treatment with the persistence of these effects at 12 months of follow-up. These results confirm previous findings [3] and demonstrate the efficacy of dapagliflozin therapy in terms not only of metabolic control but also of extraglycaemic cardiovascular benefits.

The VAI is a validated indirect index of cardiometabolic risk and a valuable index of both fat distribution and function. This has been demonstrated by the correlation between magnetic resonance imaging measurement of visceral adipose tissue and VAI, and between VAI and insulin sensitivity, evaluated by the

Table 3 Clinical, anthropometric and metabolic parameters in diabetic patients before and after triple combined therapy of dapaglifozin, metformin and long-acting insulin

Triple combined treatment (dapaglifozin + metformin + insulin)						
	Baseline Mean ± SD	6 months Mean ± SD	12 months Mean ± SD	<i>p</i> *	<i>p</i> **	<i>p</i> ***
Body mass index (kg/m ²)	33.3 ± 4.93	32.4 ± 5.17	32.5 ± 5.69	< 0.001	0.738	< 0.001
Waist circumference (cm)	113.3 ± 12.6	111.3 ± 12.2	111 ± 12.8	< 0.001	0.344	< 0.001
Systolic blood pressure (mmHg)	128.7 ± 9.15	125.1 ± 8.57	124.4 ± 7.91	0.015	0.556	0.001
Diastolic blood pressure (mmHg)	85.3 ± 9.66	81.5 ± 10.5	80.9 ± 8.01	0.027	0.730	0.002
Mean fasting glycaemia (mmol/l)	12.1 ± 3.26	8.81 ± 2.58	9.03 ± 2.83	< 0.001	0.546	< 0.001
Mean 2 h post breakfast glycaemia (mmol/l)	12.7 ± 3.34	9.51 ± 2.25	9.04 ± 2.83	< 0.001	0.510	< 0.001
Mean 2 h post-lunch glycaemia (mmol/l)	12.5 ± 2.33	9.79 ± 2.44	9.58 ± 2.69	< 0.001	0.600	< 0.001
Mean 2 h post dinner glycaemia (mmol/l)	12.8 ± 2.96	9.88 ± 2.06	9.16 ± 2.54	< 0.001	0.052	< 0.001
Total insulin requirement (U/kg)	0.52 ± 0.36	0.53 ± 0.35	0.56 ± 0.44	0.724	0.830	0.690
HbA1c (%)	9.48 ± 1.23	7.96 ± 1.14	7.95 ± 1.11	< 0.001	0.987	< 0.001
Total cholesterol (mmol/l)	4.46 ± 1.23	4.43 ± 1.07	4.36 ± 1.07	0.822	0.555	0.694
HDL-cholesterol (mmol/l)	1.16 ± 0.43	1.21 ± 0.24	1.22 ± 0.23	0.310	0.575	0.469
Triglycerides (mmol/l)	1.77 ± 0.99	1.65 ± 0.71	1.69 ± 0.77	0.257	0.194	0.968
LDL-cholesterol (mmol/l)	2.44 ± 1.04	2.48 ± 1	2.35 ± 0.95	0.743	0.238	0.469
VAI	2.95 ± 2.09	2.51 ± 1.44	2.64 ± 1.63	0.040	0.259	0.145
GOT (U/l)	23.6 ± 13.2	23.3 ± 15.3	23.6 ± 12.1	0.879	0.875	0.844
GPT (U/l)	30.8 ± 16.4	20.6 ± 12.2	19.1 ± 8.45	< 0.001	0.164	< 0.001
LAP index	95.4 ± 63.8	84.3 ± 46.8	89.6 ± 47.6	0.047	0.251	0.161
Tyg index	9.57 ± 0.63	9.25 ± 0.56	9.32 ± 0.58	< 0.001	0.232	0.003
TG/HDL-c ratio	3.97 ± 2.81	3.32 ± 1.76	3.49 ± 1.88	0.048	0.393	0.116

GPT glutamate pyruvate transaminase, *GOT* glutamate oxaloacetate transaminase, *VAI* Visceral Adiposity Index, *LAP* lipid accumulation product, *Tyg* product of triglycerides and glucose, *TG/HDL-C* triglycerides to HDL-cholesterol ratio

*Comparison between baseline and 6 months of treatment

**Comparison between 6 and 12 months of treatment

***Comparison between baseline and 12 months of treatment

hyperinsulinaemic-euglycaemic clamp [15]. Notably, VAI showed an association with the M value that was not detected by WC or BMI alone [15, 16]. Furthermore, a strong independent association between VAI and both cardiovascular and cerebrovascular events [16, 17] has been reported. In addition, VAI has been widely used in many population studies showing better

predictive power for incipient diabetes than its individual components (WC, BMI, TG and HDL) and a correlation with biochemical markers of systemic inflammation linked to adipose tissue dysfunction in patients with T2D [24, 25]. The LAP index has been proposed and demonstrated as a marker of central obesity and insulin resistance and predictive factor of

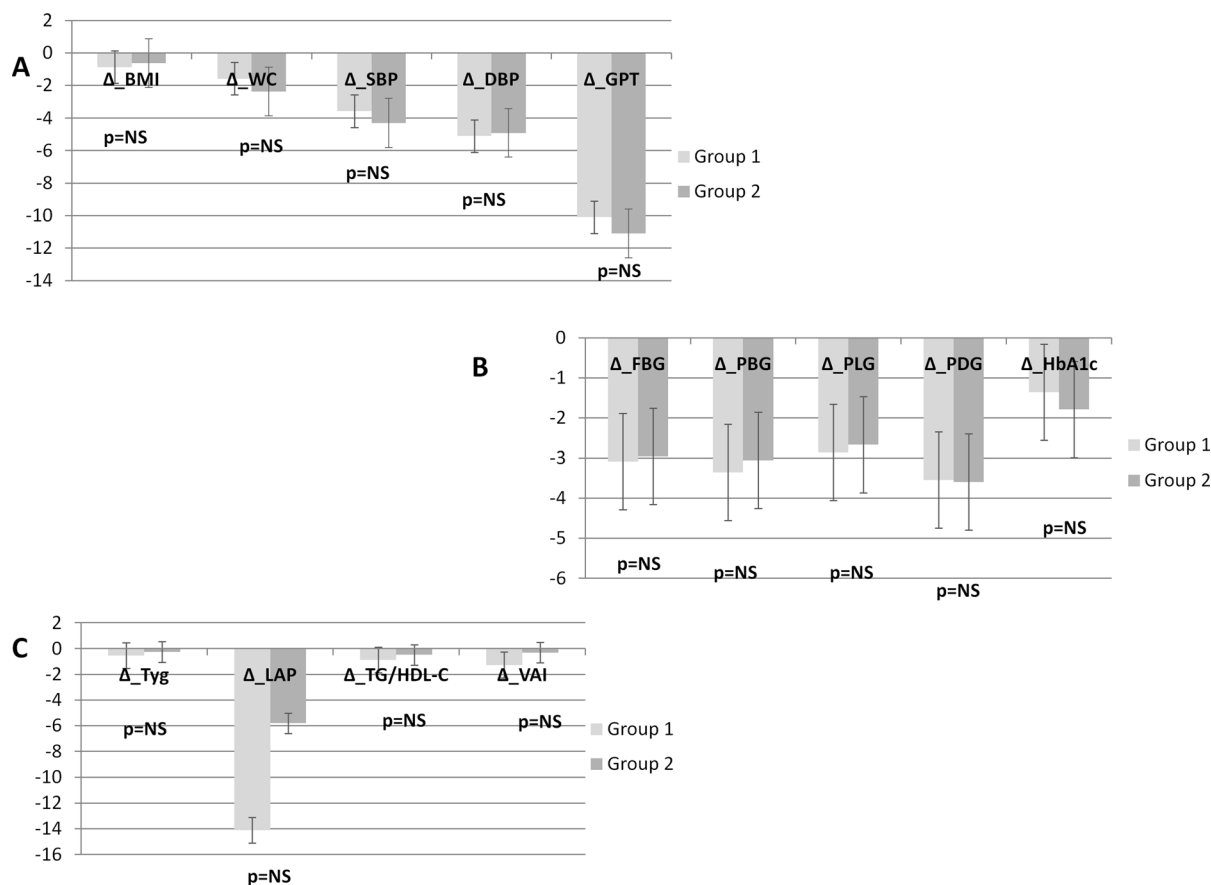


Fig. 1 Comparison of the change (Δ) from 12 months to baseline between patients on dual and triple combined treatment (groups 1 and 2) for those parameters which were statistically significant at the Student's *t*-test analysis. **a** Comparison of Δ_{BMI} , Δ_{WC} , Δ_{SBP} , Δ_{DBP} , Δ_{GPT} . **b** Comparison of Δ_{FBG} , Δ_{PBG} , Δ_{PLG} , Δ_{PDG} , Δ_{HbA1c} . **c** Comparison of Δ_{VAI} , Δ_{LAP} , Δ_{Tyg} , $\Delta_{\text{TG/HDL-C}}$. *BMI* body mass index, *WC* waist

circumference, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FBG* fasting blood glycaemia, *PBG* post-breakfast glycaemia, *PLG* post-lunch glycaemia, *PDG* post-dinner glycaemia, *VAI* Visceral Adiposity Index, *LAP* lipid accumulation product, *Tyg* product of triglycerides and glucose, *TG/HDL-C* triglycerides to HDL-cholesterol ratio

metabolic syndrome and cardiovascular disease [26, 27]. It was also used to discriminate prediabetes and diabetes and was shown to strongly correlate with HOMA-IR [28]. The Tyg index was modelled by Simental-Mendia et al. [29] and validated as a marker of insulin resistance and to discriminate diabetes status [28, 30]. The TG/HDL-C ratio is a predictor of insulin resistance and cardiometabolic risk and has been proposed as an atherogenic marker [19].

Dapagliflozin improves glucose control and induces weight loss in patients with T2D [7]. Large clinical trials have recently shown that

SGLT2i reduce major adverse cardiovascular events mainly in patients with established atherosclerotic cardiovascular disease. Remarkably, the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial found that dapagliflozin was superior to placebo at preventing cardiovascular deaths and heart failure events [25]. Several studies have reported a significant improvement in epicardial adipose tissue, a parameter reflecting visceral adiposity [6], inflammation markers [7] and hepatic fibrosis [31].

A recent randomized controlled trial on 32 patients with T2D showed a decrease in visceral adipose tissue volume measured by magnetic resonance imaging [32]. However, no effects on tissue insulin sensitivity were observed.

In the current study, an interesting positive impact of dapagliflozin on adipose tissue distribution and function indirectly expressed by VAI was found. In agreement with our findings, Neeland et al. reported a significant reduction in VAI in patients with T2D treated with empagliflozin versus placebo, although the follow-up period was short [33]. Similar effects were also found in patients treated with glucagon-like peptide-1 receptor agonists [34, 35]. In the current study, we observed a similar efficacy of dapagliflozin when added to metformin alone or metformin combined with insulin regarding the changes in VAI, suggesting an effect of the drug independent from the concomitant medications. Although, the main mechanism of action of dapagliflozin is the excretion of urinary glucose, dapagliflozin also exerts a cardio-nephroprotective action, whose mechanisms remain elusive. These different pleiotropic extraglycaemic effects have a positive impact on visceral adipose dysfunction and contribute to a decreased risk of cardiovascular events, heart failure and diabetic kidney disease progression [36]. Except for reduced body weight, an alternative hypothesis explaining loss of liver fat is the metabolic substrate shift from glucose to fatty acids and possibly increased fatty acid oxidation in the liver as previously suggested [37, 38]. Interestingly, in the current study dapagliflozin addition provided a decrease in other validated surrogate markers of insulin resistance: the LAP index, Tyg index and TG/HDL-C ratio. The positive effects of dapagliflozin on insulin resistance have been evaluated in both humans by meal test and euglycaemic hyperinsulinemic clamp [39] and transgenic rat models [40].

The main limitation of our study is the non-evaluation of adiposity by imaging techniques and neither inflammatory biomarkers nor adipokines. Another limitation is the absence of a meaningful control group made up of non-diabetic subjects or patients with T2D not treated with dapagliflozin. The strength of the study is

the evaluation of the main important validated surrogates of adiposity and insulin resistance, the VAI, LAP index, Tyg index and TG/HDL-C ratio in patients treated with dapagliflozin.

The results of the current study must be considered as preliminary. Further larger prospective studies need to be performed to confirm these results.

CONCLUSION

Our study confirms the efficacy of dapagliflozin in achieving stable metabolic and glycaemic control and contributing to the improvement in other extraglycaemic targets (BMI, WC, SBP, DBP and TG levels) in a real-life single-centre cohort of patients with T2D. In addition, changes in body composition induced by dapagliflozin improve surrogate indexes of adiposity and insulin resistance. However, further prospective studies with a high number of patients with T2D and a longer period of observation are required to confirm these preliminary data.

ACKNOWLEDGEMENTS

We thank the participants of the study.

Funding. No funding or sponsorship was received for this study or publication of this article. Editorial support was provided by Edra S.p.A, and the rapid service fee was unconditionally funded by AstraZeneca.

Disclosures. Stefano Radellini, Enrica Vigneri, Felicia Pantò, Valentina Guarnotta and Carla Giordano declare that they have no conflict of interest.

Compliance with Ethics Guidelines. Approval was obtained from the Ethics Committee of the Policlinico Paolo Giaccone Hospital, University of Palermo. All procedures were in accordance with the ethical standards of the local committee on human experimentation (institutional and national) and with the Declaration of Helsinki (1964) and its later

amendments. At the time of the first visit in our Out-Patients' Clinic, all patients provided informed consent to participate in the study and for the publication of the study.

Data Availability. All data generated or analyzed during this study are included in this published article.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Authors' Contributions. VG, SR: manuscript writing, data analysis and editing; EV, FP: data collection; CG, VG: protocol development and editing; VG, SR, EV, FP and C.G. read and approved the final manuscript for publication.

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