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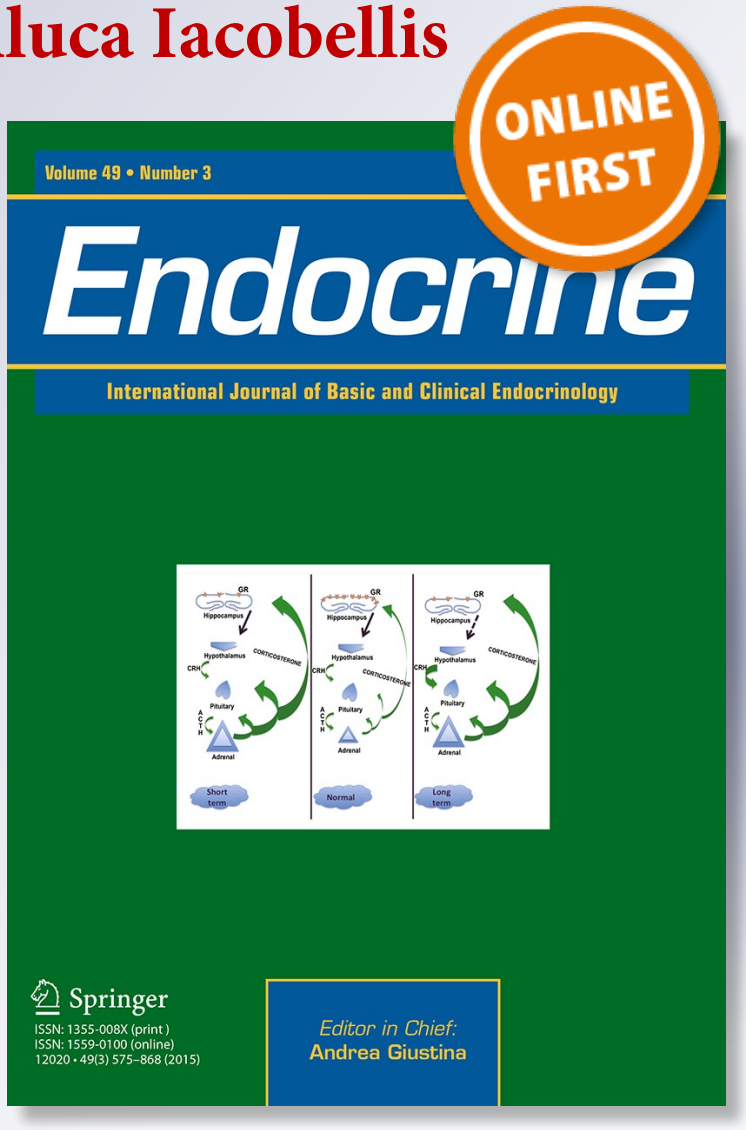

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ORIGINAL ARTICLE

Effect of sitagliptin on epicardial fat thickness in subjects with type 2 diabetes and obesity: a pilot study

Marcos M. Lima-Martínez[1,2] · Mariela Paoli[3] · Marianela Rodney[4] · Nathalie Balladares[1,2] · Miguel Contreras[5] · Luis D'Marco[6] · Gianluca Iacobellis[7]

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Abstract The aim of the study was to assess the effect of sitagliptin addition on the epicardial adipose tissue (EAT) thickness in subjects with type 2 diabetes mellitus inadequately controlled on metformin monotherapy. This was a 24-week interventional pilot study in 26 consecutive type 2 diabetic patients, 14 females and 12 males average age of 43.8 ± 9.0 years, with Hemoglobin A1c (HbA1c) ≥7 % on metformin monotherapy. Subjects who met the inclusion criteria were added on sitagliptin and started on sitagliptin/metformin combination at the dosage of 50 mg/1000 mg twice daily. EAT and visceral and total body fat were measured, respectively, with echocardiography and bioelectrical impedance analysis at baseline and after 24 weeks of sitagliptin/metformin treatment in each subject. HbA1c and plasma lipids were also measured. EAT decreased significantly from 9.98 ± 2.63 to 8.10 ± 2.11 mm, $p = 0.001$, accounting for a percentage of reduction (Δ %) of −15 % after 24 weeks of sitagliptin addition, whereas total body fat percentage, visceral fat, and body mass index (BMI), decreased by 8, 12, and 7 %, respectively ($p = 0.001$ for all). After 6 month, EAT Δ % was significantly correlated with Δ % of visceral fat ($r = 0.456$; $p = 0.01$), whereas no correlation with either BMI Δ % ($r = 0.292$; $p = 0.147$) or HbA1c Δ % was found. The addition of Sitagliptin produced a significant and rapid reduction of EAT, marker of organ-specific visceral fat, in overweight/obese individuals with type 2 diabetes inadequately controlled on metformin monotherapy. EAT as measured with ultrasound can serve as no invasive and accurate marker of visceral fat changes during pharmaceutical interventions targeting the fat.

Keywords Epicardial adipose tissue · Epicardial fat · Sitagliptin · Diet · Exercise

✉ Marcos M. Lima-Martínez
marcoslimamedical@hotmail.com

1 Departamento de Ciencias Fisiológicas, Universidad de Oriente, Núcleo Bolívar, Ciudad Bolívar, Venezuela

2 Anexo A Centro Médico Orinoco, Unidad de Endocrinología, Diabetes, Metabolismo y Nutrición, Ciudad Bolívar, Venezuela

3 Instituto Autónomo Hospital Universitario de los Andes, Unidad de Endocrinología, Mérida, Venezuela

4 Servicio de Cardiología, Hospital Universitario Ruíz y Páez, Ciudad Bolívar, Venezuela

5 Centro Médico El Valle, Nueva Esparta, Venezuela

6 Clínica Puerto Ordaz, Unidad Avanzada de Investigación y Diagnóstico Ecográfico y Renal (UNIRENAL), Ciudad Guayana, Venezuela

7 Division of Endocrinology, Department of Medicine, University of Miami Miller School of Medicine, Miami, USA

Introduction

Visceral adiposity is associated with higher cardio-metabolic risk. Quantifying visceral adipose tissue allows a better cardiovascular and metabolic risk stratification [1, 2]. The importance of the anatomical closeness of some visceral adipose tissue depots to target organs, including the heart, was recently emphasized [3]. Thus in the last few years, some non-traditional visceral adipose tissues, such as epicardial adipose tissue (EAT), have been studied and proposed as new markers of visceral adiposity [4–6]. Clinically, the thickness of epicardial fat can be easily and accurately measured with standard ultrasound techniques [7]. Echocardiographic epicardial fat strongly and independently reflects intra-abdominal visceral fat and intramyocardial fat content, as measured by magnetic resonance

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imaging (MRI) [7, 8]. Several clinical studies have shown that epicardial fat thickness is significantly related to metabolic syndrome, diabetes, and coronary artery disease (CAD) [9–13]. Given its simple objective measurability, epicardial fat can serve as target for pharmaceutical agents targeting the adipose tissue [1, 4]. Thiazolidinediones have been shown to decrease inflammatory cytokines in EAT of patients with type 2 diabetes [14], whereas metformin produced no significant effects [15]. Furthermore, EAT thickness decreased in diabetic subjects treated with atorvastatin in comparison with those who received simvastatin and ezetimibe [16]. Epicardial fat reduced also after very low calorie diet, bariatric surgery-induced weight loss, and moderate aerobic exercise [17, 18].

Dipeptidyl peptidase-4 (DPP-4) inhibitors are a relatively new class of drugs for type 2 diabetes mellitus that exert a hypoglycemic effect by inhibiting the degradation of endogenous peptides such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). Several studies have demonstrated that DPP-4 inhibitors offer a wide range of cardiovascular benefits by ameliorating risk factors such as high blood pressure, postprandial lipemia, inflammatory markers, oxidative stress, and platelet aggregation [19]. Recently, sitagliptin has shown to significantly reduce visceral adiposity, as measured with bioelectric impedance analysis (BIA) in overweight type 2 diabetes mellitus patients [20]. The combination of sitagliptin and metformin has shown to be safe and effective [21].

Nevertheless, whether sitagliptin can significantly reduce an organ-specific visceral fat depot, such as EAT is unknown and unexplored. Hence, we aimed to assess the effect of sitagliptin addition on EAT in subjects with type 2 diabetes mellitus and obesity inadequately controlled on metformin monotherapy.

Materials and methods

Subjects

Men and women with type 2 diabetes as per American Diabetes Association (ADA) [22], (18–75 years of age) who were taking metformin monotherapy at a stable dose of >1000 mg/day for at least 12 weeks prior to the screening visit and had inadequate glycemic control [defined by a HemoglobinA1c (HbA1c) level ≥7 %] were recruited for the study. Subjects were recruited from those who were referred to the Endocrinology, Diabetes, Metabolism, and Nutrition Unit of Centro Médico Orinoco in Ciudad Bolívar, Venezuela, for diabetes management and care. More than 200 subjects with type 2 diabetes were screened. Subjects with any contraindications for use of sitagliptin or DPP4 inhibitors in general, history of type 1 diabetes, family dyslipidemias, high blood pressure, other endocrine diseases such as thyroid diseases, Cushing syndrome, acromegaly, impaired renal function (creatinine clearance <60 mL/min), alanine aminotransferase, or aspartate aminotransferase levels more than twofold the upper limit of normal, as well as those using sulfonylureas, thiazolidinediones, insulin, glucagon-like peptide 1 receptor (GLP-1R) analogs, glucocorticoids, and lipid-lowering agents were excluded from the study. This study was approved by the hospital's Ethics Commission pursuant to Helsinki Declaration guidelines. Once the written informed consent form was signed, each subject was enrolled in the study.

Study design

This was a 24-week interventional pilot study. Sitagliptin was added on the ongoing Metformin therapy. Subjects were started on sitagliptin/metformin combination at the dosage of 50–1000 mg twice daily. The pre-fixed combination of sitagliptin/metformin was chosen to obtain a better compliance of the participants in taking the study medications. Metformin tablets in monotherapy were discontinued. Patients received also a detailed dietary plan (1500 kcal/day meal plan with a macronutrient distribution of 50 % carbohydrate; 30 % fat with no more than 10 % of saturated fat; and 20 % protein) and were advised to have 150 min per week of aerobic exercise as per ADA recommendations [23]. All patients were contacted every 2 months to receive dietary counseling and check their adherence to the treatment.

Study endpoints

EAT was the primary endpoint. Each subject had anthropometrics, blood tests, echocardiograms, and BIA both before and after the 24 weeks of treatment.

Methodologies

Anthropometrics

Weight and height were measured with subjects wearing only their underwear. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Waist circumference (WC) was measured midway between the underside of the lowest rib and the iliac crests, in centimeters, with subjects standing.

Biochemicals

After an overnight fast, each subject had a blood drawn to measure HbA1c, blood glucose, and lipids (total

cholesterol, triglycerides, and high-density lipoprotein-cholesterol (HDL-C). Low-density lipoprotein (LDL-C) was estimated using the Friedewald Equation, where LDL-C = Total Cholesterol − [HDL-C + (Triglycerides/5)]. HbA1c was determined in accordance with the method defined by the National Glycohemoglobin Standardization Program (NGSP), using reactants from Bio-Rad Laboratories (California, USA). Insulin was determined using an ultrasensitive ELISA double sandwich method (DRG Instruments GmbH, Germany, Inc.). Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) was calculated using the equation [fasting glucose (mg/dL) × fasting insulin (mU/mL)/405] [24].

Epicardial fat thickness

Each subject underwent a two-dimensional (2D) transthoracic echocardiogram using a Mylab 50 Xvision Esaote® scanner (Genoa, Italia). An electrocardiogram was simultaneously performed on all subjects. Echocardiograms were read by a cardiologist–echocardiographer who was blinded to patients' clinical data. EAT was measured according to the method proposed and validated by Iacobellis et al. [25]. Epicardial fat was identified as the echo-free space between the outer wall of the myocardium and the visceral layer of pericardium. Epicardial fat thickness was measured in the parasternal long-axis view, perpendicularly on the free wall of the right ventricle at end systole in three cardiac cycles. Maximum epicardial fat thickness was measured at the point on the free wall of the right ventricle along the midline of the ultrasound beam, perpendicular to the aortic annulus, used as anatomical landmark for this view. The average value of three cardiac cycles was considered. The measure was performed on the free wall of the right ventricle for two reasons: (1) it is anatomically recognized as the thickest portion of epicardial fat and (2) both the long and short parasternal axes allow for the most accurate EAT measurements on the right ventricle, with an optimal orientation of the prompter in each view. [25].

Body composition analysis

Total body and visceral fat were determined by BIA with an Omron HBF-500® (Illinois, USA).

Statistical analysis

All continuous variables are presented as mean ± standard deviation, and the categorical variables as number and percentage. As all continuous variables were normally distributed, a Student's *t* test for dependent data assessed the mean difference of the quantitative variables both before and after treatment with the sitagliptin/metformin combination. The percentage variation (Δ %) of the variables was calculated and a correlation matrix between them was performed. A $p < 0.05$ was considered statistically significant. SPSS 20 was used for the statistical analyses.

Results

Twenty-six consecutive type 2 diabetic patients, 14 females and 12 males, average age of 43.8 ± 9.0 years, average diabetes duration of 2.48 ± 1.78 years, average BMI 35.02 ± 5.91 kg/m^2 participated and completed the study. Patients well tolerated the study medications and had neither serious nor minor side effects during the 24 weeks. No patient dropped from the study.

Adiposity markers

Table 1 summarizes the body fat variables data of the participants before and after 6 months of treatment with sitagliptin/metformin. The percentage variations of the adiposity markers before and 6 months after treatment are also visualized in Fig. 1.

EAT decreased significantly from 9.98 ± 2.63 to 8.10 ± 2.11 mm, $p = 0.001$, accounting for a percentage of reduction (Δ %) = −15.23 ± 26.00. BMI reduced from 35.02 ± 5.91 to 32.15 ± 5.39 kg/m^2, with a Δ % of −7.84 ± 7.14 % ($p = 0.001$). Similarly, WC reduced by -7.54 ± 5.79 % ($p = 0.001$). Total body fat percentage as determined by BIA decreased from 41.74 ± 6.60 to 38.02 ± 6.39 % (Δ % = −8.65 ± 8.97; $p = 0.001$); and visceral fat from 14.00 ± 6.63 to 12.19 ± 6.34 % (Δ % = −12.53 ± 15.47; $p = 0.001$).

Biochemical variables

Table 2 summarizes the metabolic data of the participants before and after six months of treatment with sitagliptin/metformin. A significant decrease of fasting glucose from 164.85 ± 25.86 to 105.04 ± 19.74 mg/dL ($p = 0.0001$); insulin from 20.52 ± 6.15 to 17.13 ± 4.75 mU/mL ($p = 0.001$); HOMA-IR from 8.34 ± 2.79 to 4.39 ± 1.68 ($p = 0.0001$); and HbA1c from 7.50 ± 0.45 to 6.07 ± 0.56 % ($p = 0.001$) was observed before and after treatment with sitagliptin/metformin. Also, there was a significant improvement in the lipid parameters with a decrease of total cholesterol from 181.58 ± 32.71 to 159.23 ± 41.35 mg/dL ($p = 0.007$); LDL-C from 108.89 ± 32.74 to 92.00 ± 34.22 mg/dL ($p = 0.02$); and triglycerides from 167.06 ± 105.06 to 124.46 ± 69.57 mg/dL ($p = 0.003$). Although HDL-C

Table 1 Anthropometric variables and epicardial fat of the patients before and after 24 weeks of combined treatment with sitagliptin/metformin

Parameter	Basal	24 weeks	*p*	Δ %
Weight (kg)	95.31 ± 22.72	87.49 ± 21.18	0.001	−7.84 ± 7.14
BMI (kg/m^2)	35.02 ± 5.91	32.15 ± 5.39	0.001	−7.84 ± 7.14
WC (cm)	107.66 ± 14.08	99.50 ± 14.42	0.001	−7.54 ± 5.79
Total body fat (%)	41.74 ± 6.60	38.02 ± 6.39	0.001	−8.65 ± 8.97
Visceral fat (%)	14.00 ± 6.63	12.19 ± 6.34	0.001	−12.53 ± 15.47
Epicardial fat (mm)	9.98 ± 2.63	8.10 ± 2.11	0.01	−15.23 ± 26.00

Continuous variables are presented as X ± SD

BMI body mass index, *WC* waist circumference

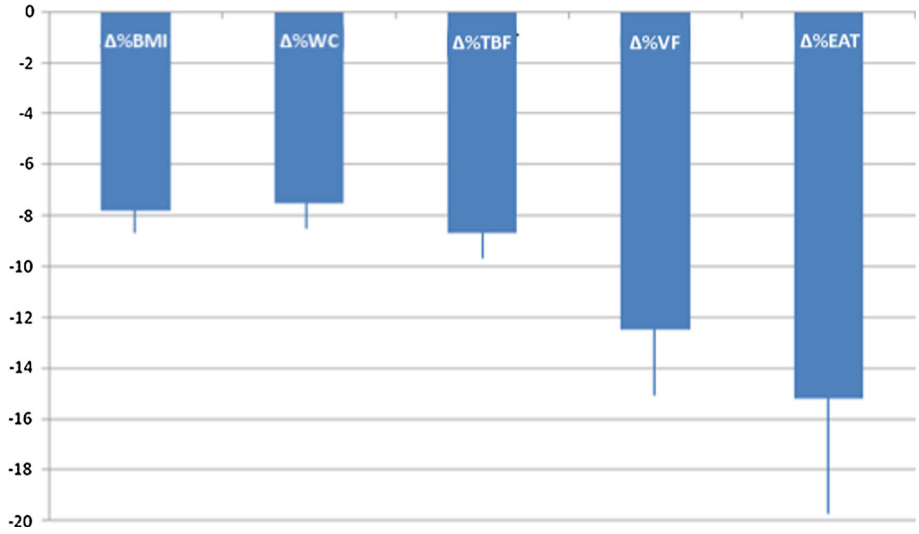

Fig. 1 Percentage variation (Δ %) of body mass index (BMI), waist circumference (WC), total body fat (TBF), visceral fat (VF), and epicardial adipose tissue (EAT) thickness after 24 weeks of treatment

Table 2 Biochemical variables of patients both prior to and 24 weeks into combined sitagliptin/metformin

Parameter	Basal	24 weeks	*p*
Glycemia (mg/dL)	164.85 ± 25.86	105.04 ± 19.74	0.0001
Insulin (mU/mL)	20.52 ± 6.15	17.13 ± 4.75	0.001
HOMA-IR	8.34 ± 2.79	4.39 ± 1.68	0.0001
HbA1c (%)	7.50 ± 0,45	6.07 ± 0,56	0.0001
Total cholesterol (mg/dL)	181.58 ± 32.71	159.23 ± 41.35	0.007
LDL-C (mg/dL)	108.89 ± 32.74	92.00 ± 34.22	0.02
HDL-C (mg/dL)	39.23 ± 8.52	42.39 ± 9.87	0.129
Triglycerides (mg(dL)	167.06 ± 105.06	124.46 ± 69.57	0.003

Continuous variables are presented as X ± SD

HOMA-IR homeostasis model assessment-insulin resistance, *HbA1c* glycosilated hemoglobin A1c, *LDL-C* low-density lipoprotein, *HDL-C* high-density lipoprotein

increased from 39.23 ± 8.52 to 42.39 ± 9.87 mg/dL, this variation was not statistically significant.

Correlates of adiposity markers

Univariate regression analysis showed that at baseline EAT was correlated with BMI ($r = 0.598$; $p = 0.001$). However, EAT Δ % after 24 weeks of treatment with sitagliptin/metformin was significantly correlated with visceral fat Δ % ($r = 0.456$; $p = 0.01$) (Fig. 2), whereas EAT change was no longer related to BMI Δ % ($r = 0.292$; $p = 0.147$) (Fig. 3). No correlation was observed between the percentage variation of HbA1c, lipids, and those of the adiposity measurements, nor

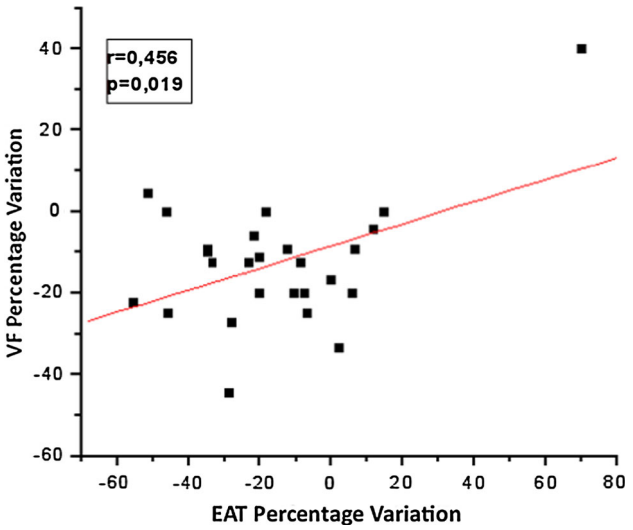

Fig. 2 Correlation between percentage variation of epicardial adipose tissue (EAT) thickness and percentage variation of visceral fat (VF) as seen after treatment

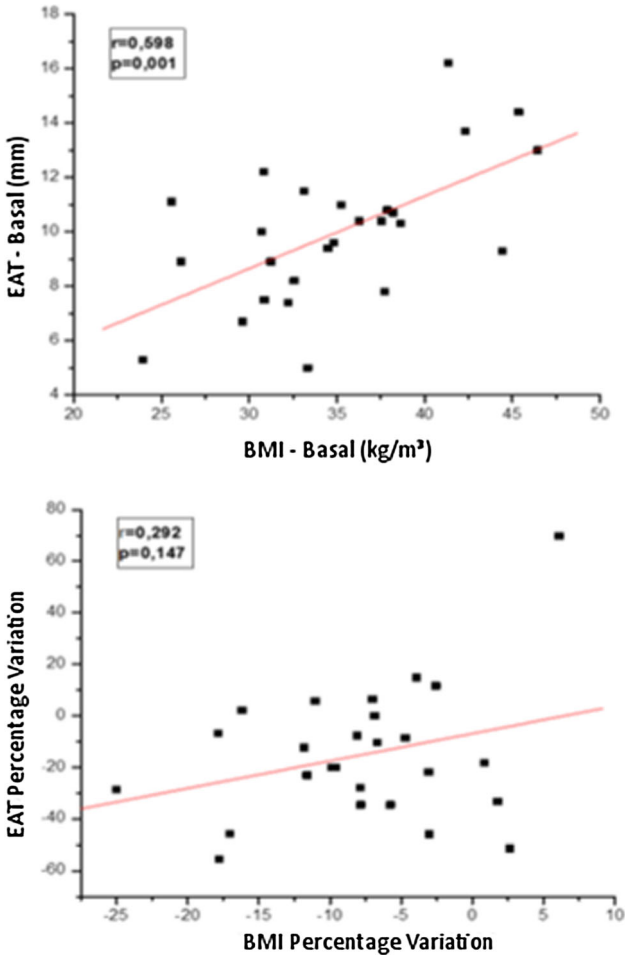

Fig. 3 Correlation between basal body mass index (BMI) and the thickness of basal epicardial tissue (EAT) (*upper panel*), and between body mass index (BMI) percentage variation and EAT percentage variation after treatment (*lower panel*)

between EAT thickness percentage variation and that of HOMA-IR ($r = 0.360$; $p = 0.07$).

Discussion

This is the first study showing an organ–visceral fat-specific effect of a DPP-4 inhibitor. In fact, we found that sitagliptin added on metformin produced a significant and rapid reduction of EAT thickness in overweight/obese type 2 diabetic subjects. Remarkably, the reduction of EAT was more pronounced than changes in BMI and waist circumference and it nicely correlated with the percentage of visceral fat decrease. The effect of sitagliptin on EAT seemed to be independent of its beneficial effects on both glucose and lipid profiles.

Epicardial fat is a marker of visceral fat. It has been also demonstrated to be an independent predictor of metabolic risk [26, 27]. EAT thickness is greater in subjects with impaired fasting glucose [28] and insulin resistance [29]. Interestingly, a thicker EAT has been observed in type 1 diabetes mellitus patients regardless of overweight [30]. Given its easy measurability and good reproducibility, EAT thickness is becoming a new therapeutic target during interventions targeting, directly or indirectly, the adipose tissue [1, 4].

Nevertheless, the effect of a DPP4 inhibitor on EAT was unexplored. The mechanism behind the effect of sitagliptin on EAT is unknown. As our patients were started on a dietary plan and lost weight, it would be intuitive to affirm that EAT reduction was reflecting the BMI reduction. A recent meta-analysis demonstrated that significant EAT reduction can be achieved with diet and bariatric surgery [31]. In some, but not all diet-based interventions, EAT reduction correlated with BMI reduction [31]. On the contrary, in our study, BMI reduction did not correlate with the decrease of EAT after 24 weeks of treatment. Our results are more consistent with earlier data by Iacobellis et al. showing that EAT decrease was higher and faster than BMI and waist circumference changes in obese subjects undergoing a very low calorie diet [17]. Our study confirmed that EAT is rather a marker of visceral fat, than overall adiposity, indicated by the BMI. It is plausible to affirm that the global body fat reduction and amelioration of the metabolic profile contributed to the EAT shrinkage on sitagliptin.

However, our data suggest that changes in EAT may be attributed to an exclusive, at least partially, effect of sitagliptin. This hypothesis may be supported by some previous observations. Sitagliptin reduced hepatic steatosis [32, 33], which is closely linked to epicardial fat, as recently reported [34]. Furthermore, GLP-1 receptor expression in adipose tissue has been established [35] and agonists of this

receptor have recently been shown to induce short term, noticeable, and significant EAT thickness reduction in type 2 diabetes patients [36], suggesting that a prolonged half-life of GLP-1 mediated by the inhibition of DPP-4 bears an important influence on the adipose reduction of this tissue.

Moreover, it has been demonstrated that inflammatory cytokine production and particularly macrophage infiltration are higher in EAT than in subcutaneous adipose tissue [37]. Interestingly, a decrease in inflammatory macrophage accumulation has been observed in adipose tissue and atherosclerotic lesions following treatment with DPP-4 inhibitors [38, 39]. It is thus possible to suggest that sitagliptin might exert an anti-inflammatory effect on EAT as recently found with other anti-inflammatory drugs [40, 41].

Another mechanism that may help elucidate the added effect of sitagliptin on visceral fat, and on EAT especially, is the fact that DPP-4 is considered an adipocytokine mainly expressed in visceral adipose tissue [42]. Evidence suggests that DPP-4 exerts a paracrine effect that hinders phosphorylation of the phosphatidylinositol 3-kinase (PI3K/Akt) signaling pathway, thus favoring the genesis and proliferation of large and immature adipocytes [42]. Blocking DPP-4 with sitagliptin, therefore, diminishes the proliferation of this type of adipocyte and favors the emergence of small and mature adiponectin-producing adipocytes [43].

Our results are in agreement with the emerging use of EAT as therapeutic target and marker of visceral fat changes. EAT is a modifiable risk factor and can be tracked with imaging methods. Waist circumference constitutes the most economic and practical marker of visceral adiposity. However, previous studies showed only a smaller change in waist circumference when compared to the percentage of change of EAT thickness. This might be explained by the moderate sensitivity and specificity of waist circumference as a marker of visceral adiposity, whereas echocardiographic assessment of epicardial fat provides a sensitive and specific measure of a true depot of visceral adiposity, thus circumventing the confusion elicited by subcutaneous abdominal fat when measuring waist circumference [17].

Our study showed for the first time that the addition of sitagliptin produced a significant reduction of EAT, marker of organ-specific visceral fat in overweight/obese individuals with type 2 diabetes inadequately controlled with metformin. EAT is a modifiable risk factor and a no invasive target of pharmaceuticals modulating the fat.

Study limitations

While our study provides novel findings, it is necessary to acknowledge some limitations. Although large enough to detect statistically significant differences both before and after treatment, the sample size was relatively small. However, previous interventional studies were able to appreciate statistically significant changes in EAT with similar sample size [36]. This can be attributed to the fast metabolism and high responsiveness of EAT [6]. We cannot rule out a potential confounding effect of lifestyle changes on EAT and the other variables. It would have been useful, therefore, to have a control group to monitor changes in lifestyle alone, without sitagliptin. Instead, patients were simply provided with lifestyle counseling rather than started on intense exercise or low calorie diet programs that could have affected the study variables. Inspired by the preliminary findings of this pilot, a larger size study will certainly include a multivariate analysis of the effect of sitagliptin on EAT. Total body fat and visceral fat were not estimated by dual-energy X-ray absorptiometry (DEXA), or computed tomography, but by BIA; although we recognize that BIA is not the gold standard technique, it is certainly no invasive, practical, affordable, and accurate [44]. Moreover, body fat composition analysis was not the primary endpoint of this pilot study.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts to disclose.

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