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ORIGINAL ARTICLE

Short-term effects of glucagon-like peptide 1 (GLP-1) receptor agonists on fat distribution in patients with type 2 diabetes mellitus: an ultrasonography study

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Abstract
Aims Glucagon-like peptide 1 receptor agonists (GLP-1 RA) induce weight loss and reduction in adipose tissue, but the effects of GLP-1 RA on the distribution of fat deposits have been poorly investigated.
Methods In 25 patients with type 2 diabetes (16 females and 9 males, mean age 63.5 ± 8.8 years), treated with GLP-1 RA (exenatide, n. 12; liraglutide, n.13), both before and 3 months after starting treatment, an abdominal ultrasonographic scan, with Doppler of renal arteries, and echocardiography were performed. Subcutaneous fat width (peri-umbilical and sub-xiphoid), deep fat deposits (pre-aortic, peri-renal, and epicardial), and renal resistive index (RI) were evaluated.
Results GLP-1 RA induced highly significant ($p < 0.001$) decrease in BMI and in fat thickness at all the assessed sites, without differences between exenatide and liraglutide treatment. A slight decrease in RI ($p = 0.055$) was also found. The percent changes of fat thickness was different between sites ($p < 0.025$), and the changes in subcutaneous deposits showed no significant correlation ($p = 0.064$) with those of deep fat deposits.
Conclusions A short course of treatment with GLP-1 RA, besides weight loss, induces a redistribution of adipose tissue deposits, possibly contributing to a better cardiovascular risk profile in patients with type 2 diabetes mellitus.

Keywords Glucagon-like peptide 1 receptor agonists · Subcutaneous fat · Deep fat · Abdominal ultrasonography · Echocardiography · Type 2 diabetes

Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1 RA) are recently introduced drugs for treatment of patients with type 2 diabetes mellitus. These analogues of the glucagon-like peptide-1 (GLP-1) incretin stimulate glucose-dependent insulin secretion induced by food ingestion and suppress inappropriately elevated glucagon secretion, thereby improving glucose homeostasis. Moreover, they show a protective effect on pancreatic beta cell mass. In addition, these drugs delay gastric empting and reduce food intake, which in turn promotes a progressive and sustained weight loss. This loss results from a reduction in fat mass rather than lean mass [1] which starts shortly after the beginning of treatment with either exenatide [2, 3] or liraglutide [1, 4]. According to a meta-analysis of randomized controlled trials, the extent of weight decrease averages 2.9 kg, with no significant difference between exenatide and liraglutide treatments [5].

Interestingly, a weight loss of such moderate entity is not unimportant. It has been shown that significant health benefits (blood pressure reduction, lipid profile

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improvement) can be achieved [6] even with modest weight reduction. In addition, GLP-1 receptor agonists induce a preferential decrease in visceral fat [7], which is characterized by proinflammatory properties. Indeed, adipose tissue is made up of distinct components with different metabolic activities, function, and health impact. For instance, visceral fat levels seem to predict the risk of cardiovascular disease better than crude anthropometric indexes as BMI or waist circumference [8].

For this reason, it should be stressed how imaging studies are highly valuable tools to investigate fat mass deposits since they allow to study not only the entity, but also the distribution of adipose tissue. It is well known that the most accurate evaluation of fat tissue deposits at a particular site is acquired through computed tomography (CT) and nuclear magnetic resonance (NMR) techniques. Ultrasonography (US) is also a valuable tool to explore several superficial and deep sites of adipose tissue deposits. However, differently from CT and NMR, US is especially useful to investigate the changes of fat deposits over time [9] because it does not imply radiation exposure is inexpensive, readily available, rather accurate and reproducible. Through renal Doppler US, it is also possible to assess the renal resistive index (RI), a measurement of renal vascular resistance which reflects systemic vascular involvement [10].

In this study, we have employed US to investigate the short-term effects of incretin therapy on the extent and distribution of adipose tissue deposits. Thus, we have measured the changes in the fat thickness of several subcutaneous and visceral fat deposits, as well as in the RI, in a group of patients with type 2 diabetes mellitus treated for 3 months with either exenatide or liraglutide according to the current Italian guidelines [11].

Materials and methods

We investigated 27 patients with type 2 diabetes mellitus, consecutively recruited, who started assuming therapy with GLP-1 receptor agonists, according to the current guidelines from Italian Public Health System Authority. All patients gave their informed consent, and the study was approved by the local ethics committee. All patients had poor metabolic control of diabetes, despite being treated with metformin at the maximal tolerated dose. One patient discontinued exenatide treatment because of intestinal side effects (nausea and vomiting), and another patient treated with liraglutide was lost at follow-up. Thus, the final investigated patient group included 25 subjects (16 females and 9 males, mean age 63.5 $\pm$ 8.8 years), who were treated subcutaneously either with exenatide (12 patients) or with liraglutide (13 patients). Patients taking exenatide were initially treated with 5.0 mcg twice daily for the first month and with 10 mcg BID thereafter. Liraglutide therapy was administered at the dose of 1.2 mg once a day.

Anthropometric parameters (BMI, waist circumference), HbA1c, creatinine for the eGFR estimate through the CKD-EPI equation [12], and lipid profile (including total, HDL-, LDL-cholesterol and triglyceride levels) were evaluated, before and after treatment, in all patients. Moreover, in all subjects, fat thickness was measured by US scans at several sites of peripheral and central fat deposits, both before and 3 months after starting GLP-1 receptor agonists treatment. In more detail, subcutaneous fat width was investigated with standard technique in the peri-umbilical (peri-umbilical fat—PUF) and sub-xiphoid (sub-xiphoid fat—SXF) region, whereas deep abdominal fat deposits were determined by scanning the peri-renal (peri-renal fat—PRF) and pre-aortic (pre-aortic fat—PAF) regions by the same well-trained operator, who also measured the RI of renal arteries by Doppler US. Epicardial fat (EpiF) thickness was measured by another specifically experienced sonographer. Both operators were blinded to the patients' data. All the abdominal measurements were made in the morning after an overnight fast by utilizing a Esaote Technos ultrasound scanner. For the investigation of subcutaneous fat pads, patients were asked to hold their breath (in the mid-expiratory phase) while the probe just touched the skin, to prevent compression. Through a longitudinal scan from the xiphoid process to the navel along the linea alba, fat thickness was measured at 5 cm from the umbilicus on the xiphoid–umbilical line and just below the xiphoid process, utilizing a linear probe (8–12.5 MHz). The probe was kept perpendicular to the skin of the upper median abdomen, and almost parallel to the surface of the liver with the convex probe (3.5–5 MHz). The peri-renal and pre-aortic fat thickness was measured with a 3.5–5 MHz convex probe. For peri-renal fat, longitudinal scanning was performed and the probe was slowly moved laterally until the optimal position was found, at which the surface of the kidney was almost parallel to the skin. Then, the thickness of fat was measured from the inner side of the abdominal musculature to the surface of the kidney, and the average of both sides was defined as fat width at that site. For pre-aortic fat thickness, in a transverse abdominal scan just above the umbilicus level, the width of the layer between the internal face of the abdominal muscle and the anterior wall of the aorta was measured [13–15]. The RI was calculated according to the formula $RI = S-D/S$, where S is the height of the systolic peak and D is the height of the end diastolic trough, as previously reported [16]. Epicardial fat was assessed with standard technique by a Esaote MyLab 30 instrument, equipped with a 2.5–3.5 MHz sectorial probe, on the free wall of right ventricle from both parasternal long- and short-axis views, and the average value was considered [17]. The within-

operator variability demonstrated a very high repeatability of the methods, as previously reported [18].

Statistical analysis

For all the parameters, the baseline values were compared to those observed after 3 months of incretin therapy by Wilcoxon's signed-rank test for repeated measurements on the same subject. A more robust standard *t* test for paired samples was applied as well. The level of significance was set at alpha = 0.05. Since the variance of the populations was not known, a Fisher's test for equality of variances was performed prior to each *t* test and the estimate of the variance population was chosen accordingly. The percent changes were also compared by Wilcoxon's test.

To determine similar patterns in the variation of fat thickness among patients, a hierarchical clustering algorithm based on ward's minimum variance method, as an exploratory technique, was employed. Such an analysis provides a hierarchy of clusters of patients, who are homogeneous inside each group for the considered variables (fat thickness changes). No structural variables such as age and BMI have been used in the clustering.

A canonical correlation analysis between subcutaneous and visceral fat variations was used to test if the overall changes of deep adipose tissue deposits somehow correlated with those of superficial fat stores.

Results

The mean serum HbA1c levels of the patient group decreased from 9.5 ± 1.2 to 8.2 ± 1.3 % (from 80.5 ± 13.0 to 66.3 ± 14.2 mmol/mol) ($p = 0.006$) after 3 months of incretin therapy. Lipid profile did not show significant variations (data not shown), except a decrease in the triglyceride levels (from 191.9 ± 74.1 to 157.3 ± 45.6 mg/dL; $p = 0.032$).

The main results concerning anthropometric and fat thickness variables are reported in Table 1 and Fig. 1. As shown, the employed drugs, besides loss of weight, BMI and waist circumference, induced a highly significant decrease in fat thickness at all the assessed sites, although the percent changes were not equal among different sites. The percent changes of SXF, PRF, and EpiF were significantly more marked than the percent changes of weight and BMI, as well as than PUF and PAF ($p < 0.025$ for all) (see Fig. 1). Since no significant difference was found between the 12 patients treated with exenatide and the 13 treated with liraglutide, their data were pooled in the subsequent analysis. A very slight decrease in renal RI (0.645 ± 0.030 vs. 0.642 ± 0.028, $p = 0.055$; $\Delta\ \% = -0.4 \pm 0.9$ %) was found, too, whereas no significant change during therapy was found in either creatinine (Cr) (0.9 ± 0.3 vs. 0.9 ± 0.2 mg/dL; $p = 0.686$) or eGFR (79.1 ± 19.7 vs. 78.7 ± 19.1 mL/min/1.73 m^2; $p = 0.903$) values. Both the parametric and the nonparametric tests gave analogous results.

The only variable showing gender-related difference in behavior was Cr ($p = 0.041$ by Wilcoxon's test). However, the cluster analysis on fat thickness changes showed that a subset of three patients had peculiar behavior, and after further scrutiny, they were considered as outliers. By performing again the tests for paired samples on the remaining patients, we confirmed the results of previous analysis, but Cr changes did not show significant difference between sexes.

Finally, when we tested the correlation between treatment-induced changes of the set of subcutaneous (PUF and SXF) and deep (PRF, PAF, and EpiF) fat deposits by canonical correlation analysis and Wilks' Lambda test, we found a value of 0.064, which implies that the changes of superficial and deep adipose tissue stores were not significantly correlated.

Discussion

Our short-term results show that the weight loss induced by GLP-1 receptor agonists reflects a significant decrease in

Table 1 Clinical and ultrasonography parameters

	Basal	3 months	*p**	Δ %
Body mass index (Kg/m^2)	35.2 ± 4.8	33.7 ± 4.6	<0.001	-4.4 ± 3.1
Weight (Kg)	89.4 ± 12.4	85.9 ± 12.9	<0.001	$-4,1 \pm 3.1$
Waist circumference (cm)	115.8 ± 11.4	113.2 ± 10.6	0.004	-2.1 ± 3.0
Fat thickness (mm)				
Peri-umbilical	56.5 ± 12.3	54.4 ± 12.1	<0.001	-3.9 ± 1.6
Sub-xyphoideal	21.4 ± 8.6	12.6 ± 8.5	<0.001	-9.0 ± 9.6
Pre-aortic	61.0 ± 13.9	58.8 ± 13.6	<0.001	-3.6 ± 1.8
Peri-renal	15.2 ± 4.9	14.2 ± 4.7	<0.001	-8.4 ± 5.5
Epicardial	9.4 ± 1.6	$8.0 \pm 1.\ 9$	0.003	-13.0 ± 23.2

* *p* by Wilcoxon's Rank test

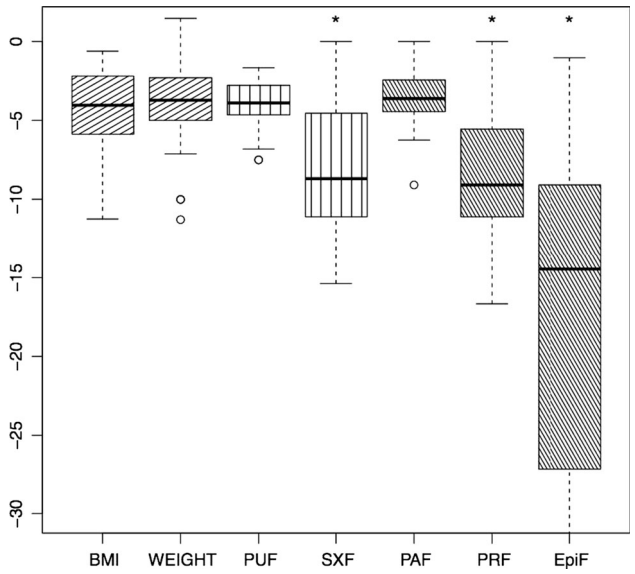

Fig. 1 The *box plots* report the percent changes of body mass index (BMI) and weight, faced to those of the fat thickness of different subcutaneous (*PUF* peri-umbilical fat, and *SXF* sub-xiphoid fat) and deep (*PAF* pre-aortic fat; *PRF* peri-renal fat; *EpiF* epicardial fat) adipose tissue deposits, following 3 months of therapy with GLP-1 receptor agonists. *$p \leq 0.02$ versus BMI, weight, PUF, PAF

fat thickness at different sites and that such changes do not homogeneously occur in different fat deposits throughout the body. A marginal effect on the RI in renal Doppler US was also found.

Also, in our sample of patients with type 2 diabetes mellitus treated with add-on incretin therapy, the loss of weight (and adipose tissue) occurred early after the beginning of therapy, according to previous reports [3, 4]. Long-term studies showed that such weight loss is then sustained, which could be a major breakthrough not only in the treatment of type 2 diabetes, but also potentially in the treatment of obesity [19–21].

Interestingly, US proved to be a valuable tool to monitor treatment-induced changes of adipose tissue storage, being radiation-free, low cost, widely diffused, and repeatable, which suggests its wider use in the common clinical practice [9, 14, 15]. In addition, since US may investigate the width of adipose tissue pads at several body sites, such a technique allowed us to investigate both subcutaneous and visceral fat deposits. For this reason, since at our knowledge no work has at present compared the effects of this therapy on different fat deposits, we investigated several storage sites indicated by previous literature reports [13–15, 17].

The latter point is crucial, at the light of many recent acquisitions on the so-called adipose organ. An increasingly accepted concept is that the latter is not homogeneous in terms of anatomy, metabolism, and physiological regulation [22, 23]. Accordingly, BMI and even waist circumference are increasingly regarded as rather gross and crude measurements of total adiposity, which could not adequately account for the morbidity and mortality risk associated with excess adiposity [8]. Instead, the regional distribution of fat stores appears to be more important than total adiposity, to induce the metabolic and vascular complications of obesity [17, 22–26]. Moreover, a recent paper in different African ethnic groups showed that abdominal fat distribution, as evaluated by US, accounted for the differences in insulin resistance and β-cells function [27].

In this view, our results are of particular interest since they show that even a short course of GLP-1 receptor agonist treatment results in a significant decrease not only of weight and BMI, but also of both subcutaneous and visceral fat deposits. The lack of significant difference between exenatide and liraglutide action seems to confirm that this is a "class" effect of these drugs [5]. Moreover, the changes of fat thickness did not show substantial gender-related differences. It should be particularly stressed how different deep deposits of adipose tissue shrank shortly after starting therapy, the decrease in certain fat pads being particularly pronounced (see Fig. 1). Differently from the changes of pre-aortic fat, particularly important, appear those observed in peri-renal and epicardial fat thickness, the percent change of which was much more marked than that of waist circumference. The latter is a simpler but crude predictor of cardiovascular risk, whose predictive ability in serial measurements has been recently questioned [28]. Our data emphasize how these deep fat deposits are rapidly affected during incretin-related weight loss [29], as after other interventions like diet [30] and exercise [31]. This let us hypothesize that the US technique could become a sensitive indicator and a useful tool for follow-up studies of the adiposopathic distribution of fat, the changes of which could influence cardiovascular risk. For this important reason, the implementation of carefully standardized US measurement protocols is crucial to obtain accurate and reliable results, particularly in longitudinal studies [32]. As a fact, visceral adipose tissue (particularly epicardial fat) seems to be metabolically more active and capable to secrete a wider arrange of cytokines than subcutaneous fat [33]. Looking at our results (see Fig. 1), and considering the loose relationships among the changes in thickness of subcutaneous and deep fat pads (and even among deep storage sites), it is apparent as GLP-1 receptor agonists not only decrease weight but also significantly influence fat distribution. Interestingly, at the light of the accumulating evidence on the beneficial cardiovascular effects of these drugs [34], the assessment of some deep fat deposits seems more predictive of increased cardiovascular risk, compared with that of other sites. Also, oxygen consumption capacity during exercise, which in turn reflects cardiorespiratory

fitness, appears to be associated to intra-abdominal fat accumulation in patients with type 2 diabetes [35]. Our finding of a slight and marginally significant reduction in the renal RI, with unchanged eGFR, should also be worth to be mentioned, since this index of renal vascular resistance was reported to be higher in patients with diabetes [10, 16].

In conclusion, our data demonstrated that even a short course of treatment with GLP-1 receptor agonists, besides weight loss, induces a redistribution of adipose tissue deposits, possibly contributing to a better cardiovascular risk profile, in patients with type 2 diabetes mellitus.

Conflict of interest No potential conflicts of interest relevant to this article were reported.

Ethical standard The protocol was approved by the Ethical Committee of Policlinico Umberto I Hospital, Sapienza University of Rome.

Human and animal rights disclosure All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5).

Informed consent disclosure Informed consent was obtained from all patients for being included in the study.

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