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Effect of Liraglutide in Different Abdominal Fat Layers Measured by Ultrasound: The Importance of Perirenal Fat Reduction

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Keywords
Pharmacological treatment · Abdominal fat · Ultrasound · Preperitoneal fat · Omental fat · Perirenal fat · Cardiometabolic risk

Abstract

Introduction: Ultrasonography (US) in patients with obesity allows us to measure different layers of abdominal fat (superficial subcutaneous, deep subcutaneous, preperitoneal, omental, and perirenal), not assessable by DEXA or CT scan. Omental and perirenal fat depots are considered predictors of metabolic complications. Liraglutide is particularly effective in reducing weight in patients with insulin-resistance, but its direct impact on each abdominal fat layer is unknown. ***Methods:*** We measured, at the L4 level, all 5 abdominal fat depots in 860 patients with obesity (72.8% women, mean age 56.6 ± 1.5 years, BMI 34.4 ± 4.7 kg/m^2, body fat 47 ± 2%, abdominal circumference 105.8 ± 3 cm), before and after 6 months of liraglutide treatment. Laboratory tests for glucose, insulin, and lipid profile were routinely done. T-student was used to compare intraindividual differences. ***Results:*** Weight loss was 7.5 ± 2.8 kg (7.96% from baseline), with no differences by sex/age/BMI. Greater loss was observed in patients with higher dosages and NAFLD. All US-measured fat layers showed a significant reduction ($p < 0.05$) at 6th months. Preperitoneal fat showed a −26 ± 5.5% reduction and 46% of the patients went below metabolic syndrome (MS) risk cut-off values. Omental fat was reduced by −17.8 ± 5% (67% of the patients below MS risk) and perirenal fat by −22.4 ± 4.4% (56% of the patients below MS). Both omental and perirenal fat reduction correlated with total and LDL cholesterol. Higher perirenal fat reduction (−28%) was seen among patients with obesity and hypertension. Perirenal fat also correlated with blood pressure reduction. ***Conclusion:*** Liraglutide induces greater fat loss in the layers involved with MS. However, the maximal reduction is seen at perirenal fat, which has been recently related with hypertension and could play an important role in modulating

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kidney's expansion and intraglomerular pressure. US is a reproducible clinical tool to assess pathologic fat depots in patients living with obesity.

Introduction

Ultrasonography (US) is an affordable technique that can be performed at the bedside of the patient, with an acceptable reproducibility, and is becoming a widely used complementary method of body composition in patients with obesity [1–3]. This procedure allows us to identify and measure 5 different stratified layers of abdominal fat (superficial subcutaneous, deep subcutaneous, preperitoneal, omental, and right perirenal) not assessable by DEXA or CT scan, considered the gold-standard imaging technique but only able to separate total subcutaneous from total visceral fat. If these anatomically separated fat depots have different metabolic functionality, is their modification after weight management, clinically relevant? [4].

Right below the dermis, superficial subcutaneous depot acts as a protective barrier against infections, whereas deep subcutaneous, highly vascularized and innervated, is considered the major adiponectin-secreting fat [5]. It is also the location where higher number of preadipocytes can be found [6] and where browning of adipose tissue takes place [7].

The 3rd consecutive measurable layer, preperitoneal fat, markedly hypoechoic, has been related to endometrial cancer risk [8], fatty liver disease [9], and cardiovascular risk both in adults [10] and adolescents [11]. Cut-off values associated with metabolic syndrome risk (11 mm [men] and 9 mm [women]) have been previously published in a Catalan cohort [1].

Deeper inside the abdominal cavity, intraperitoneal fat is composed of 2 coexisting fat tissues: mesenteric fat, rich in lymphoid and connective tissue that protects and fix abdominal organs to the dorsolumbar posterior wall (structural function) [12] and omental fat, surrounding bowels, with an important metabolic function [13, 14]. This intraperitoneal fat is usually (but wrongly) called "visceral fat," concept that should only refer to the fatty infiltration of solid organs such as liver, pancreas or kidney. It is known that omental fat interacts with upper gastrointestinal tract and its microbiota, inducing insulin-resistance [13], and is related with increased cardiovascular risk [14]. Specific cut-off measures for omental fat thickness of 37 mm (women) and 54 mm (men), for metabolic syndrome risk, have been proposed using ROC curves analysis [1].

Finally, in the retroperitoneal space, peri- and pararenal fat (spliced by a fascia) surround both kidneys [15]. Perirenal fat thickness has also been related to cardiovascular risk [1] (cut-off points 17 mm [women]/22.5 mm [men]). This relationship can be explained not only by differential adipokine expression but also by a mechanistic effect. A bigger perirenal fat depot may difficult a congestive kidney to expand, leading to increased intra-medullar pressure and consequent hypertension [16].

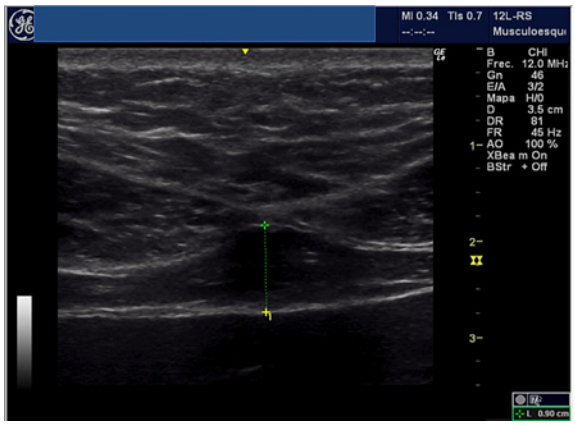
Liraglutide is an effective treatment to reduce weight in all patients living with obesity, but better results are reported in those with insulin-resistance and prediabetes [17]. We also know its beneficial effect in health status by improving lipid profile and reducing blood pressure [18]. Are these metabolic changes only related to weight loss? GLP1 receptor agonists seem to act, not only reducing food intake but also as a major insulin-sensitizing agent [19].

The specific effect of liraglutide treatment on those intraabdominal fat layers is, to this date, unknown. The aim of our study was to analyze the differential action of liraglutide in preperitoneal, omental, and perirenal and their relation with metabolic comorbidities in patients with obesity.

Material and Methods

Among n = 2,160 consecutive patients living with obesity attended at our EASO-COMM Unit (2021–2022), we analyzed data from n = 860 patients which fulfilled the inclusion/exclusion criteria.

- >18 years old (mean age 56.6 ± 1.5 years).
- Any gender (72.8% women and 27.2% men).
- BMI >30 kg/m^2.
- Included in a multidisciplinary weight-loss program with endocrinologist, dietitian, psychologist, and physical trainer follow-up for 6 months. All visits (twice monthly) should have been completed.
- Availability of all anthropometric data at baseline and 6 months.
- Availability of all laboratory testing at baseline and 6 months (lipid profile was used to classify patients with dyslipidemia. Fib-4 was used to classify NAFLD patients).
- Standardized ultrasound assessment of 5 consecutive abdominal fat layers should have been performed at baseline and 6 months.
- Different timeline blood pressure measures to diagnose hypertension.
- Availability of ultrasound assessment of fatty liver (elastography).



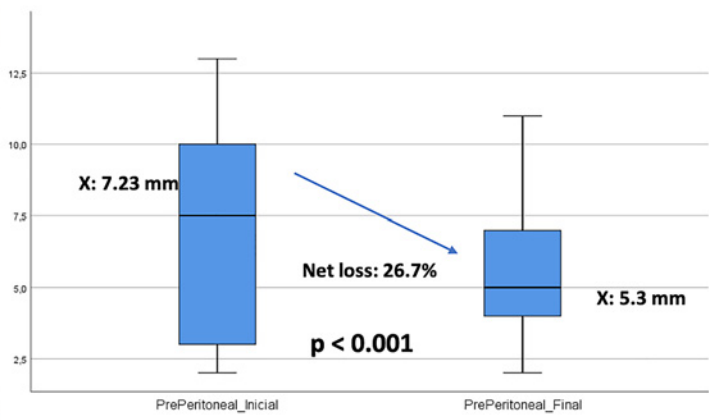


Fig. 1. Preperitoneal fat (baseline and 6 months).

- Baseline polysomnography records availability to diagnose obstructive apnea syndrome (OSAS).
- Treated with subcutaneous liraglutide for 6 months at maximum tolerated dosage (mean dosage was 2.3 ± 0.7 mg/day, and 79% of the patients were on >1.8 mg/day).

Anthropometric Data

Mean baseline BMI was 34.7 ± 0.8 kg/m^2. 56% lived with grade 1 obesity (BMI 30–35 kg/m^2), 33% grade 2 (BMI 35–40 kg/m^2), and 11% had BMI >40 kg/m^2. Mean abdominal perimeter (measured in cm, from top of both iliac crest) was 105.8 ± 3 cm at baseline. Measures >88 cm in female and >102 cm in male were considered as major criteria for metabolic syndrome definition [20]. Baseline total percentage body fat (measured by multipolar bioelectrical impedanciometry-BIA (Inbody 530©), using 15 different measures (30 s assessment) at 3 different frequencies (5–50-500 kHz) in left arm, right arm, trunk, left leg, and right leg, was 47 ± 2%.

Clinical Data

Prevalence of comorbidities were as follows: 23% patients were diagnosed of hypertension (17% treated with antihypertensive drugs), 21% lived with type 2 diabetes mellitus, 19% presented dyslipidemia (15% under cholesterol-lowering drugs), 14% fatty liver (NAFLD), and 7% were diagnosed of OSAS. 13% had 2 of these conditions together. Type 2 diabetes was diagnosed according to ADA guidelines [21]. Abnormal blood pressure was defined as a 3-times measured value >130 mm Hg for systolic and/or >85 mm Hg for diastolic blood pressure and dyslipidemia was defined as serum triglycerides (TGs) >150 mg/dL or HDL-cholesterol <40 mg/dL in men and <50 mg/dL in women [22]. NAFLD was defined as elevated liver enzymes in blood tests (Fib-4 >1.3), loss of differential ultrasound echogenicity between liver and right kidney parenchyma, and elastography >7.5 kPA [23]. Nocturnal polysomnography was used to diagnose patients with OSAS [24].

Laboratory Measurements

Measurements of fasting glucose, total cholesterol, HDL and LDL cholesterol, TGs, serum insulin (enzyme immunoanalysis ALINITY C reagents© (Abbot Diagnostics) with 3 µU/mL sensibility) were recorded at baseline and 6th month. HOMA index was also calculated and HOMA-IR >4.05 p90 was considered as marker of insulin-resistance [25].

Ultrasound Measurements

A General Electric Logic E© with a high frequency 12 MHz linear probe (superficial fat measures) and a 5 MHz convex probe (intraperitoneal and retroperitoneal fat measures) were used for the abdominal fat ultrasound assessment. Following a strict standardized protocol [1], thickness (mm) of (a) total subcutaneous tissue, divided into superficial and profound subcutaneous layers by the fascia superficialis (6), (b) preperitoneal fat, measured from the linea alba to the parietal layer of the peritoneum (Fig. 1), (c) intraperitoneal fat, including both omental and mesenteric fat and ranging from the peritoneal line to the anterior wall of the abdominal aorta (Fig. 2), and (d) perirenal fat (peri- and pararenal are measured together), starting from the renal cortex to the triangle formed by liver pole and abdominal wall musculature (for the right perirenal depot) (Fig. 3), were sequentially measured [2]. All these measures were obtained right at the exact point where the aorta bifurcates into the left and right common iliac arteries, position corresponding to the 4th lumbar vertebra level (L4), protocolized reference target when measuring visceral fat with CT or MRI [26]. As already described in previous work the correlation coefficient of the mean ultrasound distance assessed by two different sonographers at baseline is 0.94 ($p < 0.01$), with a mean difference 0.40 cm (SD 0.90), and a coefficient of variation of 5.40%, indicating good reproducibility of the ultrasound measurements [3].

Statistical Analysis

The statistical study was performed using the statistical software package SPSS version 19 [27]. Quantitative variables followed normal distribution. We compared 6th months versus baseline

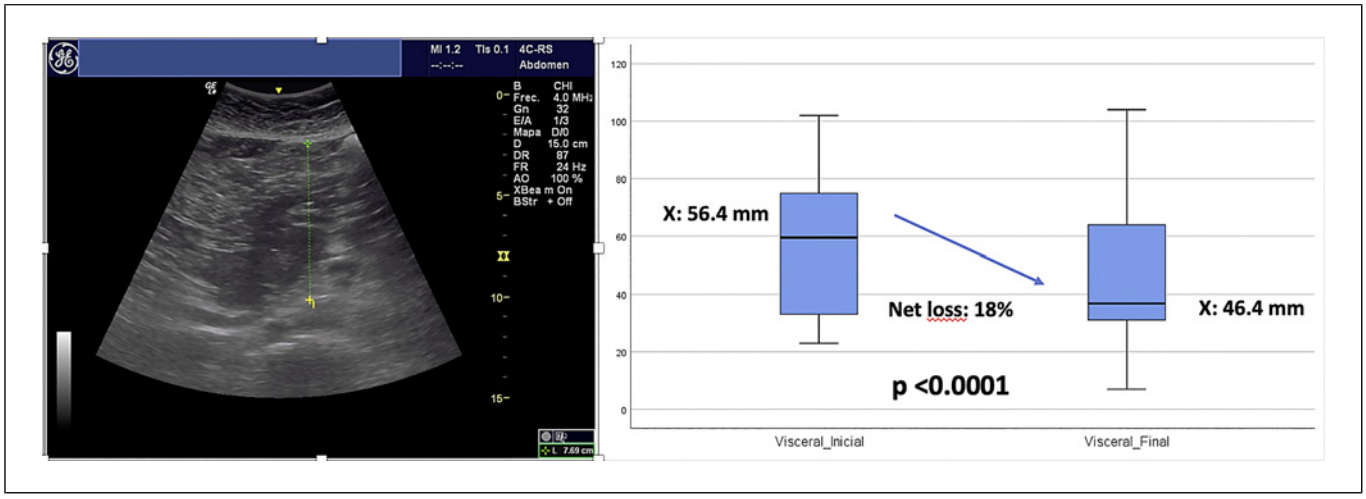


Fig. 2. Omental fat (baseline and 6 months).

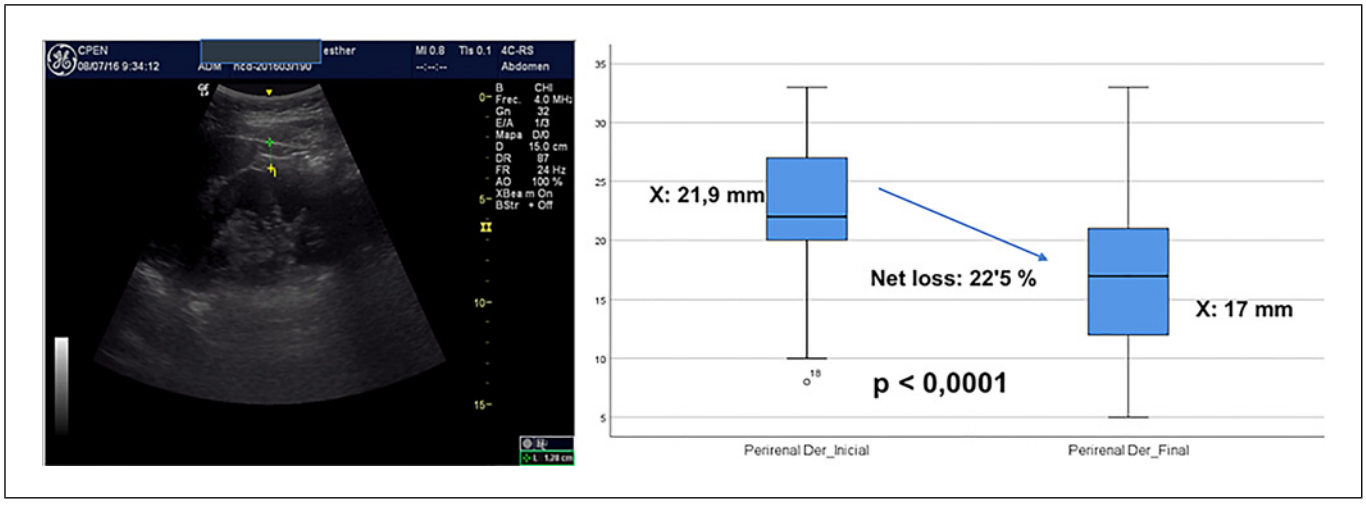


Fig. 3. Perirenal fat (baseline and 6 months).

intraindividual differences of their means and their confidence index (95%) with a Student's "*t*" test for independent related samples. Pearson's *r* test and multiple regression analysis (age, sex, initial BMI, and dosage) were used to find out correlations and eliminate confounding values, respectively.

Results

Average weight loss was 7.5 ± 2.8 kg (7.96% from the initial average weight) leading to BMI reduction of 2.7 ± 0.8 kg/m^2. Six percent of patients living with grade III obesity reached grade II. 17% of patients living with grade II obesity reached grade I ranges and 24% of grade I reached overweight values. Abdominal perimeter reduction was 10.14 ± 3.2 cm (9.6% loss) and % fat mass reduction 9.8 ± 2.8% from baseline ($p < 0.05$) (Table 1).

Greater weight loss was observed in patients with higher dosages (>1.8 mg/day) and patients with NAFLD (10.1 ± 2.4 kg) ($p < 0.05$). No differences by sex, age, initial BMI, or other baseline comorbidities, were observed.

Both BMI ($r = 0.477$; $p = 0.007$) and abdominal perimeter ($r = 0.590$ and $p = 0.043$) correlated with omental fat layer variation. Preperitoneal fat depot correlated with BIA-measured percentage of fat ($r = 0.768$ and $p = 0.002$).

Table 1. Anthropometric data, baseline and 6th-month follow-up

	Initial	Final	Difference	*p* value
Weight	94.2±17.3 kg	86.7±16.9 kg	7.5±2.8 kg (7.96%)	*<0.0001*
BMI	34.4±4.7 kg/m^2	31.7±5.1 kg/m^2	2.7±0.8 kg/m^2 (7.84%)	*<0.0001*
Abd circumference	105.8±3 cm	95.6±3.6 cm	10.1±3.2 cm	*<0.0001*
Sup Subcut. (SS)	10.4±3.8 mm	8.5±2.4 mm	18.2±5.5%	*<0.004*
Deep Subcut. (DS)	15.5±5.3 mm	12.7±5.4 mm	18±4.6%	*<0.0001*
Preperitoneal (PP)	7.23±3.6 mm	5.3±2.4 mm	26±5.5%	*<0.0001*
Omental (OM)	56.4±22.9 mm	46.4±25.6 mm	17.8±5%	*<0.0001*
R Perirenal (RK)	21.9±7.3 mm	17±7.6 mm	22.4±4.4%	*<0.0001*

No correlations were found between subcutaneous or right perirenal fat layers and standard anthropometric measures.

We found significant differences ($p < 0.05$) between final and initial glucose, HOMA index, total cholesterol, and LDL levels. However, no differences of HDL or TG were seen. Baseline fat layers measurements were superficial subcutaneous 10.4 ± 3.8 mm; deep subcutaneous 15.5 ± 5.3 mm; preperitoneal 7.2 ± 3.6 mm; omental 56.4 ± 22.9 mm; right perirenal 21.9 ± 7.3 mm. All US-measured fat strata showed a statistically significant reduction ($p < 0.05$) at the end of the study (Table 1).

Subcutaneous fat thickness showed an average −18.2 ± 5.5% reduction in the superficial and −18 ± 4.6% reduction in the deeper stratus. No significant correlations were found when comparing superficial subcutaneous fat layer with glucose or lipid profile.

Preperitoneal fat thickness showed an average −26 ± 5.5% reduction and is inversely correlated with HDL-cholesterol ($r = -0.43$; $p = 0.045$). According to the metabolic syndrome cut-off risks, 46% of the patients achieved a preperitoneal fat thickness below <11 mm (men)/<9 mm (women).

Omental fat depot showed an average −17.8 ± 5% reduction of its thickness and 67% of the patients achieved a reduction below the proposed 54 (men)/37 mm (women) risk values for metabolic syndrome. Omental fat reduction was correlated with total ($r = 0.52$; $p = 0.013$), and LDL-cholesterol ($r = 0.48$; $p = 0.023$).

Perirenal fat thickness showed an average −22.4 ± 4.4% reduction and 56% of the patients went below the proposed <22 (men)/17 mm (women) risk values for metabolic syndrome. Perirenal fat layer reduction was also correlated with total ($r = 0.58$; $p = 0.05$) and LDL-cholesterol ($r = 0.62$; $p = 0.002$). A higher right perirenal fat reduction was seen in the hypertension subgroup (28.4 ± 3.8%). There was a correlation between right perirenal fat thickness and arterial hypertension ($r = 0.56$; $p = 0.05$).

Discussion

These are the first published results on the effect of a short-acting GLP1 analog on stratified abdominal fat depots. Using a protocolized ultrasound imaging approach, we found significant reductions of preperitoneal, omental, and perirenal fat, independently of age, initial BMI category or dosage titration.

Kidney's surrounding fat seems to be the most prominent target, specially, in those patients living together with obesity and hypertension (−28% perirenal fat reduction and 56% of patients reaching the cut-off level considered at risk for metabolic syndrome comorbidities [1]. Furthermore, significant correlation was found between perirenal fat thickness and arterial blood pressure, total and LDL-cholesterol levels (despite cholesterol-lowering and antihypertensive drugs being used in those patients). The kidney involvement in metabolic and cardiovascular risk has become a breakthrough topic since the appearance of sodium-glucose cotransporter inhibitors iSLGT2 as antidiabetic drugs [28]. They have been recently approved in the treatment of renal impairment and cardiac failure [29] and many mechanisms have been proposed to explain its capacity in preventing major cardiovascular events, most of them related with natriuresis and proximal tubular changes [30]. The concept of "fat kidney" has emerged with MRI measures of renal fat infiltration, particularly in sinus [31]. But little is known about the relationship between perirenal fat and cardiovascular risk. Its relationship with intima-media thickness and pericardial fat [32] has been pointed out and is considered a marker of subclinical atherosclerosis [33].

How perirenal fat can interact and modulate blood pressure control? It has been postulated that a bigger perirenal fat depot may difficult a congestive kidney to expand, leading to increased intra-medullar pressure and consequent hypertension [34]. May GLP1 analogs

treatment be useful in preventing this "tamponade syndrome" [16]? Could this mechanistic hypothesis partially explain blood pressure improvement after liraglutide treatment observed in previous trials?

However, perirenal (retroperitoneal) fat only account for a small proportion of the observed 10% global loss of adiposity or −10 cm abdominal circumference reduction. These changes can be mainly explained by preperitoneal (−26%) and omental (−17.8%) fat layers reductions (Table 1).

These strata, both related with insulin-resistance comorbidities, share the intraperitoneal space and are included in the classic concept of "visceral" obesity when DEXA scan or CT imaging are used as imaging techniques [26]. In previous studies, preperitoneal fat has already been linked with NAFLD (9) or intima-media thickness [11] in patients with high cardiovascular risk [10]. In our study, despite a significant number of patients were already under cholesterol-lowering therapies, we also found an inverse correlation between HDL levels and preperitoneal fat layer, enhancing the idea of its relationship with increased cardiovascular risk.

Omental fat is known to induce insulin-resistance through a deleterious adipokine secretion profile [5] and is linked with cardiovascular morbidities [13]. Our study confirms previously published correlations with some of the most important cardiovascular markers: BMI, abdominal perimeter, glucose or total, and LDL-cholesterol levels [1].

Our study has some important limitations: it is a retrospective study with unblinded treatment and lacks a placebo matched (diet only) control group. Our aim was to compare the effect of liraglutide on the same patient, rather than comparing different treatment regimes. Further randomized control trials with a diet-only arm, would be desirable.

Our patients were strictly followed in a specialized obesity unit, with frequent nutritional and physical exercise assessment. Would the results be different in a less intensive weight-management approach? Almost 25% of the included patients had metabolic comorbidities (type 2 diabetes, hypertension, and/or dyslipidemia), would the results be different in non-metabolic "healthy" individuals with obesity?

Despite these limitations, this real-life clinical setting allowed us to deal with more patients and also enhances the reproducibility of the US-measurements. We are deeply convinced that the use of ultrasound in abdominal fat layers assessment can be a valuable tool to follow-up the efficacy of weight-loss therapies. It gives the healthcare professional a metabolic and cardiovascular perspective of obesity, and it can also be used as a powerful pedagogic tool (images) to explain the meaning of visceral adiposity to our patients.

Conclusion

Liraglutide treatment shows a significant reduction of perirenal fat, allowing kidney's expansion and reducing intraglomerular pressure. This is a novel proposed mechanistic effect (congestive kidney) to explain obesity-related hypertension, never studied after GLP1 analogs treatment, which may help understand its cardiovascular beneficial effects. The use of ultrasound in the assessment of abdominal fat depots has shown to be a useful clinical tool to assess pharmacological efficacy in obesity management programs.

Statement of Ethics

This study was presented at the hospital Ethics Committee (No. 2019-000979-16). Approval was granted as an observational study using retrospective data of common clinical practice (informed consent signed at first-visit). All individual patient data have been anonymized.

Conflict of Interest Statement

All the authors have declared not having any conflict of interest and send the form to the corresponding author.

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Author Contributions

Guillem Cuatrecasas, Pilar Garcia-Lorda, Elena M. Marron, and Francisco De Cabo: design and statistical analysis. Guillem Cuatrecasas, Marta Calbo, Ioana Patrascioiu, Camila Benito, Gabriel Cuatrecasas, Inaki Marina, and Silvana Di Gregorio: writing. Marta Calbo, Olga Rossell, Laia Dachs, Gerardo Aguilar, Maria-José Coves, Sonia March, Mariona Balfegó, Inaki Marina, Gabriel Cuatrecasas, and Silvana Di Gregorio: clinical data. Francisco De Cabo, Marta Calbo, Olga Rossell, and Laia Dachs: ultrasound measurements.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1 Cuatrecasas G, de Cabo F, Coves MJ, Patrascioiu I, Aguilar G, March S, et al. Ultrasound measures of abdominal fat layers correlate with metabolic syndrome features in patients with obesity. Obes Sci Pract. 2020;6(6):660–7. https://doi.org/10.1002/osp4.453

2 Azzi AJ, Lafrenière AS, Gilardino M, Hemmerling T. Ultrasonography technique in abdominal subcutaneous adipose tissue measurement: a systematic review. J Ultrasound Med. 2019;38(4):877–88. https://doi.org/10.1002/jum.14789

3 Stolk RP, Wink O, Zelissen PM, Meijer R, van Gils AP, Grobbee DE. Validity and reproducibility of ultrasonography for the measurement of intra-abdominal adipose tissue. Int J Obes Relat Metab Disord. 2001;25(9):1346–51. https://doi.org/10.1038/sj.ijo.0801734

4 Zwick RK, Guerrero-Juarez CF, Horsley V, Plikus MV. Anatomical, physiological, and functional diversity of adipose tissue. Cell Metab. 2018;27(1):68–83. https://doi.org/10.1016/j.cmet.2017.12.002

5 Schlecht I, Fischer B, Behrens G, Leitzmann MF. Relations of visceral and abdominal subcutaneous adipose tissue, body mass index, and waist circumference to serum concentrations of parameters of chronic inflammation. Obes Facts. 2016;9(3):144–57. https://doi.org/10.1159/000443691

6 Silva KR, Cortes I, Liechocki S, Carneiro JR, Souza AA, Borojevic R, et al. Characterization of stromal vascular fraction and adipose stem cells from subcutaneous, preperitoneal and visceral morbidly obese human adipose tissue depots. PLoS One. 2017;12(3):e0174115. https://doi.org/10.1371/journal.pone.0174115

7 Flynn A, Li Q, Panagia M, Abdelbaky A, MacNabb M, Samir A, et al. Contrast-enhanced ultrasound: a novel noninvasive, nonionizing method for the detection of Brown adipose tissue in humans. J Am Soc Echocardiogr. 2015;28(10):1247–54. https://doi.org/10.1016/j.echo.2015.06.014

8 Ciavattini A, Di Giuseppe J, Clemente N, Moriconi L, Carpini GD, Montik N, et al. Thickness of preperitoneal fat as a predictor of malignancy in overweight and obese women with endometrial polyps. Oncol Lett. 2016;11(3):2278–82. https://doi.org/10.3892/ol.2016.4186

9 Fukuda K, Seki Y, Ichihi M, Okada T, Hirata A, Kogita S, et al. Usefulness of ultrasonographic estimation of preperitoneal and subcutaneous fat thickness in the diagnosis of nonalcoholic fatty liver disease in diabetic patients. J Med Ultrason. 2015;42(3):357–63. https://doi.org/10.1007/s10396-015-0615-7

10 Bonjoch A, de Cabo F, Puig J, Perez-Alvarez N, Echeverria P, Clotet B, et al. Ultrasound-Based assessment of preperitoneal fat as a surrogate marker of cardiovascular risk: comparative study between people living with HIV and controls. AIDS Res Hum Retroviruses. 2022;38(3):222–7. https://doi.org/10.1089/AID.2021.0141

11 Hacihamdioğlu B, Öçal G, Berberoğlu M, Siklar Z, Fitöz S, Tutar E, et al. Preperitoneal fat tissue may be associated with arterial stiffness in obese adolescents. Ultrasound Med Biol. 2014;40(5):871–6. https://doi.org/10.1016/j.ultrasmedbio.2013.11.014

12 Buragina G, Magenta Biasina A, Carrafiello G. Clinical and radiological features of mesenteric panniculitis: a critical overview. Acta Biomed. 2019;90(4):411–22. https://doi.org/10.23750/abm.v90i4.7696

13 Uittenbogaart M, Leclercq WK, Bonouvrie D, Romeijn MM, Luijten AA, Olde Damink SW, et al. Diet-Induced alteration of microbiota and development of obesity, nonalcoholic fatty liver disease, and diabetes: study protocol of a prospective study. JMIR Res Protoc. 2019;8(6):e11553. https://doi.org/10.2196/11553

14 Shabestari AA, Bahrami-Motlagh H, Hosseinpanah F, Heidari K. Abdominal fat sonographic measurement compared to anthropometric indices for predicting the presence of coronary artery disease. J Ultrasound Med. 2013;32(11):1957–65. https://doi.org/10.7863/ultra.32.11.1957

15 Kawasaki S, Aoki K, Hasegawa O, Numata K, Tanaka K, Shibata N, et al. Sonographic evaluation of visceral fat by measuring para- and perirenal fat. J Clin Ultrasound. 2008;36(3):129–33. https://doi.org/10.1002/jcu.20426

16 Boorsma EM, Ter Maaten JM, Voors AA, van Veldhuisen DJ. Renal compression in heart failure: the renal tamponade hypothesis. JACC Heart Fail. 2022;10(3):175–83. https://doi.org/10.1016/j.jchf.2021.12.005

17 Le Roux CW, Astrup A, Fujioka K, Greenway F, Lau DCW, Van Gaal L, et al. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. Lancet. 2017;389(10077):1399–409. https://doi.org/10.1016/S0140-6736(17)30069-7

18 Helmstädter J, Frenis K, Filippou K, Grill A, Dib M, Kalinovic S, et al. Endothelial GLP-1 (Glucagon-Like peptide-1) receptor mediates cardiovascular protection by liraglutide in mice with experimental arterial hypertension. Arterioscler Thromb Vasc Biol. 2020;40(1):145–58. https://doi.org/10.1161/atv.0000615456.97862.30

19 Zhou JY, Poudel A, Welchko R, Mekala N, Chandramani-Shivalingappa P, Rosca MG, et al. Liraglutide improves insulin sensitivity in high fat diet induced diabetic mice through multiple pathways. Eur J Pharmacol. 2019;861:172594. https://doi.org/10.1016/j.ejphar.2019.172594

20 Beilby J. Definition of metabolic syndrome: Report of the National Heart, Lung, and blood institute/American heart association conference on scientific issues related to definition. Clin Biochem Rev. 2004;25(3):195–8.

21 American Diabetes Association. Classification and diagnosis of diabetes: *Standards of medical Care in diabetes-2018*. Diabetes Care. 2018;41(Suppl 1):S13–27. https://doi.org/10.2337/dc18-S002

22 American Diabetes Association. Cardiovascular disease and risk management: *Standards of medical Care in diabetes-2018*. Diabetes Care. 2018;41(Suppl 1):S86–104. https://doi.org/10.2337/dc18-S009

23 Wong VW, Chan WK, Chitturi S, Chawla Y, Dan YY, Duseja A, et al. Asia-pacific working party on non-alcoholic fatty liver disease guidelines 2017-Part 1: definition, risk factors and assessment. J Gastroenterol Hepatol. 2018;33(1):70–85. https://doi.org/10.1111/jgh.13857

24 Lee JJ, Sundar KM. Evaluation and management of adults with obstructive sleep apnea syndrome. Lung. 2021;199(2):87–101. https://doi.org/10.1007/s00408-021-00426-w

25 Gayoso-Diz P, Otero-González A, Rodriguez-Alvarez MX, Gude F, García F, De Francisco A, et al. Insulin resistance (HOMA-IR) cut-off values and the metabolic syndrome in a general adult population: effect of gender and age: EPIRCE cross-sectional study. BMC Endocr Disord. 2013;16:13–47.

26 Shen W, Wang ZM, Punyanita M, Lei J, Sinav A, Kral JG, et al. Adipose tissue quantification by imaging methods: a proposed classification. Obes Res. 2003;11(1):5–16. https://doi.org/10.1038/oby.2003.3

27 Park E, Cho M, Ki CS. Correct use of repeated measures analysis of variance. Korean J Lab Med. 2009;29:1–9. https://doi.org/10.3343/kjlm.2009.29.1.1

28 Tang H, Fang Z, Wang T, Cui W, Zhai S, Song Y. Meta-analysis of effects of sodium-glucose cotransporter 2 inhibitors on cardiovascular outcomes and all-cause mortality among patients with type 2 diabetes mellitus. Am J Cardiol. 2016;118(11):1774–80. https://doi.org/10.1016/j.amjcard.2016.08.061

29 Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383(15):1436–46. https://doi.org/10.1056/NEJMoa2024816

30 Petrie MC, Verma S, Docherty KF, Inzucchi SE, Anand I, Belohlávek J, et al. Effect of dapagliflozin on worsening heart failure and cardiovascular death in patients with heart failure with and without diabetes. JAMA. 2020;323(14):1353–68. https://doi.org/10.1001/jama.2020.1906

31 Gjela M, Askeland A, Frøkjær JB, Mellergaard M, Handberg A. MRI-based quantification of renal fat in obese individuals using different image analysis approaches. Abdom Radiol. 2022;47(10):3546–53. https://doi.org/10.1007/s00261-022-03603-4
32 López-Bermejo A, Prats-Puig A, Osiniri I, Martínez-Calcerrada JM, Bassols J. Perirenal and epicardial fat and their association with carotid intima-media thickness in children. Ann Pediatr Endocrinol Metab. 2019;24(4):220–5. https://doi.org/10.6065/apem.2019.24.4.220
33 Okeahialam BN, Sirisena AI, Ike EE, Chagok NM. Ultrasound assessed perirenal fat: an index of sub-clinical atherosclerosis. Am J Cardiovasc Dis. 2020;10(5):564–8.
34 Hall JE, do Carmo JM, da Silva AA, Wang Z, Hall ME. Obesity, kidney dysfunction and hypertension: mechanistic links. Nat Rev Nephrol. 2019;15(6):367–85. https://doi.org/10.1038/s41581-019-0145-4