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Cuatrecasas G, Calbo M, Rossell O, Dachs L, Aguilar-Soler G, Coves M-J, Patrascioiu I, Benito CE, March S, Balfegó M, Cuatrecasas G, Di Gregorio S, Marina I, Garcia-Lorda P, Munoz-Marron E, De Cabo F

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Effect of liraglutide in different abdominal fat layers measured by ultrasound. The importance of perirenal fat reduction.

Running title: *"perirenal and omental fat thickness reduction after liraglutide treatment".*

[1,2,3]Guillem Cuatrecasas, [2,3]Marta Calbo, [2,3]Olga Rossell, [2,3]Laia Dachs, [2,3]Gerardo Aguilar-Soler, [2,3]Maria-José Coves, [2,3]Ioana Patrascioiu, [2,3]Camila Eugenia Benito, [2,3] Sonia March, [1,2,3] Mariona Balfegó, [2,3,4]Gabriel Cuatrecasas, [2,3]Silvana Di Gregorio, [2,5]Inaki Marina, [6]Pilar Garcia-Lorda, [1,6]Elena Munoz-Marron, [7]Francisco De Cabo.

[1]Facultat Ciencies Salut, Open University Catalonia (UOC), Barcelona
[2]Obesity Unit, Clinica Sagrada Familia, Barcelona.
[3]CP endocrinologia SLP, Barcelona.
[4]EAP Sarrià, Barcelona.
[5]Hospital Viladecans.
[6] Cognitive NeuroLab, Barcelona.
[7]Ultrasound Department, Institut Guirado for Radiology, Barcelona

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Full correspondence address: Guillem Cuatrecasas, Director, CP Endocrinologia SLP, Barcelona 08037, Spain.
guillemcuatrecasas@gmail.com Phone: +34600550127

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Abstract

Introduction: Ultrasonography 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 intra-individual 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 6^{th} 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 Metabolic syndrome. However, the maximal reduction is seen at perirenal fat, which has been recently related with Hypertension and could play an important role in modulating kidney's expansion and intraglomerular pressure. US is a reproducible clinical tool to assess pathologic fat depots in patients living with Obesity.

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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 [1,2,3]. 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 adiponectine-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, Pre-peritoneal 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, intra-peritoneal fat is composed of 2 coexisting fat tissues: Mesenteric fat, rich in lymphoid and connective tissue that protects and fix abdominal organs to the dorso-lumbar 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 Para-renal 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 (GLP1a) seems to act, not only reducing food intake but also as a major insulin-sensitizing agent [19].
The specific effect of Liraglutide treatment on those intrabdominal 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=2160 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.

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- Availability of Ultrasound assessment of fatty liver (elastography).
- Baseline polysomnography records availability to diagnose 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 >1.8mg/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 sec. assessment) at 3 different frequencies (5-50-500kHz) 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 Obstructive apnea syndrome (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 >130mmHg for systolic and/or >85mmHg for diastolic blood pressure and Dyslipidemia was defined as serum triglycerides >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 (TC), HDL and LDL-cholesterol, triglycerides (TG), 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), was 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 (Figure 1), c) *intraperitoneal* fat, including both *omental* and *mesenteric* fat and ranging from the peritoneal line to the anterior wall of the abdominal aorta (Figure 2), and d) *perirenal* fat (*peri-* and *para-renal* are measured together), starting from the renal cortex to the triangle formed by liver pole and abdominal wall musculature (for the right *perirenal* depot) (Figure 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 vs baseline 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.

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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. 6% 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 $p=0.002$). 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, TC and LDL levels. However, no differences of HDL or TG were seen. Baseline fat layers measurements were Superficial subcutaneous 10.4±3.8mm; Deep subcutaneous 15.5±5.3mm; Preperitoneal 7.2±3.6mm; Omental 56.4±22.9mm; right Perirenal 21.9±7.3mm. 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) /37mm (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) /17mm (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 ($r=0.56$; $p=0.05$).

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Discussion:

These are the first published results on the effect of a short-acting GLP1 analogue 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 anti-hypertensive 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 analogues 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 intra-peritoneal 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.

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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 analogues treatment, which may help to understand its cardiovascular beneficial effects.
The use of ultrasound in the assessment of abdominal fat depots have shown to be a useful clinical tool to assess pharmacological efficacy in Obesity management programs.

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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 analisis.
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, Mº José Coves, Sonia March, Mariona Balfegó, Inaki Marina, Gabriel Cuatrecasas and Silvana Di Gregorio: Clinical data.
Francisco De Cabo, Marta Calbo, Olga Rossell, Laia Dachs: ultrasound measurements.

Data availability statement:
All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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Figures:

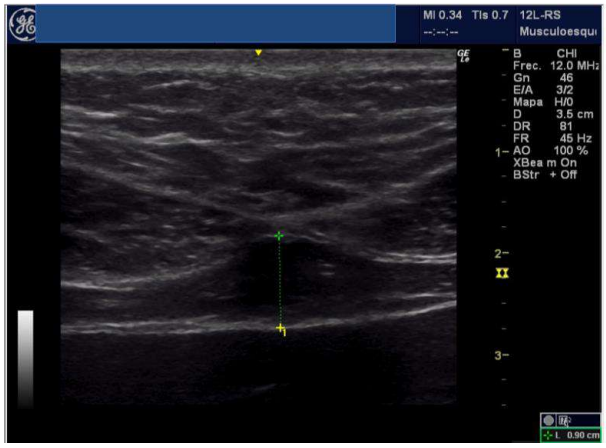
Figure 1: Preperitoneal fat (baseline and 6 month)

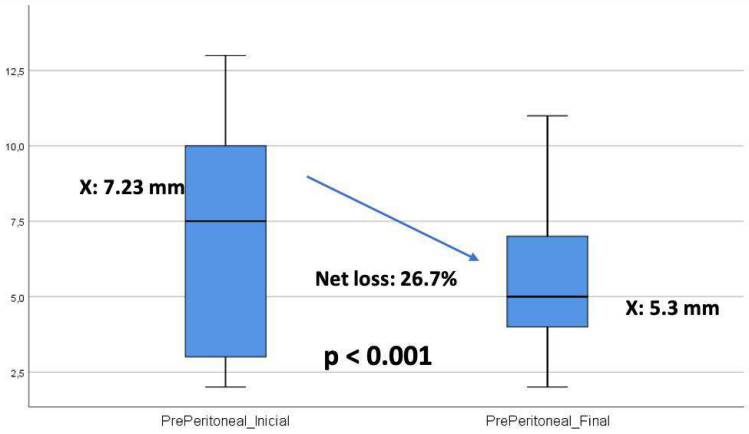
Figure 2: Omental fat (baseline and 6 month)

Figure 3: Perirenal fat (baseline and 6 month)

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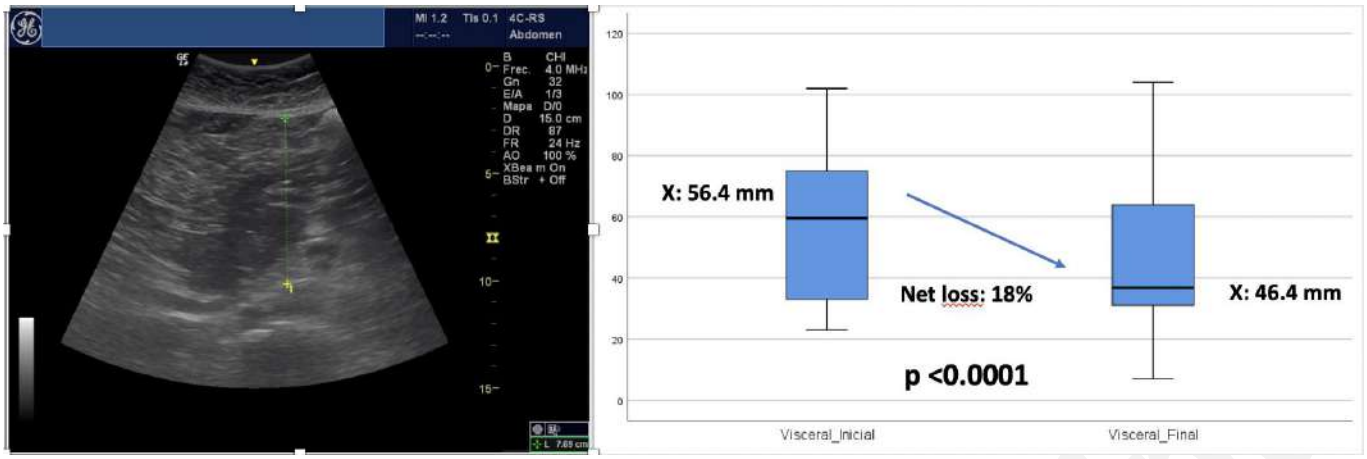
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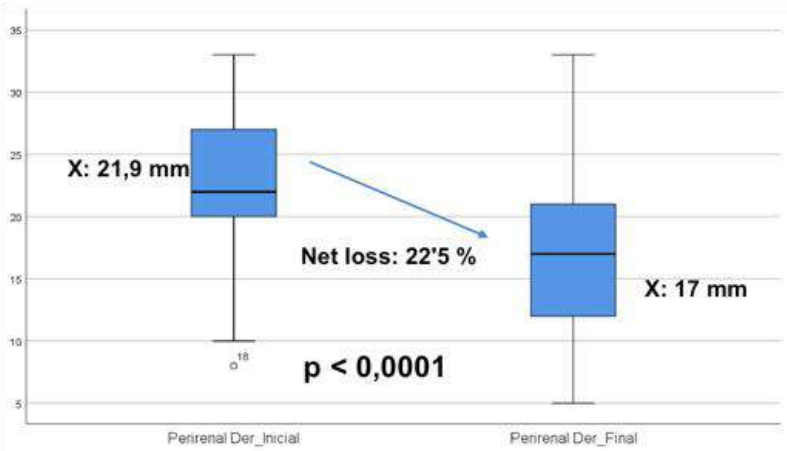
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	Initial	Final	Difference	*p*
Weight	94.2 ± 17.3 kg	86.7 ± 16.9 kg	7.5 ± 2.8 Kg (7.96 %)	*<0.0001*
BMI	34.4 ± 4.7 kg/m^2	31.7 ± 5.1 kg/m^2	2.7 ± 0.8 Kg/m^2 (7.84 %)	*<0.0001*
Abd circumference	105.8±3 cm	95.6±3.6 cm	10.1±3.2	*<0.0001*
Sup Subcut. (SS)	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 Perirrenal (RK)	21.9 ± 7.3 mm	17 ± 7.6 mm	22.4±4.4%	*<0.0001*

Table 1: Anthropometric Data, baseline and 6th month follow-up

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