International Journal of Obesity www.nature.com/ijo

ARTICLE

Bariatric Surgery

Visceral adipose tissue adiponectin predicts excess weight loss after bariatric surgery in females with severe obesity

Giulia Cantini[1], Giovanni Quartararo[2], Niccolò Ghezzi[2], Diego Assis Gonçalves[1,3], Laura Fei[1], Arianna Pia Propato[1], Luca Galtarossa[1], Marcello Lucchese[2], Mario Maggi[1] and Michaela Luconi[1]✉

OBJECTIVE: Bariatric surgery not always results in satisfactory excess weight loss (EWL) in severe obesity. Given the economic and clinical costs of bariatric surgery failure, defining predictors of successful EWL represents a relevant clinical issue for the health system to select patients benefiting from operation.
METHODS: By ELISA and Western blot analyses, we assessed the predicting value of pre-operative adiponectin (APN) locally produced in abdominal visceral (VAT) and subcutaneous (SAT) adipose tissue versus plasma levels as a novel sex-linked biomarker of EWL at different time points of follow up (6–24 months) after bariatric surgery in 43 patients (56% females) affected by severe obesity undergoing a small pilot observational study.
RESULTS: VAT-APN was lower in females and represented the only marker significantly correlated with EWL. In females, VAT-APN in the distribution upper quartile but not baseline BMI retained a statistically significant correlation with EWL at any time points (6–24 months) at multivariate analysis. The best VAT-APN cut-off value to predict 95% EWL at 12 months from surgery (98% accuracy, 100% sensitivity, 94% specificity, $p = 0.010$) was 5.1 µg/mg.
CONCLUSIONS: In this very preliminary study, APN in VAT rather than its circulating or subcutaneous levels predicts EWL after bariatric surgery as an independent factor in the female sex only, thus contributing to identify those patients who could much benefit from surgery.

International Journal of Obesity (2024) 48:247–253; https://doi.org/10.1038/s41366-023-01406-1

INTRODUCTION

The prevalence of severe obesity and its associated life-threatening comorbidities has exponentially increased worldwide in the last decades, also worriedly interesting paediatric ages [1]. Bariatric surgery should be considered as the elective strategy for patients with body mass index (BMI) ≥ 40 kg/m^2 or BMI ≥ 35–40 kg/m^2 associated with comorbidities, as it results in a rapid and important weight loss associated with a significant improvement of the comorbidities as type 2 diabetes, T2D [2] and a decrease in obesity-related long-term mortality [2–4]. A large Scandinavian population-based cohort study reported, however, that patients with severe obesity obtained a long-lasting reduction in the use of lipid-lowering and antidiabetic medications but only a transient effect for cardiovascular medications after bariatric surgery [5]. Indeed, the response to surgery is not always optimal resulting in insufficient weight loss (IWL) or weight regain (WR) even at early follow up [6]. Recent reviews evaluating the current knowledge about mechanisms and predictors of WR and IWL after bariatric surgery, came to the conclusion that these are still poorly characterized and need further investigation [7, 8]. Given the economic and clinical costs of failure of bariatric surgery in these patients, searching for predictors of successful and durable weight loss represents a relevant clinical issue for the health system [9].

Circulating levels of hormones involved in the control of energy homeostasis and metabolism, such as the gastric product, ghrelin, and the adipose tissue (AT) adipokines, leptin and adiponectin (APN), have been demonstrated to be associated with weight variations [10]. Both plasmatic ghrelin [11] and APN [10] have been suggestive as predictive of the weight loss and of the metabolic amelioration observed post-surgery. However, circulating levels of APN do not reflect the differences in the hormone production and functional significance at the level of different fat depots, being the abdominal visceral AT the most susceptible to the dysregulation occurring in obesity and the target of the main remodelling during weight loss. Local APN production in AT may represent a more penetrating and predictive marker of the effect of bariatric surgery, also reflecting potential differences between the two sexes.

Therefore, in the present paper, we assessed the putative value of pre-operative APN levels locally produced in visceral (VAT) and subcutaneous (SAT) AT, and compared it with APN plasma levels as sex-linked predictors of excess weight loss (EWL) reached after bariatric surgery.

[1]Department of Experimental and Clinical Biomedical Sciences "Mario Serio", Endocrinology Unit, University of Florence, 50139 Florence, Italy. [2]Department of Surgery, General and Bariatric Surgery Unit, Santa Maria Nuova Hospital, Piazza Santa Maria Nuova, 50122 Florence, Italy. [3]Department of Parasitology, Microbiology and Immunology, Federal University of Juiz de Fora, Juiz de Fora, Brazil. ✉email: michaela.luconi@unifi.it

Received: 25 July 2023 Revised: 14 October 2023 Accepted: 20 October 2023
Published online: 3 November 2023

Table 1. Adiponectin levels and weight data.

	TOT	F ($n = 24$)	M ($n = 17$)	*p*
APN VAT (μg/mg)	3.5[2.5–5.1]	3.2[2.4–5.1]	3.6[2.5–5.2]	0.771
APN SAT (μg/mg)	3.8[2.3–5.2]	3.6[1.9–5.7]	3.9[2.5–5.1]	0.696
APN serum (μg/ml)	8.7[5.7–12.5]	9.8[6.7–13.8]	6.3[3.9–11.2]	***0.045***
EWL 6 m (%)	58[47–70]	63[55–76]	45[33–57]	***0.004***
EWL12m (%)	73[63–83]	78[69–85]	63[52–77]	***0.003***
EWL 18 m (%)	83[72–90]	84[80–94]	74[58–85]	***0.036***
EWL 24 m (%)	82[72–93]	86[79–97]	73[52–90]	0.126
BMI 6 m (Kg/m^2)	33[30–37]	32[30–34]	35[34–41]	***0.007***
BMI 12 m (Kg/m^2)	31[28–33]	29[28–31]	34[31–37]	***0.003***
BMI 18 m (Kg/m^2)	29[27–31]	28[26–30]	31[29–33]	0.080
BMI 24 m (Kg/m^2)	28[26–31]	28[26–30]	30[28–34]	0.090

Data for the entire cohort (TOT) and after sex stratification (F, M) are reported as the median[IQR] values for adiponectin (APN) levels evaluated by ELISA in visceral (VAT) and subcutaneous (SAT) AT and in serum, as well as for EWL and BMI at 6, 12, 18 and 24 months of follow up after bariatric surgery. Statistically significant p values < 0.05 between distributions in females (F) and males (M) calculated with U Mann–Whitney's test are indicated in bold Italics.

METHODS

Patients, Study design and ethical approval

The study was performed on a series of patients suffering from severe obesity (Body Mass Index, BMI ≥ 35 kg/m^2 with comorbidities, or BMI ≥ 40 kg/m^2) referring to the Bariatric Surgery Unit at Santa Maria Nuova Hospital in Florence ($n = 43$). All patients enrolled underwent laparoscopic bariatric surgery and were followed for subsequent 24-month observation after surgery.

The study was approved by the Local Ethical Committee and Institutional Review Board (protocol number 83/13). All patients enrolled gave signed informed consent after receiving written and oral information on the study. Research has been performed in accordance with the Declaration of Helsinki. The manuscript follows the person first language guidelines for obesity.

The choice of surgery and type of laparoscopic bariatric technique (Anastomosis Gastric Bypass, Roux Y Bypass, and Sleeve Gastrectomy) was made by a team of specialists composed by a surgeon, an endocrinologist and a dietitian, depending on the overall evaluation of the patient's history.

All patients underwent a pre-surgery baseline visit (T0) at hospital admission before surgery, taking all anthropometric measures, together with blood samples drawn for routine biochemical analysis. At surgery, two small AT samples (1 cm^3) were taken from abdominal SAT and VAT, with no compromising of surgery. AT samples were snap frozen in liquid nitrogen and stored at −80 °C until use for protein extraction and analysis [12]. The follow-up evaluation was performed after 6, 12, 18 and 24 ± 2 months from surgery.

In 2 patients (1 F and 1 M), paired VAT and SAT levels of APN were not available. In 8 out of 43 patients, weight or waist circumference were not available at maximum two consecutive time points of the follow-up.

Biochemical and anthropometric measurements

1. Anthropometric measures: Height, weight, waist and hip circumference were measured for each subject at baseline and at all the follow up time points; body mass index (BMI) was calculated according to the formula BMI (Kg/m^2), EWL was calculated as: (Baseline Weight—Follow up Weight)/(Baseline Weight—Ideal Weight); Ideal Weight was considered for each patient as the weight corresponding to a BMI = 25 Kg/m^2.
2. Biochemical tests were performed on blood samples collected at baseline before surgery, after overnight fasting. Serum levels of fasting glucose, total cholesterol, HDL-cholesterol and triglycerides were measured using a colorimetric assay (Siemens Healthcare, Tarrytown, NY). LDL-cholesterol was calculated by Friedewald's formula for serum triglyceride levels <400 mg/dL. Insulin was evaluated by an electrochemiluminescence immunoassay (ECLIA, Roche Diagnostics, Mannheim, Germany) on a Cobas E601 analyzer (Roche Diagnostics). IR was estimated by the homeostasis model assessment of insulin resistance (HOMA-IR) index [Insulin (pmol/L) × Fasting blood glucose (mg/dL) / 22.5];
3. Min and Max blood pressure was measured at baseline.
4. Post-surgery complications were evaluated by the team of bariatric surgeons at each time point of the follow up, and classified as presence or absence.

Adiponectin measurement

ELISA. APN was measured by a specific ELISA kit (Sandwich Enzyme-Linked Immunosorbent Assay for Quantitative Detection of Human Adiponectin Concentrations in Cell Culture Supernatants, Serum, Plasma, Tissue Homogenates, catalogue # MBS824844, My Biosource Inc, San Diego, CA, USA) in both serum and in protein extracts from VAT and SAT, according to the manufacturer's instructions. APN was evaluated in 100 μl of serum drawn before surgery, while for intra-tissue measurement, 100 μg of protein extract obtained by homogenizer in RIPA buffer (20 mM Tris pH 7.4, 150 mM NaCl, 0.2 mM EDTA, 0.5% Triton-100, supplemented with 100× phosphatase inhibitor and 100x protease inhibitor, Sigma-Aldrich) and clarified by centrifugation (6000 rpm 10 min 4 °C), were analyzed. Sensitivity: the minimum detectable dose of Human APN is typically below 15 pg/ml; range of linearity: 62.5 pg/ml–4000 pg/ml.

Western blot semiquantitative analysis. Frozen AT samples were homogenized and extracted in RIPA buffer. Thirty micrograms of extracted proteins were separated by 4–20% reducing SDS-PAGE (Stain-free precasted gels, BIO-RAD Labs). An internal standard (IS) made of equal amount of proteins extracted from 3 SAT and 3 VAT specimens for a total of 30 μg of proteins was applied in all SDS-PAGE as an internal anchor. Total protein loading for each lane was evaluated by Stain-free technique (BIO-RAD Labs) before protein transfer to PVDF membranes. Membranes were probed with anti-APN primary antibody (Vinci Biochem) followed by peroxidase-conjugated secondary IgG [13]. Bound antibodies were revealed with ECL reagents (Immobilon, Merck Millipore). Image acquisition and densitometric analysis were performed with Quantity One software on a ChemiDoc XRS instrument (BIO-RAD Labs). All Western blots were repeated in at least three independent experiments. Semiquantitative APN expression was evaluated from Western blot after normalization of each lane for total protein loading and referred to IS expression taken as 1.

Statistical analysis

Data were expressed as mean ± SD or median [interquartile range, IQR]. Nonparametric U Mann–Whitney's test was used for comparisons of two sets of paired data and for independent data. A $P < 0.05$ value was used for statistical significance. Stepwise multiple linear regression was applied for multivariate analysis. Receiver operating characteristic

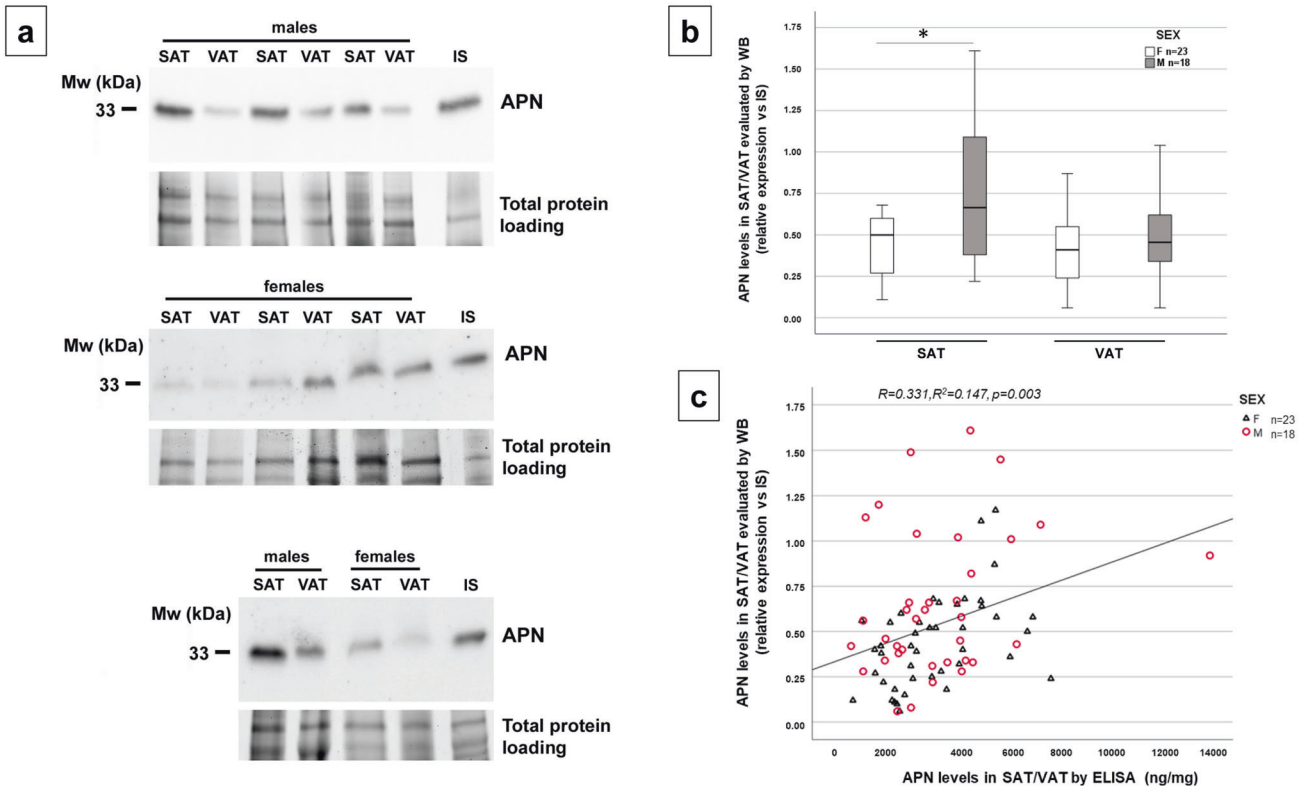

Fig. 1 APN protein expression in abdominal AT of patients with severe obesity: sex and depot differences. a Representative Western blot analysis of total protein extracts from SAT and VAT specimens of male and female patients with severe obesity shows a single band at the expected molecular weight, as revealed by the specific anti-APN antibody. An internal standard (IS) was run in all gels to enable semiquantitative relative expression of APN band intensity. Total protein loading for each lane as evaluated by Stain-free technique applied to Stain-free precasted gels (Biorad Labs). Molecular weight markers (MW in kDa) are indicated to left of the blot. **b** Box charts show the median[IQR] of semiquantitative APN levels, as evaluated in SAT and VAT protein samples evaluated by Western blot after normalization of each lane for total protein loading and referred to IS expression taken as 1. **c** Positive linear correlation between APN expression in AT (SAT and VAT) evaluated by relative semiquantitative WB analysis and by ELISA technique; females (triangle, F) and males (circle, M) are indicated.

(ROC) curve analysis for accuracy determination and all the other statistical analyses were performed on SPSS 28.0 for Windows (Chicago, USA).

RESULTS

Differences in the clinical profiles between sexes in patients affected by severe obesity

Forty-three patients affected by severe obesity and undergoing bariatric surgery at Santa Maria Nuova Hospital in Florence between 2017 and 2020 were enrolled in the study. Patients' characteristics at baseline before surgery are indicated in both the entire cohort and after stratification for sex (Table 1). Among the 24 females, 35% had T2D and 64% showed IR, while among the 19 males, 40% had T2D and 64% were insulin resistant. Anastomosis gastric bypass surgery technique was performed in 29% and 37%, Roux Y Bypass in 58% and 53%, and Sleeve Gastrectomy in 13% and 10% of the females and males, respectively. Post-surgery complications (prevalence of 46% and 18% in females and males, respectively) were all mild (dumping syndrome, gastric pyrosis, nausea) with only one severe surgery-related bleeding in a woman. Statistical analysis of data showed significantly better weight baseline parameters in females compared to males, including higher levels of HDL and a better hepatic profile (lower AST/GOT and ALT/GPT levels), Supplementary Table 1. No further differences at baseline between sexes were found when stratifying for the type of surgery (not shown).

Differences in the blood and adipose tissue levels of APN between sexes in patients affected by severe obesity

APN levels were measured before surgery in paired samples taken at surgery from abdominal SAT and VAT and compared with serum levels of APN, all evaluated with the same ELISA technique (Table 1). Circulating APN levels were confirmed to be higher in females, while to our surprise, APN content in abdominal SAT and VAT was lower than in the male sex, though the difference did not reach any statistical significance (Table 1). Differences between sexes and fat depots in APN local production in AT of patients was further confirmed by applying a semiquantitative Western blot analysis of total protein extracts from SAT and VAT specimens (Fig. 1a). APN relative expression compared to an internal standard (IS) of AT was confirmed to be higher in male vs female SAT, while the relative expression in VAT was lower and uniform among sexes (Fig. 1a, b). A statistically significant correlation was found between APN in VAT and SAT evaluated by semiquantitative WB and quantitative ELISA (Fig. 1c). When looking at the excess weight loss (EWL) as a clinical endpoint of the effects of surgery, EWL was found to be higher in females at any time points after bariatric surgery, corresponding to significantly lower BMIs reached by the first year. Differences between sexes were lost in the second year (Table 1). No significant WR was observed in our cohort even at two years from surgery. Only 7% patients (all males) experienced IWL (defined as WL < 50% EWL) [7] at 24 months from surgery.

APN levels in SAT, VAT and serum were not correlated with T2D or IR in either males and females.

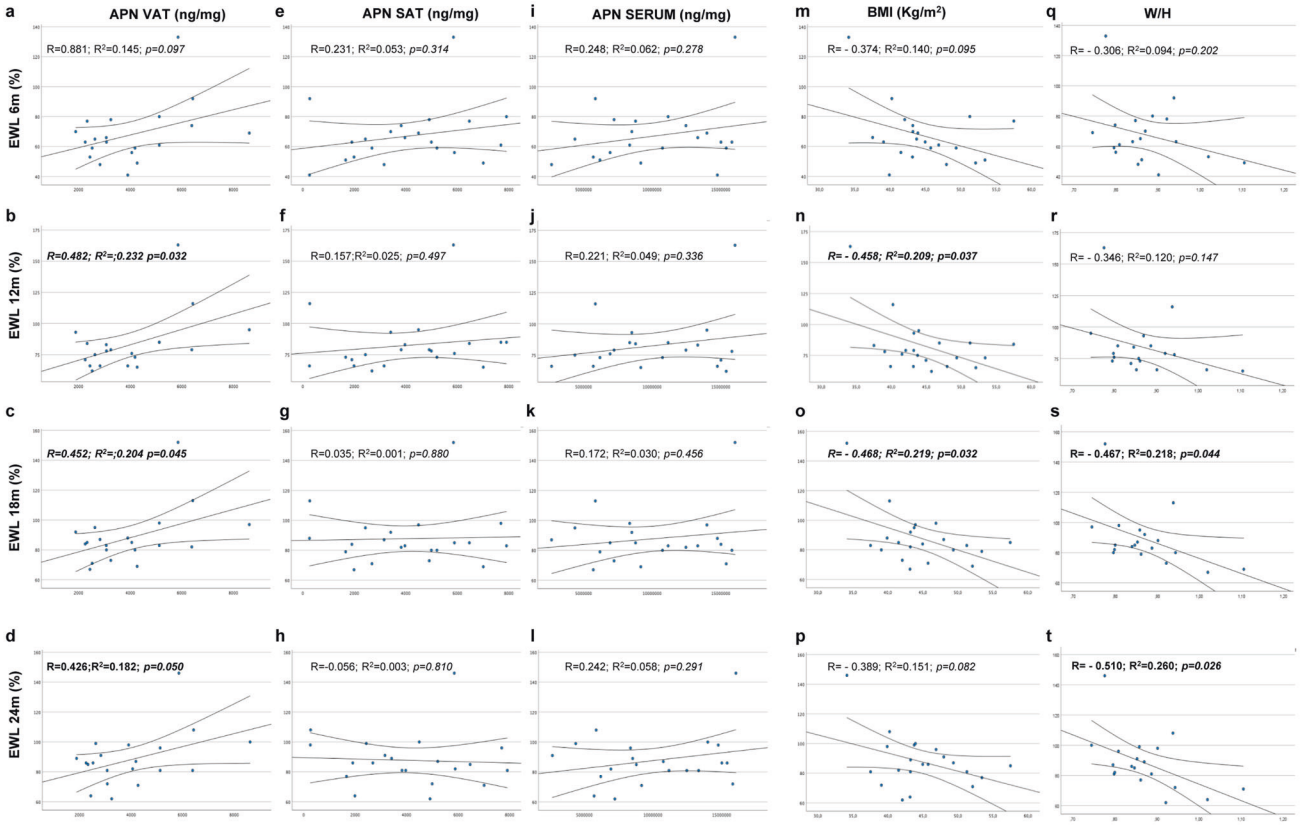

Fig. 2 EWL association with AT (SAT and VAT) or circulating APN as well as with BMI or W/H in female patients with severe obesity. Linear regression curves describe the association between EWL at 6, 12, 18, 24 months and baseline VAT APN (panels **a**–**d**), SAT APN (panels **e**–**h**), or blood APN (panels **i**–**l**), as well as baseline BMI (panels **m**–**p**) or W/H (panels **q**–**t**). For each graph, linear interpolation curves and the 25–75th CI are depicted; R, R^2, and *p* values are reported; statistically significant *p* values are indicated in bold Italics; $n = 20$ females where all EWL data were available.

VAT APN can predict EWL reached with bariatric surgery in women but not in men with severe obesity

A positive association was evident between baseline VAT APN and EWL only in females, which reached a statistical significance starting from 12 months after surgery and was also maintained at 2 years (Fig. 2a–d). On the contrary, no significant correlation was present for SAT (Fig. 2e–h) or blood (Fig. 2i–l) APN. Baseline BMI displayed a negative correlation with EWL, which was significant only at month 12 and 18 from surgery, and once again only when considering the female sex (Fig. 2m–p). No correlation was found between age and APN levels or EWL, either in the whole cohort or in females, thus excluding any putative association with menopause.

Rather than BMI, a more penetrant indicator of fat excess distributed between visceral abdominal and subcutaneous femoral/gluteal AT, is represented by the waist/hip ratio, which indicates a healthier pear-shaped or a metabolically-risky apple-shaped phenotype, defined as below or greater/equal than the sex-related cut-off (respectively 0.8 in F and 0.95 in M). In our series, W/H correlation was significant only with circulating APN levels, $r = -0.442$, $p = 0.005$. W/H was significantly correlated with EWL in females only and only starting from 12 months after surgery (Fig. 2q–t). The apple-shaped distribution was more frequent in females than males (77% vs 69%). APN in VAT was significantly higher in pear-shaped than in apple-shaped patients ($p = 0.007$), and in females ($p = 0.019$) compared to males (Table 2).

In order to define the best threshold for VAT APN able to predict EWL after surgery, patients were stratified in two classes with VAT APN levels higher/equal or lower than the cut-off value, corresponding to the upper quartile (≥75th percentile) of the APN distribution in VAT samples, and identified by ROC curve analysis. In females, baseline VAT APN, but not baseline BMI, retained a statistically significant correlation with EWL at any time points between 6 and 24 months from surgery, both at univariate and multivariate analysis (Table 3). No correlation was found for SAT APN in females or, in general, in the male sex, or with W/H pear- vs apple-shaped classes (not shown). EWL was significantly higher in the upper quartile of VAT APN compared to lower levels at any time point from surgery in females (Fig. 3a), but not in males (Fig. 3a). The type of bariatric surgery did not influence EWL percentage in either sexes (not shown). Finally, limited to the female patients, ROC analysis indicated the best cut-off values for VAT APN to predict 80% EWL at 6 months from surgery (98% accuracy, 100% sensitivity, 82% specificity, $p = 0.034$, Fig. 3c) and 95% EWL at 12 months from surgery (98% accuracy, 100% sensitivity, 94% specificity, $p = 0.010$, Fig. 3d). This analysis was not significant for male patients (not shown).

DISCUSSION

In a small pilot cohort of patients affected by severe obesity undergoing bariatric surgery with a post-surgery follow-up up to 2 years, our study explored the AT production of APN as a potential predictive marker of EWL obtained with bariatric surgery. In females, we found that APN produced in abdominal VAT was positively associated with EWL starting from 12 months from surgery, while there was no significant correlation in operated males. Neither circulating nor abdominal SAT APN displayed any significant association with EWL in either sexes. In females, VAT

Table 2. APN distribution according to pear- or apple- shape in patients with severe obesity.

	TOT ($n = 41$)		F ($n = 24$)		M ($n = 17$)	
	PEAR	APPLE	PEAR W/H < 0.8	APPLE W/H ≥ 0.8	PEAR W/H < 0.95	APPLE W/H ≥ 0.95
APN VAT (μg/mg)	5.4[4.2–6.5]***	3.2[2.3–4.8]	4.1[5.9–7.5]*	3.0[3.3–4.6]	5.3[2.9–6.1]	3.3[2.1–4.9]
APN SAT (μg/mg)	4.9[3.4–5.4]	3.2[1.9–6.2]	5.2[4.2–5.9]	3.2[1.2–5.7]	4.9[1.8–5.0]	4.5[2.6–7.0]
APN serum (μg/ml)	11.4[8.2–13.2]**	6.4[4.6–10.9]	12.5[8.8–15.0]	8.5[6.6–11.1]	11.1[6.1–12.2]	5.2[3.8–6.3]§

Median[IQR] APN in VAT, SAT and circulating levels evaluated by ELISA are reported in the entire series of patients or are stratified according to female (F) and male (M) sex. *U* Mann–Whitney's test: *$p = 0.037$, **$p = 0.019$, and ***$p = 0.007$ pear- vs apple-shape in the same sex; § $p = 0.019$ F vs M.

Table 3. Baseline visceral adiponectin is a better predictor than BMI in female morbidly obese patients of the EWL after bariatric surgery.

UNIVARIATE	EWL 6 m	EWL 12 m	EWL 18 m	EWL 24 m
VAT APN				
≥75th percentile vs <75th percentile	***r = 0.594 p = 0.005***	***r = 0.621 p = 0.003***	***r = 0.585 p = 0.005***	***r = 0.521 p = 0.015***
BMI	r = − 0.374 p = 0.095	***r = − 0.458 p = 0.037***	***r = −0.468 p = 0.032***	r = −0.389 $p = 0.082$
MULTIVARIATE	**EWL 6 m**	**EWL 12 m**	**EWL 18 m**	**EWL 24 m**
VAT APN				
≥75th percentile vs <75th percentile	***β = 0.545 p = 0.007***	***β = 0.558 p = 0.004***	***β = 0.519 p = 0.008***	***β = 0.467 p = 0.025***
BMI	β = −0.278 $p = 0.142$	***β = −0.360 p = 0.045***	***β = −0.378 p = 0.042***	β = −0.307 $p = 0.126$

Baseline VAT adiponectin (VAT APN cut off = 5.1 μg/mg corresponding to the 75th percentile of distribution) evaluated by ELISA in female bariatric patients retains a statistical significant correlation with EWL at any time points between 6 and 24 months from surgery, both at univariate and multivariate analysis with the baseline BMI as confounding factor. Regression analysis was performed with the forward selection in the model. No statistical significant correlation was found for male obese patients; $n = 21$ female patients; r, β and p are indicated. Statistically significant p values are indicated in bold Italics.

APN levels in the upper quartile maintained a significant correlation with EWL at all the four time points of follow up considered, also at multivariate regression analysis adjusted for baseline BMI. Conversely, the ability of basal BMI to predict EWL was weaker, and lost its significance at multivariate analysis. W/H was associated with EWL only at longer follow up, losing any predictive power at short time, and when clustered for pear- and apple-shaped classes. A cut-off value for VAT APN in females able to predict the 80% EWL at 6 months and 95% EWL at 12 months was identified with a predictive threshold for identifying the best responders to bariatric surgery among female patients.

Our findings suggest that APN produced by VAT in women with severe obesity may represent an independent predictor of EWL. Obesity is characterized by lower circulating levels of this adipokine, which remains higher in females than in males. High circulating APN is correlated with a better insulin sensitivity and lower abdominal visceral adiposity [14, 15]. The impact of sex and fat pad distribution on the AT local production of this hormone has been poorly investigated. This is particularly relevant in obesity, a condition characterized by a different sex-dependent distribution of the excess adiposity, which is generally concentrated in the visceral abdomen in males (apple-shaped) and in the subcutaneously peripheral fat (gluteal-femoral hip) in females (pear-shaped) [16]. The subcutaneous abdominal and hip depots are metabolically healthier than the visceral depots [17], the latter characterized by hypertrophy associated with a reduced quality of the AT [18]. These differences result in a different risk of obesity-associated comorbidities [14, 15]. Notably, we found that while circulating APN was higher in females than in males with severe obesity [19], SAT and VAT levels were generally lower in females, with significantly higher APN in the male SAT. Interestingly, when we compared APN content in fat pads, according to pear- or apple-shaped distribution of AT in severe obesity, we found that the pear-shaped content of VAT APN is significantly higher compared to apple-shaped, in particular for the female sex. Taken together these findings suggest that VAT rather than SAT APN is the relevant marker of healthier fat even in severe obesity, in particular in females. In a previous study conducted in a nonhomogeneous cohort with only 40% of subjects with severe obesity, VAT mass was negatively correlated with APN secretion from ex vivo VAT explants [20], or from in vitro cultured adipocytes isolated from VAT of women with normal weight [21]. Similar to our data, these correlations were evident in females, confirming that VAT rather than SAT APN decrease reflects increased adiposity in a sex-related manner. Though the mechanisms responsible of this paradoxically inverse association are still to be elucidated, our findings suggest that in women, VAT expansion is associated with a relevant tissue disfunction, which may explain the greater detrimental effects of central adiposity and metabolic syndrome in this sex [22]. Indeed, expansion of abdominal AT in females is characterized by different mechanisms according to the depots: while both hypertrophy and hyperplasia of adipocytes occur in SAT, fat deposition in visceral abdominal depots involves hypertrophic process resulting in altered AT functions and metabolism [23].

Circulating APN did not reflect abdominal AT production rather the contribution of subcutaneous gluteal adipose pads, which our data suggest to be deficient in men displaying apple-shape compared to women resulting in lower circulating APN.

Our data demonstrate that EWL is associated with VAT and not with SAT APN content, with no correlation with APN serum levels. It can be hypothesized that the better quality of VAT may facilitate the reaching of the ideal weight after surgery. Of note, this relation is evident only in females. Moreover, females in the upper class of VAT APN performed better than males with the same levels of VAT APN in terms of weight loss during the first year from surgery. These findings further support the concept that APN is a penetrant marker of VAT quality, also contributing to weight normalization, but only in the female context, probably as depending on the sex hormone milieu. Accordingly, it could be of help measuring APN content in VAT samples obtained during surgery to improve the patient management.

We recognize some limitations of our study, which is retrospective and small, although it is homogenous, since bariatric

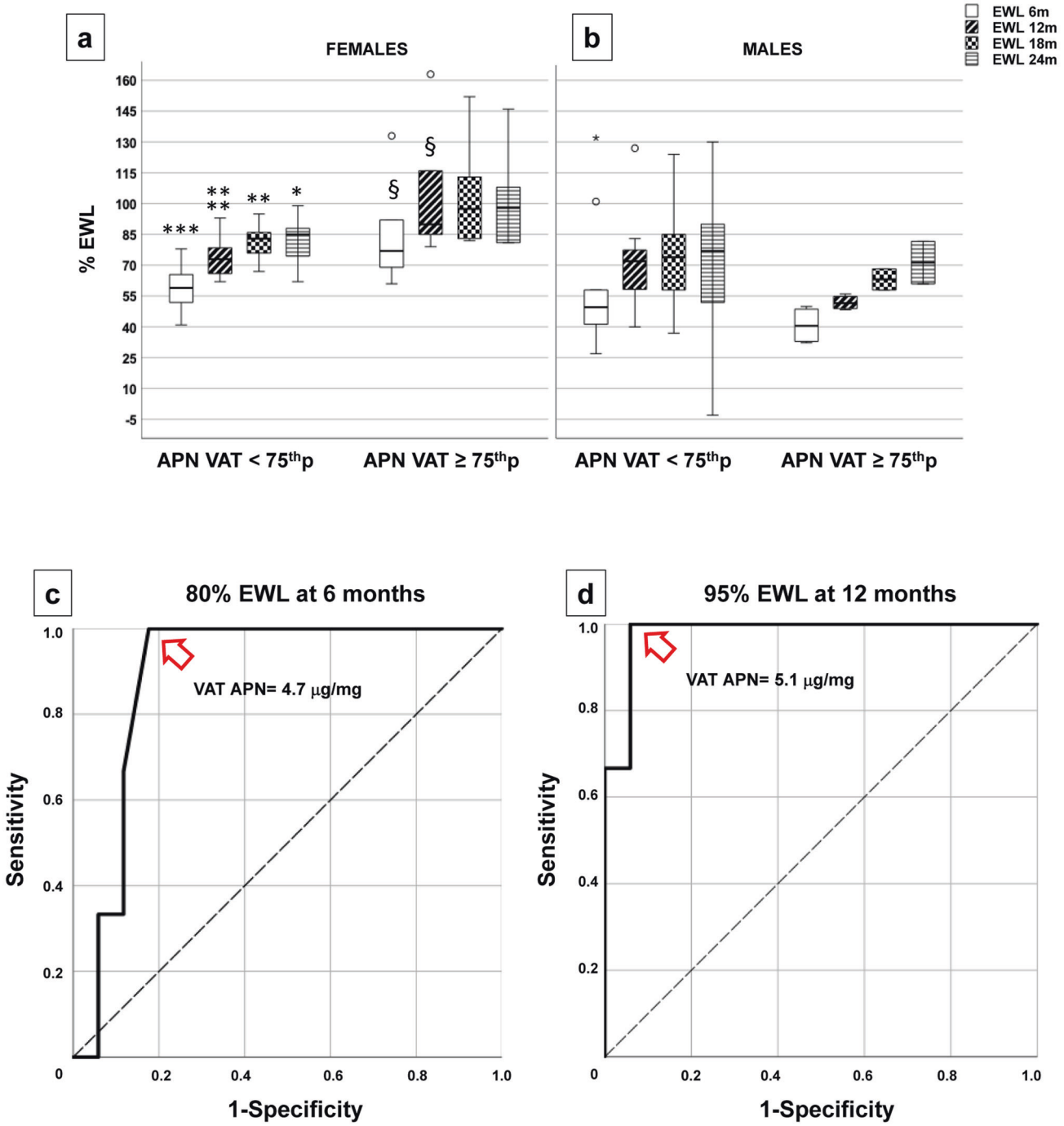

Fig. 3 High VAT adiponectin levels are associated with EWL prediction in female severe obesity. Distribution of EWL in female and male patients: female ($n = 24$, panel **a**) and male ($n = 19$, panel **b**) patients were stratified in two classes according to the VAT APN cut off = 5.1 µg/mg, corresponding to the 75th percentile of APN distribution. EWL Median[IQR] values at the different time intervals of follow up are indicated by box charts. Statistical analysis performed with *U* Mann–Whitney test: *$p < 0.05$, **$p < 0.01$, ***$p < 0.005$, ****$p < 0.001$ between VAT APN upper (≥5.1 µg/mg) and lower (<5.1 µg/mg) classes; § $p < 0.010$ between females (F) and males (M). Receiver operating characteristic (ROC) curve analysis for defining the best cut-off value of VAT APN predictive of the EWL in female patients: ROC curve analysis shown for APN concentration in VAT of 21 female patients out of 24 who had a complete follow up, and evaluated by ELISA, indicate that a cut-off of VAT APN of 4.7 µg/mg was able to predict 80% EWL at 6 months from surgery (89% accuracy, 100% sensitivity, 87% specificity, $p = 0.034$), (panel **c**), while a cut-off of 5.1 µg/ml was able to predict 95% EWL at 12 months from surgery (98% accuracy, 100% sensitivity, 94% specificity, $p = 0.010$), (panel **d**).

surgery is performed monocentrically limiting any variance related to the type of surgery. The small power derived from the low number of participants may affect results, which need to be confirmed in larger prospective studies. Moreover, the confounding effect of the different pharmacological regimen of patients has not been taken into consideration; the follow-up was short (2 years) limiting considerations on APN predictivity on WR at long follow up, and reported only the endpoints of EWL and complications. Finally, the absence of collected glycaemic, insulin, hypertensive, inflammation, and lipid profile data at follow up,

prevents from any analysis of APN as a predictive marker of recovery from associated comorbidities.

In conclusion, our findings indicate that APN produced in the abdominal VAT rather than the circulating or subcutaneous levels can predict EWL after bariatric surgery as an independent factor in the female sex. If validated in larger cohorts of patients, these results may contribute to a better management of the patients with severe obesity, enabling to identify those patients who will much benefit from surgery.

DATA AVAILABILITY

The data of this study are available from the corresponding author, ML, upon reasonable request.

REFERENCES

1. Pinhas-Hamiel O, Hamiel U, Bendor CD, Bardugo A, Twig G, Cukierman-Yaffe T. The global spread of severe obesity in toddlers, children, and adolescents: a systematic review and meta-analysis. Obes Facts. 2022;15:118–34.
2. Di Lorenzo N, Antoniou SA, Batterham RL, Busetto L, Godoroja D, Iossa A, et al. Clinical practice guidelines of the European Association for Endoscopic Surgery (EAES) on bariatric surgery: update 2020 endorsed by IFSO-EC, EASO and ESPCOP. Surg Endosc. 2020;34:2332–58.
3. Adams TD, Gress RE, Smith SC, Halverson RC, Simper SC, Rosamond WD, et al. Long-term mortality after gastric bypass surgery. N. Engl J Med. 2007;357:753–61.
4. Adams TD, Davidson LE, Litwin SE, Kim J, Kolotkin RL, Nanjee MN, et al. Weight and metabolic outcomes 12 years after gastric bypass. N. Engl J Med. 2018;378:93–96.
5. Kauppila JH, Markar S, Santoni G, Holmberg D, Lagergren J. Temporal changes in obesity-related medication after bariatric surgery vs no surgery for obesity. JAMA Surg. 2023;158:817–23.
6. Yarigholi F, Bahardoust M, Mosavari H, Tehrani FM, Gholizadeh H, Shahmiri SS, et al. Predictors of weight regain and insufficient weight loss according to different definitions after sleeve gastrectomy: a retrospective analytical study. Obes Surg. 2022;32:4040–6.
7. El Ansari W, Elhag W. Weight regain and insufficient weight loss after bariatric surgery: definitions, prevalence, mechanisms, predictors, prevention and management strategies, and knowledge gaps-a scoping review. Obes Surg. 2021;31:1755–66.
8. Pokala B, Hernandez E, Giannopoulos S, Athanasiadis DI, Timsina L, Sorg N, et al. Early postoperative weight loss predicts nadir weight and weight regain after laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass. Surg Endosc. 2023;37:4934–41.
9. Athanasiadis DI, Martin A, Kapsampelis P, Monfared S, Stefanidis D. Factors associated with weight regain post-bariatric surgery: a systematic review. Surg Endosc. 2021;35:4069–84.
10. Faraj M, Havel PJ, Phélis S, Blank D, Sniderman AD, Cianflone K. Plasma acylation-stimulating protein, adiponectin, leptin, and ghrelin before and after weight loss induced by gastric bypass surgery in morbidly obese subjects. J Clin Endocrinol Metab. 2003;88:1594–602.
11. Williams RL, Wood LG, Collins CE, Morgan PJ, Callister R. Energy homeostasis and appetite regulating hormones as predictors of weight loss in men and women. Appetite. 2016;101:1–7.
12. Di Franco A, Guasti D, Mazzanti B, Ercolino T, Francalanci M, Nesi G, et al. Dissecting the origin of inducible brown fat in adult humans through a novel adipose stem cell model from adipose tissue surrounding pheochromocytoma. J Clin Endocrinol Metab. 2014;99:E1903–12.
13. Di Franco A, Guasti D, Squecco R, Mazzanti B, Rossi F, Idrizaj E, et al. Searching for classical brown fat in humans: development of a novel human fetal brown stem cell model. Stem Cells. 2016;34:1679–91.
14. Lee JM, Okumura MJ, Davis MM, Herman WH, Gurney JG. Prevalence and determinants of insulin resistance among U.S. adolescents: a population-based study. Diabetes Care. 2006;29:2427–32.
15. Lee S, Bacha F, Gungor N, Arslanian S. Racial differences in adiponectin in youth: relationship to visceral fat and insulin sensitivity. Diabetes Care. 2006;29:51–56.
16. Alser M, Elrayess MA. From an apple to a pear: moving fat around for reversing insulin resistance. Int J Environ Res Public Health. 2022;19:14251.
17. Smith SR, Lovejoy JC, Greenway F, Ryan D, deJonge L, de la Bretonne J, et al. Contributions of total body fat, abdominal subcutaneous adipose tissue compartments, and visceral adipose tissue to the metabolic complications of obesity. Metabolism. 2001;50:425–35.
18. Delaney KZ, Santosa S. Sex differences in regional adipose tissue depots pose different threats for the development of Type 2 diabetes in males and females. Obes Rev. 2022;23:e13393.
19. Lihn AS, Bruun JM, He G, Pedersen SB, Jensen PF, Richelsen B. Lower expression of adiponectin mRNA in visceral adipose tissue in lean and obese subjects. Mol Cell Endocrinol. 2004;219:9–15.
20. Reneau J, Goldblatt M, Gould J, Kindel T, Kastenmeier A, Higgins R. et al. Effect of adiposity on tissue-specific adiponectin secretion. PLoS One. 2018;13:e0198889.
21. Drolet R, Richard C, Sniderman AD, Mailloux J, Fortier M, Huot C, et al. Hypertrophy and hyperplasia of abdominal adipose tissues in women. Int J Obes. 2008;32:283–91.
22. Sarafidis PA, McFarlane SI, Bakris GL. Gender disparity in outcomes of care and management for diabetes and the metabolic syndrome. Curr Diab Rep. 2006;6:219–24.
23. Drolet R, Bélanger C, Fortier M, Huot C, Mailloux J, Légaré D, et al. Fat depot-specific impact of visceral obesity on adipocyte adiponectin release in women. Obesity (Silver Spring). 2009;17:424–30.

ACKNOWLEDGEMENTS

The authors thank Dr. Enrico Facchiano (General and Bariatric Surgery Unit, Santa Maria Nuova Hospital) for his valuable collaboration.

AUTHOR CONTRIBUTIONS

GC, GQ, ML designed and conceive the study; GQ, NG, MaLu were responsible for patient selection and surgery and obtained patient samples; DAG, LF, AP, LG conducted experiments; GC, GQ, NG, collected patient data; GC, ML analysed data and wrote the manuscript; MM, ML interpreted results, revised the draft manuscript critically for important intellectual content. All authors were involved in writing the paper and had final approval of the submitted version.

FUNDING

This publication was produced with the co-funding European Union—Next Generation EU, in the context of The National Recovery and Resilience Plan, Investment 1.5 Ecosystems of Innovation, Project Tuscany Health Ecosystem (THE), CUP: B83C22003920001.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41366-023-01406-1.

Correspondence and requests for materials should be addressed to Michaela Luconi.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.