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Increased copeptin may reflect vasopressin-related metabolic changes after bariatric surgery

Francesca Galbiati[1] | Imen Becetti[2] | Meghan Lauze[2] | Anna Aulinas[3] | Vibha Singhal[2,4] | Miriam A. Bredella[5,6] | Elizabeth A. Lawson[1] | Madhusmita Misra[1,2,7]

[1]Neuroendocrine Unit, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA

[2]Division of Pediatric Endocrinology, Department of Pediatrics, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA

[3]Department of Endocrinology and Nutrition, Hospital de la Santa Creu i Sant Pau, IR-Sant Pau, Barcelona, Spain

[4]Department of Pediatrics, Mattel Childrens' Hospital, UCLA, Los Angeles, California, USA

[5]Department of Radiology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA

[6]Department of Radiology, NYU Langone Health and Grossman School of Medicine, New York, New York, USA

[7]Division of Pediatric Endocrinology, Department of Pediatrics, University of Virginia, Charlottesville, Virginia, USA

Correspondence
Madhusmita Misra, Division of Pediatric Endocrinology, Department of Pediatrics, University of Virginia, 6th Floor, 1204 West Main St, Charlottesville, VA 22903, USA.
Email: abp6bd@uvahealth.org

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Abstract

Objective: Mechanisms underlying metabolic improvement following metabolic and bariatric surgery (MBS) may provide insight into novel therapies. Vasopressin improves body composition and protects against hypoglycemia. Associations of copeptin, a stable cleavage product of vasopressin, with BMI and insulin resistance suggest an adaptive increase in vasopressin to counteract metabolic disruption. To our knowledge, no study has investigated copeptin before and after MBS in humans. This study's aim was to investigate copeptin changes following MBS and associations with metabolic parameters.

Methods: This was a 12-month longitudinal study of 64 youth (78% female; mean age 18.7 [SD 2.8] y) with obesity (mean BMI 45.6 [SD 6.8] kg/m^2) undergoing MBS ($n = 34$) or nonsurgical (NS) lifestyle management ($n = 30$). Fasting copeptin, hemoglobin A1c (HbA1c), homeostatic model assessment for insulin resistance (HOMA-IR), body composition, and resting energy expenditure (REE) were assessed.

Results: Over 12 months, copeptin increased more (time-by-treatment $p = 0.017$) whereas HbA1c and adiposity decreased more after MBS than NS ($ps \leq 0.036$). Copeptin changes correlated negatively with percentage fat mass and REE changes (rho ≤ -0.29; $ps \leq 0.025$) in the whole group, and they correlated positively with HbA1c and HOMA-IR (rho ≥ 0.41; false discovery rate–adjusted $p = 0.05$) and negatively with REE changes (rho $= -0.55$; false discovery rate–adjusted $p = 0.036$) in the MBS group.

Conclusions: Increases in copeptin after weight loss in MBS compared with NS were associated with lower REE and higher HbA1c/HOMA-IR values. Vasopressin may contribute to MBS-related metabolic modifications.

Miriam A. Bredella, Elizabeth A. Lawson, and Madhusmita Misra are co-senior authors and contributed equally to this work.

INTRODUCTION

The prevalence of obesity in youth is rising, and it is associated with metabolic complications including insulin resistance, type 2 diabetes mellitus, and metabolic syndrome [1]. Metabolic and bariatric surgery (MBS) has been increasingly used to effectively treat obesity in youth; however, the mechanisms for metabolic changes after MBS are still poorly understood. Our group has shown that oxytocin, a hypothalamic neurohormone known to regulate metabolism, decreases after MBS in association with decreases in lean mass [2]. Arginine vasopressin (AVP) and oxytocin are sister hormones produced in the hypothalamus, and both regulate body composition [3–6].

AVP is a hypothalamic–pituitary neurohormone known for its role in water balance [7]. However, there is a growing body of evidence demonstrating that AVP has important metabolic effects that could impact obesity pathophysiology [6]. Central leptin administration stimulated AVP in mice [8], suggesting that AVP might play a role in energy balance [9]. In animal models, AVP suppresses calorie intake [10, 11] and promotes muscle regeneration [12–14]. Preclinical data have demonstrated that AVP regulates pancreatic endocrine functions and glucose homeostasis in a context-dependent fashion by increasing insulin secretion at higher glycemic levels and glucagon at lower glycemic levels [15]. Also, intravenous AVP was protective against insulin-induced hypoglycemia in healthy men, possibly through a direct effect on glucagon secretion [16]. Further, in rodents [17] as well as humans [18], AVP has been found to be elevated in uncontrolled diabetes mellitus and in hepatic steatosis in rats [5, 19] suggesting an adaptive boost in the AVP system to counterbalance this state of metabolic derangement. Taken together, the aforementioned data indicate that intact AVP signaling may contribute to the maintenance of metabolic health.

A robust body of literature has shown that copeptin, a stable surrogate marker for AVP that is co-secreted and derives from the AVP precursor [20, 21], is directly associated with blood glucose and plasma insulin levels, as well as insulin resistance, abdominal obesity, metabolic syndrome, and body mass index (BMI) [22–26], suggesting again an adaptive increase in AVP activity in states of metabolic disruption. A few studies have investigated copeptin in metabolic dysregulation in youth [27–32] and found that copeptin correlates positively with BMI and metabolic syndrome markers in children with obesity [27, 28, 30]. However, no study in humans has investigated AVP physiology and copeptin levels in patients undergoing weight loss treatment. This is an important knowledge gap in need of elucidation to further our understanding of the role of vasopressin in metabolism.

Our objective was to assess copeptin levels in adolescents and young adults with moderate to severe obesity following MBS or lifestyle modification (nonsurgical [NS] controls). We aimed to (i) investigate copeptin levels in response to weight loss and (ii) examine the relationships between changes in copeptin levels and changes in metabolic parameters. We hypothesized that (i) copeptin levels would increase 12 months after MBS as a possible mediator of the favorable metabolic effects induced by surgery and that (ii) copeptin levels would be associated with improved metabolic parameters and lower risk of hypoglycemia.

Study Importance

What is already known?

- Metabolic and bariatric surgery is effective in treating obesity in youth.
- Arginine vasopressin (AVP) is a neurohormone that decreases food intake and promotes muscle regeneration in animals, and it is protective against hypoglycemia in animals and humans.
- Copeptin, a stable surrogate marker for AVP, is directly associated with insulin resistance, abdominal obesity, and metabolic syndrome, suggesting an adaptive increase in AVP activity in states of metabolic disruption.

What does this study add?

- Surgical weight loss treatment can impact copeptin levels at 12 months, and copeptin changes are associated with changes in fat mass and glucose homeostasis.
- Copeptin levels at 12 months after weight loss intervention were positively correlated with lean mass, suggesting a protective role of copeptin in lean mass reduction.
- Copeptin changes over 12 months correlated positively with glycated hemoglobin and homeostatic model assessment for insulin resistance, suggesting a protective role of copeptin against hypoglycemia.

How might these results change the direction of research or the focus of clinical practice?

- Future research should investigate the role of endogenous and exogenous AVP on metabolic outcomes.
- The vasopressin system might be a potential target for obesity therapeutics.

METHODS

Study population

This was a prospective cohort study of 64 adolescents and young adults (78% female) with moderate to severe obesity who were enrolled in a study comparing effects of MBS to NS controls. Thirty participants underwent NS management, and 34 underwent MBS (25 sleeve gastrectomy and 9 Roux-en-Y gastric bypass). Inclusion criteria for MBS included having BMI ≥35 with one or more obesity-related complications or having BMI ≥40. Exclusion criteria included being currently pregnant or breastfeeding, using medications that

cause weight gain (unless on stable doses), having uncontrolled thyroid disease, having a substance abuse disorder, and being a cigarette smoker, as previously described [2]. Participants were recruited from several tertiary care obesity treatment centers focused on lifestyle and surgical interventions for weight management from June 2015 through September 2019. The study was conducted in accordance with the Declaration of Helsinki, was approved by the Institutional Review Board of Massachusetts General Hospital (protocol code 2015P000360; date of initial approval 22 April 2015), and was compliant with the Health Insurance Portability and Accountability Act. Participants aged ≥18 years and parents of participants aged <18 years provided written informed consent. Participants aged <18 years provided informed assent.

Study visits and procedures

A screening visit was performed to confirm eligibility for the study. Study visits were performed at baseline (within a month prior to surgery) and 12 months after surgery. NS controls were also examined at baseline and 12 months after the baseline visit. A medical history, physical examination, and anthropometric measurements were obtained from all participants. Weight was measured to the nearest 0.1 kg using an electronic scale, and height was measured using a wall-mounted stadiometer as the mean of three measurements. BMI was calculated as weight in kilograms divided by height in meters squared. After an overnight fast with ad libitum water intake, each participant underwent blood tests for copeptin, glucose, insulin, and glycated hemoglobin (HbA1c); dual-energy x-ray absorptiometry (DXA) for body composition; and indirect calorimetry for resting energy expenditure (REE) (adjusted for lean mass) at baseline and 12 months. NS controls received standard diet and exercise counseling throughout the study from their primary care provider, specialized programs they were enrolled in, or dietitians from our Translational and Clinical Research Center.

Laboratory measures

Fasting serum copeptin levels were measured using the automated Brahms KRYPTOR assay (Thermo Fisher Scientific) with intra-assay and inter-assay coefficient of variation of 4% to 15% and 6% to 18%, respectively, at the University of Iowa. Levels of serum glucose, insulin, and HbA1c were assessed as previously described [33, 34]. The homeostatic model assessment for insulin resistance (HOMA-IR) was calculated using fasting glucose and insulin levels as follows: (fasting insulin, micro-international units per milliliter [μIU/mL]) × (fasting glucose, milligrams per deciliter [mg/dL])/405, as previously described [33].

Body composition analysis

DXA (Hologic 4500 A) was used to assess total body and percentage lean mass, fat mass, and estimated visceral adipose tissue (VAT) mass. VAT mass was measured in a 5-cm-wide region placed across the entire abdomen just above the iliac crest at a level that approximately coincided with the fourth lumbar vertebrae on the whole body DXA scan.

Resting energy expenditure

REE was assessed using indirect calorimetry using VMAX Encore 29 metabolic cart (Viasys Healthcare, CareFusion).

Statistical analysis

We performed statistical analyses using Stata statistical software (version 18.0; StataCorp LLC). For nominal variables (group differences in sex, race, and ethnicity), we applied the χ^2 test. The distribution of continuous variables was checked using the Shapiro–Wilk test and graphical methods (box plots), and log-transformation (base e) was applied as appropriate to approximate normality. We applied linear mixed-effects model regression for repeated measurements to analyze temporary and group-specific dynamics in copeptin levels before and 12 months after weight loss treatment, including the factors sex, age, BMI, and time-by-treatment interaction, and using z statistics with an unstructured covariance matrix. We investigated the relationships between absolute changes in copeptin levels from 0 to 12 months and more sophisticated DXA-acquired measures of body composition, glucose homeostasis parameters, and REE using Spearman correlation, as the absolute difference in copeptin concentrations was not normally distributed. Partial correlation analysis was applied to adjust the aforementioned correlations for BMI changes over the same duration. Effect size statistics are provided as Cohen d. Testing for multiple comparisons was performed using the false discovery rate (FDR) test for the main analyses. A sensitivity analysis on the aforementioned Spearman correlations was performed in the surgical participants who underwent sleeve gastrectomy only. Power calculation was performed to achieve a power of 0.8 with an α of 0.05 indicating that a total sample size of 52 would allow detection of a clinically significant difference in copeptin levels.

RESULTS

Participant baseline clinical characteristics and changes over 12 months

Participants in the NS versus MBS group did not differ by sex, ethnicity, race, systolic and diastolic blood pressure, HbA1c, HOMA-IR, lean mass, or REE. Participants undergoing MBS were slightly older and had higher weight, BMI, and total and percentage fat mass at baseline compared to the NS group ($p \leq 0.049$; Table 1).

Twelve months after weight loss interventions, the MBS group had lower weight, BMI, systolic and diastolic blood pressure, HOMA-IR, total fat mass, percentage fat mass, VAT, and total lean mass

TABLE 1 Participant baseline and 12-month anthropometric measures, biochemical measures, body composition, and glucose homeostasis parameters in nonsurgical and surgical groups

	Baseline				12 months			
			Statistics				Statistics	
Characteristic	Nonsurgical (n = 30)	Surgical (n = 34)	Cohen d	p (raw)	Nonsurgical (n = 30)	Surgical (n = 34)	Cohen d	p (raw)
Age (y)[a]	17.92 ± 2.91	19.28 ± 2.48	−2.01	**0.049**	19.03 ± 2.90	20.16 ± 2.17	−1.74	0.088
Biological sex[b]								
Female	22 (73%)	28 (82%)	0.76	0.384	—	—	—	—
Male	18 (27%)	6 (18%)						
Race[b]								
American Indian/Alaska Native	1 (3%)	0 (0%)	0.75	0.352	—	—	—	—
Asian	1 (3%)	0 (0%)			—	—	—	—
Black	6 (20%)	10 (29%)			—	—	—	—
More than one race	3 (10%)	3 (9%)			—	—	—	—
White	15 (50%)	20 (59%)			—	—	—	—
Not disclosed	4 (14%)	1 (3%)			—	—	—	—
Ethnicity (Hispanic/Latino ethnic group)[b]	15 (50%)	12 (35%)	1.41	0.235	—	—	—	—
Anthropometrics[c]								
Weight (kg)	118.95 (101.30–132.60)	132.70 (119.10–151.20)	−2.95	**0.005**	120.9 (102.4–135.2)	96.5 (78.7–16.7)	3.52	**0.001**
BMI (kg/m^2)	41.65 (38.30–46.51)	47.95 (42.27–53.10)	−3.44	**0.001**	42.38 ± 5.90	35.35 ± 9.07	3.58	**0.001**
Blood pressure (mmHg)[a]								
Systolic blood pressure	119.10 ± 11.57	122.21 ± 14.52	−0.94	0.351	124.87 ± 12.62	116.58 ± 12.36	2.59	**0.012**
Diastolic blood pressure	66.37 ± 8.69	66.62 ± 9.51	0.33	0.745	69.33 ± 8.38	65.61 ± 9.51	1.62	0.111
Biochemistry								
Copeptin (pmol/L)[d]	7.04 ± 0.51	6.86 ± 0.56	N/A	N/A	6.13 ± 0.48	7.60 ± 0.53	N/A	
Hemoglobin A1c (%)[c]	5.44 (5.20–5.68)	5.49 (5.28–5.70)	−0.03	0.974	5.34 (5.10–5.60)	5.20 (5.00–5.30)	1.77	0.077
HOMA-IR[c]	2.35 (0.98–3.93)	2.60 (2.05–4.30)	−0.47	0.640	2.80 (1.53–4.39)	0.91 (0.47–1.38)	5.49	**<0.001**
Body composition[a]								
Total fat mass (kg)	57.2 ± 11.9	65.5 ± 15.2	−2.39	**0.020**	56.4 ± 130.3	40.2 ± 12.4	4.88	**<0.001**
Percentage fat mass (%)	47.2 ± 4.3	49.0 ± 5.0	−1.59	**0.012**	45.9 ± 4.9	40.8 ± 6.2	3.45	**0.001**
Estimated VAT mass (kg)	0.8 ± 0.3	0.9 ± 0.3	−1.19	0.238	0.7 ± 0.2	0.05 ± 0.2	3.71	**0.001**
Total lean mass (kg)[a]	61.6 ± 11.0	64.7 ± 10.6	−1.13	0.262	61.2 (52.5–72.9)	53.9 (48.2–57.8)	3.24	**0.002**
Percentage lean mass (%)	50.9 ± 4.2	49.2 ± 5.2	1.43	0.158	52.2 ± 4.9	56.7 ± 5.8	−3.23	**0.002**

(Continues)

TABLE 1 (Continued)

Characteristic	Baseline		Statistics		12 months		Statistics	
	Nonsurgical ($n = 30$)	Surgical ($n = 34$)	Cohen *d*	*p* (raw)	Nonsurgical ($n = 30$)	Surgical ($n = 34$)	Cohen *d*	*p* (raw)
Resting energy expenditure adjusted for lean mass (kcal/d per kg)[a]	0.028 ± 0.004	0.029 ± 0.004	−0.22	0.420	0.026 (0.025–0.028)	0.027 (0.023–0.028)	−0.03	0.734

Note: Copeptin and body composition measures are reported in their original scales in the table but were statistically tested after log transformation to approximate normality. Values in bold are statistically significant.

Abbreviations: HOMA-IR, homeostatic model assessment for insulin resistance; VAT, visceral adipose tissue; N/A, not applicable.

[a]Differences across groups in normally distributed variables (according to Shapiro–Wilk normality test) were analyzed using two-sample *t* tests. Data are presented as mean ± SE.

[b]Count variables were analyzed with χ^2 or Fisher exact test. Data are presented as *N* (%).

[c]Differences across groups in non-normally distributed variables were analyzed using nonparametric Wilcoxon rank sum tests. Data are presented as median (IQR).

[d]Copeptin levels were analyzed with linear mixed effects models.

(*p*s ≤ 0.012) than the NS group (Table 1). Weight, BMI, HOMA-IR, and total lean mass decreased in the MBS group and increased in the NS group over 12 months (*p*s ≤ 0.01). Systolic blood pressure, HbA1c, total and percentage fat mass, and VAT decreased more in the MBS group compared to the NS group (*p*s ≤ 0.036; Table 2). Percentage lean mass increased in the MBS group and decreased in the NS group ($p < 0.001$; Table 2).

Baseline copeptin levels and changes over 12 months

Baseline copeptin levels did not differ across groups ($p = 0.247$). Over 12 months, weight loss treatment impacted copeptin levels from baseline to 12 months such that copeptin significantly increased at 1 year in patients undergoing MBS versus NS: MBS had a median (interquartile range [IQR]) copeptin absolute change of +1.57 (−0.23 to 3.60) pmol/L, and NS had a median (IQR) copeptin absolute change of −0.13 (−2.62 to 1.65) pmol/L ($p = 0.023$). Time-by-treatment effect was significant ($p = 0.017$; Figure 1). The time-by-treatment effect remained significant after controlling for age and BMI over time ($p = 0.048$).

Copeptin levels in relationship to body composition, glucose homeostasis, and REE

At baseline, copeptin levels were negatively associated with total fat mass (rho = −0.25; $p = 0.045$). Copeptin levels were not associated with any other body composition variables, markers of glucose homeostasis, or REE (*p* ≥ 0.051).

At the 12-month time point, copeptin levels were positively correlated with total lean mass (rho = 0.27; $p = 0.038$) and negatively correlated with REE (rho = −0.45; *p* ≤ 0.001). Copeptin levels were not associated with any other body composition variables or glucose homeostasis measures (*p*s ≥ 0.099).

We then analyzed the relationships between changes in copeptin levels and changes in body composition, glucose homeostasis, and REE 12 months following weight loss interventions. In the overall population, copeptin changes were negatively correlated with changes in percentage fat mass (rho = −0.27; $p = 0.038$) and REE (rho = −0.39; $p = 0.004$; Figure 2). After controlling for BMI changes, the correlations were no longer significant ($p = 0.777$ and $p = 0.238$, respectively). No significant correlations were found between changes in copeptin levels and other parameters (*p* ≥ 0.106).

To investigate whether the aforementioned correlations might be specific to the weight loss intervention, we analyzed the relationships between changes in copeptin levels and changes in body composition, glucose homeostasis, and REE within each group (Table 3). For HbA1c changes, we removed one high outlier showing development of new poorly controlled diabetes mellitus 12 months after bariatric surgery because it was in the opposite direction of all the other participants. In the MBS group only, copeptin changes over 12 months were positively correlated with changes in HbA1c (rho = 0.48; $p = 0.008$;

TABLE 2 Twelve-month changes in participant anthropometrics, blood pressure, biochemical measures, body composition, and resting energy expenditure

	Nonsurgical (n = 30)	Surgical (n = 34)	Cohen d	p (raw)
Anthropometrics[a]				
12-mo weight change (%)	2.00 (−2.00 to 5.00)	−28.00 (−34.00 to 21.00)	6.31	**<0.001**
12-mo change in BMI (%)	0.54 (−3.10 to 4.37)	−28.97 (−33.67 to −16.47)	5.97	**<0.001**
Blood pressure (mmHg)[a]				
12-mo change in systolic blood pressure (%)	−5.00 (−5.00 to 14.00)	−6.00 (−14.00 to 5.00)	2.59	**0.010**
12-mo change in diastolic blood pressure (%)	3.00 (−8.00 to 13.00)	0 (−13.00 to +8.00)	−0.96	0.341
Biochemistry[a]				
12-mo change in copeptin (%)	−2.0 (−34.0 to 41.0)	29.0 (−51.0 to +54.0)	−2.07	**0.038**
12-mo change in HOMA-IR (%)	36.7 (−3.3 to 124.8)	−70.0 (−77.1 to −47.8)	0.79	**<0.001**
12-mo change in hemoglobin A1c (%)	−1.8 (−5.21 to −0.4)	−7.4 (−9.1 to −3.6)	0.05	**0.001**
Body composition[a]				
12-mo change in total fat mass (%)	−0.7 (−2.9 to 0.6)	−8.0 (−13.3 to −4.3)	6.38	**<0.001**
12-mo change in percentage fat mass (%)	−1.3 (−5.7 to 1.3)	−13.0 (−24.4 to −5.4)	4.13	**<0.001**
12-mo change in estimated VAT mass (%)	−10.0 (−20.7 to 3.3)	−43.0 (−54.6 to −32.2)	0.67	**<0.001**
12-mo change in total lean mass (%)	2.5 (−0.1 to 5.5)	−16.1 (−20.2 to −9.6)	3.06	**<0.001**
12-mo change in percentage lean mass (%)	1.6 (−1.0 to 5.7)	13.8 (6.4 to 21.9)	−5.20	**<0.001**
12-mo change in resting energy expenditure (adjusted for lean mass) (%)[b]	−3.25 ± 13.28	−6.29 ± 17.56	0.20	0.482

Note: Copeptin measures, dual-energy x-ray absorptiometry measures, and HOMA-IR at 12 mo are reported in their original scales in the table but were statistically tested after log transformation to approximate normality. Values in bold are statistically significant.
Abbreviations: HOMA-IR, homeostatic model assessment for insulin resistance; VAT, visceral adipose tissue; N/A, not applicable.
[a]Differences across groups in non-normally distributed variables (according to Shapiro–Wilk normality test) were analyzed using nonparametric Wilcoxon rank sum test. Data are presented as median [IQR].
[b]Differences across groups in normally distributed variables were analyzed using two-sample t tests. Data are presented as mean ± SE.

FDR-adjusted $p = 0.012$) and HOMA-IR (rho = 0.41; $p = 0.025$; FDR-adjusted $p = 0.025$) and negatively correlated with REE (rho = −0.55; $p = 0.006$; FDR-adjusted $p = 0.012$). Figure 3 shows the relationships between copeptin changes and metabolic parameter changes that were significant in the MBS group but not NS.

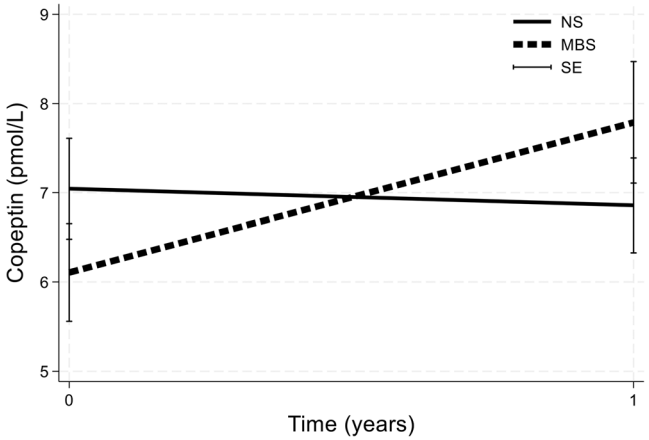

FIGURE 1 Copeptin levels before and after weight loss interventions. Copeptin significantly increased over 1 year in participants undergoing metabolic and bariatric surgery (MBS; dashed line) versus the nonsurgical (NS) group (solid line). Copeptin absolute change was −0.13 (−2.62 to 1.65) pmol/L in NS and +1.57 (−0.23 to 3.60) pmol/L in MBS ($p = 0.023$); time-by-treatment effect: $p = 0.017$. Adjusted means and SE from linear mixed effects model are reported.

After controlling for BMI changes, REE changes remained negatively correlated with copeptin changes ($p = 0.049$), whereas associations of HbA1c ($p = 0.821$) and HOMA-IR ($p = 0.095$) changes with copeptin changes were lost. No correlations were observed in the NS group ($p \geq 0.060$).

We also performed a sensitivity analysis of the aforementioned correlations in the subgroup of surgical participants who underwent sleeve gastrectomy ($n = 25$). Changes in copeptin over 12 months remained positively correlated with changes in HbA1c (rho = 0.54; $p = 0.006$; BMI-adjusted $p = 0.023$) and negatively correlated with REE (rho = −0.55; $p = 0.006$; BMI-adjusted $p = 0.049$).

DISCUSSION

To the best of our knowledge, this is the first study to demonstrate that surgical weight loss treatment can impact copeptin levels at 12 months, and that changes in copeptin levels are in turn associated with changes in fat mass, glucose homeostasis, and REE. Copeptin is a stable surrogate marker for AVP and correlates well with peripheral AVP levels [21]. Preclinical data have shown that AVP is anorexigenic [10, 11] and regulates lipolysis [35, 36]. and it is possible that increased AVP contributes

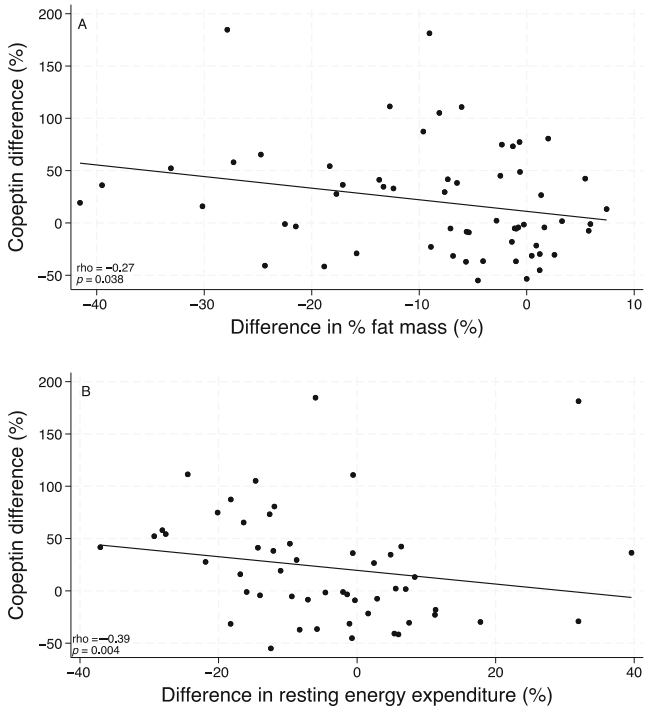

FIGURE 2 Correlations between copeptin and metabolic parameters in overall population. Overall, copeptin changes at 12 months correlated negatively with (A) percentage fat and (B) resting energy expenditure percentage changes.

TABLE 3 Spearman correlations between 12-month percentage change in metabolic parameters and 12-month percentage change in copeptin levels.

	MBS		Adjusted	NS	
	Rho	*p*	*p* (FDR)[a]	Rho	*p*
Change in BMI (%)	0.10	0.586	0.703	−0.12	0.512
Change in percentage fat mass (%)	−0.14	0.469	0.703	−0.03	0.856
Change in percentage lean mass (%)	−0.001	0.995	0.995	−0.28	0.138
Change in HbA1c[b] (%)	0.48	**0.008**	**0.012**	0.12	0.524
Change in HOMA-IR (%)	0.41	**0.025**	**0.025**	0.13	0.501
Change in REE (%)	−0.55	**0.006**	**0.012**	−0.143	0.464

Note: Values in bold are statistically significant.
Abbreviations: FDR, false discovery rate; HbA1c, hemoglobin A1c; HOMA-IR, homeostatic model assessment for insulin resistance; MBS, metabolic and bariatric surgery; NS, nonsurgical; REE, resting energy expenditure.
[a]FDR testing was applied to test for multiple comparisons.
[b]Results after exclusion of one high outlier.

to both reduced food intake and fat mass reduction following MBS, contributing to weight loss. Another explanation for the increased copeptin levels after MBS versus NS could lie in lower stress levels after MBS that would translate to lower cortisol levels. Mouse models have shown that weight loss following sleeve gastrectomy was associated with lower morning corticosterone than calorie-restriction–induced weight loss [37], and it is well known that AVP is an adrenocorticotropic hormone (ACTH) secretagogue [38] via the V1b receptor and AVP is downregulated by cortisol negative feedback. It is therefore possible that lower stress (and cortisol) levels in the MBS groups led to reduced feedback for AVP downregulation.

Our findings also showed a positive correlation between copeptin levels 12 months after weight loss intervention and total lean mass, indicating that (despite lean mass decreases with weight loss treatment) the greater the copeptin levels the lesser the lean mass reduction. This finding is consistent with preclinical data demonstrating that vasopressin promotes muscle regeneration [14], which could translate to humans. Furthermore, we showed that absolute changes in copeptin levels after weight loss treatment correlated negatively with percentage fat mass changes, suggesting that copeptin increase might enhance lipolysis and reduce fat mass, supporting a lipolytic role of AVP. Indeed, preclinical data have highlighted how AVP could be pro- or antilipolytic based on the AVP receptor subtype (V1a or V1b) activation [6, 35, 39]. In humans with AVP deficiency (formerly known as central diabetes insipidus), treatment with desmopressin (a vasopressin analogue) led to activation of lipoprotein lipase [40], suggesting that AVP promotes lipolysis, in line with our findings.

Additionally, we showed a positive correlation between copeptin level changes over 12 months and changes in HbA1c and HOMA-IR in the MBS group only. These results may initially seem discordant with the aforementioned findings of increased copeptin levels being associated with improved metabolic health. Nevertheless, the copeptin–glucose homeostasis correlation may represent a protective mechanism against post-MBS hypoglycemia possibly mediated by vasopressin. Post-MBS hypoglycemia is a serious complication affecting up to 75% of patients who have undergone MBS [41]. and few therapeutic options are available. It has also been shown that HbA1c reduction after MBS correlates with a higher risk of hypoglycemia [42]. Our findings suggest that higher copeptin levels 12 months after MBS may reduce the risk of hypoglycemia, reflected in associations with higher HbA1c and HOMA-IR values. Both preclinical and human studies have found AVP to be protective against hypoglycemia. In animal models, AVP modulated pancreatic endocrine function in a context-dependent manner, with the induction of insulin secretion under a high-glucose condition and of glucagon secretion under a low-glucose condition [43]. Additionally, a study in healthy men found that intravenous vasopressin was protective against insulin-induced hypoglycemia via glucagon stimulation [16]. Taken together, it is possible that the AVP system may represent a protective mechanism against hypoglycemia while also promoting metabolic health after MBS.

Lastly, at 12 months after weight loss intervention, we found a negative correlation between copeptin levels and REE in the overall population as well as between changes in copeptin levels and changes in REE in the MBS group only, and the latter held even after controlling for BMI changes. In line with our findings, a previous study found that dehydration status (when AVP would be expected to increase) was associated

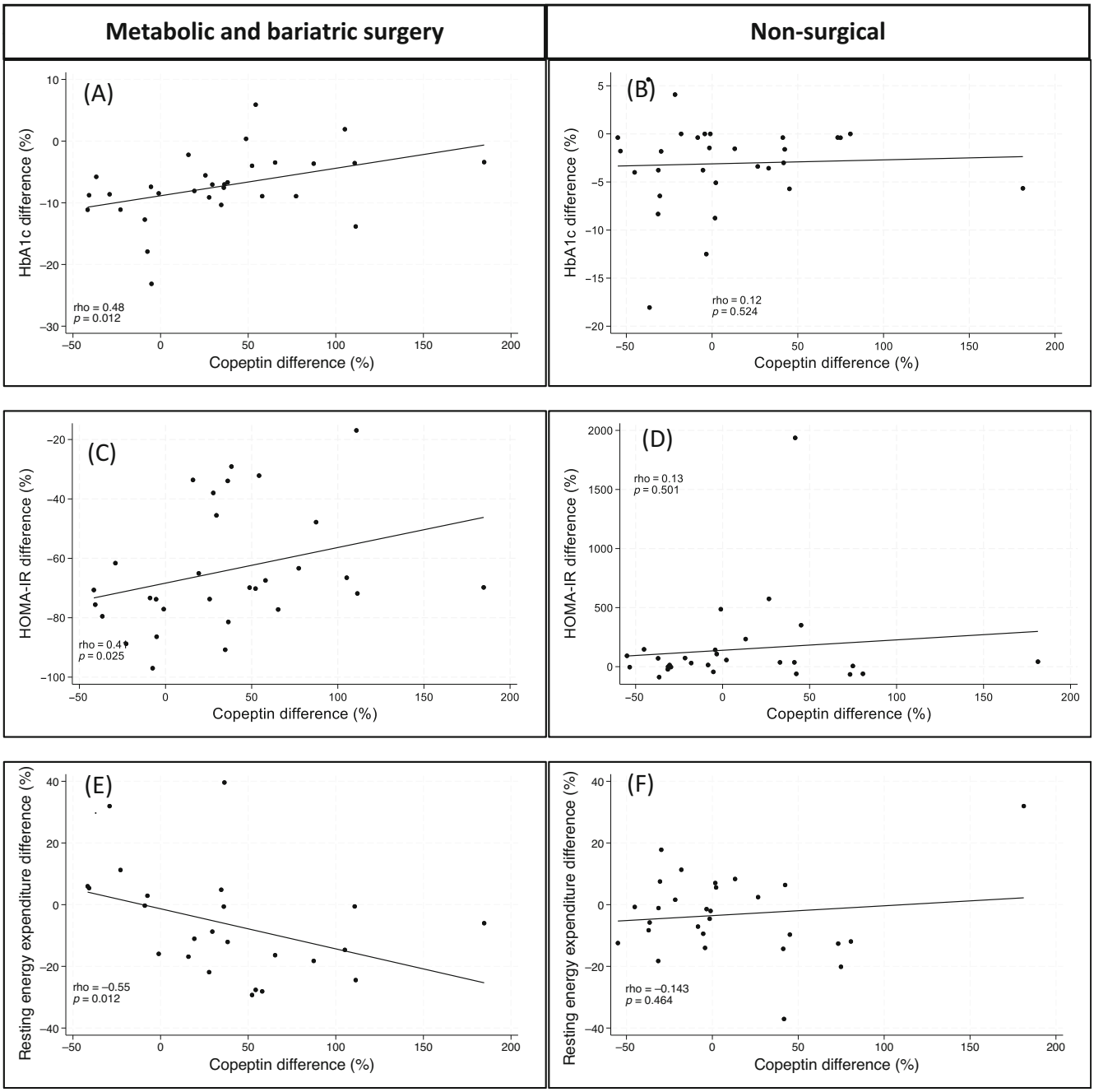

FIGURE 3 Relationships between copeptin percentage changes and metabolic parameters in the two treatment groups. Relationship between copeptin percentage changes and glycated hemoglobin (HbA1c) percentage changes in the (A) metabolic and bariatric surgery (MBS) group and (B) nonsurgical (NS) group; relationship between copeptin percentage changes and homeostatic model assessment for insulin resistance (HOMA-IR) percentage changes in (C) MBS and (D) NS; relationship between copeptin percentage changes and resting energy expenditure percentage changes in (E) MBS and (F) NS. *P* values for the MBS group are FDR-adjusted.

negatively with REE [44]. It is possible that MBS-induced weight loss causes a water shift from adipose to lean tissue impacting both copeptin levels (increased due to relatively diminished intravascular volume) and REE (decreased due to loss of adiposity). Despite the fact that fat mass reduction drives a decrease in REE, in this study, the correlation between copeptin changes and REE changes held after controlling for changes in BMI, suggesting a compensatory AVP increase to counteract reduced REE after weight loss in MBS.

Limitations of this study include the relatively small sample size, the inclusion of two different MBS techniques that may have different impacts on the AVP system and copeptin levels (partially addressed by sensitivity analysis on just the participants who underwent sleeve gastrectomy that confirmed our results), the age range of participants limiting generalizability of the results to an older population, the lack of hydration markers, and the report of baseline rather than stimulated copeptin. Previous studies have shown a blunted AVP response to

hypertonic saline in lean men versus men with obesity, indicating impairment of the AVP system in obesity [45]. It was however, beyond the scope of this study to assess AVP reactivity to hyperosmolar stimuli. Furthermore, our data for copeptin, body composition, glucose homeostasis, and REE are associative, and associations do not prove causation. Strengths of our study include the inclusion of NS controls as a comparison group, novel findings regarding copeptin levels that have not been investigated before in the bariatric surgery population, and powerful statistical analysis methods such as linear mixed effect.

CONCLUSION

For the first time, we have shown that copeptin levels are impacted by MBS and that increases in copeptin levels after weight loss are associated with improved body composition in the group as a whole and with higher HbA1c and HOMA-IR values in the MBS group, suggesting a potential dual mechanism for AVP to promote muscle preservation in weight loss and protect from post-MBS hypoglycemia. Larger studies are needed to investigate the role of AVP signaling in metabolism and identify additional therapeutic targets for obesity.O

AUTHOR CONTRIBUTIONS

Francesca Galbiati: conceptualization, methodology, investigation, data curation, formal analysis, and writing—original draft; Imen Becetti: study conduct and data management; Meghan Lauze: study conduct and data management; Anna Aulinas: writing—review and editing; Vibha Singhal: study conduct and supervision; Miriam A. Bredella: conceptualization, methodology, validation, resources, funding acquisition, writing—review and editing, supervision, and project administration; Elizabeth A. Lawson: conceptualization, writing—review and editing, and supervision; Madhusmita Misra: conceptualization, methodology, validation, resources, funding acquisition, writing—review and editing, supervision, and project administration.

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CONFLICT OF INTEREST STATEMENT

Elizabeth A. Lawson receives grant support and research study drug from Tonix Pharmaceuticals and receives royalties from UpToDate. Elizabeth A. Lawson and/or immediate family members hold stock in Thermo Fisher Scientific, Zoetis, Danaher Corporation, and Intuitive Surgical. Elizabeth A. Lawson is an inventor on US provisional patent application number 63/467,980 (Oxytocin-based therapeutics to improve cognitive control in individuals with attention deficit hyperactivity disorder). Madhusmita Misra has served as a key opinion leader for Lumos Pharmaceuticals, receives study drug donation from Tonix Pharmaceuticals, and royalties from UpToDate. The other authors declared no conflicts of interest.

CLINICAL TRIAL REGISTRATION

ClinicalTrials.gov identifier NCT02557438.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

ORCID

Francesca Galbiati https://orcid.org/0000-0003-0744-2541
Vibha Singhal https://orcid.org/0000-0002-9729-4433
Madhusmita Misra https://orcid.org/0000-0002-9405-2981

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