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HEALTH SCIENCES

An interdisciplinary therapy for lifestyle change is effective in improving psychological and inflammatory parameters in women with grade I obesity

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Abstract: Obesity and depression, disorders associated with inflammation, have high incidences in women. Understanding the derangements present in the initial phase of obesity may point to factors that could help avoiding disease aggravation. The present study aimed at investigating the effects of a 6-months interdisciplinary therapy for weight loss in women with grade I obesity. Before and after the therapy, 37 middle-aged women donated blood and responded to questionnaires for depression and anxiety symptoms. Inflammatory parameters were evaluated in serum and a preliminary screening of the plasma proteome was performed. The therapy decreased anthropometric, psychological scores, and serum levels of inflammatory parameters. Depression and anxiety scores correlated positively with some inflammatory parameters. The proteomic analysis showed changes in proteins related to cholesterol metabolism and inflammatory response. Interdisciplinary therapy improves anthropometric and inflammatory statuses and ameliorating psychological symptoms. The decrease of MCP-1 levels after interdisciplinary therapy has not been reported so far, at the best of our knowledge. The present demonstration of positive associations of inflammatory markers and psychological scores indicate that these mediators may be useful to monitor psychological status in obesity. The present proteome data, although preliminary, pointed to plasma alterations indicative of improvement of inflammation after interdisciplinary therapy.

Key words: Anxiety, depression, inflammation, obesity, proteome.

INTRODUCTION

Obesity prevalence has increased worldwide over the past 50 years, a pattern also observed in Brazil (NCD-Risk, 2016). A bidirectional link between obesity and depression has been demonstrated and inflammatory activation has been indicated as a feature shared by these disorders (Milaneschi et al. 2019). Higher incidence of both obesity and depression has been observed in women in comparison to men (Derry et al. 2015).

The involvement of inflammatory adipokines, thrombotic factors, and adhesion molecules in the pathophysiology of obesity has been evidenced. The levels of the anti-fibrinolytic protein plasminogen activator inhibitor-1 (PAI-1) associated positively with obesity and stroke (Chen et al. 2017). High plasma levels of the adhesion molecules intercellular adhesion

molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) have been observed in women with obesity and weight loss was able to decrease their concentration (Ziccard et al. 2002). The adipokine monocyte chemotactic protein-1 (MCP-1) has also been shown to increase with obesity (Panee 2012).

An association of inflammation and endothelial dysfunction with depression has been suggested (van Doreen et al. 2016). A relationship between PAI-1 and depression symptoms has been observed in patients with major depressive disorder (Girard et al. 2019). Up-regulation of PAI-1 has also been reported in a mouse model of depression (Girard et al. 2019). An association between VCAM-1 and depression symptoms has been observed in elderly individuals (Tchalla et al. 2015) and increased ICAM-1 has been detected in subjects with depression (van Doreen et al. 2016). Moreover, in adults with generalized anxiety and personality disorders, increased levels of MCP-1 have been indicated (Ogłodek et al. 2015).

Obesity treatment by a multidisciplinary therapeutic program focusing on lifestyle changes has been effective in weight loss achievement and sustaining (Bischoff et al. 2012). We have previously shown, in adult men and women with obesity, that this strategy induced weight loss, improved psychological parameters and reduced symptoms of binge eating (de Carvalho et al. 2012). In women with obesity, we have reported decreased levels of PAI-1, VCAM-1, and ICAM-1 (Jamar et al. 2016) and attenuation of depression and anxiety symptoms (Moraes et al. 2019).

The data mentioned above indicate that inflammatory factors and adhesion molecules are related to both obesity and psychological symptoms, two serious public health problems whose incidence is increased in women. Understanding these relationships may shed light on the mechanisms involved in these diseases and on their link.

The present work aimed at analyzing the effects of an interdisciplinary therapy for lifestyle change on the relationship between psychological and metabolic parameters of women with grade I obesity. The results may lead to the recognition of manageable factors present in this initial phase of the disease, helping to avoid further impairment and complications. A plasma proteomic analysis was performed for a broad inspection of the molecular mechanisms involved in the response to the lifestyle intervention.

MATERIALS AND METHODS

Study protocol

This study, performed in accordance with the principles of the Declaration of Helsinki, was approved by the Human Research Ethics Committee of the Universidade Federal de São Paulo (n° 72416/12), with Certificate of Presentation for Ethical Appreciation generated at Plataforma Brasil (CAAE number: 01888412.0.0000.5505), and registered with ClinicalTrials.gov (n° NCT02573688). All participants signed the informed consent authorizing data collection and analysis.

Thirty-seven women with grade I obesity (BMI 30-34.9 Kg/m^2, age 41.51 ± 0.89 years) were selected among the volunteers of the Group for Study of Obesity of the Universidade Federal de São Paulo (Santos, SP, Brazil). They were included in the study after verification of absence of medical restrictions, indicated by physical examination and exercise ECG, abusive alcohol or drugs consumption, pregnancy or gastroplasty. At the end of the 6-months therapy, only those women that had 75% of attendance to the treatment sections and had all measurements performed were considered

for the results analysis (final N = 15; drop-off rate = 40,5%).

The volunteers were evaluated both at baseline and after a 6-months interdisciplinary therapy for lifestyle change (IT) that included nutritional, psychological and physical exercise approaches.

Anthropometric measurements and body composition

The volunteers used light clothes and no shoes for body mass and height measurements. Body composition was assessed by tetrapolar bioelectrical impedance (RJL Systems, Quantum II, Clinton Township, Michigan, USA). Fat free mass was calculated by the equation for obese individuals (Segal et al. 1988).

Dietary intake

Dietary records were collected on 3 alternate days, including one weekend day, before and after the IT. Evaluation of energy and macronutrients intake was performed using Avanutri Software (Avanutri & Nutrição Serviços e Informática Inc., Três Rios, RJ, Brazil).

Depression and anxiety symptoms

Depression and anxiety symptoms were assessed by the Beck Depression's Inventory (BDI) and Beck Anxiety's Inventory (BAI), respectively (Beck et al. 1961, Hewitt & Norton 1993). Both questionnaires have been validated for Brazilian Portuguese (Cunha 2001).

The BDI and BAI tests consist of a self-report questionnaire with 21 questions, each one with four statements corresponding to depression and anxiety symptoms, respectively. Both tests were applied by the psychology team and the responders were instructed to consider the week previous to the test, including the test day. The answers were graded 0-3 points and the total score allowed the classification of depression degrees as "none or minimal" (0-9), "mild" (10-16), "moderate" (17-29) or "severe" (30-63) and anxiety degrees as "minimal" (0-7), "mild" (8-15), "moderate" (16-25) or "severe" (26-63) (Beck et al. 1961, Hewitt & Norton 1993).

Blood samples collection and analysis

Blood samples were collected after a 12-h overnight fast and centrifuged (20 minutes, 3000 rpm, 4 °C). ELISA was used to determined serum levels of ICAM-1, VCAM-1 and MCP-1 (Multiplex, Merck Millipore, Billerica, MA, USA) and leptin, adiponectin and PAI-1 (R&D Systems, Minneapolis, MN, USA).

For proteomic analysis, blood samples were collected under EDTA and the plasma received a protease-inhibitor mixture (150 µL/mL) (Complete Mini Protease Inhibitor Cocktail Tablets, Roche Applied Science, Penzberg, Upper Bavaria, Germany). The samples were homogenized and stored at -80 °C.

Interdisciplinary therapy

Nutritional therapy

All participants received an individual diet orientation using the predictive equation for obese individuals, according to Dietary Reference Intakes (DRI 2005). The volunteers participated in group dietary orientations (1 hour/week), aimed at promoting nutritional education for changes of eating habits. The nutritionist team presented topics such as food pyramid, food labels, food choices in social events, and other nutrition topics brought by the volunteers.

Psychological therapy

The psychological therapy (1 hour/week) was performed through group dynamics. The psychology team addressed topics such as body image, anxiety and eating behavior, emotions, family relationships, and stress management.

Contents brought by the volunteers were also discussed. Individual psychotherapy was offered only when behavioral problems were detected.

Physical exercise therapy

Physical exercise (three hours/week, 1-hour sessions on alternate days) included 30 minutes of aerobic training plus 30 minutes of resistance training per session, under the supervision of sports therapy team.

Proteomic analysis

Albumin depletion was performed in 250 µL of plasma by affinity chromatography using Blue Sepharose CL-6B (GE Healthcare Life Science, Chicago, Illinois, United States). The samples were dried under vacuum and then diluted in 400 µL of 50 mM NH_4HCO_3. Aliquots of 20 µg of protein of each sample were pooled (5 individual samples per pool). The samples in each pool were chosen randomly.

The sample pools were prepared for mass spectrometry analysis as previously reported, with minor modifications (Pedroso et al. 2017). Briefly, each pool was incubated (80°C for 15 minutes) with 25 µL of 0.2% solution of RapiGest SF (Waters, Milford, Massachusetts, US), reduced with 2.5 mM DTT (60°C for 30 minutes) and alkylated with 10 mM iodoacetamide (room temperature for 30 minutes in the dark). Proteins were digested using trypsin (Promega Corp., Madison, Wisconsin, US) at a 1:100 (wt:wt) enzyme:protein ratio (37°C overnight). Samples were then incubated with 10 µL of 5% trifluoroacetic acid (37°C for 90 minutes), centrifuged (13,000 rpm at 4°C for 10 minutes) and the supernatants were recovered.

Mass spectrometry

Peptides were analyzed in three technical replicates on a nanoAcquity UPLC system coupled with a Synapt G2 HDMS mass spectrometer (Waters). Samples were injected onto a trap column (nanoAquity C18 trap column Symmetry 180 µm x 20 mm, Waters) and then transferred by an elution gradient to an analytical column (nanoAcquity C18 BEH 75 µm x 150 mm, 1.7 mm, Waters). The mobile phase A (0.1% formic acid in water) and the mobile phase B (0.1% formic acid in acetonitrile) were used to generate a phase B elution gradient (7 to 35%) during 92 minutes at a flow rate of 275 nL/min. Data were acquired in $HDMS^E$ mode, switching the collision energy from low (4 eV) to high (ramped from 19 to 45 eV), for accurate measurement of both intact peptides and fragments. External calibration was performed with infusion of Glu-fibrinopeptide B (Waters) solution (500 fmol/mL in 50% acetonitrile, 0.1% formic acid) through a nanoLockSpray apparatus, scanned every 30 seconds.

Protein identification and relative quantitation

ProteinLynx Global Server software version 3.0.1 (Waters Corp.) was used for data processing and for database search against *Homo sapiens (Human)* sequences from UniProtKB/Swiss-Prot database (www.uniprot.org). The search parameters were as follows: cysteine carbamidomethylation as fixed modification, methionine oxidation, N-terminal acetylation, glutamine, and asparagine deamidation as variable modifications, automatic fragment and peptide mass tolerance, and up to 2 missed cleavage sites allowed for trypsin digestion. A minimum of 1 fragment ion per peptide, 5 fragment ions per protein and 2 peptides per protein were set as criteria for protein identification. The false discovery identification rate was set to 1%. Label-free quantitative assessments based on peptide intensities were performed. The integrated intensities of the three most intense peptides of each identified protein were used for relative quantitation.

Results were exported as Excel files. Only proteins identified in at least 2 technical replicates were included in statistical analysis. Additionally, proteins not detected in any replicate of one condition (indicating that the intensities were bellow the detection limit), but identified in the other condition, were listed. Normalization was performed in each sample according to the sum of protein intensities.

Statistical Analysis

Statistical analysis was performed using STATISTICA 12.0 (StatSoft, Tulsa, OK, USA).

The Shapiro-Wilk normality test was applied to all variables, with exception of proteome results. Comparisons between baseline and post-treatment values were performed by paired Student's "t" test (parametric variables) or Wilcoxon test (nonparametric variables). Pearson correlation analysis was used to evaluate the relationship between depression (BDI score) or anxiety (BAI score) symptoms with inflammatory, body composition, anthropometric and dietary intake parameters. Correlation analysis was performed with the pre- and post-IT values combined (n=30).

Protein intensities differences between baseline and post-therapy conditions were analyzed using paired Student's "t" test. Significance was set at $p \leq 0.05$. The biological process related to each significantly altered protein was assessed at the UniProtKB/Swiss-Prot database.

RESULTS

IT attenuated obesity and psychological measures

The IT was effective in decreasing body mass and BMI and in improving body composition. It also reduced the dietary intakes of calories and saturated fatty acids (Table I).

The IT reduced leptin, ICAM-1, VCAM-1, PAI-1 and MCP-1 levels while adiponectin levels did not change (Table II).

According to BDI scores, the subjects presented mild depressive symptoms at baseline while the post-therapy score indicated minimal depression symptoms. Although the BAI scores showed minimal anxiety symptoms both at baseline and after IT, the post-IT values were significantly lower than the baseline values (Table III).

Correlation analysis

The BDI scores correlated positively with ICAM-1, VCAM-1, and PAI-1 serum levels (Figure 1a-c) and the BAI scores correlated positively with MCP-1 serum levels (Figure 2). No other significant correlations were detected.

Proteomic analysis

Forty-three proteins were identified (Supplementary Table SI), of which 9 were significantly affected by the IT (Table IV and Table SI). The therapy induced downregulation of apolipoprotein A-I (APOA1), alpha-2-HS-glycoprotein (AHSG), alpha-1B-glycoprotein (A1BG), immunoglobulin heavy constant mu (IGHM), apolipoprotein A-IV (APOA4), and attractin (ATRN), which was observed exclusively at baseline. Ceruloplasmin (CP) and serum albumin (ALB) were upregulated after therapy. Moreover, immunoglobulin kappa variable 1D-12 (IGKV1D-12) was detected only after the therapy (Table IV). The biological processes in which these proteins participate are shown in table IV. They are mainly related to immune response and cholesterol metabolism.

Table I. Anthropometric and body composition measures and food intake of women with grade I obesity, at baseline and at the end of the 6-months interdisciplinary therapy (IT).

	Baseline	Confidence interval	Post-IT	Confidence interval	p-value
Body composition					
BM (Kg)	88.35 ± 1.90	84.3 – 92.4	85.19 ± 2.02	80.9 – 89.5	**<0.01[a]**
BMI (Kg/m2)	33.8 (30.1 - 34.5)	32.0 – 33.9	32.3 (28.9 – 33.5)	30.9 – 32.6	**<0.01[b]**
FFM (Kg)	50.21 ± 0.96	48.1 – 52.3	49.13 ± 1.02	46.9 – 51.3	**<0.01[a]**
FFM (%)	56.89 ± 0.44	56.0 – 57.8	57.75 ± 0.47	56.7 – 58.8	**<0.01[a]**
BF (Kg)	38.14 ± 1.06	35.9 – 40.4	36.06 ± 1.12	33.7 – 38.4	**<0.01[a]**
BF (%)	43.11 ± 0.44	42.2 – 44.0	42.25 ± 0.47	41.2 – 43.3	**<0.01[a]**
Food intake					
Total intake (Kcal)	1802.11 ± 129.44	1524.5 – 2079.7	1606.12 ± 87.85	1417.7 – 1794.5	**0.04[a]**
Carbohydrates (g)	240.22 ± 15.95	206.0 – 274.4	216.21 ± 12.72	188.9 – 243.5	0.11[a]
Proteins (g)	76.77 ± 6.95	61.9 – 91.7	71.58 ± 5.09	60.7 – 82.5	0.47[a]
Lipids (g)	59.35 ± 6.42	45.6 – 73.1	50.55 ± 3,47	43.1 – 58.8	0.08[a]
SFA (g)	15.94 ± 2.72	10.1 – 21.8	10.86 ± 1.43	7.8 – 13.9	**0.04**[a]
MUFAs (g)	10.53 (4.31 – 24.33)	8.7 – 16.8	10.07 (2.52 – 17.13)	7.8 – 12.4	0.14[b]
PUFA (g)	6.94 ± 0.94	4.9 – 9.0	7.34 ± 0.95	5.3 – 9.4	0.72[a]
Fibers (g)	11.64 ± 1.19	9.1 – 14.2	9.93 ± 1.01	7.8 – 12.1	0.12[a]

[a]Paired Student "t" test (Mean ± Standard Error); [b]Wilcoxon test (Median (Minimum - Maximum))
Abbreviations: BM = body mass; BMI = body mass index; FFM = fat free mass; BF = body fat; SFA = saturated fatty acids; MUFA = monounsaturated fatty acids; PUFA = polyunsaturated fatty acids. N = 15.

Table II. Inflammatory markers of women with grade I obesity, at baseline and at the end of the 6-months interdisciplinary therapy.

Inflammatory markers					
	Baseline	**Confidence interval**	**Post-therapy**	**Confidence interval**	**p-value**
Leptin (ng/mL)	21.32 (13.50 - 61.24)	19.2 – 36.4	14.18 (8.53 - 49.08)	13.9 – 27.8	**<0.01[b]**
Adiponectin (ug/mL)	6.99 (2.40 - 34.93)	4.6 – 14.9	4.63 (2.39 - 17.92)	4.8 – 11.0	0.26[b]
Leptin / Adiponectin	3.00 (0.53 - 25.51)	1.8 – 8.8	3.13 (0.54 - 10.90)	2.3 – 6.2	0.46[b]
ICAM-1 (ng/mL)	99.78 ± 9.56	79.3 – 120.3	62.13 ± 5.85	49.6 – 74.7	**<0.01[a]**
VCAM-1 (ng/mL)	727.00 ± 83.85	547.2 – 906.8	391.58 ± 38.72	308.5 – 474.3	**<0.01[a]**
MCP-1 (pg/mL)	280.00 (201.00 – 499.00)	272.8 – 368.6	247.00 (94.08 – 474.00)	213.1 – 315.9	**<0.01[b]**
PAI-1 (ng/mL)	88.35 ± 7.49	72.3 – 104.4	50.93 ± 6.32	37.4 – 64.5	**<0.01[a]**

[a]Paired Student "t" test (Mean ± Standard Error); [b]Wilcoxon test (Median (Minimum - Maximum))
Abbreviations: ICAM = intercellular adhesion molecule; VCAM = vascular cell adhesion molecule; MCP-1 = monocyte chemotactic protein-1; PAI-1 = plasminogen activator inhibitor-1. N = 15.

Table III. Psychological tests of women with grade I obesity, at baseline and at the end of the 6-months interdisciplinary therapy.

Psychological test					
	Baseline	Confidence interval	Post-therapy	Confidence interval	p-value
BDI	16.13 ± 2.14	11.5 – 20.7	8.00 ± 1.23	5.4 – 10.6	**<0.01**[a]
BAI	7 (0 - 35)	5.6 – 16.9	5 (0 - 23)	3.0 – 10.3	**0.02**[b]

[a]Paired Student "t" test (Mean ± Standard Error); [b]Wilcoxon test (Median (Minimum - Maximum))
Abbreviations: BDI = Beck depression inventory; BAI = Beck anxiety inventory.
N = 15.

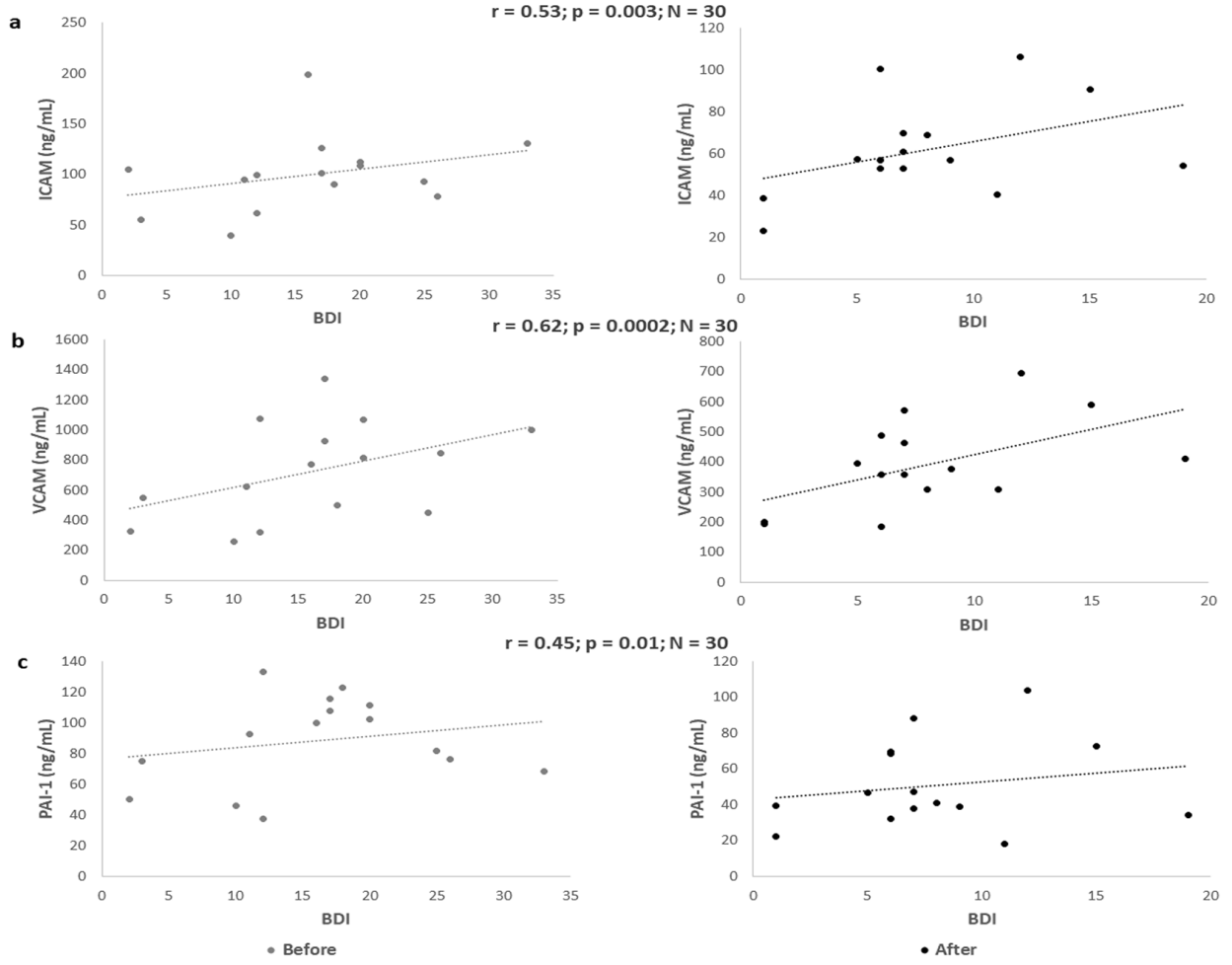

Figure 1. Relationships between BDI and ICAM-1 (a), VCAM-1 (b) and PAI-1 (c) in women with grade I obesity.

DISCUSSION

In the present investigation, we found, in women with grade I obesity, that depression symptoms had a positive correlation with PAI-1, VCAM-1, and ICAM-1, while the anxiety symptoms correlated positively with MCP-1. We also showed that the application, for 6 months, of an interdisciplinary therapy program for weigh loss (IT) was effective in improving anthropometric, inflammatory, and psychological parameters.

We observed a small 3.6% decrease in body weight in response to the IT. This was probably due to the also small decrease in total caloric intake (11%), achieved by a 32% diminished

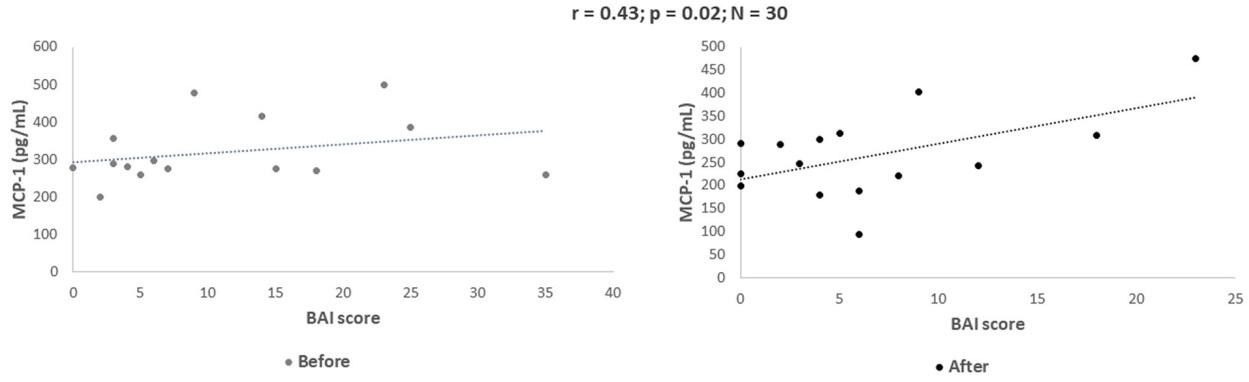

Figure 2. Relationships between BAI and MCP-1 in women with grade I obesity.

intake of saturated fatty acids. We have observed changes in body weight similar to the present observation in studies including both grade I and grade II obese subjects (de Carvalho et al. 2012, Jamar et al. 2016, Moraes et al. 2019). It is important to note that, although the decrease of body weight achieved after the 6-months IT was not sufficient to change the obesity grade, it did improve the inflammatory parameters and also affected plasma proteins, as evaluated by mass spectrometry.

The observation that the inflammatory parameters changed more prominently in comparison to the body weight changes indicates that the beneficial value of the IT may not be judged based only on its anthropometric effects. Indeed, considering the difficulties that obese subjects have to achieve body weight loss, it is important to point that even small weight losses may be relevant to the metabolic and inflammatory statuses.

The association of inflammatory activation and depression has been evidenced in both animal and human studies. The intraperitoneal injection of LPS has been shown to induce depressive-like behaviors and increased PAI-1 levels in mice (Girard et al. 2019). Increased PAI-1 levels have been reported in eutrophic men and women presenting depression symptoms (Girard et al. 2019). The present results in women with grade I obesity corroborate these findings and shows that this association is also present in obesity, indicating that obesity treatment may also be beneficial for the associated depression symptoms. Importantly, we were also able to demonstrate that the IT induced weight loss and attenuated both the levels of inflammatory markers and the depression scores.

We observed a positive correlation between ICAM-1 and VCAM-1 levels with depression symptoms in women with grade I obesity. These findings corroborate the indications of a role of microvascular disfunction, caused by adhesion molecules, in the development of depression in elderly eutrophic men and women (Tchalla et al. 2015). ICAM-1 association with depression symptoms in individuals with overweight has also been observed (van Doreen et al. 2016). Here, we report that the IT decreased ICAM-1 and VCAM-1 levels, showing that weight loss in women with grade I obesity is able to also minimize the derangements associated with depression symptoms in this population.

We also found a positive correlation between MCP-1 levels and anxiety symptoms. Moreover, both BAI scores and MCP-1 levels decreased after the IT. At the best of our knowledge, this is the first demonstration of an association of anxiety status and MCP-1 in women with grade I obesity. This chemokine has been shown to be elevated in individuals with obesity (Panee 2012) and in eutrophic adults of both genders with

Table IV. Plasma proteins significantly affected by interdisciplinary therapy.

UniProt ID	Gene name	Protein	Metabolic process	Fold-change	p-Value*
Down-regulation by IT					
P02647	APOA1	Apolipoprotein A-I	Cholesterol metabolic process	0.74	0.05
P06727	APOA4	Apolipoprotein A-IV	Cholesterol metabolic process Innate immune response in mucosa	0.80	0.05
P02765	AHSG	Alpha-2-HS-glycoprotein	Acute-phase response Neutrophil degranulation Platelet degranulation	0.63	0.02
P04217	A1BG	Alpha-1B-glycoprotein	Neutrophil degranulation Platelet degranulation	0.78	0.03
P01871	IGHM	Immunoglobulin heavy constant mu	Innate Immune response	0.61	<0.01
O75882	ATRN	Attractin	Inflammatory response	Not detected at post-therapy[1]	
Up-regulation by IT					
P00450	CP	Ceruloplasmin	Cellular iron ion homeostasis	1.64	<0.01
P02768	ALB	Serum albumin	Cellular response to starvation. Lipoprotein metabolic process	1.36	<0.01
P01611	IGKV1D-12	Immunoglobulin kappa variable 1D-12	Regulation of complement activation Immune response	Not detected at baseline[2]	

UniProt ID: UniProt Identification (acession code); Gene name: name of the gene that codes for the protein; Protein name: Uniprot recommended name; Fold-change: mean protein intensity at post-therapy/mean protein intensity at baseline. *p-Value based on Student's "t" test. [1] protein not detected in any of the 3 replicates pos-therapy and identified in at least 2 replicates at baseline, indicating down-regulation. [2] protein not detected in any of the 3 replicates at baseline and identified in at least 2 replicates post-therapy, indicating up-regulation.

generalized anxiety and personality disorders (Ogłodek et al. 2015). The present results thus corroborate the indications of a role of MCP-1 in anxiety and demonstrate this association in women with grade I obesity. Cohort studies have also found an increase of anxiety severity/symptoms with the increase of inflammation status (van Eeden et al. 2021, Vogelzangs et al. 2016).

In the present study, the women with grade I obesity showed a BAI score of minimal anxiety both before and after the IT, despite the significant decrease induced by the therapy. This discrete diminution in BAI is probably relevant, since the test considers how much the individuals have been bothered by each symptom over the past week (Beck et al. 1961, Hewitt & Norton 1993), indicating that the discrete decrease in BAI score could is due to an improvement in the symptoms. In one study demonstrating a positive correlation of anxiety and inflammation the authors suggested that if inflammatory activation in obesity is amplified by anxiety, it may contribute to some long-term complications of obesity (Pierce et al. 2017), what could indicate that the decrease found in the present study could be sufficient to cause a change in the MCP-1 levels, but more studies were needed to prove this results.

We found no significant correlations for adiponectin and observed no variations in adiponectin levels and leptin/adiponectin ratio, after the 3% weight loss induced by the IT. These results corroborate our previous findings in women with obesity, whose weight loss was of 6% after one year of IT (Moraes et al. 2019).

Absence of adiponectin variations have also been reported after 6 months of a dietary therapy

that induced a weight loss of 4.5%, in individuals with overweight and obesity. In contrast, after 2 years of therapy, those individuals showed increased adiponectin levels, while body weight was maintained at a level 2.5% lower than the initial weight (Ma et al. 2016). These results may indicate that, not only the degree of weight loss but also the long-term weight maintenance is relevant to impact on adiponectin levels.

The proteomic analysis revealed that the IT reduced the plasma levels of APOA1 and APOA4, proteins involved in cholesterol metabolism. APOA1, the main protein constituent of HDL particles, has been attributed a role as predictor of cardiovascular risk and showed an inverse correlation with adiposity (Wang & Peng 2012). The present results agree with the demonstration of reduced APOA1 levels in children with overweight and obesity, after a dietary intervention. The authors attributed the APOA1 response to the observed substantial reduction of total cholesterol levels (Vrablík et al. 2014). Decreased APOA1 levels have also been found in women and men with overweight and obesity after a dietary intervention (Tovar et al. 2015).

APOA4 participates in reverse cholesterol transport and anti-inflammatory and antioxidant properties have also been described for this protein (Raffaelli et al. 2014). Data on the response of plasma APOA4 levels to weight loss are still controversial and the studies have indicated that it may be dependent on the time course and degree of weight loss. The drastic weight loss induced by bariatric surgery in women with grade IV obesity has been shown to be accompanied by increased circulating APOA4 levels, showing a positive correlation with the increased levels of HDL-C (Raffaelli et al. 2014). In contrast, individuals with obesity submitted to gastric bypass have shown decreased APOA4 levels one month after the surgery but the levels started to increase afterwards, reaching preoperative levels 12 months after the procedure (Pardina et al. 2009). The authors attributed the APOA4 decrease to an adaptation to weight loss.

The proteomic analysis evidenced that the IT altered the plasma levels of proteins associated with inflammation. IT down-regulated AHSG, a protein expressed mainly by hepatocytes that has been associated to insulin resistance, subclinical inflammation, and cardiovascular disease (Stefan & Häring 2013). Studies in cultured cells have evidenced a role of AHSG in inflammation and atherosclerosis. High levels of MCP-1 and PAI-1 have been detected in perivascular fat cells and in endothelial cells after incubation with AHSG (Siegel-Axel et al. 2014). The AHSG decrease observed here may, thus, indicate that IT had a positive effect on pathways related with inflammation and atherosclerosis.

Despite the indication of A1BG participation in the immune system, little is known about its function. Increased A1BG levels have been reported in patients with rheumatoid arthritis and block of TNF-alpha improved protein levels (Estelius et al. 2019). Here, A1BG levels decreased after the IT, but more studies are necessary to determine the function and influence of this protein in individuals with obesity.

We observed that the IT decreased plasma levels of attractin, an enzyme expressed in monocytes plasma membranes that increases T-cell infiltration (Wrenger et al. 2006). Higher levels of monocyte attractin have been observed in adults with obesity in comparison to lean subjects (Laudes et al. 2012). The attractin reduction induced by the IT suggests that weight loss decreased inflammatory mediators.

IT led to decreased levels of IGHM, a part of immunoglobulin M (IgM). In comparison to eutrophic individuals, obese men have

shown increased basal circulating levels of B lymphocytes and an exacerbated IGHM response to influenza, in a manner proportional to BMI (Kosaraju et al. 2017). It is possible to suggest that the decrease of IGHM levels may indicate an improvement of inflammatory status induced by the IT.

IGKV1D-12 was identified in the subjects plasma only after IT, indicating up-regulation. Immunoglobulins free light chains in serum are involved in the inflammatory response, participating in the activation of mast cells and neutrophils for the release of chemotactic and pro-inflammatory cytokines and infiltration of T-lymphocytes and macrophages in tissues (Esparvarinha et al. 2017). In individuals with type 2 diabetes, decreased kappa light chain and increased lambda light chain levels have been reported (Matsumori et al. 2020). The present findings warrant further studies to understand the role of IGKV1D-12 in obesity.

The plasma samples used for the present proteomic analysis were albumin depleted, as it could impair the identification of low-abundant proteins. However, even after this procedure, we were able to detect a significant increase of albumin after the IT. Since it has been demonstrated that individuals with obesity had increased risk of hypoalbuminemia (Mosli & Mosli 2017), the present data could indicate an improvement of plasma albumin status after IT.

Our study presented some limitations, such as the sample size, since some volunteers gave up the IT and only the subjects finishing the treatment were included in the analyses. Additionally, because our goal was to conduct an initial screening of the plasma proteome response to IT in women with grade I obesity, the proteome analysis was performed in pooled samples.

The present study demonstrated the beneficial effects of a short-term interdisciplinary program for weigh loss in women with grade I obesity, a population that has drawn little attention in the literature. In summary, our findings showed that the IT, in women with grade I obesity, improved anthropometric and inflammatory parameters as well as depression and anxiety symptoms. We were also able to demonstrate that MCP-1 is among the inflammatory mediators affected by the IT, a finding that, at the best of our knowledge, has not yet been reported. Additionally, the present demonstration of positive associations of inflammatory markers and psychological symptoms indicate that these mediators may be useful to monitor depression and anxiety status in obesity. Finally, the present proteome data, although preliminary, pointed to plasma alterations indicative of improvement of inflammation after IT.

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SUPPLEMENTARY MATERIAL

Table SI

How to cite

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APS and LOTC were the main researcher, contributed to data collection and writing the manuscript. APP, ASM, MATC and ARD, also contributed to the data collection. AKT performed the proteome analysis. MMT, LMO and DAC contributed to the discussion of the manuscript. EBR was the main coordinator of the study, contributed to study design, writing, discussion and article review.