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Research Paper

Discriminatory metabolic and inflammatory parameters in serum and omental adipose tissue of obese patients with different insulin sensitivity☆

Marian Khatib [a,1], Isabel Zvibel [b,c,1], Shira Zelber-Sagi [b,d], Chen Varol [b,c], Guy Lahat [a], Subhi Abu-Abeid [a], Joseph M. Klausner [a,c], Zamir Halpern [b,c], Sigal Fishman [b,c,*]

[a] Surgery Department, Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel
[b] The Research Center for Digestive Tract and Liver Diseases, Tel-Aviv Sourasky Medical Center, Israel
[c] Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel
[d] School of Public Health, Haifa University, Haifa, Israel

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ABSTRACT

Objective: Metabolically healthy obese phenotype is defined by high insulin sensitivity and lack of metabolic syndrome, parameters regulated by omental adipose tissue inflammation, ectopic fat deposition and adipose tissue dysfunction. Our study aimed to identify novel metabolic and inflammatory markers in serum and omental adipose tissue which characterize the "unhealthy" obese patients and distinguish them from obese patients with better metabolic profile.
Design: Cross-sectional study.
Patients: Subjects included 75 obese patients undergoing bariatric surgery at the Tel-Aviv Medical Center (mean age 43.9 ± 13.9, mean BMI 41 ± 8.4). The HOMA median value was used as a cut-off to differentiate between patients with better or worse insulin resistance.
Measurements: Demographic data, fasting serum insulin, glucose, bile acids, serum metabolic and inflammatory markers were obtained. During the bariatric surgery, omental adipose tissue was harvested and analyzed for metabolic and inflammatory markers using qRT-PCR. Logistic regressions were used to calculate odds ratio and 95% confidence interval for the prediction of the metabolic profile.
Results: Serum markers that were significantly higher among the obese with HOMA >6 were total bile acids. In the omental adipose tissue the inflammatory markers TNFα and ADAM17 were significantly higher among obese patients with HOMA >6. In multivariate analysis, the strongest predictor for insulin resistance was ADAM17 (OR = 1.82, 1.06–3.14, $P = 0.031$).
Conclusions: The study highlighted the predictive value of serum bile acids in identifying obese patients at high risk. Secondly, omental adipose tissue ADAM17 was revealed as a novel and strongest independent predictor for higher insulin resistance in morbidly obese patients.

Introduction

Obesity is associated with increased risk of developing metabolic syndrome (MetS), type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) leading to higher all-cause mortality. However, accumulating evidence suggests that not all obese subjects are at increased cardiometabolic risk and that the "metabolically healthy obese" (MHO) phenotype may exist [1]. These individuals are defined as having metabolically benign obesity [2] with high levels of insulin sensitivity, normal lipid and inflammation profiles and are normotensive, despite excessive body fatness [3–5].

The molecular basis for this phenotype is not well understood but is likely to involve reduced inflammatory responses [6].

Abbreviations: ADAM17, A disintegrin and metalloproteinase; CIDE, Cell death inducing DNA fragmentation factor; HOMA, Homeostasis model assessment; TIMP, Tissue inhibitor of metalloproteinase.

Conflict of interest: The authors have no conflict of interest to declare.

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* Corresponding author. Gastroenterology Department, Tel Aviv Sourasky Medical Center, 6 Weizmann, Tel-Aviv 64239, Israel. Tel.: +972 52 4262625; fax: +972 3 6974622.
E-mail address: sigalf@tlvmc.gov.il (S. Fishman).

[1] The first two authors contributed equally to the article.

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Primeau et al. have reported a number of characteristics of the MHO, including lower omental fat accumulation, higher birth weight, adipose cell size, and gene expression-encoding markers of adipose cell differentiation [7]. Recent studies suggest that inflammation of omental adipose tissue, ectopic fat deposition and adipose tissue dysfunction mediate IR in human obesity independently of total body fat mass. This suggests that mechanisms beyond a positive caloric balance, such as inflammation and adipokine release determine the pathological metabolic consequences in patients with obesity [8].

So far, there is still limited data regarding the determinants of the MHO phenotype, which would shed light on the pathogenesis of metabolic alterations in obesity and would help in the development of new therapeutic interventions tailored to obese individuals with specific metabolic phenotype.

In the present study, we aimed to identify inflammatory and metabolic markers in serum and omental adipose tissue of morbidly obese patients which correlate with better or worse insulin resistance state. In addition, we sought whether there were any significant associations between certain metabolic and inflammatory markers.

Experimental design & methods

Study design and population

We have performed cross-sectional study in a cohort of seventy five morbidly obese patients attending the obesity clinic at the Tel-Aviv Medical Center and that underwent a bariatric surgery. All data were collected prospectively. Exclusion criteria were: type-2 diabetes treated with insulin and type-1 diabetes. The HOMA was calculated as fasting serum insulin [μU/ml] × fasting plasma glucose [mmol/l]/22.5 [9] served in the definition of the MHO (divided to percentiles as accepted [1]).

Serum tests

Serum was drawn from fasted patients before their bariatric surgery and kept frozen in aliquots at −80 °C. Serum adipokines and inflammatory cytokines (adiponectin, IL-6, resistin, progranulin) were detected by ELISA assays (R&D systems). Total glucose dependent insulinotrophic polypeptide (GIP) was detected by ELISA (EMD Millipore Corporation). Other metabolic and liver function tests (including bile acids) were assayed at the local chemistry lab. Insulin was assessed by RIA at the endocrinology lab at Tel-Aviv Sourasky Medical Center.

Quantitative real time RT-PCR from omental adipose tissue

Omental fat was taken from patients that signed the informed consent form for fat biopsy (not all subjects that agreed for their sera to be used agreed to have biopsies of fat taken) during the bariatric surgery and was used to extract total RNA using the RNeasy Lipid tissue kit (Qiagen) and 2.5 μg total RNA was reverse-transcribed using M-MLV (Promega, Madison, WI). Real time RT-PCR (qRT-PCR) was performed using the Absolute Blue QPCR SYBR green ROX mix (Thermo Fisher Scientific, Epsom, Surrey, UK) in the Corbett rotor light cycler (Corbett Robotics Pty Ltd, Brisbane, Australia). The primers used were:

Lipoprotein lipase (LPL): 5′- GGGCATGTTGACATTTACCC-3′, 5′-CTCGTGGGAGCACTTCACTA - 3′;

CIDEC: 5′- CTGGCAGGGGATACAGTGTT -3′, 5′-GTCCTGTGGGTTCAGCTTGT - 3′;

CIDEA: 5′- CCAACCATGACAGGAGCAG -3′, 5′- TCTTCCTCCAG-CACCAGAGT - 3′;

Table 1
Characteristics of the study population (mean ± SD, unless otherwise stated)

Characteristic $n = 75$	Distribution
Age (years)	43.89 ± 13.88
Gender (% men)	30.7
BMI (kg/m^2)	41.04 ± 8.36
Diabetes (%)	24.3
Oral diabetic medication (%)	12
HOMA (score)	8.10 ± 7.17
Insulin (mU/ml)	33.81 ± 24.68
ALT (U/l)	14.88 ± 18.49
AST (U/l)	23.07 ± 12.44

Perilipin (plin): 5′- GGAGTACCTCCTCCCTCCAG -3′, 5′-TCTGCACGGTGTATCGAGAG - 3′;

11β-hydroxysteroid dehydrogenase type 1 (HSD1B11): 5′-AGAGCAATTTGTTGCCCAAG -3′, 5′- AATGCTTCCATTGCTCTGCT- 3′;

Progranulin (PRGN): 5′- GCCACTCCTGCATCTTTACC -3′, 5′-GATCTTTGGAAGCAGGATCG - 3′;

Sortilin: 5′- CATTTGGGGCTTCACAGAAT -3′, 5′-TTCAGGGTCTGTGGAGTGTG- 3′;

IL-6: 5′- TACCCCCAGGAGAAGATTCC -3′, 5′-TTTTCTGCCAGTGCCTCTTT - 3′; GIP receptor (GIPR): 5′-CAATGGG-GACTTTGGAGAGA-3′,5′-AAGATGAGCAGGGCTAGCAG-3′;

TNFα: 5′- TCAGCCTCTTCTCCTTCCTG -3′, 5′- GCCA-GAGGGCTGATTAGAGA - 3′;

ADAM17: 5′- GAGGACCAGGGAGGGAAATA -3′, 5′- CTTCATC-CACCCTCGAGTTC - 3′;

TIMP3: 5′- AGGACGCCTTCTGCAACTC -3′, 5′- CTTCATCTGCTT-GATGGTGTAG - 3′;

Fractalkine: 5′- TGTGACGAAATGCAACATCA-3′, 5′-CTGTGCTGTCTCGTCTCCAA - 3′;

Osteopontin (OPN): 5′-GGCTAAACCCTGACCCATCT -3′, 5′-GTCAATGGAGTCCTGGCTGT- 3′;

CCL2: 5′- CCCCAGTCACCTGCTGTTAT -3′, 5′- AGATCTCCTTGGC-CACAATG- 3′;

CCL8: 5′- AGCCACTTTCAGCCCTCAG -3′, 5′- TCTCCAGCCTCTG-GATAGGA - 3′;

CCL20: 5′-TTTATTGTGGGCTTCACACG-3′, 5′-TCACC-CAAGTCTGTTTTGGA- 3′;

IL-1β: 5′- CTGTCCTGCGTGTTGAAAGA-3′, 5′-TTCTGCTTGA-GAGGTGCTGA-3′;

RPLPO: 5′- CCCGAGAAGACCTCCTTTTT -3′, 5′- AGGA-GAAGGGGGAGATGTTG - 3′;

Statistical analysis

Statistical analyses were performed using SPSS version 21. Continuous variables are presented as means ± SD.

To test differences in continuous variables between the two groups of metabolic status, the independent samples *t*-test and, if necessary, for non-normally distributed variables, the nonparametric Mann–Whitney test were performed (as depicted in Table 2).

Associations between nominal variables were performed with the Pearson Chi–Square test. Correlations between continuous variables were calculated with the Pearson or spearman correlation. A multivariate logistic regression analysis was performed to test the gender adjusted association between the metabolic and inflammatory parameters and the metabolic phenotype. The variables that remained significantly associated with elevated HOMA with adjustment for gender, were further tested in an expended multivariate analysis (with a stepwise entry) aimed to define the

Table 2
Comparison of patients with HOMA above and below the median (mean ± SD, unless otherwise stated)

Variable	HOMA below median (<6)	HOMA above median (>6)	*P* value
Age (years)	42.45 ± 14.37 ($n = 30$)	43.45 ± 10.31 ($n = 29$)	0.762
Gender (% men)	13.3 ($n = 30$)	51.7 ($n = 29$)	0.002
BMI (kg/m^2)	42.79 ± 7.52 ($n = 30$)	42.88 ± 6.53 ($n = 29$)	0.850[b]
ALT (U/l)	10.63 ± 4.73 ($n = 30$)	15.50 ± 9.82 ($n = 29$)	0.021
AST (U/l)	19.93 ± 7.17 ($n = 30$)	24.34 ± 10.66 ($n = 29$)	0.066
Diabetes %	20.0	39.3	0.107
HOMA (score)	4.46 ± 1.21 ($n = 30$)	12.53 ± 9.13 ($n = 29$)	**<0.001**
Serum markers			
IL-6 (pg/ml)	7.22 ± 4.26 ($n = 21$)	7.09 ± 2.57 ($n = 21$)	0.905
Resistin (ng/ml)	10.44 ± 4.75 ($n = 27$)	10.31 ± 5.86 ($n = 24$)	0.930
Adiponectin (ug/ml)	5.91 ± 4.34 ($n = 28$)	4.01 ± 2.30 ($n = 24$)	0.060
Total GIP (pg/ml)	46.39 ± 36.90 ($n = 23$)	37.10 ± 26.58 ($n = 27$)	0.763[b]
Progranulin (ng/ml)	53.75 ± 12.10 ($n = 30$)	59.17 ± 17.42 ($n = 29$)	0.172
TG (mg/dl)	146.23 ± 57.66 ($n = 30$)	190.62 ± 85.99 ($n = 29$)	**0.025**
Insulin (mU/ml)	22.27 ± 5.88 ($n = 30$)	48.72 ± 31.63 ($n = 29$)	**<0.001**[b]
Bile acids (μM)	3.17 ± 3.37 ($n = 29$)	6.22 ± 5.84 ($n = 29$)	**0.003**[b]
Visceral adipose tissue markers (AU)[a]			
Metabolic markers			
CIDEA	11.15 ± 9.34 ($n = 19$)	14.25 ± 16.26 ($n = 16$)	0.485
CIDEC	3.26 ± 1.83 ($n = 19$)	4.61 ± 2.57 ($n = 16$)	0.081
PLIN	7.11 ± 5.10 ($n = 19$)	7.68 ± 6.23 ($n = 15$)	0.774
Lipoprotein lipase	1.56 ± 1.25 ($n = 20$)	2.70 ± 2.88 ($n = 16$)	0.239[b]
HSD1B11	45.28 ± 40.72 ($n = 14$)	42.14 ± 45.10 ($n = 15$)	0.846
Sortilin	29.83 ± 88.93 ($n = 19$)	16.41 ± 13.56 ($n = 17$)	0.222[b]
GIPR	1.45 ± 1.18 ($n = 19$)	1.88 ± 1.63 ($n = 15$)	0.521[b]
Inflammatory markers (AU)[a]			
PRGN	22.92 ± 50.05 ($n = 19$)	12.03 ± 15.70 ($n = 17$)	0.692[b]
FKN	2.67 ± 2.53 ($n = 11$)	4.44 ± 2.80 ($n = 9$)	0.156
OPN	8.79 ± 7.95 ($n = 12$)	14.97 ± 16.26 ($n = 12$)	0.254
ADAM17	2.38 ± 1.26 ($n = 20$)	4.30 ± 2.21 ($n = 17$)	**0.004**
TIMP3	11.52 ± 6.35 ($n = 20$)	12.95 ± 7.85 ($n = 17$)	0.545
TNF-α	3.18 ± 2.66 ($n = 20$)	9.90 ± 12.65 ($n = 16$)	**0.004**[b]
CCL2	22.73 ± 29.81 ($n = 18$)	14.70 ± 13.54 ($n = 13$)	0.689[b]
CCL8	12.76 ± 15.52 ($n = 17$)	14.45 ± 12.31 ($n = 13$)	0.187[b]
CCL20	13.64 ± 21.23 ($n = 15$)	16.88 ± 22.26 ($n = 10$)	0.717
IL-1β	2.74 ± 3.27 ($n = 18$)	3.52 ± 2.30 ($n = 11$)	0.498
IL-6	63.81 ± 106.69 ($n = 18$)	64.12 ± 75.05 ($n = 16$)	0.629[b]

Bold values mean significance of $P < 0.05$.
[a] AU = arbitrary units: Expression of the various genes in visceral adipose tissue was assessed by qRT-PCR and normalized to expression of housekeeping gene RPLPO.
[b] Calculated by the Mann–Whitney test (for all other variables, that had normal distribution, the independent samples *t*-test was performed).

variables most strongly associated with the MHO phenotype. $P < 0.05$ was considered statistically significant for all analyses.

Ethics

The study was approved by the Tel-Aviv Sourasky Medical Center IRB and all patients signed an informed consent.

Results

Characteristics of the study population

Seventy five patients were included after exclusion of two patients treated with insulin (mean age 43.9 ± 13.9 years). The majority of the patients were women (69.3%) and about one quarter had type-2 diabetes. The characteristics of the study group are presented in Table 1.

Serum variables associated with lower insulin sensitivity among obese subjects

For the analysis of parameters of serum and adipose tissue variables associated with HOMA, 16 patients with BMI <30 were excluded, leaving 59 patients with BMI >30 and measured HOMA.

The study population was divided into two groups with lower and higher insulin sensitivity using the median HOMA value of 6. Importantly, the two groups had very similar age and BMI. The percentage of men was significantly higher among patients with a higher HOMA, and thus adjustment for gender was performed when testing the association with metabolic and inflammatory parameters that were different between groups.

The serum markers tested were several inflammatory adipose tissue derived-cytokines and adipokines, previously shown to be correlated with metabolic syndrome and insulin resistance [10,11]. However, the well-established serum markers did not differentiate between the two groups, with the exception of adiponectin, with levels reduced in the group with HOMA >6, albeit not significantly ($P = 0.060$) (Table 2).

Strikingly, bile acids levels were almost two-fold higher in group with HOMA >6 ($P = 0.003$) (Table 2). Of note, the significance was preserved even after adjustment to gender (OR = 1.21, 95% CI: 1.01–1.45, $P = 0.044$).

Serum triglycerides were also significantly increased in the group with HOMA >6, but the significance was only borderline after adjustment to gender.

Omental adipose tissue inflammatory variables associated with lower insulin sensitivity

Table 2 presents data of omental tissue variables from patients that agreed to fat biopsies. In addition, values of parameters below detection levels were not included.

Expression of TNFα, the inflammatory cytokine shown to be associated with inflammation-induced insulin resistance two

Table 3
Correlations between inflammatory markers in adipose tissue

	Correlation	FKN	OPN	CCL8	CCL2	IL1b
OPN	*r*	**0.601**	1			
	P	0.001				
CCL8	*r*	0.213	0.313	1		
	P	0.307	0.112			
CCL2	*r*	**0.397**	0.301	**0.600**	1	
	P	0.049	0.119	<0.001		
IL1b	*r*	0.102	0.037	**0.546**	**0.772**	1
	P	0.645	0.861	<0.001	<0.001	
CCL20	*r*	**0.634**	**0.547**	0.265	**0.515**	**0.439**
	P	0.002	0.005	0.136	0.002	0.015

Bold values mean significance of $P < 0.05$.

decades ago [12], was indeed three-time higher ($P = 0.004$) in the omental fat of the lower insulin sensitivity group (Table 2). Its significance was preserved after adjustment to gender (OR = 1.38, 1.04–1.84, $P = 0.026$).

A new player in obesity induced-insulin resistance is the enzyme ADAM17 [13], which among other substrates, cuts and releases the mature TNFα into the circulation [13]. Levels of ADAM17 mRNA were almost two-fold higher in the group with lower insulin sensitivity ($P = 0.004$) (Table 2) and the association remained significant after adjustment for gender (OR = 1.93, 1.09–3.40, $P = 0.024$).

Importantly, when the variables that remained significantly associated with elevated HOMA with adjustment for gender were further tested together in a stepwise logistic regression, the strongest predictor that remained in the model was ADAM17 (OR = 1.82, 1.06–3.14, $P = 0.031$).

Analysis of inflammatory cytokines and chemokines in omental adipose tissue revealed strong positive correlations between two macrophage adhesion molecules, FKN and osteopontin (OPN) (Table 3). This association become even stronger ($r = 0.916$, $P = 0.001$) when analysis was performed in the group with the lower insulin sensitivity. A remarkable significant positive correlation between levels of the two macrophage recruitment chemokines CCL2 and CCL8 and the inflammatory cytokine IL-1β was also observed (Table 3). The novel adipokine CCL20 [14] was also significantly positively correlated with the inflammatory cytokines and chemokines in omental adipose tissue (Table 3).

Lipid droplets proteins regulate the capacity of adipocytes to esterify fatty acids into triglycerides and store them within the cell in a safe manner [15]. Previous studies showed that higher expression of lipid droplet proteins perilipin, CIDEA and CIDEC were associated with higher insulin sensitivity in obese patients with similar BMI [16]. However, we have found no significant differences in the expression of lipid droplet proteins or in TG uptake enzyme lipoprotein lipase in the omental adipose tissue of both groups (Table 2).

Correlation between omental adipose tissue PRGN, sortilin and IL-6

The novel adipokine PRGN has been shown to increase insulin resistance via induction of adipose tissue IL-6 [17]. Indeed, we have found a very strong positive correlation between omental adipose tissue expression of PRGN and IL-6 (Fig. 1). The trafficking molecule sortilin is known to regulate serum levels of PRGN by internalizing it and directing it to degradatory pathways [18]. For the first time, we show a strong positive correlation between the mRNA levels of these three factors in omental adipose tissue (Fig. 1). Of note, these correlations become even stronger in the group with lower HOMA: mRNA expression of PRGN and IL-6 ($r = 0.95$, $P < 0.001$, $n = 22$); PRGN and sortilin ($r = 0.96$, $P < 0.001$, $n = 24$); sortilin and IL-6 ($r = 0.93$, $P < 0.001$, $n = 22$).

Discussion

The present study highlighted the important role of serum bile acids as predictors of increased IR among morbidly obese patients. Furthermore, our results revealed ADAM17 as a novel and strongest predictor of IR in omental adipose tissue of morbidly obese patients.

Bile acids have beneficial effects on triglyceride metabolism and improve insulin sensitivity and whole body glucose homeostasis [19,20]. Indeed, post-prandial serum bile acids were found to be increased after Roux-en-Y gastric bypass [21]. Furthermore, the role of bile acids as general metabolic integrators was shown in a murine model in which bile acids administration increased energy expenditure of brown fat and prevented obesity and IR [22]. Surprisingly, our studies demonstrated increased levels of fasting bile acids in the group with lower insulin sensitivity (Table 2). These results of higher basal serum bile acids may reflect the impaired bile acids secretory function found in fatty liver disease [23]. Consistent with our results, serum bile acids were previously shown to be increased in diabetic obese patients [24].

In adipose tissue, the lower insulin sensitivity group displayed increased mRNA levels of inflammatory and metabolic markers. Numerous studies have highlighted the role of adipose tissue inflammation in obesity and IR [25–27].

Studies performed two decades ago recognized TNFα as a pivotal non-dispensable player in obesity-induced inflammation and IR [26,27]. The TACE/ADAM17 enzyme was shown to induce the shedding of TNFα, therefore participating in IR induction. A large body of evidence suggests that ADAM17 is activated in metabolic disorders and contributes to progressive deterioration of metabolic

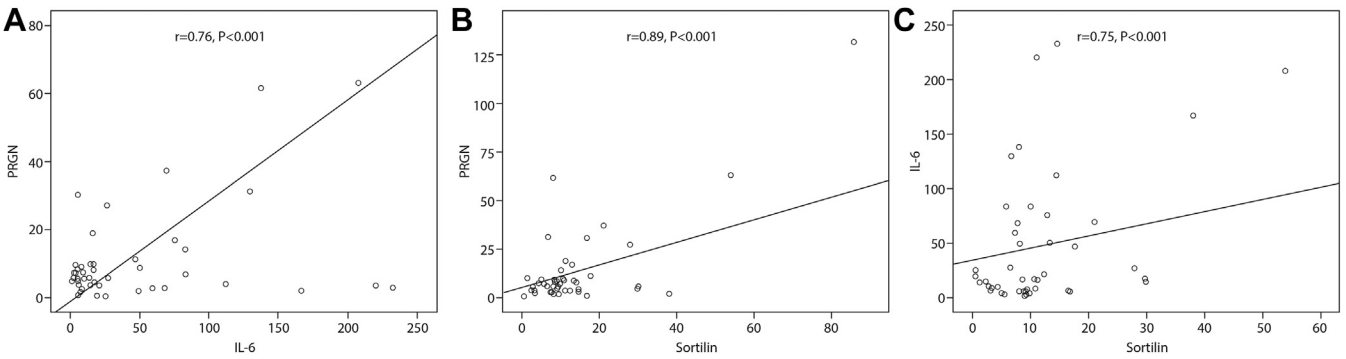

Figure. 1. Correlations between: (A) mRNA expression of PRGN and IL-6 ($n = 45$); (B) PRGN and sortilin ($n = 49$); (C) sortilin and IL-6 ($n = 45$) in omental adipose tissue of obese patients. Expression of PRGN, sortilin and IL-6 was detected by qRT-PCR and normalized to expression of RPLPO.

homeostasis via regulation of pathways involved in adipose tissue infiltration by macrophages, reduction of glucose uptake in skeletal muscle and increased lipogenesis in the liver [13]. In our study, a stepwise logistic regression analysis of the variables significantly associated with elevated HOMA revealed that the strongest predictor for IR was ADAM17, with almost two-fold increased odds per one unit increase in ADAM17 levels. Furthermore, as expected, adipose tissue TNFα mRNA expression was another inflammatory marker associated with higher IR.

PRGN is an ubiquitously secreted protein, playing roles in cancer, wound healing and neurodegeneration [17,18,28]. Importantly, it was recently identified as a novel adipokine that participates in the induction of IR via increased IL-6 secretion [17]. Indeed, our analysis of adipose tissue showed a strong association between mRNA expression of PRGN, IL-6 and also sortilin (Fig. 1). Sortilin, a trafficking molecule, regulates serum PRGN levels by directing it for degradation [29]. Here for the first time, we show an association between adipose tissue mRNA levels of sortilin and PRGN. Previous studies also support the concept of PRGN in IR, since elevated serum PRGN were associated with high levels of serum glucose and with omental obesity [30,31]. However, in our studies, we did not find any significant difference in serum PRGN levels in the two morbidly obese groups.

FKN and OPN, two chemokines involved in monocyte recruitment and adhesion and previously shown to be involved in IR [30–33], showed a two-fold increase in their mRNA expression in the omental adipose tissue of the morbidly obese patients with the lower insulin sensitivity, however this increase did not reach statistical significance, due maybe to the low number of subjects (Table 2). Notably, the expression of FKN was strongly associated with expression of OPN, and this association became even stronger in the group with lower insulin sensitivity ($r = 0.916$, $P = 0.001$).

Our study is limited by the fact that patients were recruited from the bariatric surgery clinic and all of them had some degree of IR, and therefore our cut-off was arbitrarily determined according to the median value of HOMA. Despite the markedly different HOMA averages of the two groups (4.46 ± 1.20 vs 12.53 ± 9.13), a study using "healthy obese patients" with HOMA <2 may reveal stronger differences between the groups. Another limitation stems from the cross-sectional design of the study that prevents us from inferring the direction of the associations presented in this study.

Conclusions

Our study has examined several novel predictors of IR in morbidly obese patients, including serum bile acids and ADAM17, which may serve both as diagnostic markers and also may become useful targets for treatment of the metabolic syndrome in obese patients.

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