Effect of Obesity on Growth-related Oncogene Factor-α, Thrombopoietin, and Tissue Inhibitor Metalloproteinase-1 Serum Levels

Eléonore Maury[1], Sonia M. Brichard[1], Zoltan Pataky[2], Anne Carpentier[2], Alain Golay[2] and Elisabetta Bobbioni-Harsch[2]

We have recently identified several adipokines as oversecreted by omental adipose tissue (AT) of obese subjects: two chemokines (growth-related oncogene factor-α (GRO-α), macrophage inflammatory protein-1β (MIP-1β)), a tissue inhibitor of metalloproteinases-1 (TIMP-1), an interleukin-7 (IL-7) and a megakaryocytic growth-factor (thrombopoietin (TPO)). These adipokines are involved in insulin resistance and atherosclerosis. The objectives of this study were to determine whether the circulating levels of these adipokines were increased in obesity and to identify the responsible factors. A cross-sectional study including 32 lean (BMI (kg/m^2) <25), 15 overweight (BMI: 25–29.9), 11 obese (BMI: 30–39.9), and 17 severely obese (BMI >40) age-matched women was carried out. Serum adipokine levels, insulin sensitivity, and substrate oxidation were measured by ELISA, euglycemic–hyperinsulinemic clamp, and indirect calorimetry, respectively. Circulating levels of GRO-α, TPO, and TIMP-1 were higher in obese and/or severely obese women than in lean ones (+30, 55, and 20%, respectively). Serum levels of these adipokines positively correlated with insulinemia or glycemia, and negatively with insulin sensitivity. TIMP-1 also positively correlated with blood pressure, and TPO with triglyceride levels. Multiple regression analysis showed that fat mass *per se* was an independent determinant of GRO-α, TPO, and TIMP-1 levels, suggesting that hypertrophied adipocytes and recruited macrophages in expanded AT mainly contribute to this hyperadipokinemia. Insulinemia, glycemia and resistance of glucose oxidation to insulin were additional predictors for TPO. Circulating GRO-α, TPO, and TIMP-1 levels are increased in obesity. This may be partially due to augmented adiposity *per se* and to hyperinsulinemia/insulin resistance. These high systemic levels may in turn worsen/promote insulin resistance and cardiovascular disease.

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INTRODUCTION

Obesity plays a causative role in the pathogenesis of the metabolic syndrome that clusters several abnormalities, including insulin resistance, type 2 diabetes, dyslipidemia, hypertension, cardiovascular disease, and chronic low-grade inflammation (1).

Adipokines may be involved in this adverse health profile (1,2). Increased fat mass leads to local inflammation as a consequence of adipocyte hypertrophy and associated infiltration of macrophages. Fat cell hypertrophy and recruited macrophages cause dysregulation of adipokine production with oversecretion of deleterious adipokines and hyposecretion of beneficial ones (1,3). Such a dysregulation triggers the development of a low-grade proinflammatory state in obesity, which is considered to build the common soil for the development of related circulatory and metabolic diseases (1,4–6).

We have recently identified several adipokines that are oversecreted by omental adipose tissue (AT) in obesity: two chemokines ((growth-related oncogene factor-α (GRO-α), macrophage inflammatory protein-1β (MIP-1β)), one interleukin-7 (IL-7), one tissue inhibitor of metalloproteinases-1 (TIMP-1) and one growth-factor (thrombopoietin (TPO), a megakaryocytic growth-factor) (7). The expression of these adipokines in omental adipocytes did positively correlate with several features of the metabolic syndrome, namely BMI, insulin resistance index, blood pressure, lipid levels, and hypoadiponectinemia (7). These findings support the idea that these investigated adipokines may link obesity to its cardiovascular or metabolic comorbidities.

The aims of the present study were: (i) to examine whether the increased production of these adipokines by AT was reflected by higher circulating levels in obesity and, (ii) to

The first two authors contributed equally to this work.
[1]Endocrinology and Metabolism Unit, Faculty of Medicine, University of Louvain, Brussels, Belgium; [2]Service of Therapeutic Education for Chronic Diseases, Geneva University Hospital, Geneva, Switzerland. Correspondence: Sonia M. Brichard (sonia.brichard@uclouvain.be)

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attempt to identify the potential responsible factors for this hyperadipokinemia.

METHODS AND PROCEDURES

Participants

Participants were age-matched women divided into four groups based on BMI: 32 lean (BMI <25 kg/m^2), 15 overweight (BMI between 25 and 29.9 kg/m^2), 11 obese (BMI between 30 and 39.9 kg/m^2) and 17 severely obese (BMI >40 kg/m^2) subjects. Women with diagnosed type 2 diabetes (i.e., fasting plasma glucose ≥7 mmol/l at baseline (8)) were excluded, as well as patients receiving drugs for dyslipidemia or hypertension.

All applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research. The study had the approval of the local ethics committee.

Experimental protocol

The patients were admitted to hospital in the morning (0800 h), after an overnight fast. Body weight, height, and body composition were measured. Urine was collected in order to measure urinary nitrogen. Venous catheters were inserted into a dorsal vein of the hand and into the left antecubital vein of the contra-lateral arm (for blood sampling and infusion of all test substances, respectively). Blood samples were immediately centrifuged and serum was stored at −80 °C. The patients underwent a 2 h euglycemic–hyperinsulinemic clamp. Indirect calorimetry was performed for 30 min in basal fasting conditions and repeated throughout the past 30 min of the euglycemic–hyperinsulinemic clamp.

Body composition

Body composition was measured using a body impedance analyser (Nutriguard-M, Darmstadt, Germany), with the electrodes placed on the right hand and foot. Lean body mass (LBM) was calculated according to Segal *et al.* (9).

Indirect calorimetry

This technique is widely recognized to examine rates of substrate oxidation in humans and was used in this study under conditions where interpretative pitfalls were unlikely to apply (10).

Patients were asked to avoid making intense physical activity for 48 h before the test. For the 3 days preceding the test, they were also advised to consume a balanced diet, consisting of about 50% of energy as carbohydrate, 30% as lipid and 20% as protein, without any modification of their usual energy intake. The patients were placed in a recumbent position with the head in a ventilated hood (Deltatrac; Datex, Helsinki, Finland) and oxygen consumption and carbon dioxide production were measured. After a 15 min equilibration period, gas exchange was measured for 30 min and used to calculate the respiratory quotient as well as glucose and lipid oxidation rates, according to Ferrannini (11). Protein oxidation was calculated as $6.235 \times N$ (12), where N is nitrogen excretion (mg/min) in urine measured by spectrophotometry. The lipid, glucose and protein oxidation rates were expressed as mg/kg LBM/min. Resting energy expenditure was calculated from the rates of substrate oxidation and expressed as kcal/kg LBM/day.

Euglycemic–hyperinsulinemic clamp procedure

Insulin sensitivity was evaluated by the euglycemic–hyperinsulinemic clamp procedure (13). After a priming dose (0.8 U/m^2 of body surface area over 10 min), the patients received a constant infusion of insulin at the rate of 0.04 U m^{-2} min^{-1} throughout the test. The overall duration of the test was 120 min. A 200 g/l glucose solution was infused at variable rates in order to maintain glycemia at a constant level of 5.0 mmol/l. Whole-body glucose uptake, expressed as mg/kg LBM/min, was calculated during the past 40 min period of the test, when glucose infusion reached steady state. Nonoxidative glucose disposal, which largely corresponds to glucose storage, was calculated by subtracting glucose oxidation from the total amount of glucose infused during the clamp. The insulin-induced modifications of substrate oxidative rate (Δ) were calculated as the differences between the values measured during the clamp and those measured in basal conditions.

Blood chemistry

Plasma glucose was determined enzymatically using an automated glucose analyser (Beckman Coulter, Fullerton, CA). Serum insulin, leptin, and adiponectin concentrations were measured by radioimmunoassay, using commercial kits (Linco Research, St Charles, MI). Other serum adipokine levels were quantified by specific ELISAs for human GRO-α, IL-7, MIP-1β, TIMP-1, and TPO (Quantikine or Quantikine HS (IL-7), R&D Systems, Minneapolis, MN). Serum free fatty acids were measured by an enzymatic method (WAKO, Neuss, Germany) and measurement of other lipids was performed by routine procedures in a central laboratory (Geneva University Hospital, Geneva, Switzerland). Sex hormones may influence some adipokine levels, like GRO-α in rats (14). However, whether such an influence on systemic GRO-α also exists in humans is still unclear (15,16), and we therefore did not investigate ovarian hormones in our participants.

Statistical analysis

Results are the mean ± s.e.m. The normality of data distribution was examined by the Kolmogorov–Smirnov test. Data that were not normally distributed were first log transformed before statistical processing. Comparisons between the different groups (lean, overweight, obese, and severely obese women) were made using ordinary ANOVA followed by the Dunnett's test (comparison of all groups vs. lean). Correlation analyses were performed using Pearson's test to examine the simple relationships of the investigated adipokines to selected variables (using Spearman's test for IL-7, due to the nonnormal distribution of data after the log transformation). Multiple regression analyses were used to identify the independent determinants of circulating adipokines. The predictor variables were selected from an initial set (issuing from **Table 1** and **Figure 1**: age, fat mass, basal triglycerides, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, basal and clamp free fatty acids, basal glucose, insulin and adiponectin, nonoxidative glucose utilization, Δ glucose oxidation and Δ lipid oxidation, basal and clamp energy expenditure) by the forward selection procedure (17), after exclusion of collinear parameters. Statistical analyses were performed using GraphPad InStat version 3.00 (GraphPad Software, San Diego, CA) and SAS Enterprise Guide 4.1 (SAS Institute, Cary, NC). Differences were considered statistically significant at $P < 0.05$.

RESULTS

Characteristics of the study participants

As shown in **Table 1**, obese and severely obese women exhibited several clinical or laboratory features of the metabolic syndrome. When compared to age-matched lean women, overweight, obese, and severely obese women had higher waist circumference, higher blood pressure, and hyperinsulinemia. Severely obese women also exhibited higher triglyceride levels. According to International Diabetes Federation criteria (18), half of these obese and severely obese women displayed a metabolic syndrome.

During clamp, severely obese subjects showed marked insulin resistance as assessed by decreased insulin-mediated glucose uptake at the expense of both nonoxidative and oxidative glucose disposal (**Table 1** and **Figure 1a–c**). This insulin resistance in severely obese women also caused reduced insulin suppression of lipolysis (with higher serum free fatty acids at the end of the clamp) and subsequent higher rates of

lipid oxidation (Table 1 and Figure 1d). When normalized for LBM, clamp energy expenditure was decreased in severely obese women compared to lean ones, possibly due to the lower insulin-induced glucose utilization.

Effect of obesity on GRO-α, TPO, and TIMP-1 serum levels

Serum levels of three out of the five adipokines studied were higher in severely obese women than in lean ones. Thus, when compared to lean women, serum levels of GRO-α, TPO, and TIMP-1 were increased in severely obese subjects by ~30, 55, and 20%, respectively ($P < 0.05$ or less; Figure 2). TIMP-1 was already significantly elevated in overweight and obese women ($P < 0.05$, vs. lean women). As expected, adiponectin decreased and leptin increased with increasing adiposity (Figure 2). Serum levels of GRO-α, TPO, and TIMP-1 did positively correlate with BMI, fat mass, (Figure 3) and waist circumference (Table 2), whereas no such correlations were found for MIP-1β or IL-7.

Because of the relationships between GRO-α, TPO, TIMP-1 and obesity, we merely focused on these three adipokines.

Table 1 Clinical and laboratory characteristics of lean, overweight, obese and severely obese women

	Lean	Overweight	Obese	Severely obese
Clinical parameters				
Women (*n*)	32	15	11	17
Age (years)	41.8 ± 1.6	43.4 ± 3.4	43.7 ± 2.8	37.6 ± 2.1
BMI (kg/m^2)	21.4 ± 0.3	27.0 ± 0.4**	34.1 ± 0.6**	44.5 ± 0.7**
Lean mass (LBM, kg)	42.6 ± 0.5	44.9 ± 0.9	50.6 ± 1.4**	59.9 ± 1.8**
Fat mass (kg)	14.8 ± 0.8	25.9 ± 1.3**	39.0 ± 1.6**	58.9 ± 2.4**
% Body fat	25.4 ± 0.9	35.9 ± 1.1**	43.4 ± 0.9**	49.4 ± 0.5**
Waist (cm)	72.2 ± 1.1	86.0 ± 2.3**	97.6 ± 2.5**	120.2 ± 3.1**
Waist-to-hip ratio	0.79 ± 0.01	0.86 ± 0.02**	0.86 ± 0.02*	0.89 ± 0.02**
Systolic blood pressure (mm Hg)	111 ± 2	124 ± 4**	120 ± 5	142 ± 5**
Diastolic blood pressure (mm Hg)	70 ± 1	77 ± 2*	79 ± 4**	94 ± 4**
Metabolic syndrome (%)	0	0	55**	47**
Basal serum parameters				
Triglycerides (mmol/l)	0.67 ± 0.05	0.88 ± 0.11	0.98 ± 0.10	1.26 ± 0.14**
Total cholesterol (mmol/l)	4.80 ± 0.17	5.39 ± 0.24	5.05 ± 0.17	5.04 ± 0.21
HDL-cholesterol (mmol/l)	1.45 ± 0.06	1.34 ± 0.10	1.35 ± 0.11	1.35 ± 0.06
LDL-cholesterol (mmol/l)	3.04 ± 0.15	3.65 ± 0.17*	3.22 ± 0.17	3.11 ± 0.18
FFA (mmol/l)	0.83 ± 0.04	0.84 ± 0.08	0.85 ± 0.11	0.87 ± 0.06
Glucose (mmol/l)	4.89 ± 0.05	5.01 ± 0.11	4.91 ± 0.14	4.88 ± 0.10
Insulin (ng/ml)	0.21 ± 0.02	0.40 ± 0.05*	0.46 ± 0.05**	0.85 ± 0.09**
Substrate utilization and energy expenditure				
Basal				
Glucose oxidation (mg/kg LBM/min)	1.21 ± 0.13	0.86 ± 0.26	0.76 ± 0.23	0.96 ± 0.16
Lipid oxidation (mg/kg LBM/min)	1.49 ± 0.08	1.78 ± 0.15	1.70 ± 0.10	1.66 ± 0.13
Protein oxidation (mg/kg LBM/min)	0.73 ± 0.08	0.77 ± 0.16	0.90 ± 0.20	0.86 ± 0.07
Energy expenditure (kcal/kg LBM/day)	33.78 ± 1.11	35.53 ± 1.59	33.24 ± 1.69	31.48 ± 1.02
Clamp				
FFA (mmol/l)	0.04 ± 0.01	0.06 ± 0.01	0.09 ± 0.02	0.22 ± 0.02**
Insulin (ng/ml)	2.75 ± 0.09	3.29 ± 0.22*	3.40 ± 0.18*	4.24 ± 0.23**
Glucose uptake (mg/kg LBM/min)	8.97 ± 0.37	9.06 ± 0.99	7.13 ± 0.83	4.52 ± 0.43**
Nonoxidative glucose utilization (mg/kg LBM/min)	5.72 ± 0.36	6.00 ± 0.85	4.37 ± 0.69	2.65 ± 0.46**
Glucose oxidation (mg/kg LBM/min)	3.25 ± 0.14	3.06 ± 0.35	2.76 ± 0.30	1.87 ± 0.25**
Lipid oxidation (mg/kg LBM/min)	0.78 ± 0.10	0.94 ± 0.17	0.91 ± 0.14	1.21 ± 0.10*
Energy expenditure (kcal/kg LBM/day)	35.65 ± 1.28	36.55 ± 1.53	34.47 ± 1.70	30.52 ± 1.07*

Values are mean ± s.e.m. for the number of subjects indicated at the top of each column. *$P < 0.05$, **$P < 0.01$ vs. lean women, by ANOVA followed by Dunnett's test.
FFA, free fatty acids.

Association between adipokine concentrations and metabolic parameters

We next studied the association between these three adipokines and the metabolic parameters shown in Table 1 and Figure 1. Table 2 only presents the significant relationships that were found with at least one of the three adipokines.

In the basal state, GRO-α did positively correlate with insulin, TPO with triglycerides and glycemia, and TIMP-1 with insulin and leptin. TPO did also negatively correlate with adiponectinemia.

During clamp, GRO-α, TPO, and TIMP-1 did or tended to correlate with free fatty acid levels (Table 2). GRO-α and TPO did inversely correlate with glucose uptake. When glucose uptake was normalized for clamp insulinemia (higher in overweight, obese, and severely obese women than in lean ones), this parameter was significantly inversely related to the three adipokines studied (Figure 4a). In addition, TPO levels were significantly negatively related to nonoxidative glucose utilization and Δ glucose oxidation, and positively related to Δ lipid oxidation (Figure 4b).

Determinants of the increased circulating levels of the investigated adipokines in obesity

To determine the predictive factors of this hyperadipokinemia, we performed multiple regression analysis in our entire population with the upregulated adipokines as dependent variables and with the clinical and laboratory characteristics shown in Table 1 and Figure 1 (see Methods and Procedures) as independent variables. Predictor variables were chosen by the forward selection procedure. Multiple regression analysis showed that fat mass *per se* was a significant independent determinant of GRO-α, TPO, and TIMP-1 levels ($P < 0.05$ or less).

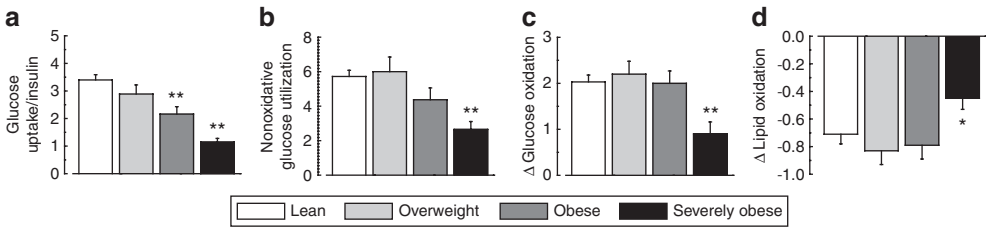

Figure 1 (**a**) Glucose uptake, (**b**) nonoxidative glucose utilization, (**c**) Δ glucose oxidation, (**d**) and Δ lipid oxidation during euglycemic–hyperinsulinemic clamp in the four groups of women. Values are mean ± s.e.m. for 32 lean, 15 overweight, 11 obese, and 17 severely obese women. Units are mg/kg LBM/min and glucose uptake was further normalized for clamp insulin concentrations. The insulin-induced modifications of substrate oxidative rate (Δ) were calculated as the differences between the values measured during the clamp and those measured in basal conditions. *$P < 0.05$, **$P < 0.01$ vs. lean women by ANOVA followed by Dunnett's test. LBM, lean body mass.

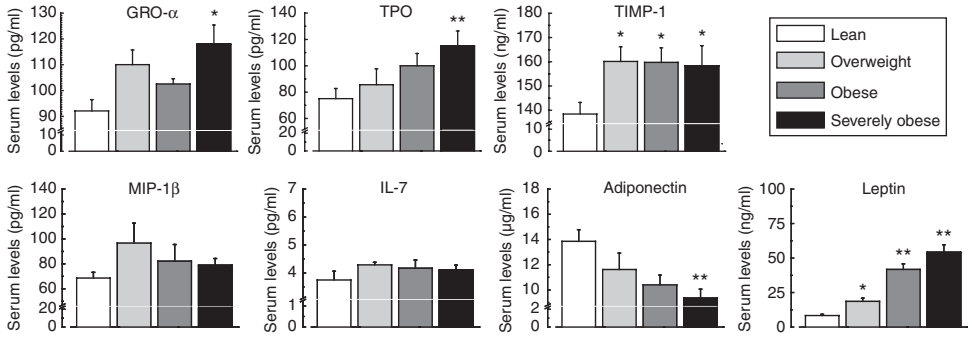

Figure 2 Serum adipokine levels in lean, overweight, obese, and severely obese women. Serum was sampled in basal conditions and adipokines were quantified by ELISA (except for leptin and adiponectin, which were measured by radioimmunoassay). Values are mean ± s.e.m. for 32 lean, 15 overweight, 11 obese, and 17 severely obese women. *$P < 0.05$, **$P < 0.01$ vs. lean women by ANOVA followed by Dunnett's test.

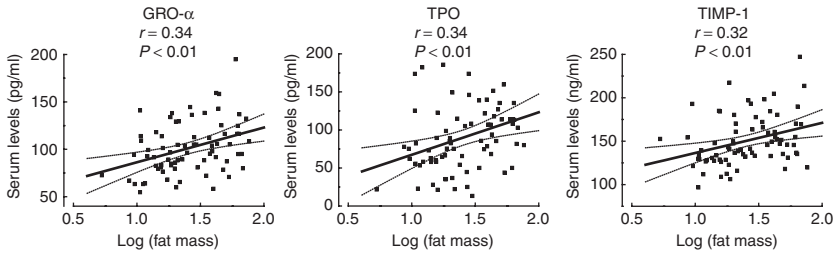

Figure 3 Relationships between serum adipokine levels and fat mass in women over a large range of BMI. Fat mass was log transformed to obtain a normal distribution. Correlation analysis was performed in the entire population (lean, overweight, obese, and severely obese groups combined, $n = 75$ women). Dotted lines correspond to the 95% confidence interval for r.

Table 2 Univariate correlation analysis between serum levels of the investigated adipokines and clinical and metabolic parameters

	GRO-α	TPO	TIMP-1
Clinical parameters			
BMI (kg/m^2)	0.33***	0.35***	0.30***
Fat mass (log (kg))	0.34***	0.34***	0.32***
Waist (cm)	0.34***	0.31***	0.32***
Systolic blood pressure (mm Hg)	0.22	0.19	0.32**
Diastolic blood pressure (mm Hg)	0.21	0.16	0.32**
Basal serum parameters			
Triglycerides (mmol/l)	0.06	0.26**	0.04
Glucose (mmol/l)	–0.04	0.23**	0.00
Insulin (ng/ml)	0.28**	0.15	0.31***
Leptin (log (ng/ml))	0.21*	0.19	0.32***
Adiponectin (μg/ml)	–0.22*	–0.26**	–0.14
Clamp substrate oxidation and energy expenditure			
FFA (log (mmol/l))	0.21*	0.26**	0.22*
Insulin (ng/ml)	0.41***	0.06	0.30***
Glucose uptake (mg/kg LBM/min)	–0.24**	–0.32***	–0.19
Nonoxidative glucose utilization (mg/kg LBM/min)	–0.20*	–0.26**	–0.14
Glucose oxidation (mg/kg LBM/min)	–0.18	–0.26**	–0.22*
Δ Glucose oxidation (mg/kg LBM/min)	–0.16	–0.35***	–0.15
Δ Lipid oxidation (mg/kg LBM/min)	0.18	0.31***	0.15
Energy expenditure (kcal/kg LBM/day)	–0.20	–0.05	–0.26***

Pearson's correlation coefficients *r* are indicated in this table. Correlation analysis was performed in the entire population (lean, overweight, obese, and severely obese groups combined, $n = 75$ women). *$P < 0.07$, **$P < 0.05$, ***$P < 0.01$. Basal serum parameters and clamp measurements (from **Table 1**) which are not presented here did not show any significant correlation with any investigated adipokines. The insulin-induced modifications of substrate oxidative rate (Δ) were calculated as the differences between the values measured during the clamp and those measured in basal conditions.
GRO-α, growth-related oncogene factor-α; TPO, thrombopoietin; TIMP-1, tissue inhibitor of metalloproteinases-1.

Basal insulinemia and glycemia, as well as the resistance of glucose oxidation to insulin (Δ glucose oxidation) were three additional independent determinants of TPO ($P \leq 0.05$ for each).

DISCUSSION

In this study, we demonstrated for the first time that circulating levels of GRO-α and TPO are increased in severely obese women and related to adiposity. GRO-α plays a role in inflammation, angiogenesis and tumorigenesis (19) and TPO stimulates the proliferation and differentiation of megakaryocytes (20). In addition, we confirmed that circulating levels of TIMP-1 did correlate with adiposity, as already shown both in a mixed population of obese subjects and in young women (21,22). However, compared with these two studies, our work by stratifying our population into different groups based on BMI further disclosed that TIMP-1 levels were already elevated in subjects who were only overweight.

The mechanisms responsible for the high systemic levels of GRO-α, TPO, and TIMP-1 in obesity have thus far not been fully elucidated. Relationships between these adipokine levels and several clinical or laboratory parameters do not necessarily imply "cause-effect" relationships. Yet, the strong relationships between these adipokines and waist circumference may suggest a contribution of central obesity. We have previously reported an exacerbated secretion of these adipokines by omental AT of obese subjects. Both adipocytes and stromal-vascular cells (i.e., nonfat cells, which mainly contain macrophages) participated to this oversecretion (7). Herein, that adiposity *per se* was an independent determinant of these high systemic levels may support the concept that hypertrophied adipocytes and surrounding recruited macrophages, both of which shift their phenotype into a proinflammatory mode, are fundamental contributors to this hyperadipokinemia (4,5,23–25). Because we did not find any relationships between MIP-1β or IL-7 and adiposity, expanded omental AT may not be a main source of these adipokines. However, it should be kept in mind that intra-abdominal fat only represents 15% of total fat in lean and obese individuals (26) and that the exact contribution of this fat depot to systemic levels of adipokines is still unsettled (25). Besides adiposity, additional factors may contribute to the observed hyperadipokinemia. More particularly, insulinemia and glycemia, as well as impaired insulin response of glucose oxidation were independent predictive factors of high circulating TPO levels. In line with this context of insulin resistance and ensuing elevated insulinemia, addition of insulin to culture medium induced the expression of TPO in a model of human adipocytes differentiated *in vitro* (27).

Whether this hyperadipokinemia may be implicated in the development/progression of obesity and its related metabolic, cardiovascular or cancer complications is still unsettled. However, some pieces of evidence support this hypothesis.

First, the development of obesity. TIMP-1 has been found to promote AT expansion. When added to the culture medium, TIMP-1 accelerated the accumulation of lipid during differentiation of 3T3-L1 adipocytes (28). Conversely, TIMP-1 knockout mice exhibited less fat mass expansion when administered a high-fat diet (29).

Second, the development of type 2 diabetes. One report suggests that GRO-α and TIMP-1 may induce insulin resistance (30). Thus, human skeletal muscle cells treated with adipocyte-conditioned medium containing these two adipokines showed impaired insulin signalling. This impairment was prevented when adipocyte-conditioned medium was generated in the presence of adiponectin, which reduced the concentrations of these two adipokines. It was further shown that this prevention was not due to a direct effect of adiponectin on myotubes but rather to secondary changes of other adipokines (30). To our knowledge, the involvement of TPO in insulin resistance

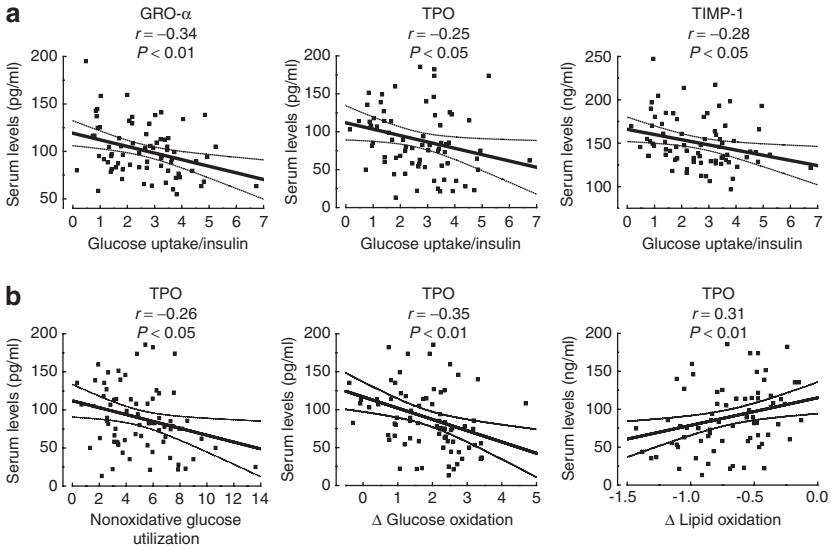

Figure 4 Relationships between (**a**) serum adipokine levels and clamp glucose uptake, (**b**) nonoxidative glucose utilization, Δ glucose oxidation and Δ lipid oxidation. Units are mg/kg LBM/min and glucose uptake was further normalized for clamp insulin concentrations. Correlation analysis was performed in the entire population (lean, overweight, obese, and severely obese groups combined, $n = 75$ women). Dotted lines correspond to the 95% confidence interval for *r*. (**a**) Clamp glucose uptake/insulin was the only metabolic parameter, which was significantly negatively correlated with the three investigated adipokines. (**b**) TPO levels were also negatively related to nonoxidative glucose utilization and Δ glucose oxidation, and positively related to Δ lipid oxidation. LBM, lean body mass.

or type 2 diabetes has never been studied. However, because glycemia, insulinemia, and insulin resistance are contributors to TPO levels and because there is a positive relationship between hyperglycemia and enhanced platelet activation in patients with acute coronary syndrome (31), it is tempting to speculate that TPO may link type 2 diabetes to cardiovascular disease.

Third, development of cardiovascular disease. Elevated serum levels of these three adipokines are risk factors for cardiovascular disease. Circulating levels of GRO-α are increased in patients with stable and more particularly in those with unstable angina. GRO-α expression is upregulated in atherosclerotic plaques and may contribute to the inflammatory recruitment of macrophages, to matrix degradation and lipid accumulation (16). Systemic TPO levels are also increased in patients with unstable angina and could participate in the pathogenesis of the acute coronary syndrome by increasing both platelet counts and size, resulting in hemostatically more active platelets (20,32). Eventually, matrix metalloproteinases and their inhibitors are involved in vascular remodelling. High systemic TIMP-1 levels have been reported to be involved in carotid plaque formation (33).

Fourth, obesity is a risk factor for several cancer types (34–37). High levels of GRO-α and TIMP-1 may contribute to link these morbidities as both are involved in tumour progression through enhancing cell proliferation, antiapoptotic activity and/or angiogenesis (38–41).

In conclusion, that adiposity *per se* predicts the high circulating levels of GRO-α, TPO, and TIMP-1 reinforces the concept that hypertrophied adipocytes and infiltrated macrophages mainly contribute to this hyperadipokinemia. Glycemia and insulinemia are additional predictive factors for TPO levels. These high systemic levels may in turn contribute to exacerbate obesity itself and also to promote insulin resistance, cardiovascular disease and cancer, thereby linking obesity to its comorbidities.

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DISCLOSURE

The authors declared no conflict of interest.

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