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Original article

Effects of glucose ingestion on circulating inflammatory mediators: Influence of sex and weight excess

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Abbreviations:
AUC
area under the curve
BMI
body mass index
E_2
total estradiol
hsCRP
high sensitivity C-reactive protein
hsIL-6
high-sensitivity interleukin-6
IL-18
interleukin-18
MCP1
monocyte chemotactic protein 1
MIF
macrophage migration inhibitory factor
MMP9
matrix metallopeptidase 9
PTX3
pentraxin-3
oGTT
oral glucose tolerance test
SHBG
sex hormone-binding globulin
T
total testosterone

SUMMARY

Background & aims: Low-grade chronic inflammation is involved in the pathophysiology of obesity. However, little is known about the influence of sex and sex hormones on surrogate inflammatory markers and mediators, particularly after glucose ingestion.
Design: Observational study.
Methods: We measured the circulating concentrations of interleukin-6, interleukin-18, macrophage migration inhibitory factor, matrix metallopeptidase-9, monocyte chemotactic protein-1 and pentraxin-3, in the fasting state and during a 75 g oral glucose tolerance test, in 24 women and 25 men. Eleven men and 11 women were lean whereas 14 men and 13 women had weight excess.
Results: Anti-inflammatory cytokines (interleukin-6 and interleukin-18) were increased in the fasting state and/or decreased in some women during the oral glucose tolerance test, as opposed to inflammatory mediators such as macrophage migration inhibitory factor and matrix metallopeptidase-9 that increased during the oral glucose tolerance test especially in subjects with weight excess. Body mass index and waist circumference were the main determinants of these changes. Fasting pentraxin-3 levels were especially increased in lean women in parallel to a decrease in free testosterone levels, and decreased during the oral glucose tolerance test as opposed to the increase in insulin concentrations.
Conclusions: The circulating concentrations of markers of low-grade chronic inflammation in young healthy adults are not only influenced by obesity but also by abdominal adiposity, fasting and glucose ingestion and, in some cases, by sex and sex hormones. These influences should be considered when these markers are used as surrogate markers of the inflammatory milieu associated with obesity.

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1. Introduction

Low grade chronic inflammation plays a central role in the development of obesity-associated insulin resistance and its association with cardiovascular disease [1]. The inflammatory milieu associated with obesity is especially dependent on abdominal adiposity [2] because visceral adipose tissue is a secretory organ that releases many inflammatory mediators among other molecules [3].

Despite the evident sexual dimorphism in the distribution of body fat in humans, with women showing a predominantly peripheral and subcutaneous deposition of adipose tissue compared with the predominantly central and visceral adipose depots characteristic of men [4,5], the possibility that sex and sex hormones influence the relationship between obesity and low-grade chronic inflammation has been recognized only recently [6].

Furthermore, most current knowledge about the association of obesity and adipose tissue dysfunction with chronic inflammation in humans has been obtained in the fasting state, even though the relationship of circulating markers of inflammation with surrogate markers of abdominal adiposity and insulin resistance may not be the same in the fasting and post-meal states [7]. Moreover, the studies addressing inflammatory markers after oral intake focused mostly on the possible pro- or anti-inflammatory roles of dietary fats and antioxidants [8–10] even though, nowadays, the search for the main dietary culprit of obesity and related metabolic disorders has shifted its focus towards dietary sugars [11,12]. Glucose ingestion, in addition to alter the concentrations of many circulating inflammatory mediators [13], has also been shown to increase reactive oxygen species generation and intranuclear nuclear factor-kappaB in mononuclear cells [14,15] and, at least in women, such effects appear to be modulated by androgens, in a manner that is independent of abdominal adiposity [16,17].

To provide new insights into these controversial and still unsolved issues we aimed to study several circulating inflammatory mediators and markers, both in the fasting state and during an oral glucose challenge, in men and women presenting with or without weight excess from whom surrogate indexes of abdominal adiposity and insulin resistance had been adequately recorded [18].

2. Materials and methods

2.1. Subjects

We studied 25 young adult men and 24 premenopausal women. Subjects were classified according to their body mass index (BMI) into lean (BMI < 25 kg/m^2, 11 men and 11 women) and weight excess (BMI ≥ 25 kg/m^2, 14 men and 13 women) subgroups. The groups were composed by patients reporting to the Department of Endocrinology and Nutrition of Hospital Ramón y Cajal because of weight excess and by healthy non-obese volunteers. Men and women were selected as to be similar in terms of age and were matched for BMI. Before enrollment, the participants had no history of obesity-associated comorbidities including disorders of glucose tolerance, hypertension, cardiovascular disease, androgen excess or sleep apnea. The subjects had not received treatment with oral contraceptives, antiandrogens, insulin sensitizers, statins, antihypertensives or drugs that might interfere with clinical/biochemical variables or influence body fat depots for at least 6 months. The local ethics committee of Hospital Universitario Ramón y Cajal approved the study and all participants gave their written informed consent.

2.2. Study protocol and assays

A complete clinical evaluation that included BMI, waist circumference and waist-hip ratio was performed in all subjects. We obtained serum and plasma samples after a 12 h overnight fasting, during the follicular phase of the menstrual cycle in women. These samples were used for the measurement of total testosterone (T), total estradiol (E_2), and sex hormone-binding globulin (SHBG). A complete lipid profile was also obtained and a 75 g oral glucose tolerance test (oGTT) was performed, assaying samples taken at 0, 30, 60, 90 and 120 min for serum insulin, plasma glucose and circulating inflammatory markers. Patients were instructed to follow a diet unrestricted in carbohydrates for 3 days before sampling the in order to avoid false positive results in the oGTT. Blood samples were immediately centrifuged, and serum and plasma were separated and frozen at -30 °C until assayed. The assays used for these measurements have been described in detail elsewhere [19,20].

Free T and free E_2 concentrations were calculated from total levels and SHBG concentrations [21]. Fasting glucose and insulin levels were used for homeostasis model assessment of insulin resistance [22] and the composite insulin sensitivity index was estimated from the glucose and insulin concentrations measured during the oGTT [23]. We used the trapezoidal rule to calculate the areas under the curve (AUC) of glucose, insulin and cytokines during the oGTT.

2.3. Assays used to measure circulating inflammatory markers

Plasma or serum concentrations of high-sensitivity C-reactive protein (hsCRP), high-sensitivity interleukin-6 (hsIL-6), interleukin-18 (IL-18), macrophage migration inhibitory factor (MIF), matrix metallopeptidase 9 (MMP9), monocyte chemotactic protein 1 (MCP1) and pentraxin-3 (PTX3) levels were assayed with commercial immunochemiluminescence or enzyme-linked immunosorbent assay kits (Immulite 2000 high-sensitivity CRP, Siemens Healthcare, Los Angeles, CA; R&D Systems, UK for hsIL-6, PTX3, MIF and MMP9; MBL, Japan for IL-18; and BioVendor, Czech Republic for MCP1). The lower limits of detection and intra- and inter-assay coefficients of variation were 0.1 mg/l and <5% at 0.2 mg/l of hsCRP; 0.039 pg/ml, 7.4% and 7.8% for hsIL-6; 12.5 pg/ml, 7.3% and 7.7% for IL-18; 0.025 ng/ml, 3.9% and 5.1% for PTX3; 0.016 ng/ml, 5.3% and 9.1% for MIF; 2.3 pg/ml, 4.7% and 8.7% for MCP1; and 0.156 ng/ml, 2.3% and 7.5% for MMP9.

2.4. Statistical analysis

Continuous variables are reported as mean ± standard deviation (text and tables) and means and 95% confidence interval or means ± standard error of the mean (figures). We used the Kolmogorov–Smirnov statistic to check continuous variables for normality, and applied logarithmic or square root transformations as needed to ensure their normal distribution.

We used univariate two-way general linear models to evaluate within a single analysis the influence of sex, weight excess and the interaction between both factors on continuous variables such as fasting circulating inflammatory markers and their AUCs. Circulating levels of glucose, insulin and inflammatory mediators were also submitted to univariate repeated-measures general linear models introducing their concentrations at the different time points of the oGTT as within-subjects effect and sex and weight groups as between-subjects effect. Mauchly's test served to assess sphericity and we applied Greenhouse-Geisser correction when required.

We used stepwise (probability to enter ≤0.05, probability to remove ≥0.10) multiple linear regression models in order to identify the main determinants of fasting concentrations and AUC of inflammatory markers in response to the oral glucose overload. Independent variables included sex, BMI, waist circumference, free T, free E_2, and fasting levels or AUC (as appropriate) of circulating glucose and insulin. We used SPSS Statistics 15.0 (SPSS Inc., Chicago, IL) for analyses. *P* values < 0.05 were considered statistically significant.

3. Results

3.1. Influence of sex and weight excess on clinical and biochemical variables

Clinical, hormonal and metabolic variables of the subjects studied here are summarized in Table 1. As expected from the study design, there were no differences among men and women in terms of age and BMI. Besides their higher total and free T levels, men also had greater waist circumference, waist-hip ratio, fasting glucose and insulin concentrations than women. Furthermore, men presented with a trend towards higher triglycerides and low-density lipoprotein-cholesterol levels compared with women that was very close to reaching statistical significance. In contrast, women had higher levels of total and free E_2, SHBG, high density-lipoprotein cholesterol and composite insulin sensitivity index values. Compared with lean individuals, subjects with weight excess had higher waist circumference, waist-hip ratio, hsCRP, fasting glucose and insulin levels and homeostasis model assessment of insulin resistance, while they presented lower levels of SHBG, high density-lipoprotein cholesterol and composite insulin sensitivity index. There were no interactions between sex and weight excess in any of these variables.

3.2. Influence of sex and weight excess on circulating inflammatory mediators in the fasting state

In the fasting state, subjects with weight excess showed higher circulating concentrations of MIF and hsIL-6 than their lean counterparts, yet the latter was only observed in women according to the statistically significant interaction observed between weight excess and sex on circulating IL-6 levels (Fig. 1). When considered as a whole, women presented with increased circulating PTX3 concentrations, yet this difference was only present in the lean subgroup since weight excess men and women presented similar PTX3 levels (Fig. 1). Weight excess, sex and their interaction did not influence the fasting concentrations of IL-18, MCP1 and MMP9 (Fig. 1).

3.3. Influence of sex and weight excess on circulating concentrations of inflammatory mediators during the oGTT

The curves for glucose, insulin and the different inflammatory mediators obtained during the oGTT according to sex and weight excess are shown in Fig. 2 and the AUCs in response to the oral glucose load are shown in Fig. 3. During the oGTT individuals with weight excess showed higher glucose and insulin levels at all time points compared with their lean counterparts, irrespective of sex (Fig. 2). Glucose concentrations were higher in men than in women throughout the curve, with the exception of time points 90 and 120 min when men and women reached similar glucose levels (Fig. 2).

When considering the AUC (Fig. 3), only men with weight excess showed greater AUC of insulin compared with lean men but such effect of weight excess was not observed in women. No differences in the AUCs of glucose were observed between subgroups.

All the inflammatory mediators changed significantly during the oGTT when considering all subjects as a whole with the exception of hsIL-6, whose levels changed only in women with weight excess (Fig. 2). In these women, hsIL-6 concentrations showed a transient decrease returning to fasting levels at the end of the oGTT (Fig. 2), yet these levels were higher compared with lean women and men throughout the oGTT, following the differences already present in the fasting state (Fig. 1). Circulating IL-18 levels decreased more markedly in lean individuals, yet the more marked decrease in lean women was close to reaching statistical significance ($P = 0.086$), in agreement with the larger negative AUC observed in women

Table 1
Influence of sex and weight excess (BMI ≥ 25 kg/m^2) on clinical, metabolic and hormonal variables.

	Men		Women		Effect of sex	Effect of weight excess	Interaction
	Lean subjects (n = 11)	Weight excess (n = 14)	Lean subjects (n = 11)	Weight excess (n = 13)	*P*	*P*	*P*
Age (yr)	32 ± 5	33 ± 6	29 ± 5	32 ± 6	0.218	0.229	0.488
Body mass index (kg/m^2)	23.9 ± 0.8	34.4 ± 9.4	21.8 ± 2.2	33.9 ± 5.2	0.433	<0.001	0.643
Waist circumference (cm)	79 ± 7	106 ± 21	66 ± 5	91 ± 11	0.001	<0.001	0.797
Waist hip ratio	0.84 ± 0.06	0.93 ± 0.09	0.71 ± 0.03	0.79 ± 0.07	<0.001	<0.001	0.721
High-sensitivity C-reactive protein (nmol/l)	8 ± 8	45 ± 48	4 ± 3	40 ± 33	0.319	<0.001	0.187
Sex hormone-binding globulin (nmol/l)	29 ± 10	26 ± 12	58 ± 22	41 ± 18	<0.001	0.042	0.127
Total testosterone (nmol/l)	18.8 ± 4.5	16.8 ± 7.4	1.6 ± 0.6	1.5 ± 0.4	<0.001	0.238	0.546
Free testosterone (pmol/l)	440 ± 101	385 ± 118	21 ± 7	21 ± 10	<0.001	0.996	0.123
Total estradiol (pmol/l)	119 ± 42	112 ± 33	296 ± 137	345 ± 277	<0.001	0.904	0.936
Free estradiol (pmol/l)	3.0 ± 1.1	2.9 ± 0.8	5.1 ± 2.2	6.9 ± 5.4	<0.001	0.630	0.557
Triglycerides (mmol/l)	1.1 ± 0.6	1.3 ± 0.6	0.8 ± 0.4	1.0 ± 0.5	0.051	0.077	0.751
Total cholesterol (mmol/l)	4.7 ± 0.6	5.2 ± 0.9	4.8 ± 0.9	4.9 ± 1.0	0.583	0.210	0.331
Low-density lipoprotein cholesterol (mmol/l)	2.8 ± 0.6	3.5 ± 0.8	2.6 ± 0.7	2.8 ± 0.7	0.051	0.066	0.269
High-density lipoprotein cholesterol (mmol/l)	1.3 ± 0.2	1.1 ± 0.3	1.8 ± 0.5	1.3 ± 0.3	0.005	0.004	0.576
Fasting glucose (mmol/l)	5.0 ± 0.4	5.5 ± 0.5	4.7 ± 0.4	5.2 ± 0.4	0.012	0.001	0.980
Fasting insulin (pmol/l)	38 ± 33	60 ± 43	24 ± 19	35 ± 20	0.045	0.028	0.812
HOMA-IR	1.2 ± 1.1	2.2 ± 1.9	0.8 ± 0.6	1.2 ± 0.7	0.085	0.027	0.795
Insulin sensitivity index	9.3 ± 5.2	5.2 ± 3.5	10.7 ± 3.1	8.7 ± 4.9	0.019	0.008	0.366

Data are means ± SD. Data were submitted to a two-way GLM after applying logarithmic transformations as needed to ensure a normal distribution of the variables. HOMA-IR, homeostasis model assessment of insulin resistance.

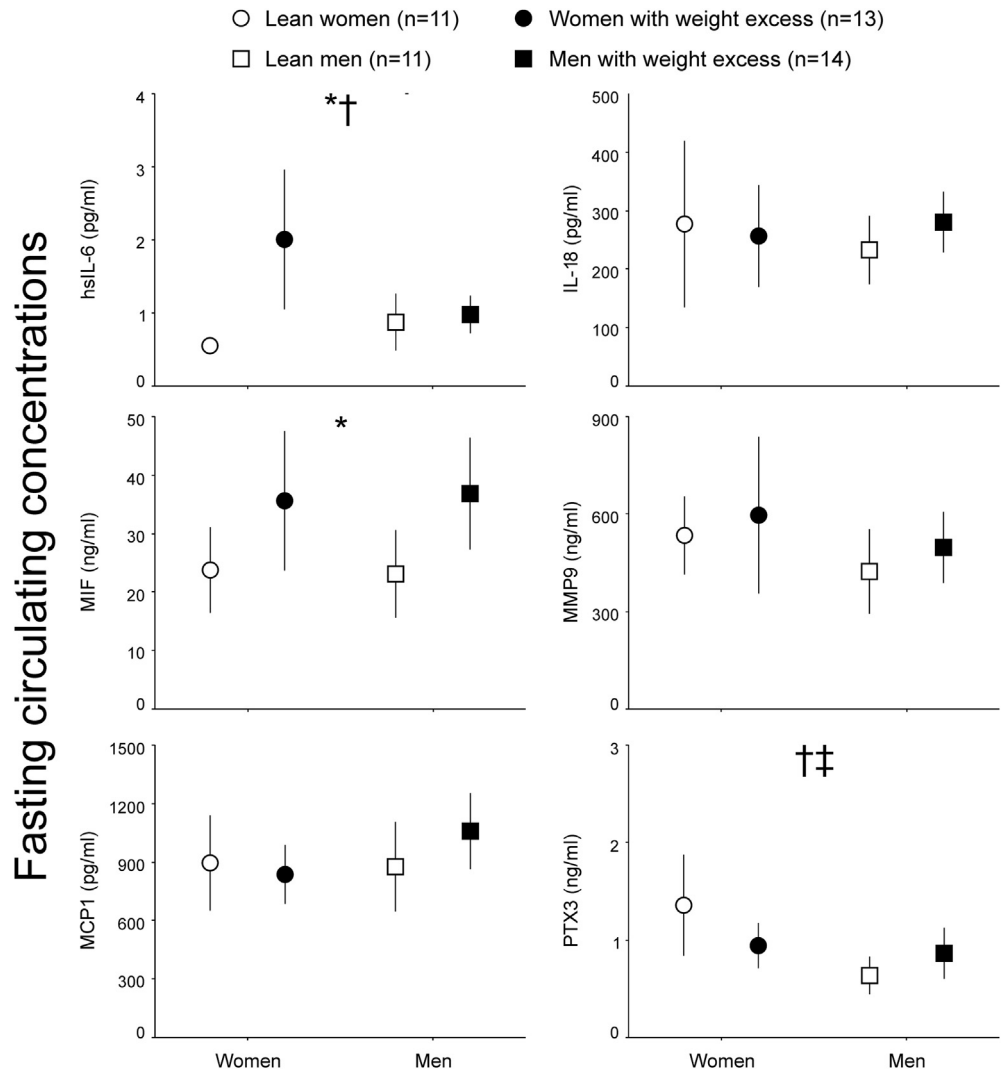

Fig. 1. Circulating concentrations of inflammatory markers in the fasting state. Data are means and 95% confidence intervals. * $P < 0.05$ for the difference between the normal and weight excess groups irrespective of sex. † $P < 0.05$ for the interaction between the effects of weight excess and sex. ‡ $P < 0.05$ for the difference between men and women irrespective of weight.

(Fig. 3). MIF was increased throughout the oGTT in subjects with weight excess compared with their lean counterparts, following their already higher fasting levels (Figs. 1 and 2). MMP9 concentrations increased during the oGTT in subjects with weight excess and decreased in lean individuals irrespective of sex (Fig. 2) and, in agreement, the AUC of MMCP9 during the oGTT was higher in subjects with weigh excess compared with their lean counterparts irrespective of sex (Fig. 3). MCP1 and PTX3 decreased slightly during the oGTT (Fig. 2) and their AUCs were similarly negative in all groups for both markers (Fig. 3), yet PTX3 concentrations were higher in women compared with men throughout the test following the differences already present at the fasting state (Figs. 1 and 2).

3.4. Main determinants of fasting levels and areas under the oGTT curve of inflammatory markers, among sex, sex hormones, glycemia and insulinemia, and surrogate clinical markers of global and regional adiposity

Multiple stepwise linear regression models were used to estimate the main contributors to the variability on fasting levels and AUCs of the inflammatory mediators studied here, which were introduced in the models as dependent variables. We introduced sex (coded as 0 for women and 1 for men), BMI, waist circumference, free T, free E_2, glycemia and insulinemia as independent variables. We used fasting glucose and insulin in the models estimating fasting levels of inflammatory markers, and AUCs of glucose and insulin in the models estimating the AUCs of the inflammatory mediators. We found that BMI was the main determinant of fasting hsIL-6 concentrations, waist circumference determined the variability of fasting MIF concentrations and of the AUC of MMP9, fasting insulin determined fasting MCP1 levels and the AUC of insulin influenced negatively the AUC of PTX3, whereas the fasting levels of the latter were influenced negatively by free T concentrations (Table 2). Of note, the variability of IL-18 concentrations was not explained by any of the independent variables studied here, and sex was not retained by any of the models (Table 2).

4. Discussion

Our present results, summarized in Table 3, indicate that the circulating concentrations of markers related to the low-grade

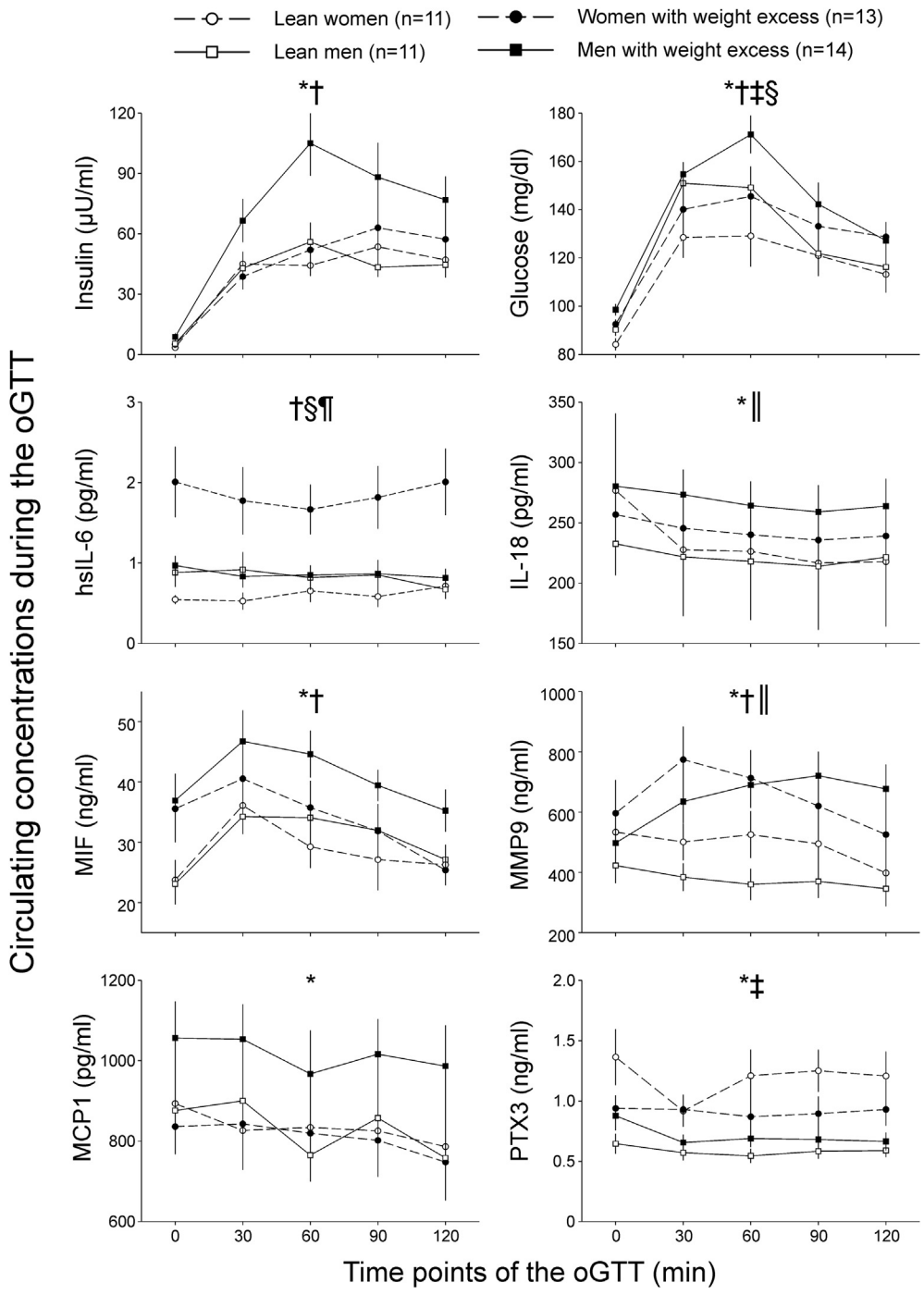

Fig. 2. Circulating concentrations of inflammatory markers in the fasting state (time point 0) and during the oral glucose tolerance test (oGTT, time points 30, 60, 90 and 120 min). Data are means ± SEM. * $P < 0.05$ for differences between time points of the oGTT irrespective of weight excess groups and sex. † $P < 0.05$ for differences between lean individuals and subjects with weight excess irrespective of sex. ‡ $P < 0.05$ for the difference between men and women irrespective of weight excess. § $P < 0.05$ for the interaction between time points of the oGTT and sex, irrespective of weight excess. ¶ $P < 0.05$ for the interaction of weight excess with sex. || $P < 0.05$ for the interaction between time points of the oGTT and weight excess, irrespective of sex.

chronic inflammatory process associated with insulin resistance – such as cytokines, chemokines, metalloproteases and pentraxins – are not only influenced by obesity but also by fasting and glucose ingestion and, in some cases, by sex.

Overall, our present results are concordant with the presumed roles of the markers studied here in the inflammatory process associated with adipose tissue dysfunction. The increased concentrations of the inflammatory cytokine MIF in subjects with weight excess, both in the fasting state and after glucose ingestion, may indicate its role in the recruitment of inflammatory cells during adipose tissue expansion and is in conceptual agreement with the increased concentrations found in obesity and insulin resistant disorders [24]. Similar considerations may apply to the increase found in MMP9 concentrations during the oGTT, since this metalloprotease participates in adipose tissue remodeling during its expansion and, accordingly,

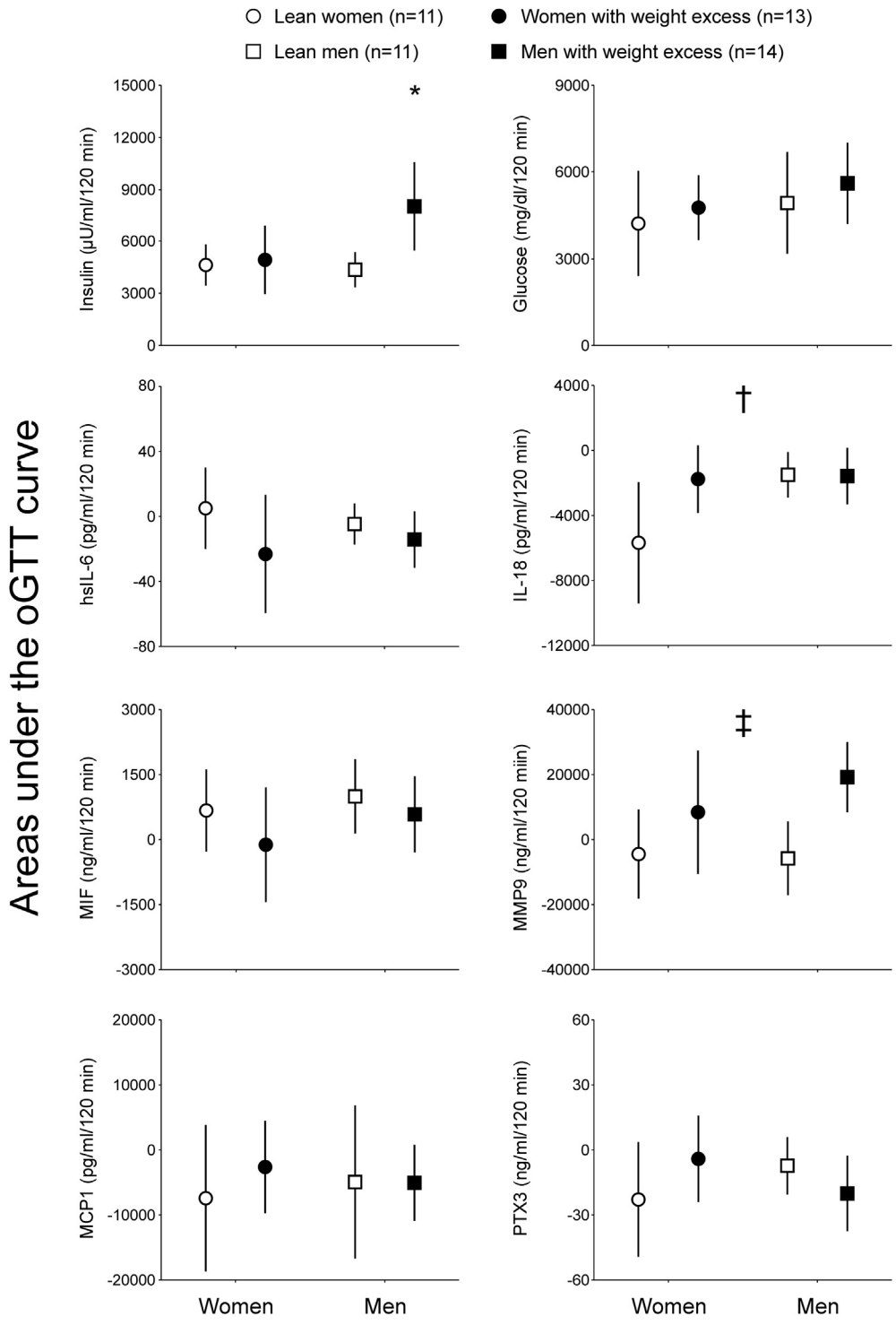

Fig. 3. Areas under the curve of circulating concentrations of inflammatory markers after oral glucose ingestion. Data are means and 95% confidence intervals. * $P < 0.05$ for the interaction between the effects of weight excess and sex. † $P < 0.05$ for the difference between men and women irrespective of weight. ‡ $P < 0.05$ for the difference between the normal and weight excess groups irrespective of sex.

increased MMP9 concentrations have been found in insulin resistance and obesity [25]. Importantly, waist circumference and not BMI was the main determinant of fasting MIF concentrations and AUC of MMP9 during the oGTT, suggesting that their increases in subjects with weight excess were mostly dependent on an abdominal deposition of body fat rather than being related to global adiposity.

Nowadays, IL-6 and IL-18 are mostly considered as anti-inflammatory cytokines that improve insulin action and/or secretion [26,27]. Hence, our current finding of increased fasting hsIL-6 levels in subjects with weight excess, with BMI being their main determinant, may indicate a compensatory rise in response to the inflammatory process associated with obesity, or the existence of resistance to their metabolic actions [27] as occurs with other

Table 2
Main determinants of fasting levels and areas under the curve (AUC) of the oral glucose tolerance test of circulating inflammatory markers among sex, sex hormones and surrogate clinical markers of global and regional adiposity.

Independent variables	Sampling condition	Variables retained by the model*	R^2	β	*P* Value
hsIL-6 (pg/ml)	Fasting	BMI (kg/m^2)	0.234	0.484	0.001
	AUC	None	–	–	–
IL-18 (pg/ml)	Fasting	None	–	–	–
	AUC	None	–	–	–
MIF (ng/ml)	Fasting	Waist circumference (cm)	0.128	0.357	0.014
	AUC	None	–	–	–
MMP9 (ng/ml)	Fasting	None	–	–	–
	AUC	Waist circumference (cm)	0.207	0.455	0.001
MCP1 (pg/ml)	Fasting	Insulin (μU/ml)	0.146	0.382	0.008
	AUC	None	–	–	–
PTX3 (ng/ml)	Fasting	Free testosterone (ng/dl)	0.165	−0.406	0.005
	AUC	AUC of insulin (μU/ml/120 min)	0.109	−0.330	0.025

Abbreviations: AUC, area under the curve; BMI, body mass index; hsIL-6, high-sensitivity interleukin-6; IL-18, interleukin-18; MCP1, monocyte chemotactic protein 1; MIF, macrophage migration inhibitory factor; MMP9, matrix metallopeptidase 9; PTX3 pentraxin-3.
The model used sex (codified as 0 for women and 1 for men), BMI, waist circumference, free testosterone and free estradiol and fasting or AUCs (as appropriate) of insulin and glucose concentrations, as independent variables. *Independent variables were introduced in the model using a stepwise method (probability to enter $\leq$ 0.05, probability to remove $\geq$ 0.10).

Table 3
Summary of effects of weight excess and sex on circulating inflammatory markers in the fasting state and during the oral glucose tolerance test.

	Fasting state (Fig. 1)	Oral glucose tolerance test	
		Time-points (Fig. 2)	AUC (Fig. 3)
hs-IL-6	↑ in women with weight excess	↓ in women with weight excess	No differences
IL-18	No differences	↓ considering all subjects as a whole	↑ negative AUC in women
MIF	↑ in subjects with weight excess	↑ considering all subjects as a whole	No differences
MMP9	No differences	↑ in subjects with weight excess ↓ in lean subjects	↑ positive AUC in subjects with weight excess
MCP1	No differences	↓ considering all subjects as a whole	No differences
PTX3	↑ in lean women	↓ considering all subjects as a whole	No differences

Abbreviations: AUC, area under the curve; BMI; hsIL-6, high-sensitivity interleukin-6; IL-18, interleukin-18; MCP1, monocyte chemotactic protein 1; MIF, macrophage migration inhibitory factor; MMP9, matrix metallopeptidase 9; PTX3 pentraxin-3.

adipokines such as leptin in obesity [28]. Also, the decreases observed in anti-inflammatory cytokines during the oGTT were especially evident in our female subjects. Circulating hsIL-6 concentrations decreased only in obese women, and women showed a larger negative AUC of circulating IL-18 compared with men, possibly indicating that loss of protection from anti-inflammatory cytokines may contribute to glucose-induced inflammation particularly in women [29]. In accordance, previous reports showed that serum IL-6 levels decreased in obese individuals after oral glucose administration [30,31] and circulating IL-18 decreased after the ingestion of a high-carbohydrate meal in subjects with or without diabetes [32].

The decrease in PTX3 concentrations observed in men and in obese women when compared with the levels obtained in lean women is in agreement with previous reports [33,34] and may suggest a beneficial role of this protein: current evidence indicates that PTX3 plays tissue protective and anti-inflammatory roles by inhibiting complement activation in serum [34,35]. The decrease in PTX3 levels during the oGTT observed in our subjects, which was mostly determined by the increase in insulin concentrations during the glucose challenge, may again indicate loss of this protective mechanism during glucose ingestion. Likewise, serum PTX3 levels correlated inversely with serum androgens in women with polycystic ovary syndrome [36].

MCP1, on the contrary, was not affected by sex or weight excess in our series, even though this chemokine has been usually found to be increased in the circulation of obese subjects in earlier reports [37] and insulin was the major determinant of its fasting levels in our series. Moreover, we have not been able to confirm previous studies about the association of MCP1 with circulating testosterone (negative) and estradiol (positive) in men, yet these associations were observed in morbidly obese subjects with obesity-associated hypogonadism and confirmed in healthy men only after substantial pharmacological modification of their sex steroids using aromatase inhibitors and estradiol patches [38].

Because we included men and women without gonadal dysfunction, and we did not modify their sex steroid concentrations by means of pharmacological intervention, we have not been able to differentiate the effects of sex from those of sex steroids. Nevertheless, our present results indicate that sexual dimorphism influenced circulating concentrations of several markers, although to a lesser extent than global and regional adiposity and insulin resistance. Women showed more pronounced changes in hsIL-6 and PTX3 concentrations in response to oral glucose ingestion, and a larger negative AUC of IL-18 levels during the oGTT, compared with men. We might hypothesize that the presence of weight excess is particularly deleterious in terms of induction of inflammation in women. On the one hand, lean women have most of the fat in the more healthy subcutaneous and peripheral depots, and the adipose tissue dysfunction only develops when weight excess is present [39]. On the other hand, a certain deposition of body fat in visceral abdominal depots is present even in lean men [39], making the consequences of increasing abdominal adiposity less noticeable in them, including the induction of low-grade chronic inflammation. Overall, our present findings further support the existence of sexual dimorphism in adipose tissue dysfunction [39,40].

In summary, the circulating concentrations of markers of low-grade chronic inflammation in young healthy adults are not only influenced by obesity but also by abdominal adiposity, fasting and glucose ingestion and, in some cases, by sex. These influences

should be considered when these markers are used as surrogate markers of the inflammatory milieu associated with insulin resistance and obesity.

Declaration of interest

The Authors have no competing interests to declare.

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