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Leptin and high-sensitivity C-reactive protein and their interaction in the metabolic syndrome in middle-aged subjects

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Abstract

High-sensitivity C-reactive protein (hsCRP) and leptin, known to interact at the molecular level, have been associated with the metabolic syndrome (MS). We examined the independent and joint effects of high leptin and hsCRP levels on the development of MS in a population-based cohort of middle-aged subjects (N = 1035). Leptin and hsCRP levels increased with an increase in the number of metabolic abnormalities ($P < .001$). However, additional adjustment for body mass index diluted the association of leptin with MS in women. In men, the association of high leptin with insulin resistance and waist circumference ($P < .001$), and in women, the association of high hsCRP with insulin resistance ($P = .029$) and waist circumference ($P = .009$) persisted in the multivariate logistic regression models. High leptin in men and high hsCRP in women were significant predictors of MS in logistic regression analysis ($P < .001$). The highest prevalence of MS (86% in men and 71% in women) was observed in the subjects who belonged to the highest quartile in both leptin and hsCRP. MS is associated independently with high leptin in men and with hsCRP in women, whereas individuals with both of these markers belong to the highest risk of metabolic cluster. The study suggests sex-specific interplay between metabolic and inflammatory markers in the pathogenesis of MS.

1. Introduction

The clustering of several cardiovascular disease and diabetes risk factors has been referred to variously as the metabolic syndrome (MS), insulin resistance syndrome, syndrome X, plurimetabolic syndrome, and the like [1-4]. The reasons for the joint occurrence of several abnormalities are still unclear. Several pathways, such as excess body fat, insulin resistance, central mechanisms, and increased peroxisome proliferator–activated γ activities can potentially lead to the development of the MS [5]. Leptin is an adipocyte-secreted hormone, and the plasma levels of leptin reflect by and large the amount of adipose tissue [6] that has been associated with the MS [7-9]. Leptin has also been shown to predict the development of the MS independently of baseline obesity [10]. Adipocytes are also a source of other cytokines, such as interleukin 6 [11], and leptin is able to induce its production [11]. This promotes the secretion of C-reactive protein (CRP) from the liver [12]. High-sensitivity CRP (hsCRP), an inflammatory marker, has been considered as an important indicator of cardiovascular risk [13] and its relationship with the MS has been shown in several studies [14-16]. It is not surprising that leptin and hsCRP levels are independently associated with each other in healthy humans [17], but the exact role of this interrelationship remains yet unknown.

In this study, we measured the fasting plasma leptin and hsCRP concentrations in a large sample of a middle-aged population. Because adiposity influences all features of the MS, the associations of high leptin and hsCRP with the MS could reflect only the obesity state. Therefore, we wanted to explore whether the earlier observed associations between high leptin and hsCRP with the MS are independent of the amount of total fat. In addition, because there is little knowledge on the joint occurrence of high leptin and hsCRP in the MS, we analyzed the interactions between leptin and hsCRP with the MS and its components as defined by the 2005 International Diabetes Federation (IDF).

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2. Subjects and methods

This study is a part of the Oulu Project Elucidating Risk of Atherosclerosis (OPERA) project, which is a population-based, epidemiologic cross-sectional study designed to address the risk factors and disease end points of atherosclerotic cardiovascular diseases. The study population and selection criteria have been described in detail [18]. In short, 600 hypertensive subjects (300 men and 300 women aged 40-59 years) were randomly selected from the national register for reimbursement of the costs of antihypertensive medication. For each hypertensive subject, an age- and sex-matched control subject was randomly selected. The study was approved by the Ethical Committee of the Faculty of Medicine, University of Oulu. Waist circumference was measured to the nearest 0.5 cm with a tape measure midway between the lower rib margin and the iliac crest in light expirium. Blood pressure (BP) was measured with an oscillometric device (Dinamap model 18465X, Criticon, Ascot, UK) according to the recommendations of the American Society of Hypertension, from the right arm, with the subjects in a sitting position, after an overnight fast and a 10- to 15-minute rest. Three measurements were made at 1-minute intervals and the means of the last 2 were used in the analyses.

All laboratory test samples were obtained after an overnight fast. Plasma was separated from venous blood and stored at 4°C. The venous blood glucose concentration was determined with the glucose dehydrogenase method. The concentrations of total cholesterol and triglycerides in the plasma and lipoprotein fractions were determined by enzymatic colorimetric methods (kits from Boehringer Diagnostica, Mannheim, Germany, catalogue nos. 236691 and 701912, respectively) using a Kone Specific analyzer (Selective Chemistry Analyser, Kone Instruments, Espoo, Finland). The very low-density lipoprotein (VLDL) fraction (d <1.006 g/mL) was separated from plasma by ultracentrifugation in a Kontron TFT 45.6 rotor at 105 000g and 15°C for 18 hours. The VLDL fraction was removed from the ultracentrifuged preparation by tube slicing. The plasma high-density lipoprotein (HDL) cholesterol concentration was determined by mixing 1 mL of the VLDL-free fraction with 25 μL of 2.8% (wt/vol) heparin and 25μL of 2 mol/L manganese chloride and by measuring the cholesterol concentration in the supernatant after centrifugation at 1000g and 4°C for 30 minutes.

Fasting plasma leptin concentrations were measured by a commercial double-antibody radioimmunoassay (Human Leptin RIA Kit; Linco Research, St Charles, MO) with an intra-assay coefficient of variation of 3.4% to 8.3% and an interassay coefficient of variation of 3.0% to 6.2%. High-sensitivity CRP was measured with commercially available enzyme-linked immunosorbent assay kits with a detection limit of 0.31 ng/mL (Diagnostic Systems Laboratories, Webster, TX).

The 2005 IDF definition of the MS was used [19]. According to the IDF definition, for persons to be defined as having the MS, they must have central obesity (defined as waist circumference ≥94 cm for Europid men and ≥80 cm for Europid women) plus any 2 of the following 4 factors: raised serum triglyceride level (≥1.7 mmol/L) or specific treatment for this lipid abnormality, reduced serum HDL cholesterol level (<1.03 mmol/L in men and <1.29 mmol/L in women) or specific treatment for this lipid abnormality, raised BP (systolic BP ≥130 mm Hg or diastolic BP ≥85 mm Hg), or treatment of previously diagnosed hypertension, impaired fasting glycemia (fasting plasma

Table 1
Main characteristics of the study subjects by gender

	Men	n	Women	n	P
Age (y)	50.7 (6.0)	520	51.8 (5.9)	525	.003
MS (%)	42.9	520	37.2	525	<.001
Type 2 diabetes mellitus (%) [a]	10.0	518	7.8	524	NS
BMI (kg/m^2)	27.9 (4.2)	520	27.4 (5.0)	525	NS
Waist circumference (cm)	97.4 (10.9)	520	83.8 (11.7)	523	<.001
Systolic BP (mm Hg)	152.0 (21.4)	520	144.6 (22.2)	525	<.001
Diastolic BP (mm Hg)	92.5 (11.2)	520	85.7 (12.2)	525	<.001
Fasting glucose (mmol/L) [b]	4.7 (1.2)	520	4.5 (1.2)	525	.001
QUICKI	0.58 (0.10)	518	0.64 (0.13)	524	<.001
Total cholesterol (mmol/L)	5.8 (1.0)	520	5.6 (1.1)	525	.023
HDL cholesterol (mmol/L) [b]	1.2 (1.3)	520	1.4 (1.3)	525	<.001
Triglycerides (mmol/L) [b]	1.6 (1.6)	520	1.2 (1.6)	525	<.001
hsCRP (μg/mL) [b]	1.7 (3.5)	512	1.6 (3.5)	523	NS
Leptin (ng/mL) [b]	5.2 (1.7)	487	12.5 (1.8)	522	<.001

Values are means (SD) or percentages. NS indicates not significant.
[a] Based on World Health Organization criteria.
[b] Logarithmic backtransformed.

Table 2
Partial correlations (adjusted for BMI) between components of MS with hsCRP and leptin in men and women

Components of MS	hsCRP		Leptin	
	R	P	R	P
Men				
BMI (kg/m^2)	0.363	.000	0.700	.000
Waist circumference (cm) [a]	0.120	.008	0.356	.000
Triglycerides (mmol/L) [a]	0.087	.057	0.212	.000
HDL cholesterol (mmol/L) [a]	−0.155	.001	−0.025	.579
Systolic BP (mm Hg) [a]	0.078	.088	0.062	.176
Fasting glucose (mmol/L) [a]	0.020	.654	0.095	.036
QUICKI [a]	−0.117	.008	−0.326	.000
Leptin (ng/mL) [a]	0.163	.000	–	–
Women				
BMI (kg/m^2)	0.441	.000	0.683	.000
Waist circumference (cm) [a]	0.168	.000	0.025	.565
Triglycerides (mmol/L) [a]	0.202	.000	0.120	.006
HDL cholesterol (mmol/L) [a]	−0.057	.193	0.055	.207
Systolic BP (mm Hg) [a]	0.029	.508	0.025	.571
Fasting glucose (mmol/L) [a]	0.203	.000	−0.090	.041
QUICKI [a]	−0.191	.000	−0.113	.010
Leptin (ng/mL) [a]	0.214	.000	–	–

[a] Adjusted for BMI.

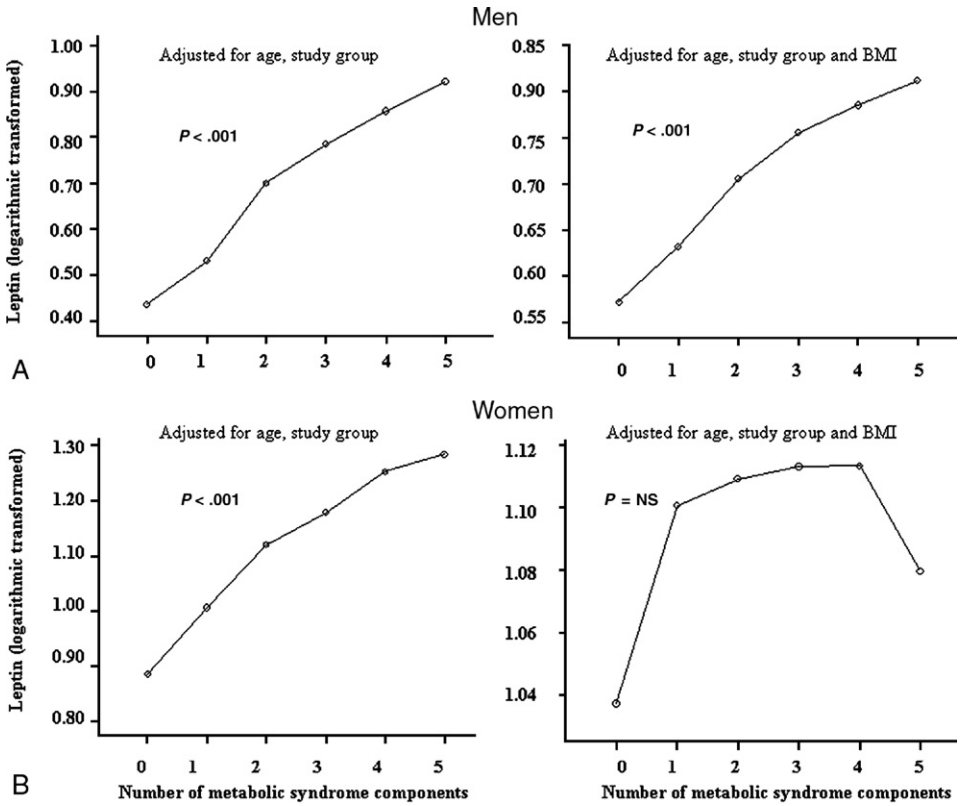

Fig. 1. Fasting plasma leptin concentrations of the study subjects in relation to the number of IDF criteria of MS in men and women. Values adjusted for age, study group (left), and age, and study group and BMI (right panels) are shown.

glucose ≥5.6 mmol/L), or previously diagnosed type 2 diabetes mellitus.

Insulin sensitivity was assessed using fasting plasma insulin concentrations and a quantitative insulin sensitivity check index (QUICKI = 1/[log(fasting insulin) + log(fasting glucose)]) [20]. The subjects with insulin sensitivity below the lowest quartile of the control cohort (QUICKI <0.563) were regarded as insulin resistant.

2.1. Statistical methods

To compare the means of the variables measured, Student *t* test and analysis of covariance were used. For evaluating differences in frequencies, the χ^2 test was used. The partial correlations between components of MS and hsCRP and leptin were calculated while controlling for body mass index (BMI). The association between leptin and hsCRP and the variables studied was assessed using linear and logistic regression analyses. The following variables were entered into the multivariate models: study group, BMI, and age. The sexes were analyzed separately because of significant differences in plasma levels of leptin between men and women. Log-transformed (leptin and hsCRP, triglycerides, HDL cholesterol, glucose, and insulin) values were used as appropriate to normalize the skewed distributions. All calculations were made with the SPSS statistical package (version 9.0, SPSS, Chicago, IL). $P < .05$ was regarded as significant.

3. Results

Table 1 shows the main characteristics of the study subjects by gender. Women were older, had lower values of waist circumference, BP, fasting glucose, total cholesterol, and triglycerides than men. HDL cholesterol, QUICKI, and leptin values were higher in women than in men. The prevalence of MS was higher in male than in female subjects.

Partial correlations (adjusted for BMI) between components of MS with hsCRP and leptin in men and women are shown in Table 2. In men, hsCRP was correlated positively with BMI and waist circumference and negatively with HDL cholesterol and QUICKI. hsCRP correlated positively with BMI, waist circumference, triglycerides, and fasting blood glucose and negatively with QUICKI in female subjects. In men, leptin correlated positively with BMI, waist circumference, triglycerides, and fasting blood glucose and negatively with QUICKI. Leptin correlated positively with BMI and triglycerides and negatively with fasting blood glucose and QUICKI in female subjects.

Leptin concentrations varied in relation to the number of MS IDF criteria met (Fig. 1). Leptin levels (adjusted for age and study group) increased with an increase in the number of metabolic abnormalities in both male and female ($P < .001$) subjects. When additional adjustment for BMI was done, the association of leptin with MS remained in male ($P < .001$) but not in female subjects.

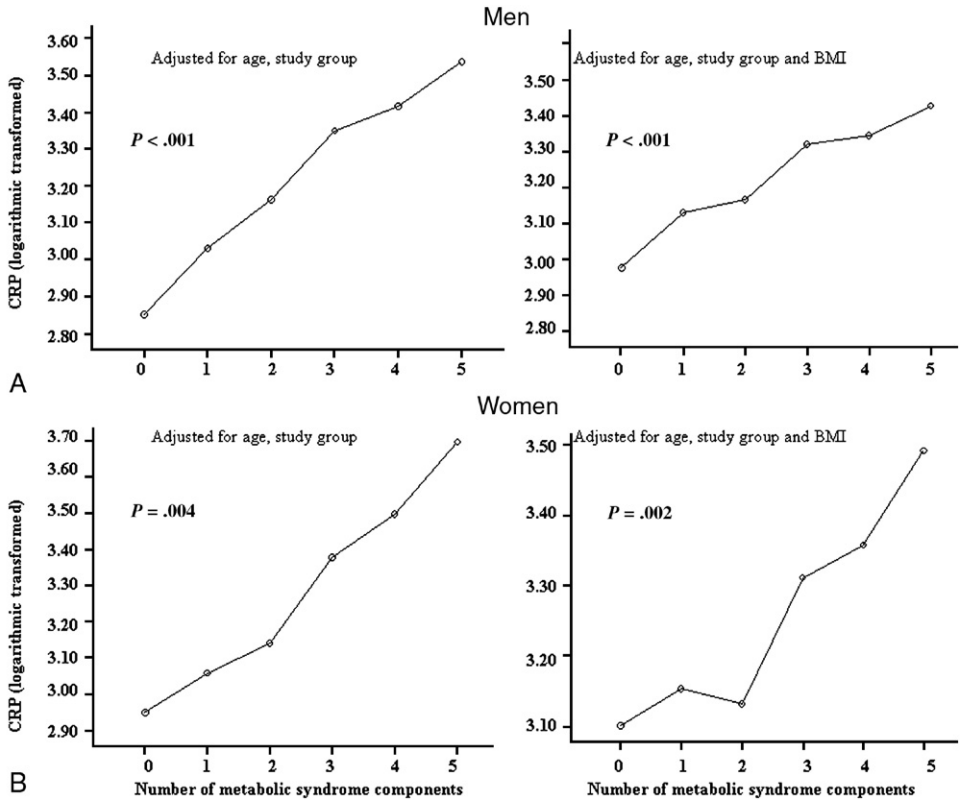

Fig. 2. Fasting plasma hsCRP concentrations of the study subjects in relation to the number of IDF criteria of MS in men and women.

In addition, hsCRP levels (adjusted for age and study group) increased with an increase in the number of metabolic abnormalities in both male and female ($P < .001$) subjects (Fig. 2). When additional adjustment for BMI was done, the association of hsCRP with MS remained significant in both male ($P = .004$) and female ($P = .002$) subjects.

In men (but not in women), the association of high leptin ($P < .001$), and in women (but not in men), the association of high hsCRP ($P = .029$) with insulin resistance (QUICKI <0.563) persisted in the multivariate logistic regression models (adjusted for study cohort, age, and BMI).

In multivariate models, the associations with central obesity (defined as waist circumference ≥94 cm for men and ≥80 cm for women) remained significant for high leptin in men ($P < .001$) and for high hsCRP in women ($P = .009$). The following variables were entered into the multivariate models: study group, BMI, and age.

Odds ratios (ORs) with 95% confidence intervals (CIs) for leptin and hsCRP quartiles for MS obtained by logistic regression analysis adjusted for age, BMI, and study group are shown in Fig. 3. Both leptin and hsCRP were included in the same model. In male individuals, high leptin was a statistically significant predictor of MS in logistic regression analysis ($P < .001$) so that the subjects in the first leptin quartile were at lower risk of having MS compared with the subjects in the fourth quartile (OR, 6.59; 95% CI, 2.93-14.79; $P < .001$). In female subjects, hsCRP was a statistically significant predictor of MS in logistic regression analysis (OR, 3.01 for the fourth quartile compared with the first quartile; 95% CI, 1.76-5.16; $P = .001$), whereas the association of high leptin with MS was not significant ($P = .075$).

We also analyzed the frequency of MS in relation to combined leptin and hsCRP quartiles in male (Fig. 4A) and female subjects (Fig. 4B). In men, hsCRP quartile did not seem be a significant predictor of MS in any of the leptin quartiles, whereas in women, the prevalence of MS was highest in the highest hsCRP quartile when leptin quartiles (except for the highest leptin quartile) were considered. The highest prevalence of MS (86% in men and 71% in women) was observed in the subjects who belonged to the highest quartile in both leptin and hsCRP.

Ten percent of men and 7.8% of women had type 2 diabetes mellitus (Table 1). We examined the predictors of type 2 diabetes mellitus in both sexes by including age, waist circumference, study group, hsCRP, and leptin in the logistic regression analysis. In female subjects, hsCRP was the strongest predictor of development of type 2 diabetes mellitus (OR, 4.50; 95% CI, 2.07-9.78; $P < .001$), although leptin was also significant but its effect was weak (OR, 0.05; 95% CI, 0.01-0.34; $P = .002$). hsCRP or leptin was not significantly associated with the development of type 2 diabetes mellitus in men. Forty-four percent of the women were premenopausal and 51%

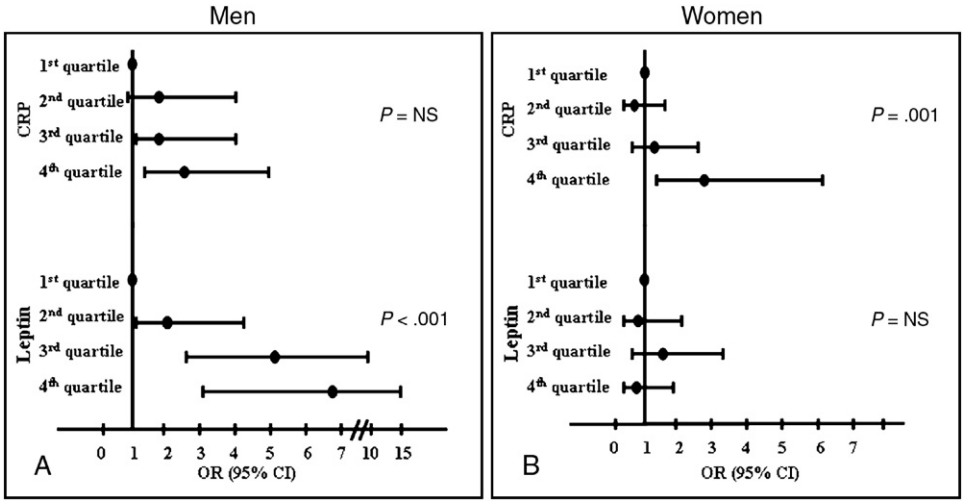

Fig. 3. ORs with 95% CI of leptin and hsCRP quartiles for MS obtained by logistic regression analysis adjusted for age, BMI and study group. The first quartile is used as a reference category.

were postmenopausal. Menopausal status could not be defined for 5% of the women. When menopausal status was included in the multivariate linear regression analysis, the results did not change.

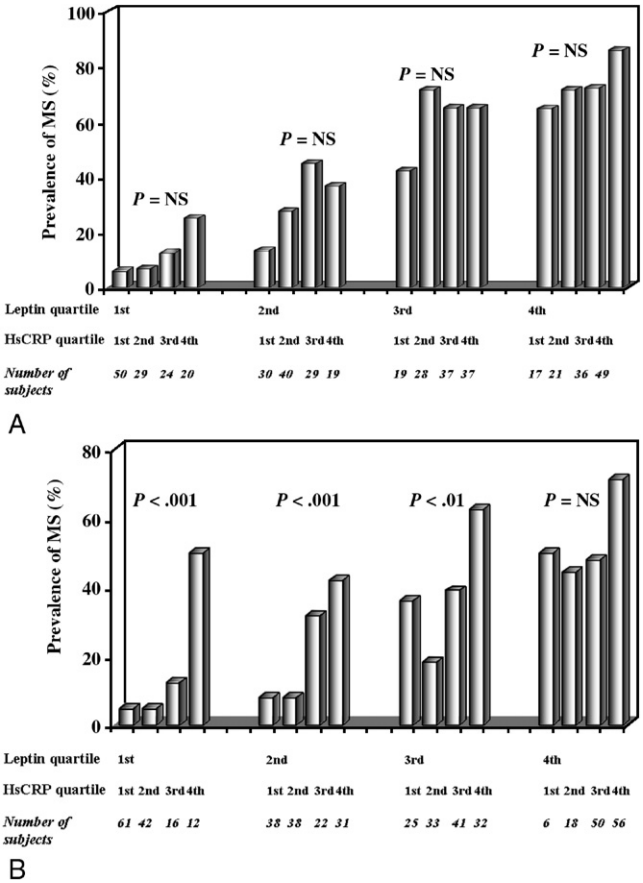

Fig. 4. The prevalence of MS in different leptin and hsCRP quartiles in men (A) and women (B).

4. Discussion

The results of the present study suggest that both leptin and hsCRP levels were correlated with several components of the MS and with metabolic cluster per se. Both leptin and hsCRP values increased with an increase in number of metabolic abnormalities. Adjustment for BMI did not change the association of leptin with MS in male but diluted the effect of leptin in female individuals. Therefore, leptin's association with MS in women seems to be more dependent on its relationship with BMI. The association of MS with hsCRP remained significant after adjustment for BMI. When both markers were considered jointly, leptin, a metabolic marker, was associated independently with MS among male subjects, whereas hsCRP, an inflammatory marker, seemed to be a stronger indicator of MS in women. Because these analyses were all carried out on data adjusted for BMI, the results provide strong support for the concept that the associations are independent of the overall level of fatness.

Decreased insulin action, or insulin resistance, has been suggested as a primary physiologic defect underlying the MS [2]. Interestingly, leptin showed a strong independent association with insulin resistance among male but not in female subjects. This is in accordance with some earlier studies [21,22] suggesting that there are important sex-based differences in the regulation and action of leptin in humans. Leptin receptors are present in a number of tissues including beta cells of the pancreas where leptin is able to suppress the secretion of insulin [23]. In the presence of leptin deficiency or resistance, leptin fails to inhibit glucose-stimulated insulin secretion, which could lead to hyperinsulinemia and insulin resistance [24]. Leptin may also have effects on insulin action [25]. Why these effects on insulin sensitivity were evident in male but not in female subjects of the present study remains unknown. Undoubtedly, the development of MS involves multiple and interactive effects of genetic,

hormonal, and environmental factors. Leptin levels are higher in women than in men [26], consistent with a state of relative leptin resistance. In female subjects in whom leptin is up-regulated, an increase in number of metabolic abnormalities does not seem anymore to lead to an increase in leptin levels when the latter are adjusted for BMI. It is interesting to note that leptin was independently associated with waist circumference among male but not in female subjects as reported earlier [22]. Excess body fat (and accumulation of fat into the abdominal region) is the single most important central feature of the MS [5].

The association of hsCRP with MS persisted after adjustment for BMI in both men and women. However, when both markers were considered together, the association of hsCRP with MS in women persisted but became nonsignificant in men. In female subjects, hsCRP was associated independently with waist circumference, a prerequisite of MS. In addition, hsCRP showed association with insulin resistance among female subjects, independent of age and BMI. Therefore, in women, who had a lower frequency of MS than men, inflammatory mechanisms seem to be associated with the insulin resistance and clustering of metabolic abnormalities. Earlier studies have demonstrated a prognostic value of hsCRP in the prediction of type 2 diabetes mellitus [27]. Our data indicate inflammation to be a strong predictor for development of type 2 diabetes mellitus in women. Our results are in line with those obtained from an earlier prospective Mexico City Diabetes Study [28]. A limitation of our study is its cross-sectional study design, which does not allow one to conclude on causality of the associations.

It is not surprising that leptin and hsCRP are tightly linked and this was true also in the current study in both men and women. Leptin is secreted from adipocytes inducing production of other adipocytokines, such as interleukin 6, that promote hsCRP synthesis by the liver. Interestingly, induction of leptin resistance through direct interaction of CRP with leptin was recently reported [29]. Therefore, leptin and hsCRP have potentially interactive and additive effects that may have clinical significance. It was interesting that leptin and hsCRP tended to have an additive effect on the prevalence of MS in the present study, with the highest prevalence of MS (86% in men and 71% in women) observed in the subjects who belonged to the highest quartile in both leptin and hsCRP.

In conclusion, the study suggests that leptin and hsCRP are strong indicators of MS in both men and women as observed in earlier studies. However, in women, the effect of leptin weakened after adjustment for BMI. Leptin was independently associated with insulin resistance and abdominal obesity in men, whereas hsCRP showed similar relationships in women. Subjects who had elevated levels of both leptin and hsCRP belonged to the highest risk of developing MS. In summary, the sex-specific interplay between metabolic and inflammatory markers may be involved in the pathogenesis of MS.

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