The Degree of Hyperinsulinemia and Impaired Glucose Tolerance Predicts Plasma Leptin Concentrations in Women Only: A New Exploratory Paradigm

Daniel Panarotto, Jean-Luc Ardilouze, Daniel Tessier, and Pierre Maheux

Plasma leptin has been shown to correlate positively with many indices of obesity, as well as insulin resistance. For a given body weight, the levels are higher in women than in men, but the reasons for this difference are not clear. Insulin has been shown to stimulate leptin production by adipose tissue in vivo and in vitro. Previous studies have reported that leptin levels are similar in diabetic and nondiabetic individuals. However, these studies were not performed in newly diagnosed diabetics, and other variables (such as gender) could have confounded the results. Therefore, the goal of the present cross-sectional study is to examine the effect of metabolic variables (such as glucose and insulin) on plasma leptin concentrations in men and women separately. We measured leptin levels in 48 subjects (17 with newly diagnosed type 2 diabetes mellitus, 13 with impaired glucose tolerance [IGT], and 18 normal individuals). The 3 groups were well matched for gender, age, and body mass index (BMI). When adjusted for the BMI and gender, a statistically significant gender-related difference in mean plasma leptin was observed across the 3 glucose tolerance subgroups ($P < .03$ by analysis of covariance [ANCOVA]). More specifically, plasma leptin levels were, on average, 44% lower in women with diabetes or IGT versus normal women ($P < .02$). No such between-group difference was observed in the men. In univariate analysis in the same female subgroup, plasma leptin correlated positively with fasting insulin ($r_s = +.43$, $P < .06$) and negatively with 2-hour post–75-g glucose load plasma glucose concentration ($r_s = -.54$, $P < .02$). In a multiple regression model controlling for the BMI in the female subgroup, circulating insulin and glucose concentrations 2 hours after the 75-g glucose load were good predictors of fasting plasma leptin ($r = +.38$, $P = .02$ and $r = -.70$, $P < .001$, respectively). Leptin levels in women appear to be influenced independently and to an important degree by ambient plasma glucose and plasma insulin concentrations. These findings suggest that the synthesis of leptin by adipose tissue is more susceptible to in vivo regulation by insulin and glucose in women than in men. Plasma leptin concentrations were also lower in women with IGT or type 2 diabetes versus normal women, suggesting that fasting and/or postprandial hyperglycemia interferes with the stimulatory effect of plasma insulin on the synthesis of leptin by adipose tissue in women only.

LEPTIN, the 167–amino acid peptide product of the *ob* gene, was cloned in 1994,[1] but its exact physiological role and mode of regulation in man is still a matter of intense discussion.[2,3] The recent interest in the measurement of leptin by radioimmunoassay has generated a huge amount of information on the principal determinants and nondeterminants of plasma leptin in a number of pathophysiological conditions in man. To date, most of the clinical data have been observational and were obtained from case-control studies in which the findings were not always interpreted with regard to all of the now well-recognized confounding variables.

The information currently available regarding the variable plasma concentrations of leptin in man illustrates 2 different and complex issues. The first is that whereas insulin regulates the expression of leptin by adipose tissue in vitro,[4-6] similar activity seems to occur in vivo in humans only after infusions of insulin lasting from 4 to 72 hours,[7-10] as compared with rodents, wherein the action appears much faster.[4,11,12] In clinical conditions characterized by insulin resistance such as impaired glucose tolerance (IGT), type 2 diabetes mellitus, and, to some extent, polycystic ovary syndrome, a defect in the action of insulin could theoretically lead either directly or indirectly to important changes in plasma leptin. One way in which this might occur is that for a given body fat mass, an impairment in the action of insulin on adipocytes leads to a reduction in the synthesis of leptin by adipose tissue. Alternatively, if insulin resistance does not blunt the effects of insulin on adipose tissue, the compensatory hyperinsulinemia found in insulin-resistant patients could lead to an increase in leptin production by adipose tissue. However, to date, the majority of researchers have found no differences in plasma leptin levels between diabetic and nondiabetic individuals[1-4] or between normal women and those with polycystic ovary syndrome.[13-15] The reason(s) for the absence of differences in plasma leptin between these insulin-sensitive and insulin-resistant populations is not clear. Even if most of these studies controlled for body adiposity, these findings suggest that other factors are involved in the regulation of leptin production.

The second important consideration arising from the available data is that for a given body mass index (BMI), plasma leptin is usually severalfold higher in women than in men.[2,16] The reasons for this dichotomy and its physiological or pathophysiological implications have not been well established. The involvement of female sex hormone levels,[2,17] the reduced androgen levels in women,[2,18] and/or the favored distribution of fat toward the subcutaneous region in women[2,19,20] have been proposed as possible explanations, but none of these fully explain the higher plasma levels of leptin in women. The situation is therefore complex and needs a more definitive answer. More specifically, what other factor(s) could be impli-

From the Division of Endocrinology and Metabolism, Department of Medicine, Université de Sherbrooke, Sherbrooke, Quebec, Canada.

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Address reprint requests to Pierre Maheux, MD, Division of Endocrinology and Metabolism, Université de Sherbrooke, 3001, 12ème Avenue Nord, Sherbrooke, Quebec, Canada J1H 5N4.

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cated and which parameters of glucose metabolism could influence this gender difference?

To address the 2 aforementioned problems, therefore, a cross-sectional study was performed (1) to explore the hypothesis that men and women differ with regard to plasma leptin levels as a result of differing regulatory effects of plasma insulin and glucose on adipose tissue, and (2) to define the precise influence of the glucose tolerance status and the degree of hyperinsulinemia on plasma leptin in both genders.

Our results not only confirm a dichotomy in plasma leptin levels in men and women, but suggest that hyperinsulinemia and hyperglycemia play independent and determinant roles in the production of leptin in women specifically.

SUBJECTS AND METHODS

Study Population

Forty-eight Caucasian subjects (age, 40 to 70 years; mean ± SD, 56 ± 8) were recruited, comprising 17 individuals with type 2 diabetes mellitus, 13 subjects with IGT, and 18 normal individuals. All subjects had recently been screened from a large community-based diabetes program in which individuals with a random capillary glucose level over 8 mmol/L were invited for an oral glucose tolerance test. The classification was based on World Health Organization (WHO) criteria[21] using a standard 2-hour 75-g glucose tolerance test administered in the morning after a 12-hour fast and preceded by 3 days of unrestricted carbohydrate intake. Therefore, all diabetic and glucose-intolerant subjects included in the present study were newly diagnosed, and none had used oral hypoglycemic agents or insulin. The mean BMI was 27.9 ± 2.5 kg/m^2 (range, 20.8 to 32.6); 44% (21 of 48) were women. Of the 21 women, 16 were postmenopausal, and of these, 7 (44%) were receiving estrogen, a replacement therapy that does not affect plasma leptin concentrations.[22] The level of physical activity (in kilojoules per day) was estimated in each subject using a questionnaire developed and validated by Sallis et al.[23]

Hormonal Assays

Plasma insulin was determined using a human insulin-specific radioimmunoassay that does not cross-react with proinsulin (Linco Research, St Louis, MO). Fasting plasma immunoreactive leptin was determined using a commercial double-antibody radioimmunoassay (Linco Research). The leptin radioimmunoassay uses a rabbit anti-human leptin antibody and detects immunoreactive human leptin with a sensitivity of 0.5 ng/mL in plasma. The intraassay coefficient of variation was less than 5% across the range of standard (1 to 100 ng/mL), whereas the interassay coefficient of variation estimated by the use of 2 control pools was 2.3 ± 0.1 ng/mL (mean ± SD) (5.1%) and 12.5 ± 0.7 ng/mL (5.3%), respectively.

Statistical Analysis

Plasma leptin, glucose, and insulin were not normally distributed variables. All statistical analyses therefore used nonparametric tests or logarithmically transformed variables. Between-group comparisons of variables were performed using the Mann-Whitney *U* rank-sum test or the Kruskal-Wallis test, depending on the number of groups to be compared. Relationships between plasma leptin and independent variables were assessed using the Spearman rank correlation coefficient (r_s). Comparisons of continuous variables among the 3 groups were made using analysis of covariance (ANCOVA) to control for the influence of confounding variables (gender and BMI) on leptin concentrations across the different subgroups of glucose tolerance. To validate the results obtained with ANCOVA, several multiple regression models were established using the log-transformed leptin concentration as the dependent variable. Data are presented as the mean ± SEM unless otherwise indicated. Differences were considered significant at a *P* value less than .05. All statistical analyses were performed with the software StatView 5.0 for Windows (SAS Institute, Chicago, IL). A power calculation analysis for the multiple linear regression was performed a posteriori using the software nQuery Advisor 3.0 for Windows (Statistical Solutions, Saugus, MA) and following guidelines established by Cohen.[24]

RESULTS

Patients' Baseline Characteristics

The physical and metabolic characteristics of the subjects in this protocol are summarized in Table 1 according to gender and glucose tolerance status. The subjects were comparable for most variables, with the exception of a higher body weight and waist to hip ratio in the male subgroup. Subjects with diabetes

Table 1. Comparison of Subjects by Gender and Diagnosis of Glucose Tolerance

Variable	Men (n = 27)				Women (n = 21)			
	Normal	IGT	Diabetic	*P**	Normal	IGT	Diabetic	*P**
No. of subjects	10	8	9		8	5	8	
Age (yr)	55 ± 10	58 ± 9	59 ± 6	NS	56 ± 7	54 ± 5	55 ± 9	NS
BMI (kg/m^2)	27.4 ± 2.1	28.8 ± 2.5	27.6 ± 2.4	NS	27.9 ± 2.5	26.0 ± 3.3	28.9 ± 2.3	NS
Weight (kg)	80.4 ± 11.5	81.9 ± 10.3	82.2 ± 8.4	NS	74.3 ± 11.5	65.2 ± 4.8	70.0 ± 7.6	NS
Waist to hip ratio	0.91 ± 0.04	0.90 ± 0.08	0.93 ± 0.05	NS	0.83 ± 0.03	0.85 ± 0.08	0.86 ± 0.06	NS
Physical activity (kJ/d)	559 ± 300	725 ± 293	515 ± 361	NS	545 ± 274	684 ± 315	737 ± 399	NS
Systolic blood pressure (mm Hg)	136 ± 15	133 ± 11	147 ± 11	NS	142 ± 12	138 ± 7	136 ± 20	NS
Diastolic blood pressure (mm Hg)	89 ± 8	85 ± 8	89 ± 7	NS	92 ± 9	88 ± 8	90 ± 9	NS
Plasma glucose (mmol/L)								
Fasting	4.6 ± 0.3	5.5 ± 0.8	7.1 ± 1.6	<.001	4.8 ± 0.4	4.7 ± 0.3	7.1 ± 1.5	<.001
2-h post–75-g load	5.7 ± 1.5	9.1 ± 1.2	15.1 ± 3.2	<.001	5.0 ± 1.1	8.9 ± 1.2	15.6 ± 2.6	<.001
Plasma insulin (pmol/L)								
Fasting	58 ± 15	99 ± 46	83 ± 37	NS	73 ± 21	72 ± 22	82 ± 25	NS
2-h post–75-g load	416 ± 314	793 ± 634	358 ± 235	NS	349 ± 215	618 ± 312	388 ± 190	NS
Plasma leptin (ng/mL)	4.7 ± 2.4	5.3 ± 3.1	5.1 ± 3.1	NS	23.9 ± 12.6	14.1 ± 6.6	13.1 ± 2.3	<.07

NOTE. Results are the mean ± SD.

*Kruskal-Wallis test in each gender subgroup.

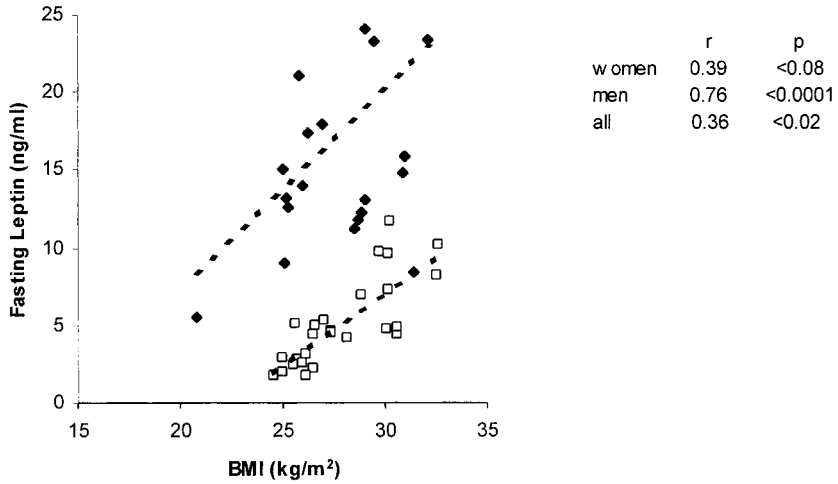

Fig 1. Relationship between fasting plasma leptin and the BMI in men (□) and women (◆). Spearman correlation coefficients (r_s) and associated *P* values are shown.

exhibited, on average, mildly elevated fasting plasma glucose, confirming that these were newly diagnosed diabetics. Despite this specific characteristic of the diabetic subgroup, fasting and 2-hour post–75-g glucose load insulin did not differ significantly versus normal subjects in each gender subgroup. However, when plasma insulin data from both gender subgroups were pooled for analysis, subjects with IGT had, on average, plasma insulin concentrations that were significantly higher ($P < .02$) versus the normal and diabetic subjects (normal 386 ± 264, IGT 726 ± 524, and diabetics 372 ± 209 pmol/L, mean ± SD). This latter analysis therefore confirms the presence of compensatory hyperinsulinemia in the IGT subgroup and some signs of impaired insulin secretion in the subjects with diabetes.

Figure 1 shows that the fasting leptin concentration correlated positively with the BMI ($r_s = .36$, $P < .02$ across the entire group, Spearman rank correlation coefficient) and was, in general 3-fold higher in women versus men. The correlation between the BMI and fasting leptin was stronger in men versus women (men, $r_s = .76$, $P < .0001$; women, $r_s = .39$, $P < .08$, Spearman rank correlation coefficient).

Differences in Plasma Leptin Across Glucose Tolerance Diagnoses

On the whole and independent of gender, there was no statistically significant apparent difference in mean fasting leptin concentrations between the 3 glucose tolerance subgroups (normal 13.2 ± 3.0, IGT 8.7 ± 1.8, and diabetic 8.9 ± 1.2 ng/mL, $P > .05$, Kruskal-Wallis test; combined data not shown in Table 1). Controlling for gender and the BMI, a statistically significant ($P < .03$ by ANCOVA) gender-related difference in the mean plasma leptin level was revealed (Fig 2). Plasma leptin levels were, on average, 44% lower ($P < .02$ by ANCOVA controlling for BMI) in women with diabetes or IGT versus normal women. No such between-group difference was observed in the men ($P > .05$ by ANCOVA controlling for BMI).

Correlations Between Plasma Leptin and Glucose Concentrations

To define more specifically the relationship between the glucose tolerance status and plasma leptin, simple correlation analyses were performed using plasma glucose as a continuous variable. The relationship between fasting plasma leptin and 2-hour post–75-g glucose load plasma glucose showed clear sex differences (Fig 3), being statistically significant in women ($r_s = -.54$, $P < .02$) but not in men. No significant correlations were apparent in either sex between plasma leptin and fasting glucose ($r_s = -.32$, $P > .05$).

The use of a multiple regression analysis model showed an independent effect of plasma glucose on fasting leptin in the female subgroup specifically. In this model (using log-transformed fasting leptin as the dependent variable), both the

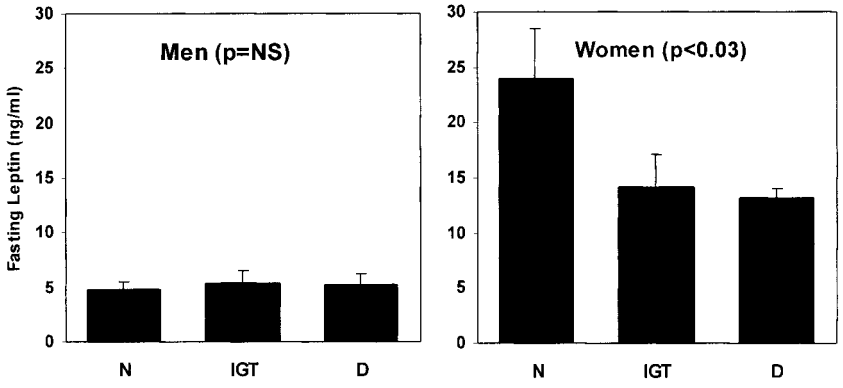

Fig 2. Differences in fasting plasma leptin in men and women in the 3 groups, normal (N), IGT, and D (diabetes). *P* values obtained by ANCOVA (controlling for BMI) are shown for each gender subgroup. Data are the mean ± SEM.

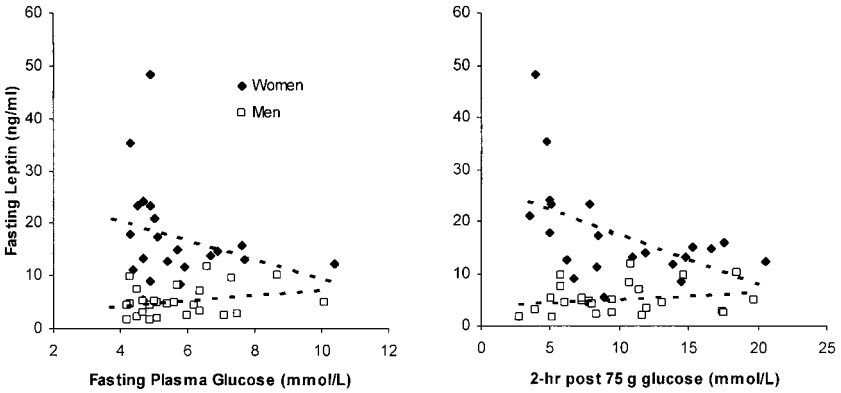

Fig 3. Relationships between fasting plasma leptin and fasting plasma glucose and 2-hour post–75-g load plasma glucose in men (□) and women (◆). Spearman correlation coefficients (r_s) and associated *P* values are shown for each gender subgroup. For women, the r_s for fasting plasma glucose was −.31 (*P* = .16), and for 2-hour post–75-g load glucose, −.54 (*P* < .02). For men, the r_s for fasting plasma glucose was +.24 (*P* = .23), and for 2 hour post–75-g load glucose, +.15 (*P* = .45).

BMI and log-transformed 2-hour post–75-g glucose load glucose levels were strong and independent predictors of plasma leptin in women ($r = +.53$, $P < .003$ and $r = -.62$, $P < .001$, respectively). When the 2-hour post–75-g glucose load glucose concentration was replaced in this model by the log-transformed fasting glucose concentration, the latter variable had a predictive value that tended toward significance ($r = -.39$, $P = .06$).

Correlations Between Plasma Leptin and Insulin Concentrations

Univariate and multivariate analyses were performed between fasting plasma leptin and fasting plasma insulin concentrations (Fig 4). Fasting insulin correlated positively with fasting leptin across the entire group ($r_s = .35$, $P < .02$, Spearman rank correlation coefficient). When the analyses were controlled for gender, a correlation between leptin and insulin was again apparent and was generally stronger in both sexes (women, $r_s = .42$, $P < .06$; men, $r_s = .42$, $P < .04$).

Several regression models were used to clarify the relationship between plasma leptin and insulin concentrations (Table 2). In these analyses, plasma insulin, BMI, and plasma glucose were used as the independent variables. Since the 2-hour level was more strongly correlated with plasma leptin than the fasting plasma glucose concentration, we present results obtained with the 2-hour post–75-g glucose load glucose and insulin concentrations in Table 2. Analyses performed with the fasting glucose and insulin concentrations showed more or less the same results, but the standardized coefficients and R^2 were noticeably less strong (data not shown). The first analysis was performed for the entire study group and included gender as an independent variable. In this model (Table 2), the BMI, gender, 2-hour post–75-g glucose load glucose and insulin concentrations were all independent predictors of fasting plasma leptin. The model for the entire study group had predictive values (R^2) of .79, thus explaining approximately 80% of the total variability of fasting plasma leptin. Because of the significant gender differences observed in this study, multiple regression analyses were also performed within each gender subgroup (Table 2). A marked correlation between female gender and fasting plasma leptin was again observed: the BMI, 2-hour post–75-g load insulin, and 2-hour post–75-g load glucose were all independent predictors of fasting plasma leptin. In the male subgroup, neither the 2-hour post–75-g load insulin nor the 2-hour post–75-g load glucose had a statistically significant association with plasma leptin. In women, the standardized coefficients for the 2-hour post–75-g load insulin and glucose were not only statistically significant but also several-fold higher than those calculated for the entire study sample or for the male subgroup. The statistical power for the 3 regression models has been carefully calculated using a 2-tailed α level of .05 and taking into account the respective sample size, the number of covariates, and the adjusted R^2 obtained. The statistical power of each

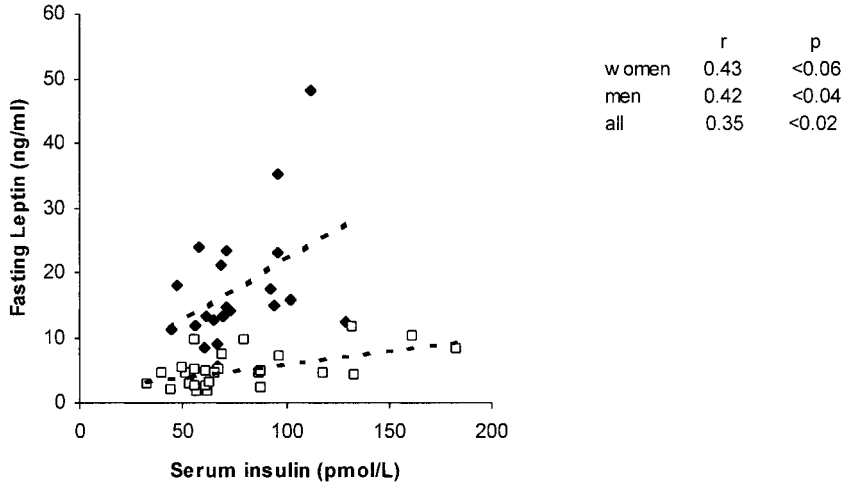

Fig 4. Relationship between fasting plasma leptin, and fasting plasma insulin in men (□) and women (◆). Spearman correlation coefficients (r_s) and associated *P* values are shown for each gender subgroup and for the entire study sample.

Table 2. Regression Models With Fasting Plasma Leptin (log-transformed) as the Dependent Variable

Independent Variable	Coefficient	Standardized Coefficient	*t*	*P*
Entire study group (N = 48)				
Intercept	−0.969	−0.969	−3.495	.001
M/F	0.550	0.777	11.611	<.001
BMI (kg/m^2)	0.054	0.385	5.474	<.001
2-h post–75-g load insulin (pmol/L)*	0.184	0.163	2.314	.026
2-h post–75-g load glucose (mmol/L)*	−0.244	−0.150	−2.195	.034
R^2 = .80, adjusted R^2 = .79				
Female subgroup (n = 21)				
Intercept	−0.197	−0.197	−0.476	.640
BMI (kg/m^2)	0.051	0.671	4.735	<.001
2-h post–75-g load insulin (pmol/L)*	0.316	0.384	2.686	.016
2-h post–75-g load glucose (mmol/L)*	−0.623	−0.695	−5.150	<.001
R^2 = .71, adjusted R^2 = .66				
Male subgroup (n = 27)				
Intercept	−1.669	−1.669	−4.370	<.001
BMI (kg/m^2)	0.080	0.787	4.469	<.001
2-h post–75-g load insulin (pmol/L)*	0.000	0.000	0.000	.999
2-h post–75-g load glucose (mmol/L)*	0.087	0.077	0.609	.548
R^2 = .65, adjusted R^2 = .61				

*Log-transformed variables.

of the models presented in Table 2 was uniformly and individually 99%, confirming that our analyses were based on a sufficient number of subjects.

DISCUSSION

Plasma leptin levels were measured in a population of 48 Caucasian subjects who had undergone a standard diagnostic 2-hour oral glucose tolerance test. The specific aim of the study was to explore the relationships between serum fasting leptin and other parameters such as plasma glucose and plasma insulin across genders. The study population contained subjects of both sexes who were not morbidly obese but had 1 of 3 different glucose tolerance phenotypes. As expected, women were found to have higher plasma leptin levels than men and plasma leptin correlated positively with the BMI, confirming that the study sample was comparable to other cohorts.[2,16,25,26] The diabetic subgroup included mostly patients with mild and newly diagnosed diabetes mellitus, none of whom were taking any hypoglycemic agents or insulin, which could theoretically influence plasma leptin.

When mean plasma leptin levels in the 3 groups were initially compared, no differences were apparent, a finding that corresponded with many previously published studies.[25-30] However, when the analysis was controlled for gender and the BMI, statistically significant differences in leptin levels were revealed in women between the diabetic and IGT groups and the normal group. This finding emphasizes the problem of comparing leptin levels solely in univariate analyses. It is not clear why our data are different from those previously published. One explanation could be that the diabetic patients included in previous studies were not recently diagnosed and consequently had treatments that could have theoretically influenced plasma insulin concentrations, the degree of insulin resistance, and/or plasma leptin concentrations.[2,25-28]

To further explore the apparent differences in leptin concentrations between normal, IGT, and diabetic individuals, another series of statistical analyses were conducted using plasma glucose not as a categorical and diagnostic variable as suggested by the WHO[21] but rather as a continuous variable. In these analyses, 2-hour post–75-g load plasma glucose correlated inversely with plasma leptin in women only, supporting the aforementioned results obtained with ANCOVA in subjects categorized according to 2-hour post–75-g load plasma glucose concentrations (WHO criteria) and gender. To our knowledge, only one research group[31] has shown an independent link between plasma leptin and plasma glucose. That group reported lower leptin levels in poorly controlled and morbidly obese diabetics compared with well-controlled diabetics, glucose-intolerant subjects, or normal subjects. However, the study was conducted in subjects with a BMI greater than 40 kg/m^2, and the reduction in plasma leptin was largely confined to the uppermost quartile of the plasma glucose distribution (up to 25.5 mmol/L), which corresponded to poorly controlled diabetes. More recently, one group has shown that HbA_{1c} was negatively correlated with serum leptin concentrations in patients with an established diagnosis of diabetes mellitus.[32] However, our study is the first to show that an independent link between plasma leptin and plasma glucose is not unique to obese and very hyperglycemic individuals.

The apparently more important predictive value of 2-hour post–75-g load glucose (*v* fasting glucose) in our study is probably related to the fact that the former was the variable used for determining the glucose tolerance status of each participant. However, one could also speculate that the 2-hour post–75-g load plasma glucose level may be more important for the regulation of leptin production by adipose tissue. To our knowledge, no in vitro study has demonstrated a direct effect of glucose, independent of insulin, on the adipose tissue expression of leptin in animals or humans. A direct effect of glucose on the expression of other genes has been described,[33] but such an inhibitory effect on leptin production would need further investigation.

Finally, we examined the link between plasma leptin and insulin concentrations and found, like others,[7,16,34,35] a positive correlation between plasma leptin and plasma insulin in univariate and multivariate analysis. Our multivariate regression analysis was performed to control for gender, BMI, and 2-hour post–75-g load plasma glucose, and the results confirmed that plasma insulin was an independent predictor of plasma leptin. Here, again, this finding was specific for the female subgroup, as shown by the multiple regression models within each gender subgroup (Table 2). In the specific regression model outlined in the female subgroup, both the 2-hour post–75-g load plasma insulin and the 2-hour post–75-g load plasma glucose correlated with fasting plasma leptin, which further supports the data

presented. In other words, circulating glucose and insulin concentrations appear to have important and independent effects on plasma leptin in women.

A priori, our data suggest that a chronic state of hyperinsulinemia in women, as demonstrated by an increase in plasma insulin, is likely to increase plasma leptin. A number of researchers have reported higher fasting leptin levels in insulin-resistant subjects,[34,36] but it is not always easy to confirm whether the increased synthesis of leptin by adipose tissue is caused by the insulin resistance defect or by the compensatory hyperinsulinemia. Three lines of evidence favor the latter explanation. First, insulin has been shown to directly increase the expression of *ob* gene and mRNA levels in animals[4,5,11,12] and in humans.[7-10] Second, when insulin resistance and plasma insulin levels are measured in the same subjects and entered in the same regression models, plasma insulin is clearly a significant predictor of plasma leptin, whereas insulin resistance unexpectedly loses its predictive value.[35,37,38] Third, one study[39] has shown that prepubertal type 1 diabetics have higher leptin levels than nondiabetics and that this association was probably caused by the hyperinsulinemia present in these patients, further supporting the role of chronic hyperinsulinemia in leptin secretion. These observations suggest that the response of adipose tissue to leptin is therefore not affected by the insulin resistance phenomenon. Our data go further by suggesting that this regulatory effect of insulin on leptin seems to occur in women only. This effect is important but not unique to insulin, as indicated by our finding that plasma glucose also has a significant impact on plasma leptin.

Unanswered at present is the question of why women are more susceptible than men to the regulation of leptin by ambient glucose or insulin. The significance of this gender dichotomy in plasma leptin and its metabolic determinants are also unclear. The hypothesis that men and women differ with regard to plasma leptin responsiveness is a fairly new and unexplored area. Women may have higher absolute leptin levels than men, but it has recently been shown that they have relatively lower diurnal leptin amplitude than men, for a given fat mass.[40] The fact that hyperinsulinemia acutely increases plasma leptin only in women when euglycemia is maintained[29] is another point corroborating our findings, even though a recent study showed a responsiveness to insulin of cultured adipose tissue in obese men and women.[41] A complete discussion on the observed dichotomy of plasma leptin is beyond the scope of this study. However, we suggest that in women adipose tissue may be constantly stimulated by metabolic or hormonal signals, of which plasma glucose and plasma insulin would appear to be pivotal. For example, female adipose tissue may be more sensitive to insulin than male adipose tissue, which could lead to a chronic upregulation of leptin production with a subsequent basal hyperleptinemia and a blunting of the diurnal rhythmicity of leptin. An increase in subcutaneous adipose tissue could also be in itself the reason that this regulation is different in women and men.[20,41] We acknowledge that our lack of information with regard to body composition and percent body fat can somewhat limit the interpretation of our data, but still very few published articles have focused on the types of gender differences outlined herein. To our knowledge, only 2 groups showed that the correlation between insulin and leptin was maintained only in women (as compared with men) when corrected for fat mass.[42,43] The usefulness of such gender dimorphism for leptin is not well understood, but could be related to a putative role for leptin in reproduction.[2,44,45]

Finally, a puzzling paradox arises from our data. If female patients with IGT are insulin-resistant and therefore have increased insulin concentrations, why are they not hyperleptinemic? We have found that insulin-resistant subjects have lower plasma leptin levels than normal individuals independently of the BMI, and that the more impaired the glucose tolerance of a woman, the lower her plasma leptin. These data become less contradictory in view of the apparent suppressive effect of plasma glucose on plasma leptin that we have observed in women only. Therefore, is leptin important in type 2 diabetes and IGT? From our data, it would appear that the answer to this question is ''yes'' and that such a role is predominantly important in women. We hypothesize that insulin resistance leads to a compensatory state of hyperinsulinemia that increases the production of leptin by adipose tissue, theoretically preventing a further weight gain and a further increase in the insulin resistance defect. With β-cell exhaustion (as in our subjects with diabetes), hyperglycemia arises and it is hypothesized to have a restraining effect on the production of leptin by adipose tissue. Our data suggest that postprandial hyperglycemia such as that observed in the early phase of type 2 diabetes (at a time when plasma insulin has returned to levels similar to the values of normal individuals) can impede the synthesis of leptin by adipocytes. Such a reduction in plasma leptin in patients with IGT or type 2 diabetes could therefore ultimately lead to an increase in appetite and to difficulty in achieving normal body weight.

In conclusion, this study has demonstrated that in addition to the BMI, plasma glucose and ambient hyperinsulinemia are strong, independent, and unique predictors of plasma leptin in women only. That these associations were not observed in men suggests that adipose tissue in women has the unique feature of being subject to close regulation by circulating glucose and insulin. Taking into account some important confounding variables, our study has shown that nonmorbidly obese women with IGT or newly diagnosed type 2 diabetes have lower plasma leptin than normal women. We hypothesize that postprandial and, albeit to a lesser extent, fasting hyperglycemia restrain the stimulatory effect of plasma insulin on the synthesis of leptin by adipose tissue. There are obviously many factors that can influence plasma leptin, but it should be remembered that our regression model, which controlled for the BMI, gender, glucose, and insulin, was able to explain 80% of the observed variability in fasting leptin. These results provide new insights into the potential mechanisms underlying the differences in plasma leptin between men and women. Further studies focusing on the mechanisms of leptin regulation by insulin and glucose in women will help to further clarify leptin physiology.

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