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Leptin and Variables of Body Adiposity, Energy Balance, and Insulin Resistance in a Population-Based Study

The Hoorn Study

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OBJECTIVE — Leptin is thought to play a key role in the control of body weight. There is a complex interrelationship between leptin and insulin or insulin resistance, but it is unknown how leptin is regulated. We therefore explored, in a large population-based study of 2,484 Caucasian subjects aged 50–74 years, the relationship between leptin and variables of body adiposity, energy balance, and insulin resistance.

RESEARCH DESIGN AND METHODS — Leptin was measured by means of a radioimmunoassay. Multiple linear regression analyses were performed with leptin as dependent variable and age, sex, BMI, waist circumference, daily energy intake, physical activity, smoking, hypertension, fasting triglyceride concentrations, HDL cholesterol, fasting plasma glucose, and fasting plasma insulin concentrations as independent variables (determinants).

RESULTS — Leptin concentrations were found to be four times higher in women than in men. Effect modification between sex and potential determinants was expected, and the analyses were performed separately for women and men. BMI was the strongest determinant of leptin in women and waist circumference the strongest determinant in men. BMI, waist circumference, insulin, and triglyceride concentrations were independently and significantly ($P < 0.05$) associated with leptin, while inverse associations were shown for smoking and daily energy intake (borderline significance).

CONCLUSIONS — This study confirms the relationship between insulin and leptin and, in addition, suggests a relationship between triglyceride concentrations and leptin independent of sex, BMI, waist circumference, and insulin.

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The recent discovery of leptin is potentially important for research into obesity and related diseases (1). Leptin is a hormone produced by the fat cells, and is

thought to play a key role in the control of body weight (2,3). Leptin is hypothetically involved in a feedback loop linking fat and a satiety/energy expenditure center in the

hypothalamus. This feedback loop appears to be disturbed in obesity (4,5). Obesity is also often accompanied by disturbances in blood pressure or lipid metabolism related to insulin resistance (decreased tissue sensitivity to insulin) (6,7). Recent studies suggest a complex interrelationship between leptin and insulin or insulin resistance (2). Experimental studies in mice and rats show that insulin affects leptin concentrations (4) and that recombinant leptin influences insulin resistance and triglyceride metabolism (8,9). Human studies confirm a relationship between insulin and leptin (10,11), but are controversial with regard to the involvement of leptin in insulin resistance or triglyceride metabolism (3,12–16). This controversy might partly be explained by the selection of specific study populations or by small sample sizes. Another explanation might be the role of leptin in a feedback loop, which would differentiate cause and effect. For example, some investigators have hypothesized that leptin has an influence on insulin resistance (12), others that insulin resistance has an influence on leptin (17). The purpose of the present study was to gain insight into the regulation of leptin concentrations. We therefore explored, in a large cross-sectional population-based study, the influence on serum leptin concentrations of potential determinants related to body adiposity, energy balance, and insulin resistance.

RESEARCH DESIGN AND METHODS

Subjects

A random sample of 50- to 74-year-old subjects was taken from the population register of the town of Hoorn in the Netherlands (57,000 inhabitants). Of the 3,553 subjects invited, 2,540 (71.5%) participated, of whom 56 were excluded from the analyses because they were non-Caucasian. Thus, the final cohort consisted of 2,484 subjects (18). Subjects who reported having diabetes ($n = 104$) were excluded from the present analyses to

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W.F.B. holds stock in Eli Lilly.

Abbreviations: HOMA, homeostasis model assessment.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

prevent any possible influence from blood glucose-lowering treatment or diet. Subjects with missing measurements of leptin concentrations due to lost serum samples were also excluded ($n = 35$).

Survey procedures

Detailed information on the Hoorn Study population has already been published (18). Participants underwent a 75-g oral glucose tolerance test and were classified according to the 1985 World Health Organization criteria (19). Height, weight, and waist and hip circumference were measured as described elsewhere (20) and used to calculate BMI (kg/m^2) and the waist-to-hip ratio. Hypertension was defined as current treatment with antihypertensive drugs or an elevated blood pressure (diastolic ≥ 95 mmHg or systolic ≥ 160 mmHg). Physical activity was estimated by asking nine equally weighted yes or no questions about regular performance of the following activities: sport, cycling, gardening, walking, doing odd jobs, going up stairs at home, household activities, daily food shopping, and working, whether paid or unpaid. Daily energy intake (kilocalories) was measured by means of a self-administered validated semiquantitative food-frequency questionnaire (21).

Laboratory analyses

Leptin was measured in banked serum samples. Detailed information on the radioimmunoassay used to measure serum leptin concentrations (micrograms per liter) has been published recently (22). Fasting and 2-h plasma glucose concentrations (millimoles per liter) were determined according to a glucose dehydrogenase method (Merck, Darmstadt, Germany). HDL cholesterol and triglycerides (millimoles per liter) were measured by means of enzymatic techniques (Boehringer Mannheim, Mannheim, Germany). One radioimmunoassay was used to measure insulin (picomoles per liter), and had $<0.2\%$ cross-reactivity with proinsulin and des-31,32-proinsulin (Linco Research, St. Louis, MO). A second radioimmunoassay was also used to measure insulin, and had $\pm 80\%$ cross-reactivity with proinsulin and des-31,32-proinsulin (Novo Nordisk, Copenhagen, Denmark). The latter measurement was used to calculate insulin resistance by the homeostasis model assessment (HOMA) method because it is thought to be more similar to the assay of the HOMA method validation study (23).

Table 1—Clinical and biochemical characteristics of study population stratified for sex

	Women	Men
<i>n</i>	1,254	1,091
Leptin ($\mu\text{g/l}$)	14.4 (8.2–23.7)	3.4 (1.9–5.8)
Age (years)	61 (55–68)	60 (55–67)
Variables related to body adiposity		
BMI (kg/m^2)	26.3 (24.0–29.1)	26.0 (24.2–27.8)
Waist (m)	0.86 (0.79–0.94)	0.95 (0.89–1.00)
Waist-to-hip ratio	0.84 (0.79–0.89)	0.95 (0.91–0.99)
Variables related to energy balance		
Daily energy intake ($\text{kcal} \times 1,000$)	1.8 (1.5–2.1)	2.3 (1.9–2.7)
Physical activities (<i>n</i>)	6 (4–7)	6 (5–7)
Current smoking (% yes)	28	36
Variables related to insulin resistance		
Fasting plasma glucose (mmol/l)	5.3 (5.0–5.8)	5.5 (5.2–5.9)
2-h plasma glucose (mmol/l)	5.6 (4.7–6.8)	5.4 (4.3–6.6)
Fasting specific insulin (pmol/l)	76 (60–99)	77 (61–101)
Fasting nonspecific insulin (pmol/l)	84 (61–123)	90 (65–124)
Calculated insulin resistance (HOMA)	3.3 (2.3–5.2)	3.7 (2.6–5.3)
Triglycerides (mmol/l)	1.3 (1.0–1.8)	1.4 (1.1–2.0)
HDL cholesterol (mmol/l)	1.4 (1.2–1.7)	1.1 (1.0–1.4)
Hypertension (% yes)	31	30

Data are medians (interquartile range), unless otherwise indicated. Scale of physical activities: 1–9; 1 = low, 9 = high.

Calculation of insulin resistance

Insulin resistance was calculated by the HOMA method, using fasting plasma glucose and insulin concentrations (23). Assuming that normal-weight normal subjects <35 years of age have an insulin resistance of 1, the value for insulin resistance can be assessed by the formula: fasting insulin ($\mu\text{U/ml}$) $\times$ fasting glucose (mmol/l) / 22.5 (23). Results from HOMA correlate well with measurements obtained by means of the euglycemic clamp technique, as was shown in the HOMA method validation study (23) and by a separate study in 16 subjects (J.B.R., J.M.D., C. Popp-Snijders, P.J.K., G.N., C.D.A.S., L.M.B., R.J.H., unpublished observations).

Statistical analysis

A first impression of relationships of leptin was provided by graphs and Spearman's rank correlation coefficients. Subsequently, multiple linear regression models were constructed to explore in detail the relationship between serum leptin concentrations and determinants related to body adiposity, energy balance, and insulin resistance. Effect modification was expected to occur between sex and potential determinants, so the analyses were performed separately for women and men (1). The associations between leptin and potential determinants

explored in the first models were adjusted for age; in the subsequent models, they were adjusted for age and BMI; and in a final model, they were adjusted for age, BMI, and each other. The distribution of leptin was normalized by transformation into its natural logarithm to improve the plots of residual analyses. Results are expressed as percentage differences in serum leptin concentrations associated with the interquartile range of potential determinants (in the final model, 95% CIs are also provided). A zero within the 95% CI implies that no independent statistically significant ($P < 0.05$) association could be established. The proportion of variation in leptin (R^2) explained by a potential determinant in the final model is also provided. All data were analyzed with an SPSS-PC software package (SPSS, Chicago).

RESULTS — Medians and interquartile ranges of serum leptin concentrations were four times higher in women, 14.4 $\mu\text{g/l}$ (8.2–23.7), than in men, 3.4 $\mu\text{g/l}$ (1.9–5.8). Characteristics of determinants related to body adiposity, energy balance, and insulin resistance of the study population were stratified for sex, and are shown in Table 1. The correlation between leptin and BMI, fasting plasma insulin, calculated insulin resistance, and triglycerides is shown in

Figs. 1–4. BMI was the strongest determinant of leptin in women, and waist circumference was the strongest determinant in men, as can be seen in Tables 2 and 3, respectively. However, to study associations that are independent of body fat mass, adjustments were made for BMI in both women and men (Tables 2 and 3). The strong influence of BMI on the association of determinants related to energy balance and insulin resistance suggests that body adiposity may, at least partially, play an intermediate role.

Daily energy intake and physical activity were inversely associated with leptin. The association with daily energy intake was statistically of borderline significance ($P = 0.07$) in women and significant ($P < 0.05$) in men (Tables 4 and 5, respectively). Smoking was inversely associated with leptin in both sexes, after adjustment for determinants related to body adiposity, energy balance, and insulin resistance (Tables 2–5).

All regression models showed an independent association between fasting triglyceride concentrations and leptin (Tables 2–5). Thus, in both sexes, triglyceride concentrations were positively associated with leptin, independent of BMI, waist circumference, and insulin. The regression models used for Tables 4 and 5 suggested that the relationships between triglyceride and leptin and between insulin and leptin are of the same magnitude. Individuals at the 75th percentile had 5–10% higher serum leptin concentrations compared with those at the 25th percentile of triglyceride and insulin distribution, after adjustment for BMI and waist circumference (Tables 4 and 5). Calculated insulin resistance was associated with leptin in such a way that insulin-resistant subjects had high serum leptin concentrations. In the same way, fasting plasma insulin concentrations were associated with leptin. One regression model with $\ln(\text{leptin})$ as dependent variable that included both insulin and insulin resistance suggested weakly independent associations for both determinants in men only (data not shown). Applying calculated insulin resistance instead of insulin and fasting glucose in the models shown in Tables 4 and 5 resulted in similar coefficients for the remaining determinants (data not shown). In women, fasting plasma glucose was inversely associated with leptin, after adjustment for determinants related to body adiposity and insulin resistance (Table 4). Results did not essentially change when 2-h plasma glucose was included in the model instead of fasting plasma glucose (data not

Figure 1—Correlation between leptin and BMI in a 50- to 74-year-old general Dutch population: 0.68 for women (□) ($P < 0.001$) and 0.59 for men (■) ($P < 0.001$).

Figure 2—Correlation between leptin and fasting plasma insulin in a 50- to 74-year-old general Dutch population: 0.47 for women (□) ($P < 0.001$) and 0.53 for men (■) ($P < 0.001$).

Figure 3—Correlation between leptin and calculated insulin resistance in a 50- to 74-year-old general Dutch population: 0.46 for women (□) ($P < 0.001$) and 0.52 for men (○) ($P < 0.001$).

Figure 4—Correlation between leptin and triglycerides in a 50- to 74-year-old general Dutch population: 0.32 for women (□) ($P < 0.001$) and 0.28 for men (○) ($P < 0.001$).

shown). Apart from differences between the sexes with regard to associations of body adiposity and leptin, hypertension and HDL cholesterol were positively associated with leptin in men only, after adjustment for determinants related to body adiposity and insulin resistance (Table 5).

To estimate the possible residual influence of the amount of body adiposity on the final conclusions, an alternative strategy was implemented. A reference range of serum leptin concentrations, based on BMI and sex, was used to create categories of individuals according to leptin concentrations: below the 5th percentile, between the 5th and the 95th percentiles, and above the 95th percentile (1). The same determinants of leptin as those mentioned in Table 1 were compared in the three categories. The results were essentially the same, and were therefore omitted from the present paper.

CONCLUSIONS — The present large cross-sectional population-based study suggests that various determinants related to body adiposity, energy balance, and insulin resistance are involved in the regulation of serum leptin concentrations.

Body adiposity may play an intermediate role. Various studies have shown that body adiposity is the major determinant of leptin (24,25). We wanted to study the association of leptin with determinants related to energy balance and insulin resistance, independent of body adiposity. However, accurate methods to estimate body adiposity, such as hydrodensitometry, were not feasible in the present study. Adjustment for body adiposity was, therefore, imperfect, and residual confounding cannot be excluded. Nevertheless, the final conclusions of the present study were supported by similar results when an alternative strategy based on a leptin reference line (1) was used to adjust for body adiposity.

Body adiposity has also been suggested to be the main contributor to the difference of serum leptin concentrations between the sexes (24,25). Both sex and determinants related to body adiposity appeared to be modifiers of serum leptin concentrations. BMI appeared to be the strongest determinant of leptin in women, and waist circumference the strongest determinant in men. In the Rancho Bernardo Heart Study, waist circumference appeared to be a better anthropometric estimate of obesity and fat distribution than the waist-to-hip ratio (26). The contribution of body adiposity

Table 2—Percentage difference in serum leptin concentrations associated with a change from the 25th to the 75th percentile of potential determinants of leptin in women

Potential determinants (IQR)	Linear regression models with ln(leptin) as dependent variable			
	Adjusted for age		Adjusted for age and BMI	
	% Difference in leptin	R ² model (%)	% Difference in leptin	R ² model (%)
Age (12.5 years)	20	1.8*	—	—
BMI (5.1 kg/m ²)	101	41.7*	—	—
Waist circumference (0.15 m)	67	35.8*	29	1.5*
Waist-to-hip ratio (0.10)	48	11.2*	8	0.3*
Daily energy intake (0.6 kcal × 1,000)	−7	0.5*	−3	—
Physical activities (3)	−17	1.4*	−3	—
Current smoking (yes vs. no)	−24	2.1*	−14	0.7*
Fasting plasma glucose (0.8 mmol/l)	8	1.4*	—	—
2-h plasma glucose value (2.1 mmol/l)	9	1.7*	2	—
Fasting specific insulin (39 pmol/l)	23	8.7*	8	0.7*
Fasting nonspecific insulin (62 pmol/l)	39	15.4*	15	1.9*
Calculated insulin resistance (2.9)	28	11.4*	8	0.8*
Triglycerides (0.8 mmol/l)	23	5.5*	8	0.7*
HDL cholesterol (0.5 mmol/l)	−19	3.4*	−3	—
Hypertension (yes vs. no)	36	2.8*	6	—

Data for current smoking and hypertension represent the percentage difference in serum leptin concentration associated with yes vs. no. Scale of physical activities: 1–9; 1 = low; 9 = high. R² is the proportion of the variation in leptin (ln) explained by the potential determinant in the left margin (%). IQR; interquartile range or a change from the 25th to the 75th percentile. *P < 0.01.

to serum leptin concentrations could further depend on its location. Subcutaneous and visceral adiposity are supposed to contribute differently (27,28). In addition, androgens may have affected the difference in serum leptin concentrations between the sexes (25).

Smoking was independently and inversely associated with serum leptin concentrations in both men and women, which is in line with an existing report that suggested that smoking may modify the sensitivity of hypothalamic leptin receptors and, consequently, mod-

ulate leptin synthesis and reduce body weight (29).

Mechanisms underlying the association between serum triglyceride and leptin concentrations are unclear. Serum triglyceride concentrations may lead to expansion of the volume of fat cells, which, in turn,

Table 3—Percentage difference in serum leptin concentrations associated with a change from the 25th to the 75th percentile of potential determinants of leptin in men

Potential determinants (IQR)	Linear regression models with ln(leptin) as dependent variable			
	Adjusted for age		Adjusted for age and BMI	
	% Difference in leptin	R ² model (%)	% Difference in leptin	R ² model (%)
Age (12 years)	23	1.9*	—	—
BMI (3.6 kg/m ²)	94	36.3*	—	—
Waist circumference (0.11 m)	106	42.3*	70	7.3*
Waist-to-hip ratio (0.11)	84	26.6*	35	4.5*
Daily energy intake (0.8 kcal × 1,000)	−11	1.0*	−9	0.6*
Physical activities (2)	−12	1.5*	−8	0.6*
Current smoking (yes vs. no)	−26	2.5*	−8	0.2
Fasting plasma glucose (0.7 mmol/l)	11	3.0*	2	—
2-h plasma glucose value (2.3 mmol/l)	21	6.8*	9	1.2*
Fasting specific insulin (40 pmol/l)	22	9.5*	10	2.4*
Fasting nonspecific insulin (59 pmol/l)	50	20.9*	23	4.9*
Calculated insulin resistance (2.7)	32	15.7*	14	3.1*
Triglycerides (0.9 mmol/l)	26	7.3*	11	1.4*
HDL cholesterol (0.5 mmol/l)	−13	1.3*	—	—
Hypertension (yes vs. no)	54	4.6*	25	1.2*

Data for current smoking and hypertension represent the percentage difference in serum leptin concentration associated with yes vs. no. Scale of physical activities: 1–9; 1 = low; 9 = high. R² is the proportion of the variation in leptin (ln) explained by the potential determinant in the left margin (%). IQR; interquartile range or a change from the 25th to the 75th percentile. *P < 0.01.

Table 4—Percentage difference in serum leptin concentrations associated with a change from the 25th to the 75th percentile of potential determinants of leptin in women, using a single linear regression model ($R^2 = 47\%$)

Potential determinant (IQR)	% Difference in leptin (95% CI)
Constant	−60 (−78 to −31)
Age (12.5 years)	−3 (−9 to 3)
BMI (5.1 kg/m ²)	62 (49 to 75)
Waist circumference (0.15 m)	25 (15 to 37)
Daily energy intake (0.6 kcal × 1,000)	−4 (−8 to 0)
Physical activities (3)	−4 (−11 to 3)
Current smoking (yes vs. no)	−18 (−24 to −11)
Fasting plasma glucose (0.8 mmol/l)	−3 (−6 to 0)
Fasting specific insulin (39 pmol/l)	6 (3 to 10)
Triglycerides (0.8 mmol/l)	7 (2 to 11)
HDL cholesterol (0.5 mmol/l)	2 (−3 to 8)
Hypertension (yes vs. no)	2 (−6 to 10)

Data for current smoking and hypertension represent the percentage difference in serum leptin concentration associated with yes vs. no. Scale of physical activities: 1–9; 1 = low, 9 = high. R^2 is the proportion of the variation in leptin (ln) explained by the complete model. IQR, interquartile range or a change from the 25th to the 75th percentile.

may lead to an increase in *ob* gene expression and serum leptin concentrations. It is also possible that serum triglyceride concentrations are affected by leptin, e.g., by indirect mechanisms involved in insulin resistance (8,9). A recent study in rats reported a triglyceride-lowering effect of leptin (9), and a study in mice reported an attenuating effect of leptin on the lipogenic effect of insulin in skeletal muscle (8). Skeletal muscle triglyceride concentrations have been shown to be related to insulin resistance in humans (30). Studies in humans on the relationship between triglyceride concentrations and leptin have so far reported controversial observations. Apart from the present study, two other studies found an association of triglycerides with leptin in men after adjustment for percentage body fat assessed by skinfold measurements (3) or after adjustment for BMI and insulin sensitivity (12). One study in humans found no association between triglycerides and leptin after adjustment for body fat mass estimated according to the hydrostatic weighing technique (16). However, that particular study also failed to demonstrate an independent association between insulin and leptin in men, and methodological shortcomings in that study are therefore also plausible.

The relationship between insulin and leptin, which was also found in this study, is in concordance with reported findings in humans showing an induction of *ob* gene expression and an increase in leptin concentrations by insulin infusion, possibly

due to the trophic effect of insulin on adipocytes (10,31,32). In this study, an association between insulin resistance and leptin was found that was limited in precision because the HOMA method was used to calculate insulin resistance (23). Nevertheless, an association between insulin resistance and leptin remains a highly intriguing finding, since insulin resistance was proposed as an adaptation for weight maintenance many years before the discovery of leptin (33). The recent literature is controversial with regard to the relation-

ship between insulin resistance and leptin. A number of studies have reported associations between insulin resistance and leptin in normal glucose-tolerant subjects (13, 14,34), but one did not (35). Other studies reported no association between insulin resistance and leptin in subjects with diabetes (15,36). The findings are in line with the possibility of hyperinsulinemia inducing hyperleptinemia and leptin resistance (15) or, alternatively, of leptin inducing insulin resistance, which, in turn, causes hyperinsulinemia. Downregulation of leptin transport in the brain (5) may result in reduced cerebrospinal fluid leptin concentrations, despite increased serum leptin concentrations. Reduced cerebrospinal fluid leptin concentrations are assumed to promote an increase in food ingestion, an increase in adiposity mass, and, subsequently, an increase in insulin resistance (37). We also found that hypertension and HDL cholesterol were independently associated with leptin in men and that fasting plasma glucose was independently associated with leptin in women. A study in Western Samoa found an association between diastolic blood pressure and leptin in men, but no relationship between HDL cholesterol and leptin (12). Another study involving a Canadian Aboriginal population found an independent and inverse association of glucose tolerance status with leptin levels in women (38), which was confirmed by the present study. A possible indirect relationship between

Table 5—Percentage difference in serum leptin concentrations associated with a change from the 25th to the 75th percentile of potential determinants of leptin in men, using a single linear regression model ($R^2 = 49\%$)

Potential determinant (IQR)	% Difference in leptin (95% CI)
Constant	−99 (−100 to −98)
Age (12 years)	5 (−3 to 13)
BMI (3.6 kg/m ²)	35 (19 to 53)
Waist circumference (0.11 m)	90 (68 to 114)
Daily energy intake (0.8 kcal × 1,000)	−6 (−10 to −2)
Physical activities (2)	−8 (−14 to 0)
Current smoking (yes vs. no)	−12 (−19 to −3)
Fasting plasma glucose (0.7 mmol/l)	−2 (−6 to 1)
Fasting specific insulin (40 pmol/l)	7 (3 to 10)
Triglycerides (0.9 mmol/l)	9 (5 to 14)
HDL cholesterol (0.5 mmol/l)	8 (1 to 16)
Hypertension (yes vs. no)	12 (2 to 23)

Data for current smoking and hypertension represent the percentage difference in serum leptin concentration associated with yes vs. no. Scale of physical activities: 1–9; 1 = low, 9 = high. R^2 is the proportion of the variation in leptin (ln) explained by the complete model. IQR, interquartile range or a change from the 25th to the 75th percentile.

regulators of the glucose metabolism and leptin seems therefore possible, despite negative results of former studies (34,39). Future studies in humans are warranted to confirm these findings. Differences in associations between the sexes may be explained by resistance to leptin, which is assumed to be more prominent in women, since the absolute serum leptin concentrations are four times higher in women than in men (25).

In conclusion, determinants related to body adiposity, energy balance, and insulin resistance are associated with serum leptin concentrations. BMI and waist circumference are positively associated, whereas physical activity (only in men), daily energy intake, and smoking are negatively associated with serum leptin concentrations. The relationship between leptin and lipid and glucose metabolism remains complex. Triglyceride concentrations and insulin are positively associated with leptin, independent of BMI, waist circumference, and each other. Hypertension and HDL cholesterol are positively associated with leptin in men, and fasting plasma glucose is negatively associated with leptin in women, independent of BMI, waist circumference, and insulin and triglyceride concentrations.

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