Overweight Is Associated With Lower Serum Leptin in Peruvian Indian Than in Caucasian Women: A Dissociation Contributing to Low Blood Pressure?

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We tested whether plasma levels of leptin and insulin are associated with the lower blood pressure in women of Peruvian Indian heritage compared with Caucasian women. A total of 181 women from Peru and 85 from Sweden, aged 20 to 60 years, with normal plasma glucose levels participated in the study. Measurements of anthropometry, blood pressure, and blood tests were performed after overnight fasting. Compared with women from Umeå in Sweden, women from Lima, Peru had higher body mass index (BMI) (26.2 ± 4.9 *v* 24.4 ± 3.8 kg/m²), waist circumference (85 ± 11 *v* 79 ± 10 cm), lower systolic blood pressure (99 ± 15 *v* 114 ± 14 mm; *P* < .001) and diastolic blood pressure (67 ± 7 *v* 74 ± 10 mm; *P* < .001). In addition, they had a reduction of the ratio of plasma leptin to BMI (0.52 ± 0.22 *v* 0.61 ± 0.36; *P* <.001), greater plasma insulin (80 ± 42 *v* 41 ± 21 pmol/L), but lower plasma glucose (4.2 ± 0.5 *v* 5.1 ± 0.5 mmol/L; *P* < .001). Furthermore, the 181 women from Lima had higher plasma triglyceride levels (1.5 ± 0.8 *v* 1.3 ± 0.7; *P* = .039), but lower plasma high-density lipoprotein (HDL)-cholesterol (1.0 ± 0.2 *v* 1.5 ± 0.4 mmol/L; *P* < .001) and total plasma cholesterol (5.0 ± 1.1 *v* 5.9 ± 1.3 mmol/L; *P* < .001) levels. Plasma leptin correlated with blood pressure and BMI in both populations (*P* < .001). In multiple regression analysis, BMI, but not log leptin, emerged as the determinant for systolic blood pressure. We concluded that women living in Lima have significant lower blood pressure levels in association with elevated plasma insulin concentrations, but lower plasma leptin values adjusted for BMI in comparison with women from northern Sweden. This may suggest that the concept of metabolic syndrome is different among women with Peruvian Indian heritage in comparison to a Caucasian population.

EPIDEMIOLOGIC SURVEYS in populations of different ethnic origins find a close correlation between obesity, measured as visceral or total body fat, and blood pressure. The clustering of these conditions has been named the metabolic syndrome or syndrome X and has been shown to be associated with development of type 2 diabetes and cardiovascular diseases. Reaven et al[1] postulated that insulin resistance plays a central role in this syndrome, mediated by compensatory hyperinsulinemia, which in turn, directly increases blood pressure and alters lipid metabolism. Furthermore, insulin resistance has been shown to be an independent risk marker for cardiovascular diseases.[2] However, the mechanisms of the relationship between these classical risk factors and insulin resistance is not established, and it has not been established whether this clustering of factors is restricted to westernized populations only.

Leptin has during recent years been associated with the metabolic syndrome due to its association with adiposity.[3] Furthermore, leptin has been suggested to increase blood pressure. A significant correlation exists between circulating leptin and blood pressure in healthy subjects,[4] and leptin administration to rats is followed by increased blood pressure.[5,6] Administration of leptin increases the sympathetic nerve activity, which might be a mechanism underlying the increase in blood pressure.[5,6] Interestingly, leptin is an independent predictor of hemorrhagic stroke[7] and myocardial infarction.[8]

Women living in the northern urban area of Lima, Peru, have abdominal obesity with high waist circumference and body mass index (BMI) in combination with low blood pressure when compared with western populations, despite low income and high unemployment rates, factors often associated with increased heart disease mortality[9] and risk factors for cardiovascular disease.[10] This paradoxical clinical observation initiated the present study to examine the distribution of circulating insulin, leptin, and lipids versus blood pressure, BMI, and waist circumference in this population. The results were compared with the same measurements obtained from a population-based sample from northern Sweden within the World Health Organization (WHO) Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) study. Details of the background, objectives, and recruitment of the subjects in this study have previously been reported.[11]

SUBJECTS AND METHODS

Lima, Peru

Alternativa, a nongovernmental organization, was founded 20 years ago as a "Center for Social Research and Popular Education" and is working on topics related to urban poverty in the district of San Martin de Porres in the "Northen Cone of Lima". Alternativa is working with community kitchens, which are organized by women, and face the nourishment problem by collective cooking of the main meal (lunch). There are, according to official information, about 10,000 community kitchen in Peru. About 15 to 20 families constitute each kitchen in the district of San Martin de Porres. Women at the age of 20 to 60 years were invited from 14 community kitchens to the Department of Nutrition and Health Education of Alternativa. A total of 184 subjects were

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Table 1. Mean ± SD of Variables in the Two Populations

Variable	Lima (n = 181)	Umeå (n = 85)	P
Age (yr)	42 ± 10	40 ± 10	NS
BMI (kg/m²)	26.2 ± 4.9	24.4 ± 3.8	<.001
Waist circumference (cm)	85 ± 11	79 ± 10	<.001
Leptin (ng/mL)	14.4 ± 7.5	16.1 ± 11.3	NS
Leptin/BMI	0.52 ± 0.22	0.61 ± 0.36	.020
Insulin (pmol/L)	80 ± 42	41 ± 21	<.001
Cholesterol (mmol/L)	5.0 ± 1.1	5.9 ± 1.3	<.001
HDL-cholesterol (mmol/L)	1.0 ± 0.2	1.5 ± 0.4	<.001
Triglycerides (mmol/L)	1.5 ± 0.8	1.3 ± 0.7	.039
Glucose (mmol/L)	4.2 ± 0.5	5.1 ± 0.5	<.001
SBP (mm Hg)	99 ± 15	114 ± 14	<.001
DBP (mm Hg)	67 ± 7	74 ± 10	<.001

NOTE. *P* indicates the probability level of random difference between the populations.

Abbreviation: NS, not significant.

studied, and of those, 3 were excluded due to a baseline plasma in glucose level exceeding 7.0 mmol/L.

A migration antecedent from indigenous Andean communities in Peru was identified in all subjects. Of the subjects, 89% had been residents of Lima for more than 20 years. In a few subjects, genetic influences from Caucasian ancestors were obvious. We have no genetic markers to determine to which degree the study population was representative of Peruvian Indians, but the migration from rural Andean regions indicates that the dominant genetic background is American Indian.

Umeå, Sweden

A random age-matched sample of 85 women with fasting plasma glucose levels below 7.0 mmol/L and without any hypertensive treatment from the population-based Northern Sweden WHO Monitoring Trends and Determinants in Cardiovascular Diseases (MONICA) Study served as controls. The recruitment of this study group has been previously described.[11]

The 2 populations are both random samples of the total population. Therefore, they are not a priori matched to each other. Information regarding smoking, physical activity, and family history of hypertension and diabetes is lacking. The examinations were performed by Peruvian personnel in Lima and by Swedish personnel in Umeå. One of the authors (F.L.) trained the Peruvian personnel, nurses, and laboratory technicians regarding the methods used. Equipment for obtaining venous blood was brought from Sweden to Lima. In both populations, body height (m), weight (kg), hip, and waist circumferences (cm) were measured after an overnight fast. Blood pressure was measured using a standard mercury sphygmomanometer after the subjects had rested for at least 10 minutes. Venous blood samples were obtained in the morning after a 12-hour fast and centrifuged. In samples taken in Peru, plasma was separated and stored at –20°C for 1 week and then brought to Sweden for analyses. Insulin and leptin were analyzed with double-antibody radioimmunoassay techniques using guinea pig antihuman insulin antibodies, human insulin standard, and mono-^{125}I-Tyr-human insulin and rabbit antihuman leptin antibodies,^{125}I-labelled human leptin and human leptin as standard, respectively (Linco Research, St Charles, MO). In the control study in Umeå, leptin was determined by radioimmunoassay (Linco), whereas insulin was determined by enzyme-linked immunosorbent assay.[12] Plasma glucose was determined using the glucose oxidase procedure. Approval for the study had been given by the Ethics Committees of Lund and Umeå Universities and San Martin University Hospital in Lima.

Statistical Analyses

All results are presented as mean values ± SD. Due to skewed distribution of fasting insulin and leptin levels (Kolmogorov-Smirnov goodness of fit test; $P < .05$), these levels were logarithmically transformed for the analyses of group differences. Differences between the groups were analyzed using Mann-Whitney *U* test.

RESULTS

As shown in Table 1, women in Lima had higher BMI and waist circumference, but lower mean height, systolic blood pressure (SBP), and diastolic blood pressure (DBP) in comparison to Swedish women of the same age. Furthermore, fasting insulin and triglyceride levels were increased, and plasma glucose, high-density lipoprotein (HDL), and leptin values were lower in the Lima population.

In both populations, strong positive correlations were found between BMI and leptin, waist, insulin, SBP, DBP, triglycerides, and plasma glucose (Table 2; $P < .001$). In contrast, no relationship was found with age.

As BMI positively correlated to these variables and because the 2 populations were not a priori matched with regard to BMI, we formed quintiles of BMI of the 2 populations, and the mean values of systolic blood pressure, plasma insulin, and plasma leptin for each quintile of BMI are shown in Fig 1. As expected, women from Lima who are more obese (increased BMI and waist circumference) also had much higher insulin levels than Swedish women. Despite marked hyperinsulinaemia, women from Lima are characterized by lower SBP recordings in all BMI quintiles. Furthermore, plasma leptin values among overweight subjects (BMI > 25) were significantly lower in the Peruvian women.

Leptin ($r = .36$ in Lima and $r = .37$ in Umeå, both $P < .001$) (Fig 2), and BMI ($r = .38$ in Lima and $r = .45$ in Umeå; both $P < .001$) correlated with SBP. To ascertain which of these factors independently influenced blood pressure, log leptin and BMI were both entered in a forward stepwise multiple regression with SBP as the dependent variable. It was found that BMI emerged as the independent determinant for SBP and not leptin, both in Lima and in Umeå. This shows that the main influence on blood pressure in these populations is BMI independent of leptin. Figure 2 illustrates this relationship. Blood pressure and BMI are shown in different quintiles of circulating leptin in the 2 populations. As the 2 populations were not a priori matched for BMI, a subanalysis of the data was performed in the narrow

Table 2. Regression Coefficient of the Univariate Correlations Between BMI and Leptin, Waist, SBP, DBP, Triglycerides, and Glucose in the Two Populations

Variable	Lima	Umeå
Leptin	.70	.73
Waist circumference	.92	.85
SBP	.38	.44
DBP	.37	.50
Triglycerides	.41	.46
Glucose	.38	.29

NOTE. All correlations were significant at the $P < .001$ level, except for the correlation between BMI and glucose in Umeå, being significant at $P = .028$.

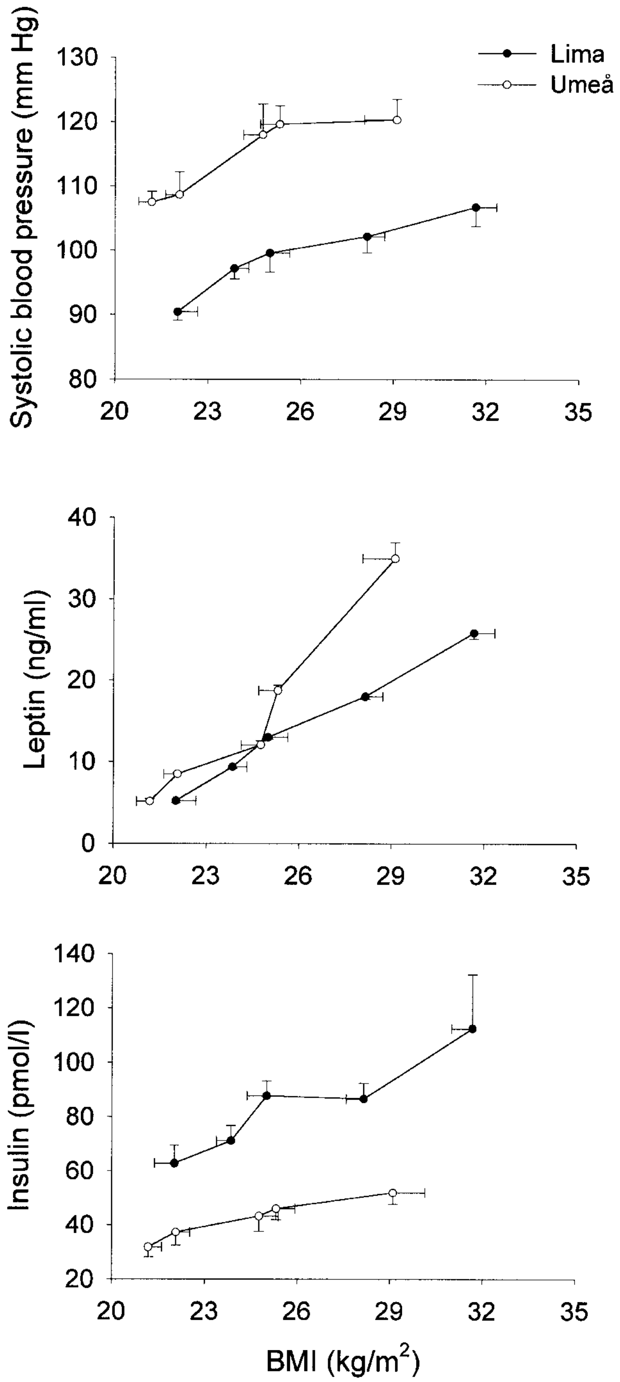

Fig 1. SBP and circulating levels of leptin and insulin in the populations of women from Lima and Umeå, as divided in quintiles with regard to BMI. Mean ± SEM is shown.

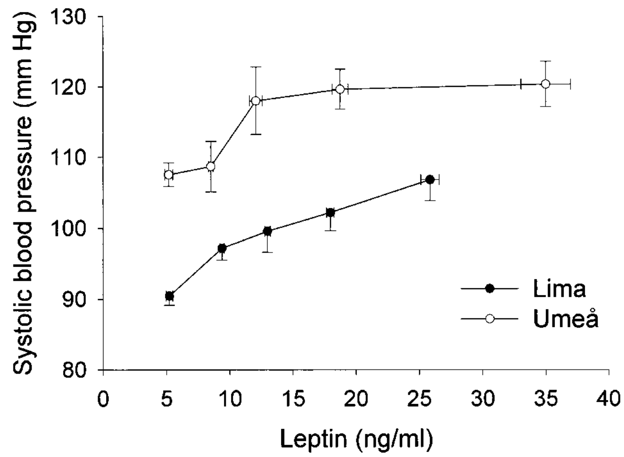

Fig 2. SBP in the populations of women from Lima and Umeå, as divided in quintiles with regard to circulating leptin. Mean ± SEM is shown.

interval of 28 to 32 kg/m^2 of BMI (Table 3). As can be seen, also in this narrow BMI interval, blood pressure and leptin were higher in Umeå, whereas insulin was higher in Lima.

DISCUSSION

Women living in the urban area of greater Lima are more obese than Swedish women of the same age, but have nevertheless lower SBP and DBP. In accordance with the higher degree of obesity, the Peruvian women had elevated insulin levels. However, there is a clear difference in the relationship between leptin per unit of BMI between Peruvian and Swedish women. Different regulation of blood pressure and insulin levels are characteristics of the Lima population when compared with the Umeå population, illustrating important population differences in the expression of the metabolic syndrome.

An intriguing issue is whether the lower expression of leptin in Lima explains the lower blood pressure, ie, whether leptin contributes to the higher blood pressure in Sweden. In fact, several previous studies have shown a relationship between leptin and blood pressure. Thus, plasma levels of leptin are elevated in patients with essential hypertension, as observed in healthy offspring of patients with hypertension.[13] Furthermore, experimental studies have shown that leptin administration increases the sympathetic nervous activity,[5] and long-term leptin administration increases the arterial blood pressure.[6] Also, in the present study, leptin correlated with blood pressure. Because this influence of leptin on SBP was dependent on BMI, it is suggested that the hypertension associated with BMI is partially due to leptin. Therefore, because both populations examined in the present study showed correlation between

Table 3. Circulating Leptin and Insulin and Blood Pressure in Subjects of the Two Populations Within the Narrow BMI Limit of 28 to 32 kg/m^2

Variable	Lima (n = 42)	Umeå (n = 12)	*P*
BMI (kg/m^2)	29.9 ± 1.1	29.8 ± 1.4	NS
Leptin (ng/mL)	18.7 ± 6.4	28.7 ± 11.1	<.001
Leptin/BMI	0.63 ± 0.21	0.95 ± 0.33	.007
Insulin (pmol/L)	95 ± 41	53 ± 15	<.001
SBP (mm Hg)	101 ± 13	120 ± 8	<.001
DBP (mm Hg)	68 ± 6	76 ± 7	<.001

NOTE. Means ± SD are shown. *P* indicates the probability level of random difference between the populations.

Abbreviation: NS, not significantly different.

leptin levels and blood pressure, it is possible that the lower blood pressure in subjects from Lima is explained by the lower leptin levels in the subjects with BMI exceeding 25 kg/m^2.

Another intriguing issue is the mechanism of the different plasma leptin levels in the 2 populations studied. The most obvious difference was the high BMI levels, suggesting that it is the regulation of the expression of leptin at increasing adiposity, which is different between women in Peru and Sweden. Hence, in obesity, the adiposity in Swedish exhibit increased leptin levels when compared with the Peruvian population. Because the range of blood pressure was similar in the 2 study groups and the association between plasma leptin and SBP recordings were identical (r = .36 and r = .38, respectively), despite the great difference in mean blood pressure values, it is possible that the the lower leptin levels in the Peruvian women is an effect of confounding environmental factors.

One environmental factor of potential importance is different types of diet in the 2 populations. Diet is considered an important environmental factor influencing lipid metabolism, blood pressure, insulin secretion, and insulin-mediated glucose uptake. Preliminary results from diet history recall in the Peruvian group show very low-fat (18% calorie) and high-carbohydrate intake (68% calorie). In contrast, a previous study has shown that in Umeå, the percentage calorie intake of fat is 35%.[14] Short-term consumption of a high-carbohydrate, low-fat diet is known to be accompanied by beneficial changes in blood pressure and in glucose tolerance.[15] Insulin sensitivity is improved, but neither stimulated or fasting plasma insulin are altered when the diet is changed from high- to low-fat intake.

The present study also showed lower fasting blood glucose levels and blood pressure in Peruvian women when compared with Swedish women, which indicates lower insulin sensitivity in the Peruvian women. Furthermore, plasma insulin levels were higher in Peruvian women than in Swedish women. The most likely explanation for this paradoxical finding is that the high-carbohydrate load in the diet stimulates insulin secretion inadequately in relationship to the insulin sensitivity. Our findings are consistent with other reports that indicate insulin resistance may be more important than hyperinsulinemia as a determinant of blood pressure and other cardiovascular risk factors.[16,17] Conversely, serum leptin may be positively associated with excess fat intake independent of obesity.[18,19] Thus, a possible explanation for the observed divergence from the features of the metabolic syndrome, eg, low blood pressure and plasma leptin, is a diet with extremely low-fat intake.

However, genetic factors may also influence leptin levels. A previous study from South Africa showed that leptin concentrations were higher and insulin levels lower in black compared with white women, despite similar BMI and body fat mass.[20] In contrast, no significant differences in plasma leptin levels and resting metabolic rates were observed in lean Pima Indians and non-Pima Mexicans living at high altitude in a rural area.[21] This is in line with the present study, as the difference in leptin level was observed only in overweight and obese subjects.

It is of interest to speculate whether the different leptin levels achieved at similar adiposity in the 2 populations have any consequences for satiety or energy expenditure, the 2 main functions of leptin.[22] Indeed, in a previous study, it was found that leptin levels correlate negatively to food intake determined as total energy intake in humans.[23] Therefore, it may be speculated that the low-leptin levels in the Peruvian population contribute both to the higher waist and degree of obesity and to the lower blood pressure. This is in line with previous suggestions that low-plasma leptin concentrations are associated with weight gain, perhaps through increased appetite, low-daily energy expenditure, and low-sympathetic nervous system activity,[24] although the importance of leptin for the regulation of energy expenditure in humans is still controversial.[25,26]

In this context, it is necessary to add a note of caution, because we have not measured body fat mass and its distribution, physical activity, or smoking habits in the 2 populations. Differences in body proportions of the trunk and legs may distort the meaning of BMI as a measure of obesity in the different ethnic groups.[27] This possible bias might play a role in the cross-ethnic comparison of leptin levels in obese and lean subjects classified using critical points of BMI. However, the differences in leptin and insulin levels between black and white women were observed at similar BMI and body fat mass.[20] Although the Peruvian women might be more physically active, this would not explain the lower level of lepin per unit BMI, because leptin has not been shown to be dependent on physical activity independent from changes in BMI.[28] Similarly, smoking has been shown to have no independent influence on leptin.[29] Another note of caution is that the 2 populations were selected randomly from the background population, and they were matched only for age and gender. However, even if the analyses were performed within narrow limits of BMI in overweight subjects, when the BMI did not differ between the groups, the differences in blood pressure, leptin, and insulin persist, as is evident from Table 3, showing the analysis in the BMI interval of 28 to 32 kg/m^2.

In summary, we have detected significant lower blood pressure levels, elevated plasma insulin concentrations, but lower plasma leptin values adjusted for BMI, in women living in Lima compared with women from northern Sweden. The relationship between variables suggested to be important for the development or complications of the metabolic syndrome or syndrome X obviously is different among obese women with Peruvian Indian heritage in comparison to a Caucasian population.

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