Elevated Plasma Leptin Levels Pre-exist in Healthy Descendants of Patients with Essential Hypertension

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Introduction: Plasma leptin and insulin levels have been found to be elevated in patients with essential hypertension (EH) and have been suggested to be components of the metabolic syndrome. Increased heart rate (HR) may predict the development of EH in normal or borderline hypertensive individuals. The aim of our study was to test the hypothesis that elevated plasma leptin and insulin levels as well as systolic blood pressure (SBP) and diastolic blood pressure (DBP) and increased resting HR pre-exist in the healthy descendants of patients with EH.

Methods: Twenty-six (12 male) healthy descendants of hypertensive patients, mean age 16±2.5 years and body mass index (BMI) of 21.5±2.8kg/m^2 (group A), and 30 (14 male) healthy descendants of normotensive patients, mean age 17±2.3 years and BMI of 21.9±2.4 kg/m^2 (group B), were studied. The two groups were matched for sex, age, and BMI. Mean SBP, DBP, resting HR, plasma leptin, and plasma insulin levels (radioimmunoassay method) were determined in the whole study population.

Results: Mean SBP, DBP, and resting HR were significantly higher in group A than in group B (120±12 vs 112±9.5 mmHg, 77±9 vs 72±7 mmHg, 79±8 vs 75±5 beats/min, $P<0.01$, $P<0.05$, and $P<0.05$, respectively). Plasma leptin and insulin levels were significantly higher in group A than in group B (9±5.06 vs 5.6±2.5 ng/mL and 20.11±11.3 vs 14.8±5.2 μIU/mL, $P<0.01$ and $P<0.05$, respectively).

Conclusions: Our findings support the hypothesis that hyperleptinemia, hyperinsulinemia, and elevated blood pressure and resting HR preexists in the healthy descendants of patients with EH.

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The metabolic syndrome was first described almost 30 years ago[1] but it was recently redefined by Reaven[2] based on the theory that reduced glucose tolerance, hyperinsulinemia, central obesity, increased VLDL cholesterol and triglyceride levels, decreased HDL cholesterol levels and essential hypertension (EH) are consequences of insulin resistance[3,4]. It has been found that these metabolic disorders are associated with an increased risk of coronary artery disease[5].

Insulin resistance and the subsequent hyperinsulinemia are thought to cause an increase in blood pressure (BP) levels through a variety of mechanisms, such as stimulation of the sympathetic nervous system[6], renal reabsorption of Na[7], activation of the renin-angiotensin axis and the accumulation of calcium ions in the vascular smooth muscle fibers. Nevertheless, several areas of the pathogenetic mechanism remain questionable[8].

Leptin is a recently discovered hormone[9], produced by the adipocyte-specific ob gene. Leptin provides the brain with information about the existence of excess adipose tissue, thereby linking dietary habits, metabolism and endocrine activity to the state of nutrition of the body. Recently, plasma leptin levels have been associated with several characteristics of the metabolic syndrome, such as EH[10], obesity[11], insulin-resistance[12] and HDL cholesterol levels[13].

In recent years, many data support the hypothesis that heart rate (HR) strongly correlates with the occurrence of hypertension and may be predictive of the development of permanent hypertension in individuals with normal or borderline increased BP values, while at the same time it is associated with increased cardiovascular morbidity and mortality[14]. The aim of our study was to test the hypothesis that elevated plasma leptin and insulin levels as well as BP and increased resting HR pre-exist in the healthy descendants of patients with hypertension, compared to the descendants of individuals without a history of hypertension or cardiovascular disease.

Material and methods

We studied 26 healthy individuals, descendants of patients with hypertension (12 men and 14 women) with a mean age of 16±2.5 and body mass index (BMI) of 21.5±2.8 kg/m^2 (Group A) and 30 healthy individuals, descendants of subjects without a history of hypertension, cardiovascular disease or diabetes mellitus (14 men and 16 women), with a mean age of 17±2.3 years, and BMI 21.9±2.4 Kg/m^2 (Group B). Group A individuals were healthy children of hypertensive parents, who are followed in the antihypertensive unit of our Hospital, did not take any medication and were non-smokers. Alcohol consumption, calculated in grams per day, was determined according to a comprehensive questionnaire, while at the same time, we recorded information with respect to the physical activity of the subjects also by means of a special questionnaire[15]. Before the study, all participants signed an informed consent form and underwent a routine thorough clinical examination. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) values were determined based on the 1st and 5th Korotkoff sounds, respectively. The measurements were taken using a mercury sphygmomanometer placed to the right forearm, in the supine position, after the person under examination had rested for 15 minutes. HR was measured under the same conditions with an electrocardiogram (ECG), calculated as the average of 9 R – R intervals[14]. The final measurement results were the mean results of at least 3 consecutive visits of the persons examined. The measurements were taken by the same examiner, who was not familiar with the family history of the persons examined. Blood samples to measure insulin and leptin were taken between 8-9 am, after a 12-hour fast.

Laboratory analysis

Immunoactive insulin (Insulin - CT RIA kit, CIS bio International, Gif Sur Yvette, France) and leptin levels (P-leptin) (Human Leptin RIA kit, Linco Research Inc) were determined by radioimmunoassay method. The investigators conducting the analysis did not know the origin of the blood samples.

Statistical analysis

The data were expressed as mean values ± standard deviation (SD). The differences between the two groups were tested using the Student's t-test. The data were analysed further using a parametric method of linear regression analysis with leptin as a dependent variable. All analyses were performed using the statistical analysis software SPSS.

Results

No significant difference was found between the two groups with respect to age, sex and BMI. The study results and the comparisons between the two groups are listed in Table 1. Mean SBP was significantly higher in group A compared to group B (120±12 vs 112±9.5 mmHg, $p<0.01$). Mean DBP was also significantly higher in group A compared to group B (77±9 vs 72±7 mmHg, $p<0.05$), as well as mean HR (79±8 vs 75±5 bpm, $p<0.05$). Significantly higher leptin levels ($p<0.01$) were observed in group A (9.0±5.06 ng/ml) compared to group B (5.6±2.5 ng/ml). Significantly higher insulin levels ($p<0.05$) were also found in group A (20.11±11.3 μIU/ml) compared to group B (14.8±5.2 μIU/ml) (Table 1, Figure 1). Leptin levels were significantly higher in both male and female descendants of hypertensives compared to the respective male and female descendants of the control group (7.65±5.06 vs 3.8±1.7 ng/ml, $p<0.005$ and 11.05±4.77 vs 7.87±2.15 ng/ml, $p<0.05$, respectively). Statistical analysis using leptin

Table I. The results and the comparison between the two groups.

	Group A	Group B	P
SBP (mmHg)	120±12	112±9.5	<0.01
DBP (mmHg)	77±9	72±7	<0.05
Heart rate (bpm)	79±8	75±5	<0.05
Leptin (ng/ml)	9.0±5.06	5.6±2.5	<0.01
Insulin (μIU/ml)	20.11±11.3	14.8±5.2	<0.05

SBP: systolic blood pressure; DBP: diastolic blood pressure

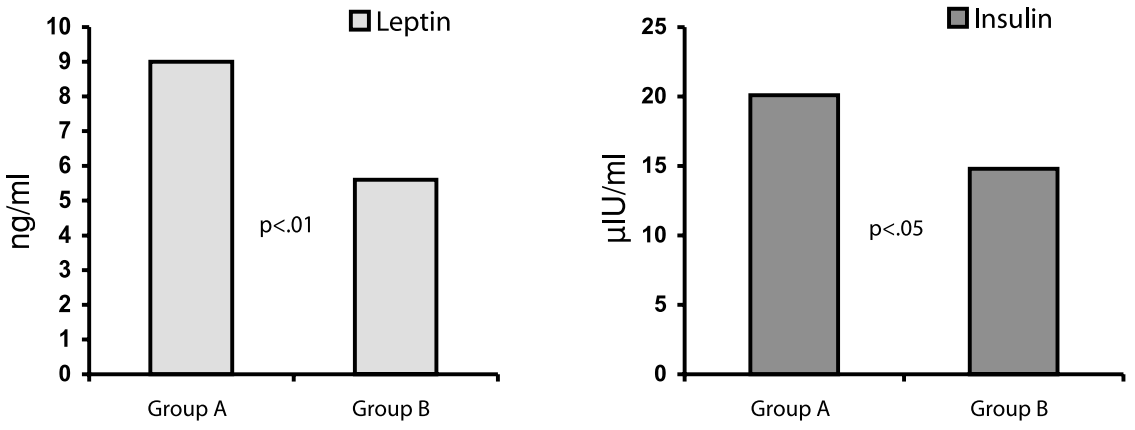

Figure 1. Plasma leptin and insulin levels in the descendants of hypertensives (Group A) are significantly higher than in the descendants of normotensives (Group B, $p<0.01$ and $p<0.05$, respectively).

as a dependent variable did not show a correlation of the latter with BMI ($r=0.065$, $p=NS$) or with insulin ($r=0.22$, $p=NS$). It should be noted that no differences were found between the two groups with respect to physical activity and alcohol consumption.

Discussion

The present study showed that leptin levels were significantly higher in healthy descendants of patients with EH, compared to the healthy descendants of normotensive individuals, while there were no significant differences between the two groups with respect to age, sex and BMI. The study also indicates that the descendants of patients with EH seem to have significantly higher insulin levels, SBP and DBP values, and resting HR, compared to the descendants of individuals without a history of cardiovascular disease, diabetes mellitus or EH.

In contrast to literature data, no correlation was found between BMI and leptin levels, a fact which is attributed to the small variability of BMI values observed in this group of young adults[16,17]. No correlation was found between insulin and leptin levels. Although most studies show a correlation between insulin and leptin levels, in the study by Agata et al[10], similar to our study, no correlation was found between the two substances, even when the most sensitive technique was used (euglycemic hyperinsulinemic glucose clamp technique). In this study[10], hypertensive patients were found to be insulin-resistant but also to have hyperleptinemia. It is possible that in order to show this correlation a larger population needs to be studied.

Another possible explanation is that hyperleptinemia is usually preceded by a prolonged period of hyperinsulinemia, thus this biological consequence may not be obvious in the young people studied due to their age. By combining the aforementioned explanations, it can be said that the observed hyperleptinemia in group A is directly and independently related to a family history of EH.

This implies that there is a possible genetic connection between hyperleptinemia and EH, although this was not shown in a recent study by Onions et al[18]. In this study, no data were obtained supporting a connection between the four polymorphic indices of the gene locus of leptin and the EH phenotype. However, the study population included clearly overweight persons (BMI >27 Kg/m^2) and African Americans. With this material, it is possible that additional pathophysiological mechanisms are related to the occurrence of EH. Besides, the inclusion of African Americans, as mentioned also by the authors, should be taken into account in the evaluation of results.

In our study, the descendants of patients with EH had also significantly higher plasma insulin levels compared to the healthy descendants of normotensive individuals ($p<0.05$), a fact which is in line with the previous observations[19].

A limitation of our study is that insulin-resistance was not measured, while as far as HR and BP are concerned, our findings agree with previous studies[14]. The mechanisms affecting the increase of leptin levels in EH are not clear. This increase seems to result from: 1) stimulation by hyperinsulinemia, caused by insulin-resistance often observed in hyper-

tensive patients[20], 2) the difference in the quantity of body fat between normotensives and hypertensives, despite the similar values of BMI, 3) the difference in the metabolic characteristics of the fat cells of the subjects in the two groups and 4) the leptin-resistance in the hypertensive patients[10]. It should be stressed that there are very few data concerning the plasma leptin levels of healthy descendants of hypertensive patients[21].

It has been suggested recently that hyperleptinemia should be included in the metabolic syndrome, since leptin is associated with several of its components[12,22]. It has been found that leptin decreases the levels of the neuropeptide Y in the hypothalamus, a fact which is related to the activation of the sympathetic nervous system[23]. This can explain the coexistence of increased HR and BP and increased insulin and leptin levels in the individuals of group A. However, in a recent study of a group of hypertensive mice[24], no correlation was found between leptin and EH. Clearly further studies are needed and a larger number of samples in order to confirm these correlations. Also, it is known that the value of BMI in the calculation of body fat is limited and possibly more precise methods of calculating adipose tissue are necessary. However, it should be stressed that many studies carried out with the application of alternative methods, such as biopsy of subcutaneous fat[25] from the abdominal region or computer tomography imaging, have shown correlations with the leptin levels, similar to those reported in our study[12,26].

Conclusions

Our findings imply that increased values of HR, SBP, DBP and plasma insulin and leptin levels preexist in the healthy descendants of hypertensive patients. Further studies are necessary in order to document these initial observations, which support the practice of examining children and young adults in order to determine cardiovascular risk, as a basis of preventing cardiovascular events in later adult life.

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