Circulating leptin levels predict the development of metabolic syndrome in middle-aged men: an 8-year follow-up study

Ferruccio Galletti\textsuperscript{a}, Antonio Barbato\textsuperscript{a}, Marco Versiero\textsuperscript{a}, Roberto Iacone\textsuperscript{a}, Ornella Russo\textsuperscript{a}, Gianvincenzo Barba\textsuperscript{b}, Alfonso Siani\textsuperscript{b}, Francesco P. Cappuccio\textsuperscript{c}, Eduardo Farinaro\textsuperscript{d}, Elisabetta della Valle\textsuperscript{d} and Pasquale Strazzullo\textsuperscript{a}

**Background** Because high circulating plasma leptin is associated with many features of the metabolic syndrome (MS), such as abdominal obesity, insulin resistance and high blood pressure (BP), we analysed the ability of plasma leptin concentration to predict the risk of developing MS in a prospective investigation of adult male participants of the Olivetti Heart Study (OHS).

**Methods and Results** Three hundred and sixty out of 907 men participating in the 1994–95 and 2002–04 OHS examinations (mean age at baseline 50.4 years, range 25–73 years) were free of MS at first visit according to NCEP-ATP III criteria (modified for the lack of high-density lipoprotein-cholesterol measurement at baseline). During an average follow-up period of 8 years, there were 52 incident cases of MS (14.5%) due, in particular, to a rise in the prevalence of high BP (42.4%), abdominal obesity (16.4%) and impaired fasting glucose (IFG, 6.1%). In multivariate analyses, a one standard deviation difference in baseline plasma leptin concentration was associated with a 1.58-fold greater risk of developing MS (95% confidence interval = 1.10–2.30, \( P = 0.016 \)) accounting for age, waist circumference, homeostatic assessment model index, smoking, alcohol consumption and physical activity. In particular, plasma leptin was positively associated with the risk of developing high BP (0.006) and IFG (0.014), after adjustment for confounders.

**Conclusion** In this sample of an adult male population free of MS at baseline, circulating plasma leptin was a significant predictor of the risk of MS and, in particular, of its high BP and IFG components, independently of potential confounders. *J Hypertens* 25:000–000 © 2007 Lippincott Williams & Wilkins.

**Keywords:** hypertension, insulin resistance, leptin, metabolic syndrome, salt-sensitive hypertension

\textsuperscript{a}Department of Clinical and Experimental Medicine, Federico II University of Naples Medical School, Naples, Italy, \textsuperscript{b}Epidemiology and Population Genetics, Institute of Food Science, CNR, Avellino, Italy, \textsuperscript{c}Clinical Sciences Research Institute, Warwick Medical School, Coventry, UK and \textsuperscript{d}Institutes of Preventive Medical Sciences, Federico II University of Naples, Medical School, Naples, Italy

Correspondence and requests for reprints to Dr Ferruccio Galletti, Department of Clinical & Experimental Medicine, Faculty of Medicine, Via S. Pansini 5, 80131 Naples, Italy Tel: +39 0817 464301; fax: +39 0815 466152; e-mail: galletti@unina.it, strazzul@unina.it

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**Introduction**

The metabolic syndrome (MS) is thought to have its roots in the age-related development of abdominal obesity and its pathophysiological hallmark in reduced insulin sensitivity. Some of the definitions proposed for MS [1–3] are actually based on objective indicators of insulin resistance. However, when using the widely accepted NCEP-ATP III diagnostic criteria [4], a significant proportion of the individuals meeting these criteria have no evidence of insulin resistance [5,6], suggesting that, in a large number of subjects, other pathogenic factors must be operating to produce an altered metabolic profile.

Elevated serum leptin concentration is a feature of obesity and abdominal adiposity and, albeit not considered among the diagnostic criteria for MS, has been found to be increased in subjects with MS [7–9]. Leptin is produced by differentiated adipocytes in white adipose tissue, but also in other organs, such as the hypothalamic region of the brain [10]. It physiologically acts on specific structures in the hypothalamus, suppressing the desire for food and increasing energy expenditure by a sympathetically-mediated rise of thermogenesis in brown adipose tissue [10,11]. In addition, leptin might heighten insulin sensitivity by the skeletal muscle [12]. Elevated levels of plasma leptin are a common feature of human obesity: the higher the body mass index (BMI) or the waist circumference, the higher the serum leptin level [13]. Moreover, serum leptin concentration has been reported to be directly associated with serum insulin concentration [14–18] and with blood pressure (BP) [19]. In this regard, it is noteworthy that central sympathetic activation by adipose tissue-derived, and possibly also by locally produced leptin [10], is translated into increased sympathetic...
discharge not only to brown adipose tissue, but also to other organs and, in particular, to the kidney, as recently shown by Exler et al. [20], with possible effects on BP homeostatic control.

In several respects, leptin and hyperleptinemia appear to be crucial factors in the complex interplay of metabolic alterations clustering in the form of MS. We thus decided to prospectively evaluate the role of leptin in the process of the development of MS and its individual components, taking into account the other relevant factors involved, namely abdominal adiposity and insulin resistance. To this purpose, we used the database of the Olivetti Heart Study, an epidemiological investigation of the metabolic, nutritional and genetic precursors of cardiovascular diseases in an unselected sample of adult male population in southern Italy.

**Methods**

**Population**

The Olivetti Heart Study population is given by the male workforce of the Olivetti factories of Pozzuoli (Naples) and Marcianise (Caserta). The general characteristics of the study and its methodological procedures have been previously described [21]. The local Ethics Committee approved the study protocol, and participants provided their informed consent to participate. A total of 1085 individuals aged 25–74 years (mean ± SD = 51.5 ± 7.2 years) were examined in 1994–5: of these, 907 (83.6%) were seen again in 2002–4 and were considered eligible for the present analysis.

**Diagnosis of metabolic syndrome**

For the purpose of analysing the role of leptin and related variables in the development of MS, we identified all the subjects who were certainly free of MS at baseline. The diagnosis of MS was based on the NCEP/ATPIII criteria [4]. However, because the measurement of serum high-density lipoprotein (HDL)-cholesterol level was not available at this time, a positive diagnosis of MS at baseline was made only if at least three of the other four components of the syndrome (i.e. waist circumference ≥102 cm, serum triglyceride ≥1.70 mmol/l or current triglyceride-lowering therapy, fasting glucose ≥6.10 mmol/l or known type 2 diabetes or current hypoglycemic therapy, BP ≥130 and/or 85 mmHg or current antihypertensive therapy) were present in a given participant. On the other hand, a negative diagnosis of MS was made in those cases in which only one or none of these components were present, allowing for the possibility of an HDL-cholesterol level in the abnormal range. The subjects in which only two elements of the NCEP/ATPIII criteria were present were excluded and thus the possibility of a false negative diagnosis was eliminated. Three hundred and sixty participants were certainly free of MS at the baseline visit and were the object of our prospective evaluation.

**Examination procedures**

Body weight and height were measured on a standard beam balance scale with an attached ruler. Body weight was measured to the nearest 0.1 kg and body height was measured to the nearest 1.0 cm, with subjects wearing light indoor clothing without shoes. BMI was calculated according to the standard formula. Being overweight was defined as a BMI ≥25 and obesity as a BMI ≥30. The waist circumference, taken as an index of abdominal adiposity, was measured at the umbilicus level with the subject standing erect with abdomen relaxed, arms at the sides, and feet together; measurements were performed to the nearest 0.1 cm with a flexible inextensible plastic tape.

Smoking habits, alcohol consumption and degree of habitual physical activity were investigated by a standardized questionnaire.

Systolic and diastolic (phase V) BP were taken three times 2 min apart with a random zero sphygmomanometer (Gelman Hawksley Ltd, Sussex, UK) after the subject had been sitting for at least 10 min. The average of the second and third reading was recorded. Hypertension was defined as BP ≥140 and/or 90 mmHg or current antihypertensive drug treatment. The resting supine heart rate was measured. A fasting venous blood sample was taken in the seated position between 08.00 h and 10.00 h, after the BP measurements, for determination of serum leptin and serum insulin, lipids and glucose.

The blood specimens were immediately centrifuged and stored at −70°C until analysed. Serum leptin was measured by an enzyme-linked immunosorbent assay (R&D System GmbH, Wiesbaden-Nordenstadt, Germany). Intra- and inter-assay coefficient of variation were less than 3% and 5.4%, respectively [22].

Serum total and HDL-cholesterol, triglyceride and glucose levels were measured with automated methods (Cobas-Mira, Roche, Italy). Serum insulin was determined by radioimmunoassay (Insulin Lisophage; Technogenetics, Milan, Italy). The homeostatic assessment model (HOMA) index was used to estimate insulin resistance and calculated as fasting serum insulin (μU/ml) × fasting serum glucose (mM)/22.5, as described by Matthews et al. [23].

**Statistical analysis**

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS-PC, version 12; SPSS, Inc., Chicago, Illinois, USA). Because the distributions of leptin, glucose, triglyceride and HOMA index deviated significantly from normal, they were normalized by log-transformation, and log-transformed values were used in the analysis. Logistic regression was used to estimate the predictive role of selected variables with
respect to the incidence of MS. Logistic regression was also adopted to estimate the risk of developing each individual component of MS as a function of the baseline serum leptin level and accounting for possible confounders. In all logistic regression analyses, the independent variables included in the equation were expressed as their respective z-scores to normalize for SD; these were calculated by standard formulae (e.g. age z-score = (age – μ age)/σ age, where μ age is the age of a given participant, μ age is the average age of the study population and σ age is the age SD). Results were expressed as mean±SD or 95% confidence interval (CI), unless otherwise indicated. P < 0.05 (two-sided) was considered statistically significant.

Results

At baseline, 67% of the participants were overweight, 5.8% were obese, 24% were hypertensive and 0.8% were diabetic. Thirty-six percent of the hypertensive participants were on regular antihypertensive treatment prescribed by their physician, 9.7% of the population were receiving treatment with hypolipidemic drugs and 0.3% were receiving treatment with hypoglycaemic agents because of type 2 diabetes.

At the end of the 8-year follow-up period, 52 individuals had developed MS (14.5%). According to the NCEP-ATPIII criteria, the prevalence of high BP rose from 37.8% to 80.2%, abdominal adiposity from 2.2% to 16.8%, and impaired fasting glucose (IFG) from 4.7% to 9.4%. The prevalence of hypertriglyceridemia remained unchanged (from 19.4% to 19.7%). Twenty-two percent of participants had a low serum HDL-cholesterol level by NCEP/ATPIII criteria at follow-up examination (the baseline prevalence was not known).

All the differences observed at baseline between the two groups became more marked at follow-up examination (Table 1); in addition, significant differences became apparent with regard to BP (despite the influence of concomitant pharmacological therapy) and to serum HDL-cholesterol concentration (which was not available at baseline).

When the study population was stratified by tertile of baseline serum leptin concentration (Fig. 1), the incidence of MS increased linearly across serum leptin categories (χ² = 12.1, P = 0.002). With respect to the single components of MS (according to the NCEP-ATPIII definition), as shown in Fig. 2, the incidence of abdominal adiposity, IFG and high BP all rose linearly across leptin tertiles. By contrast, there was no difference in the incidence of hypertriglyceridemia (P = 0.106).

<table>
<thead>
<tr>
<th>Table 1 Differences in selected variables at baseline and follow-up examination between participants who did or did not develop the metabolic syndrome (MS) (n = 360)</th>
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<td>1994–95 examination</td>
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<td>2002–04 examination</td>
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<tr>
<td>Age (years)</td>
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<tr>
<td>Body mass index (kg/m²)</td>
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<td>Waist circumference (cm)</td>
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<td>Serum glucose (mmol/l)</td>
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<td>HOMA index</td>
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<td>Baseline serum leptin (ng/ml)*</td>
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<td>SBP (mmHg)</td>
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<td>DBP (mmHg)</td>
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*Geometric mean (SD). **P < 0.05, ***P < 0.001, MS+ vs. MS− participants. HOMA, homeostatic assessment model index; HDL, high-density lipoprotein; SBP, Systolic blood pressure; DBP, diastolic blood pressure.
Logistic regression analysis was used to estimate the predictive role of baseline serum leptin concentration as a continuous variable with regard to the risk of developing MS over 8 years. In a model including baseline values of serum leptin, waist circumference, HOMA index, age, smoking, alcohol consumption and habitual physical activity with MS as dependent variable, serum leptin and the HOMA index were both independent predictors of MS. The risk of developing MS was 1.8-fold greater for 1 SD increment in HOMA index (95% CI = 1.31–2.48; P < 0.001) and 1.58-fold greater (95% CI = 1.10–2.30, P = 0.016) for 1 SD difference in serum leptin concentration. In this model, waist circumference did not further add to the risk of MS (relative risk = 1.00, 95% CI = 0.68–1.48 for 1 SD increment in waist circumference). In a similar logistic regression equation in which waist circumference was replaced by BMI as covariate, BMI was the main predictor of MS with an increase in risk of 1.86-fold (95% CI = 1.23–2.81, P = 0.003) for each SD increase in BMI, whereas the relative risk linked to a 1 SD difference in leptin fell to 1.32 (95% CI = 0.90–1.94, P = 0.149).

In addition, we analysed the value of baseline serum leptin concentration as predictor of incident cases of each single component of MS. This analysis was carried out in two steps. In the first step, the effect of leptin was evaluated using a logistic regression model with leptin as independent variable and age, smoking habits, alcohol intake and degree of habitual physical activity as covariates. Four different equations were run, with abdominal adiposity, high BP, IFG and elevated serum triglyceride at follow-up examination (as defined by the NCEP/ATPIII criteria) as dependent variables. With respect to the end-point variables, each analysis included only those participants who had normal values of that variable at baseline. This analysis could not be effected for low HDL-cholesterol because baseline values were not available in this case. As shown in Table 2, baseline serum leptin concentration was significantly associated to the risk of developing three components of MS, namely abdominal obesity, high BP and IFG, whereas it was not predictive of the risk of hypertriglyceridemia.

As a second step, two logistic regression models were prepared that, in addition to leptin, included waist circumference or HOMA index as independent variables, plus age, smoking, alcohol intake and degree of habitual physical activity as covariates. For each of the two models,

Table 2  Multivariate logistic regression analysis: relative risk (RR) of developing the specified metabolic syndrome components over 8 years according to 1 SD increase in baseline serum leptin concentration

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>First step $^a$</th>
<th>Model A $^a$</th>
<th>Model B $^a$</th>
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<tbody>
<tr>
<td></td>
<td>Independent variable: leptin (z-score)</td>
<td>RR (95%CI)</td>
<td>P</td>
</tr>
<tr>
<td>Equation 1: Abdominal adiposity</td>
<td>2.02 (1.43–2.86)</td>
<td>&lt; 0.001</td>
<td>1.02 (0.68–1.53)</td>
</tr>
<tr>
<td>Equation 2: High BP</td>
<td>1.55 (1.13–2.13)</td>
<td>0.007</td>
<td>1.53 (1.06–2.21)</td>
</tr>
<tr>
<td>Equation 3: IFG</td>
<td>1.89 (1.22–2.95)</td>
<td>0.004</td>
<td>2.19 (1.32–3.81)</td>
</tr>
<tr>
<td>Equation 4: Hypertriglyceridemia</td>
<td>0.76 (0.52–1.12)</td>
<td>0.166</td>
<td>0.63 (0.50–1.24)</td>
</tr>
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$^a$ Covariates in the model: age, smoking, alcohol intake and physical activity.

$^b$ Covariates in the model: same as in the first step plus baseline waist circumference.

$^c$ Covariates in the model: same as in the first step plus baseline homeostatic assessment model index. RR, relative risk; BP, blood pressure; IFG, impaired fasting glucose.
again, four different equations were run, with abdominal adiposity, high BP, IFG and hypertriglyceridemia at follow-up examination as dependent variables (Table 2). Also in this case, each analysis included only those participants who had normal values of the respective dependent variable at baseline. In model A, which accounted for the concomitant effect of waist circumference, baseline serum leptin remained a significant predictor of IFG and high BP, whereas it lost its effect on the risk of abdominal adiposity. In model B, which accounted for the concomitant effect of HOMA index, baseline serum leptin again remained a significant predictor of IFG and high BP but it was also a significant predictor of the development of abdominal obesity.

Finally, the ability of serum leptin to predict the rate of high BP was also evaluated by accounting for the basal levels of systolic and diastolic BP values (data not shown). In both equations, leptin remained a highly significant predictor of incident high BP with a relative risk of 2.07 (1.34–3.21) and 2.02 (1.30–3.15), respectively, for 1 SD difference in serum leptin concentration.

**Discussion**

The metabolic syndrome is generally considered to have its most common precursor in abdominal obesity and its pathophysiological hallmark in reduced insulin sensitivity. However, applying the widely accepted NCEP-ATP III diagnostic criteria for MS to the Olivetti Heart Study population, more than 40% of the individuals meeting these criteria had a HOMA index of insulin sensitivity below the 80th percentile for a comparable population of adult, normal weight, non-diabetic individuals [24], thus being in the normal range or not particularly elevated (unpublished data). In all evidence, in this large number of subjects, other metabolic factors are responsible for the altered metabolic profile and possibly for the increase in BP clustering in the MS.

Increased serum leptin is a feature of obesity and abdominal adiposity, and itself is often associated with impaired insulin sensitivity and found to be elevated in subjects with MS [7–9]. This was also the case in the present study, where the serum leptin concentration was significantly associated at univariate analysis with all the components of MS and with the HOMA index of insulin sensitivity in the baseline evaluation of our study population.

To hypothesize a causal role for elevated leptin levels in the occurrence of MS, it is essential to demonstrate its ability to predict the risk of developing MS over time independently of confounders. To this end, we analysed a group of individuals who attended the 1994–95 examination of the Olivetti Prospective Heart Study and were found to not have MS by NCEP-ATP III criteria at that time. This group of participants was examined again after 8 years. The main finding of this prospective evaluation was that baseline serum leptin concentration did predict the risk of MS over the 8-year follow-up period, which is the primary outcome of our study. To our knowledge, this is the first report of a predictive role of leptin with regard to the incidence of MS as defined by conventional criteria in a population-based investigation. However, another recent study has reported that serum leptin concentration predicts the worsening of some features of metabolic syndrome over time [25].

The association between baseline serum leptin concentration and the risk of developing MS was continuous through the entire range of serum leptin levels and was found to be at least partly independent of both waist circumference and degree of insulin sensitivity determined at baseline. Elevated levels of plasma leptin in man are most often felt to be a consequence of obesity; nevertheless, a sizable leptin production also occurs in other organs, including the brain [26]. It must be noted that, in this cohort, abdominal obesity at baseline was markedly under-represented given the deliberate exclusion of individuals with pre-existing MS. Notwithstanding, there was a substantial number of individuals who had relatively elevated serum leptin levels considering the degree that they were overweight and their abdominal adiposity. Our findings lead us to speculate that excess circulating plasma leptin plays a specific role along the pathway leading to the development of MS, irrespective of other possible mechanisms related to obesity and insulin resistance. Besides waist circumference, serum leptin was also strongly associated with BMI in our baseline observation. Because the increase in plasma leptin is at least in part a consequence of obesity, the fact that plasma leptin concentration lost a major portion of its predictive value with respect to MS when accounting for BMI might be parsimoniously explained by a direct cause–effect relationship between obesity and plasma leptin. Alternatively, it is possible that, given the high degree of collinearity between plasma leptin and BMI, the latter tends to over-ride the effect of leptin on the risk of MS in multivariate analysis because of the much stronger regression dilution bias affecting the estimate of plasma leptin compared to that of BMI. This point needs to be further evaluated in future studies.

The secondary outcome of our study was the exploration of the relationships between baseline leptin levels and the risk of developing any single component of MS. Multivariate analyses of these relationships, accounting for the effects of age, smoking, drinking habits and habitual physical activity, indicated that serum leptin had the ability to predict the development of several components of MS: the higher the serum leptin level at baseline, the greater the probability to develop abdominal obesity, IFG or high BP over time. Accounting for the effect of HOMA index or BP at baseline did not alter
these relationships whereas, in a model also including waist circumference, the association of leptin with the risk of abdominal obesity was lost but leptin remained a significant predictor of both high BP and IFG.

We have previously reported cross-sectional data from the 1994–95 examination of the Olivetti Heart Study showing a significant direct association between serum leptin and BP, independently of age and abdominal adiposity [19]. Animal experimental studies are in favour of a prohypertensive effect of leptin [27–31]. The best known physiological action of leptin is the promotion of weight loss by a reduction of appetite and increased energy expenditure through a central stimulatory action on sympathetic nervous system activity [11]. Although most obese humans are thought to be leptin-resistant because hyperleptinaemia fails to normalize adipose tissue mass in these subjects, such resistance appears to be selective for the metabolic actions of leptin while sparing other effects prompted by the hormone due to differential mechanistic pathways [11]. In particular, there is compelling evidence provided by studies in human volunteers with very different values of body mass index indicating a strong direct association between circulating leptin levels and sympathetic discharge to the kidney estimated by norepinephrine spillover, irrespective of body fat mass [10]. Experimentally, step-by-step increases in sympathetic stimulation to the kidney have been shown to be associated with increases in renin secretion, enhanced proximal tubular sodium and water reabsorption and, eventually, a reduction in renal plasma flow and glomerular filtration rate [24]. All of these actions may contribute to a rise in BP, possibly due to a long-standing increase in circulating plasma leptin levels.

An explanation for the association between baseline plasma leptin and the risk of developing IFG in our study population is less straightforward. Whether leptin physiologically has a direct effect on insulin sensitivity is still controversial. Total body glucose utilization increases after acute leptin administration in rodents [32]. Long-term treatment with leptin in rats was reported to ameliorate insulin sensitivity by improving insulin-stimulated glucose transport in skeletal muscle [33,34]. Other recent studies suggest that leptin could inhibit the incorporation of free fatty acids into triglycerides [35] and thus reduce triglyceride deposits [12]. However, other studies of the effects of leptin on glucose metabolism of skeletal muscle have provided discrepant results [36–40]. Thus, in conclusion, for clarification, this issue warrants further investigation.

**Study limitations**

One limitation of the present work is that the Olivetti study cohort comprised white male participants only; thus, its results may be generalized only to a comparable white male population. The lack of measurement of HDL-cholesterol at the 1994–95 baseline examination placed some restraint on our analysis at baseline. However, we did have the HDL-cholesterol measurement at the 8-year follow-up examination, and we are confident that this problem does not affect the interpretation of our main findings. Another limitation is that our findings are relative to a population with an average age at baseline of 50 years, albeit with a widespread age distribution. We cannot exclude that the features (and possibly the mechanisms) of MS developing at an earlier age might be different, to some extent, from those observed in this cohort of middle-age and elderly subjects. In particular, the very low number of new incident cases of hypertriglyceridemia during the 8-year follow-up period is not surprising given the relatively advanced age of our study population and the notion that serum triglyceride concentration tends to be stable after age 50 years [41].

Finally, a sizable proportion of the study participants was receiving some pharmacological treatment prescribed by their personal physician. Because current treatment of any single component of MS is taken care of by the NCEP-ATPIII diagnostic criteria, this factor could not affect the correct diagnosis of MS; however, it is theoretically possible that some of these treatments may have exerted an effect on metabolic parameters, such as insulin sensitivity, and, in turn, serum glucose levels. Notwithstanding, this possible confounding effect of treatment is more likely to have led to an underestimation of the biological and clinical associations observed.

**Conclusions and perspectives**

In summary, our study demonstrated the ability of plasma leptin concentration to predict the risk of developing the metabolic syndrome as defined by NCEP-ATPIII diagnostic criteria in a sample from an adult male population. It also showed that leptin was a predictor of incident hypertension and IFG, after adjustment for age, degree of abdominal adiposity, insulin resistance, BP, smoking, drinking habits and habitual physical activity at baseline. These results support the evidence provided by previous human and animal studies in favour of a pathogenic role of hyperleptinemia in the development of some of the features of metabolic syndrome, particularly high BP. Given the strong association between being overweight and hyperleptinemia, our findings also imply the need to prevent and/or treat being overweight and obesity as a fundamental tool against the development of metabolic syndrome.

**References**

Leptin predicts metabolic syndrome Galletti et al. 7


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