# Heredity and obesity-associated hypertension: impact of hormonal characteristics and left ventricular mass

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**Objectives:** To investigate the influence of heredity on obesity-associated hypertension, we evaluated casual and 24-h blood pressure, left ventricular mass and some metabolic and hormonal measurements in normotensive obese subjects.

**Design:** Healthy, normotensive obese subjects (n = 81) with positive or negative family history of hypertension were studied. Both groups were also subdivided according to a positive or a negative family history of obesity. Accordingly, 45 obese subjects had a positive family history of hypertension, 25 of these having a positive (subgroup A) and 20 having a negative family history of obesity (subgroup B). The other 36 obese subjects had a negative family history of hypertension, 19 of these having a positive (subgroup C) and 17 having a negative family history of obesity (subgroup D).

**Methods:** Casual and 24-h systolic (SBP), diastolic (DBP) and mean blood pressure (MBP) were evaluated. Serum fasting blood sugar, total cholesterol and triglycerides levels, urinary excretion of sodium, immunoreactive fasting insulin, plasma ANF levels, plasma renin activity (PRA), plasma aldosterone level, plasma adrenaline and noradrenaline levels and echocardiographic total left ventricular mass (LVM) and LVM : height ratio were also calculated.

**Results:** Twenty-four-hour DBP, 24-h MBP, LVM, LVM : height ratio, total cholesterol and PRA values were significantly higher in normotensive obese offspring of hypertensive parents than in obese offspring of normotensive parents. Twenty-four-hour DBP and MBP, LVM, LVM : height ratio, insulin level, insulin : glucose ratio and PRA were significantly higher in subgroup A than in subgroup B. Fasting blood sugar level, 24-h DBP and MBP, insulin level, insulin : glucose ratio, PRA, noradrenaline, adrenaline and plasma aldosterone levels were significantly higher in subgroup C than in subgroup D. Multivariate analysis also indicated that 24-h MBP and PRA levels were significantly influenced by the association between a positive family history of hypertension and obesity.

**Conclusions:** The present results suggest that a family history of obesity might increase the risk of developing hypertension in obese subjects. An elevated PRA may precede the development of hypertension in obese subjects who are at risk for developing hypertension.

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**Keywords: Obesity, hypertension, family genetics, renin–angiotensin system.**

## Introduction

The relationship between blood pressure and obesity has long been recognized [1–3]. A weight gain has been reported in some prospective studies to be positively associated with future blood pressure level [4]. However, lean hypertensives may also be subject to the subsequent development of obesity [1].

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Some studies [5,6] have indicated that a positive family history of hypertension can predispose to the development of hypertension. It has also been reported [7] that blood pressure correlates well between blood relatives and poorly between spouses and between parents with adoptive offspring. A study of twins [8] has emphasized the importance of genetic factors on the pathogenesis of hypertension. However, indices of insulin and lipid metabolism [9], sodium-regulating hormones [10], renal function [11] and left ventricular structure and function [12] may be altered early in the course of hypertension. Indeed, these findings have raised the possibility that measurable metabolic, hormonal and cardiovascular changes may precede the increase in blood pressure [10].

Moreover, genetic and environmental contributions to obesity have been investigated using a variety of study designs, including monozygotic or dizygotic twin pairs, or both [13], multiple biologically related family members [14] and adopted families [15]. An increase in body weight is among the environmental factors which have been reported to be related to familial aggregation of blood pressure [10,14]. However, the significance of this association may be confounded by the fact that the familial resemblance of body weight appears to be determined as genetically as that of blood pressure [14].

Although hypertension in obese subjects might be considered as a distinct type of hypertension [16], no study has addressed the influence of heredity on the mechanisms responsible for this strong association (between hypertension and obesity). Kawabe *et al.* [17] recently reported a significant correlation between body weight or body mass index and home systolic blood pressure (SBP) in subjects with a family history of hypertension. To explain this finding, those authors suggested that it is possible that several of the offspring of hypertensive parents also had a positive family history of obesity.

Searching for hereditary or familial defects that may underlie essential hypertension, it is plausible to evaluate currently normotensive obese offspring of hypertensive parents, some of whom could be in a prehypertensive stage.

In the present study we evaluated casual and 24-h blood pressure, left ventricular mass (LVM) and some metabolic and hormonal measurements in healthy normotensive obese offspring of hypertensive and of normotensive parents. To strengthen the role of family history on obesity-induced hypertension, both groups were also subgrouped according to the positive or negative family history of obesity.

## Subjects and methods

### Subjects

Two groups of consecutive normotensive obese subjects were studied. One group included offspring of normotensive families, the other consisting of offspring having one parent with essential hypertension. Subjects were considered eligible for the study if their age was <40 years, with body mass index >30 kg/m$^2$ for males and >27.3 kg/m$^2$ for females, according to the cutoff values reported at the Italian Consensus Conference on Obesity [18], with blood pressure consistently below 140/90 mmHg, and if they were not taking any drugs.

Physical health was assessed by routine clinical examination. Thereafter, informed consent was obtained to assess the family history of essential hypertension and obesity. Subjects with an uncertain family history of hypertension or obesity, or both, and with parents or siblings with diabetes mellitus type I or II, were excluded from the study. All subjects with cardiovascular or endocrine diseases, renal impairment, psychiatric problems or alcoholism were also excluded from the study.

Data on the presence or absence of hypertension or obesity, or both, in parents and siblings were obtained according to the methodology described by Hunt *et al.* [19]. However, to avoid bias the family history information was in all cases collected by physicians who were unaware of the purpose and the results of the study. The following procedure was used.

Information on blood pressure and body weight, the use of antihypertensive drugs or hypo-energetic diet and cardiovascular complications in parents and siblings was obtained from the family physician and, in essential hypertensive and obese parents attending our clinic as regular outpatients, also from the clinic records. The historical information was further validated by direct questioning of all parents. The blood pressure, body weight, body height, body mass index and body fat distribution of the parents were determined by one of the authors. In the hypertensive and in the obese parents, secondary forms of these conditions were excluded by clinical examination and specific laboratory investigations.

A negative family history of essential hypertension and obesity was recorded when neither parent and none of the siblings of the subjects had experienced any previous episode of high blood pressure or weight gain, myocardial or cerebral ischaemic disease, their current blood pressure was normal and body mass index values were <25 kg/m$^2$ for males and <24.7 kg/m$^2$ for females. From 95 subjects who fulfilled the eligibility criteria, 14 were excluded because of an uncertain family history of essential hypertension or obesity, or both. Therefore, 81 obese normotensive subjects were studied. They were grouped as follows.

*Group 1*

Group 1 consisted of offspring of parents with essential hypertension, and contained 45 subjects (20 male, 25 female; mean±SD age 38.2±2.3 years), 25 (11 male, 14 female) having a positive (subgroup A) and 20 (nine male, 11 female) having a negative family history of obesity (subgroup B). All subjects with a positive family history had one parent with essential hypertension or obesity, or both. The mean±SD untreated

blood pressure in the hypertensive parents averaged 180±5/110±2 mmHg, and the mean±SD waist:hip ratio in the parents was 0.93±0.06.

*Group 2*

Group 2 consisted of offspring of parents without essential hypertension, and contained 36 subjects (17 male, 19 female; mean±SD age 37±3.5 years), 19 (nine male, 10 female) having a positive (subgroup C) and 17 (eight male, nine female) having a negative family history of obesity (subgroup D). The current mean±SD blood pressure in the normotensive parents averaged 125±2/77±1 mmHg, and the mean±SD waist:hip ratio in the parents was 0.92±0.07.

Of the 45 obese subjects in group 1, 30 had one hypertensive parent and 15 had two hypertensive parents. Of the 44 obese subjects with positive family history of obesity, 29 had one obese parent and 15 had two obese parents. None of the subjects were adopted offspring.

We did not subgroup the subjects according to the presence or absence of one or both parents with essential hypertension or obesity, because the groups were too small for further subgrouping.

## Methods

All subjects gave informed consent to undergo the following investigations. The present study was also approved by the Ethics Committee of the University of Palermo.

*Anthropometric measurements*

Body weight was measured with the subjects lightly dressed, using a level balance, to the nearest 0.1 kg. Body height was measured without shoes and to the nearest 0.5 cm. Body mass index was calculated as weight (in kg)/[height (in m)]$^2$. The waist:hip ratio was determined as the ratio of the waist circumference at the umbilical level to the hip circumference at the level of the anterior iliac spine in the standing position [20,21], according to the World Health Organization recommendation. Following the recommendations of the Italian Consensus Conference on Obesity [18], waist:hip ratio values ≥0.81 for females and ≥0.92 for males indicated a central fat distribution. Conversely, a peripheral fat distribution was considered when the respective ratios were <0.81 and <0.92. The waist:hip ratio has been reported to be both a useful index to measure the body fat distribution and a reliable predictor of upper or lower obesity [18,22]. It has also been associated with the risk of cardiovascular disease in a large epidemiological study [22].

The duration of obesity was calculated by accurate history-taking as reported previously [16,20,21,23].

*Casual and 24-h blood pressures*

The casual SBP and diastolic blood pressure (DBP) were measured in triplicate, using a mercury sphygmomanometer, with the subject supine. Casual DBP refers to the Korotkoff phase V. The casual mean blood pressure (MBP) was calculated as casual DBP + 1/3(arterial pulse pressure).

Arterial pressure was measured with an appropriate large cuff in all subjects [20,21,23,24]. Heart rate was evaluated by electrocardiogram.

Ambulatory blood pressure was recorded by the portable fully automatic Takeda TM2420 system (A & D Co. Ltd, Tokyo, Japan) connected through the serial interface (RS232) to an IBM personal system 2 computer, which in our laboratory showed a correlation of r=0.96 with both casual SBP and casual DBP [25]. The reading, editing and summary analysis of data provided by the unit were done by dedicated software. The unit was set to take readings automatically every 20 min throughout the 24-h period. This approach was tolerated well by all of the subjects who were recruited.

The 24-h mean SBP, DBP and mean blood pressure (MBP) were calculated. Criteria for deleting individual blood pressure readings included a pulse pressure of <12 mmHg or an inconsistent increase and decrease in SBP or DBP of >30 mmHg from previous or subsequent readings.

Recordings were included in the study only if at least 80% of the maximal number of 72 readings during the 24-h period passed the deletion criteria.

Journals of activity, symptoms and emotions were carefully kept by the subjects for aid in the editing process.

*Left ventricular mass*

LVM and LVM:height ratio were calculated by echocardiographic findings as reported previously [24].

Two-dimensional and M-mode echocardiographic examination was performed, using an Esaote Biomedica computer-aided ultrasound system (Cansalop SpA, Florence, Italy) equipped with 2.5- and 3.5-MHz phased-array transducers, and a standard VHS video system was used to record the signal. Echocardiograms were analysed by one reader with no knowledge of either the clinical data or the study group of which the subject was a member.

*Analytic methods*

Venous blood samples were drawn after an overweight fast for determination of fasting blood sugar, total cholesterol, triglycerides, immunoreactive insulin and ANF levels, plasma renin activity (PRA), and plasma aldosterone and plasma catecholamines levels. All blood samples were collected on ice, the plasma then being separated and frozen until assay.

Fasting blood sugar was measured in triplicate with an autoanalyser (model AA II; Technicon Corporation, Tarrytown, New York, USA) by the glucose oxidase technique. Serum total plasma cholesterol and triglycerides levels were measured by enzymatic methods (Boehringer–Mannheim, Mannheim, Germany).

### Insulin
Immunoreactive insulin levels were detected by the radioimmunoassay double-antibody method using a commercial kit (Sorin Biomedica SpA, Saluggia, Italy). The intra-assay variation was 7.5% and the interassay variation 8%. The sensitivity for detection of insulin was 17 pmol/l. The insulin : glucose ratio was also calculated.

### Plasma catecholamines
Samples were prepared and assayed by high-performance liquid chromatography as described by Goldstein *et al.* [25]. The sensitivity for detection of noradrenaline was 0.08 nmol/l and for adrenaline 136 pmol/l.

### Atrial natriuretic factor
Plasma ANF levels were determined by radioimmunoassay as described previously by Volpe *et al.* [26], using rabbit antiserum (RAS 8978; Peninsula Laboratories Inc., Belmont, California, USA), iodinated human ANF ($7.4 \times 10^{13}$ Bq/mmol: Amersham International plc, Little Chalfont, Buckinghamshire, UK) and α-human ANF (Bissendorf GmbH peptide, Wedemark, Germany) as a standard. ANF was extracted from plasma with Sep-Pak cartridges (Waters Associates Inc., Milford, Massachusetts, USA). The recoveries were determined on each plasma sample by adding to it a minimal amount of radiolabelled ANF, ranging from 74 to 90%.

The intra-assay and interassay coefficients of variation were 6.5 and 10.5%, respectively. The radioimmunoassay sensitivity was 1 fmol/tube.

### Plasma renin activity and plasma aldosterone
PRA and plasma aldosterone levels were measured by radioimmunoassay using a commercial kit (Sorin Biomedica SpA). The samples for PRA and plasma aldosterone evaluation were obtained with the subject upright and walking for 1 h.

The intra-assay variations were 5% for PRA and 9.5% for plasma aldosterone, and the respective interassay variations were 7 and 11.2%. The sensitivities of the methods were 0.03 ng/l per s for PRA and 40 pmol/l for plasma aldosterone.

### Urinary sodium excretion
To evaluate the urinary sodium excretion, three consecutive 24-h urine collections were used. Values used are the mean values of the three determinations. The sodium levels in urine were measured by the standard ion-selective electrodes method (Beckman).

### Statistical analysis
One-way analysis of variance for comparison of means and the Student–Neumann–Keuls *post hoc* test for comparison of subgroups were performed. A multivariate analysis of variance was performed using a full factorial model. We used PRA, plasma insulin, left ventricular mass and mean 24-h blood pressure as the dependent variables. A family history of hypertension and of obesity were entered as categorical predictor variables. Each factor was transformed into deviation contrasts. Finally, BMI, waist : hip ratio and age were used as covariates. $P < 0.05$ was considered statistically significant. All values are expressed as means ± SD.

## Results
The two groups of obese subjects were comparable in clinical characteristics. No significant differences in age, body weight, body height, waist : hip ratio or duration of obesity were observed. However, body mass index values were significantly ($P < 0.02$) higher in obese subjects with negative family history of hypertension (Table 1).

**Table 1.** Clinical characteristics in normotensive obese subjects with a positive or negative family history of hypertension.

| | Family history of hypertension | |
|---|---|---|
| | Positive | Negative |
| Cases | 45 | 36 |
| Male : female | 20 : 25 | 17 : 19 |
| Age (years) | 38.2 ± 2.3 | 37 ± 3.5 |
| Body weight (kg) | 88.7 ± 20.5 | 97 ± 17 |
| Body height (cm) | 161 ± 9.4 | 161 ± 12 |
| Body mass index (kg/m²) | 33.6 ± 5.4 | 37.2 ± 5.6† |
| Waist : hip ratio (%) | 0.92 ± 0.07 | 0.94 ± 0.08 |
| Duration of obesity (months) | 161.4 ± 94.9 | 182.4 ± 112.9 |
| Blood pressures (mmHg) | | |
| Casual SBP | 127.6 ± 13 | 126 ± 10 |
| Casual DBP | 79.4 ± 9 | 76.4 ± 8 |
| Casual MPB | 93.5 ± 9.3 | 93.1 ± 6.6 |
| 24-h SBP | 116.4 ± 6.3 | 115 ± 6 |
| 24-h DBP | 74 ± 6 | 70 ± 4.5** |
| 24-h MBP | 88 ± 5.3 | 85 ± 3.6† |
| Heart rate (beats/min) | 73.6 ± 5.6 | 72.8 ± 5.8 |
| LVM (g) | 196.3 ± 40 | 153.6 ± 30*** |
| LVM : height ratio (g/m) | 122 ± 50 | 95.4 ± 38* |

Values are expressed as means ± SD. *$P < 0.03$, †$P < 0.02$, **$P < 0.006$, ***$P < 0.001$, versus positive history. SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; LVM, left ventricular mass.

### Normotensive obese offspring of hypertensive parents versus normotensive obese offspring of normotensive parents
In normotensive obese offspring of hypertensive parents 24-h DBP ($P < 0.006$), 24-h MBP ($P < 0.02$), LVM ($P < 0.001$) and LVM : height ratio ($P < 0.03$) were significantly higher than in normotensive obese offspring of normotensive parents (Table 1).

Metabolic and hormonal measurements [total plasma cholesterol ($P < 0.008$) and PRA ($P < 0.001$)] values were also significantly higher in obese offspring of hypertensives (Table 2).

**Table 2.** Metabolic and hormonal measurements in normotensive obese subjects with a positive or negative family history of hypertension.

| | Family history of hypertension | |
|---|---|---|
| | Positive | Negative |
| Cases | 45 | 36 |
| Fasting blood sugar (mmol/l) | 5.2±0.4 | 5.0±0.4 |
| Serum total cholesterol (mmol/l) | 5.1±1 | 4.5±0.7** |
| Serum triglycerides (mmol/l) | 1.4±0.3 | 1.4±0.3 |
| Immunoreactive fasting serum insulin (pmol/l) | 103±63 | 124±53 |
| Insulin : glucose ratio | 19±11 | 22±8 |
| Plasma noradrenaline (nmol/l) | 2.0±0.3 | 1.9±0.5 |
| Plasma adrenaline (pmol/l) | 1032±273 | 928±349 |
| ANF (pmol/l) | 64±19 | 62±18 |
| PRA (ng/l per s) | 0.6±0.05 | 0.5±0.05*** |
| Plasma aldosterone (pmol/l) | 455±79 | 450±88 |
| Urinary sodium excretion (mmol/24 h) | 141.3±63 | 144±58 |

Values are expressed as means±SD. **$P<0.008$, ***$P<0.001$, versus positive history. PRA, plasma renin activity.

## Influence of family history of obesity on normotensive obese offspring of hypertensive parents

Normotensive obese offspring of hypertensives were subgrouped according to the presence or absence of a family history of obesity. The two subgroups were comparable in age, body height, body mass index and waist : hip ratio. However, body weight and duration of obesity were significantly higher ($P<0.05$) in those with than in those without a family history of obesity (Table 3). Twenty-four-hour DBP, 24-h MBP, LVM and LVM : height ratio were significantly higher ($P<0.05$) in those with than in those without a family history of obesity (Table 3). Also, immunoreactive insulin, insulin : glucose ratio and PRA values were significantly higher ($P<0.05$) in those with than in those without a family history of obesity (Table 4).

## Influence of family history of obesity on normotensive obese offspring of normotensive parents

Normotensive obese offspring of normotensive parents were subgrouped to the presence or absence of a family history of obesity. The two subgroups of subjects were comparable in age, body height and waist : hip ratio. However, body weight, body mass index and duration of obesity were significantly higher ($P<0.05$) in those with than in those without a family history of obesity (Table 3).

Twenty-four-hour DBP and 24-h MBP were significantly greater ($P<0.05$) in those with than in those without a family history of obesity (Table 3). Also, fasting blood sugar, immunoreactive insulin, insulin : glucose ratio, PRA, plasma noradrenaline, adrenaline and aldosterone levels were significantly higher ($P<0.05$) in those with than in those without a family history of obesity (Table 4).

## Multivariate analysis

Multivariate analysis indicated that between dependent variables only 24-h MBP and PRA were influenced sig-

**Table 3.** Clinical characteristics in normotensive obese subjects with a positive or negative family history of hypertension subgrouped according to a positive (groups A and C) or negative (groups B and D) family history of obesity.

| | Family history of hypertension | | | |
|---|---|---|---|---|
| | Positive | | Negative | |
| | Group A | Group B | Group C | Group D |
| Cases | 25 | 20 | 19 | 17 |
| Male : female | 11 : 14 | 9 : 11 | 9 : 10 | 8 : 9 |
| Age (years) | 37.6±2 | 38.5±2.1 | 36±3 | 37.9±2.5 |
| Body weight (kg) | 92.6±6.2*† | 83.5±7.1† | 106±17‡ | 84.8±10.3 |
| Body height (cm) | 161.5±10 | 160.5±8.9 | 163±13 | 160±11.6 |
| Body mass index (kg/m$^2$) | 35.7±6† | 32.6±4.7† | 40±3.4‡ | 33.6±6 |
| Waist : hip ratio (%) | 0.94±0.07 | 0.90±0.07† | 0.97±0.07 | 0.91±0.09 |
| Duration of obesity (months) | 203±90*† | 99.2±58.9† | 237±92‡ | 109.5±100 |
| Blood pressures (mmHg) | | | | |
| Casual SBP | 128.6±13.8 | 126.2±13.8 | 128±11.6 | 124±8.6 |
| Casual DBP | 78.6±11.2 | 80.3±5.7 | 79.1±8.6 | 75±7.6 |
| Casual MBP | 95.3±11 | 95.6±7.1 | 94.4±7 | 92±6.6 |
| 24-h SBP | 117±7 | 115.6±5.5 | 116±5.3 | 114±7.7 |
| 24-h DBP | 76±5.7*‡ | 72±5‡ | 73±2.7‡ | 68±4.8 |
| 24-h MBP | 90.2±5*†‡ | 84±6 | 87±3.0‡ | 83±3.3 |
| Heart rate (beats/min) | 73±6 | 74.5±5 | 73.2±4.1 | 72.1±8 |
| LVM (g) | 210±46*†‡ | 172±45.6 | 155±54 | 150.5±54 |
| LVM : height ratio (g/m) | 130±32*†‡ | 105±27 | 95.1±31.5 | 94.1±30 |

Values are expressed as means±SD. *$P<0.05$, versus group B; †$P<0.05$, versus group C; ‡$P<0.05$, versus group D (all by Neumann–Keuls *post hoc* test). SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; LVM, left ventricular mass.

**Table 4.** Metabolic and hormonal measurements in normotensive obese subjects with a positive or negative family history of hypertension subgrouped according to positive (groups A and C) or negative (groups B and D) family history of obesity.

| | Family history of hypertension | | | |
|---|---|---|---|---|
| | Positive | | Negative | |
| | Group A | Group B | Group C | Group D |
| Cases | 25 | 20 | 19 | 17 |
| Fasting blood sugar (mmol/l) | 5.1±0.2‡ | 5.2±0.3‡ | 5.2±0.3‡ | 4.8±0.4 |
| Total serum cholesterol (mmol/l) | 5.2±1† | 4.9±0.7 | 4.5±0.8 | 4.5±0.7 |
| Serum triglycerides (mmol/l) | 1.3±0.5 | 1.5±0.9 | 1.4±0.3 | 1.4±0.2 |
| Immunoreactive fasting serum insulin (pmol/l) | 126±72*† | 74±32† | 153±49‡ | 86±27 |
| Insulin : glucose ratio | 25±16* | 14±6† | 29±6‡ | 18±10 |
| Plasma noradrenaline (nmol/l) | 2.0±0.3 | 2.0±0.4 | 2.1±0.5‡ | 1.7±0.3 |
| Plasma adrenaline (pmol/l) | 1064±306 | 982±235 | 1228±393‡ | 780±246 |
| ANF (pmol/l) | 67±10† | 62±14† | 99±42‡ | 77±14 |
| PRA (ng/l per s) | 0.7±0.08*‡ | 0.5±0.05† | 0.6±0.08‡ | 0.4±0.08 |
| Plasma aldosterone (pmol/l) | 494±70† | 432±77† | 580±88‡ | 330±90 |
| Urinary sodium excretion (mmol/24 h) | 149±75 | 131±46 | 157±60 | 127±47 |

Values are expressed as means±SD. *$P<0.05$, versus group B; †$P<0.05$, versus group C; ‡$P<0.05$, versus group D (all by Neumann–Keuls *post hoc* test). PRA, plasma renin activity.

nificantly ($P<0.01$) by the association of a positive family history of hypertension and a positive family history of obesity. These relationships remained independent when age, BMI and waist : hip ratio were considered in the analysis.

## Discussion

The present study was the first to analyse contemporaneously the role of a family history of both hypertension and obesity on the mechanisms responsible for obesity-associated hypertension.

Our data indicate that normotensive obese offspring of hypertensive parents were characterized by higher blood pressure values than those in comparable obese offspring of normotensive parents. The concomitant presence of a positive family history of obesity appears to strengthen this finding.

Also, 24-h DBP and MBP were higher in the subjects with a positive family history of obesity, independently of the family history of hypertension. Moreover, a family history of obesity might be predictive of the metabolic and hormone changes responsible for obesity-associated hypertension. This finding seems interesting, and is consistent with other data indicating that body weight might play a more important role for the prediction of baseline blood pressure level, rather than family history of hypertension [10].

Watt *et al.* [27] have also reported that an increasing blood pressure would be anticipated especially in subjects with a positive family history of hypertension and a considerable weight gain.

It has been emphasized that some data [6] indicate that a positive family history of hypertension on the mother's side might be of greater pathogenic importance than a positive history on the father's side. Because of the small numbers of subjects, we were unable to analyse this in the present study. More studies are needed to address this question. However, some studies [28–30] have suggested that a family history of hypertension may be predictive of the endocrine and metabolic changes that characterize hypertension, even in the absence of increased blood pressure. In the present study obese offspring of parents with hypertension and obesity were characterized by increased PRA and LVM. Also, higher blood pressure values were associated with increased levels of plasma insulin or insulin : glucose ratio, catecholamines and ANF in those subjects. However, the differences in these last variables do not appear to be related to a positive family history of hypertension, but may represent the secondary effects of obesity [3,31,32]. In fact, all these measurements were significantly higher in the obese subgroup characterized by negative family history of hypertension and positive family history of obesity.

It is therefore necessary to emphasize that we excluded from the present study all obese subjects with a familial predisposition to diabetes, because it is known well that there are common elements involved in the risk factors for diabetes, obesity and hypertension [3,18,29,32,33]. Moreover, it has recently been reported by Warram *et al.* [33] that obese offspring with diabetic parents had fasting and stimulated insulin levels that were almost double those found in comparable obese control subjects. Accordingly, a genetic predisposition to diabetes may modify the association between obesity and insulin resistance, so that obese subjects with these genes are more resistant to insulin than obese subjects without this predisposition.

Conversely, PRA levels were higher both in obese offspring of parents with both hypertension and obesity, and in obese offspring of normotensive but obese parents. Both of these subgroups had higher 24-h DBP and 24-h MBP than their control subjects with non-obese

parents. This finding was also supported by multivariate analysis, indicating that the association between a family history of hypertension and obesity can influence 24-h MBP and PRA levels in these subjects. These data are consistent with the results of Ravogli *et al.* [34] and with those reported by Grim *et al.* [35], indicating that subjects who can be considered to be in a prehypertensive condition, such as offspring of hypertensive parents, had higher 24-h blood pressure and renin levels and decreased natriuretic responses to a saline load. The possibility that these genetic influences may act through the renin–angiotensin system was supported by a study of renal haemodynamics in children of normotensive and hypertensive parents [36]. Other data indicate that abnormalities in the renin–angiotensin system may help to explain the genetic predisposition to high blood pressure [27].

In addition, our previous data [37,38] indicated that an altered response of salt-regulating hormones to saline loading might be related to the higher susceptibility of obese subjects to developing hypertension.

More specifically, in normotensive obese subjects the major physiological adjustments occurring to an acute saline load, namely suppression of PRA and plasma aldosterone levels and increased urinary sodium excretion values, were found to be significantly smaller and delayed compared with those found in matched lean subjects. The physiological secretory response of ANF promoted by a saline load in lean subjects was not detectable in obese subjects. In fact, ANF levels were slightly reduced in normotensive obese subjects [37].

PRA has also been reported to be an independent variable that may influence blood pressure in hypertensive subjects with central obesity [38].

In our opinion the results of the current study may be very important in view of the fact that higher PRA values are associated with an increased risk of myocardial infarction in hypertensive subjects [39].

Moreover, obese offspring of parents who are both hypertensive and obese had an increased LVM. This finding has been reported frequently in the offspring of hypertensive parents [10,12,34,40–42]. Accordingly, some of these data indicated that an increased 24-h blood pressure was accompanied by early cardiovascular structural changes [34,41] and that initial modifications in left ventricular structure were related to exercise blood pressure and should represent a specific marker for normotensive subjects with hypertensive parents [12,40]. Also, the hypertension in pregnancy offspring study has recently reported [42] that blood pressure in children predicts their future blood pressure, and that an early increased LVM is an independent predictor of increased LVM in adolescence.

Our data therefore suggest that the association between a family history of hypertension and obesity may impair the cardiovascular risk habitus of these subjects. However, the increase in LVM was not correlated with a family history of obesity in obese subjects who had no family history of hypertension. This might indicate that increased LVM is more strongly dependent on a family history of hypertension than on a family history of obesity.

In conclusion, the present results suggest that a family history of obesity might increase the risk of developing hypertension in obese subjects. Also, elevated PRA levels may precede the development of hypertension in these subjects. Accordingly, it is possible to recognize a particular subset of obese subjects at high risk of developing hypertension. These could be characterized by a positive family history of both hypertension and obesity and high PRA levels. However, additional prospective data need to be provided to prove whether this is the case.

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