Central Obesity and Hypertension
The Role of Plasma Endothelin

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Hypertension and central obesity are two conditions closely linked, but the mechanisms responsible for obesity-associated hypertension are still unclear. In the last few years, several studies addressed the role of endothelin-1 (ET-1) in the development and maintenance of hypertension. This study was designed to evaluate plasma ET-1 in normotensive and hypertensive central obese subjects compared with a lean healthy group. Our final goal was to analyze the relationship between plasma ET-1, blood pressure, and left ventricular structure and function in central obese subjects (both normotensives and hypertensives). ET-levels have been assessed by the radioimmunoassay method in 20 lean normotensives and in 57 central obese subjects; 30 of them were hypertensives and 27 of them were normotensives. Twenty-four-hour mean blood pressure (MBP/24 h) by noninvasive ambulatory blood pressure monitoring, left ventricular mass/height (LVM/H), and left ventricular ejection fraction (LVEF) by echocardiography and peak filling rate (PFR) by radionuclide study were also measured. ET levels were significantly ($P < .05$) higher in obese hypertensives and obese normotensives than in lean normotensives. In addition, ET levels were significantly ($P < .05$) higher in obese hypertensives than in obese normotensives. ET were directly related to LVM/H ($r = 0.86$; $P < .001$) and MBP/24 h ($r = 0.48$; $P < .009$) but only in obese hypertensives. Multiple regression analysis indicated that ET-1 plasma levels remain an independent predictor of MBP/24 h and LVM/H also when age was included in the analysis. These data suggest that obesity-associated hypertension is characterized by an endothelial dysfunction that may contribute to the higher cardiovascular risk detectable in these patients. © 1996 American Journal of Hypertension, Ltd. **Am J Hypertens 1996;9:1186–1191**

KEY WORDS: **Obesity, central fat distribution, hypertension, endothelin.**

Hypertension and obesity are disorders that are closely linked, especially when obesity is characterized by central fat distribution.[1,2] Although this strong association, the mechanisms of obesity-associated hypertension are still unclear.[2–4] Some abnormalities have been recently reported to explain the higher susceptibility of obese subjects to develop hypertension. They include increased plasma volume and cardiac output,[4] hyperinsulinemia, and insulin-resistance,[5,6] enhanced sympathetic nervous system activity,[7] sodium retention and dysregulation in salt-regulating hormones.[8,9] In addition, recent our data indicated that an impaired homeostatic function may be early detectable in central obese subjects.[10] On the other hand, hypertension is characterized by altered hemodynamic balance, in particular, increased peripheral vascular resistances. The discovery that endothelial cells also secrete potent vasoactive substances, such as endothelin (ET), further supports the concept that the endothelial organ may play

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an important role in hypertension both as a mediator and target of the disease.[11] In the last years, several studies addressed the role of endothelin-1 (ET-1) in the development and maintenance of hypertension.[12–14] Several factors including arginine-vasopressin, angiotensin II, and insulin stimulate the release of ET-1, whereas others inhibit the production of this vasoconstricting hormone.[15] Although these evidences, little is known about the relationship between central fat distribution and ET release in obesity-associated hypertension.

This study was designed to evaluate plasma ET-1 in normotensive and hypertensive central obese subjects compared with a lean healthy group. Our final goal was to analyze the relationship between plasma ET-1, blood pressure and left ventricular structure and function in central obese subjects both normotensives and hypertensives.

SUBJECTS AND METHODS

Subjects A total of 77 subjects, 57 with central obesity and 20 lean healthy controls, all younger than 40 years, were included in this study. Obese subjects were recruited from the obese population attending the obesity center of the Internal Medicine Department at the University of Palermo (Italy). Lean normotensives were volunteer subjects chosen from a group of subjects undergoing a clinical check-up and found to be healthy. The subjects were considered as obese according to gender-specific 85th percentile of body mass index (BMI) values proposed by the Italian Consensus Conference on Obesity.[16] The cut-off value for obesity was $\geq$30.5 kg/m^2 for men and $\geq$27.3 kg/m^2 for women. Lean subjects were selected on the basis of BMI values of less than 25 kg/m^2 for men and 24.7 kg/m^2 for women.[16,17] Each subject's fat distribution was assessed by measuring the waist-to-hip ratio (WHR) in the standing position, as previously reported.[17,18] Central fat distribution was defined on the basis of gender-specific 85th percentile of WHR values.[16] The cut-off value of central obesity was considered $\geq$ 0.81 for women and $\geq$ 0.92 for men.[16] According to JNC-V criteria,[19] essential hypertension was defined by a diastolic blood pressure $\geq$90 mm Hg with the subjects in the supine position on at least three visits at 1-week intervals. Arterial pressure was measured with an appropriate large cuff in obese subjects.[2,17,18]

All the subjects included in the study were subdivided as follows: 1) Lean normotensives. This group consisted of subjects (10 men and 10 women) aged 29 to 39 years (mean age 34 $\pm$ 5 years) with a BMI mean value of 22 $\pm$ 1.5 and WHR mean value of 0.87 $\pm$ 0.07. 2) Obese normotensives. This group consisted of subjects (13 men and 14 women) aged 30 to 39 years (mean age 37 $\pm$ 2 years) with a BMI mean value of 34 $\pm$ 5 and WHR mean value of 0.94 $\pm$ 0.07. 3) Obese hypertensives. This group consisted of subjects (14 men and 16 women) aged 33 to 39 years (mean age 37 $\pm$ 2 years) with a BMI mean value of 35 $\pm$ 7 and WHR mean value of 0.95 $\pm$ 0.06. All the groups were comparable with regard to age, gender, and height. Both obese groups were comparable with regard to BMI and WHR. Both normotensive groups were comparable with regard to casual mean blood pressure (MBPc).

Exclusion criteria comprised severe hypertension, cardiovascular and renal diseases, insulin-dependent or -independent diabetes mellitus, hyperlipoproteinemia, electrolyte imbalances, smoking habit, alcoholism, or psychiatric problem. 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.

Laboratory Methods *Casual and 24-h Blood Pressure* The casual systolic (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 MBPc was calculated as casual DBP + $^1/_3$ arterial pulse pressure.

Heart rate was evaluated by electrocardiogram.

Ambulatory blood pressure was recorded by the portable, fully automatic Takeda TM 2420 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.[20] 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 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 mm Hg or an inconsistent increase and decrease in SBP or DBP $>$ 30 mm Hg 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 and Function Left ventricular mass (LVM) and LVM: height ratio (LVM/H) were calculated by echocardiographic findings as reported previously.[21]

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 analyzed by one reader with no knowledge of either the clinical data or the study group of which the subjects was a member.

Left ventricular ejection fraction (LVEF) and peak filling rate (PFR) were calculated by radionuclide angiography according to Bonow method.[22] This method is currently utilized in our laboratory also in obese subjects.

Analytic Method Venous blood samples were drawn after an overnight fast for determination of plasma ET-1.

Radioimmunoassay method, after extraction, was used to measure plasma ET-1. The antibody used has 100% cross-reactivity with ET-1 and the intra- and interassay variation was 4.5% and 6.8%.[23]

Statistical Analysis Differences among the groups were analyzed by one-way analysis of variance and Student-Newman-Keuls post hoc test.

Linear and multiple regression analyses were used to determine coefficients of correlation among plasma ET-1 levels and all measurements we have detected. All data are expressed as mean value ± standard deviation. A $P < .05$ was considered statistically significant.

RESULTS

Characteristics of Lean and Obese Subjects The three groups were comparable with regard to gender, age and body height. Lean and obese normotensives were also comparable with regard to casual and 24-h mean blood pressure. Both obese groups were comparable for BMI and WHR (Table 1).

Obese Versus Lean Subjects ET-1 levels were significantly higher ($P < .05$) in obese normotensives and hypertensives than in lean controls. LVM/H were significantly higher ($P < .05$), and LVEF and PFR were significantly lower ($P < .05$), in both obese groups than in lean controls. Heart rate (HR) was significantly higher ($P < .05$) only in obese hypertensives than in lean controls (Table 1).

Obese Normotensives Versus Obese Hypertensives ET-1 levels, MBPc, MBP/24-h were significantly higher ($P < .05$), and LVEF and PFR were significantly lower ($P < .05$), in obese hypertensives than in obese normotensives (Table 1).

Correlations In all the obese subjects ET-1 correlated directly with MBP/24-h ($r = 0.40$; $P < .05$) and with LVM/H ($r = 0.48$; $P < .05$), but these relations remained significant only in obese hypertensives (respectively $r = 0.48$, $P < .009$ and $r = 0.86$, $P < .001$) when linear regression analysis was made separately in both groups (Figures 1 and 2). No correlation was found between ET-1 and the remaining measurements we have detected.

TABLE 1. DETAILS OF GROUPS

	Lean Controls	Obese Normotensives	Obese Hypertensives
Cases (n)	20	27	30
Gender (M/F)	10/10	13/14	14/16
Age (yrs)	37 ± 2	34 ± 6	37.5 ± 4
Height (cm)	166 ± 9	161 ± 11	160 ± 9
BMI (kg/m^2)	22 ± 1.5	34 ± 5*	35 ± 7*
WHR (%)	0.87 ± 0.07	0.94 ± 0.07*	0.95 ± 0.06*
ET-1 (pg/mL)	3.5 ± 1.3	5 ± 2.6*	8.4 ± 2.5*†
MBPc (mm Hg)	93 ± 7	94 ± 8	121 ± 10*†
MBP/24 h (mm Hg)	84 ± 4	87 ± 5	109 ± 15*†
LVM/H (g/cm)	81 ± 25	111 ± 41*	127 ± 31*
LVEF (%)	65 ± 2	61 ± 5*	58 ± 5*†
PFR (EDV/sec)	3.6 ± 0.2	2.9 ± 0.6*	2.7 ± 0.6*†
HR (beats/min)	71 ± 4	72 ± 4	76 ± 10*†

BMI, body mass index; WHR, waist to hip ratio, ET-1, endothelin-1; MBPc, casual mean blood pressure; MBP/24 h, 24-h mean blood pressure; LVM/H, left ventricular mass/height; LVEF, left ventricular ejection fraction; PFR, peak filling rate; HR, heart rate.

* P < .05 v *lean controls.*

† P < .05 v *obese normotensives.*

Multiple Regression Analysis Multiple regression analysis indicated that ET-1 levels remain an independent predictor of MBP/24-h and LVM/H also when age was included in the analysis.

DISCUSSION AND CONCLUSION

Our study demonstrated that plasma ET-1 levels were significantly higher in normotensive and hypertensive obese subjects than in lean controls, and in hypertensive than in normotensive central obese subjects. Moreover, circulating ET-levels correlated with MBP/24-h and LVM/H but only in hypertensive obese subjects. These results are consistent with the indication that endothelial dysfunction may be early detectable in central obese subjects. It appears to be involved in the pathophysiology of obesity-related hypertension and it is associated to clearcut markers of cardiovascular damage in hypertensive central obese subjects.

On the other hand, Miyauchi et al[13] have recently reported an age–sex related variation of plasma ET-1 concentration in normotensive and hypertensive subjects. According to these results, our subjects have been matched for age and sex to eliminate these misleading factors. To our knowledge, this study is the first to analyze relationship between plasma ET, blood pressure and left ventricular structure and function in central obese subjects. In view of this, it has to be emphasized that central obese subjects may be considered at higher

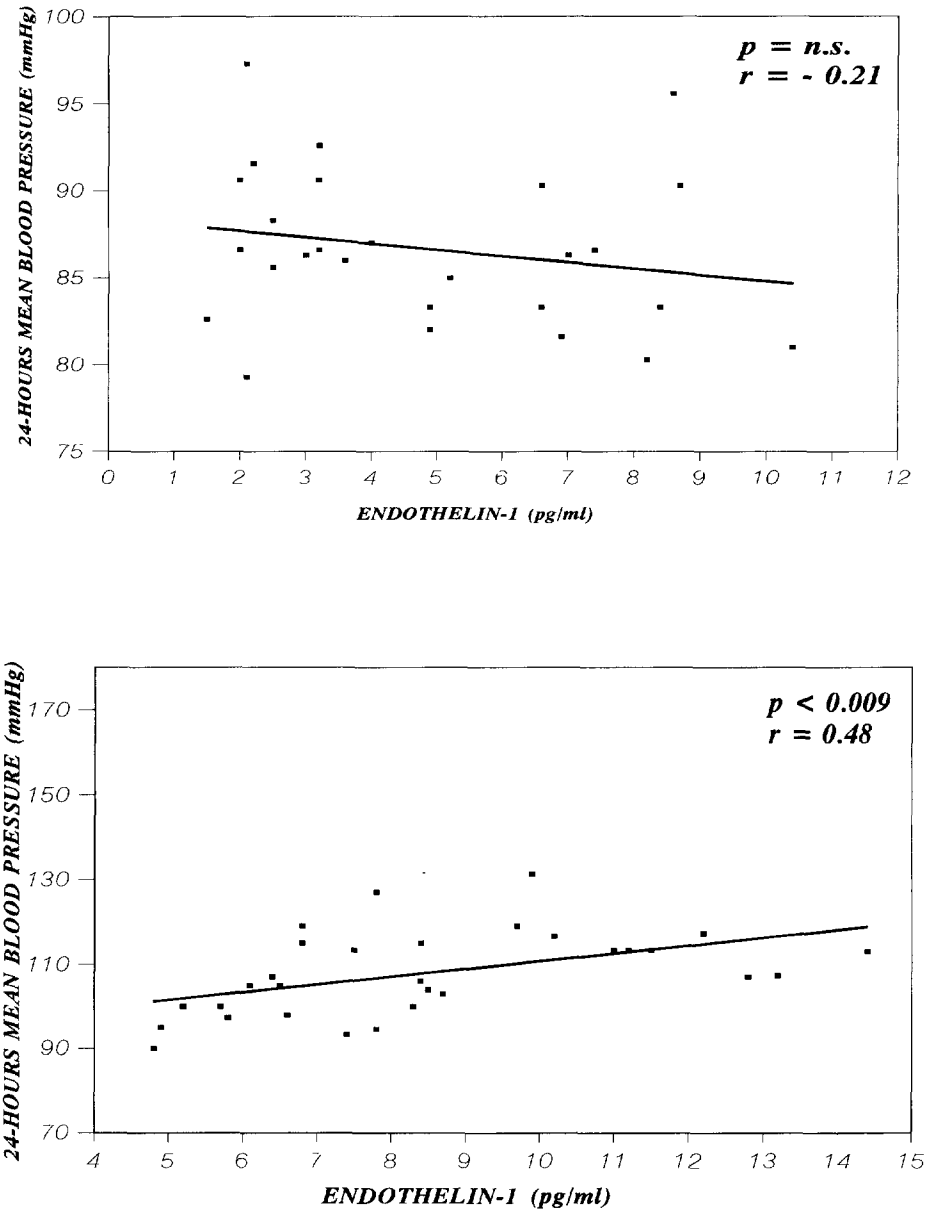
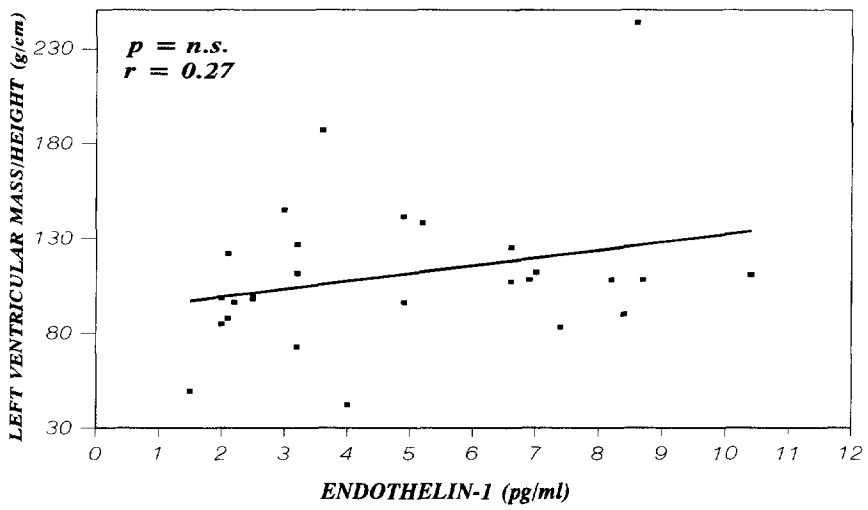


FIGURE 1. *Relationship between endothelin-1 and 24-h mean blood pressure in normotensive (***upper panel***) and hypertensive (***lower panel***) central obese subjects.*

risk to developing hypertension and cardiovascular disease.[1,10,20,24,25] In fact, in these subjects it is possible to detect an atherogenic lipidic profile, a prothrombotic and hypofibrinolitic pattern, and silent left ventricular dysfunction.[10,17,18,24] Other our previous data indicated an important role attributable to salt regulating hormone,[9] renin-angiotensin system, and renal hemodynamics[9,15,25] in obesity-associated hypertension. On the other hand, the role of ET-1 in the determination of increased systemic and regional vascular resistances has been well reported.[15] Accordingly, increased ET levels might be related to the mechanisms of obesity-associated hypertension. In fact, they were higher in both obese groups than in lean controls, but also in obese hypertensives than in obese normotensives. The detection of higher ET-1 levels in normotensive central obese subjects than in lean controls is consistent with our indication that normotensive central obese subjects might be considered in a prehypertensive condition.[25] This finding was further supported by the fact that an association between family history of obesity and hypertension may strengthen the risk to developing hypertension in these subjects.[20] Relationships found by us between ET levels and MBP / 24-h and LVM / H in hypertensive obese subjects are consistent with the suggestion that increased ET levels may be associated with cardiovascular damage in these subjects.[11,26] In fact, it is well known that MBP / 24-h and LVM values are the most important predictors of cardiovascular damage in hypertensive subjects.[27] Moreover, this hypothesis was



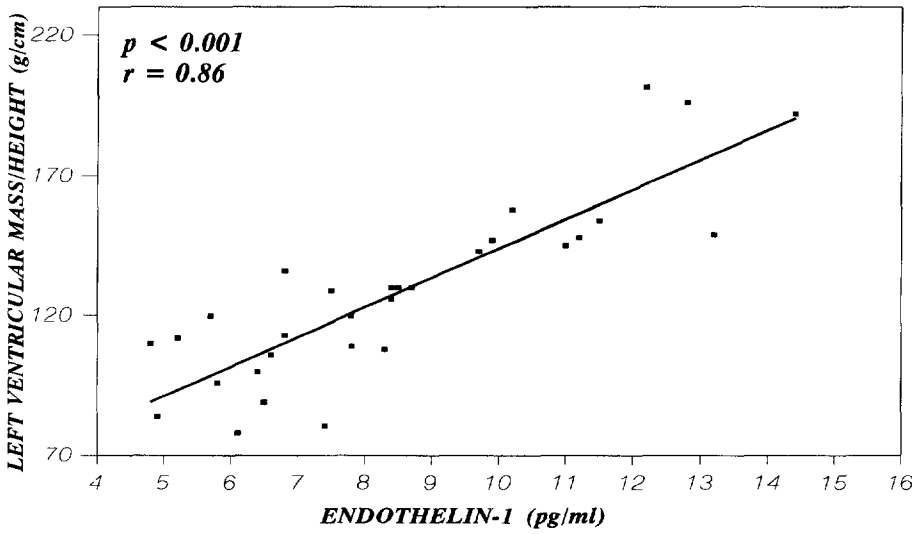


FIGURE 2. *Relationship between endothelin-1 and left ventricular mass/height in normotensive (***upper panel***) and hypertensive (***lower panel***) central obese subjects.*

further supported by multiple regression analysis indicating an independent role of ET-1 levels to influence MBP / 24-h and LVM / H values in obese hypertensives. The role of ET-1 on vascular damage has been well investigated in the last years, and it has been reported that ET levels are higher in patients with acute myocardial infarction,[28] vasospastic angina,[29] and subarachnoid hemorrhage.[30] The mechanisms responsible for elevated plasma ET levels in normotensive and hypertensive central obese subjects remain unknown. This might be related to some abnormalities detectable early in normotensive and hypertensive central obese subjects, contributing to the higher cardiovascular risk in these subjects and able to interact with ET-1 release.[15] They include insulin resistance and hyperinsulinemia,[6] enhanced adrenergic activity,[7] and dysregulation in the renin-angiotensin system.[2,9] In conclusion, our results indicate that endothelial dysfunction may be considered an important contributing factor to the obesity-associated hypertension and an early marker of cardiovascular damage in hypertensive central obese subjects. Of course, if it is the case, it has to be investigated by a prospective study to evaluate whether a higher incidence of events may be recognized in central obese subjects with higher ET plasma levels.

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