Early Upregulation of Endothelial Adhesion Molecules in Obese Hypertensive Men

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Abstract—Upregulation of endothelial adhesion molecules is the earliest step of atherogenesis. Whether obesity induces endothelial adhesin upregulation is unknown. To address this topic, circulating vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), E-selectin, and von Willebrand factor (vWF) concentrations were evaluated in 22 obese hypertensive (51.4±4.6 years [mean±SD age]), 19 obese normotensive (50.6±3.8 years), 18 nonobese hypertensive (52.3±3.9 years), and 16 nonobese normotensive (52.4±3.5 years) men without other risk factors or overt atherosclerosis. All measurements were repeated in the obese subgroups after weight loss induced by 12 weeks of caloric restriction. Basal circulating VCAM-1 levels were similar between the 2 obese groups but were higher (P<0.0001) than in the 2 nonobese groups. No differences were found between nonobese hypertensives and normotensives. Serum low density lipoprotein cholesterol was weakly correlated with plasma soluble VCAM-1 levels in pooled, obese subjects (r=0.362, P=0.02). Plasma soluble adhesin and vWF concentrations decreased significantly after weight loss in obese hypertensives (VCAM-1 P=0.03, ICAM-1 P=0.004, E-selectin P<0.0001, and vWF P=0.003) and normotensives (VCAM-1 P=0.003, E-selectin P<0.0001, and vWF P<0.0001). Body mass index was correlated with plasma E-selectin concentrations at baseline and after weight loss in obese hypertensives (r=0.501, P=0.018 and r=0.466, P=0.03, respectively) and obese normotensives (r=0.523, P=0.021 and r=0.460, P=0.05, respectively). In conclusion, our data show that obesity per se induces early endothelial activation in hypertensive and normotensive men. Weight loss counteracted endothelial activation in both obese hypertensive and normotensive men. (Hypertension. 1999;34:568-573.)

Key Words: hypertension □ obesity □ endothelium □ adhesion molecules □ risk factors

Obesity increases the risk of cardiovascular death in adult subjects.1 Although cardiovascular risk factors2 are often present in obese subjects, obesity per se might favor the development of atherosclerosis.2,3 Cardiovascular diseases increase with body weight independent of other risk factors.3 Obesity and central body fat disposition have been correlated with a higher prevalence of cardiovascular death in low-risk subjects.4 The relative risk of cardiovascular death associated with a higher prevalence of cardiovascular death in low-risk subjects.4 The relative risk of cardiovascular death associated with an increment of 1 kg/m² in body mass index (BMI) is 1.10 and 1.08 for adult men and women, respectively.1 Thus, although the influence of other risk factors such as low physical activity and excess alcohol intake2 cannot be excluded, obesity acts as an independent cardiovascular risk factor.

Upregulation of endothelial adhesins of the selectin family5 (E-selectin and P-selectin) and of the immunoglobulin superfamily6 [intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1)] allows the attachment of circulating cells to the endothelium and represents the initiating event in atherogenesis.7,8 Upregulation of adhesin genes leads to the expression of membrane-associated adhesins and release of their soluble forms. Thus, circulating soluble adhesin levels act as markers of in vivo adhesin expression.5–11 Accordingly, plasma soluble E-selectin concentrations were found to be elevated in conditions associated with increased risk for developing atherosclerosis, ie, type 2 diabetes12,13 and hypertension.14 Similarly, plasma soluble VCAM-1, ICAM-1, and E-selectin concentrations were found to be elevated in glucose-intolerant hypertensives.15 Augmented levels of circulating von Willebrand factor (vWF), a marker of in vivo endothelial damage,16 were found in nonatherosclerotic obese persons.17 Furthermore, circulating levels of endothelin-118 and tissue plasminogen activator-119 were increased while endothelium-dependent vasodilation20 was reduced in normotensive obese individuals.

Taken together, the above data support the concept that obesity per se might induce early endothelial activation in humans. In view of the possible relationship between such endothelial activation and obesity, we evaluated circulating

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soluble VCAM-1, ICAM-1, and E-selectin concentrations in low-risk, obese subjects who had no conditions known to affect circulating adhesion levels. Estrogen influence on soluble adhesins21 was excluded by studying a male population. Plasma soluble adhesion levels were assessed both before and after weight loss resulting from caloric restriction. To evaluate the influence of weight loss–related changes in blood pressure modifications, we also studied obese hypertensives before and after the same caloric restriction. Nonobese hypertensive and normotensive groups served as controls.

Methods

Patient Recruitment
The study was conducted in 19 normotensive obese men (mean±SD age, 50.6±3.8 years) and 22 obese male outpatients with untreated essential hypertension (51.4±4.6 years). Most patients had participated in a previous study by our group,18 and we used previously collected, stored plasma samples for this study. After approval from our Ethics Committee, informed consent was obtained from the patients selected for being white, nonsmokers, and with a BMI >30 kg/m2. Glucose tolerance was normal, and serum cholesterol and triglycerides were <5.5 mmol/L and 1.8 mmol/L, respectively. In obese hypertensives and normotensives, supine diastolic blood pressure levels were 95 to 114 mm Hg and <90 mm Hg, respectively, on 4 different visits at 1-week intervals. Serum creatinine was <100 µmol/L, and albuminuria was <20 µg/min. Clinical and ultrasound examinations of neck and limb vessels were normal. Patients with an abnormal electrocardiogram, positive histories of angina or vascular diseases, or a parental history of vascular diseases before the age of 60 were excluded. Patients had no concomitant diseases, allergies, or recent acute infectious or inflammatory diseases.

After recruitment, the outpatients began a weight-maintaining diet for 1 week. Then, after an overnight fast, they were admitted to our unit at 8 AM. A forearm vein was cannulated, and after 1 hour in a supine position, venous blood samples for plasma adhesion and vWF assays were collected in prechilled tubes containing EDTA. Tubes were centrifuged at 3000 rpm and plasma aliquots were stored at −80°C until assayed.

After blood sampling, the patients were given an 800 kcal/d diet for 12 weeks. Then blood sampling for plasma adhesion and vWF assays was repeated. Twenty-four-hour urine volumes for urinary albumin excretion were also collected. Anthropometric variables including body weight (light clothes, shoes off), waist-to-hip ratio, and subcapular skinfold thickness were measured. Blood pressure levels were measured at baseline and then each 15 days during caloric restriction by using a standard Riva-Rocci sphygmomanometer and stethoscope. Four sitting blood pressure measurements were taken at 3-minute intervals, and the mean of the latter 3 readings was calculated. Cuffs of appropriate size were used.

Laboratory Methods

Circulating E-selectin (R&D Systems), ICAM-1 (R&D), and VCAM-1 (R&D) levels were assessed by immunoenzymatic methods. Plasma vWF levels were also measured by an immunoenzymatic method (Boehringer Mannheim Co). Plasma insulin levels were assayed by radioimmunoassay (Ares Serono). Serum total cholesterol, HDL cholesterol, and triglyceride levels were assessed by enzymatic methods (Boehringer Mannheim); in the case of HDL cholesterol, it was measured after precipitation of LDL and VLDL cholesterol fractions by phosphotungstate. LDL and VLDL cholesterol levels were assessed by the Friedewald method. Urinary albumin was evaluated by nephelometry.

Control Groups
Circulating soluble E-selectin, ICAM-1, VCAM-1, and vWF concentrations were assessed mostly from stored plasma samples from the already described18 nonobese control subjects (n=16, 52.4±3.5 years) and nonobese hypertensive patients (n=18, 52.3±3.9 years). Procedures and criteria were identical to those used for the obese groups, but nonobese subjects had a BMI <26 kg/m2.

Statistical Analysis
Statistical significance values among the examined groups were evaluated by 1-way ANOVA followed by Bonferroni’s test and the Newman-Keuls test for pairwise comparisons. Multiple comparisons were tested by ANOVA, followed by post hoc analysis for adjusting the significance levels. Linear regression and correlation were used to evaluate relationships between variables. Statistical significance was considered at a value of P<0.05. All data are presented as mean±SD.

Results

Baseline Data
Obese hypertensives and normotensives had higher fasting insulin levels than did nonobese subjects (the Table). Although normal, urinary albumin excretion values were higher in obese hypertensives than in obese normotensives and controls but not in nonobese hypertensives. This latter group and the obese normotensives showed a higher urinary albumin excretion compared with controls. Urinary albumin was correlated with mean blood pressure levels in obese hypertensives (r=0.572, P=0.005), obese normotensives (r=0.588, P=0.008), nonobese hypertensives (r=0.561, P=0.024), and nonobese normotensives (r=0.490, P=0.039). Serum lipid levels were not significantly different among the groups evaluated (the Table).

Obese hypertensives and normotensives had similar levels of circulating VCAM-1, ICAM-1, and E-selectin (Figures 1A, 1B, and 1C, respectively) as well as of vWF (Figure 1D). By contrast, the above variables were significantly higher in the 2 obese subgroups than in their nonobese counterparts (Figure 1). Circulating levels of soluble adhesins and of vWF did not differ between nonobese hypertensives and normotensives (Figure 1).

Considered together, obese hypertensives and obese normotensives had plasma concentrations of soluble VCAM-1 that were significantly correlated with plasma LDL levels (Figure 2A), whereas plasma soluble E-selectin levels were directly correlated with BMI (Figure 2B) but not with waist-to-hip ratio or subscapular skinfold thickness. The correlation between plasma E-selectin levels and BMI was also evident in obese hypertensives (P=0.018) and obese normotensive patients (P=0.021) considered separately. A direct correlation was found between plasma vWF levels and BMI in obese hypertensives (r=0.512, P=0.015) and obese normotensives (r=0.477, P=0.039). Plasma vWF levels were not correlated with waist-to-hip ratio or subscapular skinfold thickness. In the nonobese subgroups, neither circulating soluble adhesion molecule nor plasma vWF levels were correlated with any variable.

Effects of Weight Loss in Obese Hypertensives
The 12 weeks of caloric restriction reduced BMI (from 33.2±1.7 to 30.6±1.5 kg/m2, P<0.0001), systolic blood pressure levels were 95 to 114 mm Hg and <90 mm Hg, respectively, on 4 different visits at 1-week intervals. Serum creatinine was <100 µmol/L, and albuminuria was <20 µg/min. Clinical and ultrasound examinations of neck and limb vessels were normal. Patients with an abnormal electrocardiogram, positive histories of angina or vascular diseases, or a parental history of vascular diseases before the age of 60 were excluded. Patients had no concomitant diseases, allergies, or recent acute infectious or inflammatory diseases.

After recruitment, the outpatients began a weight-maintaining diet for 1 week. Then, after an overnight fast, they were admitted to our unit at 8 AM. A forearm vein was cannulated, and after 1 hour in a supine position, venous blood samples for plasma adhesion and vWF assays were collected in prechilled tubes containing EDTA. Tubes were centrifuged at 3000 rpm and plasma aliquots were stored at −80°C until assayed.

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Laboratory Methods

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The 12 weeks of caloric restriction significantly reduced BMI (6.4 mm Hg, $P = 0.026$), blood pressure (from 165.6 to 156.2 mm Hg, $P = 0.003$), fasting plasma insulin (from 118.6 to 106.3 pmol/L, $P = 0.026$), and vWF levels (from 1.71 to 1.48 KU/L, $P < 0.0001$) but not serum cholesterol, cholesterol subfractions, triglyceride, or plasma glucose levels.

Circulating soluble VCAM-1, ICAM-1, and E-selectin levels significantly decreased after caloric restriction (Figures 3A, 3B, and 3C, respectively). As in obese hypertensives, plasma soluble E-selectin levels after weight loss were directly correlated with corresponding values of BMI (Figure 4B).

### Discussion

The current report shows increased levels of circulating VCAM-1, ICAM-1, and E-selectin in obese hypertensive and normotensive men. Endothelial activation was unrelated to the presence of hypertension and/or other cardiovascular risk factors. Indeed, plasma soluble adhesion molecule concentrations were elevated in both normotensive and hypertensive obese subjects. Furthermore, obese patients were nondiabetic and nonhyperlipidemic and had no evidence of overt atherosclerosis and/or a parental history of vascular diseases before the age of 60. Moreover, both normotensive and hypertensive obese patients manifested increased levels of the well-known marker of endothelial activation, vWF. Although the urinary albumin excretion rate was correlated with blood pressure levels rather than body weight, this marker of endothelial damage was also higher in obese than in nonobese subgroups. Thus, our data confirm the presence of endothelial activation, vWF. Furthermore, the same data show that obesity per se promotes early endothelial activation, which involves adhesion molecules and the procoagulant agent vWF, and which is accompanied by an increase in circulating vWF levels. The current findings suggest that endothelial activation is not activated in uncomplicated hypertension. Instead, it may be related to an increase in proinflammatory cytokines, which have been shown to be associated with obesity and hypertension. Furthermore, the increased levels of vWF in obese hypertensive patients may be reflecting a compensatory mechanism to maintain vascular homeostasis in the face of endothelial damage.

### Effects of Weight Loss in Obese Normotensives

The 12 weeks of caloric restriction significantly reduced BMI (from 32.9 ± 1.8 to 31.2 ± 2.1, $P = 0.02$), urinary albumin (from 14.6 ± 2.3 to 12.2 ± 2.6 µg/min, $P = 0.005$), fasting plasma insulin (from 118.6 ± 38.3 to 94.4 ± 24.4 pmol/L, $P = 0.026$), and vWF levels (from 1.71 ± 0.18 to 1.48 ± 0.16 KU/L, $P < 0.0001$) but not serum cholesterol, cholesterol subfractions, triglyceride, or plasma glucose levels.
elevated urinary albumin excretion. Consistent with this, weight loss counteracted such endothelial activation, as indicated by the simultaneous decrements of urinary albumin excretion, plasma vWF, and soluble adhesin levels occurring after 12 weeks of caloric restriction.

As is known, obesity is correlated with an increased risk for developing atherosclerosis. In spite of the association of obesity with hypertension, hyperlipidemia, hyperinsulinemia, elevated alcohol consumption, physical inactivity, and cigarette smoking, some evidence supports the concept that obesity per se might increase cardiovascular risk, independent of other risk factors.

In this regard, the initiating event in atheroma formation is upregulation of endothelial adhesion molecules and the consequent transendothelial migration of circulating leukocytes and monocytes. Although adhesin expression on the endothelial cell surface cannot be investigated in vivo, the soluble forms of endothelial adhesins have been found in the circulation. Indeed, a proteolytic process leads to the release of soluble VCAM-1, ICAM-1, and E-selectin from activated human cultured cells simultaneously with the expression of their membrane-associated forms. Accordingly, significant increments of plasma soluble ICAM-1 levels have been described after a 2-hour angiotensin II infusion, ie, the same time course for maximal expression of membrane-associated ICAM-1 by human endothelial cells stimulated with either angiotensin II or various cytokines. Therefore, the level of circulating adhesins can be considered a marker of their in vivo expression.

In keeping with this, high plasma adhesin concentrations have been found in atherosclerosis and in conditions associated with increased cardiovascular risk, ie, type 2 diabetes and impaired glucose tolerance. Whereas ICAM-1 is broadly distributed in tissues, VCAM-1 and E-selectin are mainly and exclusively expressed, respectively, by vascular endothelial cells. Thus, the increased levels of plasma soluble E-selectin and VCAM-1 found in obese patients strongly suggest that the vascular endothelium is activated in human obesity. Again, the elevation of urinary albumin excretion and plasma vWF levels in obese patients and their significant decrements after weight loss further support this hypothesis.

The reasons leading to endothelial adhesin upregulation in human obesity are unclear. A direct relationship between plasma soluble VCAM-1 and LDL levels was found in obese patients. Lysophosphatidylcholine, a component of oxidized...
LDL, upregulates VCAM-1 expression in human cultured endothelial cells. In hyperlipidemic animals, VCAM-1 up-regulation is associated with early atherosclerosis. Hypercholesterolemia has been associated with increased plasma soluble VCAM-1 concentrations in humans, suggesting that circulating LDL may upregulate VCAM-1 in obese subjects due to LDL oxidation. In contrast to this hypothesis, a correlation between circulating LDL and soluble VCAM-1 levels was weak, and our obese patients had normal serum LDL levels. Furthermore, although obese patients manifested increased plasma E-selectin and ICAM-1 concentrations, these latter 2 and the circulating LDL levels were not correlated. Moreover, reduction of circulating LDL levels by 51% was reported to not affect plasma soluble VCAM-1 concentrations in hypercholesterolemic patients. Therefore, our data cannot support a role for circulating LDL in favoring VCAM-1 upregulation in obese subjects.

Another possible explanation for our findings could be related to insulin levels and glucose metabolism. Plasma E-selectin and ICAM-1 levels were elevated in hyperglycemic type 2 diabetics. High glucose levels upregulate E-selectin and ICAM-1 expression in human endothelial cells. Thus, changes in plasma glucose levels could upregulate endothelial adhesins in obese people. Against this hypothesis, we studied only euglycemic patients and found no correlations between plasma adhesion and glucose levels. Thus, our data do not support the hypothesis that changes of plasma glucose levels within the normal range might upregulate endothelial adhesion molecules in obese people. Similarly, obese subjects can be significantly insulin resistant and hyperinsulinemic. However, plasma insulin and adhesion concentrations were also unrelated in our patients. Thus, further studies are needed to evaluate the possible intriguing relationships among insulin, glucose, and soluble adhesion molecule levels in obese people.

Figure 3. Effects of weight loss due to 12 weeks of caloric restriction on plasma soluble VCAM-1 (A), ICAM-1 (B), E-selectin (C), and vWF (D) levels (mean±SD) in obese hypertensive (n=22) and obese normotensive (n=19) subjects.

Figure 4. Direct relationship between levels of plasma soluble E-selectin and BMI in obese hypertensives (A, n=22) and obese normotensives (B, n=19) after weight loss due to 12 weeks of caloric restriction.

In this regard, our data suggest that obesity per se could overstimulate E-selectin and vWF production. Indeed, we found a significant correlation between circulating E-selectin levels and BMI in both obese hypertensive and obese normotensive groups (Figure 2B). Values of BMI after weight loss were directly correlated with soluble E-selectin levels in both groups (Figures 4A and 4B). Additionally, plasma vWF concentrations were elevated and directly correlated with BMI in obese subjects. In keeping with this, waist-to-hip ratio and subscapular skinfold thickness were unrelated to plasma vWF and E-selectin levels. Unfortunately, no relationship was found between changes in plasma E-selectin and BMI after weight loss. Thus, the role of obesity as a promoter of E-selectin activation needs to be confirmed by further studies.

At variance from our data, 2 elegant reports showed increased plasma soluble E-selectin and vWF levels in hypertensive patients. However, after exclusion of those with uncontrolled hypertension, vascular damage, severe hypercholesterolemia, and smoking, neither vWF nor E-selectin...
levels were elevated in hypertensives versus normoten-
sives. Furthermore, uncontrolled hypertensives were not
selected for having ultrasonographically normal arteries and
normal glucose tolerance, and approximately two thirds of the
study populations were constituted by fertile women. As
a consequence, discrepancies between our data and previous
data simply reflect differences in patient selection.

In conclusion, the current report demonstrates increased levels of plasma soluble E-selectin, ICAM-1, VCAM-1, and vWF and elevated urinary albumin excretion in obese essential hyperten-
sive and normotensive men without atherosclerosis and/or other
concomitant risk factors. The pivotal role of obesity as the main
promoter of endothelial activation was clearly demonstrated by
the marked reductions of soluble adhesin levels observed after
weight loss due to caloric restriction. Although normal, circu-
lating glucose and insulin levels were both higher in obese than
nonobese groups, suggesting that abnormalities in glucose me-
tabolism might simultaneously induce adipose tissue accumula-
tion and endothelial adhesion upregulation. Whether the observed
endothelial activation plays a role in obesity-related atherogen-
esis remains unsettled and needs further clarification by longi-
tudinal follow-up studies.

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