Abstract—Structural alterations of subcutaneous small resistance arteries, as indicated by an increased media:lumen ratio, are frequently present in hypertensive and/or diabetic patients and may represent the earliest alteration observed. In addition, media:lumen ratios of small arteries have a strong prognostic significance. However, no data are available about the structure of small resistance arteries of obese patients, particularly after weight loss. We have investigated 27 patients with severe obesity. Twelve of them were normotensive, and 15 were hypertensive. All of the obese patients underwent bariatric surgery. We compared results obtained with those observed in 13 normotensive lean controls and in 13 hypertensive lean patients. All of the subjects and patients underwent a biopsy of subcutaneous fat during surgical intervention. In 8 obese patients, a second biopsy was obtained after consistent weight loss, during a surgical intervention for abdominoplasty. Subcutaneous small resistance arteries were dissected and mounted on a wire myograph, and structural parameters were measured. A concentration-response curve to acetylcholine was performed to evaluate endothelial function. Obese patients, independent from the presence of hypertension, show the presence of an increased media:lumen ratio and media cross-sectional area, together with an impaired endothelial-dependent vasodilatation. After surgical correction of obesity and consistent weight loss, a significant improvement of microvascular structure and of some oxidative stress/inflammation markers were observed. In conclusion, our data suggest that the presence of obesity is associated with structural alterations of subcutaneous small resistance arteries, mainly characterized by hypertrophic remodeling. Weight loss may improve microvascular structure. (Hypertension. 2011;58:29-36.)

Key Words: remodeling • hypertension • obesity • microcirculation • small arteries

Alterations in the microcirculation are common accompaniments of cardiovascular and metabolic diseases1-2 and may involve small resistance arteries, arterioles, capillaries, and postcapillary venules.3 In particular, the structure of subcutaneous1-3 and cerebral4 small resistance arteries (lumen diameter: 100 to 300 μm) may be altered in the presence of cardiovascular or metabolic diseases. Essential hypertension is associated with a narrowing of the internal lumen and with an increase of media wall thickness, with consequent increase in the media:lumen ratio.1 The observed increase in the media:lumen ratio may be the consequence of an eutrophic remodeling (rearrangement of otherwise normal material around a narrowed lumen) or of a hypertrophic remodeling (vascular smooth muscle cell hypertrophy or hyperplasia).5 Eutrophic remodeling of subcutaneous small arteries is commonly seen in essential hypertension, whereas an inward hypertrophic remodeling, with evident smooth muscle cell growth, was shown in patients with type 2 diabetes mellitus, regardless of the presence of elevated or normal blood pressure levels,6 as well as in some forms of secondary hypertension.7 Several mechanisms were advocated to explain the development of vascular remodeling. In the development of eutrophic remodeling, an alteration of integrin pattern might be involved,8 together with an increased blood pressure in the presence of a tonic vasoconstrictor response, which maintains wall stress constant.9 On the contrary, a hypertrophic remodeling might be ascribed to the direct vascular effect of humoral growth factors, including angiotensin II7 and insulin/insulin-like growth factor 1,6,10 and/or to the impairment of myogenic responses (vasoconstriction to increased intravascular pressure) with consequent increase in wall stress.11

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From the Clinica Medica, Department of Medical and Surgical Sciences (C.D.C., E.P., D.R., C.Co., E.L.B., G.E.M.B., A.P., C.A.R., E.A.R.) and the Chair of General Surgery, Department of Medical and Surgical Sciences (F.M., E.D.B., C.Ca., R.N.) and the Chair of Clinical Biochemistry, Department of Biomedical Sciences and Biotechnology (G.R., L.C.), University of Brescia, Brescia, Italy.
Correspondence to Damiano Rizzoni, Department of Medical and Surgical Sciences, University of Brescia, c/o 2a Medicina Spedali Civili di Brescia, Piazza Spedali Civili 1, 25100 Brescia, Italy. E-mail rizzoni@med.unibs.it
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It was demonstrated previously that an increase in the media:lumen ratio of subcutaneous small arteries is a powerful predictor of cardiovascular events in hypertension and that hypertrophic remodeling seems to be associated with an even higher incidence of events, compared with eutrophic remodeling. Structural alterations in the subcutaneous vascular district might, at least partly, reflect similar alterations in the vasculature of target organs, such as the heart, although relationships observed were relatively not close.

Not only may microvascular structure be altered in cardiovascular and/or metabolic diseases but also functional responses, in particular, the endothelium-mediated ones. In fact, an impairment of the endothelial function, as evaluated by the vasodilator response to acetylcholine, has been detected in human small arteries in essential hypertension, as well as in type 2 diabetes mellitus.

The growing incidence and prevalence of obesity across developed economies worldwide (obesity “epidemic”) has an enormous impact on increasing cardiovascular risk. Obesity is frequently associated with increased systemic oxidative stress/inflammation, as suggested by the observation of an increased production of circulating indicators, such as C-reactive protein, tumor necrosis factor-α, and interleukin 6.

However, few data are presently available about the structure of small arteries in obese patients, in particular in those without the concomitant presence of diabetes mellitus and/or hypertension. Grassi et al have demonstrated the presence of an increased media:lumen ratio of subcutaneous small resistance arteries of normotensive and hypertensive patients with severe obesity, attributed to the presence of hypertrophic remodeling. In the same study the presence of endothelial dysfunction was also detected. The same authors confirmed these data in a population of severely obese patients with metabolic syndrome. However, no data are presently available about the effect of a pronounced weight loss on the structure of small resistance arteries in obese patients.

### Patients and Methods

#### Basal Study

We have investigated 27 patients with abdominal severe obesity, according to current definitions, admitted to the surgical department of our hospital for indication to bariatric surgery (jejuno-ileal bypass or bilipancreatic derivation). Indication to bariatric surgery was made according to current clinical practice and ethics guidelines. Twelve of them were normotensive and 15 hypertensive, according to the European Society of Hypertension and of the European Society of Cardiology guidelines from 2007. As control groups, we investigated also 13 lean normotensive subjects and 13 lean patients with essential hypertension who were undergoing standard surgery. None of the subjects took cardiovascular medication or antioxidant vitamins. The major part of the 15 hypertensive obese patients and of the 13 hypertensive lean patients were treated previously, for various periods of time, with antihypertensive drugs (antihypertensive treatment was withdrawn 2 weeks before enrollment). There was no difference in the proportion of treated patients or in the classes of antihypertensive drugs between the 2 groups. Venous blood samples were taken with the participants in the supine position, after a therapeutic wash out period of ≥2 weeks, for standard hematologic and serum biochemistry tests (including triglycerides and total cholesterol), as well as for evaluation of indices of inflammation and oxidative stress in obese patients and in normotensive lean subjects.

#### Follow-Up Study

Eight obese patients (6 hypertensives and 2 normotensives) were re-evaluated after an average time of 14 months (418±56 days). All of them were submitted to a second surgical intervention of abdominoplasty as a consequence of a pronounced weight loss. Indication for the second intervention was made in the surgical department, according to common clinical practice. Surgeons had no access to the database and were completely unaware of morphological and laboratory findings. No patients received treatment for hypertension or dyslipidemia, because their blood pressure and cholesterol levels remained below the current cut points for intervention throughout the follow-up period (only in 2 cases was a calcium channel blocker maintained for ~2 months). No one had diabetes mellitus.

#### Micromyography

All of the subjects were submitted to a biopsy of subcutaneous fat from the anterior abdominal region. The biopsy of the abdominal subcutaneous fat was taken during a surgical procedure (bariatric surgery in obese patients and laparoscopic cholecystectomy or other minor surgery in lean normotensives and essential hypertensives). Surgery was never performed in patients with sign of systemic inflammation, and this was a necessary condition for enrollment.

In 8 obese patients, a second biopsy was obtained during the second surgical intervention after weight loss. Small arteries (~100 to 280 μm of average diameter in relaxed conditions, 2 mm long) were dissected from the subcutaneous fat of the biopsies and mounted as a ring preparation on an isometric myograph (410 A, Danish Myo Technology, Aarhus, Denmark), by threading onto 2 stainless steel wires (40 μm diameter). Details about the micromyographic technique of evaluation of small artery morphology were reported previously. A calculation of the remodeling and growth indices was then performed, according to the methods of Heagerty et al. The remodeling index quantifies how much of the vascular structural alteration may be explained by a rearrangement of the same material around a narrowed lumen, without cell growth. The growth index quantifies the relative component of vascular smooth muscle cell growth.

Cross-sectional area (CSA) was calculated as follows: $\text{CSA} = \pi(D / 2)^2$, where “D” is inner diameter and “WT” the wall thickness. The remodeling index was calculated as follows: 100[(D1c – D1remodel)/(D1c – D1o)], where “D1c” and “D1o” are the internal diameters of vessels control and obese subjects, respectively, and “D1remodel” is the remodelled internal diameter. (D1remodel × 4CSA/m2) was calculated as [(D1o – D1c)/2]2, where “D1o” is the external diameter of the obese vessel and “CSA” is the media CSA of control vessels. The growth index was calculated as (CSA – CSAi)/CSAi, where “CSAi” and “CSA” are the media CSA of vessels belonging to control and obese subjects, respectively.

Endothelium-dependent responses were evaluated as a cumulative concentration–response curve to acetylcholine at the following concentrations, 10⁻⁹, 10⁻⁸, 10⁻⁷, 10⁻⁶, and 10⁻⁵ mol/L, at 3 minutes per concentration, after precontraction with 10 μmol/L of norepinephrine. Also, a concentration–response curve to sodium nitroprusside (10⁻⁹, 10⁻⁸, 10⁻⁷, 10⁻⁶, and 10⁻⁵ mol/L) was performed to assess endothelium-independent vasodilatation. The average values obtained from 2 vessels in each experiment were considered. The response to acetylcholine and sodium nitroprusside was expressed as the percentage decrease of the wall tension. For further details see also References 6 and 7. The protocol of the study was approved by the ethics committee of our institution (Medical School, University of Brescia), and informed consent was obtained from each participant. The procedures followed were in accordance with institutional guidelines.

#### Evaluation of Circulating Inflammatory Markers and Oxidative Stress

Blood samples were collected between 8:00 and 9:00 AM while participants were in a fasting state. After blood collection, plasma...
and serum were frozen in aliquots at −80°C immediately after centrifugation (4°C, 3000 rpm for 10 minutes). Circulating levels of C-reactive protein (Bender MedSystems, Austria, Europe), proinflammatory cytokines interleukin (IL) 6 and IL-18, macrophage chemotactic factor 1, plasminogen activator inhibitor-1, soluble vascular cell adhesion molecule 1, and soluble intercellular adhesion molecule 1 (Bender MedSystems) have been measured in plasma by ELISA technique following the directions of the supplier company. Further details about the methods used are reported in Reference.27

### Statistical Analysis

All of the analyses were carried out with the BMDP statistical package (BMDP software programs 7D, 8D, 1V, 2V; BMDP Statistical Software Inc, Los Angeles, CA).

### Results

#### Demographic Data

The demographic, hemodynamic, and humoral data are reported in Table 1. As expected, systolic and diastolic blood pressures were significantly higher in hypertensive obese or lean patients compared with normotensive lean subjects or normotensive obese patients. Fasting glucose was not different between groups, although hypertensive obese patients tended to have higher values.

Body weight and body mass index were significantly higher in obese patients compared with lean patients and subjects. Serum cholesterol or triglycerides were not significantly different among the groups, although hypertensive patients tended to have higher values, whereas the proportion of dyslipidemic patients was significantly different between groups. No signs of renal impairment were observed; serum creatinine values were lower in obese patients. Only 3 obese patients had overt diabetes mellitus.

### Table 1. Demographic, Hemodynamic, and Humoral Data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1, Normotensive Lean Subjects (n=13)</th>
<th>Group 2, Hypertensive Lean Patients (n=13)</th>
<th>Group 3, Normotensive Obese Patients (n=12)</th>
<th>Group 4, Hypertensive Obese Patients (n=15)</th>
<th>P Between Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>43.00±3.04</td>
<td>50.00±2.53</td>
<td>33.00±2.32</td>
<td>41.00±3.38</td>
<td>3 vs 1: P=0.019; 3 vs 2: P=0.00013</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>6/7</td>
<td>8/5</td>
<td>1/11</td>
<td>3/12</td>
<td>3 vs 1: P=0.00014; 3 vs 2: P=0.00002</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>59.00±2.50</td>
<td>77.00±3.87</td>
<td>120.00±5.95</td>
<td>114.00±11.00</td>
<td>3 vs 1: P=0.00014; 3 vs 2: P=0.00002</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>22.10±0.82</td>
<td>25.40±1.17</td>
<td>45.00±2.09</td>
<td>49.70±2.28</td>
<td>3 vs 1: P=0.00021; 3 vs 2: P=0.000004; 4 vs 2: P=0.0000001</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>89.50±3.53</td>
<td>97.40±6.42</td>
<td>91.80±2.21</td>
<td>130.00±19.10</td>
<td>3 vs 1: P=0.000051; 3 vs 2: P=0.00000032; 4 vs 2: P=0.000013</td>
</tr>
<tr>
<td>Serum nitrogen, mg/dL</td>
<td>28.50±3.98</td>
<td>35.90±2.74</td>
<td>29.90±1.31</td>
<td>36.90±2.60</td>
<td>3 vs 1: P=0.000001; 3 vs 2: P=0.0013; 4 vs 2: P=0.011</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.14±0.07</td>
<td>0.96±0.08</td>
<td>0.69±0.03</td>
<td>0.69±0.03</td>
<td>3 vs 1: P=0.000051; 4 vs 2: P=0.0000032; 3 vs 2: P=0.0013; 4 vs 2: P=0.011</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>195.00±15.30</td>
<td>210.00±15.30</td>
<td>175.00±6.16</td>
<td>209.00±8.68</td>
<td>3 vs 1: P=0.0035; 2 vs 3: P=0.00000061; 4 vs 3: P=0.00189</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>126.00±16.00</td>
<td>155.00±19.10</td>
<td>87.80±6.94</td>
<td>145.00±20.20</td>
<td>2 vs 1: P=0.000024; 2 vs 3: P=0.0000061; 4 vs 1: P=0.0035; 4 vs 3: P=0.00189</td>
</tr>
<tr>
<td>Diabetic patients</td>
<td>0/13</td>
<td>0/13</td>
<td>0/12</td>
<td>3/15</td>
<td>2 vs 1: P=0.0035; 2 vs 3: P=0.00000061; 4 vs 3: P=0.00189</td>
</tr>
<tr>
<td>Dyslipidemic patients</td>
<td>0/13</td>
<td>7/13</td>
<td>1/12</td>
<td>7/15</td>
<td>2 vs 1: P=0.000033; 2 vs 3: P=0.00014; 4 vs 1: P=0.027</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>127.00±2.40</td>
<td>160.00±1.50</td>
<td>120.00±2.18</td>
<td>140.00±3.98</td>
<td>2 vs 1: P=0.0035; 2 vs 3: P=0.00000061; 4 vs 3: P=0.00189</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>79.00±2.10</td>
<td>99.00±1.70</td>
<td>77.30±1.62</td>
<td>87.90±3.75</td>
<td>2 vs 1: P=0.000033; 2 vs 3: P=0.00014; 4 vs 1: P=0.027</td>
</tr>
</tbody>
</table>

M indicates male; F, female.
Subcutaneous Small Arteries

Media:lumen ratio, media thickness, and wall thickness were significantly greater in the normotensive lean subjects and significantly smaller in obese patients compared with the remaining 2 groups (Table 2). Hypertensive lean patients showed the presence of eutrophic remodeling, as suggested by a remodeling index close to 100%, whereas normotensive and hypertensive obese patients showed a remodeling index, respectively, of 14% and 49%, with a relevant component of vascular smooth muscle cell growth (growth index: 86% and 119%; Table 2). A χ² analysis did...
not show that any effect of sex was detected on media:lumen ratio.

**Endothelial Function**
The vasodilatation to acetylcholine was significantly reduced in hypertensive lean patients and in hypertensive or normotensive obese patients compared with normotensive lean subjects (ANOVA; P<0.001 in any case; Figure 1 and Table 2). No difference among groups was observed in the responses to sodium nitroprusside (Figure 1).

**Circulating Indices of Inflammation and Oxidative Stress**
A statistically significant difference between normotensive lean subjects and hypertensive or normotensive obese patients was observed for circulating levels of IL-6 (1.26±0.64 versus 5.02±0.71 pg/mL; P=0.039), soluble vascular cell adhesion molecule (941.0±96.3 versus 1556.0±1390 ng/mL; P=0.029), and C-reactive protein (287.0±87.9 versus 1114.0±107.0 ng/mL; P=0.000038). No difference was observed for total antioxidant power, lipid peroxidation, malonyldialdehyde, macrophage chemotactic factor 1, IL-18, soluble intercellular adhesion molecule, and plasminogen activator inhibitor 1. Similar data were obtained when normotensive lean subject were separately compared with normotensive and hypertensive obese patients (Table 2).

**Effect of Weight Loss**
A marked decrease in body weight and body mass index was observed in obese patients >1 year after bariatric surgery (Table 3), together with a reduction in fasting glucose, serum cholesterol, triglycerides, lipid peroxidation, malonyldialdehyde, IL-6, soluble intercellular adhesion molecule, and C-reactive protein. No change in blood pressure values was observed.

A statistically significant reduction in media:lumen ratio, media thickness, and media cross-sectional area was also observed (Table 3 and Figure 2). A clear shift from hypertrophic to mainly eutrophic remodeling was observed, as suggested by the observation of an increased remodeling index (from 33% to 140%) and the decrease of the growth index (from >110% to 22%; Table 3). An improvement of endothelial function as evaluated by vasodilatation to acetyl-
Table 3. Demographic, Humoral Data, and Morphological Characteristics of the Subcutaneous Small Arteries and Circulating Indices of Oxidative Stress/Inflammation Before and After Weight Loss in Obese Patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Obese Patients Before Weight Loss (n=8)</th>
<th>Obese Patients After Weight Loss (n=8)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic and humoral data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>36.40±6.46</td>
<td>. . .</td>
<td></td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>1/7</td>
<td>. . .</td>
<td></td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>127.00±3.02</td>
<td>83.30±6.93</td>
<td>0.0028</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>138.00±4.03</td>
<td>135.00±3.87</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>88.10±3.98</td>
<td>86.30±3.52</td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>45.80±2.16</td>
<td>27.40±1.42</td>
<td>0.00016</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>137.0±35.1</td>
<td>85.2±3.7</td>
<td>0.036</td>
</tr>
<tr>
<td>Serum nitrogen, mg/dL</td>
<td>37.8±4.65</td>
<td>32.70±4.47</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>0.66±0.05</td>
<td>0.64±0.05</td>
<td></td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>190.00±10.80</td>
<td>122.00±7.42</td>
<td>0.0053</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>152.0±41.9</td>
<td>91.0±13.5</td>
<td>0.028</td>
</tr>
<tr>
<td>Glycosylated hemoglobin, HbA1c, %</td>
<td>5.11±0.22</td>
<td>4.75±0.14</td>
<td></td>
</tr>
<tr>
<td>Oxidative stress and inflammation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total antioxidant power, μM</td>
<td>261.0±46.0</td>
<td>215.0±24.5</td>
<td>0.041</td>
</tr>
<tr>
<td>LPO, μmol/L</td>
<td>1.59±0.18</td>
<td>0.97±0.10</td>
<td>0.049</td>
</tr>
<tr>
<td>MDA, μmol/L</td>
<td>0.63±0.10</td>
<td>0.34±0.04</td>
<td>0.031</td>
</tr>
<tr>
<td>MCP-1, pg/mL</td>
<td>114.00±6.86</td>
<td>113.00±14.20</td>
<td></td>
</tr>
<tr>
<td>IL-6, pg/mL</td>
<td>4.29±1.16</td>
<td>2.18±0.76</td>
<td>0.017</td>
</tr>
<tr>
<td>IL-18, pg/mL</td>
<td>495.0±74.6</td>
<td>452.0±32.4</td>
<td></td>
</tr>
<tr>
<td>sICAM-1, ng/mL</td>
<td>633.0±56.6</td>
<td>473.0±41.4</td>
<td>0.047</td>
</tr>
<tr>
<td>sVCAM-1, ng/mL</td>
<td>912±200</td>
<td>1078±115</td>
<td></td>
</tr>
<tr>
<td>PAI-1, ng/dL</td>
<td>7.80±1.85</td>
<td>5.50±1.33</td>
<td></td>
</tr>
<tr>
<td>CRP, ng/mL</td>
<td>1465±334</td>
<td>726±300</td>
<td>0.037</td>
</tr>
</tbody>
</table>

CRP indicates C-reactive protein; PAI, plasminogen activator inhibitor; sICAM, soluble vascular cell adhesion molecule; sCAM, soluble intercellular adhesion molecule; IL, interleukin; MCP, macrophage chemotactic factor; MDA, malonyldialdehyde; LPO, lipid peroxidation; M, male; F, female.

Discussion

Alterations in the microcirculation represent a common finding in patients with hypertension30 and also in those with diabetes mellitus6; remodeling of small resistance arteries is an important mechanism involved in the development of organ damage, as well as of clinical events.12,13 In fact, structural alterations of small arteries are associated with an increased cardiovascular risk in hypertensive and diabetic patients, perhaps as a consequence of an impaired organ flow reserve in several relevant vascular districts.9,14,15

The presence of obesity,21 with or without other components of the metabolic syndrome,22 seems to be associated with hypertrophic remodeling of subcutaneous small vessels. Hypertrophic remodeling, such as that observed in diabetic or obese patients, seems to be associated with an even worse prognosis14 compared with eutrophic remodeling. The present study confirmed the presence of hypertrophic remodeling in the subcutaneous vessels of patients with obesity, regardless of the presence of hypertension, diabetes mellitus, and dyslipidemia. In addition, for the first time, the present study demonstrated the possibility to regress vascular structural alterations through a persistent and pronounced weight loss, in our case obtained with bariatric surgery. Weight loss through bariatric surgery was demonstrated previously to be able to reduce overall mortality29 and to induce remission of type 2 diabetes mellitus.30

Figure 2. Media:lumen values before and after weight loss in obese patients, P<0.05 vs before weight loss. Data are shown as mean±SEM.

Figure 3. Line graphs show a concentration-response curve to acetylcholine (ACH) in subcutaneous small arteries of obese patients (n=4) before and after weight loss (ANOVA, P<0.05). Data are shown as mean±SEM.

Choline was observed after weight loss in the small number of patients in which such data were available (Figure 3).
and body mass index, waist circumference, plasma insulin levels, and homeostatic model assessment index, thus suggesting an important role of humoral factors, such as insulin/insulin resistance in the development of vascular structural alterations, whereas blood pressure overload seems to play a minor role. It is, therefore, possible that, similarly, humoral/metabolic factors might be involved in the observed regression of such alterations. In our study, however, glycosylated hemoglobin was below normal limits both before and after weight loss.

Interestingly enough, in the previously mentioned study, as well as in our investigation, a pronounced endothelial dysfunction was observed, as suggested by the presence of a clearly impaired vasodilator response to acetylcholine. Although functional and structural alterations in the microvasculature are not necessarily interrelated, it is possible that oxidative stress/inflammation might be involved in the development (and possibly in the regression) of both types of vascular damage. Endothelial function, when evaluated in the coronary vessels or as flow-mediated dilatation of the brachial artery, seems to be a potent predictor of cardiovascular events, although data about acetylcholine-induced dilatation of small resistance artery are less positive in this regard.

Several pathophysiological mechanisms are possibly involved in the interactions among obesity, cardiovascular alterations, and hypertension, including an activation of the sympathetic nervous system, of the renin-angiotensin system, insulin resistance, increased leptin levels, systemic inflammation, endothelial dysfunction, and oxidative stress. Some of them were investigated in the present study, although no definite conclusion about mechanistic relations between development and/or regression of vascular structural alterations might be drawn from our data. After bariatric surgery, there were a number of changes in addition to weight loss. These changes included reduction in fasting glucose, serum cholesterol, and triglycerides; therefore, it is unclear to what extent these changes, per se, contribute to the observed differences in resistance artery structure and function.

Structural remodeling of the microvascular networks also includes rarefaction in the most distal part, as suggested by the observation, in hypertension, diabetes mellitus, and obesity, of a reduction in the density of microvessels and capillaries, with potential consequences for tissue perfusion and exchange of transport of nutrients. A close correlation between media:lumen ratio of subcutaneous small arteries and capillary density in the skin was observed previously, thus suggesting that vascular remodeling and rarefaction occur in parallel, and, therefore, that vascular abnormalities at different levels are quantitatively and qualitatively similar. Exercise training seems to have beneficial effects in terms of blunting microvessel loss in the obese, insulin-resistant individuals; however, mechanisms involved are still elusive and warrant future investigation.

**Limitation of the Study**

Because of the relatively low number of patients evaluated in the present study, correlation analyses did not provide enough information about mechanisms involved in the observed vascular alterations and especially about causality of mechanisms advocated in the regression of microvascular changes observed after weight loss. In addition, it should be mentioned that remodeling and growth indices provide qualitative, not quantitative, information on vascular remodeling. Because of the methods of calculation, values obtained in the different groups may far exceed 100%, and the sum between remodeling index and growth index is not necessarily close to 100%. We did not measure circulating indices of oxidative stress/inflammation in lean hypertensive patients. There is general agreement about the fact that consistent weight loss is associated with a reduction in inflammation and oxidative stress, and this might have contributed to our observed findings. Obese patients have a greater prevalence of women compared with the remaining groups. However, such a difference in sex distribution is unlikely to have influence our results, because no difference in vascular morphology or in inflammation/oxidative stress markers between sexes was demonstrated previously and confirmed by analysis in our study. Finally, we did not specifically evaluate adipoocyte-derived hormones, although adipokines might play a relevant role in the development of vascular structural and functional alterations.

**Perspectives**

Our data confirm that the presence of obesity is associated with structural alterations of subcutaneous small resistance arteries, mainly characterized by hypertrophic remodeling. For the first time, our data suggest that weight loss obtained by bariatric surgery may improve microvascular structure. However, it is not presently known whether weight loss obtained by a hypocaloric diet may have similar effects.

**Acknowledgments**

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**Disclosures**

None.

**References**

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