# Reduction of Inflammatory Cytokine Concentrations and Improvement of Endothelial Functions in Obese Women After Weight Loss Over One Year

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***Background***—Visceral fat is a key regulator site for the process of inflammation, and atherosclerotic lesions are essentially an inflammatory response.

***Methods and Results***—Fifty-six healthy premenopausal obese women (age range 25 to 44 years, body mass index 37.2±2.2, waist to hip ratio range 0.78 to 0.92) and 40 age-matched normal weight women were studied. Compared with nonobese women, obese women had increased basal concentrations of tumor necrosis factor-$\alpha$ (TNF-$\alpha$, $P<0.01$), interleukin-6 (IL-6, $P<0.01$), P-selectin ($P<0.01$), intercellular adhesion molecule-1 (ICAM-1, $P<0.02$), and vascular adhesion molecule-1 (VCAM-1, $P<0.05$). Vascular responses to L-arginine (3 g IV), the natural precursor of nitric oxide, were impaired in obese women: reductions in mean blood pressure ($P<0.02$), platelet aggregation to adenosine diphosphate ($P<0.05$), and blood viscosity ($P<0.05$) were significantly lower as compared with those in the nonobese group. Concentrations of TNF-$\alpha$ and IL-6 were related ($P<0.01$) to visceral obesity, as well as to adhesin levels and responses to L-arginine. After 1 year of a multidisciplinary program of weight reduction (diet, exercise, behavioral counseling), all obese women lost at least 10% of their original weight (9.8±1.5 kg, range 7.5 to 13 kg). Compared with baseline, sustained weight loss was associated with reduction of cytokine ($P<0.01$) and adhesin ($P<0.02$) concentrations and with improvement of vascular responses to L-arginine.

***Conclusion***—In obese women, endothelial activation correlates with visceral body fat, possibly through inappropriate secretion of cytokines. Weight loss represents a safe method for downregulating the inflammatory state and ameliorating endothelial dysfunction in obese women. **(*Circulation*. 2002;105:804-809.)**

**Key Words:** obesity ■ weight loss ■ cell adhesion molecules ■ interleukins ■ endothelium

Obese individuals with excess fat in intraabdominal depots are at particular risk of negative health consequences; visceral fat is a better predictor of cardiovascular and metabolic disease risk than the amount of body fat alone.[1] A growing body of evidence implicates adipose tissue in general, and visceral adiposity in particular, as key regulators of inflammation, coagulation, and fibrinolysis.[2] Adipose tissue secretes proinflammatory cytokines and fibrinolytic regulators, such as plasminogen activator inhibitor-1.[3] Among the various cytokines, tumor necrosis factor-$\alpha$ (TNF-$\alpha$) and interleukin-6 (IL-6) seem to play a major role because they are expressed in and released by adipose tissue,[4,5] can influence endothelial function,[6] and induce endothelial expression of chemokines and adhesion molecules,[7] which are central in the early stage of the atherogenetic process.[8] Inflammation blood markers, such as C-reactive protein (CRP), predict future cardiovascular events in healthy subjects,[9] suggesting a role for inflammation in the initiation of atherosclerosis, as well as in the precipitation on an acute event. The synthesis of CRP is mostly under the control of IL-6.[10]

There are very few studies addressing the relationship between circulating levels of proinflammatory cytokines, adhesion molecules, and the distribution of body fat in humans. One study reports higher levels of circulating intercellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1), and E-selectin in obese men as compared with nonobese men, irrespective of the presence of hypertension.[11] Yudkin et al[12] found in healthy subjects a close relationship between circulating CRP and cytokine (TNF-$\alpha$, IL-6) concentrations and anthropometric measures of obesity, although the subjects they studied were mostly overweight. However, no previous study evaluated the relationship between circulating concentrations of cytokines and

Received September 27, 2001; revision received December 11, 2001; accepted December 21, 2001.

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***Circulation*** **is available at http://www.circulationaha.org** **DOI: 10.1161/hc0702.104279**

endothelial functions in obese people, nor was there any study investigating the influence of substantial weight loss. The aim of the present study was to evaluate whether endothelial functions and circulating levels of proinflammatory cytokines and adhesion molecules were abnormal in obese people. The answers to these questions were sought in obese women without additional cardiovascular risk factors by (1) measuring circulating levels of TNF-$\alpha$, IL-6, ICAM-1, VCAM-1, and P-selectin; (2) characterizing the vascular responses to L-arginine, the natural precursor of nitric oxide (NO); (3) relating indexes of body fat distribution with measures of endothelial activation; and (4) evaluating the effect of sustained weight loss (at least 10% of the initial body weight).

## Methods

Obese and nonobese premenopausal women, aged 25 to 44 years, were recruited from the outpatient department of the teaching hospital at the Second University of Naples, Italy. All obese women (n=56) were sedentary (less than 1-hour per week of physical activity) with no evidence of participation in diet reduction programs within the last 6 months. All subjects were asked to complete a personal health and medical history questionnaire, which served as a screening tool; women were excluded from the study if they had type 2 diabetes mellitus, hypertension, cardiovascular disease, psychiatric problems, a story of alcohol abuse, or if they smoked or took any medication. All women had laboratory data (urea nitrogen, creatinine, electrolytes, liver function tests, uric acid, tiroxine, and complete blood count), chest x-ray, and ECG normal. Forty sedentary, healthy nonobese women, matched for age (by group) to the obese women, served as control group. They were nonsmoker and took no medication. All women (both groups) had normal glucose tolerance (2-hour post load plasma glucose $<$7.8 mmol/L) and were studied in the follicular phase of the cycle, within the first week after menstrual bleeding stop.

Each women gave informed written consent to participate in this study, which was approved by the institutional committee of ethical practice of our institution.

All women were studied after a 14-hour overnight fast and were required to refrain from drinking alcohol in the previous 10 days. Subjects were measured at the nearest 0.5 cm in height and 100 g in weight. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m$^2$). Waist-to-hip ratio (WHR) was calculated as waist circumference in centimeters divided by hip circumference in centimeters.

Endothelial functions in the form of hemodynamic and rheologic responses to L-arginine were assessed as previously described.[13] In brief, the women were placed in a supine comfortable position with a room temperature between 20 and 24°C; following cannulation of a large antecubital vein with an intravenous line kept open with a 0.9% saline drip, the women's blood pressure was automatically recorded with a noninvasive technique (Finapres Ohmeda 2003). Blood pressure was also recorded with a random zero sphygmomanometer. After a 10-minute equilibration period, an intravenous bolus of 3 g of L-arginine (10 mL of a ready 30% solution of L-arginine monochloride) was injected within 60 seconds. Blood pressure, platelet aggregation response to adenosine diphosphate, and blood viscosity were measured before the L-arginine injection and 10 minutes later.

In order to ensure the greatest adhesion to the treatment program, obese women were treated with a multidisciplinary approach consisting of diet, exercise, behavioral and nutritional counseling, and liposuction surgery for those who were candidates and agreed for the procedure. The mean daily caloric intake was 1300 kcal, ranging from 1250 to 1350 kcal. The composition of the dietary regimen was the following (in grams): carbohydrates 178, proteins 73, saturated fat 9, monounsaturated fat 17, polyunsaturated fat 8, sodium 1.1, potassium 3, calcium 0.5, phosphorus 1.2, and fiber 25. This regimen was very similar to the Mediterranean-style Step I diet, which is under active evaluation by the American Heart Association as a possible tool to lower cardiovascular risk in the population.[14] All women were encouraged to have physical activity (at least 1-hour walk three times a week).

In 15 women with focal areas of lipodystrophy resistant to conventional mean of improvement, a single-site (thighs or legs) 2-L liposuction surgery was performed during the study period with local anesthesia alone (tumescent technique). In brief,[15] a diluted mixture of lidocaine and epinephrine in a crystalloid solution was infiltrated into the subcutaneous fat to provide anesthesia, analgesia, and hemostasis; then, subcutaneous fat was dislodged by means of metal cannulas placed through small skin incisions and aspirated with negative pressure. Liposuction was done at least 3 months before plasma assays. Patients were advised to wear an elastic compression garment for several weeks and resumed their normal activities within a few days after the procedure. All women were followed on an outpatient basis, at 1 month intervals.

Assays for serum total and high-density lipoprotein cholesterol, triglyceride, and glucose levels were performed in the hospital's chemistry laboratory. Plasma insulin levels were assayed by radioimmunoassay (Ares Serono). Serum samples for cytokine and adhesin levels were stored at −80°C until assay. Serum concentrations of TNF-$\alpha$, IL-6, ICAM-1, VCAM-1, and P-selectin were determined in duplicate using commercially available immunosorbent kits (R&D Systems). Dilution curves of serum samples were parallel those of standard. Intraassay and interassay coefficients of variation were below 4.5% and 7%, respectively, for all kits. Platelet aggregation was determined according to the method of Born.[16] The aggregometer was adjusted before each test, and aggregation was induced using a final concentration of 1.25 $\mu$mol/L of adenosine diphosphate. Blood viscosity at high rates of shear (225/sec$^{-1}$) was assessed with a digital viscosimeter 0.8° cone, using aliquots of blood anticoagulated with 0.77 mol/L of EDTA (ratio of blood to EDTA, 1:20). The coefficient of variation was 2% for blood viscosity and 4.5% for platelet aggregation. The overall reproducibility of the L-arginine test was 0.75% (SD of the difference between 2 tests performed in 10 women at baseline) and the coefficient of variation was 2.9%.

### Statistical Analysis

Data are presented as group mean±SD. For a desired value of $P$=0.05 and 80% power to detect an actual difference, a sample size of 20 per group was considered satisfactory. One-way ANOVA was used to compare baseline data, followed by Scheffé's test for pairwise comparisons. Multiple comparisons were made with ANOVA followed by post hoc analysis (Student-Newmann-Keuls test) to locate the significant difference indicated with ANOVA. Linear regression and correlation were used to evaluated relationships between variables. Multivariate regression analysis tested the independent association and contribution of changes in BMI, WHR, physical activity, and plasma cytokine concentrations with the dependent variables (indexes of endothelial activation). A value of $P<0.05$ was considered significant. All calculations were made on an IBM PC computer (SPSS, Inc, version 9.0).

## Results

### Baseline Data

The characteristics of these white women with normal glucose tolerance are shown in Table 1. Compared with nonobese women, obese women had higher fasting glucose and insulin concentrations; by contrast, serum lipid and blood pressure levels were not different between the 2 groups. Levels of circulating TNF-$\alpha$ ($P<0.01$), IL-6 ($P<0.01$), P-selectin ($P<0.01$), ICAM-1 ($P<0.02$), and VCAM-1 ($P<0.02$) were significantly higher in the obese group than in the nonobese group. Moreover, baseline levels of circulating TNF-$\alpha$ (5.7±1.7 pg/mL), IL-6 (3.12±1.0 pg/mL), P-selectin (89.7±29.5 ng/mL), ICAM-1 (304±73 ng/mL), and

**TABLE 1. Clinical Characteristics of the Study Women**

| | Obese (n=56) | Nonobese (n=40) | P |
|---|---|---|---|
| Age, years | 35.3±4.8 | 34.1±5.2 | NS |
| BMI, kg/m$^2$ | 37.2±2.2 | 23.5±1.7 | <0.001 |
| WHR | 0.84±0.06 | 0.72±0.05 | <0.001 |
| SBP, mm Hg | 123.3±6.2 | 121.7±5.3 | NS |
| DBP, mm Hg | 83.5±3.9 | 82.1±3.7 | NS |
| Fasting glucose, mmol/L | 5.5±0.4 | 4.9±0.3 | <0.05 |
| Fasting insulin, pmol/L | 115.4±37.7 | 68.4±23.2 | <0.02 |
| Total cholesterol, mmol/L | 4.9±0.5 | 4.8±0.5 | NS |
| LDL cholesterol, mmol/L | 3.4±0.4 | 3.3±0.4 | NS |
| HDL cholesterol, mmol/L | 1.0±0.2 | 1.1±0.2 | NS |
| Triglyceride, mmol/L | 1.5±0.3 | 1.3±0.2 | NS |
| TNF-$\alpha$, pg/mL | 5.8±1.5 | 3.6±0.9 | <0.01 |
| IL-6, pg/mL | 3.18±0.9 | 1.4±0.5 | <0.01 |
| P-selectin, ng/mL | 87.5±27.4 | 52.3±15.8 | <0.01 |
| ICAM-1, ng/mL | 315±67 | 201±54 | <0.02 |
| VCAM-1, ng/mL | 708±162 | 547±123 | <0.02 |

NS indicates not significant; BMI, body mass index; WHR, waist-to-hip ratio; SBP, systolic blood pressure; and DBP, diastolic blood pressure.

VCAM-1 (687±154 ng/mL) in women who underwent liposuction were not significantly different from the other obese women. Hemodynamic and rheologic responses to L-arginine were impaired in the obese group: mean blood pressure decrease following the L-arginine bolus (difference between basal and 10 minute values) was −2.0±1.5 mm Hg, the decrease of platelet aggregation was −4.5±2.7%, and that of blood viscosity was −0.05±0.04 cp. The corresponding values in nonobese women were −6.2±1.7 mm Hg ($P<0.01$), −12±4.5% ($P<0.05$), and −0.1±0.05 cp ($P<0.05$), respectively.

Concentrations of TNF-$\alpha$, IL-6, and adhesion molecules were related to measures of total (BMI), and particularly central (WHR), obesity (Table 2). Mean blood pressure and platelet aggregation responses to L-arginine were inversely related to measures of total and central adiposity. In Table 3, the relationships of concentrations of TNF-$\alpha$ and IL-6 with concentrations of adhesion molecules, measures of endothelial functions, and metabolic parameters are shown. Univariate correlations are given as these were little affected by adjustment for age. Concentrations of TNF-$\alpha$ and IL-6 were related to adhesin concentrations and to vascular responses to L-arginine, but not to lipid parameters, glucose, and insulin. Concentrations of TNF-$\alpha$ correlated with those of IL-6 ($r=0.45$, $P<0.01$).

**TABLE 2. Relationships of Anthropometric Measures of Obesity With Concentrations of Proinflammatory Cytokines, Adhesion Molecules, and Indexes of Endothelial Functions in Obese Women**

| | BMI | WHR |
|---|---|---|
| TNF-$\alpha$* | 0.40‡ | 0.55§ |
| IL-6* | 0.26† | 0.45§ |
| P-selectin | 0.35‡ | 0.41‡ |
| VCAM-1 | 0.29† | 0.33‡ |
| ICAM-1 | 0.27† | 0.29† |
| MBP response to L-arginine | −0.25† | −0.41§ |
| PA response to L-arginine | −0.19† | −0.34‡ |

*Log-transformed; †$P<0.05$; ‡$P<0.02$; §$P<0.01$. BMI indicates body mass index; WHR, waist-to-hip ratio; MBP, mean blood pressure; and PA, platelet aggregation.

**TABLE 3. Relationships of Concentrations of Proinflammatory Cytokines With Metabolic Parameters and Indexes of Endothelial Functions in Obese Women**

| | TNF-$\alpha$* | IL-6* |
|---|---|---|
| P-selectin | 0.31‡ | 0.37‡ |
| VCAM-1 | 0.24† | 0.19† |
| ICAM-1 | 0.23† | 0.21† |
| MBP response to L-arginine | −0.27‡ | −0.29‡ |
| PA response to L-arginine | −0.21† | −0.24† |
| LDL-cholesterol | 0.09 | 0.06 |
| HDL-cholesterol | 0.17 | 0.15 |
| Triglyceride | 0.14 | 0.09 |
| Glucose | 0.15 | 0.10 |
| Insulin | 0.11 | 0.09 |
| IL-6 | 0.45§ | – |

*Log-transformed; †$P<0.05$; ‡$P<0.02$; §$P<0.01$. MBP indicates mean blood pressure; and PA, platelet aggregation.

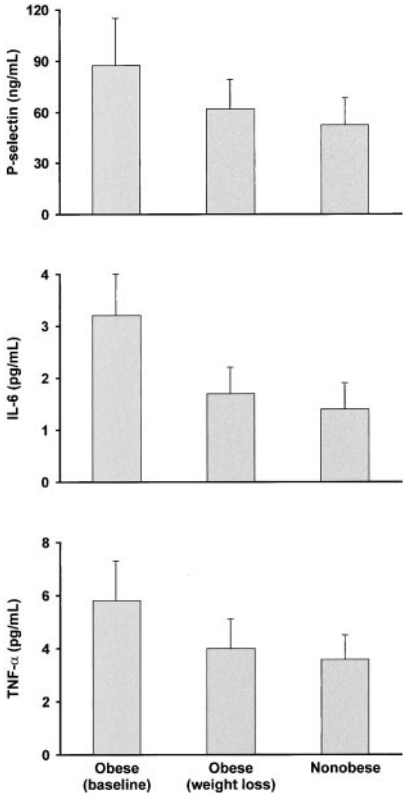
## Effects of Weight Loss in Obese Women

All obese women were reexamined after 12 months. They lost at least 10% of their initial body weight with a mean decrease of 9.8±1.5 kg (range 7.5 to 13 kg). All women increased the level of their physical activity, from a basal value of 46±12 to 131±29 minutes/week ($P<0.01$). Compared with baseline values, sustained weight loss was associated with significant reductions of BMI, WHR, fasting glucose and insulin levels, TNF-$\alpha$, IL-6, and adhesin concentrations (Table 4, Figure). Vascular responses to L-arginine significantly improved after weight loss and were not different from those of the nonobese

**TABLE 4. Effects of Weight Loss in Obese Women**

| | Baseline | 12 Months | P |
|---|---|---|---|
| BMI, kg/m$^2$ | 37.2±2.2 | 32.5±1.5 | <0.001 |
| WHR | 0.84±0.06 | 0.78±0.04 | <0.001 |
| Fasting glucose, mmol/L | 5.5±0.4 | 5.1±0.4 | <0.05 |
| Fasting insulin, pmol/L | 115.4±37.7 | 89.8±34.3 | <0.02 |
| TNF-$\alpha$, pg/mL | 5.8±1.5 | 4.0±1.1 | <0.01 |
| IL-6, pg/mL | 3.18±0.9 | 1.7±0.5 | <0.01 |
| P-selectin, ng/mL | 87.5±27.4 | 61.5±17.4 | <0.01 |
| ICAM-1, ng/mL | 315±67 | 234±51 | <0.02 |
| VCAM-1, ng/mL | 708±162 | 590±134 | <0.02 |
| Responses to L-arginine | | | |
| MBP, mm Hg | −2.0±1.5 | −5±1.7 | <0.01 |
| PA, % | −4.5±2.7 | −11±3.9 | <0.02 |
| BV, centipoises | −0.05±0.05 | −0.1±0.05 | <0.02 |

BV indicates blood viscosity; BMI, body mass index; WHR, waist-to-hip ratio; MBP, mean blood pressure; and PA, platelet aggregation.




Concentrations of P-selectin, IL-6, and TNF-$\alpha$ in obese women before and after weight loss and in control normal weight women.

group. Serum total cholesterol, cholesterol subfractions, triglyceride, and blood pressure values were not significantly decreased after the same period. The changes in cytokine and adhesin concentrations, and in vascular responses to L-arginine after weight loss in the 15 obese women who underwent liposuction surgery were not significantly different from those observed in the other obese women.

Changes in cytokine and adhesin concentrations, and vascular responses to L-arginine after weight loss were related to reductions in BMI and WHR (Table 5), as well as to increases in physical activity ($r=-0.21$ for IL-6, $P<0.05$; $r=-0.25$ for TNF-$\alpha$, $P<0.02$; $r=0.23$ to 0.26 for responses to L-arginine, $P<0.05$). After weight loss, the changes in adhesin levels and in vascular responses to L-arginine correlated with the decline in serum TNF-$\alpha$ and IL-6. For evaluating the independent association of changes in markers of endothelial activation and function with changes in serum TNF-$\alpha$ and IL-6 levels, a multivariate analysis was performed in which P-selectin or blood pressure response to L-arginine were the dependent variables and BMI, WHR, level of physical activity, serum TNF-$\alpha$, and IL-6 concentrations were the independent variables. The model explained 65% of the variability in the change of P-selectin level and about 60% of the MBP response to L-arginine with changes in TNF-$\alpha$ and IL-6 concentrations.

**TABLE 5. Relationships of Reduction of Anthropometric Measures After Weight Loss in Obese Women With Reduction of Proinflammatory Cytokines and Adhesion Molecules and Improvement of Endothelial Functions**

| | BMI | WHR |
|---|---|---|
| TNF-$\alpha$* | 0.35‡ | 0.54§ |
| IL-6* | 0.31‡ | 0.45§ |
| P-selectin | 0.29‡ | 0.34‡ |
| VCAM-1 | 0.25† | 0.29‡ |
| ICAM-1 | 0.22† | 0.25† |
| MBP response to L-arginine | −0.24† | −0.29‡ |
| PA response to L-arginine | −0.21† | −0.24† |

*Log-transformed; †$P<0.05$; ‡$P<0.02$; §$P<0.01$. MBP indicates mean blood pressure; and PA, platelet aggregation.

## Discussion

To our knowledge, this is the first study to prospectively investigate the effect of sustained weight loss on circulating levels of proinflammatory cytokines and on endothelial functions in apparently health obese women with different degrees of central adiposity. The main findings of our study are that circulating levels of TNF-$\alpha$ and IL-6, and the adhesion molecules VCAM-1, ICAM-1, and P-selectin are elevated in obese women and correlate with indexes of adiposity, particularly central adiposity, and that reduction of body weight results in significant amelioration of endothelial activation strictly correlated with reduction of cytokine levels.

Obesity is associated with an increased risk of developing atherosclerosis, irrespective of the presence of other risk factors associated, such as hypertension, hyperlipidemia, diabetes mellitus, hyperinsulinemia, elevated alcohol consumption, and smoking.[1,17] Many of these associated factors were, by inclusion criteria, not present in our population of obese women; this seems to suggest that the elevated levels of proinflammatory cytokines and adhesion molecules in obese women we studied represent the effect of obesity per se independent of other confounding factors. Circulating soluble adhesion molecule levels are considered to be markers of in vivo adhesin expression[18] and also a marker of atherosclerosis. For example, soluble P-selectin levels are elevated among apparently healthy women at risk for future cardiovascular events,[19] and elevated ICAM-1 levels are associated with increased risk of future myocardial infarction in apparently healthy men.[20] Upregulation of endothelial adhesion molecules initiates atheroma formation through the consequent transendothelial migration of circulating leukocytes and monocytes.[21] Accordingly, high plasma adhesin concentrations have been found in atherosclerosis,[22] as well as in conditions associated with increased cardiovascular risk such as type 2 diabetes[23,24] and hypertension.[11,25]

IL-6 and TNF-$\alpha$ are expressed in adipose tissue: systemic concentrations of IL-6 increase with adiposity, and it has been suggested that about 30% of total circulating IL-6 originates from adipose tissue;[5] moreover, in vitro release of TNF-$\alpha$ by adipocytes has been reported.[4] Circulating concentrations of TNF-$\alpha$ or IL-6 have been found associated with BMI,[12,26] a finding confirmed by our data. In addition, body fat distribution more than total fat may influence cytokine levels and hence endothelial activation. Many lines of thought support this: (1) TNF-$\alpha$ induces production of IL-6 by adipose

tissue,[27] compatible with the correlation we found between the concentrations of these 2 cytokines in the serum of obese women; (2) IL-6 may induce endothelial expression of chemokines and adhesion molecules,[7] and its plasma concentrations are predictive of future myocardial infarction among apparently healthy men[28]; and (3) there is a close relationship between cytokines levels and indexes of endothelial activation. Accordingly, the concentrations of TNF-$\alpha$ and IL-6 were positively related to circulating levels of adhesion molecules, and negatively related to blood pressure and platelet aggregation fall after L-arginine. All this seems to suggest that cytokines, arising in part from adipose tissue, mainly visceral, might be partly responsible for endothelial activation and endothelial dysfunction observed in obese women, particularly those with visceral obesity.

Other possible explanations for our findings could be related to other metabolic parameters that have been associated with increased plasma levels of adhesins in humans. For instance, plasma VCAM-1 concentrations have been found elevated in hypercholesterolemic subjects,[29] and plasma ICAM-1 and E-selectin circulating levels are reported to be higher in type 2 diabetic subjects,[23,24,30] supporting a role for oxidized LDL and high glucose to upregulate adhesin expression in humans, as occurs in human endothelial cells.[31,32] Against this possibility, the obese women we studied had normal concentrations of LDL; furthermore, no association between serum LDL and adhesin concentrations was found, nor was there any relationship between plasma glucose or insulin and any of the adhesion molecule concentrations.

The results obtained after weight loss in obese women also support a role for visceral fat as a key factor predisposing toward atherosclerotic disease, possibly through inappropriate cytokine secretion. In fact, at the same level of body weight reduction, women with the greatest degree of visceral obesity had the greatest decrease of cytokine and adhesin levels and the greatest improvement of endothelial functions. On the other hand, the multivariate analysis of data showed that changes in cytokine concentrations were associated with changes in adhesin concentrations or indexes of endothelial function independently of changes in BMI. Thus, the improvement of endothelial functions after weight loss in obese women was more marked in those who lost more visceral fat and was strictly associated with a decrease in cytokine concentrations.

The women who underwent a single 2-L liposuction surgery as an adjunctive step to the multidisciplinary approach to weight loss presented a response that was not different from the other women. In particular, the exclusion of these 15 women from the analysis did not change the significance of the associations between WHR decrease and amelioration of endothelial functions, both in univariate and in multivariate analyses. Thus, in selected candidates, liposuction may be safely used in management of weight loss of the obese patient.

## Clinical Implications

This study shows that in obese women endothelial dysfunction is associated with increased body fat, in particular with visceral fat. A likely mechanism for this association is through the plasma cytokine levels, which correlated with indexes of endothelial activation (plasma adhesin concentrations) and functions (hemodynamic and rheologic responses to L-arginine) both at baseline and after sustained weight loss. Studies in cell biology, animal models, clinical research, and epidemiology have been remarkably consistent suggesting that atherosclerotic lesions are essentially an inflammatory response.[21] This hypothesis has found convincing support, particularly in the linking of inflammation to cardiovascular risk through changes in endothelial functions.[33,34] However, inflammation may be a modifiable risk factor amenable to correction by drugs[4] or lifestyle modifications.[35] Because of the powerful association with obesity, weight loss may be another safe method for downregulating the inflammatory status of obese subjects with the goal to reduce their cardiovascular risk.

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