Role of Subcutaneous Abdominal Fat on Cardiac Function and Proinflammatory Cytokines in Premenopausal Obese Women

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Abstract: The role of surgically removing subcutaneous fat by abdominoplasty on circulating inflammatory markers and myocardial dysfunction, evaluated by myocardial performance index (MPI), were investigated. Twenty volunteers submitted to the abdominoplasty (abdominoplasty group), and other 28 women treated by hypocaloric diet (diet group) were evaluated. Echocardiographic parameters of MPI, circulating levels of tumor necrosis factor (TNF)-α and interleukin (IL)-6, were performed at baseline and 2 months later. Compared with nonobese women, obese women had increased concentrations of TNF-α ($P < 0.01$), IL-6 ($P < 0.01$), and higher MPI ($P < 0.02$), indicating ventricular dysfunction. Subcutaneous fat concentrations of TNF-α and IL-6 were related to MPI impairment. After 60 days, waist-to hip ratio was significantly reduced in the abdominoplasty group. Anthropometric changes were accompanied by a significant decline in plasma concentrations of TNF-α and IL-6 levels as well as by significant improvements of MPI in abdominoplasty group compared with diet group. Abdominoplasty may represent a safe method for ameliorating cardiac function in obese women.

Key Words: abdominoplastic surgery, cardiac function, inflammation

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Many studies show that in obese patients heart contractile dysfunction is associated with increased body fat and particularly visceral fat.[1] A likely mechanism for this association may be through plasma cytokine levels, which correlated with myocardial performance index (MPI), a useful method to estimate heart function, both at baseline and after sustained weight loss.[2] Indeed, circulating mediators of inflammation participate in the mechanisms of myocardial damage,[3,4] and many of these inflammatory proteins are secreted directly from adipocytes and adipose tissue-derived macrophages: adipose tissue synthesize and secrete several cytokines, including tumor necrosis factor (TNF)-α[5] and interleukin (IL)-6.[6] Elevated levels of TNF-α and IL-6 have been found to be associated with proxy indicators of elevated body fat[7] and with risk of heart failure.[8,9] The progressive increase in adipose tissue, produced by long-term disequilibria in energy balance, may evoke these pro-inflammatory properties of adipocytes as well as adipose tissue-derived macrophages.[10] Prior literature has emphasized the important relations of visceral adiposity with inflammation and related cardiometabolic risk, whereas recent data show that both subcutaneous and visceral adipose tissues appear to be associated with chronic inflammation.[11] Therefore, as subcutaneous adipose tissue may have multiple metabolic and endocrinologic properties that have previously been ascribed only to visceral adipose tissue,[11] we thought that a surgical massive excision of these "pathologic" fat cells through abdominal dermolipectomy could be able to ameliorate the inflammatory pattern as well as cardiac function in patients with visceral obesity. Although metabolic benefits of abdominal liposuction on cardiovascular system, insulin sensitivity and diabetes are controversial,[12,13] no study has evaluated the possibility that massive excision of abdominal fat tissue through abdominal dermolipectomy may affect the inflammatory state and cardiac function in obese patients. Therefore, the aim of the present study was to evaluate whether myocardial dysfunction, evaluated by MPI, was associated with proinflammatory cytokines produced by subcutaneous adipose tissue in premenopausal obese women. Moreover, the role of surgically removing subcutaneous fat by abdominoplasty on circulating inflammatory markers as well as on cardiac function was also investigated and compared with the effects of 2 months of hypocaloric diet intervention.

RESEARCH DESIGN AND METHODS

We reviewed clinical data and echocardiograms for 48 obese women who had standard indications for abdominoplastic surgery.[14] Twenty obese women who had volunteered to undergo abdominoplastic surgery were included in the abdominoplasty group of this study; further 28 obese patients without surgical obesity treatment were included in the diet group (Fig. 1). Nonobese (body mass index [BMI] <25) healthy women matched for age to obese women served as control group. All study groups volunteered for repeated clinical evaluations and laboratory analyses as well as echocardiography. In the abdominoplasty group, for avoiding the confounding effect of abdominoplasty-related changing in body weight in the follow-up period, a weight-maintaining diet consisting of 55% carbohydrates, 30% lipid, and 15% protein was administered for 2 months on an outpatient basis. In the diet group, women were treated with a multidisciplinary approach consisting of diet, exercise, and behavioral and nutritional counseling. The mean recommended daily caloric intake was 1300 kcal, ranging from 1250 to 1350 kcal. The recommended composition of the dietary regimen was 55% carbohydrates, 30% lipid, and 15% protein, and were followed on an outpatient basis until 2 months This regimen was very similar to the Mediterranean-Style step I diet.[15] All obese women were sedentary (<1 h/wk of physical activity), with no evidence of participation in diet reduction programs within the last 6 months. Women were excluded from the study if they had type 2 diabetes, hypertension, cardiovascular disease, psychiatric problems, a history of alcohol abuse, or if they smoked or took any medication. All women had normal results for laboratory data (urea nitrogen, creatinine, electrolytes, liver function tests, uric acid, thyroxin, and complete blood count), chest x-rays, and electrocardiograms. All women had

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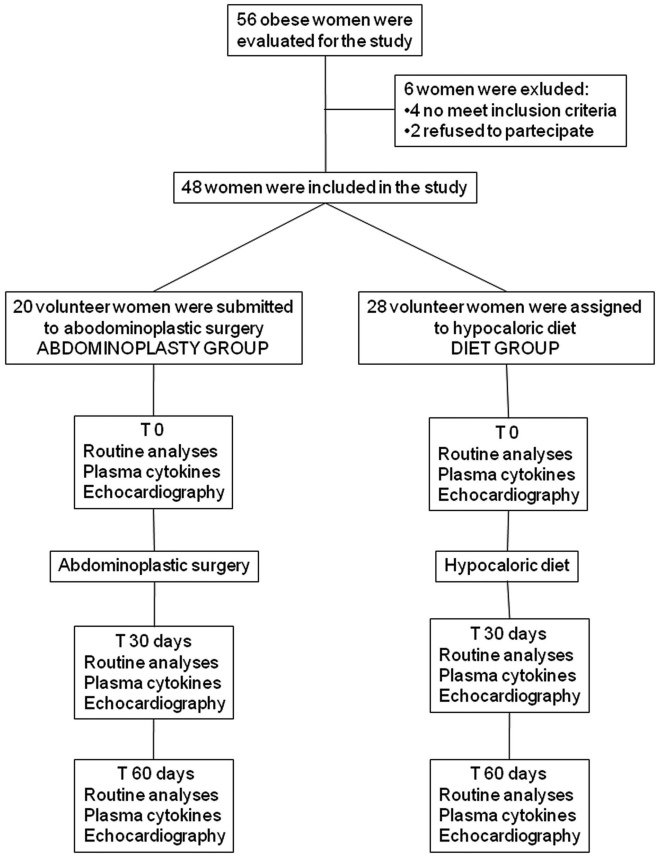

FIGURE 1. Study protocol.

normal glucose tolerance (2-hour postload plasma glucose <7.4 mmol/L) and were studied in the same phase of the menstrual cycle. All women were studied after a 14-hour overnight fast and were required to refrain from drinking alcohol over the previous 10 days. All women were evaluated at baseline and 2 months later.

Anthropometrics Parameters

Women were measured to the nearest 0.5 cm in height and 100 g in weight. Height was determined with the subject standing without shoes and weight with the subject in stockinged feet, using a mechanical scale. BMI was calculated as weight in kilograms divided by the square of height in meters. Waist-to hip ratio (WHR) was calculated as waist circumference in centimeters divided by hip circumference in centimeters.

Echocardiography

All women underwent 2-dimensional and Doppler echocardiography, with measurements taken according to the American Society of Echocardiography recommendations.[16] Only frames with optimal visualization of interfaces and simultaneously showing septum, left ventricular internal diameter, and posterior wall were used for reading. Two observers read the tracings, and the mean value from at least 5 measurements per observer were computed. The readers of the echo were blinded. Left ventricular mass was calculated according to Troy et al[17] and was normalized by both body surface area and height[18] to correct for the effect of overweight. The ejection fraction was calculated from area measurements using the area-length method applied to the average apical area.[19] MPI was measured as previously described.[20] Doppler velocities and time intervals were measured from mitral inflow and left ventricular outflow recordings. Isovolumetric relaxation time (IRT) was the time interval from cessation of left ventricular outflow to onset of mitral inflow. ET was the time interval from the onset and cessation of left ventricular outflow, and mitral early diastolic flow deceleration time was the time interval between the peak early diastolic velocity and the end of early diastolic flow. Total systolic time interval was measured from the cessation of one mitral flow to the beginning of the following mitral inflow. Isovolumetric contracting time (ICT) was calculated by subtracting ET and IRT from the total systolic time interval. The ratio of velocity time intervals of mitral early and late diastolic flows was calculated. MPI was calculated by using the formula MPI = (IRT + ICT)/ET.[20,21]

Analyses of Blood Samples

Serum samples for cytokine levels were stored at T −80°C until assayed. Serum concentrations of TNF-α and IL-6 were determined in duplicate using a highly sensitive quantitative sandwich enzyme assay (Quantikine HS; R&D Systems, Minneapolis, MN). 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, Italy). Insulin resistance in the fasting state was assessed with homeostasis model assessment (HOMA) and calculated with the following formula: fasting plasma glucose (millimoles per liter) times fasting serum insulin (microunits per milliliter) divided by 25, as described by Matthews et al.[22]

Abdominal Dermolipectomy

Patients underwent conventional abdominoplasty surgical procedure, with umbiliculum transposition and cutaneous adipose mass tissue excision ranging from 2878 ± 200 gr. Patients were mobilized 24 hours after surgery, anti-inflammatory therapy (nonsteroidal anti-inflammatory drugs) was suspended after 48 hour and were discharged 72 hours following with antibiotic therapy.

Analyses of Adipose Tissue

After surgery, the specimens were cut parallel to the long axis into 2 halves. The first half was frozen in liquid nitrogen for the following enzyme-linked immunosorbent assay analysis. A portion of the other half specimen was immediately immersion fixed in 10% buffered formalin. Sections were serially cut at 5 μm, mounted on lysine-coated slides, and stained with hematoxylin/eosin and with the trichrome method. Specimens were analyzed by light microscopy.

Biochemical Adipose Tissue Assays

Specimens were lysed and centrifuged for 10 minutes at 10,000g at 4°C. After centrifugation, 20 μg of each sample were analyzed for quantification of IL-6 and TNF-α levels using a specific enzyme-linked immunosorbent assay kits (Santa Cruz).

Immunohistochemistry

After the surgical procedure, samples were immediately frozen in isopentane and cooled in liquid nitrogen. Serial sections were incubated with specific antibodies antinitrotyrosine and anti-CD68 (Dako), anti–TNF-α, anti-IL-6 (R&D).

Analysis of immunohistochemistry was performed with a personal computer–based quantitative 24-bit color image analysis system (IM500, Leica Microsystem AG).

Each woman provided informed written consent to participate in this study, which was approved by the institutional committee of ethical practice of our institution. The patients subscribed a separate informed consent to undergo abdominoplasty.

Statistical Analysis

Data are presented as group means ± SD. One-way analysis of variance (ANOVA) was used to compare baseline data, followed by Scheffes 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. Simple and partial correlation were used to evaluate relationships between variables. A value of $P < 0.05$ was considered significant. All calculations were made on an IBM PC (version 12.0; SPSS, Chicago, IL).

RESULTS

The characteristics of study groups are shown in Table 1. The mean age was similar among the obese and nonobese groups, and BMI and WHR were significantly higher in the obese group. Compared with nonobese women, obese women had higher fasting glucose and insulin concentrations and HOMA scores. As expected for an obese female population, serum TNF-α ($P < 0.01$) and IL-6 ($P < 0.01$) levels were higher than those of nonobese women (Table 1). Serum cytokine levels and HOMA scores were related to measures of total (BMI) and, particularly, central (WHR) obesity (Table 2). Echocardiographic/Doppler measurements are presented in Table 1. Compared with nonobese women, all obese women had longer left ventricular internal diastolic diameter ($P < 0.01$), thicker interventricular septum ($P < 0.05$), and left ventricular posterior wall ($P < 0.04$), but lower ejection fraction ($P < 0.05$) (Table 1). Moreover, obese women had higher MPI ($P < 0.02$), indicating ventricular dysfunction (Table 1). Measures of total and central adiposity were inversely related to ejection fraction, and directly related to MPI (Table 2). Concentrations of TNF-α and IL-6 were inversely related to ejection fraction, and directly related to MPI (Table 2). Before abdominoplastic surgery and diet, there were no significant differences in all study parameters between abdominoplasty and diet obese groups (Table 3). After abdominoplasty, the mean fat tissue removed was 3.2 kg. A great portion of adipose tissue was occupied by macrophages, as well as both immunohistochemistry and quantitative analyses revealed high staining and levels of TNF-α and IL-6 (Fig. 2). Notably, adipose tissue concentrations of TNF-α and IL-6 were directly related to MPI (Fig. 2).

TABLE 1. Clinical Characteristics of the Obese Women (Abdominoplasty Group = 20; Diet Group = 28) and Nonobese Women

	Obese Women	Nonobese Women
n	48	20
Age (yr)	40.5 ± 5	39 ± 5
BMI (kg/m^2)	33.8 ± 3.1*	23.8 ± 1.8
WHR	0.90 ± 0.01*	0.79 ± 0.04
Systolic blood pressure (mm Hg)	117.3 ± 4.1	117.8 ± 5.2
Diastolic blood pressure (mm Hg)	80.2 ± 3.3	78.9 ± 3.9
Fasting glucose (mmol/L)	5.3 ± 0.3*	4.8 ± 0.4
Fasting insulin (μU/mL)	16.7 ± 4.8*	7.9 ± 2.5
HOMA	3.6 ± 0.5*	1.6 ± 0.4
Total cholesterol (mmol/L)	5.1 ± 0.4	5.0 ± 0.6
LDL cholesterol (mmol/L)	3.0 ± 0.3	3.2 ± 0.3
HDL cholesterol (mmol/L)	1.1 ± 0.2	1.1 ± 0.3
Triglyceride (mmol/L)	1.4 ± 0.5	1.4 ± 0.5
TNF-α (pg/mL)	6.1 ± 1.8*	2.2 ± 0.7
IL-6 (pg/mL)	4.1 ± 0.7*	2.5 ± 0.9
LVM/BSA (g/m^2)	95.1 ± 13*	71.8 ± 12
LVM/h2 (g/m^2)	64.6 ± 7*	46.9 ± 9
IVS (mm)	11.1 ± 1.4*	8.3 ± 1.0
MPI	0.57 ± 0.05*	0.35 ± 0.05
Ejection fraction (%)	51 ± 5*	65 ± 8

Data are group means ± SD.
*$P < 0.05$ compared with nonobese women.
IVS indicates interventricular septum; LVM/BSA, left ventricular mass index/body surface area; LVM/h^2, left ventricular mass index/height squared.

TABLE 2. Relationships of Anthropometric Measures of Obesity and Concentrations of Proinflammatory Cytokines With Echocardiographic Parameters in Obese Women

	BMI	WHR	TNF-α	IL-6
TNF-α*	0.28†	0.43‡	—	0.10
IL-6*	0.38‡	0.55§	0.10	—
HOMA	0.33‡	0.53§	0.36‡	0.29†
Ejection fraction	−0.10	−0.38‡	−0.36‡	−0.28†
MPI	0.12	0.37‡	0.36‡	0.26†

Measures of total and central adiposity as well as proinflammatory cytokines were inversely related to ejection fraction, and directly related to MPI.
*Log transformed.
$^\dagger P < 0.05$.
$^\ddagger P < 0.02$.
$^\S P < 0.01$.

Cardiovascular Effects of Abdominoplasty

Two months after both abdominoplastic surgery or diet program, BMI was significantly reduced in both abdominoplasty and diet groups, without significant differences between the groups, while WHR was significantly reduced only in the abdominoplasty group (Table 3). A significant and similar decline in fasting plasma insulin, plasma triglycerides and HOMA scores were observed in both groups (Table 3). Serum total cholesterol, cholesterol subfractions, and fasting plasma glucose values were unaffected after the same period in both groups (Table 3). In contrast inflammatory pattern (plasma TNF-α and IL-6 levels) as well as in echocardiographic parameters (MPI, ejection fraction) were significantly improved in abdominoplasty group either versus baseline condition or versus diet treated obese group at the end of the same follow-up period (60 days) (Table 3). In addiction changes in inflammatory patterns were also related to decline in WHR (Table 4). Interestingly enough, changes in WHR correlated with improvements in cardiac function (MPI, ejection fraction) (Table 4). Such correlation was lost after adjustment for BMI. In nonobese women, anthropometric, metabolic, and echocardiographic parameters were not different from baseline after 60 days (data not shown).

CONCLUSIONS

The main findings of this study are that MPI, an index of heart dysfunction, positively correlated with proinflammatory cytokine levels in subcutaneous fat tissue and that surgically removing subcutaneous fat by abdominoplasty resulted in significant improvement of the sequelae of ventricular dysfunction evidenced by MPI. Such improvements are mainly associated with a significant decline in circulating pro-inflammatory cytokines. Because any associated conditions could be ruled out through clinical investigation and close laboratory evaluation, it is reasonable to hypothesize that in the clinical setting, any changes in cardiac function can be interpreted as a consequence of massive excision of fat cells through abdominal abdominoplastic surgery.

TABLE 3. Clinical Characteristics, Metabolic Profile and Cardiac Parameters Before and 60 d After Abdominoplastic Surgery (Abdominoplasty Group) and After Diet (Diet Group)

	Abdominoplasty Group			Diet Group		
	Before	**After 60 d**	***P***	**Before**	**After 60 d**	***P***
n	20	20	—	28	28	—
Age (yr)	40 ± 4	—		41 ± 5	—	—
BMI (kg/m^2)	33.8 ± 2.8	32.2 ± 0.9	0.021	33.7 ± 3.2	32.4 ± 1.1	0.047
WHR	0.90 ± 0.01	0.87 ± 0.02*	0.001	0.90 ± 0.02	0.89 ± 0.04	0.242
Fasting glucose (mmol/L)	5.3 ± 0.3	5.2 ± 0.2	0.222	5.3 ± 0.4	5.2 ± 0.1	0,285
Fasting insulin (μU/mL)	16.6 ± 4.7	13.4 ± 5.1	0.046	16.9 ± 4.6	14.0 ± 4.9	0.026
HOMA	3.6 ± 0.5	2.8 ± 0.7	0.013	3.5 ± 0.4	2.9 ± 0.5	0.016
Cholesterol (mmol/L)	5.1 ± 0.5	5.0 ± 0.6	0.570	5.1 ± 0.4	5.1 ± 0.2	0.845
LDL cholesterol (mmol/L)	3.0 ± 0.2	3.0 ± 0.4	0.987	3.1 ± 0.1	3.0 ± 0.3	0.165
HDL cholesterol (mmol/L)	1.1 ± 0.2	1.2 ± 0.3	0.222	1.1 ± 0.3	1.1 ± 0.4	0.898
Triglyceride (mmol/L)	1.4 ± 0.3	1.2 ± 0.1	0.006	1.5 ± 0.3	1.3 ± 0.2	0.005
TNF-α (pg/mL)	6.0 ± 1.7	4.3 ± 1.6*	0.002	6.1 ± 1.8	5.9 ± 2.1	0.703
IL-6 (pg/mL)	4.1 ± 0.6	2.9 ± 0.9*	0.001	4.2 ± 0.9	3.9 ± 1.2	0.295
MPI	0.57 ± 0.06	0.43 ± 0.08*	0.001	0.56 ± 0.04	0.54 ± 0.06	0.148
Ejection fraction (%)	51 ± 4	56 ± 3*	0.001	50 ± 6	53 ± 6	0.067

Data are as means ± SD.
*$P < 0.05$ compared with diet group.

Studies have identified MPI as an independent predictor cardiac mortality in patients with heart failure.[23] Obesity is associated with an increased risk of developing heart failure, irrespective of the presence of other associated risk factors, such as hypertension, hyperlipidemia, hyperinsulinemia, diabetes, elevated alcohol consumption, and smoking.[1] Many of these associated factors were, by inclusion criteria, not present in our population of obese women; this seems to suggest that the morphologic and functional echocardiographic alterations are due to obesity. The increase of MPI indicates a worse functional outcome in obese women. MPI is a Doppler index of combined systolic and diastolic function[24] derived from aortic and mitral flows and has been shown to be related to morbidity and mortality in patients with various cardiovascular disorders, including heart failure.[20,21] The present study provides evidence of an association between MPI abnormalities and subcutaneous abdominal fat in obese women. As for the background of this association, obesity may be responsible for an increased inflammatory process and a poor cardiac contractile function may be linked to a greater inflammatory process in the subcutaneous fat. More than 25 years ago, Lefer and Rovetto[25] reported that the sera of septic patients and experimental animals contained a "myocardial depressant factor," the molecular nature of which has eluded definitive identification in the intervening years. During the past decade, TNF-α and IL-1 were shown to be present in the sera of septic patients and responsible for most, if not all, of the reversible cardiac depression often seen with this syndrome.[26] These data are consistent with earlier reports[27] that soluble inflammatory mediators in medium conditioned by activated immunocytes altered the contractile responsiveness of beating cardiac muscle cells to beta-adrenergic agonists, an effect that could be mimicked in this in vitro preparation by recombinant TNF-α or IL-1β. Accordingly, the subcutaneous fat concentrations of TNF-α and IL-6 were positively related to MPI and negatively related to ejection fraction. All of this seems to suggest that cytokines elaborated by subcutaneous adipocytes and macrophages may be partly responsible for cardiac dysfunction observed in obese women. The present finding underscores the positive association of abdominal subcutaneous adipose tissue with circulating markers of inflammation. Although prior literature has emphasized the important relations of visceral adiposity with inflammation and related cardiac dysfunction,[28] the role of subcutaneous fat are not yet completely characterized. However, recent research has shown that both visceral and subcutaneous adipose tissue are related to markers of inflammation and oxidative stress.[11] Moreover, a very recent data suggest that adipose tissue macrophages may be active players in the process of adipose tissue development through the extension of the capillary network and in the genesis of obesity-associated cardiovascular pathologies through their production of the metalloproteinase-9,[29] a key enzyme involved in cardiac remodeling processes.[30] Accordingly, we show that also abdominal subcutaneous adipose tissue appears to be associated with both chronic inflammation and heart dysfunction. Therefore, abdominal subcutaneous adipose tissue may be not simply an inert storage deposit for lipids, but may represent an important endocrine organ regulating whole-body metabolism and other vital functions related to inflammation and immune responses that have previously been ascribed only to visceral adipose tissue.

The results obtained after dermolipectomy in obese women also support a role for subcutaneous fat as a key factor predisposing toward cardiac dysfunction, possibly through inappropriate cytokine secretion. In fact, at the same level of body weight reduction, women subjected to massive excision of abdominal fat cells had the greatest decrease of cytokine levels and the greatest improvement of cardiac functions 2 months after the abdominoplastic surgery compared with women treated with diet program. Thus, the improvement of cardiac function in obese women was more marked in those who lost more subcutaneous abdominal fat and was strictly associated with a decrease in cytokine concentrations. Liposuction and abdominoplasty are the most frequently used methods to address obesity by plastic surgery techniques. As far as liposuction is concerned, contrasting data regarding the role of liposuction on insulin resistance and pro-inflammatory markers have been reported.[12] By contrast, in the present study we investigated the possible beneficial effect of abdominoplastic surgery, an alternative and safe method by which a reduction in abdominal fat is achieved without an intensive surgical approach.[31] Our data seem to

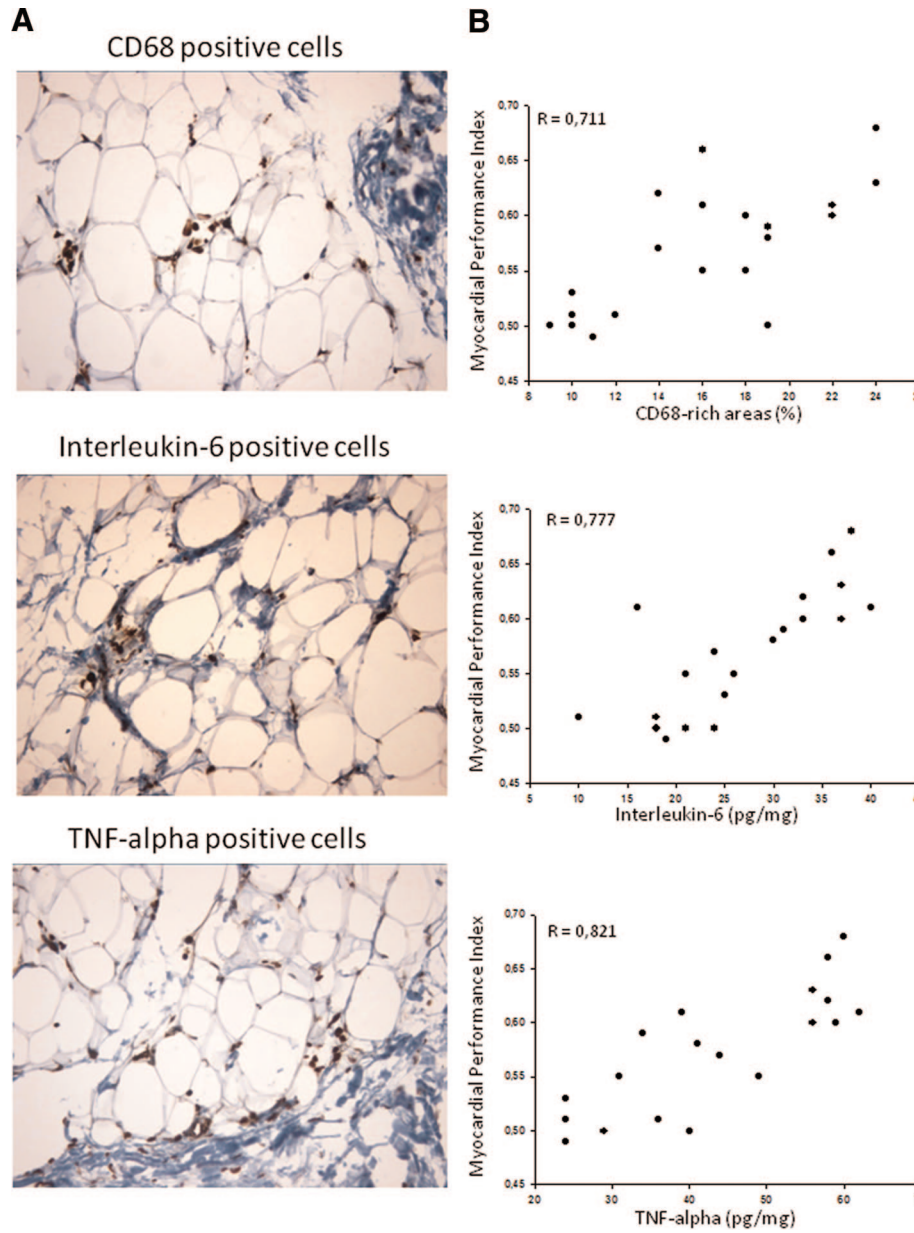

FIGURE 2. Representative immunohistochemical analysis of macrophages (CD68), interleukin-6 and tumor necrosis factor (TNF)-α from subcutaneous adipose tissue specimens of obese women undergoing to abdominoplastic surgery ($\times$600) (A). Correlations between myocardial performace index and adipose tissue levels of CD68, TNF-α and interleukin-6 (B).

TABLE 4. Relationships Between the Anthropometric Changes After Abdominoplastic Surgery and Proinflammatory Cytokines and Echocardiographic Parameters

	BMI	WHR
TNF-α*	−0.18	−0.33†
IL-6*	−0.20	−0.42‡
HOMA	−0.30§	−0.51‡
Ejection fraction	−0.11	−0.31†
MPI	0.10	0.37†

*Log transformed.
$^{\dagger}P < 0.02$.
$^{\ddagger}P < 0.01$.
$^{\S}P < 0.05$.

indicate that abdominoplasty is more useful than liposuction in cardiac function and lowering pro-inflammatory markers. The differences between liposuction and abdominoplastic surgery might be found in the possibility that abdominoplasty may remove a larger amount of abdominal fat than liposuction, and thus have a greater lowering effect on tissue release from abdominal fat.

In conclusion, our study demonstrates that, in obese patients, abdominoplastic surgery is associated with weight loss, improved cardiac function and a lower degree of inflammation. Because of the particular goal of the abdominoplasty, our study was carried out only in women and we acknowledge that this could be a potential limitation of our study. Thus, further long-term studies will be needed to confirm our finding in a larger population (also including men) and to determine if the cardiac effect of abdominoplastic surgery will translate into a reduced incidence of cardiovascular disease.

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