RESEARCH ARTICLE

Gender effect on vascular inflammation following bariatric surgery

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ABSTRACT. Studies have shown that mortality was reduced by 31.6% in patients that underwent bariatric surgery compared with the non-operative control group. However, in most surgical series the majority of patients were women, and men had higher post-operative mortality rates and a higher postoperative morbidity, regardless of weight. Our primary end point was to study gender effects on vascular inflammation following bariatric surgery for weight loss. ***Methods.*** **A prospective study evaluated vascular inflammation in obese patients before and three months after bariatric surgery. Markers of vascular inflammation were measured - before surgery and three months afterwards.** ***Results.*** **One hundred and two patients (73 women and 29 men, 40.5 ± 12.3 years old) underwent bariatric surgery. Correlation was found between BMI change and waist circumference change ($r = 0.658$, $P<0.001$). Three months post-surgery, BMI was significantly decreased ($p<0.001$) (a decrease of 8.82), waist circumference was reduced ($p<0.001$) (a decrease of 17.33 cm). ICAM-1 levels and hs-CRP levels were decreased (both $P = 0.0001$). Gender differences seem to be borderline significant with respect to the prevalence of type II diabetes mellitus (men > women; $P = 0.05$) and hypertension (men > women; $P = 0.06$). In women, following bariatric surgery, BMI was decreased ($p<0.001$) (a decrease of 9.25), waist circumference was reduced ($p<0.001$) (a decrease of 18.8cm). ICAM-1 levels were decreased ($p = 0.002$) and hs-CRP levels were also decreased ($P = 0.0001$). In men, following bariatric surgery, BMI was decreased ($p = 0.001$) (a decrease of 8.1), waist circumference was reduced ($p<0.005$) (a decrease of 14.6cm); however, although ICAM-1 levels and hs-CRP levels were decreased the decreases were non-significant (both $P = 0.09$).** ***Discussion.*** **Our study examined gender effects of bariatric surgery on vascular inflammation. Bariatric surgery had no significant effect on biochemical inflammatory markers in male patients, while females undergoing the same kind of bariatric surgery for weight loss showed a significant decrease in these markers of inflammation. These results may explain the epidemiological data that described higher morbidity and mortality among obese men undergoing bariatric operation for weight loss. This is the first study that has demonstrated a gender difference in the inflammatory responses that may affect clinical outcome, and cardiovascular morbidity and mortality.**

Key words: gender, inflammation, weight loss, bariatric surgery

Obesity, particularly abdominal obesity, is associated with increased risks of hypertension, diabetes mellitus, hyperlipidemia, sleep apnea, coronary artery disease, stroke, and mortality [1, 2]. Weight loss surgery is the most effective treatment for morbid obesity, mainly because medical and dietary treatments have been proven insufficient in the long run [3, 4]. A meta-analysis by Buchwald *et al.* found that 77% of patients with preoperative DM type II improved postoperatively [5]. Similar findings were reported for patients with hyperlipidemia, hypertension, and sleep apnea syndrome [5]. Sjostrom has shown that mortality was reduced by 31.6% in patients who underwent bariatric surgery compared with non-operative controls [6]. However, in most surgical series the majority of patients were women, and studies have shown that men had higher postoperative mortality and morbidity rates [7-10] regardless of weight [10]. In a propensity score-adjusted analysis of older, severely obese male patients the use of bariatric surgery compared with the usual care, was not associated with a decreased mortality rate during a mean 6.7 years of follow-up [11].

Our primary end point was to identify any effect of gender on vascular inflammation three months post-bariatric surgery.

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DONORS AND METHODS

The study was a prospective study. Patients were evaluated one day before and three months after bariatric surgery for weight loss. The surgery was a restrictive surgery ("sleeve" operation for 93 patients, and gastric "band" operation for nine patients). The study was approved by the Internal Review Board (IRB) of the hospital, and all patients signed a consent form before enrollment. Inflammatory markers were measured one day before and three months after surgery.

Body mass index (BMI) is a standardized measure of the relationship of body mass to height. The BMI is calculated by dividing the weight in kilograms by the height [2] in meters (kg/m^2). Waist circumference was measured on a bare abdomen, just above a hip bone while the patient was standing relaxed. A high-risk waist circumference is gender-dependent - a male with a waist measurement over 40 inches (102 cm), and a female with a waist measurement over 35 inches (88 cm) are considered at risk. Waist circumference represents abdominal adiposity.

Biochemical analysis

High sensitivity C reactive protein (hs-CRP) was measured using Quantikine Human C-Reactive Protein, cat. No. DCRP00 R&D System Inc.614 McKinley Place NE Minneapolis, MN 55413, USA.

Serum-soluble Intercellular Cell Adhesion Molecule (ICAM-1) levels were measured using Quantikine Human sICAM-1/CD54 Immunoassay, Cat. No. DCD540, R&D Systems, Inc. 614 McKinley Place NE Minneapolis, MN 55413, USA

Statistical analysis

Distributions of the study variables are described by percentages (categorical variables) or means and standard deviations (SDs), as appropriate. Student's T tests were used to compare means of different clinical and biochemical parameters measured before and after the procedure. A two-sided χ^2 test was used to compare distribution differences by gender. The Pearson correlation was used to study correlations between mean parameters and between the changes in the different parameters

RESULTS

The study was performed in a Regional Governmental Hospital in the north of Israel (Galilee). Overall, 102 patients from the north of Israel were recruited into the study (73 women and 29 men, mean age 40.5 ± 12.3 years old) (*table 1*). Smoking prevalence (6%) was lower than expected for the Israeli population (22.8% overall). The high prevalence of hypertension and type II diabetes mellitus was expected owing to the weight of the population studied. A significant correlation was found between BMI change and waist circumference change ($r = 0.658$, $P<0.001$). Three months after the bariatric surgery, BMI had decreased from 43.7 ± 5.6 to 34.8 ± 5.8 ($p<0.001$) (a decrease of 8.82), waist circumference was reduced from 129.0 ± 13.6 cm to 111.7 ± 13.9 cm ($p<0.001$) (a decrease of 17.33 cm) (*table 2*). ICAM-1 levels had decreased from 244.1 ± 115.8 pg/mL to 189.1 ± 89.5 pg/mL ($P = 0.0008$) and hs-CRP levels had decreased from 11,339 ± 7,897 pg/mL to 6,224 ± 5,710 pg/mL ($P = 0.0001$) (*table 3*).

Table 1
Clinical parameters.

	Whole group	Women	Men	p-value
Number	102	73	29	
Age	40.5 ± 12.3	39.8 ± 11.9	43.0 ± 13.0	NS
Smokers	7	4 (5%)	3 (10%)	0.41
Type II DM	21	11 (15%)	10 (34%)	0.05
HTN	33	19 (26%)	14 (48%)	0.06

Type 2 diabetes - Following the bariatric surgery, 12 of the 21 patients with type 2diabetes did not need any medications for the diabetes (HbA1c% less than 6.5%). All other diabetic patients showed improved diabetes mellitus status; those who used insulin did not need it anymore and started using oral medications with good glycemic control. Those who took oral medications before the bariatric surgery needed a much smaller amount after the surgery. Only baseline BMI predicted postoperative BMI ($P<0.001$). We also found a positive correlation between BMI change and waist circumference change (0.658, $P<0.001$; Pearson's correlation).

Gender effects

Gender seemed to affect the prevalence of type II diabetes mellitus (men 34%, women 15%; $P = 0.05$) and hypertension (men 48%, women 26%; $P = 0.06$). Seventy three women (mean age 39.8 ± 11.9 years old) underwent bariatric surgery. Four were smokers (5%), 11 had type II diabetes mellitus (15%), and 19 had high blood pressure (26%) (*table 1*); following bariatric surgery BMI was decreased from 44.1 ± 5.2 to 34.9 ± 5.5 ($p<0.001$) (a decrease of 9.25), waist circumference was reduced from 127.9 ± 13.6 cm to 109.1 ± 12.7 cm ($p<0.001$) (a decrease of 18.8 cm) (*table 2*). ICAM-1 levels had decreased from 233.6 ± 106.9 pg/mL to 180.0 ± 73.4 pg/mL ($p = 0.002$) and hs-CRP levels decreased from 12,072 ± 7,653 pg/mL to 6,394 ± 5,536 pg/mL ($P = 0.0001$) (*table 3*). Twenty nine men underwent bariatric surgery (mean age 43.0 ± 13.0 years old). Three were smokers (10%), 10 had type II diabetes mellitus (34%), 14 had hypertension (48%) (*table 1*); following bariatric surgery BMI was decreased from 42.6 ± 6.7 to 34.5 ± 7.0 ($p = 0.001$) (a decrease of 8.1), waist circumference was reduced from 131.8 ± 13.9 cm to 117.3 ± 15.6 cm ($p<0.005$) (a decrease of 14.6 cm) (*table 2*). ICAM-1 levels were non-significantly decreased from 270.2 ± 134.0 pg/mL to 208.3 ± 116.1 pg/mL ($p = 0.09$) and hs-CRP levels were non-significantly decreased from 9,467 ± 8,345 pg/mL to 5,850 ± 6,208 pg/mL ($P = 0.09$) (*table 3*).

DISCUSSION

Our study found that women benefited more than men from bariatric surgery for weight loss, because surgery had no effect on inflammatory markers in males, while females showed a significant decrease in these markers of inflammation.

Table 2
Metabolic parameter changes three months after bariatric surgery.

	BMI 1	BMI 2	p-value	WC 1	WC 2	p-value
Whole group	43.7 ± 5.6	34.8 ± 5.8	**<0.001**	129.0 ± 13.6	111.7 ± 13.9	**<0.001**
Women	44.1 ± 5.2	34.9 ± 5.5	**<0.001**	127.9 ± 13.5	109.1 ± 12.7	**<0.001**
Men	42.5 ± 6.7	34.5 ± 7.0	**0.0001**	131.8 ± 13.9	117.3 ± 15.6	**0.005**

BMI 1 – basal metabolic index before the operation; **BMI 2** - basal metabolic index after the operation **WC 1** – waist circumference before the operation; **WC 2** - waist circumference after the operation

Table 3
Levels of inflammatory markers before and three months after bariatric surgery.

	ICAM-1/1 pg/mL	ICAM-1/2 pg/mL	p-value	CRP 1 pg/mL	CRP 2 pg/mL	p-value
Whole group	244.1 ± 115.8	189.1±89.5	**0.0008**	11,339 ± 7,897	62,24 ± 5,710	**0.0001**
Women	233.6 ± 106.9	180.0±73.4	**0.002**	12,072 ± 7,653	6,394 ± 5,536	**0.0001**
Men	270.2 ± 134.0	208.3±116.1	**0.09**	9,467 ± 8,345	5,850 ± 6,208	**0.09**

ICAM-1/1 – ICAM-1 level before the operation**; ICAM-1/2 –** ICAM-1 level after the operation, **CRP 1 –** C-reactive protein level before the operation, **CRP 2 –** C-reactive protein level after the operation

In most surgical series the majority of patients are women, and several studies have shown that mortality rates are higher in men [7-9]. Livingston *et al.* [7] demonstrated higher postoperative morbidity in men, regardless of weight, and a recent study showed that men have higher rates of co-morbid disease than women with the same BMI [10]. A Swedish cohort study found that the adjusted mortality risk was 1.5 when the obese surgical cohort was compared with the general control cohort [12]. When postoperative morbidity was compared with the general control cohort, the relative risk of myocardial infarction was two-fold higher and the risk of stroke four-fold higher. However, this surgery results in lower morbidity rates with diabetes mellitus and hyperlipidemia than the non-surgical cohort; still, an increased risk remained for all co-morbidities in comparison with the general population [12]. A Swedish study (including all patients who underwent bariatric surgery in Sweden between 1980 and 2006), found that after surgery the overall risk remained increased for myocardial infarction, angina pectoris, stroke, diabetes mellitus, and death compared with the general population [13]. An American retrospective cohort study examined the mortality rate of 850 veterans (74% males) between 2000 and 2006 and found that the use of bariatric surgery compared with the usual care was not associated with decreased mortality during a mean 6.7 years of follow-up [11]. On the other hand, the prospective Swedish study that followed 4,047 obese subjects for 10.9 years and found that bariatric surgery for severe obesity was associated with long-term weight loss and decreased overall mortality [14]. A recent analysis by the American College of Surgeons found that increased body mass index, increased age, and undergoing Roux-en-Y gastric bypass were associated with increased rates of postoperative complications. They also found that Hispanic and African American patients had increased rates of postoperative complications [15]. The Longitudinal Assessment of Bariatric Surgery Consortium (4,776 patients) found that extreme values of BMI were significantly associated with an increased risk of the composite end point (death, venous thromboembolism, re-intervention), while age, gender, race, and ethnic group were not [16]. It is important to mention that in this study only 21% of the patients were males.

In our series, the "sleeve" operation was performed in 93 patients and the gastric "band" operation in nine patients – all nine of the patients undergoing "band" surgery were women.

It might be that if we had used a more advanced surgical approach we may have obtained different results. The effect of the surgical approach on markers of inflammation and the gender effect following these procedures should be studied in the future.

The effect of bariatric surgery on vascular inflammation

Hs-CRP levels were only significantly reduced in patients that underwent bariatric surgery for weight loss [17]. Following bariatric surgery, levels of VEGF, leptin, gherlin and insulin decreased significantly in parallel with weight reduction [18-20], with a greater weight loss seen when compared with medical treatment [21]. Significant reductions in markers of inflammation were detected following bariatric surgery [22]. However, in most studies women were the majority of the population studied (80% women), with no gender effect analysis having been performed.

ICAM-1 and hs-CRP are markers of vascular inflammation and may represent atherosclerotic processes – both insidious and clinical– that involve a cascade of events that start with reactive oxygen species damaging the arterial wall followed by long-standing endothelial dysfunction and inflammation of the arterial wall with the eventual development of atherosclerosis and atherosclerotic plaques [23, 24]. Most of the bariatric surgery studies that have been reported were conducted in women, with a very small number of men undergoing this procedure. This explains the lack of data for men, including our study as there were fewer men than women. However, there were enough for a statistical calculation for comparing any difference before and after surgery. Our data have highlighted the relative lack of benefit observed in men undergoing this operation, and this has not been shown before. Epidemiological data

have demonstrated a lack of any dramatic effect of bariatric surgery for obesity in men, but this has always been related to the higher complication rate in men, the older age, higher frequency of type 2 diabetes, hypertension and other, co-morbid conditions – and indeed, in our study we too noticed a higher rate of co-morbid conditions in men (relative to women undergoing the surgery) – our male population had higher rate of type 2 diabetes and hypertension.

Summary

This is the first study that has demonstrated a post-operative, gender effect on vascular inflammation with beneficial results in females that may partly explain the more favorable clinical outcome in females undergoing this procedure.

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