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Gender Effect on vascular responsiveness after bariatric surgery

Research Article

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Abstract: Obesity, particularly abdominal obesity, is associated with increased risks of arterial hypertension, diabetes mellitus, hyperlipidemia, sleep apnea, coronary artery disease, stroke and mortality. 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. Our primary end point was to study the gender effect on vascular responsiveness (endothelial function and the ankle brachial index [ABI]) 3 months post bariatric surgery. Our secondary end points were to study the effect of gender on antropometric parameters (BMI, waist circumference) and chronic diseases (diabetes mellitus type II, arterial hypertension) 3 months following bariatric surgery, and to find independent variables that may affect and predict the post-operative clinical outcome. Methods: In this prospective study, patients were evaluated one day before surgery and 3 months afterwards. Ankle brachial index was measured while the patient was supine after 15 minutes rest and measurement of the systolic blood pressure in all four extremities was done. The brachial artery method was used to measure endothelial function expressed as flow mediated diameter percent change (FMD %). FMD% more than 10% is considered a normal response. Results: Compared with diabetic females, diabetic males had a higher postoperative BMI (men with diabetes mellitus did not lose weight as much as diabetic women) (β=-0.299; P=0.04), while women with diabetes mellitus had a more significant reduction in BMI postoperatively (β=+0.287; P=0.04). Following bariatric surgery, 12 of the 21 patients with diabetes mellitus type II did not need any medications for diabetes (kept HbA1c% less than 6.5%). All other diabetic patients improved their diabetes mellitus status. Women significantly improved their ABI (average increase of 0.07, p=0.04) and their endothelial function (FMD% change was improved from -3.5$\pm$9.0% to 14.8$\pm$8.1%, an improvement of 18.3%, p<0.001). Systolic blood pressure was decreased significantly (by 6.6 mmHg, p=0.04). Men improved their endothelial function (FMD% change was improved from -1.3$\pm$10.1% to 11.7$\pm$6.2%, p<0.001), but no significant change was observed in systolic blood pressure (p=0.29) nor in ABI (P=0.8). A linear regression analysis found that a higher baseline FMD% significantly predicted a higher postoperative FMD% (β=0.294, P=0.03). In obese males, the higher the baseline BMI the worse the post operative endothelial function (β=-0.921, P<0.001) and the same adverse effect was documented for hypertensive men (β=-0.380, P=0.05). For females, the higher the baseline FMD% the higher the postoperative FMD% (β=+0.397; P=0.01) [a favorable outcome]. Discussion: Our study has demonstrated a possible mechanistic insight into gender effects observed in epidemiological studies through improvement in vascular response in females undergoing this operation including a better reduction in systolic blood pressure and a better weight reduction in diabetic women with improvement in ABI; unlike males, who did not improve their ABI and did not decrease systolic blood pressure, and the finding that obese diabetic males and obese hypertensive males did the worst.

Keywords: *Gender • Obesity • Endothelial function • Hypertension • Bariatric surgery*

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1. Background

Obesity, particularly abdominal obesity, is associated with increased risks of arterial 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]. Improvements in metabolic conditions associated with obesity have been reported after bariatric surgery, and in a meta analysis by Buchwald et al. 77% of patients with preoperative diabetes mellitus type II improved after the operation [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 that underwent bariatric surgery compared with the non-operative control group [6]. However, in most surgical series, the majority of patients were women, and men had higher postoperative mortality rates [7-9] and a higher postoperative morbidity regardless of weight [10]. In a propensity score-adjusted analysis of older severely obese male patients, the use of bariatric surgery compared with usual care was not associated with decreased mortality during a mean 6.7 years of follow-up [11].

Our primary end point was to study the gender effect on vascular responsiveness (endothelial function and the ankle brachial index) 3 months post bariatric surgery.

Our secondary end points were to study the effect of gender on anthropometric parameters (BMI, waist circumference) and chronic diseases (diabetes mellitus type II, high blood pressure) 3 months following bariatric surgery, and to find independent variables that may affect and predict the postoperative clinical outcome.

2. Methods

This was a prospective study. Patients were evaluated one day before surgery and 3 months afterwards. The bariatric surgery was restrictive (“sleeve” operation for 93 patients and gastric “band” operation for 9 patients). The study was approved by the Internal Review Board (IRB) of the hospital and all patients signed a consent form before enrollment. All patients had a medical history and examination, vascular measurements and fasting blood withdrawn early in the morning one day before surgery and 3 months afterwards (at the same diurnal time schedules).

2.1 Vascular measurements

Ankle brachial index (ABI) was measured while the patient was supine after 15 minutes rest and measurement of the systolic blood pressure in all four extremities was done. To measure an ankle systolic pressure, a standard adult blood pressure cuff was placed around the ankle just above the malleoli. While using the Doppler flow-meter to monitor the signal from the anterior tibial artery, distal to the cuff, the cuff was inflated to a pressure approximately 30 mm Hg above the systolic pressure to occlude flow temporarily. As the cuff was slowly deflated (2 to 5 mm Hg/s), the pressure at which the Doppler flow signal was first heard and recorded was the ankle systolic pressure. An ABI was calculated by dividing the ankle systolic blood pressure by the greater of the two systolic upper extremity systolic blood pressures. An ABI between 0.9–1.3 is considered normal. An ABI below 0.9 is indicative of peripheral artery disease. An ABI below 0.5 is indicative of severe arterial stenosis.

The brachial artery method to measure endothelial function - all measurements of the flow mediated diameter percent change (FMD %) were performed early in the morning, in a quiet and dark room and at controlled ambient temperatures between 20°C and 26°C. The patients had been fasted overnight for at least 10 hours (water was permitted), were supine and had 10 minutes rest. The subject’s right arm was comfortably immobilized in the extending position, allowing for ultrasound scanning of the brachial artery 5–10 cm above the antecubital fossa. In each examination, recording of vessel images were followed by inflation of a cuff to supra-systolic pressure (40 to 50 mmHg above systolic pressure) for 5 minutes. Then the cuff was deflated and the brachial artery diameter was imaged and recorded for 3 minutes. FMD% more than 10% is considered a normal response. An FMD% lower than 10% reflects endothelial dysfunction, which suggests a high likelihood of developing a cardiovascular event in the future. Subjects with a negative FMD% result (the artery is constricted after stress and not dilated as expected) have the worst prognosis.

2.2 Metabolic measurements

The 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 square of the height in meters (kg/m^2).

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Waist circumference was measured on a bare abdomen just above the iliac crests while the patient was standing relaxed. A high-risk waist circumference is gender-dependent: males with waist measurement over 40 inches (102 cm) and females with waist measurement over 35 inches (88 cm) are considered at risk. Waist circumference reflects abdominal adiposity.

Blood pressure was measured twice after the patient was sitting for at least 15 minutes in a comfortable chair, and an average of 2 measurements with a rest period of 2 minutes between them was recorded. Blood pressure was taken early in the morning while patients were still fasting and before performing the other vascular measurements.

2.3 Statistical analysis

Distributions of the study variables are described by percentages (categorical variables) or means and standard deviations (SDs), as appropriate. Students' t-tests were used to compare means of different clinical and biochemical parameters measured before and after the procedure. A two-sided chi-squared test was used to compare distribution differences by gender. Pearson correlation was used to study correlations between mean parameters and between the changes in the different parameters. In order to explore the correlates most affecting a change in %FMD, a linear regression model was used where FMD% change following bariatric surgery was the dependent variable. Age, smoking, prevalence of diabetes mellitus type II, prevalence of hypertension, FMD% before the procedure and BMI change (difference in pre- and postoperative BMI) were used to assess the independent impact of each of these variables by gender.

3. Results

The study was done in a Regional Governmental Hospital in the north of Israel (Galilee). Overall, 102 patients from the north of Israel were recruited to the study (73 women and 29 men, mean age 40.5±12.3 years) (Table 1).

Table 1. Clinical parameters.

	All Subjects	Women	Men	p-value
Number	102	73	29	
Age (years)	40.5±12.3	39.8±11.9	43.0±13.0	NS
Smokers	7	4 (5%)	3 (10%)	0.41
DM type 2	21	11 (15%)	10 (34%)	**0.05**
HTN	33	19 (26%)	14 (48%)	0.06

DM type II – diabetes mellitus type 2; HTN – arterial hypertension

Smoking prevalence (6%) was lower than expected for the Israeli population (22.8% overall). The high prevalence of arterial hypertension and diabetes mellitus type II were expected due to the obesity of the population studied. A significant positive correlation was found between BMI change and waist circumference change (r=0.658, P<0.001). Three months after bariatric surgery, BMI was decreased (from 43.7±5.6 to 34.8±5.8, p<0.001), waist circumference was reduced (from 129.0±13.6 cm to 111.7±13.9 cm, p<0.001) (Table 2), ABI was improved (from 1.14±0.19 to 1.19±0.16, p=0.01), and FMD% was improved (from -2.9±9.3% to 13.8±7.6%, p<0.001). Systolic blood pressure also decreased (from 135.7±15.1 mmHg to 129±16.6 mmHg, p=0.02) (Table 3).

3.1 Gender effect on weight loss

Compared with diabetic females, diabetic males had a higher post operative BMI (men with diabetes mel-

Table 2. Metabolic parameters change 3 months after bariatric surgery.

	BMI 1	BMI 2	p-value	WC 1 (cm)	WC 2 (cm)	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 – body mass index before the operation; BMI 2 - body mass index after the operation;
WC 1 – waist circumference before the operation; WC 2 - waist circumference after the operation

Table 3. Vascular parameters before and 3 months after bariatric surgery.

	FMD1%	FMD2%	p-value	ABI1	ABI2	p-value	BP 1	BP 2	p-value
Whole Group	-2.9±9.3	13.8±7.6	**<0.001**	1.14±0.2	1.19±0.2	**0.01**	135.7±15.1	129.2±16.6	**0.02**
Women	-3.5±9.0	14.8±8.1	**<0.001**	1.15±0.2	1.21±0.1	**0.04**	135.6±14.2	129.0±16.2	**0.04**
Men	-1.3±10.1	11.7±6.2	**<0.001**	1.15±0.2	1.14±0.2	**0.82**	136.1±17.5	130.1±17.5	**0.29**

FMD1% - flow mediated diameter percent change before the operation; FMD2% - flow mediated diameter percent change after the operation; ABI1 – ankle brachial index before the operation; ABI2 - ankle brachial index after the operation; BP 1 – blood pressure before the operation; BP 2 – blood pressure after the operation

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litus did not lose weight as much as diabetic women) (β=-0.299; P=0.04) while women with diabetes mellitus had a more significant reduction in BMI postoperatively (β=+0.287; P=0.04).

A linear regression model found that the only variable that predicted post-procedural waist circumference was the baseline waist circumference (P<0.001). In both genders, baseline waist circumference predicted post-operative waist circumference - in men (β=0.687, P=0.003) and in women (β=0.511, P=0.002).

3.2 Diabetes mellitus type II

Following the bariatric surgery, 12 of the 21 patients with diabetes mellitus type II did not need any medications for diabetes (kept HbA1c% less than 6.5%). All other diabetic patients improved their diabetes mellitus status; those who previously used insulin no longer needed it and commenced oral medications with a good glycemic control. Those who took oral medications before surgery required less intensive therapy.

In order to find an independent variable that could predict BMI reduction a linear regression model was used with postoperative BMI as a continuous outcome. Only baseline BMI predicted postoperative BMI (P<0.001). We also found a positive correlation between BMI change and waist circumference change (r=0.658, P<0.001; Pearson's correlation).

3.3 Gender effects on diabetes mellitus and on arterial hypertension

Gender differences seem to be borderline significant with respect to the prevalence of diabetes mellitus type II (men 34%, women 15%; P=0.05) and arterial hypertension (men 48%, women 26%; P=0.06). Seventy three women (mean age 39.8±11.9 years) underwent the bariatric surgery. Four were smokers (5%), 11 had diabetes mellitus type II (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), waist circumference was reduced (from 127.9±13.6 cm to 109.1±12.7 cm, p<0.001) (Table 2), ABI was improved (from 1.14±0.2 to 1.21±0.14, p=0.04), FMD% change was improved (from -3.5±9.0% to 14.8±8.1%, p<0.001), and systolic blood pressure was decreased (from 135.6±14.3 mmHg to 129±16.2 mmHg, p=0.04, Table 3).

Twenty nine men underwent the bariatric surgery (mean age 43.0±13.0 years). Three were smokers (10%), 10 had diabetes mellitus type II (34%) and 14 had hypertension (48%) (Table 1). Following bariatric surgery, BMI decreased (from 42.6±6.7 to 34.5±7.0, p=0.001), waist circumference was reduced (from 131.8±13.9 cm to 117.3±15.6 cm, p<0.005, Table 2), and FMD% change improved (from -1.3±10.1% to 11.7±6.2%, p<0.001). No significant change was observed in either systolic blood pressure (decreased from 136.1±17.5 mmHg to 130.1±17.5 mmHg, p=0.29) or ABI (from 1.15±0.2 to 1.14±0.2, P=0.8, Table 3).

3.4 Gender effect on endothelial function

A linear regression analysis studied the change in FMD% following bariatric surgery and found that the only significant predictor was baseline FMD% – a higher baseline FMD% significantly predicted a higher post-operative FMD% (β=0.294, P=0.03). However, when this model was stratified by gender, it was found that in male patients, baseline FMD% did not predict the postoperative FMD%. When the same linear regression analysis was done with baseline BMI as an independent variable it was found that in obese males the higher the baseline BMI the worse the postoperative endothelial function (β=-0.921, P<0.001) and the same adverse effect was documented for hypertensive men (β=-0.380, P=0.05). For females, the only variable that predicted postoperative FMD% was baseline FMD%, the higher the baseline FMD% the higher the postoperative FMD% (β=+0.397; P=0.01).

4. Discussion

Our study examined the effect of restrictive bariatric surgery on the clinical outcome of obese patients with a specific emphasis on gender effects. Our study has demonstrated that women may benefit more than men from weight loss bariatric surgery. Women tended to improve their endothelial function and ABI, and lower systolic blood pressure more effectively compared with men three months following surgery. BMI was reduced more favorably in women with diabetes mellitus type II than men with diabetes mellitus, who lost less weight compared to obese men without diabetes mellitus. Men did not reduce significantly their systolic blood pressure and no change was observed in their ABI (even though both genders had normal values, in women it tended to improve significantly). Interestingly, obese patients that underwent the bariatric operation had a lower incidence of smoking compared to the north of Israel (5% of the women in our study were smokers compared to 12.9% of the female population in the north of Israel, and only 10% of the male population in our study were smokers compared to 42.7% of the male population in the north of Israel). Men had a higher prevalence of diabetes mellitus type II and arterial hypertension compared with

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women in our study, and it may explain, in part, the less favorable outcome observed in obese male patients with diabetes mellitus or arterial hypertension undergoing this bariatric operation compared with women.

In most surgical series the majority of patients were women, and several studies have shown that mortality rates were higher in men [7-9]. The reason for this is not clear, although higher BMI and later presentation were part of the explanation. Livingston et al. [7]. demonstrated higher postoperative morbidity among 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 comparison of all cause mortality for obese surgical and non-surgical cohorts gave an adjusted mortality risk of 0.7. The adjusted mortality risk was 1.5 when the obese surgical cohort was compared with the general control cohort [12]. When the postoperative morbidity was compared with the general control cohort, the relative risk of myocardial infarction was two-fold higher and the risk for stroke four-fold higher. Despite surgery resulting in lower morbidity rates of diabetes mellitus and hyperlipidemia than the non-surgical cohort, an increased risk remained for all co-morbidities in comparison with the general population [12]. A nationwide, population-based cohort study that was conducted on 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]. However, the 4161 patients that underwent gastric bypass surgery no longer had a higher risk of diabetes mellitus or myocardial infarction (while these 2 morbidities remained increased after restrictive type surgery in 7855 patients) [13]. The adjusted mortality remained higher after both gastric bypass and restrictive surgery with no gender effect on mortality or morbidity [13]. An American retrospective cohort study of bariatric surgery programs done in Veterans Affairs medical centers 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 it is important to remember the prospective Swedish study that followed 4047 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]. These differences in postoperative mortality rates could be attributed to the different populations that were studied, the relative lack of participation of women in the VA study, the kind of bariatric operation used (gastric bypass vs. restrictive), the age of the participants, the more complicated condition of patients with co-morbid diseases that complicated the post-surgical recovery and outcome, or because of ethnicity. A recent analysis of 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 (4776 patients) found that extreme BMI values were significantly associated with an increased risk of a 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 – so actually it was a study that predominantly evaluated females.

It is possible that the gender related differences that were observed in our study are associated with inflammatory proteins and peptides that were found to be affected differently and more favorably among women (personal unpublished data). Another possibility is a different effect on hormones that have been shown to be affected by the bariatric surgery, starting a few days postoperatively, and that may have longstanding effects on the liver, pancreas and other organs. It is possible that the hormonal regulation has a more favorable long-term effect on the cardiovascular system and may explain the beneficial clinical outcome in women that has not been demonstrated in men.

4.1 The effect of bariatric surgery on diabetes mellitus

Our study has shown that patients that underwent bariatric surgery had a significant improvement in their diabetes mellitus status. Diabetes mellitus has disappeared in almost half of previously affected patients, and the other diabetic patients needed fewer medications (i.e. the ones who needed insulin no longer required it, and the ones who were treated with oral hypoglygemic medications reduced the frequency and the dosage of these medications). Surprisingly, these effects were noted soon after the operation, within the first month, and in some patients even within the first week after the bariatric surgery. It has been described before that hyperglycemia is resolved quickly after bariatric surgery but the underlying mechanism is still unclear. Comparing gastric bypass versus gastric restrictive surgery it was found that both had a similar effect on weight loss and reduction in fasting glucose. However, insulin sensitivity increased only after gastric bypass surgery and was

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not changed following the restrictive surgery, and there was a robust increase in insulin secretion, glucagon-like peptide 1 and beta cell sensitivity to glucose only after gastric bypass surgery [17]. A study that examined multiethnic adults showed that among 1603 adults (66% Hispanic, 77% females) who underwent bariatric surgery, 377 patients had diabetes mellitus type II, 107 had fasting plasma glucose >126 mg/dL, and 276 were pre-diabetic. Three years after surgery, all groups had a normal fasting plasma glucose and patients who had diabetes mellitus decreased their HBA1C% by 2.3%. Patients with pre-diabetes had the most dramatic weight loss [18]. In order to determine the impact of the bariatric procedure performed, a meta-analysis found that 78% of diabetic patients had complete resolution, and diabetes was improved in 87% of patients. Weight loss and diabetic resolution were greatest in patients undergoing biliopancreatic diversion/duodenal switch, followed by gastric bypass, and least for restrictive procedures [18].

We found a gender effect on weight lose among obese diabetic patients. Diabetic males had a higher postoperative BMI (compared with men without diabetes mellitus), while diabetic females had a more significant reduction in BMI after the procedure. Again, we demonstrate a favorable effect for females, especially in the high-risk group of obese patients with diabetes mellitus type II.

4.2 The bariatric surgery effect on endothelial function

Obesity is associated with an increased cardiovascular risk. Endothelial function is impaired in obesity and represents the earliest stage of clinical atherosclerosis. Abnormalities of endothelial function worsen with increased weight owing to several mechanisms associated with excess fat mass including impaired glucose tolerance, insulin resistance, metabolic dysregulation, adipocytokine release and systemic inflammation that play a key role in the evolution and clinical expression of cardiovascular disease [19,20]. It has been demonstrated that short term weight loss (not by surgery) improves endothelial function within weeks via mechanisms that were related more to metabolic changes than the degree of weight loss [21-24]. Following non-surgical sustained weight loss, FMD increased significantly but remained blunted in patients without weight decline, and the vascular improvement was correlated most strongly with glucose levels and was independent of weight change [25]. Bariatric surgery resulted in a decrease in BMI with improvement in glucose and lipid metabolism, the carotid intima thickness was diminished significantly and the flow mediated diameter improved from severe dysfunction to normal values. Both carotid intima thickness and FMD% were associated with intra-abdominal fat [26]. A study that compared FMD% and coronary blood flow (CBF) in 50 obese patients who underwent bariatric surgery and in 20 comparable obese controls found that baseline FMD% and CBF were similar in the two groups, but after three months FMD% and CBF were significantly improved in patients who underwent the bariatric surgery but not in patients in the control group. C-reactive protein (CRP) levels were also significantly reduced after 3 months in patients who underwent the bariatric surgery, with no change in CRP level in the control group; however, the favorable vascular effects observed in the bariatric surgery group were independent of other cardiovascular risk factors, basal values or changes in CRP [27]. Other studies describe the same phenomena of a significant decrease of VEGF, leptin, ghrelin and insulin following bariatric surgery (some of them only with gastric bypass surgery) in parallel with weight reduction [28,29], with a greater weight loss and a more pronounced improvement in endothelial function following surgical intervention compared with medical treatment alone [29]. Following surgery there was a significant reduction in levels of different markers of inflammation – like intercellular cell adhesion molecule 1 and E-selectin - that take an active part in endothelial activation and atherogenesis [30,31]. It is important to mention that in all studies that were reported in relation to endothelial function and inflammation, the population studied included more than 80% women, and no gender effect analysis was done. In our study, we found a difference in vascular responsiveness - only females improved their ABI and significantly reduced their systolic blood pressure following the bariatric surgery, while males did not demonstrate such favorable effects.

5. Summary

Bariatric surgery is considered the best treatment for long-term weight reduction, with favorable effects on metabolic and endocrine parameters and a significant improvement in endothelial function and reduction in cardiovascular risk. However, most of the studies were done mainly on women and some epidemiological studies raised doubts about the efficiency and benefit of these bariatric operations for weight reduction in obese males. Several explanations were suggested including the possibility that obese male patients have more comorbid conditions and have more complications due to these conditions.

Our study has demonstrated a possible mechanistic insight into these gender effects on the clinical outcome

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post bariatric surgery and has shown clearly that women gain more than men – in improving vascular response, a better weight reduction (especially in diabetic women), and a significant reduction in systolic blood pressure. We also found that, unlike diabetic obese women, diabetic and non-diabetic obese men who had hypertension did much worse than men without these co-morbidities.

These results may explain in part the epidemiological data that described more morbidity and mortality among obese men that underwent the bariatric operation for weight loss, especially older men, and the ones who had diabetes mellitus and hypertension.

This is the first study that has demonstrated a gender related difference in the post-bariatric surgery vascular responses that may affect clinical outcome and the cardiovascular morbidity and mortality.

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