Effect of bariatric surgery on flow-mediated dilation and carotid intima-media thickness in patients with morbid obesity: 1-year follow-up study

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Abstract

Objective: Obesity is associated with increased cardiovascular (CV) mortality and morbidity. Bariatric surgery (BS) is currently an established therapeutic approach for severely obese patients. Carotid intima-media thickness (CIMT) and brachial artery flow-mediated dilation (FMD) provide important prognostic information beyond traditional CV risk factors. This study aimed to examine the effect of bariatric surgery-induced weight loss on CIMT and brachial artery FMD in morbidly obese patients.

Methods: A total of 23 morbidly obese patients (40.4±5.6 years, 13 females) were examined before and after BS for 1 year with 3-month periods. CIMT, FMD, body composition, and metabolic parameters were determined.

Results: All the patients exhibited significant weight loss following BS ($p<0.001$). Carotid intima-media thickness reduction was not significant from baseline to 6 months ($p=0.069$), but at 9 months ($p=0.004$), it became significant. Similarly, the difference between the preoperative and 6-month FMD assessments was not significant ($p=0.057$), but at 9 months ($p<0.001$), it became significant.

Conclusion: Our study reveals that weight loss following BS causes improvements in CV risk factors, which is evident after 9 months of surgery. *(Anatol J Cardiol 2020; 23: 218-22)*

Keywords: atherosclerosis, obesity, bariatric surgery, weight loss, intima-media thickness flow-mediated vasodilation

Introduction

Obesity is one of the most significant and increasing health problems worldwide. It is associated with increased cardiovascular (CV) mortality and morbidity (1). The burden of excess weight is related to the development of most CV risk factors, such as type 2 diabetes mellitus (DM), hypertension (HT), and dyslipidemia (1). Furthermore, obesity has direct negative effects on the atherosclerotic process and on endothelial function (2, 3). In obese patients, subclinical atherosclerosis and endothelial dysfunction are substrates for CV disease and robust predictors of future CV events (4, 5).

Bariatric surgery (BS) is currently an established therapeutic approach for severely obese patients. The indications for BS in patients aged 18–65 years include a body mass index (BMI) ≥40 kg/m^2 (defined as morbid obesity) or BMI of 35–40 kg/m^2 with co-morbidities, the severity of which is expected to decrease with weight reduction (6).

Carotid intima-media thickness (CIMT) is a marker of subclinical atherosclerosis and is widely accepted as one of the significant predictors of CV events (7-10). Similarly, brachial artery flow-mediated dilation (FMD) is recognized as a surrogate marker of endothelial dysfunction and an independent predictor of CV events (11, 12). Both CIMT and FMD provide important prognostic information beyond traditional CV risk factors.

Bariatric surgery (BS) has been shown to result in an effective, long-term weight loss and in the amelioration of the most obesity associated risk factors of obesity (13, 14). In morbidly obese patients, few data exist on significant weight loss-induced changes in CIMT and impaired endothelial function as defined by brachial artery FMD (15, 16). The present study aimed to examine the effect of BS-induced weight loss on CIMT and brachial artery FMD in patients with morbid obesity.

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Methods

Twenty-three severely obese patients (40.4±5.6 years, 13 females) undergoing BS (Roux-en-Y gastric bypass) were enrolled in our study. Patients desiring surgical intervention for the treatment of obesity were initially referred to the surgical department to determine their eligibility for surgery. If a subject was eligible, an operation was scheduled after workup at the outpatient clinic for metabolism, where patients were consecutively screened for eligibility and enrolled when informed consent was given. Exclusion criteria were overt DM, HT, history of CV disease, secondary causes of obesity, pregnancy, lipid-lowering medication, acute or chronic liver diseases, chronic kidney disease, chronic obstructive pulmonary disease, smoking (>10 cigarettes/day), obstructive sleep apnea, and a history of an average alcohol consumption of more than 20 g alcohol per day. Patients with acute infectious and inflammatory diseases were excluded by taking a medical history and conducting physical and laboratory examinations. In all patients included in the study, physical examination, medical interview, and basic laboratory tests were conducted and electrocardiography performed. Body composition (lean mass and fat mass) was determined by impedance analysis using Body Composition Analyzer from Biospace Europe (Germany) with an integrated scale. All measurements were performed in the morning in the fasted state. The study was approved by the Local Ethics Committee of İstanbul University İstanbul Faculty of Medicine.

Flow-mediated dilation evaluation by brachial artery high-resolution ultrasound imaging

FMD was measured according to guideline (17) with ultrasound unit electronic calipers (VIVID 7 General Electric, Wisconsin, and USA) and 10 MHz linear array transducer. To best visualize the brachial artery, the arm was comfortably immobilized in the extended position, and the brachial artery was scanned in a longitudinal section 3–5 cm above the antecubital fossa. The diameter of the artery is measured in basal conditions. A pneumatic cuff, inflated to a pressure higher than the subject's systolic blood pressure, is used to induce compression for 5 min, after which the cuff is deflated and the diameter of the artery is measured again. FMD is calculated as the percentage difference between the maximum postischemic diameter and the average basal diameter:

FMD=[(postischemic diameter–basal diameter)/basal diameter]×100.

Measurements of carotid intima-media thickness

Carotid intima-media thickness was measured according to the method described previously (18). Longitudinal scanning was performed from the common carotid artery to the bifurcation point, with the subject in the supine position. After bifurcation of the common carotid artery had been confirmed, CIMT was measured from the far wall of the internal carotid artery within 10 mm proximal to the bifurcation. Three points were measured on one scan, which was synchronized with R-wave peaks on the electrocardiogram to avoid possible errors resulting from variable arterial compliance. The mean CIMT was calculated from six measurements on two scans by two different observers.

Instrumental investigations and blood tests were repeated 3, 6, 9, and 12 months after surgery for comparison with the preoperative findings.

Statistical analysis

Data were tested for normality using the Shapiro–Wilk test. Normally distributed data are expressed as mean ± SD, whereas data that are not normally distributed are expressed as median and interquartile range. Analysis of variance in parametric repeated measurements and non-parametric Friedman test for non-parametric measurements were used to compare repeated measurements, and post hoc analysis of the measurements were tested using the Bonferroni (Dunn) test in both groups. A two-sided p-value smaller or equal to 0.05 was considered statistically significant. All analyses were conducted using SPSS 16 for Windows (SPSS, Chicago, IL, USA).

Results

All morbidly obese patients (BMI 52±6.9 kg/m^2) were reassessed at 3, 6, 9, and 12 months after surgery in order for them to undergo postoperative evaluation. A comparison of basic anthropometric and biochemical parameters in patients before and after BS is presented in Tables 1, 2. All patients exhibited significant weight loss following BS. Moreover, the BMI reduction in patients, both from baseline to 6 months and from 6 to 12 months, was statistically significant (p<0.001).

Statistically significant differences were found in glucose, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, and high-sensitivity C-reactive protein (hsCRP) concentrations. The difference in LDL cholesterol levels between the preoperative and the 3-month

Table 1. Anthropometric measurements before and after bariatric surgery

Parameter (n=23)	Baseline	Follow-up		*P*-value
		3 months	12 months	
Weight (kg)	[a]148±27	[b]121±21	[c]108±20	<0.001
BMI (kg/m^2)	[a]52±6.9	[b]43±6.3	[c]38±5.8	<0.001
Fat mass (%)	[a]48.7±7.1	[b]40.9±7.2	[c]37.6±8.1	<0.001
Fat mass (kg)	[a]71.8±16.8	[b]49.9±12.9	[c]41.3±13.7	<0.001
Lean mass (kg)	[a]75.9±17.3	[b]71.7±15.1	[c]67.1±13.2	<0.001

Values are expressed as mean±SD; BMI - body mass index; a, b, c are expressed for statistically significant difference from each measurement

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Table 2. Biochemical measurements before and after bariatric surgery

Parameter (n=23)	Baseline	Follow-up				*P*-value
		3 months	6 months	9 months	12 months	
Triglyceride (mg/dL)	[a]148±70	[a]112±40	[b]98±35	[b]93±35	[c]87±36	<0.001
HDL (mg/dL)	[a]41±7	[a]42±6	[a]43±6	[a]45±7	[b]47±7	<0.05
LDL (mg/dL)	[a]126±33	[a]108±36	[a]106±34	[b]106±47	[c]104±47	<0.001
Glucose (mg/dL)	[a]106±18	[a]95±16	[a]87±13	[b]85±11	[c]83±11	<0.001
BUN (mg/dL)	[a]6.1±1.4	[a]5.9±1.8	[a]5.1±1.8	[a]6±2	[a]5.9±1.8	0.056
Creatinine (mg/dL)	[a]0.8±0.2	[a]0.8±0.2	[a]0.8±0.1	[b]0.8±0.2	[b]0.7±0.1	<0.001
Sodium (mEq/L)	[a]140±2	[a]142±2	[a]142±1.5	[a]142±1.4	[a]141±1.5	0.249
Potassium (mEq/L)	[a]4.3±0.3	[a]4.2±0.4	[a]4.2±0.3	[a]4.4±0.3	[a]4.4±0.3	0.092
hsCRP (mg/dL)	[a]10.1±6.9	[a]7.7±7.8	[b]4.1±3.3	[b]3.2±3.0	[b]4.1±4.0	<0.001
WBC (10^3/mm^3)	[a]8.7±1.9	[b]7.1±1.2	[b]7.6±1.4	[b]7.9±2.2	[b]7.7±1.9	0.014
RBC (10^6/mm^3)	[a]4.7±0.5	[a]4.7±0.6	[a]4.6±0.6	[a]4.6±0.4	[b]4.6±0.4	0.047
HGB (g/dL)	[a]12.9±1.5	[a]12.6±1.5	[a]12.8±1.6	[a]13±1.2	[a]12.8±1.3	0.47
HCT (%)	[a]39.6±4.6	[a]38.9±4.5	[a]39±4.9	[a]39.5±3.7	[a]38.8±3.8	0.453
PLT (10^3/mm^3)	[a]291±74	[a]274±110	[a]265±69	[a]267±67	[b]255±61	<0.001

Values are expressed as mean±SD. HDL - high-density lipoprotein, LDL - low-density lipoprotein, BUN - blood urea nitrogen, hsCRP - high-sensitivity C-reactive protein, WBC - white blood cell, RBC - red blood cell, HGB - hemoglobin, HCT - hematocrit, PLT – platelet; a, b, c are expressed for statistically significant difference from each measurement

values was significant (p<0.001), but the further improvement, between 3 and 12 months, was not (p=0.32). Similarly, the difference in triglyceride and hsCRP levels between the preoperative and the 3-month values was significant (p<0.001), but the further improvement, between 3 and 12 months, was not (p=0.26). The HDL cholesterol improvements were less significant (p=0.038). The results of the comparative analysis of the markers of artery function in patients qualified for BS are summarized in Table 3. CIMT reduction was not significant from baseline to 6 months (p=0.069), but at 9 months (p=0.004), it became significant. Similarly, the difference between the preoperative and 6-month FMD assessments was not significant (p=0.057), but at 9 months (p<0.001), it became significant. The measurements in basal (0 month) and the follow-up after surgery on 3, 6, 9, and 12 months were compared in Table 4. Interobserver correlation for determining CIMT was assessed using the intraclass correlation coefficient (ICC) test, and a strong correlation between the observers was found (ICC: 0.96, p<0.001).

Discussion

Obesity is classified as a major and modifiable risk factor for CV disease and is associated with metabolic disorders, such as dyslipidemia, insulin resistance, and DM, which are also known as significant CV risk factors (19). Bariatric surgery has become the most efficient treatment option for morbidly obese patients by inducing prominent and sustained weight loss with beneficial effects on CV risk factors. In this study, we investigated the impact of BS on weight loss in morbidly obese subjects in addition to its effects on CIMT and brachial artery FMD as instrumental parameters for CV risk assessment.

Weight loss by either sleeve gastrectomy or gastric bypass results in the majority of patients in a shift toward a more favorable lipid profile with reduced LDL cholesterol, improved HDL cholesterol, and lower triglyceride levels, as well as lower fasting glucose levels (20, 21).

Laimer et al. (22) found that CRP, which is one of the most important biomarkers of atherosclerosis and chronic inflammation,

Table 3. Measurements of CIMT and FMD before and after bariatric surgery

Parameter (n=23)	Baseline	Follow up				*P*-value
		3 months	6 months	9 months	12 months	
CIMT (mm)	[a]0.79±0.19	[a]0.73±0.14	[a]0.71±0.13	[b]0.68±0.12	[b]0.65±0.11	<0.001
FMD (%)	[a]6.8±2.6	[a]6.5±2.6	[b]8±3	[b]8.9±2.4	[b]8.4±2.2	<0.001

CIMT - carotid intima-media thickness, FMD - flow-mediated dilation; a, b, c are expressed for statistically significant difference from each measurement

Table 4. Comparison of the measurements in basal (0. month) and follow-up after surgery on 3, 6, 9, and 12 months

Parameters	Measurements in 0, 3, 6, 9, and 12 months					*P*-value
	Basal (0)	3 months	6 months	9 months	12 months	
τWeight (kg)	[a]148.35±27.1	[b]121.72±21.2	-	-	[c]108.36±21.2	<0.001
τBMI (kg/m²)	[a]52.08±6.98	[b]43.17±6.37	-	-	[c]38.2±5.84	<0.001
πTrigyliceride (mg/dL)	[a]148±70	[a]112±40	[b]98±35	[b]93±35	[c]87±36	<0.001
πHDL (mg/dL)	[a]41±7	[a]42±6	[a]43±6	[a]45±7	[b]47±7	<0.001
πLDL (mg/dL)	[a]126±33	[a]108±36	[a]106±34	[b]106±47	[c]104±47	<0.001
πFasting glucose (mg/dL)	[a]106±28	[a]95±16	[a]87±13	[b]85±11	[c]83±11	<0.001
πhsCRP (mg/dL)	[a]10.1±6.9	[a]7.7±7.8	[b]4.1±3.3	[b]3.2±3.0	[b]4.1±4.0	<0.001
πFMD (%)	[a]6.8±2.6	[a]6.5±2.6	[b]8±3	[b]8.9±2.4	[b]8.4±2.2	<0.001
πCIMT (mm)	[a]0.79±0.19	[a]0.73±0.14	[a]0.71±0.13	[b]0.68±0.12	[b]0.65±0.11	<0.001

τAnalysis of variance in repeated parametric measurements and πnon-parametric Friedman test were used as appropriate. a, b, c are expressed for statistically significant difference from each measurements. Values are expressed as mean±SD. BMI - body mass index, HDL - high-density lipoprotein, LDL - low-density lipoprotein, hsCRP - high-sensitivity C-reactive protein, CIMT - carotid intima-media thickness, FMD - flow-mediated dilation

is modified by pronounced weight loss. Adipose tissue promotes a state of inflammation through secretion of several cytokines, such as CRP and interleukin-6 in obese subjects (23). A In published a meta-analysis marked that BS can decrease the low-grade inflammation related with obesity by reducing the levels of systemic inflammatory markers (24).

In our study, significant reductions were observed in LDL cholesterol, glucose, hsCRP levels, and triglyceride values at 3 months follow-up. The HDL cholesterol improvements were less marked in this follow-up period. These multiple beneficial metabolic effects can be explained by efficient weight loss by BS.

It has been previously determined that CIMT and FMD provide distinct independent information about atherosclerosis (25). FMD identifies abnormalities of the endothelial function preceding the development of a structural lesion. Carotid intima-media thickness indicates the presence of vascular damage, which is suggestive of a more advanced stage of atherosclerosis.

Arkin et al. (26), in their study on 203 obese patients, found that body weight is a significant predictor of vessel dysfunction. The FMD values negatively correlated with body weight. Lupoli et al. (27) conducted a meta-analysis assessing changes in CIMT and FMD in obese patients following BS. Only 10 articles met the inclusion criteria, and 314 obese patients were analyzed. Consequently, BS was associated with a significant improvement in structural and functional markers of atherosclerosis and beneficial effects on subclinical atherosclerosis and on endothelial function. A significant reduction of CIMT (–0.17 mm), accompanied by a 5.6% increase in FMD, was also reported (27).

In the present study, CIMT reduction was not significant from baseline to 6 months follow-up, but at 9 months follow-up, it became significant. Similarly, the difference between the preoperative and 6-month FMD assessments was not significant, but at 9 months follow-up, it became significant. Accordingly, we demonstrated that changes in CIMT and FMD are significant at 9 months follow-up after the improvement in metabolic parameters. These clear effects may be related to a substantial reduction of the obesity-related inflammatory status occurring after BS. Moreover, hsCRP reduction after BS can also be accompanied by early improvements in cholesterol levels that can potentially further develop structural and functional markers of atherosclerosis. This study provides novel 1-year follow-up data on the effects of pronounced weight loss following BS on surrogate measures of atherosclerosis.

Study limitations

Our study was designed to assess the 1-year follow-up of BS on CIMT and FMD.

For this reason, different studies should express if these effects are maintained at long-term follow-up and how they relate to the beneficial effects on CV risk factors. Other limitations of our study are the relatively small sample size and the lack of a control group (morbidly obese subjects who did not undergo BS for some reason). Comparison of the degrees of improvement in CIMT and FMD between the BS group and the control group could have better demonstrated the beneficial effects of BS on CIMT and FMD. Finally, as a limitation, the final publication, "Expert consensus and evidence-based recommendations for the assessment of FMD in humans" (28), recommends the administration of sublingual nitroglycerin to evaluate non-endothelium-dependent vasodilatation. But we didn't use sublingual nitroglycerin because patients were normotensive, and some similar studies which were made without using sublingual nitroglycerin exist.

Conclusion

Our study revealed that BS is important not only in weight reduction but also in the correction of CV risk factors. Bariatric surgery-induced weight loss improves both the functional and structural markers of early atherosclerosis, which could poten-

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tially reduce future CV risk. The main results of our study are that CIMT and FMD improve significantly after the BS-induced reduction of body weight and subsequent improvements in CV risk factors. These observations merit further investigation on the beneficial effects of BS-induced weight loss on CV health in more comprehensive trials.

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