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Effect of bariatric surgery on peripheral flow-mediated dilation and coronary microvascular function

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Abstract *Background and aims:* To assess the effects of bariatric surgery (BS) on peripheral endothelial function and on coronary microvascular dilator function.
Methods and results: We studied 50 morbidly obese patients (age 38 ± 9, 13 M) who underwent BS and 20 comparable obese controls (age 41 ± 11, 6 M) without any evidence of cardiovascular disease. Peripheral vascular dilator function was assessed by brachial artery diameter changes in response to post-ischemic forearm hyperaemia (flow-mediated dilation, FMD). Coronary microvascular function was assessed by measuring coronary blood flow (CBF) velocity response to i.v. adenosine and to cold pressor test (CPT) in the left anterior descending coronary artery by transthoracic Doppler echocardiography. The tests were performed at baseline and at 3-month follow-up. At baseline, FMD and CBF response to adenosine and CPT were similar in the 2 groups. Compared to baseline, FMD at follow-up improved significantly in BS patients (5.9 ± 2.7% to 8.8 ± 2.4%, $p < 0.01$), but not in controls (6.3 ± 3.2% vs. 6.4 ± 3.1%, $p = 0.41$). Similarly, a significant improvement of CBF response to adenosine (1.63 ± 0.47 to 2.45 ± 0.57, $p < 0.01$) and to CPT (1.43 ± 0.26 to 2.13 ± 0.55, $p < 0.01$) was observed in BS patients but not in controls (1.55 ± 0.38 vs. 1.53 ± 0.37, $p = 0.85$; and 1.37 ± 0.26 vs. 1.34 ± 0.21, $p = 0.48$, respectively). The favourable vascular effects of BS were similar independently of the presence and changes of other known cardiovascular risk factors and of basal values and changes of serum C-reactive protein levels.
Conclusions: Our data show that, in morbidly obese patients, together with peripheral endothelial function, BS also improves coronary microvascular function. These effects suggest

Abbreviations: BMI, body mass index; BS, bariatric surgery; CAD, coronary artery disease; CBF, coronary blood flow; CMVD, coronary microvascular dysfunction; CPT, cold-pressor test; CRP, C-reactive protein; CVRF, cardiovascular risk factor; FMD, flow-mediated dilation; LAD, left anterior descending; NMD, nitrate mediated dilation; WHR, waist to hip ratio.

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global improvement of vascular function which can contribute significantly to the reduction of cardiovascular risk by BS reported in previous studies.

Introduction

Previous studies have shown that obesity is associated with systemic endothelial dysfunction [1] and with coronary microvascular dysfunction (CMVD) [2], both of which may predict the development of obstructive coronary artery disease as well as of cardiovascular events [3–5].

The mechanisms responsible for the negative effects of obesity on vascular function, however, are not completely clear yet. The high frequency of classical cardiovascular risk factors (CVRFs) associated with obesity can play a role. However, visceral fat is also an important endocrine and paracrine organ which secretes substances (e.g., inflammatory cytokines, angiotensin II, leptin and resistin) that can alter vascular function through direct negative effects [6] or even indirectly through induction of insulin resistance [7,8].

In obese patients bariatric surgery (BS) results in a significant reduction of body weight. Widely accepted indications to BS currently include body mass index (BMI) $\geq$40 kg/m^2 or BMI $\geq$ 35 kg/m^2 in presence of important comorbidities. Long-term follow-up of patients has shown that BS is associated with a significant decrease in global and cardiac mortality in these patients [9,10].

The reasons for the reduced cardiovascular risk associated with BS are likely multiple [11,12], but an improvement of vascular function might play a significant role. While previous reports showed an improvement of peripheral endothelial function by BS [13], no previous study investigated whether BS improves coronary microvascular function. In this study we investigated this issue, also assessing whether the effects of BS on coronary microvascular function showed any relation with those on peripheral endothelial function.

Methods

Subjects

We studied 50 consecutive subjects (age 38 $\pm$ 9 years, 13 men) with a diagnosis of morbid obesity according to the World Health Organization (WHO) guidelines [14], who were admitted to the BS Unit of our University hospital, to undergo BS intervention.

As a control group, we studied 20 consecutive subjects who decided not to undergo BS and were comparable as to age (41 $\pm$ 11 years, 6 men).

Both BS and control patients were excluded if they had any suspect of cardiovascular disease, according to clinical history, physical examination, electrocardiogram and 2D-color Doppler echocardiogram. Patients were also excluded if they had any acute or chronic inflammatory disease, malignant disease, asthma or any history of alcohol or drug abuse.

The presence of CVRFs was carefully assessed in all patients. Hypertension was diagnosed if blood pressure was >140/90 mmHg or the subject was taking any anti-hypertensive drugs. Hypercholesterolemia was diagnosed if either total blood cholesterol level was >200 mg/dL, LDL cholesterol was >130 mg/dL or the subject was taking any anti-cholesterolemic drugs. Active smoking was diagnosed if the subjects had smoked any cigarette in the last month. Diabetes was diagnosed if fasting blood glucose was >126 mg/dL or it was $\geq$200 mg/dL at 2 h of a tolerance test with 75 g of glucose (OGTT) [15]. Impaired glucose tolerance (IGT) was diagnosed when blood glucose was $\geq$140 and $\leq$200 mg/dL at 2 h of an OGTT [15].

Study protocol

At baseline all patients underwent assessment of peripheral flow-mediated dilation (FMD) and nitrate mediated dilation (NMD), and assessment of coronary blood flow (CBF) response to adenosine and to cold pressor test (CPT). The same tests were repeated 3-months after BS in the study group and at 3-month follow-up in the control group.

All study investigations were carried out in the early afternoon hours, in a fasting state, after washout of medications for at least 5 half-lives. All patients gave informed consent to participate in the study. The study was approved by the Review Board of our Institution.

Flow-mediated dilation (FMD)

The FMD tests were all performed by the same expert operator. Subjects rested in the supine position for at least 10 min in a warm, quiet room (22–24 °C) before testing. A 10 MHz multi frequency linear array probe attached to a high-resolution ultrasound machine (Siemens® Acuson Sequoia) was used to acquire images of the right brachial artery.

Brachial artery diameter was measured throughout the whole test using a totally automated system, described in detail elsewhere [16]. By this system, after the operator has chosen the arterial segment to analyze, the software automatically identifies the internal edges of the vessel and tracks the walls of the artery via the brightness intensity of the walls vs. the lumen of the vessel. Then the software provides a diameter measurement every second throughout the test. Importantly, the probe is kept in a fixed position by a mechanical support throughout the examination.

In our patients, after baseline images of the brachial artery were obtained for 1 min, a forearm cuff, positioned 1 cm under the antecubital fossa, was inflated to 250 mm Hg. The cuff was released 5 min after the inflation with a consequent forearm reactive hyperaemia. The basal diameter was defined as the average of all measures collected during the first minute, and FMD was calculated by the software as the maximum percent change of the brachial artery diameter following hyperaemia compared to the basal diameter [16]. Maximal Doppler flow velocity was also measured at baseline and at peak of forearm