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RESEARCH ARTICLE

Association of Carotid Intima-media Thickness and Cardiovascular Risk Factors in Women Pre- and Post-bariatric Surgery

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Abstract
Background Obesity is associated with cardiovascular risk factors (CVRFs), such as hypertension, hypertriglyceridemia, and low levels of high-density cholesterol (HDL-C). In obese patients with a body mass index (BMI) of ≥40 kg/m^2 or 35–40 kg/m^2 associated with CVRFs, weight loss may be achieved more effectively by bariatric surgery on reducing several CVRFs. Carotid intima-media thickness (C-IMT) is an indicator of early atherosclerosis, and may be correlated with CVRFs. Our objective was to correlate C-IMT with CVRFs before (baseline data) and after surgery, and to observe whether weight loss is followed by a regression of C-IMT.
Methods Eighteen women who had undergone bariatric surgery participated in this study. Assessments were carried out on the baseline date, and 3, 6, and 12 months after surgery. Some of the CVRFs analyzed were: total cholesterol (TC) levels, HDL-C, triglycerides to HDL-C ratio (TG/HDL-C) and fasting plasma glucose. C-IMT was measured by B-mode ultrasound.
Results A positive correlation was found between C-IMT and age and triglyceride level (p=0.002 and p=0.02, respectively). Six months after surgery, we found a significant reduction in C-IMT (p<0.05), which was significantly correlated with TG level and systolic pressure (p<0.05).
Conclusion The weight loss achieved with bariatric surgery resulted in regression of C-IMT. This regression could be observed 6 months following surgery, with an additional benefit at 12 months. Also, this finding was correlated with a reduction in triglyceride levels and systolic blood pressure.

Keywords Cardiovascular risk · Weight loss · Bariatric surgery · Intima-media thickness

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Introduction

According to the World Health Organization (WHO), there are approximately one billion overweight people worldwide. Of these, 300 million are obese [1]. Hypertriglyceridemia, low-plasma high-density cholesterol (HDL-C) levels, and glucose abnormalities associated with obesity also represent risk factors (RF) predictive of cardiovascular disease

(CVD). These metabolic changes are components of the so-called metabolic syndrome (MS) [2, 3]. Metabolic syndrome is not clearly defined in the literature, and this definition has been continuously modified over the last few years [4–6].

Despite the link between MS and obesity, not all obese patients have the metabolic abnormalities of MS. In a review of several studies, Sims describes “metabolically healthy obese patients” who lack any of the components of this syndrome [7]. On the other hand, patients with normal BMI, but increased intra-abdominal adiposity may show some criteria for the diagnosis of MS [8]. The literature shows computed tomography to be the gold standard in assessing intra-abdominal adiposity [2]; however, the measurement of waist circumference has been widely used as a surrogate assessment. Waist circumference provides a more practical way of estimating intra-abdominal adiposity, and has also shown a better correlation with metabolic risk factors than high body mass index (BMI) [8].

Atherogenic dyslipidemia is defined by high levels of LDL-cholesterol (LDL-C), triglycerides (TG), triglycerides/HDL-C (TG/HDL-C) ratio >3 and low levels of HDL-cholesterol (HDL-C) [9]. The particle size of LDL-C (dense, small particles) is strongly associated with TG/HDL-C ratio [10] and increased cardiovascular risk. LDL-C particle size has also been linked with a high incidence of CVD [11], increased incidence of angiographically proven coronary artery disease [12], and increased carotid intima-media thickness (C-IMT) [13]. The thickening of the intima-media layer is described as an early atherosclerotic change, and is also correlated with the cardiovascular risk factors (CVRFs) [11].

It is well-known that weight loss is one of the most effective measures for reducing atherogenic dyslipidemia, insulin resistance, and therefore CVRFs. [9, 14]. In patients with a BMI≥40 kg/m^2 or 35–40 kg/m^2 associated with cardiovascular risk factors [15], weight reduction may be more efficiently achieved by surgical procedures (bariatric surgery) compared to diets, physical activity, and/or pharmacological treatment [9, 15]. Surgical outcome is considered successful when a stable and significant weight reduction [20–30 kg] is obtained and maintained for at least 1 year after surgery [15], and when there is a significant reduction in cardiovascular risk factors [16].

Consequently, a reduction in body weight may normalize the metabolic parameters related to metabolic syndrome in most patients [15, 17], and may also affect some markers of early atherosclerotic changes such as C-IMT [18]. However, the benefits of weight loss obtained by bariatric surgery, and its association with C-IMT changes, are not well defined in the literature [19]. Thus, the purpose of this study was to evaluate the influence of weight loss on cardiovascular risk factors and C-IMT thickening, and the association between C-IMT and changes in cardiovascular risk factors.

Methods

Thirty-nine women who underwent bariatric surgery between September 2005 and September 2006 were initially included in this study. Of these, eighteen were able to be monitored during the 12-month period following surgery. The main inclusion criteria for this study were: patients with a BMI>40 kg/m^2 (grade 3 obesity) or between 35 and 40 kg/m^2 (grade 2 obesity) in association with cardiovascular risk factors such as hypertension, dyslipidemia, glucose abnormalities, and a history of smoking [16]. All the surgeries were performed using the Fobi–Capella technique (Roux-en-Y gastric bypass) [15, 20, 21].

The patients were also evaluated for metabolic syndrome, according to the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III criteria (NCEP ATPIII) [4]. The patients were diagnosed as having metabolic syndrome if they met three or more of the NCEP ATP III criteria. At the baseline, none of the patients were taking any type of lipid-lowering agent. Ten patients (57%) were diagnosed with hypertension at the baseline, and three (16.7%) had type 2 diabetes mellitus.

The study consisted of a five-stage protocol, as follows:

1. Prior medical history including age, previous history, and duration of type 2 diabetes, hypertension, smoking history, and current medications.
2. Anthropometric measurements such as weight (kg), height (m), and waist circumference (cm) were performed with the patient wearing light clothes and no shoes. BMI was calculated as weight (kg) divided by height squared (m^2) and waist circumference was measured at the umbilicus using a tape measure, with the patient supine.
3. A fasting venous blood sample was collected. The parameters assessed were as follows: fasting plasma glucose (FPG), total cholesterol (TC), HDL-C, LDL-C, and triglycerides. The triglycerides/HDL ratio was calculated as an atherogenic index, as previously described in the literature [10]
4. Systolic (SBP) and diastolic blood pressure (DBP) were obtained with the patient in the seated position, after 5 min of rest, using a calibrated sphygmomanometer. Three consecutive measurements were carried out and the mean was used for the analysis.
5. C-IMT was measured by B-mode ultrasound (General Electric-GE, Logik Book) with a linear transducer of

7.5 to 10 MHz [22]. The patients were examined lying on their backs, by a physician who was blind for the patients' cardiovascular risk factors and weight loss status. Three equidistant measurements were taken on the posterior wall of the right and left common carotid artery, at a distance of 1 to 1.5 cm from the bulb. The lumen diameters of both common carotid arteries were also measured. The mean value of these six equidistant measurements was calculated and used in the data analysis.

Twenty one patients who did not complete the 1-year follow-up were not included in the final analysis.

All the above-mentioned assessments were carried out at the baseline and at 3, 6, and 12 months after surgery. The timeframe for blood sample collection, blood pressure determination, waist circumference measurement, and ultrasound exam did not exceed 21 days. All the subjects were informed about the study protocol, and signed an informed consent form prior to any study-related procedures. This study was previously approved by the Ethics Committee of the Federal University of São Paulo.

Results

Table 1 shows clinical data for the patients studied. The mean age was 44.1±9.8 years and the mean BMI was 44.3±6.4 kg/m^2. At the baseline, we found that 55.6% of the patients had low HDL-C levels, 50% had high levels of total cholesterol, and 33.4% had high levels of triglycerides. Ten (47%) out of the eighteen patients with high blood pressure were receiving treatment for hypertension. Three (16.6%) were diagnosed with type 2 diabetes mellitus, of which two were being treated pharmacologically with an oral agent. Twelve (67%) of the patients presented three or more components of the metabolic syndrome at the baseline. At the end of the 6-month follow-up period, three of the patients still showed criteria for MS, compared with one patient at the end of the 12-month follow-up period. Due to the small sample size, no statistical analysis was performed in this subgroup.

A total of 144 ultrasound measurements were performed on the 18 patients who successfully completed the 1-year study period. At the baseline, C-IMT ranged from 0.53 mm to 0.84 mm, with a mean of 0.73±0.12 mm. Three carotid bulbs showed calcified plaques resulting in clinically insignificant stenosis (less than 50% of the lumen). There were no changes in the degree of stenosis during the study period. A higher C-IMT was associated with older patients and with a higher triglyceride level in the baseline measurements ($p<0.05$).

There was a statistically significant decrease in C-IMT at 6 and 12 months post-surgery, from 0.73±0.12 at the baseline to 0.63±0.12 ($p<0.05$) and 0.60±0.12 ($p<0.05$) at 6 and 12 months, respectively (Fig. 1). We did not find any statistical difference in C-IMT between the baseline and month 3 and between months 6 and 12. Also, there was no change in lumen diameter throughout the study. Reductions in waist circumference, BMI, plasma levels of LDL-C, triglycerides, and TG/HDL-C ratio were statistically significant (Fig. 2; $p<0.05$), although we did not find any correlation in between C-IMT and these measurements (Table 1). Reductions in plasma levels of HDL-C and fasting plasma glucose were not significant (Table 1).

The regression of C-IMT during the study period showed a statistically significant correlation with the reduction in triglyceride levels ($p=0.03$) and systolic blood pressure ($p=0.03$). Regarding the metabolic syndrome criteria, we noted that FPG and HDL-C did not change with weight loss during the 12 months of follow-up. The triglyceride value showed a gradual decrease with reduction in weight after surgery. This change was observed from month 3 to month 12 (96.4±23.9; 84.3±26; 71.8±22.2;

Table 1 C-IMT and in clinical and metabolic variables along the 12-month monitoring ($n=18$)

Variable	Baseline	3 months after the surgery	6 months after the surgery	12 months after the surgery
C-IMT (mm)	0.73±0.12	0.79±0.08	0.63±0.12*	0.60±0.12*
FPG (mg/dl)	97.9±29.6	84.7±7.3	81.2±13.7	86.9±10.2
Triglycerides (mg/dl)	145.7±72.7	96.4±23.9**	84.3±26**	71.8±22,2**
HDL-C	51.9±15.7	47.7±10.7	51.8±12.9	54.2±9.9
LDL-C	108.5±33.6	93.5±20.9	84.3±21.3*	83.2±21.8*
SBP (mmHg)	131.1±14.5	125.7±21.1	118.6±20.3	110.9±14.8*
DBP (mmHg)	88.7±8.9	85.3±15.6	79.9±11.3	76.8±9.6*
BMI (kg/m2)	44.3±6.4**	36±6.3	31.8±4.7	27.4±8.1
WC (cm)	120.2±12.8	104.4±12.8*	97.3±13.2*	89.2±11.9*
Trig/HDL ratio	2.56 (1.77–3.75)	1.97(1.59–2.59)	1.64 (1.32–1.78)**	1.15 (0.98–1.78)**

*$p<0.05$ vs. baseline
**$p<0.001$ vs. baseline

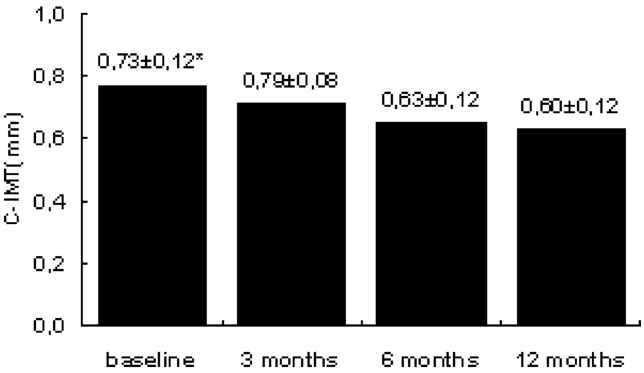

Fig. 1 C-IMT regression during 12 months of study (*$p<0.05$ vs. 6 and 12 months after the surgery)

Fig. 2). For both systolic and diastolic blood pressure, we found a similar profile to that seen for triglycerides, i.e., the patients had a mean decrease of 20.2 mmHg in SBP and 11.9 mmHg in DBP, as shown in Table 1. A non-significant decrease in LDL-C levels was observed in the first 3 months after surgery. This decrease became statistically significant 6 months after surgery (Table 1) and remained so for up to 1 year.

As expected, BMI and waist circumference showed a progressive decrease during the observation period. The percent change in BMI from the baseline to month 12 was 38.1% (44.3±6.4 vs. 27.4±8.1, $p<0.001$) while the percentage change in waist circumference was 25.8% (120.2±12.8 vs. 89.2±11.9, $p<0.05$). The greatest impact on CVRFs was observed 6 months after surgery, with a slight but non-significant additional improvement after 1 year.

Discussion

This study showed that a rapid and marked reduction in weight after bariatric surgery in a high-risk population of grade 2 or 3 obese female subjects was followed by a regression in C-IMT, as well as a reduction in triglyceride levels, TG/HDL ratio, and blood pressure, with a non-significant increase in HDL-C levels. Six months after surgery, we found that the reduction of systolic blood pressure and triglycerides was correlated with C-IMT ($p<0.05$).

It is well established in the literature that bariatric surgery is more effective than non-surgical treatment for weight loss in patients with a BMI of 40 kg/m^2 or above [15, 23]. In these patients, obesity is associated with an increase in the inflammatory response, which is linked to the development of atherosclerosis. Weight loss has been shown to reduce inflammatory markers and C-IMT measurements in obese premenopausal women [24]. In addition, weight loss has shown a positive effect on cardiovascular risk factors [14, 25]. Previous studies analyzing the effects of lifestyle changes in obese patients [9, 14, 26] have only shown moderate effects on total cholesterol levels, with a more relevant effect on triglyceride levels. Normalization of hyperlipidemia was achieved in 70% of the cases, regardless of the technique applied [14, 26].

The TG/HDL-C ratio provides indirect evidence that LDL-C particle size is a predictor of triglyceride metabolism [10]. The serum plasma level of small LDL-C particles was proportional to TG plasma concentration and inversely proportional to HDL-C concentration, showing greater atherogenic potential at a value greater than 3.0 [10]. In our study, a baseline index of over 3.0 was found, which showed a significant reduction three months after surgery ($p<0.05$).

Since C-IMT is considered a marker of early atherosclerosis, our findings suggest an improvement in overall atherosclerotic profile after bariatric surgery, and a potential reduction in cardiovascular events later in life. The use of the C-IMT measurement as a surrogate indicator of generalized atherosclerosis is based on three factors: First, the technique used to measure C-IMT is sufficiently accurate and reproducible. Second, the resulting images reflect the presence or absence of atherosclerosis, and finally, the presence of carotid atherosclerosis may indicate that other vascular beds may also be affected by this process [18]. Several studies have evaluated C-IMT measurements at specific sites and its relationship to cardiovascular risk factors [12, 13, 27, 28]. The carotid artery bifurcation and the internal carotid artery were shown to be the preferred sites for the development of atherosclerotic plaques. Therefore, the measurement of C-IMT at these sites should estimate early atherosclerosis better than measurements of the common carotid artery. In our study, we used the common carotid artery measurements, since these are anatomically more accessible and technically feasible in obese patients.

Some studies show an actual regression in C-IMT after weight loss [22, 24] while others show only a reduction in

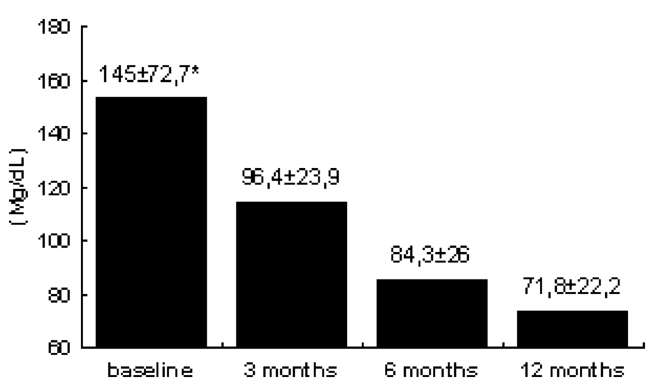

Fig. 2 Reduction in triglyceride levels in 1 year (*$p<0.001$ vs. 6 and 12 months)

the annual C-IMT progression rate [29]. These differences could result from inadequate weight loss, inability to maintain weight loss, or small sample sizes [22]. C-IMT regression was not observed following weight loss lasting only a few weeks [14], but may occur with weight loss lasting several months or more [22, 24].

An increase in C-IMT is usually associated with the aging process [30 and cardiovascular risk factors [12, 18, 30]. A previous study carried out by our group showed that in addition to age, BMI has a statistically significant association with C-IMT ($p=0.0005$) [30].

As observed in our study, the rapid and sustained weight loss achieved with bariatric surgery results in regression of C-IMT. This regression was observed 6 months after surgery, with additional benefit at 12 months. This finding was also correlated with a reduction in both triglyceride levels and systolic blood pressure. Therefore, even when C-IMT is within the normal range, as in our study sample, weight loss results in a significant decrease in blood pressure and triglyceride level. The main limitation of our study, however, was the small sample size that remained by the end of the follow-up time.

In conclusion, our study showed that in grade 2 or 3 obese female patients, bariatric surgery was able to reduce not only metabolic abnormalities, but also provided a significant decrease in carotid intima-media thickness. Furthermore, since C-IMT is an early marker of atherosclerosis, our data suggest that a decrease in body weight with bariatric surgery may prevent or delay the atherosclerotic process in this high-risk obese population.

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