ORIGINAL CONTRIBUTIONS





Mammary Volume-to-Body Mass Index Ratio: Preoperative Predictor of Cardiovascular Risk Factor and Indicator of Long-term Postoperative Remission of Comorbidities in Premenopausal Women Undergoing Sleeve Gastrectomy

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Abstract

Purpose A correct preoperative selection of candidates to undergo a sleeve gastrectomy (SG) is advisable. However, there is a dearth of available literature addressing outcome predictors after SG, besides surgical factors. To assess the accuracy of the mammary volume-to-body mass index (MV-BMI) ratio as an indicator of cardiovascular disease (CVD) risk in morbidly obese patients and as a preoperative predictor of long-term outcomes after SG.

Materials and Methods A prospective observational study of 100 consecutive females under 40 years old and planned to undergo a SG was performed. Mammary volume was calculated based on a geometry of the breast model. Correlation of the preoperative MV-BMI ratio with preoperative Framingham risk score (FRS) and triglyceride/HDL-cholesterol ratio was investigated. The correlation of preoperative MV-BMI with 5-year postoperative remission of comorbidities was also assessed.

Results Preoperative MV-BMI showed an inverse correlation with preoperative FRS and triglyceride/high-density lipoproteincholesterol ratio. It also showed a direct correlation with long-term T2D, hypertension, and dyslipidemia remission after SG. A cutoff point of MV-BMI 60 has been established as the most accurate predictive value.

Conclusion MV-BMI can be used as a predictive factor of long-term outcome after SG in premenopausal women.

Keywords Mammary volume \cdot Cardiovascular risk score \cdot Outcome \cdot Type 2 diabetes mellitus remission \cdot Hypertension remission \cdot Dyslipidemia remission \cdot Sleeve gastrectomy

Introduction

Obesity is actually a life-threatening entity and a growing burden in high-income countries but is also on startling rise in the developing world as well. Therefore, it is considered as a modern global epidemic disease [1]. Obesity has been linked to a broad spectrum of cardiovascular diseases (CVD), including type 2 diabetes mellitus (T2D), hypertension (HT), and dyslipidemia (DL), among others. Altogether, they imply an increasement of long-term cardiovascular morbidity and mortality, a loss of

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disease-free years, and a reduction of quality of life. Cardiovascular disease and diabetes are the leading causes of death and disability-adjusted life years related to high body mass index (BMI) [2].

Different multivariable models are used to assess CVD risk. However, the Framingham risk score (FRS) is the most widely used on clinical practice. The FRS defines the cardiovascular risk as the risk of suffering a first event of coronary heart disease, cerebrovascular disease, peripheral artery disease, and heart failure in the next 10 years. FRS was calculated on an algorithm including age, gender, total cholesterol, systolic blood pressure, smoking status, and the presence of T2D [3]. Other CVD risk scores include different analytical values, such as the ratio of triglycerides to high-density lipoprotein-cholesterol (HDL-cholesterol), which has demonstrated to be a strong predictor of myocardial infarction, especially when the values overcome 4.5 [4, 5]. Finally, several anthropometric parameters, like the waist-

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to-hip ratio [6] or the waist-to-height ratio [7], have demonstrated a certain predictive effect on the CVD risk.

Reducing the CVD risk constitutes a primary public health imperative, and weight loss is the most effective strategy to achieve this goal. The first therapeutic steps to achieve weight loss are lifestyle changes, including hypocaloric diets and physical exercise and pharmacological treatments. However, their efficacy is limited and a weight regain after 1 year is a constant. In contrast, bariatric surgery is an efficient and long-lasting strategy of weight loss, improves obesity-associated comorbidities, and reduces cardiovascular mortality [8].

Sleeve gastrectomy (SG) is actually the most commonly performed procedure in the world. Its performance has significantly increased in the last decade, since it is associated with good short- and mid-term outcomes, in terms of weight loss and remission of comorbidities, with low complications rate and nutritional sequelae [9]. However, recent reports have demonstrated a trend towards long-term weight regain and recurrence of comorbidities [10, 11]. Thus, a correct preoperative selection of candidates to undergo a SG is advisable [12]. There is a dearth of available literature addressing outcome predictors after SG, besides surgical factors [13].

The aim of this study was to assess the accuracy of the mammary volume-to-BMI ratio as an indicator of CVD risk in morbidly obese patients and as a preoperative predictor of long-term outcomes after SG.

Patients and Methods

A prospective observational study of 100 consecutive females under 40 years old, undergoing a SG between 2013 and 2014, was performed. Inclusion criteria were patients with body mass index (BMI) > 40 kg/m² or BMI > 35 kg/ m² with the presence of obesity-related comorbidities, undergoing a SG as bariatric procedure. Exclusion criteria included all kinds of previous breast surgeries and preoperative tobacco habit. Patients who started menopause or smoking during the follow-up period were excluded from analysis.

Preoperative Evaluation

All the candidates were evaluated by a multidisciplinary team, including surgeons, endocrinologists, psychiatrists and psychologists, anesthesiologists, and dietitians. A preoperative weight loss of at least 10% of the patient's weight was considered an indispensable condition to be selected as candidate for a SG.

Surgical Technique

The short gastric vessels of the major curvature were divided with harmonic scalpel (Ultracision®, Ethicon Endosurgery, USA). A 40-French bougie was used for the calibration of the sleeve. A longitudinal resection with mechanical endostapler (Echelon Flex®, Ethicon Endosurgery, USA) was performed from 4 cm orally to the pylorus up to the angle of His. A staple line reinforcement was performed with a continuous oversewing of polypropylene 2/0, before extracting the bougie.

Clinical Follow-up

Follow-up rate was 94%. All the patients were followed up by the surgeon and the endocrinologist at 3, 6, and 12 months during the first postoperative year. Then, patients continued their follow-up with yearly visits. Evaluation included physical examination, anthropometric measurement, and blood analysis.

Changes in comorbidities were strictly controlled, adjusting the medical treatment. Multivitamin supplements were daily prescribed.

Definitions

Mammary ptosis was defined as the clavicle-nipple length. Projection was measured as the distance between the points of implantation of the breast in the chest up to the nipple in a standing patient.

Mammary volume was calculated based on the geometry of the breast model, as reported by Copcu [14]. Following this model, we developed the following formula: The upper part of the breast is a half cone and the lower part is a half globe (Fig. 1). Therefore, the volume of half globe is calculated following the formula:

$$\frac{1}{2} \times \text{Pi} \times r \text{ (cm)}^3$$
. $r = \text{Projection (cm)}/2$

The volume of the half cone is calculated using the following formula:

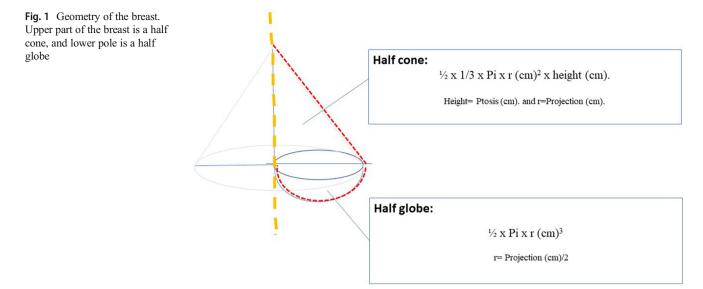
$$1/2 \times 1/3 \times \text{Pi} \times r(\text{cm})^2 \times \text{height(cm)}.$$

Height = Ptosis (cm) and r = Projection (cm).

The complete formula for the total mammary volume is as follows:

$$(1/2 \times \text{Pi} \times (\text{Projection}(\text{cm})/2)^3)$$

+ $(1/2 \times 1/3 \times \text{Pi} \times \text{Projection}(\text{cm})^2 \times \text{Ptosis}(\text{cm}))$



The mammary volume-to-body mass index (MV-BMI) ratio is calculated using the following formula:

$$\left[\left(1/2 \times \text{Pi} \times \left(\text{Projection(cm)}/2\right)^3\right) + \left(1/2 \times \left(1/3 \times \text{Pi} \times \text{Projection(cm)}^2 \times \text{Ptosis(cm)}\right)\right] / \left[\text{Weight(kg)}/\text{Height(m)}^2\right]\right] = \frac{1}{2} \left[\frac{1}{2} \times \frac{1}{2} \times \frac{1$$

Mammary measurements were done 7 days after menstruation

Variables

Anthropometric measurements included age, BMI, mammary projection, and ptosis measurement. BMI and excess BMI loss (EBMIL) were used to determine postoperative weight loss 5 years after surgery.

Cardiovascular risk factor were assessed by the Framingham cardiovascular risk score (FRS) [3] and by the triglyceride/HDL-cholesterol ratio [4, 5] at baseline and 5 years after surgery.

The MV-BMI ratio was investigated as cardiovascular risk factor and predictor of postoperative comorbidities remission. The results of this ratio are expressed as $(cm^3/(kg/m^2))$.

Remission of Comorbidities

Remission of type 2 diabetes mellitus was defined as plasma glucose below 100 mg/dl and glycated hemoglobin (A1c) below 6% in the absence of hypoglycemic treatment. Remission of hypertension was defined as blood pressure below 135/85 mmHg in the absence of antihypertensive treatment; remission of dyslipidemia was defined as fasting plasma LDL cholesterol below 130 mg/dl, plasma triglycerides below 150 mg/dl, total cholesterol below 200 mg/dl, and HDL-cholesterol over 40 mg/dl, in the absence of pharmacological therapy.

Remission of comorbidities was also assessed 5 years after surgery.

Statistical Analysis

Statistical analysis was performed using SPSS version 22.0 (SPSS Inc., Chicago, IL).

Quantitative variables were defined by mean and standard deviation (median and range in non-Gaussian variables). Qualitative variables were defined by number of cases and percentages.

Correlation between quantitative variables was performed with Pearson's and Spearman correlation tests. Paired Student's t tests were used to compare data before and after surgery.

Values of p < 0.05 were considered significant. Receiver operating characteristic (ROC) curve analysis was performed, and the respective areas under the curve (AUC) were calculated to evaluate predictive values for the investigated analytical values. Cutoff points were investigated. Sensitivity and specificity of these parameters were then calculated.

The study was approved by the local Ethics Committee. A written consent was obtained from all the patients for the surgery and for the inclusion of their data in the database.

Results

A total of 100 premenopausal women were initially included, with a mean age of 36.9 ± 7.6 years and a mean BMI of 46.6 ± 5.3 kg/m².Preoperative comorbidities included diabetes mellitus in 20% of the patients, dyslipidemia in 36%, hypertension in 24%, and obstructive sleep in 48%. Preoperative anthropometric measurements are described in Table 1.

All the patients underwent laparoscopic SG as bariatric procedure. Postoperative staple line leaks appeared in 3 patients (3%), all of them conservatively managed with an endoscopic stent placement.

Five-Year Follow-up

Five years after surgery, 6 patients were lost to follow-up, 3 patients started with tobacco habit, and one patient presented early menopause. Thus, 90 patients were included for analysis. Mean BMI was $28.1 + 4.4 \text{ kg/m}^2$, with an EBMIL of 85.7 + 8.3%. Remission rate of T2D was 80% (16 out of 20 patients), and hypertension remission rate was 68.2% (15 out of 22). Referring to dyslipidemia, hypertriglyceridemia was solved in all the cases, but hypercholesterolemia was cured in only 27.3% of the cases.

Cardiovascular Risk Factor Assessment

The mean preoperative cardiovascular risk in the next 10 years following the FRS was $0.9 \pm 0.06\%$. The mean postoperative FRS values 5 years after surgery decreased to $0.5 \pm 0.02\%$ (p < 0.001). The mean preoperative triglycerides to HDL ratio was 4.1 ± 0.3 and decreased to 3.5 ± 0.4 (p = 0.006).

Correlation Between Preoperative MV-BMI Ratio and Cardiovascular Risk Factors

Preoperative MV-BMI showed an inverse correlation with preoperative FRS (Spearman -0.721; p = 0.011) and an inverse correlation with triglyceride/HDL-cholesterol ratio (Spearman -0.703; p = 0.019).

Establishing a FRS < 1% as ideal, a ROC curve analysis was performed in order to identify the most accurate cutoff of MV-BMI, which was established at MV-BMI ratio of 60, with

BMI (kg/m ²)	46.6 <u>+</u> 5.3
Mammary projection (cm)	13.3 <u>+</u> 2.1
Ptosis (cm)	24.7 <u>+</u> 3.1
Mammary volume (cm ³)	2649.5 <u>+</u> 684.2
Mammary volume/BMI ratio (cm ³ /(kg/m ²))	56.8 + 5.3

BMI body mass index

87.7% sensibility and 84.8% specificity for presenting a FRS < 1% (AUC 0.717; CI 95% 0.631–0.823; *p* = 0.000) (Fig. 2).

Correlation Between Preoperative MV-BMI Ratio and Postoperative Remission of T2D, HT, and DL

Preoperative MV-BMI showed a direct correlation with T2D remission (Spearman 0.779; p = 0.011), a direct correlation with HT remission (Spearman 0.712; p = 0.018), and a direct correlation with DL remission (Spearman 0.664; p = 0.032). Establishing a MV-BMI cutoff value of 60 for T2D remission, 84.2% sensibility and 79.6% specificity was obtained (AUC 0.725; CI 95% 0.612–0.841; p = 0.000) (Fig. 3). Establishing a MV-BMI cutoff value of 60 for HT remission, 82.3% sensibility and 73.1% specificity were obtained (AUC 0.692; CI 95% 0.598–0.773; p = 0.01) (Fig. 4). Establishing a MV-BMI cutoff value of 60 for DL remission, 76.2% sensibility and 67.6% specificity were obtained (AUC 0.613; CI9 5% (0.554–0.712; p = 0.023) (Fig. 5).

There were no correlations between preoperative MV-BMI and preoperative BMI or long-term postoperative EBMIL.

Results of the Application of Cutoff Point MV-BMI 60 cm³/(kg/m²)

Preoperative cardiovascular risk factors were significantly lower among females with MV-BMI ratio > $60 \text{ cm}^3/(\text{kg/m}^2)$. These women also showed a significantly greater postoperative remission of DL. Despite those women with preoperative MV-BMI > $60 \text{ cm}^3/(\text{kg/m}^2)$ showed 100% remission of T2D

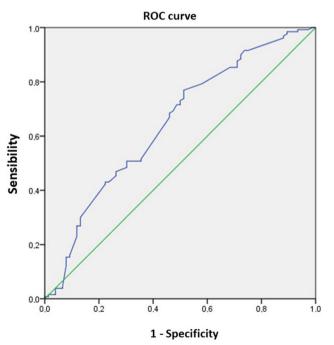


Fig. 2 ROC curve of MV-BMI for a preoperative FRS < 1%

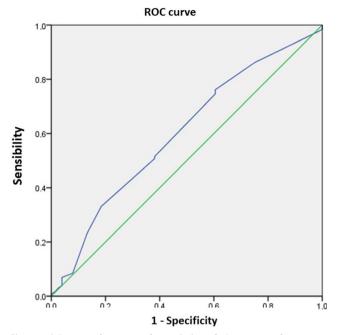


Fig. 3 ROC curve of MV-BMI for remission of T2D 5 years after surgery

and HT, the sample size was not enough to obtain significant differences between groups (Table 2).

Discussion

The breast of the woman is composed of the mammary gland and connective/adipose tissue. Because these tissues have

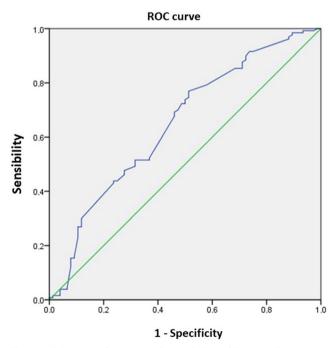


Fig. 4 ROC curve of MV-BMI for remission of hypertension 5 years after surgery

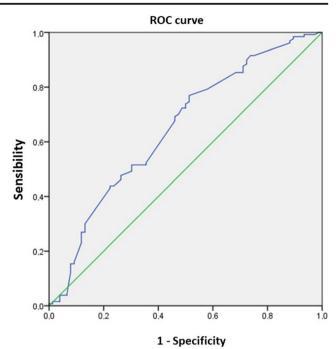


Fig. 5 ROC curve of MV-BMI for remission of dyslipidemia 5 years after surgery

hormone receptors, their sizes and volumes fluctuate according to the hormonal changes. The adipose component increases with obesity. However, the excess fat distribution is not homogeneous among different women. Some obese women develop big breasts with the weight increasement, whereas other subjects show a different distribution of the adiposity and do not significantly increase the size of their breasts [15, 16].

The female sex hormones (principally estrogens) in conjunction with growth hormone promote the sprouting, growth, and development of the breasts. At menopause, breast atrophy occurs, coinciding the decrease in size with the decline of the levels of circulating estrogen [17]. Several studies have hypothesized that the volume of the mammary glandular tissue in women is associated with the estrogen levels, whereas BMI correlates with fatty breast areas [18, 19].

It is widely known that the premenopausal estrogen release acts as a cardiovascular protector factor, while after the menopause, this estrogen decrease elevates the CVD risk up to similar levels to the males [20]. As the estrogen segregation differs in the diverse moments of the menstrual cycle, it is difficult to establish a total amount of this hormone, but altogether, it may have a trophic effect on the development of the mammary glandular tissue. The effect of the estrogenic status can also be reflected in the reduction of the CVD risk. In our series, those women with a MV-BMI over 60 cm³/(kg/m²) had significantly lower values of preoperative FRS and triglyceride-to-HDL ratios and lower preoperative T2D, hypertension, and dyslipidemia rates, without significant differences in BMI. Janiszewski et al. reported that the breast volume was an independent predictor of visceral fat in
 Table 2
 Application of the cutoff

 point MV-BMI ratio 60 on an thropometric measurements, pre

 operative cardiovascular risk fac tors and comorbidities, and post

 operative remission of
 comorbidities

	MV-BMI > 60 (cm ³ /(kg/m ²))	MV-BMI < $60 (\text{cm}^3/(\text{kg/m}^2))$	р
N	35	65	
Preoperative	55	05	
Age (years)	37.2 ± 7.8	36.6 ± 7.5	0.836
BMI (kg/m ²)	45.8 ± 5.3	47 <u>+</u> 5.4	0.762
Framingham risk score (%)	0.5 + 0.03	1.2 + 0.07	0.017
Triglyceride/HDL-cholesterol ratio	3.6 + 0.3	4.5 + 0.5	0.001
Type 2 diabetes mellitus (N)	2	18	0.009
Hypertension (N)	4	20	0.031
Dyslipidemia (N)	7	29	0.014
Postoperative			
Ν	32	58	
BMI (kg/m ²)	27.6 + 4.1	28.9 + 4.3	0.721
Excess BMI loss (%)	87.2 + 8.5	82.5 + 8.1	0.695
Type 2 diabetes mellitus remission	100% (2 out of 2)	77.8% (14 out of 18)	0.456
Hypertension remission	100% (4 out of 4)	61.1% (11 out of 18)	0.131
Dyslipidemia remission	71.4% (5 out of 7)	15.4% (4 out of 26)	0.003

MV-BMI mammary volume-to-body mass index ratio, BMI body mass index

premenopausal women, and this can be considered as a CVD risk factor. However, they failed to demonstrate a significant association with the lipid or glycemic profile [21].

Referring to long-term postoperative outcomes, our global results are excellent in terms of EBMIL and remission of comorbidities, which is consistent with the results reported in previous publications of our group. We justify these results in the exhaustive selection of candidates, based on preoperative weight loss as a reflection of adhesion to the postoperative correct diet and on the psychological evaluation [12]. However, the results obtained in women with preoperative MV-BMI > 60 cm³/(kg/m²) are even better, with significantly higher remission rates of dyslipidemia and a trend towards greater remission rates of T2D and hypertension. Given that dyslipidemia is the obesity-related comorbidity with lowest remission rates after SG, the preoperative MV-BMI can be a useful tool to predict the postoperative outcome of this comorbidity.

According to the results obtained in the present study, it seems that obese premenopausal women with bigger breasts have a better metabolic profile overall and carry a better prognosis concerning amelioration of comorbidities after SG. It looks like obese women with higher MV to BMI ratio have a more "gynecoid" type of obesity and have a better metabolic profile and postoperative prognosis, whereas women with lower MV-BMI ratio might correspond to a more "android" type of obesity, which could be associated with a worse metabolic profile and a less satisfactory postoperative amelioration of metabolic comorbidities [2].

The present study has several limitations. The first one is the formula to calculate the mammary volume, which can be considered as an approximative method. Handheld 3dimensional scanners with specific software and MRI are considered the most accurate methods for this calculation [21, 22]. However, specific software are not universally available and morbid obesity is often a limitation to undergo a MRI. Thus, this formula can be considered a useful tool to evaluate a new outcome predictor after bariatric surgery.

Second, this formula has been applied to severely obese premenopausal women candidates to bariatric surgery and undergoing SG. It must be elucidated if this formula is also applicable for postmenopausal women or for women with overweight or mild obesity, as a predictive factor for CVD. Moreover, it should be investigated if this parameter can also be an outcome predictor after other bariatric techniques.

Further limitations of the present study include a small sample size and the absence of comparison of MV-BMI with other parameters correlated with FRS or comorbidities remissions, such as waist circumference, waist-to-hip ratio, or waist-to-height ratio (not collected parameter in the present study). These would have been helpful for the validations of the present formula. Future studies should include a higher number of patients and a comparison with other anthropometric measurements correlated with cardiovascular risk scores or outcome predictors for bariatric surgery.

Conclusion

Preoperative MV-BMI showed an inverse correlation with preoperative FRS and triglyceride/HDL-cholesterol ratio. It also showed a direct correlation with long-term T2D,

hypertension, and dyslipidemia remission after SG. A cutoff point of 60 has been established as the most accurate predictive value. MV-BMI can be used as a predictive factor of longterm remission of dyslipidemia after SG in premenopausal women.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Statement of Informed Consent Informed consent was obtained from all individual participants included in the study.

Statement of Human Rights All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments.

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