Greco *et al. Metab Target Organ Damage* 2022;2:16
DOI: 10.20517/mtod.2022.22

Metabolism and Target Organ Damage

Original Article

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Effects of bariatric and metabolic surgical procedures on dyslipidemia: a retrospective, observational analysis

Carla Greco[1,2], Francesca Passerini[3,4], Silvia Coluccia[1,2], Mario Bondi[2], Fouzia Mecheri[5], Vincenzo Trapani[5], Alessandro Volpe[5], Patrizia Toschi[6], Francesca Carubbi[3,4], Manuela Simoni[1,2], Daniele Santi[1,2]

[1]Unit of Endocrinology, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena 41125, Italy.
[2]Unit of Endocrinology, Department of Medical Specialties, Azienda Ospedaliero-Universitaria di Modena, Ospedale Civile di Baggiovara, Modena 41126, Italy.
[3]Division of Internal Medicine and Metabolism, Department of Internal Medicine, Azienda Ospedaliero-Universitaria di Modena, Ospedale Civile di Baggiovara, Modena 41126, Italy.
[4]Unit of Internal and Metabolic Medicine, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena 41125, Italy.
[5]Division of General, Emergency Surgery and New Technologies, Ospedale Civile di Baggiovara, Modena 41126, Italy.
[6]Department of Metabolic Diseases and Clinical Nutrition, Azienda Ospedaliero-Universitaria of Modena, Modena 41126, Italy.

Correspondence to: Dr. Carla Greco, Unit of Endocrinology, University of Modena and Reggio Emilia, Via Campi 287, Modena 41125, Italy. E-mail: carlagreco@unimore.it

How to cite this article: Greco C, Passerini F, Coluccia S, Bondi M, Mecheri F, Trapani V, Volpe A, Toschi P, Carubbi F, Simoni M, Santi D. Effects of bariatric and metabolic surgical procedures on dyslipidemia: a retrospective, observational analysis. *Metab Target Organ Damage* 2022;2:16. https://dx.doi.org/10.20517/mtod.2022.22

Received: 21 Jul 2022 **First Decision:** 11 Aug 2022 **Revised:** 29 Aug 2022 **Accepted:** 20 Sep 2022 **Published:** 30 Sep 2022

Academic Editor: Amedeo Lonardo **Copy Editor:** Jia-Xin Zhang **Production Editor:** Jia-Xin Zhang

Abstract

Aim: Obesity and co-existing metabolic comorbidities are associated with increased cardiovascular (CV) morbidity and mortality risks, generally clustered to risk factors such as dyslipidemia. The aim of this study was to evaluate the lipid profile changes in subjects with severe obesity undergoing different procedures of bariatric and metabolic surgery (BMS), sleeve gastrectomy (SG), and Roux-en-Y gastric bypass (RYGB) in a real-world, clinical setting.

Methods: A single-center, retrospective, observational clinical study was performed enrolling patients undergoing BMS. The primary outcome was the change in total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) cholesterol, and triglycerides.

Results: In total, 123 patients were enrolled (males 25.2% and females 74.8%) with a mean age of 48.2 ± 7.9 years and a mean BMI of 47.0 ± 9.1 kg/m^2. All patients were evaluated until 16.9 ± 8.1 months after surgery. Total and HDL cholesterol did not change after surgery, while a significant reduction in triglyceride levels was recorded. Moreover, a rapid decline of both LDL and non-HDL cholesterol among follow-up visits was observed. In particular, significant inverse correlations were found between total cholesterol, LDL cholesterol, non-HDL cholesterol, and triglycerides and the number of months elapsed after bariatric surgery. Similarly, a direct correlation was found considering HDL cholesterol. Moreover, total cholesterol, LDL cholesterol, non-HDL cholesterol, and triglycerides significantly changed among visits after RYGB, while no changes were observed in the SG group. Finally, considering lipid-lowering therapies, the improvement in lipid asset was detected only in non-treated patients.

Conclusion: This study corroborates the knowledge of the improvement in lipid profile with BMS in clinical practice. Together with sustained weight loss, the BMS approach efficiently corrects dyslipidemia, contributing to decreasing the CV risk.

Keywords: Severe obesity, bariatric and metabolic surgery, lipid-lipoprotein profile, dyslipidemia

INTRODUCTION

Obesity is recognized as one of the most relevant public health problems in the world. This epidemic condition has nearly tripled since the 1980s[1], and it is associated with a wide range of co-morbid conditions, such as metabolic syndrome, cardiovascular (CV) diseases, gall bladder disease, osteoarthritis, sleep disorders, and certain types of cancer[2].

Severe obesity is defined by a body mass index (BMI) higher than 40 kg/m^2, with co-existing metabolic comorbidities, which could lead to substantially increased CV morbidity and mortality risks[2]. Indeed, severe obesity is associated with up to 9.8 years of life lost compared to normal BMI subjects[3]. In particular, morbidity and mortality appear to be determined by the clustering of CV risk factors in obese individuals[2,4]. Among these, dyslipidemia is a common condition related to both severe obesity and CV risk[5,6]. The alteration of the lipid profile encountered in patients with obesity is frequently characterized by high levels of triglycerides (TG) and low-density lipoprotein (LDL) cholesterol and by low levels of high-density lipoprotein (HDL) cholesterol[7,8].

In general, the management of obesity conventionally includes lifestyle modification, pharmacotherapy, and bariatric surgery. Bariatric surgery is the most effective long-term therapy for weight loss, with the concomitant beneficial effect of improving comorbidities and decreasing mortality[9]. The most common bariatric procedures worldwide were once divided into restrictive procedures, such as sleeve gastrectomy (SG) and adjustable gastric banding (AGB); malabsorptive procedures, such as biliopancreatic diversion with duodenal switch (BPD/DS); and mixed malabsorptive and restrictive surgery procedure, such as the Roux-en-Y gastric bypass (RYGB)[10,11]. Currently, the recognition that gastro-intestinal bariatric operations induce not simply mechanical but also metabolic changes provides a rationale for the surgical treatment of diabetes and metabolic disease[12]. Indeed, bariatric surgery is effective in weight loss and carbohydrate metabolism improvement[13,14]. Moreover, it is also effective to improve the lipid profile in patients with obesity, although differences among procedures have been detected[7,9]. For these reasons, bariatric surgery has been redefined as "bariatric and metabolic surgery (BMS)" for its intent to treat metabolic disorders as opposed to traditional bariatric surgery intended as mere weight-reduction therapy[15].

In the literature, approximately 60% of patients with severe obesity qualifying for BMS have dyslipidemia[16]. The obesity-related alteration of the lipid profile is characterized by increased triglycerides and LDL

cholesterol serum levels, together with a reduction in HDL values[8]. These abnormalities in severe obesity play a central role in the development of atherosclerosis, contributing to the residual cardiovascular risk[17]. BMS results in an atheroprotective change in lipid abnormalities, with a reduction in both fasting and postprandial triglycerides serum levels, an increase in HDL cholesterol levels, and changes in LDL and HDL composition[9,18-22]. Several studies have shown the effect of BMS on lipid asset. Mid- and long-term follow-up period prospective studies[19,22] and meta-analytic evaluations have widely demonstrated hypercholesterolemia and hypertriglyceridemia improvement across surgery[9,23,24].

Considering these metabolic effects of obesity surgery, we wanted to verify the direct action of bariatric surgery on lipid metabolism in clinical practice. With this in mind, this study aimed to evaluate lipid profile component changes in subjects with severe obesity undergoing different procedures of BMS performed in our hospital, considering both RYGB and SG.

METHODS

A single-center, retrospective, observational clinical study was performed enrolling patients with severe obesity undergoing BMS and followed up from 2010 to May 2021 at the Unit of Endocrinology of University Hospital of Modena, Italy. Routinely, patients were evaluated by a multidisciplinary team consisting of endocrinologists, bariatric surgeons, nutritionists, psychologists, and dieticians. According to the assessment of the multidisciplinary team, patients were treated with two different BMS approaches, Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG).

The following inclusion criteria were considered: (i) age higher than 18 years; (ii) BMS performed at the Modena Hospital; and (iii) follow-up performed at the Unit of Endocrinology. No specific exclusion criteria were considered.

Study design

All visits performed immediately before and after BMS until May 2021 were collected. The routine endocrinology practice provided a baseline visit, followed by other visits one month after surgery (Visit 1), three months after (Visit 2), and 6, 12, 18, and 24 months after surgery (Visits 3-6), and then annually thereafter. This follow-up period was not fixed, since it could be adjusted and tailored to the patient for specific clinical reasons.

Demographic (age and sex), anthropometric (height and weight), pharmacological (medication), and laboratory data were obtained preoperatively and during follow-up visits and were collected in specific case report forms (CRFs). BMI was expressed in units of weight (kg)/height (m^2), ideal body weight as that equivalent to a BMI of 25 kg/m^2, and excess weight (EW) as the weight excess between preoperative weight and ideal weight. The percentage of excess weight loss (%EWL) was calculated by the formula: [(initial weight - follow-up weight)/(initial weight - ideal weight)] × 100. The percentage of total weight loss (%TWL) was calculated by the formula: [(initial weight - follow-up weight)/initial weight] × 100[25].

The primary outcome of our study was the change of lipid profile components, consisting of total cholesterol (mg/dL), LDL cholesterol (mg/dL), HDL cholesterol (mg/dL), and triglycerides (mg/dL). When not available, both LDL and non-HDL cholesterol values were calculated according to the Friedewald's formula[26]. Ongoing lipid-lowering therapies were collected at each visit. Liver tests [glutamic-oxaloacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT), and gamma-glutamyl transferase (γ-GT)], transferrin as a nutritional index, and uric acid were considered as secondary endpoints.

The study was performed in accordance with the Declaration of Helsinki. Source documents of research material in the form of paper files and electronic files, and all datasets are deposited at the Unit of Endocrinology of University Hospital of Modena (Italy) and are available upon request. The Institutional Review Board of Modena and the Ethical Committee of Modena approved the study (code 0022400/21, approved on 21 July 2021).

Bariatric procedures

RYGB and SG are the most frequently performed BMS procedures worldwide for morbid obesity[11]. This technique consists of the creation of a gastric pouch by using the upper part of the stomach near the gastroesophageal junction. The remaining stomach and duodenum are then anastomosed at the distal end to an area lower down the jejunum (biliopancreatic limb) that drains gastric and pancreas secretions and bile into the small intestine[27]. A gastrojejunostomy is then performed to create the alimentary limb. The distance between the two anastomoses is measured by an average of 120 cm. In SG, part of the greater curvature of the stomach is removed, reducing its capacity by approximately two-thirds and thus limiting the intake of food. Additionally, removing the part of the stomach that secretes hormones causes hunger to decrease[28]. The decision regarding the type of surgery was based on patients' conditions (in particular, basal BMI), considering patients' comorbidities and preoperative clinical/metabolic status. Surgeries were performed in accordance with standard techniques and were generally performed by laparoscopy.

Statistical analysis

Descriptive analyses were performed considering the baseline visit. We evaluated the mid-term BMS effect considering the visits in which all patients enrolled were evaluated. In particular, the mid-term analysis evaluated patients until Visit 5 (i.e., approximately 18 months after surgery). The long-term analysis considered all visits available for each patient. In these analyses, Visit 1 was not considered since it corresponded to the first control one month after surgery and blood examinations were not performed. Differences between pre- and post-surgery and among visits were evaluated for continuous data using ANOVA univariate or Mann-Whitney U-test for normally or not-normally distributed parameters, respectively. Categorical variables were compared before and after surgery using chi-squared test. The correlation analysis was performed among continuous variables, applying Rho's Spearman analysis.

Patients were classified according to normal ranges for total, HDL, and LDL cholesterols and triglycerides. In particular, normal ranges of total cholesterol serum levels were 200 ng/dL[29]. HDL cholesterol was considered normal above 50 mg/dL in women and when higher than 40 mg/dL in men[29,30]. LDL cholesterol was considered normal below 116 mg/dL[29,31], and triglycerides lower than 150 mg/dL F[29,30]. The rate of lipid profile alterations was calculated, and the change of these rates after surgery was described. Multivariate logistic regression analyses were performed by setting the lipid profile alteration as the dependent variable and the patient's age and gender, the time elapsed after surgery, lipid-lowering therapies, and anthropometrical variables (i.e., weight, BMI, initial weight, %EWL, and %TWL) as independent variables.

These analyses were repeated, dividing the cohort of patients considering the surgical procedures used. Statistics were performed using Statistical Package for the Social Science software for Windows (version 27.0 SPSS Inc, Chicago, IL). Statistical significance was considered for $P < 0.05$.

RESULTS

In total, 123 patients were enrolled, 31 men (25.2%) and 92 women (74.8%), with a mean age of 48.2 ± 7.9 years [Table 1]. Surgical adverse events occurred in seven patients (5.6%), five after RYGB (4%) and two

Table 1. Anthropometric and laboratory analyses at each visit until Visit 5D

	Baseline	Visit 2	Visit 3	Visit 4	Visit 5	*P*-value
Weight (kg)	128.1 + 27.9	104.2 + 24.5§*	96.0 + 22.6§*	89.7 + 19.0§*	87.1 + 18.1*	**< 0.001**
BMI (kg/m^2)	47.0 + 9.1	38.2 + 7.9§*	35.2 + 7.3§*	32.9 + 6.1§*	32.1 + 5.1*	**< 0.001**
%EWL	-	42.8 + 23.7§*	57.4 + 24.3§*	63.4 + 19.7§*	70.5 + 17.9*	**< 0.001**
%TWL	-	18.3 + 7.0§*	25.0 + 7.5§*	29.6 + 8.5§*	31.8 + 8.2*	**< 0.001**
RBC (millions/mL)	4.9 + 0.5	4.8 + 0.4	4.7 + 0.5	4.6 + 0.5	4.6 + 0.5	0.125
Hb (g/dL)	13.6 + 1.6	13.6 + 1.1	13.4 + 1.1	13.8 + 4.0	13.5 + 1.3	0.807
Ht (%)	41.5 + 3.5	41.4 + 3.1	40.8 + 3.3	40.7 + 3.3	40.2 + 5.5	0.197
Glycaemia (mg/dL)	105.7 + 33.6	96.2 + 18.8	93.9 + 19.7	99.4 + 28.2	84.3 + 25.5*	0.007
Creatinine (mg/dL)	0.8 + 0.2	0.8 + 0.2	0.9 + 0.4	0.8 + 0.2	0.8 + 0.2	0.282
Uric acid (mg/dL)	5.7 + 1.3	5.7 + 0.2	5.2 + 1.2	5.2 + 0.9	4.8 + 1.2*	0.001
Total cholesterol (mg/dL)	207.6 + 40.5	191.6 + 59.9	181.1 + 50.0	190.7 + 40.9	195.8 + 38.2	0.060
HDL cholesterol (mg/dL)	50.2 + 12.4	49.5 + 14.1	53.6 + 15.6	53.2 + 10.6	57.2 + 13.1	0.202
LDL cholesterol (mg/dL)	132.0 + 33.2	123.5 + 52.9	104.3 + 34.1*	116.3 + 39.9	123.2 + 34.3	**< 0.001**
Non-HDL cholesterol (mg/dL)	157.4 + 38.2	143.5 + 56.8	127.6 + 49.1*	136.8 + 44.0	142.0 + 37.7	**< 0.001**
Triglycerides (mg/dL)	143.0 + 96.1	121.8 + 59.3	101.0 + 43.8	99.3 + 46.9	85.3 + 35.0*	0.006
AST (IU/L)	26.6 + 10.1	26.4 + 8.1	26.5 + 15.9	22.9 + 8.2	22.8 + 11.0*	0.043
ALT (IU/L)	29.3 + 18.5	29.8 + 12.4	25.0 + 9.7	22.2 + 9.9	21.0 + 8.6*	0.008
γ-GT (IU/L)	33.2 + 25.3	23.9 + 19.4	32.8 + 35.1	26.9 + 33.2	17.9 + 8.7*	0.047
Total AP (IU/L)	86.7 + 32.0	88.8 + 29.6	98.9 + 43.1	100.3 + 49.1	83.0 + 46.7	0.308
Transferrin (mg/dL)	286.5 + 87.7	248.9 + 51.1*	248.4 + 40.5*	252.3 + 45.1*	261.4 + 46.9	**< 0.001**
Ferritin (ng/mL)	80.9 + 81.2	82.6 + 92.4	70.3 + 99.0	66.0 + 58.7	53.8 + 46.8	0.148
Comorbidities						
Hypertension n(%)	65 (52.8)	62 (50.4)	61 (49.6)	59 (47.9)	56 (49.6)	
Diabetes mellitus n(%)	20 (16.3)	20 (16.3)	20 (16.3)	20 (16.5)	20 (17.7)	
OSAS n(%)	1 (0.8)	0 (0)	1 (0.8)	1 (0.8)	0 (0)	
Osteoporosis n(%)	2 (1.6)	2 (1.6)	2 (1.6)	2 (1.7)	3 (2.7)	

Data are expressed as mean ± standard deviation. Significantly different at post hoc analysis (Tukey test) compared to baseline * or previous visit §. AP: Alkaline phosphatase; BMI: body mass index; EWL: excess weight loss; GOT: glutamic-oxaloacetic transaminase; GPT: glutamic-pyruvic transaminase; γ-GT: gamma-glutamyl transferase; Hb: hemoglobin; HDL: high-density lipoprotein; Ht: hematocrit; LDL: low-density lipoprotein; RBC: Red blood cells; TWL: total weight loss.

after SG (1.6%). No cases of cancer or gallstones were reported.

Supplementary Table 1 reports the number of patients evaluated at each visit and the interval that occurred since metabolic surgery. The first visit after follow-up was performed 2.0 ± 2.2 months after metabolic surgery, and the first five visits were performed on all patients.

Anthropometric changes after bariatric surgery

Patients' weight and BMI significantly decreased after BMS, together with both %EWL and %TWL, confirming the progressive decline of body weight and the maintenance of the metabolic surgery result [Table 1]. Considering the longest follow-up available for each patient, both weight (Beta = -0.537; $P < 0.001$) and BMI (Beta = -0.193; $P < 0.001$) were significantly inversely related to months after surgery [Figure 1]. Similarly, both %EWL (Beta = -0.157; $P = 0.001$) and %TWL (Beta = -0.439; $P < 0.001$) showed a significant direct relationship with months after surgery [Figure 1].

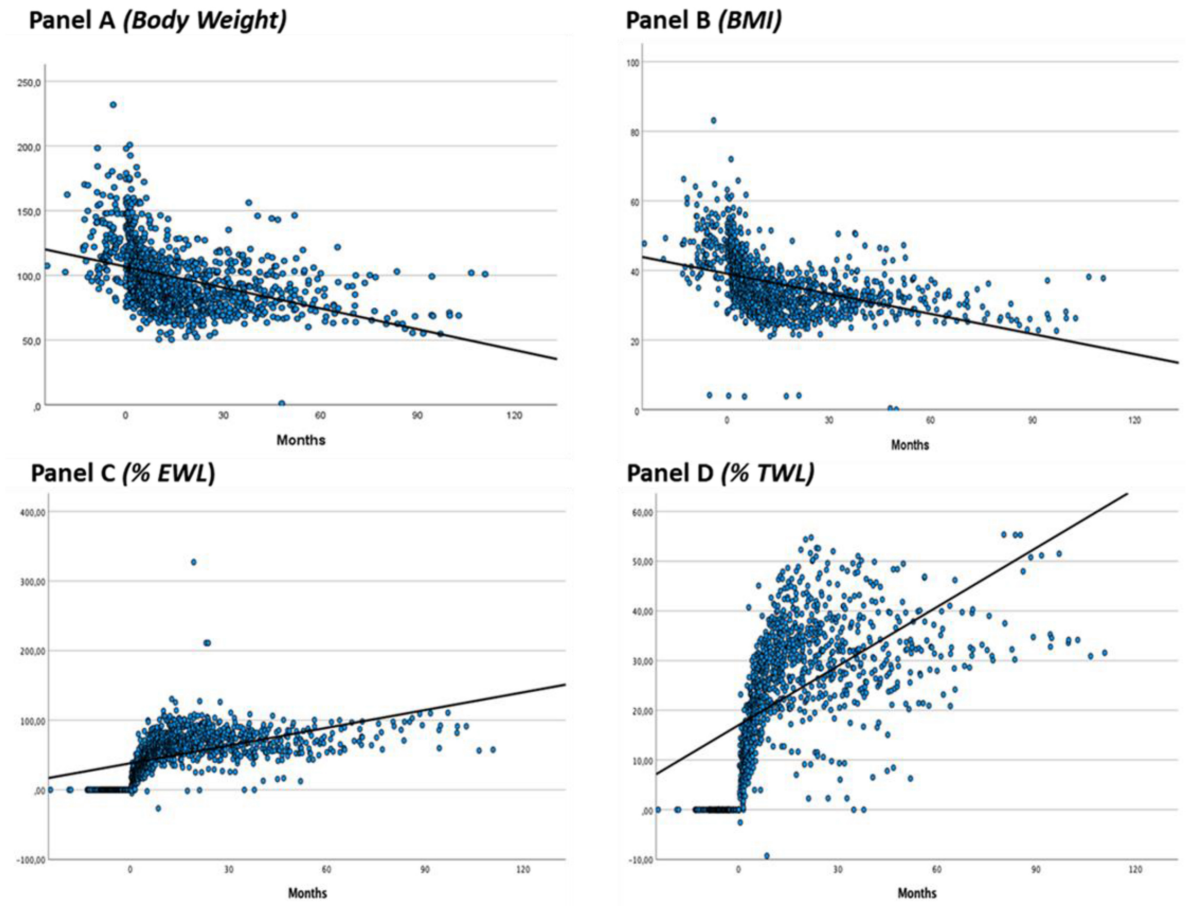

Figure 1. Linear regression analysis of months elapsed after bariatric and metabolic surgery (BMS) with: (A) body weight; (B) body mass index (BMI); (C) percentage of excess weight loss (%EWL); and (D) percentage of total weight loss (%TWL).

By classifying patients according to the BMS technique applied, we confirmed that weight and BMI significantly decreased after surgery [Table 2]. The patient's weight and BMI were significantly higher at baseline in the SG group compared to the RYGB group (P = 0.004 and P = 0.005, respectively). Although both surgical approaches led to weight reduction, weight and BMI remained significantly higher in the SG group compared to the RYGB group, and both surgical techniques led to a significant increase in both %EWL and %TWL across visits [Table 3]. Considering routine blood analysis, uric acid significantly decreased after BMS (P = 0.001), together with significant changes in AST, ALT, gamma-GT, and transferrin serum levels [Table 1].

Lipid profile

Considering lipid profile, total and HDL cholesterol did not change after BMS [Table 1]. On the contrary, a significant decrease in triglyceride serum levels was recorded (P = 0.006), with lower values at Visit 5 compared to baseline (P = 0.029) [Table 2]. Moreover, both LDL and non-HDL cholesterol were significantly reduced among visits (P < 0.001) [Table 2]. Significant direct correlations were found between total (Beta = -0.741; P = 0.014) [Figure 2], LDL (Beta = -0.751; P = 0.013) [Figure 2], non-HDL cholesterol (Beta = -0.916, P = 0.003) [Figure 2], and triglycerides (Beta = -0.159, P = 0.016) [Figure 2] and months elapsed after BMS. Similarly, a direct correlation was found between HDL cholesterol and months after surgery (Beta = 0.196; P = 0.036) [Figure 2]. HDL cholesterol serum levels were significantly inversely related to patients' weight (Beta = -0.196; P = 0.001), but not to BMI (Beta = 0.171; P = 0.314), as measured at

Table 2. Anthropometric and laboratory analyses at each visit until Visit 5, dividing patients according to the metabolic surgery applied

	Baseline	Visit 2	Visit 3	Visit 4	Visit 5	*P*-value
RYGB 77 patients (62.6%)						
Weight (kg)	122.6 + 22.8	100.2 + 21.3§*	91.9 + 19.7§*	86.7 + 17.8§*	83.7 + 17.4*	**< 0.001**
BMI (kg/m^2)	45.3 + 7.9	36.9 + 7.1§*	33.7 + 6.4§*	31.8 + 6.0§*	31.1 + 4.5*	**< 0.001**
%EWL	-	43.5 + 25.9§*	58.9 + 26.4§*	65.9 + 20.2§*	72.0 + 18.7*	**< 0.001**
%TWL	-	18.0 + 6.6§*	24.8 + 7.6§*	28.8 + 8.7§*	30.8 + 8.4*	**< 0.001**
RBC (millions/mL)	4.9 + 0.5	4.8 + 0.4	4.7 + 0.5	4.6 + 0.5	4.6 + 0.5	0.125
Hb (g/dL)	13.5 + 1.8	13.5 + 1.1	13.3 + 1.1	13.9 + 4.9	13.5 + 1.4	0.752
Ht(%)	41.6 + 3.7	41.4 + 3.3	40.7 + 3.4	40.7 + 3.5	40.4 + 5.3	0.328
Glycaemia (mg/dL)	106.6 + 35.2	97.6 + 19.8	96.1 + 22.8	102.1 + 32.4	83.0 + 31.4	0.094
Creatinine (mg/dL)	0.8 + 0.2	0.8 + 0.2	0.9 + 0.5	0.7 + 0.2	0.7 + 0.2	0.316
Uric acid (mg/dL)	5.6 + 1.1	5.6 + 1.4	4.9 + 1.3	5.0 + 1.0	4.6 + 1.4*	**0.012**
Total cholesterol (mg/dL)	267.0 + 38.0	155.4 + 37.4§*	172.3 + 36.3*	167.5 + 26.8*	173.2 + 29.0	**< 0.001**
HDL cholesterol (mg/dL)	51.5 + 11.8	47.7 + 9.1	55.5 + 7.1	59.7 + 8.4	55.7 + 12.1	0.142
LDL cholesterol (mg/dL)	130.3 + 29.0	105.7 + 27.3§*	101.8 + 31.2*	92.0 + 26.2*	107.9 + 22.4	**< 0.001**
Non-HDL cholesterol (mg/dL)	154.9 + 36.3	107.6 + 37.0§*	118.0 + 31.7*	107.8 + 28.8*	122.1 + 28.8	**< 0.001**
Triglycerides (mg/dL)	134.5 + 88.4	115.0 + 76.1	82.1 + 23.7	79.2 + 26.6	70.1 + 37.8	**0.021**
AST (IU/L)	24.4 + 10.9	26.4 + 7.9	31.3 + 22.5	23.4 + 7.9	26.2 + 13.4	0.343
ALT (IU/L)	30.2 + 20.1	26.4 + 11.6	28.0 + 9.8	24.6 + 9.9	22.6 + 9.3	0.426
γ-GT (IU/L)	32.1 + 24.8	19.5 + 10.7	29.4 + 39.4	22.0 + 22.4	15.2 + 9.2	0.149
Total AP (IU/L)	86.7 + 32.0	88.8 + 29.6	98.9 + 43.1	100.3 + 49.1	83.0 + 46.7	0.308
Transferrin (mg/dL)	296.3+ 89.2	251.3+ 55.2§*	249.3+ 41.2*	250.1+ 47.6*	260.2+ 47.0	**0.020**
Ferritin (ng/mL)	67.8 + 58.5	64.3 + 57.9	52.8 + 45.8	51.3 + 44.2	41.3 + 37.3	0.257
SG 46 patients (37.4%)						
Weight (kg)	137.4 + 33.2	111.1 + 28.2§*	102.9 + 25.5§*	94.9 + 20.0*	92.7 + 18.0*	**< 0.001**
BMI (kg/m^2)	50.0 + 10.3	40.5 + 8.7§*	37.6 + 8.1§*	34.7 + 6.0*	33.9 + 5.7*	**< 0.001**
%EWL	-	41.6 + 19.5§*	55.0 + 20.5§*	64.5 + 18.9§*	68.1 + 16.2*	**< 0.001**
%TWL	-	19.0 + 7.7§*	25.2 + 7.4§*	31.0 + 8.1§*	33.5 + 7.8*	**< 0.001**
RBC (millions/mL)	4.8 + 0.3	4.7 + 0.4	4.6 + 0.4	4.5 + 0.4	4.5 + 0.3	0.106
Hb (g/dL)	13.7 + 1.2	13.7 + 1.0	13.6 + 1.1	13.5 + 1.0	13.5 + 1.1	0.964
Ht (%)	41.4 + 3.2	41.3 + 2.7	41.1 + 3.1	40.7 + 3.1	39.9 + 5.9	0.413
Glycaemia (mg/dL)	104.2 + 31.0	94.7 + 17.7	90.3 + 13.6	96.2 + 23.5	86.4 + 13.9	0.170
Creatinine (mg/dL)	0.7 + 0.2	0.8 + 0.2	0.8 + 0.2	0.8 + 0.2	0.8 + 0.2	0.344
Uric acid (mg/dL)	5.8 + 1.5	5.8 + 1.3	5.4 + 1.1	5.4 + 0.6	5.0 + 1.0	0.070
Total cholesterol (mg/dL)	210.4 + 44.9	220.0 + 58.0	189.2 + 60.3	216.6 + 39.0	216.2 + 34.6	0.511
HDL cholesterol (mg/dL)	47.9 + 13.1	51.0 + 17.5	51.7 + 14.4	46.7 + 8.5	58.3 + 14.3	0.274
LDL cholesterol (mg/dL)	135.0 + 40.6	149.7 + 50.8	107.3 + 38.8	146.8 + 33.8	136.8 + 38.47	0.167
Non-HDL cholesterol (mg/dL)	161.9 + 41.3	173.9 + 53.5	137.2 + 62.0	169.1 + 34.8	157.9 + 37.6	0.345
Triglycerides (mg/dL)	159.1 + 109.1	126.2 + 47.5	118.5 + 51.3	117.6 + 54.6	100.6 + 25.5	0.205
AST (IU/L)	22.1 + 8.5	26.3 + 8.6	22.6 + 6.2	22.5 + 8.7	20.9 + 6.4	0.224
ALT (IU/L)	27.9 + 15.9	30.4 + 13.8	22.3 + 9.0	19.4 + 9.5	19.3 + 7.9*	**0.016**
γ-GT (IU/L)	34.9 + 26.3	29.4 + 25.9	35.8 + 31.9	31.0 + 40.7	20.7 + 7.8	0.651
Total AP (IU/L)	86.7 + 32.0	88.8 + 29.6	98.9 + 43.1	100.3 + 49.1	83.0 + 46.7	0.308
Transferrin (mg/dL)	278.6 + 60.8	243.6 + 48.8§*	235.3 + 41.3	236.7 + 40.3	245.8 + 41.8	**0.002**
Ferritin(ng/mL)	107.6 + 110.8	121.0 + 132.8	105.9 + 155.5	92.3 + 71.9	75.1 + 54.0	0.626

Data are expressed as mean ± standard deviation. Significantly different at post hoc analysis (Tukey test) compared to baseline * or previous visit

§. AP: Alkaline phosphatase; BMI: body mass index; EWL: excess weight loss; GOT: glutamic-oxaloacetic transaminase; GPT: glutamic-pyruvic transaminase; γ-GT: gamma-glutamyl transferase; Hb: hemoglobin; HDL: high-density lipoprotein; Ht: hematocrit; LDL: low-density lipoprotein; RBC: red blood cells; RYGB: Roux-en-Y gastric bypass; SG: sleeve gastrectomy; TWL: total weight loss.

Table 3. Correlation analyses (Spearman's Rho) among lipid profile variables and percentage of excess and total weight loss (%EWL and %TWL)

	Total cholesterol	HDL	LDL	Non-HDL	Triglycerides
%EWL	Rho = -0.247; *P* = 0.001	Rho = 0.201; *P* = 0.006	Rho = -0.251; *P* = 0.001	Rho = -0.312; *P* < 0.001	Rho = -0.404; *P* < 0.001
%TWL	Rho = -0.202; *P* = 0.005	Rho = 0.181; *P* = 0.013	Rho = -0.205; *P* = 0.009	Rho = -0.269; *P* < 0.001	Rho = -0.377; *P* < 0.001

EWL: Excess weight loss; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TWL: total weight loss.

each visit. Similarly, triglyceride serum levels were inversely related to patients' weight (Beta = -0.798; $P = 0.009$), but not to BMI (Beta = -0.231; $P = 0.794$). On the contrary, total (Beta = -0.132; $P = 0.488$; and Beta = 0.986; $P = 0.088$, respectively) and LDL cholesterol (Beta = -0.058; $P = 0.759$; and Beta = 0.921; $P = 0.103$, respectively) were not related to patient's weight and BMI decrease. Moreover, lipid profile changes were significantly related to both %EWL and %TWL [Table 3].

Considering the longest follow-up available in our cohort (i.e., Visit 15), a significant trend of triglycerides reduction after BMS was confirmed (Beta = -0.691; $P < 0.001$) [Figure 3], as well as after adjustment for lipid-lowering therapies (Beta = -0.952; $P < 0.001$). Similarly, the increase in HDL cholesterol after surgery remained significantly related to the months elapsed since surgery for the longest follow-up available (Beta = 0.171; $P < 0.001$) [Figure 3], although the result is not significant after adjusting lipid-lowering therapies (Beta =0.126; $P = 0.175$). On the contrary, the total (Beta = -0.231; $P = 0.056$) and LDL (Beta = -0.182; $P = 0.075$) cholesterol reductions were lost considering the longest follow-up.

The duration of lipid-lowering drug administration before patients' enrolment was not available in our cohort since this therapy is generally prescribed and managed by a general practitioner. We could only evaluate the duration of lipid-lowering drug administration during the study period. In particular, the mean lipid-lowering medication duration was 36.8 ± 11.3 months. The treatment was performed using statin therapy with several medium- to high-dose molecules. Furthermore, since the lipid asset was influenced by lipid-lowering therapies, the prescription of these drugs was evaluated at each visit. Lipid-lowering therapies were prescribed to 21 patients (17.1%) at baseline, 24 (19.5%) at Visit 2, 25 (20.3%) at Visits 3 and 4 (17.9%), and 22 at Visit 5. Classifying patients between treated and not-treated with lipid-lowering drugs, a significant improvement in the lipid profile was detected in all non-treated patients, with a significant decrease in total, LDL, and non-HDL cholesterol and triglycerides, together with an HDL cholesterol increase [Table 4]. Thus, adjusting the regression analyses previously performed by the presence of lipid-lowering therapy, statistical significance was lost for total (Beta = -0.665; $P = 0.448$), HDL (Beta = -0.872; $P = 0.401$), LDL (Beta = -0.186; $P = 0.835$), and non-HDL cholesterol (Beta = -0.916; $P = 0.289$). However, triglycerides significantly decreased with months after surgery (Beta = -0.296; $P = 0.027$).

Considering the two different surgical approaches, total cholesterol, LDL cholesterol, non-HDL cholesterol and triglycerides significantly changed among visits in RYGB treated patients ($P < 0.001$) [Table 2]. The lipid profile did not change among visits considering the SG group [Table 2].

Total cholesterol serum levels were defined as elevated for values higher than 200 mg/dL. Overall, 45.5% of the cohort (56 patients) showed high total cholesterol serum levels at baseline, and this percentage

Table 4. Lipid profile at each visit until Visit 5

	Baseline	Visit 2	Visit 3	Visit 4	Visit 5	*P*-value
Patients not treated with lipid-lowering drugs						
Total cholesterol (mg/dL)	204.7 + 39.1	176.5 + 50.6*	178.7 + 37.6*	174.9 + 29.6*	192.2 + 43.7*	**< 0.001**
HDL cholesterol (mg/dL)	50.4 + 10.7	46.8 + 7.5	52.8 + 13.8	53.9 + 10.2	60.2 + 12.5*	**0.010**
LDL cholesterol (mg/dL)	131.9 + 31.7	110.6 + 46.7	109.6 + 46.7*	104.0 + 30.0*	120.3 + 39.3	**< 0.001**
Non-HDL cholesterol (mg/dL)	154.7 + 37.5	130.9 + 51.9	125.8 + 35.8*	121.0 + 33.0*	137.2 + 42.3	**< 0.001**
Triglycerides (mg/dL)	133.4 + 90.1	121.2 + 64.2	89.9 + 29.8*	85.1 + 29.3*	69.2 + 24.0*	**0.008**
Patients treated with lipid-lowering drugs						
Total cholesterol (mg/dL)	221.8 + 45.0	239.2 + 62.4	197.4 + 77.0	225.0 + 43.0	202.0 + 28.3	0.080
HDL cholesterol (mg/dL)	50.9 + 18.7	57.7 + 24.8	55.4 + 20.1	51.9 + 12.1	52.4 + 12.3	0.771
LDL cholesterol (mg/dL)	132.0 + 44.5	157.9 + 56.9	126.4 + 34.5	148.5 + 47.8	127.4 + 28.0	0.163
Non-HDL cholesterol (mg/dL)	171.2 + 39.5	181.5 + 58.0	132.8 + 81.8	171.2 + 48.0	149.6 + 30.6	0.062
Triglycerides (mg/dL)	183.7 + 112.6	123.7 + 45.6	119.8 + 57.8	122.5 + 61.7	110.7 + 35.8	0.213

Data are expressed as mean + standard deviation. Significantly different at post hoc analysis (Tukey test) compared to baseline * or previous visit§.

significantly decreased during the follow-up visits, shifting to 7.3% (8 patients) at Visit 2 and 5.3% (6 patients) at Visit 5 ($P < 0.001$). Multivariate logistic regression analysis showed that normalization of total cholesterol was predicted by time after surgery ($P = 0.039$) and lipid-lowering therapy ($P = 0.029$) [Table 5].

Considering HDL cholesterol serum levels, 25.2% of the cohort (31 patients) showed low HDL cholesterol serum levels at baseline, and this percentage significantly decreased during the follow-up visits, shifting to 7.3% (9 patients) at Visit 2, 6.5% (8 patients) at Visit 3, 3.2% (4 patients) at Visit 4, and 1.9% (2 patients) at Visit 5 ($P < 0.001$). Multivariate logistic regression analysis showed that normalization of HDL cholesterol was predicted by patient's weight ($P = 0.001$) and %TWL ($P = 0.041$) [Table 6].

Considering LDL cholesterol serum levels, 39.8% of the cohort (49 patients) showed altered LDL cholesterol serum levels at baseline, and this percentage significantly decreased during the follow-up visits, shifting to 8.9% (11 patients) at Visit 2, 7.4% (9 patients) at Visits 3 and 4, and 6.8% (8 patients) at Visit 5 ($P < 0.001$). Multivariate logistic regression analysis did not identify predictive variables.

Regarding triglycerides serum levels, 33.3% of the entire cohort (41 patients) showed altered triglycerides serum levels at baseline, and this percentage significantly decreased during the follow-up visits, shifting to 16.2% (20 patients) at Visit 2, 13.0% (16 patients) at Visit 3, 12.2% (15 patients) at Visit 4, and 11.4% (14 patients) at Visit 5 ($P < 0.001$). Multivariate logistic regression analysis was performed, including altered triglycerides as the dependent variable and patient's age, months after surgery, weight, BMI, type of surgery, and lipid-lowering therapies as dependent variables. The normalization of triglycerides was predicted only by lipid-lowering therapy ($P = 0.028$) [Table 7].

Finally, the same significant regressions were obtained considering males and females separately (data not shown).

DISCUSSION

This retrospective study proves the improvement of lipid-lipoprotein profile in a high number of subjects with severe obesity who underwent RYGB or SG. The atherogenic lipid profile decrease is directly related to

Table 5. Multivariate logistic regression analysis considering the alteration of total cholesterol as the dependent variable

	B	Standard error	Wald	*P*-value	Exp(B)	95% confidence interval	
						Upper limit	Lower limit
Intercept	-16.825	7.570	4.940	0.026			
Age	0.025	0.019	1.710	0.191	1.025	0.988	1.064
Gender	0.343	0.547	0.393	0.531	1.409	0.483	4.112
Months after surgery	-0.039	0.020	3.838	**0.039**	0.961	0.924	1.000
Weight	-0.009	0.009	1.013	0.314	0.991	0.973	1.009
BMI	0.039	0.029	1.773	0.183	1.040	0.982	1.102
%EWL	0.011	0.030	0.138	0.711	1.011	0.953	1.073
%TWL	0.112	0.127	0.784	0.376	1.119	0.872	1.436
Surgery type	-0.574	0.305	3.554	0.059	0.563	0.310	1.023
Lipid-lowering therapy	-0.773	0.355	4.740	**0.029**	0.462	0.230	0.926

Table 6. Multivariate logistic regression analysis considering the alteration of high-density lipoprotein (HDL) cholesterol as the dependent variable

	B	Standard error	Wald	*P*-value	Exp(B)	95% confidence interval	
						Upper limit	Lower limit
Intercept	-0.747	1.401	0.284	0.594			
Age	-0.027	0.020	1.810	0.178	0.973	0.935	1.013
Gender	-0.887	0.600	2.185	0.139	0.412	0.127	1.335
Months after surgery	0.006	0.020	0.092	0.762	1.006	0.968	1.046
Weight	-0.034	0.010	11.858	**0.001**	1.035	1.015	1.055
BMI	-0.048	0.030	2.523	0.112	0.953	0.898	1.011
%EWL	0.046	0.029	2.569	0.109	1.047	0.990	1.108
%TWL	-0.286	0.141	4.158	**0.041**	0.751	0.570	0.989
Surgery type	-0.453	0.329	1.896	0.168	0.636	0.333	1.212
Lipid-lowering therapy	-0.751	0.385	3.810	0.051	0.472	0.222	1.003

Table 7. Multivariate logistic regression analysis considering the alteration of triglycerides as the dependent variable

	B	Standard error	Wald	*P*-value	Exp(B)	95% confidence interval	
						Upper limit	Lower limit
Intercept	-1.715	1.929	0.790	0.374			
Age	-0.018	0.027	0.457	0.499	0.982	0.932	1.035
Gender	-0.713	0.702	1.030	0.310	0.490	0.124	1.942
Months after surgery	-0.024	0.031	0.623	0.430	0.976	0.918	1.037
Weight	0.019	0.013	2.245	0.134	1.019	0.994	1.045
BMI	-0.015	0.040	0.140	0.708	0.985	0.911	1.066
%EWL	0.002	0.036	0.002	0.966	1.002	0.934	1.074
%TWL	0.046	0.158	0.085	0.771	1.047	0.769	1.427
Surgery type	-0.390	0.468	0.695	0.404	0.677	0.271	1.694
Lipid-lowering therapy	-1.079	0.490	4.845	**0.028**	0.340	0.130	0.888

the time elapsed since surgery. Available literature shows the effect of BMS on dyslipidemia[9,19,22-24], and, in this context, the present analysis reflects the trend of the alteration of lipid metabolism in real-life clinical practice.

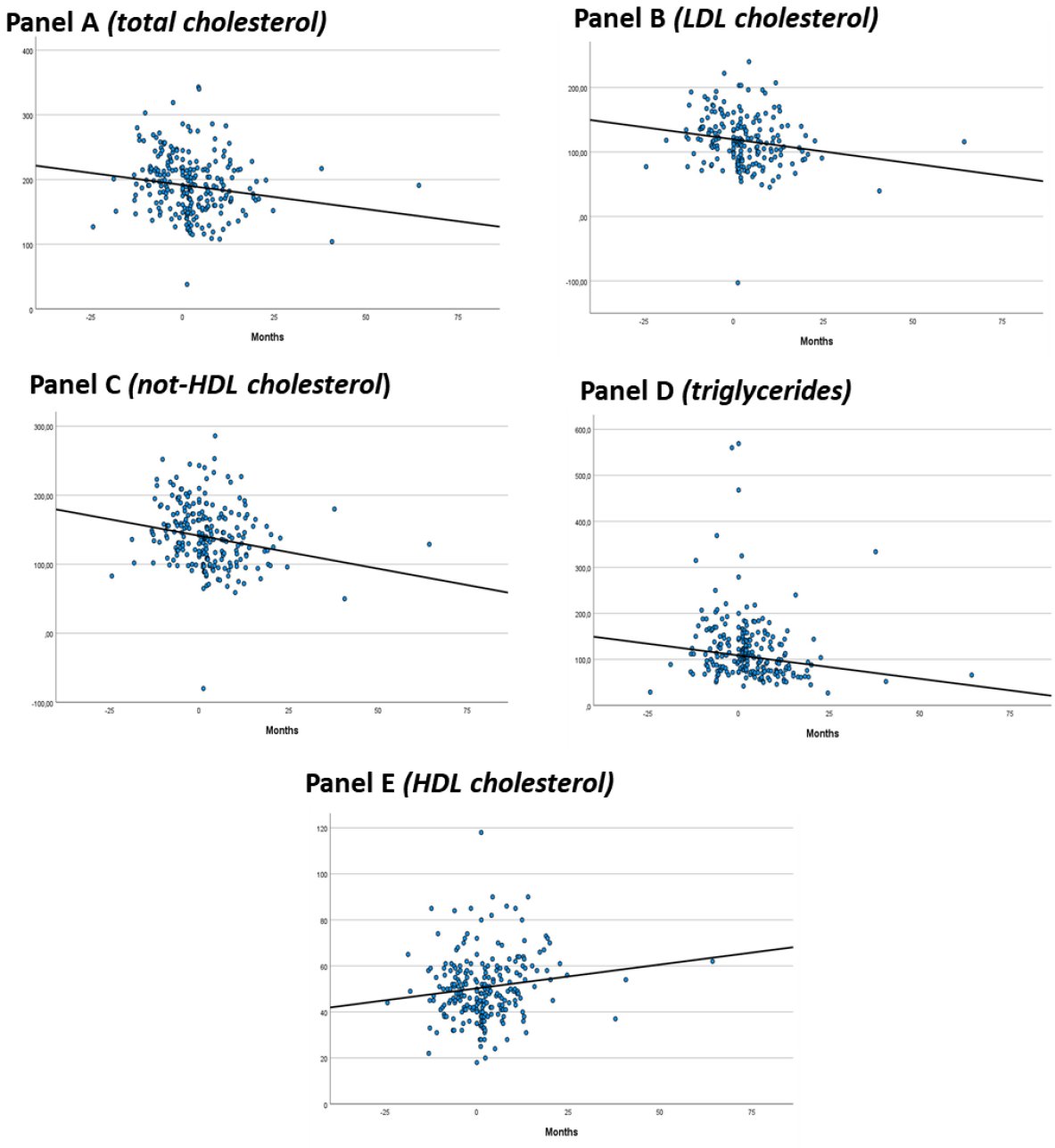

Figure 2. Linear regression analysis of months elapsed after bariatric and metabolic surgery (BMS) with: (A) total cholesterol serum levels; (B) LDL; (C) non-HDL; (D) triglycerides; and (E) HDL cholesterol.

Considering our baseline data, we found a similar dyslipidemia prevalence for total and LDL cholesterols, detected in 45.5% and 39.8% of the analyzed group, respectively. On the contrary, a lower prevalence was detected for baseline altered HDL cholesterol and triglycerides serum levels (25.2% and 33.3%, respectively). After surgery, we described a particular dynamic of cholesterol decrease, with a rapid decrease for LDL and non-HDL cholesterol and a slow change for triglycerides. Moreover, we demonstrated that considering the longest follow-up available, i.e., up to seven years after surgery, only triglycerides reduction and HDL increase progressively continue, irrespective of medical lipid-lowering therapy. On the contrary, as we

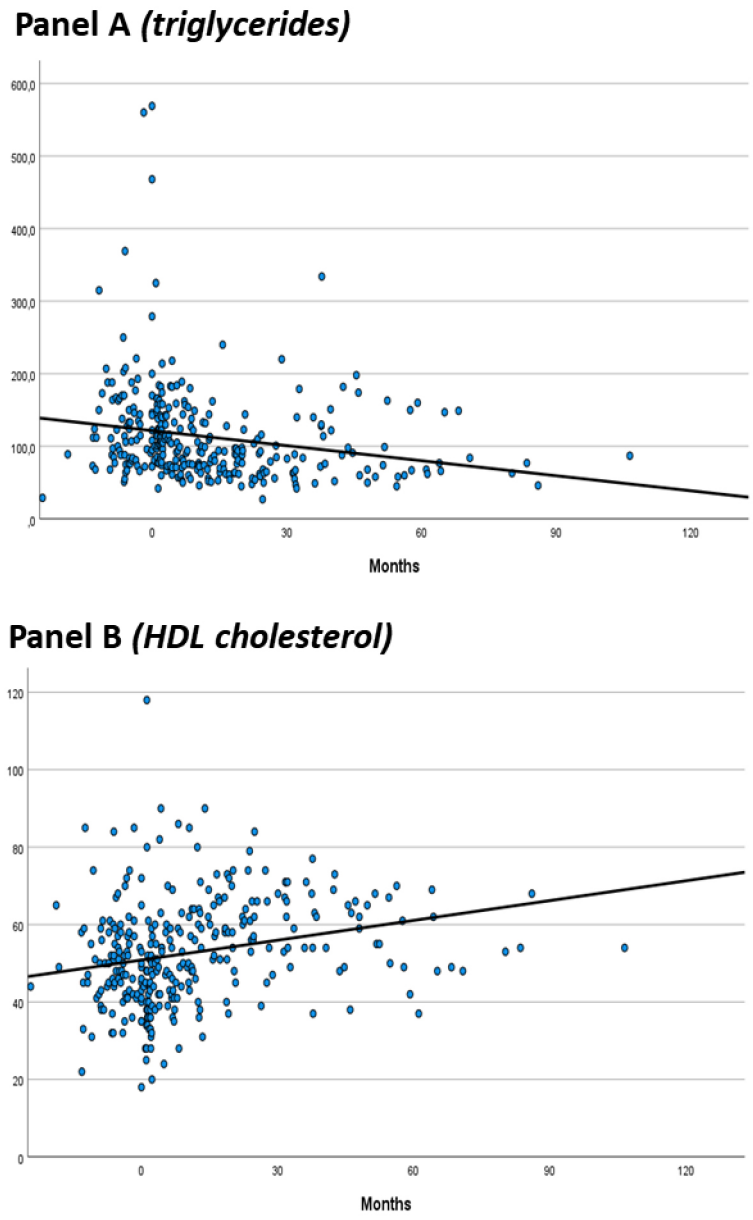

Figure 3. Linear regression analysis of months occurred after bariatric and metabolic surgery (BMS) considering the entire follow-up available in the cohort with: (A) triglycerides; and (B) HDL cholesterol.

moved further away from surgery, the rapid improvement in total and non-HDL cholesterol serum levels was progressively lost.

Dyslipidemia prevalence decreased after BMS, and it was significantly predicted by patient's weight and %TWL, thus confirming the decisive role of adipose tissue reduction in the lipid profile changes. Indeed, the adipose tissue depots in severe obesity influence the lipid-lipoprotein profile[20] and the cardio-metabolic risk[32]. The excessive visceral adipose tissue accumulation is associated with increased whole-body lipolysis and increased delivery of non-esterified fatty acids (NEFA) to the liver with the overproduction of triglyceride-rich lipoproteins[32-34]. Accordingly, cholesterol reduction after BMS is directly related to patients' weight, suggesting that the greater the weight loss, the greater the decline in serum cholesterol

levels. Similarly, HDL serum levels also showed such significant correlation with patient's weight, although a clear increase was not detected after surgery.

Moreover, as is known, obesity is related to a hypertriglyceridemic state with metabolic abnormalities in all triglyceride-rich lipoproteins. The liver plays a central role in determining this condition[35]. Indeed, subjects with severe obesity show an altered hepatic fatty acids trafficking: intra-hepatic fatty acids are shifted towards very-low LDL (VLDL) and triglycerides production rather than oxidative pathways[36]. These mechanisms may explain the different lipid profiles detected in subjects with severe obesity. Furthermore, the BMS, such as in RYGB, determines an increase in circulating fasting bile acid levels[37]. These changes in bile acid physiology after RYGB likely support weight loss and promote sustained metabolic improvements in terms of glucose and lipid metabolism[38], recognizing the bile acids as endogenous entero-hormones with a possible pivotal role in BMS. In our observations, at 16.9 ± 8.1 months of follow-up (Visit 5), the lipid profile change seemed to be flattened, not reaching statistical significance. This effect appeared more evident in the RYGB than in the SG group. This trend seemed to be in line with the weight change trend during the long follow-up. In this context, an adaptation of the enterohepatic circulation and bile acid physiology at a distance from surgery cannot be excluded.

Furthermore, it is obvious that lipid asset is influenced by lipid-lowering therapies, which were prescribed in 17.1% of our cohort of patients at baseline. Interestingly, the lipid profile improvement after BMS was detected only in patients not treated with lipid-lowering therapies. However, the analysis of the lipid-lowering therapy-free patients clearly showed a positive effect of BMS-induced weight loss on atherogenic dyslipidemia in patients with obesity. In addition, in our cohort, only the reduction in altered total cholesterol and triglycerides serum levels was predicted by lipid-lowering therapy, confirming that the regulation of lipid profile is more complex and several variables play a role in dyslipidemia development. Moreover, several studies have suggested a potential different ability to impact the lipid profile of BMS procedures, with greater benefits of malabsorptive-mixed rather than restrictive operations[9,39,40].

Finally, in our cohort, the majority of patients enrolled were females. It is widely acknowledged that the genetic, epigenetic, and hormonal conditions of sex influence physiology, disease, and therapeutic responses. In particular, sex plays a pivotal role as a modifier of the major causes of death and morbidity[41], including lipid disease. Thus, we performed stratified analyses according to sex, and no significant differences in outcomes were observed.

This study has some limitations. First, data regarding the genetic aspect of lipid profile alteration in our cohort were not available. Indeed, genetics plays an important role in determining cholesterol levels and response to treatment. Furthermore, dyslipidemia can be genetically determined (primary or familial dyslipidemia) or secondary to other conditions (such as diabetes mellitus, obesity, or an unhealthy lifestyle), the latter being more common. Thus, genetic and epigenetic influences on response to treatment with BMS in terms of lipid change cannot be excluded. Moreover, other limits intrinsic to the study design must be considered. The retrospective collection of real-life data did not allow the consideration of data related to some aspects relevant to lipid profile, such as compliance to either diet or exercise. Indeed, it is widely acknowledged that serum cholesterol levels are heavily affected by the intake of saturated, unsaturated, and polyunsaturated fats and are also determined by physical training[42]. Considering dietary compliance after BMS, no data on the long-term effect on the lipid profile are available. Although the role of the dietary approach before and after surgery is important, the beneficial effect of the surgery on the lipid profile and cardiovascular risk factors is confirmed in the long term[43]. Moreover, physical exercise is a vital part of weight management programs for enhancing weight loss, keeping ideal body weight, and preventing weight

regain. This important role is also confirmed after the bariatric approach[44]. Furthermore, collecting all clinical elements to calculate the cardiovascular risk by standardized scoring systems before and after surgery was not routinely performed, and both the number of subjects and the duration of the follow-up are limited. Indeed, follow-up reaches one year for all subjects, but a more extensive follow-up, up to seven years, is available only for a small group of patients. In addition, we were not able to evaluate the body composition, hepatic dysfunction, and insulin resistance status. Despite these limitations, our study thoroughly analyzed the lipid profile and evolution in an interval in subjects with severe obesity undergoing surgery and compared the two most common BMS procedures in a routine clinical setting. Although randomized clinical trials remain the most important source of clinical evidence, the stringent constraints of a clinical trial setting may limit the generalizability of these trial results to routine clinical practice[45]. Thus, even more relevance was provided by this real-world data analysis which could be used to fill this gap, providing new insights and better describing the usual clinical practice in a specific condition.

In conclusion, our data suggest that BMS procedures for morbid obesity not only allow sustained weight loss but also are an efficacious treatment to correct dyslipidemia in complicated obese individuals. This could provide a basis for clinical decision-making and help clinicians develop a personalized approach to managing severe obesity and associated dyslipidemia. Additionally, these changes demonstrate benefits from weight loss after BMS, including decreased risk for cardiovascular diseases.

DECLARATIONS

Authors' contributions

Conception or design: Greco C, Santi D
Extracted data: Passerini F, Coluccia S
Acquisition, analysis, or interpretation of data: Greco C, Santi D
Drafting the work or revising: Greco C, Bondi M, Trapani V, Volpe A, Carubbi F, Simoni M, Santi D
Final approval of the manuscript: Greco C, Passerini F, Coluccia S, Bondi M, Mecheri F, Trapani V, Volpe A, Toschi P, Carubbi F, Simoni M, Santi D

Availability of data and materials

Derived data supporting the findings of this study are available from the corresponding author on request.

Financial support and sponsorship

None.

Conflicts of Interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

The study was performed in accordance with the Declaration of Helsinki. The Institutional Review Board of Modena and the Ethical Committee of Modena approved the study (code 0022400/21, approved on 21th July 2021).

Consent for publication

Not applicable.

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