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ORIGINAL CONTRIBUTIONS

Effects of Bariatric Surgery on HDL Cholesterol

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Abstract

Background Low levels of high-density lipoprotein cholesterol (HDLc) are independent predictive factors of coronary heart disease. Bariatric surgery increases HDLc concentration, but the chronology and predictors of this improvement in HDLc levels are not well-established. The aim of the present study was to analyse the changes over time in HDLc concentrations after bariatric surgery and to determine the predictors of their increase.

Subjects and Methods This was a retrospective, observational study. The medical records of patients who had undergone bariatric surgery at a tertiary care hospital between January 2007 and March 2015 were reviewed. Patients who underwent revisional surgery or were treated with fibrates were excluded from the analysis.

Results A total of 185 patients were included in the study. Follow-up rates were as follows: 87% (year 2) and 28% (year 5). At postoperative month 3, HDLc levels decreased significantly versus baseline (− 11.1%; $p = 0.000$), at which point they began to rise, reaching their maximum level 2 years after bariatric surgery (26.2% increase from baseline; $p = 0.000$). The increase in HDLc concentration 2 years after surgery correlated with the preoperative HDLc level ($r = -0.292$, $p = 0.001$), and it was greater in patients who underwent sleeve gastrectomy versus gastric bypass (0.36 ± 0.4 vs. 0.18 ± 0.4 mmol/L, respectively; $p = 0.018$).

Conclusion Bariatric surgery has a beneficial effect on HDLc levels. The maximum increase in postoperative HDLc concentrations is observed 2 years after surgery. Preoperative HDLc and the type of surgery are both significant predictors of the maximum increase in HDLc levels.

Keywords Bariatric surgery · Lipid profile · HDL cholesterol

Introduction

Obesity is associated with an increased risk of cardiovascular mortality [1]. Bariatric surgery lowers this risk [2–6] by reducing the inflammatory milieu that is characteristic of obesity and by improving the metabolic comorbidities—including quantitative and functional changes in the lipoprotein profile [7]—associated with obesity, among others.

Atherogenic dyslipidaemia in patients with obesity is characterized by increased serum concentrations of triglycerides, decreased high-density lipoprotein cholesterol (HDLc) levels and by the presence of small, dense low-density lipoprotein cholesterol (LDLc) particles [8]. Low HDLc levels are an independent predictor of the risk of coronary heart disease and there is a strong, inverse association between HDLc levels and the rates of incident coronary heart disease events [9].

Bariatric surgery has a beneficial effect on lipid profile [10], including an increase in HDLc concentrations [11–14].

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However, the chronology and predictors of this improvement in HDLc levels have not been well-established. Thus, the aim of this study was to evaluate the changes over time in HDLc concentrations after bariatric surgery and to determine the predictive factors of these changes.

Materials and Methods

This was a retrospective, observational study. We reviewed the medical records of all patients ($n = 200$) who underwent bariatric surgery and subsequently followed at our tertiary care centre (Hospital de la Santa Creu i Sant Pau, Barcelona, Spain) from January 2007 to March 2015. All patients met the National Institute of Health criteria for bariatric surgery [15]. Patients who required revisional surgery ($n = 5$) or who received pre- or postoperative treatment with fibrates ($n = 10$) were excluded from the analysis.

An ad hoc questionnaire was developed to collect demographic, anthropometric, and clinical data about the presence and treatment of obesity-related metabolic comorbidities (diabetes, hypertension, dyslipidaemia, and obstructive sleep apnoea [OSA] syndrome). Hypertension was defined according to the criteria established by the European Society of Hypertension (ESH)/European Society of Cardiology (ESC) [16]. Diabetes was defined according to the criteria of the American Diabetes Association [17]. Dyslipidaemia was defined as the presence of any of the following: triglyceride concentrations ≥ 1.7 mmol/L, HDLc concentrations < 1 mmol/L in men or < 1.3 mmol/l in women, LDLc concentrations > 4.14 mmol/L, or hypolipidemic treatment.

Clinical and laboratory data were registered at baseline and postoperatively at months 3, 6, and 12 and then annually for the next 4 years. Laboratory assays were performed to determine levels of the following variables: glycaemia, glycosylated haemoglobin (HbA1c), and lipid profile (total cholesterol, HDLc, LDLc, and triglycerides). Total cholesterol and triglycerides were determined using an enzymatic method (Architect platform ci16000, Abbott Diagnostics). LDLc levels were estimated by the Friedewald formula when triglycerides levels were < 3 mmol/L or by ultracentrifugation when triglyceride levels were > 3 mmol/L. Glycaemia was determined by the hexokinase/glucose 6 phosphate dehydrogenase enzymatic method. HbA1c was measured using ion-exchange high-performance liquid chromatography assay (VARIANT II TURBO, BIO-RAD, Inc., Hercules, CA).

Descriptive statistics were used to analyse clinical characteristics. Means ± standard deviation (SD) were calculated for continuous variables. Categorical variables were reported as absolute numbers with percentages. The Kolmogorov–Smirnov test was used to assess data distribution normality. Associations between qualitative variables were assessed using the chi-square test. The *t* test and Mann–Whitney test were used to analyse independent samples. The paired *t* test and the Wilcoxon test were used to analyse changes between baseline and follow-up data. Pearson's and Spearman's correlation coefficients were calculated to determine correlations between quantitative variables. Multivariate linear regression analysis was performed to identify the factors independently associated with the maximal increase in HDLc levels over time. Statistical significance was set at $p < 0.05$. Data were analysed using the SPSS statistical software package (v. 24) for Windows.

Results

A total of 185 patients were included in the study. Baseline characteristics are shown in Table 1. Of these 185 patients, 121 (65%) underwent sleeve gastrectomy and 64 (35%) gastric bypass. No between-group differences in baseline characteristics were observed. Follow-up rates for the entire cohort were as follows: 97% (year 1), 87% (year 2), 65% (year 3), 46% (year 4), and 28% (year 5).

The changes in the anthropometric and biochemical parameters during the entire follow-up period are shown in Table 2. Changes in weight for the whole cohort and according to the type of surgery are shown in Fig. 1.

HDLc levels decreased significantly 3 months after surgery (− 11.1%; $p < 0.001$ vs. baseline). Thereafter, HDLc levels began to rise, reaching their maximum level 2 years after surgery, with a 26.2% increase compared to baseline ($p < 0.001$) (Fig. 2a,b). The percentage of patients with low HDLc levels at baseline was 47%; after surgery, these percentages were 85%, 37%, and 46%, respectively, at month 3 and at 2 and 5 years. At month 6, a higher proportion of patients in the bypass group presented low HDLc concentrations compared to the sleeve group (70% vs. 50%, respectively; $p = 0.012$). However, there were no significant differences between the groups in terms of the proportion of patients with low HDLc at the other follow-up points.

The maximum increase in HDLc concentrations (ΔHDLc) 2 years after bariatric surgery was inversely correlated with the baseline level of HDLc ($r = -0.292$; $p = 0.001$). The sleeve gastrectomy group presented a greater increase in HDLc concentration at 2 years than the gastric bypass group (0.36 ± 0.4 vs. 0.18 ± 0.4 mmol/L, respectively; $p = 0.018$). These associations remained significant on the multivariate analysis (Table 3). At 3, 4, and 5 years after surgery, the ΔHDLc appeared to remain higher in the sleeve group, without reaching statistical significance (0.26 ± 0.2 vs. 0.20 ± 0.37; 0.27 ± 0.35 vs. 0.20 ± 0.39 and 0.25 ± 0.32 vs. 0.21 ± 0.59 mmol/L at 3, 4 and 5 year respectively). At the 2-year follow-up, 17 patients showed no increase in HDLc levels versus baseline (9.2%), which related to the presence of

Table 1 Baseline clinical and biochemical characteristics of the 185 patients included in the study

	Total ($n = 185$)	Sleeve ($n = 121$)	Bypass ($n = 64$)	p**
Sex, % male	30	34	22	$p = 0.089$
Age (years)	49 ± 10	50 ± 11	47 ± 9	$p = 0.131$
BMI (kg/m^2)	46 ± 5.7	45.6 ± 6.7	46.2 ± 3	$p = 0.602$
Hypertension, n (%)	108 (58)	74 (61.16)	34 (53.1)	$p = 0.292$
DM, n (%)	65 (35)	46 (38)	19 (30)	$p = 0.528$
OSA, n (%)	99 (53.5)	69 (57)	30 (46.8)	$p = 0.188$
Dyslipidaemia, n (%)	126 (68.1%)	84 (69.4)	42 (65.6)	$p = 0.328$
HbA1c (%)	6.5 ± 1.1	6.6 ± 1.1	6.3 ± 1.1	$p = 0.157$
Fasting glycaemia (mmol/L)	6.3 ± 2.0	6.3 ± 2.0	6.3 ± 1.9	$p = 0.849$
Triglycerides (mmol/L)	1.6 ± 0.8	1.6 ± 0.8	1.6 ± 0.7	$p = 0.986$
Total cholesterol (mmol/L)	4.9 ± 0.9	4.8 ± 0.8	5.0 ± 1.0	$p = 0.223$
LDLc (mmol/L)	3.0 ± 0.8	2.9 ± 0.7	3.0 ± 0.9	$p = 0.577$
HDLc (mmol/L)	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.4	$p = 0.303$
Low HDLc*, n (%)	87 (47.3)	61 (58.8)	26 (40.6)	$p = 0.187$

BMI body mass index, *DM* diabetes mellitus, *OSA* obstructive sleep apnoea, *LDLc* low-density lipoprotein cholesterol, *cHDL* high-density lipoprotein cholesterol

*< 1.3 mmol/L in women or < 1 mmol/L in men

**p values according to Student's T test, Mann-Whitney test or chi-square test when indicated

normal HDLc levels at baseline ($p = 0.001$) and the type of surgery (9% in sleeve gastrectomy did not present an increase vs. 23% in gastric bypass; $p = 0.038$).

Discussion

The present study confirms the beneficial effects of bariatric surgery on HDLc concentrations and adds new data about the variation in these levels over time and the predictive factors associated with this effect. Our findings show that HDLc levels initially decrease but then start to rise, reaching their maximum levels 2 years after bariatric surgery. The main determinants of the maximal increase in HDLc after bariatric surgery were preoperative HDLc levels and the type of surgery performed (greater increase in sleeve gastrectomy group).

The large increase (26.2%) in HDLc concentrations 2 years after bariatric surgery in this study was greater than the increase achieved with current commercialized hypolipidemic drugs known to raise HDLc concentrations [18–22] or with lifestyle changes (diet and/or exercise) [23, 24]. This increase was similar in magnitude to that produced by niacin [18, 19, 25], whose use is limited by its adverse side effects and lower than the increase in HDLc produced by cholesteryl ester transfer protein (CETP) inhibitors. However, despite the dramatic capacity of CETP inhibitors to raise HDLc and lower LDLc levels, their development has been halted due to safety and efficacy issues [26–28]. Therefore, bariatric surgery is currently the most effective method to achieve meaningful increases in HDLc levels.

The mean baseline HDLc concentrations and the proportion of patients with low HDLc levels in our cohort were similar to those described in previous studies that have evaluated the effects of bariatric surgery on lipid parameters [6, 14, 29]. In terms of the chronology of HDLc changes, we found an initial reduction in HDLc levels 3 months after bariatric surgery, a finding that has been previously described during the first phase of weight loss after different weight loss strategies [10, 30]. The subsequent increase in HDLc concentrations seen in our study is also congruent with previous reports [11–14, 31, 32]; however, unlike other studies, we have evaluated the variations in HDLc levels over an extended follow-up period (5 years). A novel finding of this study is that the maximum increase in HDLc concentrations occurred 2 years after surgery, remaining elevated throughout the 5-year follow-up period, despite the progressive weight regain observed in our cohort.

Research has shown that patients with more adverse pretreatment lipid profiles experience greater improvement from any effective therapy than patients with less adverse profiles. This is likely the main explanation for the observed association between baseline HDLc levels and the maximal increase 2 years after surgery. More intriguing is our finding that sleeve gastrectomy induced a greater increase in HDLc levels over time than bypass surgery. In line with our results, some other studies [14, 33, 34] also found a greater postoperative increase (at month 12) in HDLc concentrations among patients who underwent sleeve gastrectomy compared to patients submitted to gastric bypass. A small study conducted by Heffron et al. [35] also found a greater increase in HDLc levels and cholesterol efflux capacity in patients treated with

Table 2 Changes in anthropometric and biochemical parameters

	Baseline	3 m *N* = 167	6 m *N* = 163	1 year *N* = 179	2 years *N* = 161	3 years *N* = 120	4 years *N* = 85	5 years *N* = 52
% Sleeve	65%	65%	66%	65%	65%	63%	60%	63%
%EWL	–	39 ± 13.5	59 ± 16.4	73 ± 21.1	71 ± 23.4	67 ± 25	59 ± 27.1	53 ± 24.4
BMI (kg/m^2)	46 ± 5.7	38 ± 5.6*	34 ± 5.1*	31 ± 5.6*	31 ± 5.6*	32 ± 6.0*	34 ± 6.6*	35 ± 5.5*
Fasting plasma glucose (mmol/L)	6.3 ± 2.0	5.3 ± 1.4*	5.8 ± 6.4	5.2 ± 1.3*	5.2 ± 1.4*	5.5 ± 2.0*	5.7 ± 2.2*	5.9 ± 2.7*
HbA1c (%)	6.5 ± 1.1	5.8 ± 1*	5.8 ± 1*	5.6 ± 0.9*	5.8 ± 1*	5.9 ± 0.9*	6 ± 1.3*	6.2 ± 1.6
Tg (mmol/L)	1.6 ± 0.8	1.4 ± 0.7*	1.2 ± 0.5*	1.0 ± 0.4*	1.0 ± 0.4*	1.0 ± 0.5*	1.1 ± 0.5*	1.0 ± 0.5*
TC (mmol/L)	4.9 ± 0.9	4.5 ± 1.0*	4.8 ± 1	4.7 ± 0.9*	4.8 ± 0.9	4.8 ± 0.9	4.8 ± 0.9	4.9 ± 1.0
LDLc (mmol/L)	3.0 ± 0.8	2.9 ± 0.8	3.2 ± 2.5	2.8 ± 0.8*	2.8 ± 0.7*	2.8 ± 0.8	2.7 ± 0.7	2.9 ± 0.9

%EWL percentage of excess weight loss, *BMI* body mass index, *Tg* triglycerides, *TC* total cholesterol, *LDLc* low-density lipoprotein cholesterol
*$p < 0.05$ vs. baseline

sleeve gastrectomy compared to gastric bypass 6 months after bariatric surgery. Various mechanisms have been proposed to explain these differences, with some authors postulating that gastric bypass may lead to lower HDLc concentrations due to an increase in circulating bile acids, which may inhibit ApoA1 synthesis. This hypothesis is further supported by the fact that this surgical technique bypasses the duodenum and part of the jejunum, where ApoA1 synthesis takes place. Conversely, sleeve gastrectomy has been reported to increase the expression of PPARα in animal models, which may contribute to accelerated synthesis and decreased clearance of ApoA1 levels [35]. Finally, resection of the gastric fundus in sleeve gastrectomy reduces ghrelin levels, a hormone known to be correlated with HDLc concentrations [14]. Notwithstanding the aforementioned results, more studies are needed to better understand these theoretical mechanisms. Furthermore, a recent long-term study has reported a similar rate of low HDLc remission at 5 years of follow-up [36] and 2 clinical trials [37, 38] have reported comparable HDLc concentrations with both techniques at 5 years of follow-up. None of these studies, however, analysed the changes in HDLc concentrations as the outcome variable. We also did not find differences between sleeve gastrectomy and gastric bypass in the improvement in HDLc concentrations at 5 years of follow-up, but we cannot rule out if it could be to a lack of power to detect differences due to the small number of patients. Therefore, more long-term studies are needed to clarify this.

The increase in HDLc concentrations after bariatric surgery may be one of the mechanisms involved in cardiovascular protective effects and decreased mortality observed in these patients [6]. However, previous strategies aimed at increasing HDLc levels (e.g., niacin or CETP inhibitors) have not demonstrated a reduction in cardiovascular mortality [39] and have been even linked to a higher risk of death and cardiac

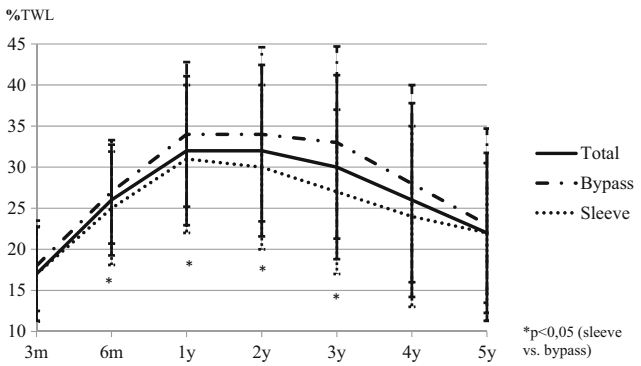

Fig. 1 Weight change as percent of total weight loss (%TWL) during the five-year follow-up period in the full cohort and by treatment group (sleeve gastrectomy vs. gastric bypass)

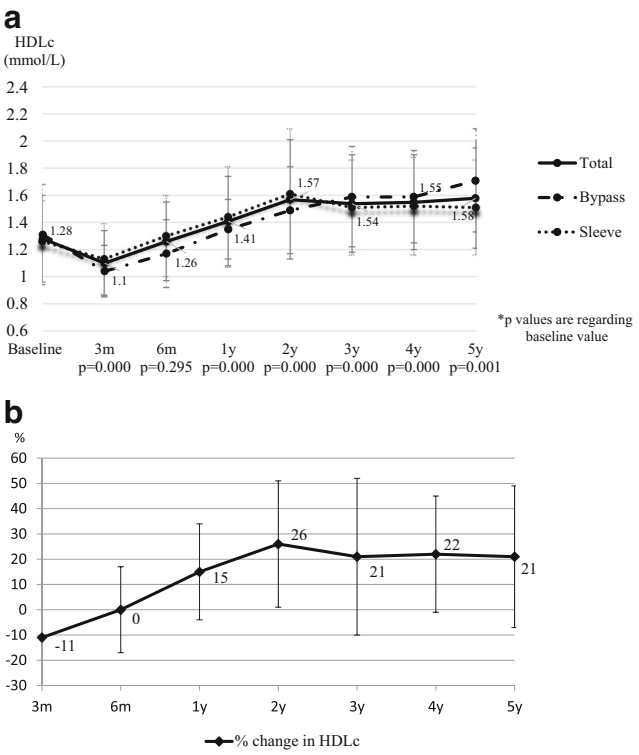

Fig. 2 **a** Changes in HDLc mean levels after bariatric surgery in the full cohort and by treatment group (sleeve gastrectomy and gastric bypass). **b** Percentage change versus baseline in HDLc values after bariatric surgery

Table 3 Predictors of the increase in HDLc concentrations at 2 years after bariatric surgery

Dependent variable	Independent variables	*Ꞵ* (95% CI)	*p* value	R^2
ΔHDLc	Constant	1.008 (0.353 to 1.663)	0.003	0.167
	Δ BMI	− 0.003 (− 0.017 to 0.011)	0.632	
	Δ Triglycerides	0.044 (− 0.088 to 0.176)	0.512	
	Sex	0.163 (− 0.011 to 0.338)	0.067	
	Age	− 0.005 (− 0.013 to 0.004)	0.264	
	Type of surgery	− 0.211 (− 0.362 to − 0.059)	0.007	
	Baseline HDLc	− 0.381 (− 0.620 to − 0.142)	0.002	

ΔHDLc: Increase in HDLc concentrations at 2 years of follow-up (FU); Δ BMI: Change in BMI at 2 years of FU; Δ Triglycerides: Change in Triglycerides at 2 years of FU

events [26]. The fact that not all the strategies known to raise HDLc concentrations have demonstrated a reduction in cardiovascular mortality may reflect the importance not only of changes in HDLc levels but also of changes in HDL composition and functionality [40]. In this context, more studies are needed to determine changes in HDL particle composition and functionality after bariatric surgery to better characterize the putative cardiovascular effects of this treatment. Complementary data—specifically, determining the predictors and mechanisms of increase in HDL levels—is crucial to better understand the antiatherogenic mechanisms of HDL, which would in term allow for the development of new drugs to improve HDL levels and composition to reduce cardiovascular-related mortality.

The main limitations of the present study include its retrospective nature and the absence of data concerning HDL functionality. The main strengths include the large sample size, long follow-up (up to 5 years), and the rigorous patient selection process in which patients on fibrates (which are known to influence HDLc concentrations) and patients submitted to a revisional surgery were excluded.

In conclusion, bariatric surgery is currently the most effective treatment to raise HDLc levels, and this increase may be related with the reduction in mortality rates seen in observational studies. Future studies are needed to clarify the cardiovascular benefits of this postoperative increase in HDLc and to identify the mechanisms involved. A better understanding of these aspects would be valuable to develop new strategies to reduce the risks of developing cardiovascular disease by increasing HDL levels.

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Compliance with Ethical Standards

Competing Interests The authors declare that they have no conflict of interest.

Ethics Statement and Informed Consent For this type of study, formal consent is not required.

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