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KEYWORDS:
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HDL;
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Triglyceride-rich lipoprotein

BACKGROUND: Elevated apolipoprotein C-III (apoC-III) has been postulated to contribute to the atherogenic dyslipidemia seen in obesity and insulin-resistant states, mainly by impairing plasma triglyceride-rich lipoprotein (TRL) metabolism. Bariatric surgery is associated with improvements of several obesity-associated metabolic abnormalities, including a reduction in plasma triglycerides (TGs) and an increase in plasma high-density lipoprotein cholesterol (HDL-C).

OBJECTIVES: We investigated the specific effect of bariatric surgery on apoC-III concentrations in plasma, non-HDL, and HDL fractions in relation to lipid profile parameters evolution.

METHODS: A total of 132 obese subjects undergoing bariatric surgery, gastric bypass ($n = 61$) or sleeve gastrectomy ($n = 71$), were studied 1 month before surgery and 6 and 12 months after surgery.

RESULTS: Plasma apoC-III, non-HDL-apoC-III, and HDL-apoC-III concentrations were markedly reduced after surgery and strongly associated with reduction in plasma TG. This decrease was

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accompanied by a redistribution of apoC-III from TRL to HDL fractions. In multivariate analysis, plasma apoC-III was the strongest predictor of TG reduction after surgery, and the increase of HDL-C was positively associated with plasma adiponectin and negatively with body mass index.

CONCLUSION: Marked reduction of apoC-III and changes in its distribution between TRL and HDL consistent with a better lipid profile are achieved in obese patients after bariatric surgery. These apoC-III beneficial modifications may have implications in dyslipidemia improvement and contribute to cardiovascular risk reduction after surgery.

Introduction

The global epidemic of obesity represents a major public health threat.[1] The relationship between the severity of obesity and increased risk of mortality and morbidity has been demonstrated in several studies.[2,3] Cardiovascular disease is the dominant cause of mortality and morbidity in obesity.[4] Dyslipidemia is often present in obesity and represents a major cardiovascular risk factor. This typical dyslipidemia of obese, insulin-resistant individuals is characterized by a quartet of abnormalities: hypertriglyceridemia, reduction in high-density lipoprotein cholesterol (HDL-C), increase of small and dense low-density lipoprotein (LDL) and postprandial hyperlipidemia.[5] The pathophysiology of this dyslipidemia is widely explained by the blood accumulation of triglyceride-rich lipoproteins (TRL) from liver (very-low-density lipoprotein [VLDL]) and intestine (chylomicrons) origin. This accumulation has been attributed to the overproduction of both VLDL[6] and chylomicrons[7] and to a defective TRL removal process because of a number of associated mechanisms: reduction of lipoprotein lipase (LPL) activity,[8] changes in the apolipoprotein composition of TRL[9] impairing particle clearance, and defect in the hepatic uptake of TRL and their remnants.[8]

Apolipoprotein C-III (apoC-III) is synthesized by the liver and to a lesser extent by the intestine.[10] In healthy individuals, plasma apoC-III is mainly present in TRL (VLDL and chylomicrons) and HDL and is redistributed from HDL to TRL in the postprandial state.[11] Indeed, rapid exchanges occur between these particles, although nonexchangeable pools of TRL-apoC-III and HDL-apoC-III have been described.[12] In hypertriglyceridemic subjects, apoC-III levels proportion bound to TRL are increased in the fasting state.[13] Plasma apoC-III concentration is strongly correlated with plasma triglyceride (TG) concentration[14,15] and is increased in insulin-resistant states (overweight or obesity[15] and type II diabetes[16,17]). Elevated apoC-III has been postulated to contribute to the atherogenic dyslipidemia by the impairment of TRL and HDL metabolism including increased VLDL production and secretion,[18] disturbance of TRL clearance by inhibiting LPL[19] or hepatic lipase,[20] and interfering with TRL and their remnant binding to hepatic lipoprotein receptors.[21,22] Beyond the effects of apoC-III on TRL and HDL metabolism, this apolipoprotein has also been shown to promote inflammation and endothelial cell dysfunction, potentially contributing to atherosclerosis and cardiovascular disease.[23,24] In several clinical studies, elevated apoC-III in HDL and non-HDL fractions was a significant predictor of coronary events and progression of coronary artery disease.[25–28] More recently, genetic variants resulting in a loss of function and reduced apoC-III concentrations were associated with a reduction in the risk of coronary heart disease.[29,30]

Considering the increased mortality in obesity and the relative long-term ineffectiveness of conventional weight-reducing treatments, bariatric surgery is now an accepted therapy worldwide for classes II and III of obesity. Two main procedures are performed: gastric bypass (GBP) and sleeve gastrectomy (SG). In long-term studies, bariatric surgery has been associated with a reduction of 29% in overall mortality compared with obese controls treated with conventional strategies. An important part of this decrease is due to the reduction of deaths from myocardial infarction in the surgery group.[31] Reduction in several cardiovascular risk factors (hypertriglyceridemia, low HDL-C, diabetes, and hypertension) at 2 and 10 years follow-up could contribute to the improvement in the cardiovascular outcome.[32] We have recently demonstrated a reduction in TRL production and an increase in particle clearance of obese subjects after bariatric surgery.[33] However, the drastic improvement of dyslipidemia after bariatric surgery is not fully explained and to date, no study has been conducted to specifically investigate the effect of bariatric surgery on apoC-III.

In the present study, we investigated the effect of GBP and SG on plasma apoC-III concentration, its distribution in the lipoprotein fractions, and its relation to plasma lipid profile. We hypothesized that the improvement of lipid parameters including plasma TG reduction and HDL-C increase after bariatric surgery could be associated with a reduction of plasma apoC-III concentration and a favorable change in apoC-III distribution between TRL and HDL fractions.

Materials and methods

Subjects

A total of 132 obese patients referred to our Nutrition Department with an indication for bariatric surgery were recruited for this study. All participants were examined

and followed by a multidisciplinary and integrated medical team consisting of an endocrinologist, a bariatric surgeon, a psychiatrist, and a dietician for at least 6 months before surgery. All the subjects met the indication criteria for bariatric surgery.[34] The choice of the surgical procedure was not randomized but made by the patient and the multidisciplinary team, after a full explanation of the risks and possible benefits of each procedure. Bariatric surgery was performed by a single surgeon in the General and Endocrine Surgery Department. Sixty-one patients undergoing GBP and 71 patients undergoing SG were consecutively included. The clinical evaluation and laboratory tests were conducted at our Nutrition Department. The subjects were examined and followed by the multidisciplinary team before surgery and at least at 1, 3, 6, 9, and 12 months postsurgery with laboratory tests 1 month before and 6 and 12 months after surgery. Patients with type II diabetes met the diagnostic criteria for diabetes.[35] The presurgery antidiabetic and hypolipidemic treatments of the patients are presented in Supplementary Table 1. This study was conducted in accordance with the Declaration of Helsinki, approved by the Research Ethics Board of Aix-Marseille University, and all subjects gave written informed consent.

Study design

Weight, fasting biochemical parameters, body composition, and energy intake (the diet of each subject was assessed by a dietician using a self-administered food diary completed during 3 days) were measured 1 month before surgery (M0) and at 6 months (M6) and 12 months (M12) after surgery. Our study was not powered or designed to compare the effectiveness of the 2 surgical procedures, one against the other.

Laboratory methods

Blood samples were collected after an overnight fast. Plasma was immediately separated by centrifugation at 2000*g* for 15 minutes at 4°C. Plasma TG, total cholesterol, HDL-C, and LDL-C were measured using an enzymatic colorimetric kit (cobas 6000 c 501 analyzer; Roche Diagnostics, Mannheim, Germany). Plasma glucose was assayed using the hexokinase oxidase method (cobas 6000 c 501 analyzer). Plasma insulin concentrations were determined using electrochemiluminescence method (cobas 6000 e 601 analyzer). Insulin resistance was estimated using the homeostasis model assessment as homeostasis model assessment-insulin resistance (HOMA-IR) = fasting insulin (mUI/L) × fasting glucose (mmol/L)/22.5.[36] HOMA-IR was not calculated for those patients with diabetes to avoid the miscalculation of HOMA-IR due to the antidiabetic drugs taken by the patients. Total apoB and apoA-I plasma concentrations were determined by immunonephelometry assay (Roche Diagnostics) using a BN ProSpec analyzer (Siemens Healthineers, Erlangen, Germany) and total plasma apoC-III and apoC-II levels by immunoturbidimetric assay (Kamiya Biomedical Company, Seattle, WA) using a cobas 6000 c 501 analyzer. HDL-apoC-III and HDL-apoC-II levels were measured in the supernatant after precipitation of TRL with phosphotungstic acid and magnesium chloride (bioMerieux, Marcy-l'Etoile, France). Non-HDL-apoC-III and non-HDL-apoC-II concentrations were calculated by subtracting HDL-apoC-III and HDL-apoC-II values from total plasma apoC-III and C-II measured levels. Specific enzyme-linked immunosorbent assay kit was used to measure serum levels of adiponectin (Quantikine Human Adiponectin; R&D Systems, Minneapolis, MN). Body composition was assessed using dual-energy x-ray absorptiometry method (Lunar iDXA, GE Healthcare, Chalfont, St Giles, UK).

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics 20.0 (IBM Inc, NY) and managed by a statistician. Results are expressed as mean ± standard deviation. Student *t*-test was used to compare GBP and SG surgical groups at M0 and at M6 and M12 after surgery. Paired *t*-test was used to compare the evolution of variables measured at different time points (ΔM6-M0, ΔM12-M0, and ΔM12-M6). Pearson correlation coefficient was used to study the association between the different continuous variables. Backward stepwise linear regression models were used to study the independent predictors of ΔM12-M0 TG. Full model 1 was computed among total obese subjects cohort and included ΔM12-M0 of total apoC-II, non-HDL-apoC-II, total apoC-III, non-HDL-apoC-III, body mass index (BMI), apoB, apoA-I, fasting glucose. Full model 2 was computed among nondiabetic subjects and included the same variables as in the model 1 plus ΔM12-M0 HOMA-IR. All tests were 2 sided, and $P < .05$ was considered statistically significant.

Results

Presurgery baseline demographic characteristics, fasting biochemical parameters, body composition, and energy intake of obese subjects

At baseline, the GBP group was older ($P < .05$) and more obese ($P < .05$) compared with the SG group. There were more patients with diabetes and the fasting plasma glucose was higher in the GBP compared with the SG group ($P < .05$ for all). We found no significant differences in sex ratio, energy intake, fat mass, lipid, apolipoprotein, and hormonal profiles between GBP and SG groups (Table 1).

Table 1 Mean baseline demographic characteristics, fasting biochemical parameters, body composition, and energy intake in the GBP and SG groups of obese subjects

Characteristics	GBP (n = 61)	SG (n = 71)
Age (y)	46.2 ± 9.6	42.3 ± 11.5[a]
Sex ratio (F/M [% women])	43/18 (70.5)	57/14 (80.3)
Weight (kg)	124.6 ± 21.6	115.7 ± 16.5[b]
BMI (kg/m^2)	44.9 ± 6.4	42.4 ± 5.3[a]
Type II diabetics, n	24	15[a]
Fasting glucose (mmol/L)	6.8 ± 3.2	5.8 ± 1.7[a]
HOMA-IR (nondiabetic cohort)	6.09 ± 4.44	5.06 ± 3.21
Adiponectin (μg/mL)	5.88 ± 3.69	6.56 ± 3.47
TG (mmol/L)	1.53 ± 0.98	1.60 ± 0.95
TC (mmol/L)	4.77 ± 0.83	4.82 ± 0.83
HDL-C (mmol/L)	1.08 ± 0.34	1.11 ± 0.34
LDL-C (mmol/L)	3.17 ± 0.75	3.12 ± 0.65
ApoA-I (g/L)	1.45 ± 0.22	1.49 ± 0.22
ApoB (g/L)	0.95 ± 0.20	0.96 ± 0.18
ApoC-II (mg/L)	43.85 ± 14.48	41.21 ± 18.64
ApoC-III (mg/L)	116.26 ± 42.70	121.50 ± 58.21
Energy intake (kJ/d)	8853 ± 3257	9239 ± 3403
Fat mass (%)	50.9 ± 5.1	50.4 ± 4.9

Apo, apolipoprotein; BMI, body mass index; GBP, gastric bypass; HDL-C, high-density lipoprotein-cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; LDL-C, low-density lipoprotein-cholesterol; SG, sleeve gastrectomy; TC, total cholesterol; TG, triglycerides.

Data are means ± standard deviation. Mean data were compared in presurgery (M0) between GBP and SG groups ([a]$P < .05$; [b]$P < .01$).

Effects of bariatric surgery on BMI, insulin resistance, adiponectin, body composition, and energy intake

When we compared presurgery to postsurgery (1 month before vs 6 or 12 months after surgery: ΔM6-M0 or ΔM12-M0) parameters, we found a significant and similar reduction in weight, BMI, plasma fasting glucose, HOMA-IR, energy intake, and fat mass and a significant and similar increase in adiponectin after surgery in both GBP and SG groups ($P < .001$ for all these parameters except ΔM6-M0 for HOMA-IR in GBP, $P < .01$; Table 2).

Effects of bariatric surgery on plasma lipids

In ΔM6-M0 and ΔM12-M0 analyses of plasma lipid concentrations, we found a significant and similar reduction in plasma TG after surgery in both GBP ($P < .01$ at M6 and $P < .001$ at M12) and SG groups ($P < .001$ at M6 and M12) and a significant and similar increase in HDL-C at M12 in both GBP ($P < .01$) and SG ($P < .001$) groups. At M6, HDL-C increased significantly only in the SG group ($P < .05$; Table 3).

We found a significant reduction in plasma TC and LDL-C only in the GBP group at M6 and M12 ($P < .01$ for TC and $P < .001$ for LDL-C; Table 3).

Effects of bariatric surgery on apolipoproteins and distribution of apoC-III and apoC-II in HDL and non-HDL fractions

After surgery, there was a significant reduction in plasma apoB in the GBP group at M6 ($P < .01$) and M12 ($P < .001$) and in the SG group only at M12 ($P < .05$) and the reduction in apoB was significantly greater in the GBP compared with the SG group at M6 and M12 ($P < .05$ for both). ApoA-I decreased significantly in the GBP group at M6 ($P < .01$) but with no change at M12 compared with presurgery and increased significantly in the SG group at M12 only ($P < .01$). Between M6 and M12, apoA-I increased significantly in both groups ($P < .001$; Table 3).

In ΔM6-M0 and ΔM12-M0 analyses, we found a significant and similar reduction in total apoC-III, total apoC-II, non-HDL-apoC-III, HDL-apoC-III, and apoC-III/apoC-II ratio after surgery in both GBP and SG groups. In ΔM12-M6, there was a significant increase in HDL-apoC-III in GBP ($P < .05$) and reduction in non-HDL-apoC-III in SG ($P < .01$). There was a significant reduction in HDL-apoC-II in ΔM12-M0 in both groups ($P < .01$), in ΔM6-M0 in the SG ($P < .01$) and in ΔM12-M6 in the GBP group ($P < .05$) and a significant reduction in non HDL-apoC-II in ΔM12-M0 in the SG group ($P < .01$). There were no significant reductions in plasma apoC-III, apoC-II, or apoC-III/apoC-II ratio in ΔM12-M6 in either group (Tables 3 and 4).

In statistical analyses of the total group of obese subjects undergoing either bariatric surgical procedure, we found a significant reduction in plasma apoC-III and apoC-II in ΔM6-M0 (−28% and −9% respectively; $P < .001$ and $P < .01$ respectively), in ΔM12-M0 (−31% and −18% respectively; $P < .001$ for both) but a significant reduction only for apoC-II in ΔM12-M6 ($P < .05$; Fig. 1, Table 5).

When we compared the concentrations of apoC-III and apoC-II in non-HDL and HDL fractions for the total group of obese subjects, we found a significant reduction of apoC-III in non-HDL and HDL fractions at M6 and M12 ($P < .001$ for all). In ΔM12-M6-specific analyses, we found a significant reduction in non-HDL-apoC-III ($P < .05$) and a significant increase in HDL-apoC-III ($P < .01$). For apoC-II, we found a significant reduction in non-HDL and HDL fractions at M6 ($P < .05$ for both) and at M12 ($P < .01$ for both) but no change in ΔM12-M6 (Fig. 2A and B, Table 5).

When we considered the distribution of apoC-III between non-HDL and HDL fractions, we found no change at M6 of apoC-III distribution between fractions (55% at M0 vs 55% at M6 for non-HDL-apoC-III fraction and 45% at M0 vs 45% at M6 for HDL-apoC-III fraction). In ΔM12-M6 analysis, we found a significant change in the

Table 2 Mean presurgery (M0) and postsurgery evolution at 6 months (M6) and at 12 months (M12) of weight, BMI, insulin resistance, adiponectin, energy expenditure, and energy intake in the GBP and SG groups of obese subjects

	GBP			SG		
Parameters	M0	ΔM6-M0	ΔM12-M0	M0	ΔM6-M0	ΔM12-M0
Weight (kg)	124.6 ± 21.6	−28.0 ± 10.3[b]	−35.6 ± 14.5[b]	115.7 ± 16.5[d]	−28.2 ± 9.1[b]	−32.24 ± 12.0[b]
BMI (kg/m^2)	44.9 ± 6.4	−10.0 ± 3.3[b]	−12.6 ± 4.8[b]	42.4 ± 5.3[c]	−10.3 ± 3.2[b]	−11.8 ± 4.4[b]
Fasting glucose (mmol/L)	6.8 ± 3.2	−1.3 ± 2.6[b]	−1.3 ± 2.3[b]	5.8 ± 1.7[c]	−0.8 ± 1.6[b]	−0.9 ± 1.4[b]
HOMA-IR (nondiabetic cohort)	6.09 ± 4.44	−3.85 ± 4.72[a]	−3.39 ± 3.19[b]	5.06 ± 3.21	−3.15 ± 2.43[b]	−3.53 ± 2.70[b]
Adiponectin (μg/mL)	5.88 ± 3.69	2.41 ± 2.94[b]	4.25 ± 4.59[b]	6.56 ± 3.47	2.17 ± 2.85[b]	4.39 ± 4.16[b]
Energy intake (kJ/d)	8853 ± 3257	−4420 ± 3361[b]	−3914 ± 3621[b]	9239 ± 3403	−4642 ± 3169[b]	−4333 ± 3470[b]
Fat mass (%)	50.9 ± 5.1	−7.81 ± 3.47[b]	−12.28 ± 5.92[b]	50.4 ± 4.9	−8.64 ± 4.05[b]	−12.21 ± 5.26[b]

BMI, body mass index; GBP, gastric bypass; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment-insulin resistance; SG, sleeve gastrectomy.

Data are means ± standard deviation. Mean data were compared between presurgery (M0) and postsurgery (M6 or M12) in each group ([a]$P < .01$; [b]$P < .001$) and between GBP and SG groups ([c]$P < .05$; [d]$P < .01$).

distribution of apoC-III between fractions (55% at M0 vs 50% at M12 for non-HDL-apoC-III fraction and 45% at M0 vs 50% at M12 for HDL-apoC-III fraction; $P < .01$ for both). For apoC-II, we found no change in non-HDL and HDL distribution between pre- and postsurgery (Fig. 2A and B, Table 5).

Presurgery (M0), postsurgery (M12) and delta post- vs pre-surgery (ΔM12-M0) correlations between lipids, apolipoproteins, biochemical, body composition, and energy intake parameters in the total cohort of obese subjects

M0 and M12 univariate analyses are presented in Supplementary Tables 2 and 3 respectively.

In ΔM12-M0 univariate analyses, we found strong positive associations between ΔTG and ΔapoC-III, Δnon-HDL-apoC-III, ΔHDL-apoC-III, ΔapoC-II, Δnon HDL-apoC-II, and ΔHDL-apoC-II ($r > 0.45$ and $P < .001$ for all). There was a significant positive association between ΔHDL-C and Δadiponectin ($r = 0.304$ and $P < .01$) and a significant negative association between ΔHDL-C and ΔBMI ($r = -0.223$ and $P < .05$; Table 6).

In ΔM12-M0 multivariate regression model analyses, ΔapoC-III in model 1 (total obese cohort) explained 56% of TG variation (full model adjusted $R^2 = 0.582$; final model adjusted $R^2 = 0.556$) and ΔapoC-III and ΔapoA-I in model 2 (nondiabetic cohort) explained 71% of TG variation (full model adjusted $R^2 = 0.689$; final model adjusted $R^2 = 0.713$; Table 7).

Discussion

In the present study, we report the effects of 2 types of bariatric surgery (GBP and SG) on apoC-III that include a marked reduction in plasma apoC-III, non-HDL-apoC-III, and HDL-apoC-III concentrations and a redistribution of apoC-III from non-HDL to HDL fraction, consistent with an improved lipid profile.

Here, the marked and similar reductions in BMI, fat mass, energy intake and the improvement in insulin sensitivity after bariatric surgery in both GBP and SG groups were accompanied by a significant reduction in fasting plasma TG and an increase in HDL-C. These findings confirm the results of several studies and meta-analyses in short-term (6–12 months) and long-term (≥12 months) follow-up after bariatric surgery.[32,37]

We found a specific decrease in plasma TC and LDL-C after GBP but not after SG. These findings are in keeping with other studies showing that mixed malabsorptive and restrictive surgery (GBP) is more effective than restrictive surgery (SG) in reducing cholesterol levels[37,38] and more specifically that TC and LDL-C are significantly reduced 12 months after GBP but not after SG.[39] In malabsorptive surgery, it has been shown that intestinal cholesterol absorption decreases leading to decreased plasma TC and LDL-C concentrations, accompanied by enhanced hepatic cholesterol synthesis and catabolism.[40] In the present study, the greater reduction in total apoB in GBP compared with SG could be explained by a specific reduction of LDL particle numbers in GBP.

Our findings are in keeping with the recently published scientific statement on lipids and bariatric procedures.[41,42]

In a recent lipoprotein kinetic study, we have shown improved TRL metabolism after bariatric surgery (GBP and SG) in nondiabetic, obese, insulin-resistant humans with normolipidemia or mild dyslipidemia. This improvement was manifested by decreased production of VLDL and chylomicrons and increased clearance of VLDL.[33] VLDL and chylomicrons are overproduced in insulin-resistant subjects compared with healthy controls,[6,7,43–46] and this overproduction seems to result, in part, from decreased sensitivity to the acute inhibitory effect of insulin on

Table 3 Mean presurgery (M0) and postsurgery evolution at 6 months (M6) and at 12 months (M12) of lipid and apolipoprotein parameters in the GBP and SG groups of obese subjects

	GBP				SG			
Parameters	M0	ΔM6-M0	ΔM12-M0	ΔM12-M6	M0	ΔM6-M0	ΔM12-M0	ΔM12-M6
TG (mmol/L)	1.53 ± 0.98	−0.42 ± 0.93[b]	−0.44 ± 0.66[c]	−0.13 ± 0.49	1.60 ± 0.95	−0.50 ± 0.75[c]	−0.64 ± 0.73[c]	−0.08 ± 0.36
TC (mmol/L)	4.77 ± 0.83	−0.41 ± 0.83[b]	−0.44 ± 1.01[b]	0.08 ± 0.83	4.82 ± 0.83	0.05 ± 0.83[e]	0.08 ± 0.90[e]	0.03 ± 0.65
HDL-C (mmol/L)	1.08 ± 0.34	0.03 ± 0.23	0.15 ± 0.31[b]	0.21 ± 0.21[c]	1.11 ± 0.34	0.10 ± 0.31[a]	0.21 ± 0.34[c]	0.15 ± 0.21[c]
LDL-C (mmol/L)	3.17 ± 0.75	−0.39 ± 0.72[c]	−0.57 ± 0.88[c]	−0.13 ± 0.72	3.12 ± 0.65	0.03 ± 0.67[e]	0.03 ± 0.83[e]	−0.03 ± 0.62
ApoA-I (g/L)	1.45 ± 0.22	−0.08 ± 0.16[b]	0.04 ± 0.18	0.15 ± 0.15[c]	1.49 ± 0.22	−0.01 ± 0.17[d]	0.11 ± 0.22[b]	0.12 ± 0.19[c]
ApoB (g/L)	0.95 ± 0.20	−0.10 ± 0.21[b]	−0.15 ± 0.20[c]	−0.02 ± 0.17	0.96 ± 0.18	−0.02 ± 0.15[d]	−0.07 ± 0.18[a,d]	−0.03 ± 0.13
ApoC-II (mg/L)	43.85 ± 14.48	−3.78 ± 12.36[a]	−7.82 ± 12.78[c]	−2.63 ± 10.29	41.21 ± 18.64	−4.15 ± 13.79[a]	−7.64 ± 13.53[c]	−1.43 ± 9.96
ApoC-III (mg/L)	116.26 ± 42.70	−34.42 ± 33.89[c]	−32.84 ± 33.00[c]	−1.08 ± 27.82	121.50 ± 58.21	−32.10 ± 41.51[c]	−38.15 ± 45.07[c]	−0.13 ± 20.66
ApoC-III/ApoC-II ratio	2.72 ± 0.84	−0.62 ± 0.74[c]	−0.38 ± 0.74[b]	0.12 ± 0.44	3.08 ± 0.91[d]	−0.66 ± 0.84[c]	−0.49 ± 0.91[c]	0.19 ± 0.82

Apo, apolipoprotein; GBP, gastric bypass; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SG, sleeve gastrectomy; TC, total cholesterol; TG, triglycerides.

Data are means ± standard deviation. Mean data were compared between presurgery (M0) and postsurgery (M6 or M12) and between postsurgery (M6 and M12) in each group ([a]$P < .05$; [b]$P < .01$; [c]$P < .001$) and between GBP and SG groups ([d]$P < .05$; [e]$P < .01$).

Table 4 Mean presurgery (M0) and postsurgery evolution at 6 months (M6) and at 12 months (M12) of apoC-II and apoC-III in HDL and non-HDL fractions in the GBP and SG groups of obese subjects

	GBP				SG			
Parameters	M0	Δ M6-M0	Δ M12-M0	Δ M12-M6	M0	Δ M6-M0	Δ M12-M0	Δ M12-M6
HDL-apoC-II (mg/L)	27.13 ± 8.89	−1.05 ± 8.48	−4.90 ± 8.75[b]	−2.26 ± 6.46[a]	26.38 ± 11.30	−2.63 ± 9.06[b]	−4.37 ± 9.90[b]	−0.49 ± 7.96
non HDL-apoC-II (mg/L)	15.60 ± 8.93	−1.43 ± 9.31	−1.99 ± 8.73	−1.13 ± 8.48	15.93 ± 8.88	−2.18 ± 8.50	−4.15 ± 8.28[b]	−1.20 ± 8.27
HDL-apoC-III (mg/L)	52.56 ± 24.13	−17.12 ± 19.14[c]	−12.27 ± 16.64[c]	3.79 ± 11.01[a]	56.39 ± 32.69	−16.85 ± 25.09[c]	−15.75 ± 27.80[c]	3.96 ± 13.92
non HDL-apoC-III (mg/L)	64.64 ± 25.39	−18.21 ± 24.15[c]	−20.30 ± 19.82[c]	−4.23 ± 22.95	65.85 ± 32.68	−15.91 ± 25.26[c]	−24.62 ± 28.58[c]	−6.66 ± 14.40[b]

Apo, apolipoprotein; GBP, gastric bypass; HDL, high-density lipoprotein; NS, not significant; SG, sleeve gastrectomy.

Data are means ± standard deviation. Mean data were compared between presurgery (M0) and postsurgery (M6 or M12) and between postsurgery (M6 and M12) in each group ([a]$P < .05$; [b]$P < .01$; [c]$P < .001$) and between GBP and SG groups (NS).

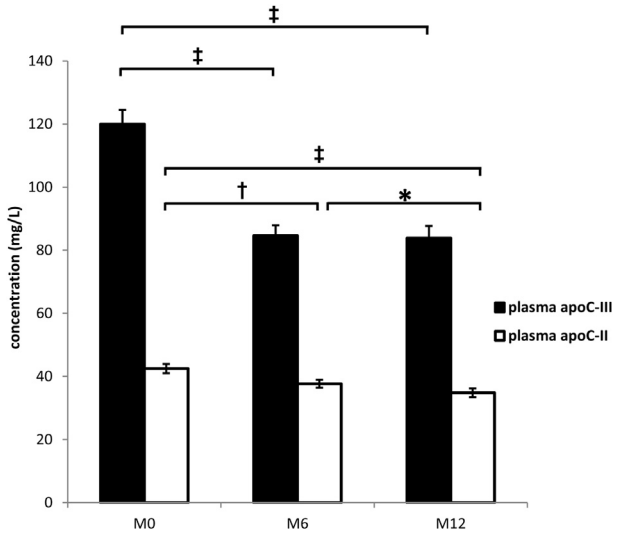

Figure 1 ApoC-III and apoC-II in presurgery (M0) and in postsurgery (at 6 months [M6] and at 12 months [M12]) in the total cohort of obese subjects. Data are means ± standard error of the mean. Mean data were compared between presurgery (M0) and postsurgery (M6 and M12) and between M12 and M6 after surgery ($^{*}P < .05$; $^{\dagger}P < .01$; $^{\ddagger}P < .001$). Apo, apolipoprotein.

VLDL and chylomicron secretion.[5] Moreover, reduced activity of LPL has been shown in insulin-resistant subjects compared with control subjects in fasting and postprandial states.[47,48] This reduction in lipolytic activity seems also to be related to insulin resistance, insulin being a potent activator of LPL.[49] In the present study, the marked improvement in insulin sensitivity after bariatric surgery and its effects on TRL production and LPL activity could explain the decrease in plasma TG concentrations. Hypertriglyceridemia is a major factor contributing to HDL catabolism and to the increased formation of atherogenic small and dense LDL particles.[49] The decrease in plasma TG could partly explain the increase in HDL-C after surgery. Our univariate analyses showed a significant negative association between TG and HDL-C at M0 and M12. Our multivariate regression model analysis confirmed the significant and negative association between the changes (ΔM12-M0) in plasma TG and apoA-I (model 2). We found a positive association between plasma TG and HOMA-IR and a negative association between HDL-C and HOMA-IR at M6 and M12 after surgery. Moreover, it has been shown in subjects with abdominal obesity that the fractional catabolic rate (FCR) of apoA-I is independently associated with both catabolism and production of $VLDL_1$-TG.[50] We also found a significant positive association between the increase in plasma adiponectin and the increase in HDL-C (ΔM12-M0). A significant negative correlation has already been reported between HDL-apoA-I catabolism and plasma adiponectin, independent of insulin resistance and plasma lipids, suggesting as in our study a direct effect of adiponectin on HDL metabolism.[49]

We found a marked, significant reduction of total plasma apoC-III and non-HDL-apoC-III concentrations after GBP and SG and strong positive associations between plasma apoC-III or non-HDL-apoC-III and plasma TG in M0, M12, and ΔM12-M0 univariate analyses.

There are various explanations accounting for the relationship between the reduction in TRL and apoC-III after bariatric surgery. One possibility is that the reduction in TRL production and the increase in TRL catabolism previously shown after bariatric surgery, in the context of weight loss and a clear improvement in insulin sensitivity,[33] may lead to a reduction of apoC-III, which is mainly bound to TRL. This explanation may also apply to the parallel significant reduction of total plasma apoC-II and non-HDL-apoC-II after GBP and SG and the strong positive associations between plasma apoC-II or non-HDL-apoC-II and plasma TG in M0, M12, and ΔM12-M0 analyses, despite the stimulating role of apoC-II on TRL catabolism. ApoC-III and apoC-II are bound to the same lipoproteins, mainly TRL and HDL, and we found a strong positive association between all the following parameters: plasma apoC-III, non-HDL-apoC-III, plasma apoC-II, non-HDL-apoC-II levels in M0, M12, and ΔM12-M0 analyses.

An alternative explanation is that the reduction in non-HDL-apoC-III after bariatric surgery could partly explain the reduction in plasma TG by the actions of apoC-III on TRL metabolism. First, apoC-III has been shown to

Table 5 Mean presurgery (M0) and postsurgery evolution at 6 months (M6) and at 12 months (M12) of apoC-II and apoC-III in plasma, HDL, and non-HDL fractions in the total cohort of obese subjects

Parameters	M0	ΔM6-M0	ΔM12-M0	ΔM12-M6
ApoC-II (mg/L)	42.50 ± 16.43	−3.74 ± 13.09^{b}	−7.71 ± 12.92^{c}	−2.52 ± 9.88^{a}
HDL-apoC-II (mg/L)	26.72 ± 10.23	−1.91 ± 8.79^{a}	−4.64 ± 9.29^{b}	−1.35 ± 7.28
Non-HDL-apoC-II (mg/L)	15.78 ± 8.87	−1.84 ± 8.85^{a}	−3.07 ± 8.53^{b}	−1.17 ± 8.32
ApoC-III (mg/L)	119.96 ± 51.29	−33.94 ± 37.88^{c}	−36.72 ± 38.64^{c}	−1.58 ± 23.03
HDL-apoC-III (mg/L)	54.66 ± 29.08	−16.97 ± 22.46^{c}	−14.12 ± 23.21^{c}	3.88 ± 12.49^{b}
Non-HDL-apoC-III (mg/L)	65.30 ± 29.50	−16.97 ± 24.67^{c}	−22.60 ± 24.84^{c}	−5.46 ± 19.02^{a}

Apo, apolipoprotein; HDL, high-density lipoprotein.

Data are means ± standard deviation. Mean data were compared between presurgery (M0) and postsurgery (M6 or M12) and between postsurgery (M6 and M12) in the total cohort of obese subjects ($^{a}P < .05$; $^{b}P < .01$; $^{c}P < .001$).

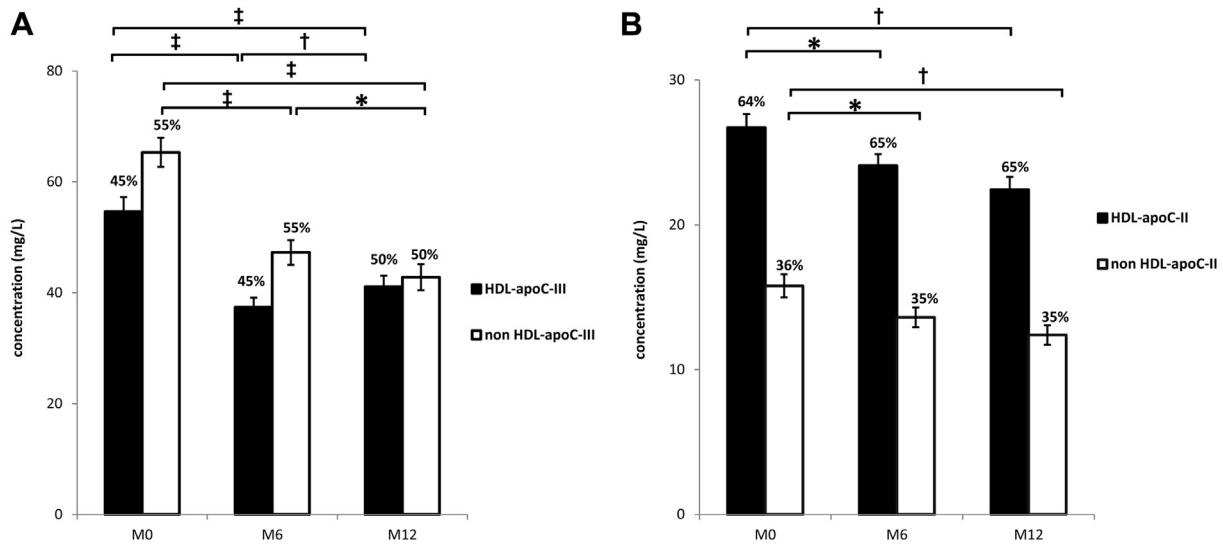

Figure 2 ApoC-III (A) and apoC-II (B) in HDL and non-HDL fractions in presurgery (M0) and in postsurgery (at 6 months [M6] and at 12 months [M12]) in the total cohort of obese subjects. Data are means ± standard error of the mean. Mean data were compared between presurgery (M0) and postsurgery (M6 and M12) and between M12 and M6 after surgery ($^{*}P < .05$; $^{\dagger}P < .01$; $^{\ddagger}P < .001$). Apo, apolipoprotein; HDL, high-density lipoprotein.

promote hepatic VLDL1 production.[18] ApoC-III is mainly synthesized in the liver and its expression is suppressed by insulin[51] and stimulated by glucose.[52] Here, the significant decrease of fasting glucose and the improvement of insulin sensitivity after GBP and SG could have played a role in reducing hepatic apoC-III expression, with subsequent reduction in VLDL1 production. Second, it is well known that apoC-III is an inhibitor of LPL activity.[19] Third, several studies have shown that apoC-III inhibits receptor-mediated uptake of TRL by the liver.[21,22]

Kinetic studies using tracer methodology have confirmed that VLDL-apoC-III is overproduced in overweight insulin-resistant subjects,[15] in hypertriglyceridemic subjects compared with controls,[53] and in centrally, obese men compared with controls.[54] Increased plasma concentrations of apoC-III are associated with impaired VLDL1 clearance in obese insulin-resistant men[55] and VLDL-apoC-III clearance is reduced in centrally obese men compared with controls.[54] Furthermore, plasma TG concentrations in abdominal obesity are determined by the kinetics of $VLDL_1$ particles, their catabolism being mainly dependent on apoC-III concentration[56] and apoC-III levels have been identified as significant determinants of the kinetics and plasma concentrations of TRLs.[57] VLDL-apoC-III concentration was also shown to be positively, independently, and significantly associated with HDL-apoA-I clearance.[54] We found a significant decrease of non HDL-apoC-III, which inhibits LPL, and of non-HDL-apoC-II, which stimulates LPL. However, the reduction in non-HDL-apoC-III was clearly higher than that in non-HDL-apoC-II for both GBP and SG at M6 and M12, leading to a significant reduction in total plasma apoC-III/apoC-II ratio after surgery. For the total cohort, the decrease in non-HDL-apoC-III was also higher than that of non-HDL-apoC-II (−26% vs −12% at M6 and −35% vs −20% at M12). Our ΔM12-M0 multivariate regression model analyses confirmed the strong and significant positive association between plasma TG and total plasma apoC-III (models 1 and 2), apoC-III being the strongest predictor of TG variation after surgery. From all these data, we suggest that the marked reduction in plasma apoC-III or more particularly non-HDL-apoC-III after bariatric surgery might have contributed to the improvement of TRL metabolism, that is, decreased production and increased clearance of TRL, leading to a reduction in plasma TG and an increase in HDL-C.

Both of the previously mentioned changes (ie, reductions in TRL and apoC-III) could occur concurrently, with one affecting the other. Reductions in TRL secondary to marked reductions in body weight, energy intake, and insulin resistance post-bariatric surgery reduce the concentration of apoC-III bound to the TRL fraction. Redistribution of apoC-III from TRL to HDL fractions after bariatric surgery may further contribute to this reduction in TRL-associated apoC-III. Reductions in TRL-bound apo-CIII in turn play an active role in contributing to further reductions in TRL concentrations. Definitive proof of a bidirectional causative relationship between TRL and apoC-III reductions awaits further mechanistic study.

Change occurring in the distribution of apoC-III between non-HDL and HDL fractions is another important finding of our study. Here, we confirmed the results of several studies showing that apoC-III levels associated with TRL in the fasted state are increased in hypertriglyceridemic subjects.[13,58] After a parallel decrease in apoC-III in non-HDL and HDL fractions with no change in the distribution of apoC-III between non-HDL (55%) and HDL (45%) fractions at M6 after surgery, we found a divergent

Table 6 Delta postsurgery vs presurgery (ΔM12-M0) Pearson correlations between lipids, apolipoproteins, biochemical, body composition, and energy intake parameters in the total cohort of obese subjects

Parameters	TC	TG	HDL-C	LDL-C	ApoC-II	HDL-apoC-II	Non-HDL-apoC-II	ApoC-III	HDL-apoC-III	Non-HDL-apoC-III
TC										
TG	0.360[c]									
HDL-C	0.257[a]	−0.072								
LDL-C	0.888[c]	0.144	0.049							
ApoC-II	0.384[c]	0.618[c]	0.003	0.248[a]						
HDL-apoC-II	0.449[c]	0.490[c]	0.081	0.315[b]	0.752[c]					
Non-HDL-apoC-II	0.180	0.465[c]	−0.087	0.072	0.696[c]	0.050				
ApoC-III	0.283[b]	0.712[c]	0.075	0.098	0.760[c]	0.530[c]	0.568[c]			
HDL-apoC-III	0.360[c]	0.681[c]	0.129	0.125	0.643[c]	0.517[c]	0.383[c]	0.789[c]		
Non-HDL-apoC-III	0.199	0.535[c]	0.035	0.041	0.602[c]	0.341[b]	0.523[c]	0.819[c]	0.293[b]	
ApoA-I	0.312[b]	0.010	0.654[c]	0.144	0.040	0.035	0.033	0.169	0.197	0.067
ApoB	0.845[c]	0.327[b]	0.005	0.835[c]	0.477[c]	0.452[c]	0.268[a]	0.344[b]	0.297[b]	0.296[b]
BMI	−0.039	−0.041	−0.223[a]	0.022	−0.057	0.030	−0.088	−0.075	−0.029	−0.100
Fasting glucose	0.247[a]	0.097	0.100	0.224[a]	0.121	0.052	0.113	0.180	0.128	0.139
HOMA-IR (nondiabetic cohort)	−0.232	0.028	−0.184	−0.155	−0.091	0.004	−0.115	−0.084	0.062	−0.202
Adiponectin	0.058	−0.004	0.304[b]	−0.017	−0.065	−0.107	0.073	−0.002	0.092	−0.056
Fat mass	0.021	−0.056	−0.203	0.052	−0.017	0.058	−0.195	0.073	0.041	−0.067
Energy intake	−0.106	0.151	−0.080	−0.212	0.090	0.099	−0.025	0.093	0.206	0.039

Apo, apolipoprotein; BMI, body mass index; HDL-C, high-density lipoprotein-cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; LDL-C, low-density lipoprotein-cholesterol; TC, total cholesterol; TG, triglycerides.

Data are Pearson correlation coefficients ($^aP < .05$; $^bP < .01$; $^cP < .001$). Light gray = positive correlations and dark gray = negative correlations.

Table 7 Multiple linear regression models predicting delta M12-M0 triglycerides evolution (final model after backward stepwise selection with a threshold for exclusion at $P < .05$)

Models	Regression coefficient	95% confidence interval	*P* value
Model 1 ($n = 81$)			
Delta M12-M0, per 1 unit increase			
ApoC-III	0.012	0.010 to 0.015	<.001
Constant	−0.050		
Model 2 ($n = 41$)			
Delta M12-M0, per 1 unit increase			
ApoC-III	0.016	0.013 to 0.019	<.001
ApoA-I	−0.697	−1.254 to −0.14	.016
Constant	0.143		

Apo, apolipoprotein.

Full model 1 was computed among total obese cohort subjects and included ΔM12-M0 of apoC-II, non-HDL-apoC-II, apoC-III, non-HDL-apoC-III, BMI, apoB, apoA-I, fasting glucose (full model adjusted $R^2 = 0.582$; final model adjusted $R^2 = 0.556$). Full model 2 was computed among nondiabetic subjects and included the same variables as model 1 and ΔM12-M0 HOMA-IR (full model adjusted $R^2 = 0.689$; final model adjusted $R^2 = 0.713$).

evolution of the distribution of apoC-III in non-HDL and HDL between M6 and M12 after surgery with a significant increase in HDL-apoC-III (+4%) and a significant decrease in non-HDL-apoC-III (−5%) in the total cohort. These changes led to a redistribution of apoC-III from non-HDL (decreasing from 55% to 50%) to HDL (increasing from 45% to 50%) fractions without a significant change in total plasma apoC-III concentrations. As already discussed, apoC-III concentrations play an important role in TRL metabolism but also in HDL metabolism. Indeed, it has been shown in nonobese subjects that HDL-apoC-III concentration was positively associated with HDL-apoA-I concentration and inversely with HDL-apoA-I FCR.[59] Moreover, HDL-apoC-III production rate was correlated with HDL-apoA-I concentration and resident time in healthy subjects.[60] In another study, HDL-apoC-III concentration was significantly elevated in centrally obese men compared with nonobese men and was significantly and directly correlated with production rate but also FCR of HDL-apoA-I in centrally obese men. Both VLDL apoC-III and HDL-apoC-III concentrations were positively associated with HDL-apoA-I hypercatabolism independently of BMI and insulin resistance.[54] One can speculate that the quantitative and relative redistribution of apoC-III between TRL and HDL fractions after bariatric surgery, leading to an improved apoC-III distribution profile in lipoproteins, may have contributed to the improvement in TRL and HDL metabolism and finally to the reduction in plasma TG and the increase in HDL-C. Selective oligonucleotide antisense inhibition of apoC-IIII synthesis are currently being developed. This therapy causes a marked reduction in plasma apoC-III and TG concentration and an increase in HDL-C, highlighting the major role of apoC-III in TRL and HDL metabolism.[61] Moreover, the efficiency of this treatment in TG reduction in familial chylomicronemia syndrome with LPL activity below 5% also underlines the role of apoC-III as a key regulator of LPL-independent pathways of TG metabolism.[62]

In conclusion, we have described, the evolution of apoC-III after bariatric surgery in humans. We showed, for the first time, marked reduction of total plasma apoC-III and non-HDL-apoC-III occurring after both GBP and SG. These quantitative changes were associated with a redistribution of apoC-III between TRL and HDL fractions consistent with a better lipid profile. Reduction of apoC-III and its lipoprotein redistribution after bariatric surgery may have implications in dyslipidemia improvement and could contribute to the reduction in cardiovascular morbidity and mortality that has been demonstrated after this effective treatment of obesity. Beyond a better understanding of the apoC-III role in the dyslipidemia of insulin-resistant subjects, the present study could help the physicians to choose among other parameters the most appropriate bariatric surgery procedure depending on the lipid profile before surgery. Moreover, this study has confirmed apoC-III as an attractive clinical target in the fields of hypertriglyceridemia, atherogenic dyslipidemia, and cardiovascular disease.

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Appendix

Supplementary Table 1 Presurgery (M0) antidiabetic and hypolipidemic treatments in the GBP and SG groups of obese subjects

Treatments	GBP ($n = 61$)	SG ($n = 71$)
Lifestyle counseling alone	1	2
Oral antidiabetic drugs	16	8
Insulin	1	2
Oral antidiabetic drugs and insulin	6	3
Statin	12	7
Fibrate	0	2
Fibrate and ezetimibe	2	0

GBP, gastric bypass; SG, sleeve gastrectomy.

Data are numbers of subjects treated with anti-diabetic and hypolipidemic treatment at pre-surgery (M0) in GBP and SG groups.

Supplementary Table 2 Presurgery (M0) Pearson correlations between lipids, apolipoproteins, biochemical, body composition, and energy intake parameters in the total cohort of obese subjects

Parameters	TC	TG	HDL-C	LDL-C	ApoC-II	HDL-apoC-II	Non-HDL-apoC-II	ApoC-III	HDL-apoC-III	Non-HDL-apoC-III
TC										
TG	0.321[c]									
HDL-C	0.294[b]	−0.255[b]								
LDL-C	0.819[c]	0.101	0.026							
ApoC-II	0.424[c]	0.694[c]	−0.017	0.154						
HDL-apoC-II	0.395[c]	0.521[c]	0.090	0.120	0.881[c]					
Non-HDL-apoC-II	0.363[c]	0.702[c]	−0.140	0.184[a]	0.837[c]	0.478[c]				
ApoC-III	0.458[c]	0.736[c]	0.036	0.150	0.773[c]	0.639[c]	0.662[c]			
HDL-apoC-III	0.476[c]	0.712[c]	0.075	0.143	0.760[c]	0.703[c]	0.569[c]	0.874[c]		
Non-HDL-apoC-III	0.396[c]	0.605[c]	−0.06	0.174	0.598[c]	0.416[c]	0.597[c]	0.877[c]	0.533[c]	
ApoA-I	0.262[b]	−0.127	0.737[c]	0.022	−0.077	−0.062	−0.136	0.121	0.137	0.046
ApoB	0.723[c]	0.510[c]	−0.098	0.709[c]	0.461[c]	0.340[c]	0.470[c]	0.425[c]	0.417[c]	0.370[c]
BMI	0.002	0.013	−0.101	0.155	−0.011	0.059	0.000	−0.092	−0.001	−0.097
Fasting glucose	0.142	0.377[c]	−0.011	0.079	0.366[c]	0.257[b]	0.348[c]	0.344[c]	0.381[c]	0.214[a]
HOMA-IR (nondiabetic cohort)	−0.042	0.190	−0.293[a]	0.007	0.067	0.103	0.005	0.026	0.091	−0.042
Adiponectin	0.230[b]	−0.148	0.500[c]	0.050	−0.104	0.003	−0.142	0.083	0.011	0.121
Fat mass	0.089	−0.190	0.200	0.090	−0.162	−0.133	−0.044	−0.174	−0.086	−0.155
Energy intake	−0.102	0.175	−0.210[a]	−0.233[a]	0.255[a]	0.235[a]	0.139	0.234[a]	0.232[a]	0.251[a]

Apo, apolipoprotein; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

Data are Pearson correlation coefficients ($^aP < .05$; $^bP < .01$; $^cP < .001$). Light gray = positive correlations and dark gray = negative correlations.

Supplementary Table 3 Postsurgery (M12) Pearson correlations between lipids, apolipoproteins, biochemical, body composition, and energy intake parameters in the total cohort of obese subjects

Parameters	TC	TG	HDL-C	LDL-C	ApoC-II	HDL-apoC-II	Non-HDL-apoC-II	ApoC-III	HDL-apoC-III	Non-HDL-apoC-III
TC										
TG	0.336[b]									
HDL-C	0.260[a]	−0.332[b]								
LDL-C	0.944[c]	0.228[a]	0.049							
ApoC-II	0.412[c]	0.680[c]	−0.013	0.315[b]						
HDL-apoC-II	0.378[c]	0.613[c]	0.013	0.288[b]	0.907[c]					
Non-HDL-apoC-II	0.339[b]	0.571[c]	−0.064	0.273[b]	0.836[c]	0.526[c]				
ApoC-III	0.443[c]	0.731[c]	0.068	0.246[a]	0.739[c]	0.691[c]	0.606[c]			
HDL-apoC-III	0.478[c]	0.630[c]	0.203	0.305[b]	0.724[c]	0.729[c]	0.511[c]	0.867[c]		
Non-HDL-apoC-III	0.306[b]	0.660[c]	−0.051	0.131	0.604[c]	0.539[c]	0.565[c]	0.908[c]	0.578[c]	
ApoA-I	0.351[c]	−0.054	0.799[c]	0.184	0.084	0.122	−0.017	0.331[b]	0.390[c]	0.193
ApoB	0.889[c]	0.424[c]	−0.031	0.910[c]	0.478[c]	0.402[c]	0.434[c]	0.412[c]	0.382[c]	0.323[b]
BMI	−0.055	0.128	−0.162	−0.061	0.160	0.205	0.04	0.156	0.074	0.141
Fasting glucose	−0.017	0.370[c]	−0.303[b]	0.019	0.301[b]	0.325[b]	0.225[a]	0.236[a]	0.219[a]	0.213[a]
HOMA-IR (nondiabetic cohort)	0.317[a]	0.503[c]	−0.378[b]	0.319[a]	0.451[b]	0.454[b]	0.374[b]	0.543[c]	0.413[b]	0.522[c]
Adiponectin	0.200[a]	−0.250[a]	0.518[c]	0.113	−0.095	−0.144	−0.040	0.076	0.126	0.046
Fat mass	0.096	−0.050	0.094	0.104	0.038	0.090	−0.050	0.105	0.055	0.077
Energy intake	0.055	0.089	−0.146	0.053	0.030	0.093	−0.033	0.057	−0.029	0.088

Apo, apolipoprotein; BMI, body mass index; HDL-C, high-density lipoprotein-cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; LDL-C, low-density lipoprotein-cholesterol; TC, total cholesterol; TG, triglycerides.

Data are Pearson correlation coefficients ($^aP < .05$; $^bP < .01$; $^cP < .001$). Light gray = positive correlations and dark gray = negative correlations.