Changes in High-Density Lipoprotein Cholesterol Efflux Capacity After Bariatric Surgery Are Procedure Dependent

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Objective—High-density lipoprotein cholesterol efflux capacity (CEC) is inversely associated with incident cardiovascular events, independent of high-density lipoprotein cholesterol. Obesity is often characterized by impaired high-density lipoprotein function. However, the effects of different bariatric surgical techniques on CEC have not been compared. This study sought to determine the effects of Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) on CEC.

Approach and Results—We prospectively studied severely obese, nondiabetic, premenopausal Hispanic women not using lipid medications undergoing RYGB (n=31) or SG (n=36). Subjects were examined before and at 6 and 12 months after surgery. There were no differences in baseline characteristics between surgical groups. Preoperative CEC correlated most strongly with Apo A1 (apolipoprotein A1) concentration but did not correlate with body mass index, waist:hip, high-sensitivity C-reactive protein, or measures of insulin resistance. After 6 months, SG produced superior response in high-density lipoprotein cholesterol and Apo A1 quantity, as well as global and non-ABCA1 (ATP-binding cassette transporter A1)–mediated CEC (P=0.048, P=0.018, respectively) versus RYGB. In multivariable regression models, only procedure type was predictive of changes in CEC (P=0.05). At 12 months after SG, CEC was equivalent to that of normal body mass index control subjects, whereas it remained impaired after RYGB.

Conclusions—SG and RYGB produce similar weight loss, but contrasting effects on CEC. These findings may be relevant in discussions about the type of procedure that is most appropriate for a particular obese patient. Further study of the mechanisms underlying these changes may lead to improved understanding of the factors governing CEC and potential therapeutic interventions to maximally reduce cardiovascular disease risk in both obese and nonobese patients.

Visual Overview—An online visual overview is available for this article. **(*Arterioscler Thromb Vasc Biol*. 2018;38:245-254. DOI: 10.1161/ATVBAHA.117.310102.)**

Key Words: bariatric surgery ■ gastric bypass ■ obesity ■ sleeve gastrectomy ■ weight loss

The World Health Organization estimates that nearly one quarter of the worldwide cardiovascular disease (CVD) burden is attributable to obesity.[1] Dyslipidemia, frequently present in obesity, seems to explain much of the increased risk for CVD.[2] Obesity is often characterized by low levels of high-density lipoprotein cholesterol (HDL-C), as well as impaired HDL function.[3–11] HDL has antioxidative, anti-inflammatory, and antithrombotic actions,[12–14] but HDL's participation in cholesterol efflux—removal of cholesterol from the periphery and atherosclerotic plaques as the first step within the process of reverse cholesterol transport—has been considered to be the foremost mechanism for its association with reduced CVD risk.[12] Over the past several years, many prospective studies have demonstrated inverse associations between cholesterol efflux capacity (CEC) and incident cardiovascular events.[4,5,15,16]

The effects of weight loss on plasma HDL-C levels have been well studied.[17–20] Previous work has determined that the weight loss modality—be it dietary modification, exercise, or bariatric surgery—influences the changes in HDL-C, as does the degree of weight loss.[21] Less characterized are the effects of weight loss on HDL function in CEC, which is only modestly associated with HDL-C, and has not been found to improve with nonsurgical weight loss.[10,22,23] The few published assessments of the effect of bariatric surgery on CEC are limited by short durations of follow-up and sample sizes.[3,24,25] Further, no head-to-head comparison of the effects of bariatric procedures on CEC has been performed.

To date, there has been little investigation of the effects of surgical weight loss on HDL function, and specifically on CEC—the only measure of HDL function independently associated with prospective cardiovascular events. Identifying interventions which avoid loss of HDL function and, ideally, produce sustained enhancement may aid in determining the most appropriate procedure for a particular patient pursuing bariatric

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Nonstandard Abbreviations and Acronyms

ABCA1	ATP-binding cassette transporter A1
ABCG1	ATP-binding cassette transporter G1
Apo	apolipoprotein
BMI	body mass index
CEC	cholesterol efflux capacity
CVD	cardiovascular disease
HDL-C	high-density lipoprotein cholesterol
RYGB	Roux-en-Y gastric bypass
SG	sleeve gastrectomy

surgery. It may also provide insight on factors governing CEC, and in turn, potential therapeutic interventions to reduce CVD risk in both obese and nonobese patients. With this background, the present study sought to prospectively investigate the effect of the 2 most commonly performed bariatric surgical procedures, Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG), on HDL function in CEC, using the common assay using J774A.1 cells and ApoB (apolipoprotein B)-depleted serum.[26]

Materials and Methods

Materials and Methods are available in the online-only Data Supplement.

Results

Eight hundred fifty-eight patients were screened, with 109 satisfying enrollment criteria and consenting to participate in the study (Figure I in the online-only Data Supplement). Seventy-four women presented for baseline testing and underwent surgery. One subject became pregnant before her 6 month follow-up visit, another started an exclusionary medication after surgery, and 5 did not return for 6-month visits.

Subjects were young (32.7±8.0 years) and severely obese (43.8±6.4 kg/m^2), and although none required medications to treat insulin resistance or dyslipidemia, half of subjects undergoing each procedure met criteria for the metabolic syndrome[27] before surgery (Table 1). Other than those subjects undergoing SG being slightly older (34.0±8.0 versus 30.4±7.3 years; P=0.02), there were no statistically significant differences in baseline characteristics between surgical groups.

Table 1. Baseline Characteristics of Obese Participants [Mean (SD) or Median [Interquartile Range]]

	All Subjects (n=74)	Subjects Attending 6-Month Follow-Up (n=67)	RYGB (n=31)	SG (n=36)
Age, y	32.4 (7.7)	32.7 (8.0)	30.4 (7.3)*	34.0 (7.9)
BMI, kg/m^2	44.1 (6.4)	43.8 (6.4)	43.1 (5.7)	45.0 (7.0)
Metabolic syndrome present	38/74	33/67	16/31	17/36
Weight, kg	112.5 (17.6)	111.0 (16.7)	111.2 (16.4)	110.9 (17.3)
Waist circumference, cm	115.9 (12.6)	114.9 (12.1)	115.3 (11.2)	114.6 (13.0)
Systolic blood pressure, mm Hg	121 (9)	121 (9)	120 (8)	122 (9)
Diastolic blood pressure, mm Hg	73 (8)	73 (8)	72 (8)	74 (9)
Total cholesterol, mg/dL	173 (33)	173 (33)	167 (22)	177 (40)
LDL cholesterol, mg/dL	110 (29)	110 (29)	104 (22)	114 (32)
HDL cholesterol, mg/dL	46.8 (10.4)	47.0 (10.2)	48.2 (9.8)	46.0 (10.6)
Apo A1, mg/dL	130.1 (24.5)	130.3 (23.9)	133.6 (25.2)	127.8 (24.1)
HDL particles, μmol/L	31.8 (5.5)	32.0 (5.6)	32.5 (6.0)	31.2 (5.2)
Large HDL particles, μmol/L	5.1 (2.9)	5.1 (2.8)	5.4 (3.2)	5.1 (2.7)
Small HDL particles, μmol/L	15.3 (5.0)	15.4 (5.2)	15.4 (4.9)	15.2 (5.2)
Triglycerides, mg/dL	95 [77–136]	101 [77–138]	92 [77–138]	110 [82–144]
HOMA-IR	6.0 (3.7)	6.0 (3.7)	6.1 (3.9)	5.9 (3.7)
Hemoglobin A1c (%)	5.6 (0.6)	5.6 (0.6)	5.7 (0.7)	5.5 (0.6)
CETP activity, pmol μL^{-1} h^{-1}		21.0 (8.3)	21.6 (9.3)	20.0 (7.5)
Adiponectin, μg/mL		11.7 (6.5)	11.8 (7.0)	11.7 (6.1)
hsCRP, mg/L	8.0 [3.7–14.3]	8.6 [4.6–14.3]	11.5 [5.4–14.9]	8 [3.7–14]
Global cholesterol efflux capacity (%)	8.3 (2.2)	8.2 (2.2)	8.3 (1.8)	8.1 (2.5)
cAMP-inducible efflux capacity (%)	3.3 (1.4)	3.3 (1.4)	3.1 (1.2)	3.4 (1.5)
Non-ABCA1–mediated efflux capacity (%)	5.1 (1.0)	5.0 (1.0)	5.2 (1.1)	4.9 (0.9)

ABCA1 indicates ATP-binding cassette transporter A1; Apo A1, apolipoprotein A1; BMI, body mass index; CETP, cholesterol ester transfer protein; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment–insulin resistance; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; RYGB, Roux-en-Y gastric bypass; and SG, sleeve gastrectomy.

*P<0.05, RYGB vs SG.

In comparison to normal body mass index (BMI) subjects (n=8) recruited from the same outpatient population, obese subjects had similar concentrations of total HDL particles, but lower HDL-C and fewer large HDL particles, with a trend toward lower Apo A1 concentrations (P=0.10; Table I in the online-only Data Supplement). Obese subjects also exhibited significantly lower global and non-ABCA1 (ATP-binding cassette transporter A1)–mediated CEC than normal BMI subjects.

Effects of Bariatric Surgery

At 6 months, both surgical procedures had reduced mean BMI, waist circumference, blood pressure, triglycerides, high-sensitivity C-reactive protein, homeostatic model assessment–insulin resistance, and hemoglobin A1c, while increasing average adiponectin and large HDL particles (Table 2). Average percent change from preoperative values for several variables differed significantly between procedures, notably, concentrations of HDL-C, HDL particles, and Apo A1 (Figure 1; Table II in the online-only Data Supplement).

SG and RYGB produced contrasting effects on CEC, with RYGB reducing and SG increasing global and non-ABCA1–mediated CEC at 6 months (Figure 2). Both procedures were associated with decreased cAMP-inducible (for the upregulation of ABCA1 in J774A.1 cells) CEC, with a trend toward greater reductions after RYGB. Fewer than one third of RYGB subjects (10/31) manifest improved global CEC, whereas more than half of SG subjects (20/36) exhibited improved global CEC, at 6 months (P=0.05). The proportion of subjects with increased non-ABCA1–mediated CEC (25/36 versus 13/31; P=0.03) was also greater after SG than RYGB, with cAMP-inducible CEC exhibiting a trend toward a difference between procedures (13/36 versus 6/31; P=0.13).

Predictors of CEC

Preoperative CEC was associated most strongly with plasma Apo A1 concentrations. There were also strong correlations with HDL-C, HDL particle concentration, and large HDL particles (particularly with non-ABCA1–mediated CEC; Table 3). Of note, correlations between CEC and these variables were stronger in our normal BMI cohort (Table III in the online-only Data Supplement). After surgery, the strengths of association between HDL parameters and CEC increased (Table 4).

Notably, the only preoperative variable predictive of response in CEC at 6 months in multivariable regression models was surgical procedure (Tables IV through VI in the online-only Data Supplement). No preoperative anthropometric or blood measures were predictive of the response of CEC postoperatively. Linear regression modeling incorporating

Table 2. Characteristics at 6 Months After Surgery [Mean Value (SD) or Median [Interquartile Range]]

	All Subjects (n=67)	RYGB (n=31)	SG (n=36)
BMI, kg/m^2	31.7 (5.6)*	30.5 (5.0)*	32.7 (5.9)*
Weight, kg	80.4 (14.2)*	78.8 (14.1)*	81.8 (14.3)*
Waist circumference, cm	91.5 (10.4)*	91.3 (9.8)*	91.7 (11.0)*
Systolic blood pressure, mm Hg	113 (12)*	112 (11)*	113 (12)*
Diastolic blood pressure, mm Hg	68 (9)*	66 (8)*	70 (10)*
Total cholesterol, mg/dL	161 (37)*	142 (23)*†	177 (38)
LDL cholesterol, mg/dL	96 (31)*	78 (17)*†	111 (31)
HDL cholesterol, mg/dL	50.4 (15)‡	48.0 (14.5)	50.9 (13.3)*
Apo A1, mg/dL	132.8 (27.8)	128.9 (27.5)	135.8 (27.6)*
HDL particles, μmol/L	29.8 (5.7)*	29.0 (5.2)*	30.0 (6.1)
Large HDL particles, μmol/L	7.3 (3.5)*	7.1 (3.6)*	7.5 (3.4)*
Small HDL particles, μmol/L	15.4 (4.6)	15.3 (4.7)	15.5 (4.5)
CETP activity, pmol μL^{-1} h^{-1}	19.1 (8.0)	16.5 (6.8)‡§	21.1 (8.3)
Triglycerides, mg/dL	82 (30)*	76 (24)*	87 (33)*
hsCRP, mg/L	1.7 [1.0–3.6]*	1.7 [1.0–2.8]*	1.6 [1.0–4.8]*
HOMA-IR	2.5 (1.5)*	2.8 (1.7)*	2.2 (1.4)*
Hemoglobin A1c (%)	5.0 (0.3)*	4.9 (0.3)*§	5.1 (0.4)*
Adiponectin, μg/mL	18.3 [13.5–32.1]*	16.2 [10.3–32.3]*	19.2 [14.0–31.5]‡

Apo A1 indicates apolipoprotein A1; BMI, body mass index; CETP, cholesterol ester transfer protein; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment–insulin resistance; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; RYGB, Roux-en-Y gastric bypass; and SG, sleeve gastrectomy.

*P<0.01, preoperative vs 6 mo post-operative.

†P<0.01, 6-mo postoperative values, RYGB vs SG.

‡P<0.05, preoperative vs 6 mo post-operative.

§P<0.05, 6-mo postoperative values, RYGB vs SG.

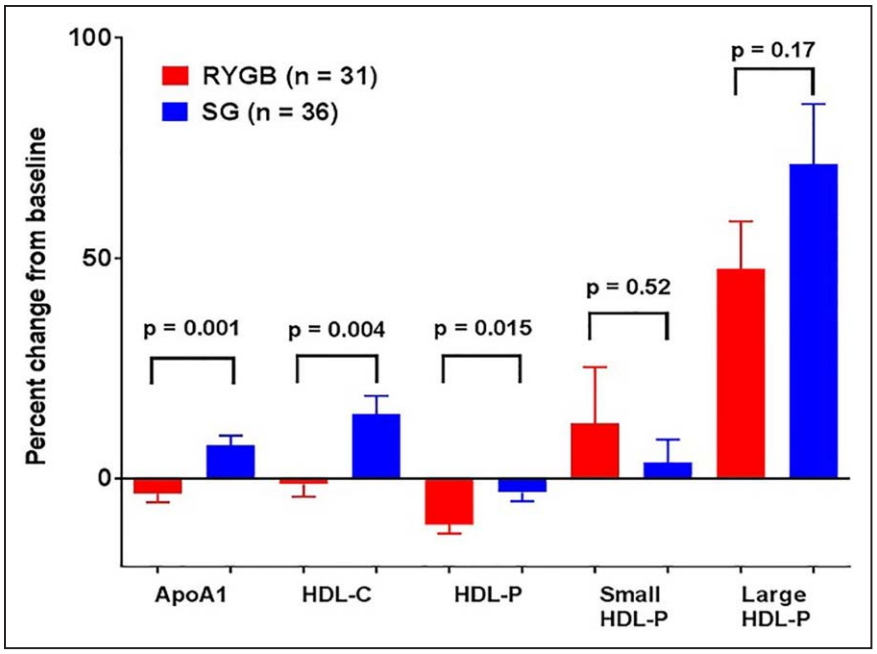

Figure 1. Percent change in high-density lipoprotein (HDL)–related parameters from baseline at 6 mo after Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG). Error bars indicate SEM. Apo A1 indicates apolipoprotein A1; and HDL-P, HDL-particles.

postoperative changes in clinical and hematologic variables revealed that changes in Apo A1 concentration were most predictive of global and non-ABCA1–mediated CEC and that changes in HDL-C were most predictive of cAMP-inducible CEC, at 6 months after surgery (Tables 5 through 7). These associations held regardless of procedure (data not shown).

The associations of several blood measures with CEC differed before and after bariatric surgery (Tables 8 and 9). Most notably, HDL-C, HDL particles, and Apo A1 (Figure 3) were no longer associated with cAMP-inducible CEC at 6 months after RYGB, but continued to be associated with this measure after SG.

Sensitivity Analyses

To obtain more specific assessments of the effects of the procedures on CEC, we compared 6-month postoperative CEC response by procedure in 4 sensitivity analyses described in Methods. These analyses demonstrated identical findings to those of data from the entire cohort—superior changes in CEC after SG, relative to RYGB. Notably, the magnitudes of differences in postoperative changes in CEC between procedures in sensitivity analyses were larger than in the cohort as a whole (Figures II through V in the online-only Data Supplement), suggesting that our observations in the full cohort potentially underestimate the size of the actual difference between procedures.

Twelve-Month Data

Although our a priori primary aim was to compare the change in global CEC between RYGB and SG at 6 months postoperatively, all subjects were invited to return for 12-month follow-up testing. However, 4 subjects became pregnant, 2 started exclusionary medications, and 6 subjects did not present for 12-month visits. Thus, 55 subjects (SG, n=32; RYGB, n=23) attended 1-year follow-up assessments. Relative to CEC at 6 months, both surgical procedures produced similar improvements at 12 months after surgery (Figure VI in the online-only Data Supplement). However, despite these similar late changes, SG produced overall superior improvement in CEC from preoperative levels. In contrast to SG, at 1 year after surgery, post-RYGB subjects persistently exhibited significantly impaired global and cAMP-inducible CEC relative to normal BMI subjects (Table 10).

Discussion

We report the largest and longest study of HDL function after bariatric surgery to date and the first to compare the 2 most commonly performed procedures. This study also equals the length for the longest prospective study of the effects of any type of intervention on CEC.[24,28,29] Notably, we found that RYGB and SG differ significantly in the provoked changes in

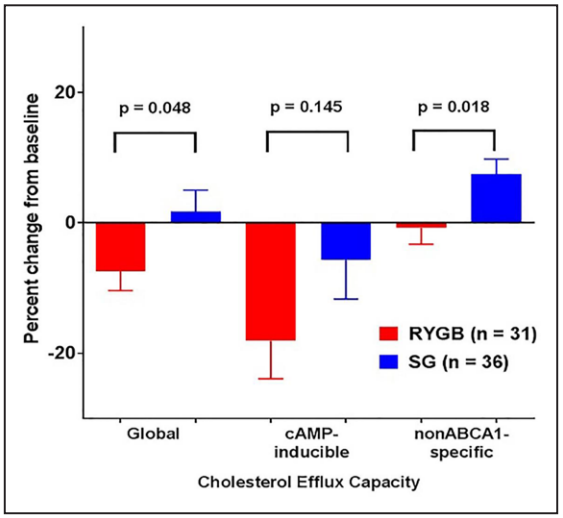

Figure 2. Percent change in global, cAMP-inducible, and non-ABCA1 (ATP-binding cassette transporter A1)–specific cholesterol efflux capacity from baseline at 6 mo after Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG). Error bars indicate SEM.

Table 3. Pearson Correlation Coefficients (*r*) for Preoperative Cholesterol Efflux Capacity With Preoperative Anthropometric Measures and Metabolic Variables

	Global	cAMP Inducible	Non-ABCA1
BMI, kg/m^2	0.07	0.17	–0.08
Body weight, kg	0.11	0.15	0.02
Waist:hip ratio	0.15	0.17	0.01
LDL cholesterol, mg/dL	0.15	0.26*	–0.06
HDL cholesterol, mg/dL	0.57†	0.34†	0.81†
Apo A1, mg/dL	0.61†	0.37†	0.85†
HDL particles, μmol/L	0.56†	0.35†	0.80†
Large HDL particles, μmol/L	0.53†	0.31†	0.75†
Small HDL particles, μmol/L	0.16	0.18	0.04
CETP activity, pmol μL^{-1} h^{-1}	0.01	0.00	–0.03
Log triglycerides	0.28*	0.43†	0.11
HOMA-IR	–0.05	0.01	–0.11
Log Adiponectin, μg/mL	0.35†	0.28*	0.32*
Log hsCRP, mg/L	–0.20	–0.22	–0.10

ABCA1 indicates ATP-binding cassette transporter A1; Apo A1, apolipoprotein A1; BMI, body mass index; CETP, cholesterol ester transfer protein; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment–insulin resistance; hsCRP, high-sensitivity C-reactive protein; and LDL, low-density lipoprotein.

*P<0.05.

†P<0.01.

Table 4. Pearson Correlation Coefficients (*r*) for 6-Month Postoperative Cholesterol Efflux Capacity With Anthropometric Measures and Metabolic Variables at 6 Months After Surgery

	Global	cAMP Inducible	Non-ABCA1
BMI, kg/m^2	0.11	0.12	0.05
Body weight, kg	0.10	0.08	0.11
Waist:hip ratio	0.06	0.10	0.00
LDL cholesterol, mg/dL	0.20	0.34*	0.02
HDL cholesterol, mg/dL	0.76*	0.54*	0.81*
Apo A1, mg/dL	0.81*	0.57*	0.83*
HDL particles, μmol/L	0.73*	0.54*	0.71*
Large HDL particles, μmol/L	0.64*	0.39*	0.77*
Small HDL particles, μmol/L	0.39*	0.39*	0.12
CETP activity, pmol μL^{-1} h^{-1}	0.14	0.18	–0.01
Log triglycerides	0.43*	0.49*	0.13
HOMA-IR	0.07	0.00	0.01
Log adiponectin, μg/mL	0.45*	0.38*	0.39*
Log hsCRP, mg/L	0.04	0.01	0.07

ABCA1 indicates ATP-binding cassette transporter A1; Apo A1, apolipoprotein A1; BMI, body mass index; CETP, cholesterol ester transfer protein; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment–insulin resistance; hsCRP, high-sensitivity C-reactive protein; and LDL, low-density lipoprotein.

*P<0.01.

CEC that occur after surgery. The changes in CEC and differences in response between procedures at 6 months after surgery seem to be largely, but incompletely, explained by changes in Apo A1 and circulating HDL particles, which differed significantly between procedures irrespective of weight loss. However, among all subjects, despite loss of nearly one third of their body weight, and exhibiting increased HDL-C by 1 year after surgery, only half experienced improved CEC, a measure independently associated with incident cardiovascular events.[4,5]

In the current study, in agreement with others, we found obese subjects to have reduced CEC[3,11] and weaker associations of CEC with HDL parameters, than normal BMI subjects.[26] Obese subjects also exhibited significantly lower concentrations of large HDL particles. This is particularly relevant, given 1 hypothesis for why HDL exhibits varying ability to perform cholesterol efflux. HDL particles are heterogeneous, and the concentrations of certain specific subclasses, such as large HDL_2 and the smallest pre-β1 particles, are felt to be most important in regard to mediating CEC and CVD protection.[30,31]

Previously, a 6-month study of premenopausal women without the metabolic syndrome undergoing RYGB found impaired ABCA1-mediated CEC after RYGB,[25] in agreement with our findings in cAMP-inducible CEC. Subjects in that study exhibited increased HDL-C and large HDL_2 particles, as well as SR-BI (scavenger receptor class B type I)–mediated and ABCG1 (ATP-binding cassette transporter G1)-mediated CEC at 6 months after surgery. Postoperative HDL_2 particles, specifically, were found to have greater ability to mediate cholesterol efflux via SR-BI relative to preoperative HDL_2. In contrast, in our cohort of equal numbers of subjects with and without the metabolic syndrome before surgery, RYGB did not improve non-ABCA1–specific CEC. Further, changes in the concentration of large HDL particles were not associated with the observed changes in non-ABCA1–specific CEC after RYGB.

In our direct comparison of procedures, SG produced superior changes to measures of HDL function in CEC relative to RYGB. Recently, in a very small group of adolescent males who underwent SG, Davidson et al[24] observed a 12% increase in global CEC at 1 year (nearly identical to the improvement we observed in SG subjects). In their study, in which Apo A1 was not quantified, the authors suggested that an increase specifically in large HDL particles was responsible for the observed improvement in CEC. Similar to both of the above-cited studies, we found concentrations of large HDL particles increased substantially and similarly after both procedures. However, in contrast to the findings in those smaller studies, the change specifically of large HDL particles was not predictive of changes in CEC in our subjects. We did observe strong associations of CEC changes with changes in HDL-C, total HDL particles, and Apo A1, all particles which exhibited preferable changes after SG versus RYGB, and seem to partially explain the superiority of the former procedure on the outcome of CEC.

Although both achieve marked and rapid weight loss, RYGB and SG are very different surgical procedures. SG, a relatively new bariatric surgical technique,[32] has rapidly become the most commonly performed bariatric procedure in the United States.[33] However, the metabolic changes after this procedure, and the mechanisms driving these changes,

Table 5. Multivariable Linear Regression Models of Changes in Baseline Variables Predicting Change in Global Cholesterol Efflux Capacity at 6 Months After Surgery

	Univariate Analysis		Multivariable Analysis	
	β (SE)	*P* Value	β (SE)	*P* Value
Body weight	1.35 (0.45)	0.004		
Waist circumference	0.80 (0.36)	0.03		
Hip circumference	1.51 (0.58)	0.01		
Log LDL-C	14.15 (6.08)	0.02		
Log HDL-C	26.97 (4.00)	<0.001		
Apo A1	0.98 (0.12)	<0.001	1.02 (0.12)	<0.001
Log HDL particles	34.82 (7.71)	<0.001		
Log large HDL particles	12.95 (7.69)	0.10		
Small HDL particles	0.08 (0.04)	0.07		
Log CETP activity	13.11 (4.91)	0.01		
Log triglycerides	15.84 (7.95)	0.05		
HOMA-IR	0.05 (0.10)	0.64		
Adiponectin	0.01 (0.01)	0.34		
hsCRP	0.13 (0.11)	0.28		

Apo A1 indicates apolipoprotein A1; CETP, cholesterol ester transfer protein; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment–insulin resistance; hsCRP, high-sensitivity C-reactive protein; and LDL-C, low-density lipoprotein cholesterol.

remain poorly understood. RYGB involves creation of a small proximal gastric pouch that is anastomosed to the jejunum. The excluded, but retained, stomach and duodenum are anastomosed to the distal jejunum. SG consists of the removal of the gastric fundus and most of the gastric body, but no anastomoses. Given the considerable differences in gastrointestinal anatomy between procedures, it is perhaps not surprising that they produce differing effects on lipid metabolism, including HDL function. For example, the bypass of the duodenum and part of the jejunum, locations of Apo A1 synthesis,

Table 6. Multivariable Linear Regression Models of Changes in Baseline Variables Predicting Change in cAMP-Inducible Cholesterol Efflux Capacity at 6 Months After Surgery

	Univariate Analysis		Multivariable Analysis	
	β (SE)	*P* Value	β (SE)	*P* Value
Body weight	2.52 (0.82)	0.003		
Waist circumference	1.54 (0.65)	0.02		
Hip circumference	2.96 (1.05)	0.01		
Log LDL-C	20.68 (11.30)	0.07		
Log HDL-C	36.23 (8.49)	<0.001	41.95 (8.32)	<0.001
Apo A1	1.25 (0.27)	<0.001		
Log HDL particles	51.95 (14.77)	0.001		
Log Large HDL particles	18.68 (14.10)	0.19		
Small HDL particles	0.22 (0.08)	0.01		
Log CETP activity	20.17 (9.22)	0.03		
Log triglycerides	19.98 (14.80)	0.18		
HOMA-IR	0.08 (0.16)	0.63		
Adiponectin	0.01 (0.02)	0.70		
hsCRP	0.12 (0.21)	0.58		

Apo A1 indicates apolipoprotein A1; CETP, cholesterol ester transfer protein; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment–insulin resistance; hsCRP, high-sensitivity C-reactive protein; and LDL-C, low-density lipoprotein cholesterol.

Table 7. Multivariable Linear Regression Models of Changes in Baseline Variables Predicting Non-ABCA1–Mediated Cholesterol Efflux Capacity at 6 Months After Surgery

	Univariate Analysis		Multivariable Analysis	
	β (SE)	*P* Value	β (SE)	*P* Value
Body weight	0.70 (0.36)	0.06		
Waist circumference	0.29 (0.28)	0.31		
Hip circumference	0.70 (0.45)	0.13		
Log LDL-C	7.68 (4.74)	0.11	−7.92 (2.84)	0.01
Log HDL-C	22.67 (2.87)	<0.001		
Apo A1	0.81 (0.08)	<0.001	0.90 (0.09)	<0.001
Log HDL particles	25.53 (5.89)	<0.001		
Log Large HDL particles	9.61 (5.84)	0.11		
Small HDL particles	0.02 (0.03)	0.64		
Log CETP activity	9.07 (3.74)	0.02		
Log triglycerides	12.13 (6.12)	0.05		
HOMA-IR	0.01 (0.07)	0.91		
Adiponectin	0.01 (0.01)	0.13		
hsCRP	0.13 (0.08)	0.13		

ABCA1 indicates ATP-binding cassette transporter A1; Apo A1, apolipoprotein A1; CETP, cholesterol ester transfer protein; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment–insulin resistance; hsCRP, high-sensitivity C-reactive protein; and LDL-C, low-density lipoprotein cholesterol.

in RYGB but not SG, may at least partly explain the contrasting response of the 2 procedures. Reductions in HDL-C observed with the use of a duodenal liner device lend support to this hypothesis.[34] Another potential mechanism, suggested by animal models, is the increased expression of PPARα (peroxisome proliferator-activated receptor alpha) after SG.[35] Increased PPARα signaling upregulates Apo A1 production[36] and may suppress Apo A1 turnover and increase CEC,[37] as we observed in subjects after SG. Finally, the anatomic rearrangement of RYGB is known to increase levels of circulating bile acids,[38] compounds which have been shown to reduce Apo A1 expression via their agonism of the farsenoid X receptor.[39]

Our novel observations open up many interesting questions to pursue in future studies. Foremost are the reasons behind the differences in response by surgery and variation in response of apparently similar patients undergoing the same procedure. In addition, after SG, but not RYGB, we found strong correlations of changes in Apo A1 and small HDL particles with cAMP-inducible CEC. This observation suggests that some unmeasured characteristics of the particles, or other factors, that are differentially affected by the 2 procedures, may partially modulate HDL function in obesity. One possibility may be pre-β HDL, which was not measured in this study. It is delipidated Apo A1 and small HDL particles which mediate efflux through ABCA1, which our cAMP-inducible CEC measure attempts to represent.[40] Asztalos et al[41] observed increased HDL-C, but decreased pre-β_1 HDL at 12 months after RYGB, in 19 severely obese women. The effects of SG on this particle are unknown and could partially explain the different effects of procedures on cAMP-inducible CEC and lack of postoperative associations with HDL-related parameters with this specific measure after RYGB.

Additional prominent hypotheses for varied HDL functionality include variations within the protein cargo and the burden of post-translational inflammatory Apo A1 modifications

Table 8. Pearson Correlation Coefficients (*r*) for 6-Month Postoperative Cholesterol Efflux Capacity With Anthropometric Measures and Metabolic Variables at 6 Months After Surgery (RYGB Only)

	Global	cAMP Inducible	Non-ABCA1
BMI, kg/m^2	−0.08	0.06	−0.16
Body weight, kg	−0.02	0.06	−0.07
Waist:hip ratio	0.08	−0.07	0.18
LDL cholesterol, mg/dL	−0.06	0.05	−0.14
HDL cholesterol, mg/dL	0.66*	0.32	0.83*
Apo A1, mg/dL	0.75*	0.27	0.85*
HDL particles, μmol/L	0.62*	0.18	0.72*
Large HDL particles, μmol/L	0.72*	0.26	0.82*
Small HDL particles, μmol/L	0.05	0.26	−0.15
CETP activity, pmol μL^{-1} h^{-1}	−0.01	0.11	−0.11
Log triglycerides	0.22	0.25	0.10
HOMA-IR	0.04	0.10	−0.04
Log adiponectin, μg/mL	0.38	0.35	0.24
Log hsCRP, mg/L	0.08	0.15	−0.02

ABCA1 indicates ATP-binding cassette transporter A1; Apo A1, apolipoprotein A1; BMI, body mass index; CETP, cholesterol ester transfer protein; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment–insulin resistance; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; and RYGB, Roux-en-Y gastric bypass.

*P<0.01.

Table 9. Pearson Correlation Coefficients (*r*) for 6-Month Postoperative Cholesterol Efflux Capacity With Anthropometric Measures and Metabolic Variables at 6 Months After Surgery (SG Only)

	Global	cAMP Inducible	Non-ABCA1
BMI, kg/m^2	0.15	0.09	0.20
Body weight, kg	0.15	0.06	0.27
Waist:hip ratio	0.09	0.22	–0.15
LDL cholesterol, mg/dL	0.21	0.33	0.05
HDL cholesterol, mg/dL	0.80*	0.68*	0.79*
Apo A1, mg/dL	0.86*	0.72*	0.83*
HDL particles, µmol/L	0.78*	0.67*	0.70*
Large HDL particles, µmol/L	0.63*	0.47*	0.72*
Small HDL particles, µmol/L	0.55*	0.46†	0.40†
CETP activity, pmol µL^{-1} h^{-1}	0.14	0.13	0.01
Log triglycerides	0.51*	0.57*	0.15
HOMA-IR	0.12	0.00	0.09
Adiponectin, µg/mL	0.49*	0.38†	0.53*
hsCRP, mg/L	–001	–0.09	0.13

ABCA1 indicates ATP-binding cassette transporter A1; Apo A1, apolipoprotein A1; BMI, body mass index; CETP, cholesterol ester transfer protein; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment–insulin resistance; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; and SG, sleeve gastrectomy.

*P<0.01.

†P<0.05.

on HDL particles, which have been demonstrated to influence CEC.[6,42–44] We hypothesized that reducing the systemic inflammation associated with obesity[45] via bariatric surgery would lead to improved HDL function in CEC. However, despite marked and similar reductions in markers of systemic inflammation among both procedures, there were differential responses in CEC as discussed above. Further, levels of serum inflammatory markers did not associate with preoperative CEC or with postoperative changes in CEC. The absence of association of serum inflammatory markers with CEC was also noted in the Dallas Heart Study,[5] suggesting that these nonspecific blood measures may not represent the propensity for inflammatory modification of HDL particles or at least any associated dysfunction.

Limitations

Our study has many limitations. Assignment to undergo the particular surgical procedure performed was not random. However, the only difference in preoperative characteristics between the 2 groups was a slight, not clinically significant, difference in age. In addition, our study sample consisted of a relatively homogenous population that both reflected the predominant composition of our clinical population and served to reduce confounding in our small sample. As a result, we cannot necessarily extrapolate our findings to other groups, such as older patients, other races, and men.

Another limitation is that the method for assessing CEC does not involve an individual's macrophages, but cultured macrophages in vitro. This may be particularly relevant; as recently, expressions of ABCA1 and ABCG1 were reported to be decreased in the monocytes of obese individuals,[46] calling into question how representative of in vivo CEC our measure may be. Further, we assessed cholesterol efflux to apoB-depleted serum. These assays do not allow for determination of bidirectional efflux driven by whole serum or that mediated specifically by ABCG1 or SR-BI. Nonetheless, the assay used in this study has been inversely associated with prevalent and incident CVD in multiple, diverse populations.[4,26]

Conclusions

This is the largest and longest study of CEC after bariatric surgery to date and the only parallel prospective comparison of 2

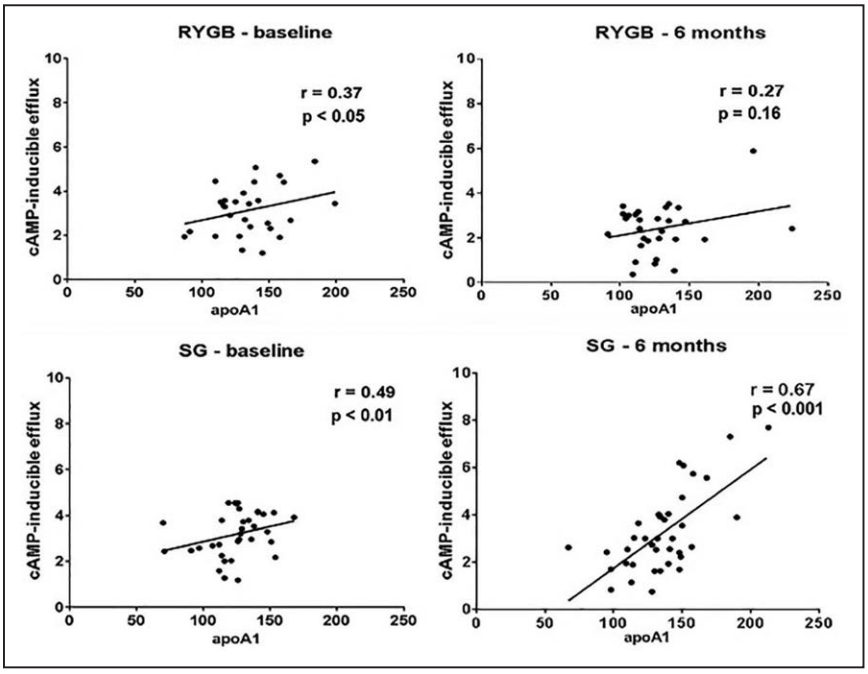

Figure 3. Correlations of Apo A1 (apolipoprotein 1A) concentration (mg/dL) with cAMP-inducible efflux (percent) before and 6 mo after Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG). *P* value from Fisher Z-transformation for comparison of SG and RYGB at baseline (P=0.57) and at 6 mo (P<0.05).

Table 10. Cholesterol Efflux Capacity of Normal BMI Subjects and Obese Subjects 12 Months After RYGB or SG [mean (SD)]

	Normal BMI	RYGB 12 mo	SG 12 mo
Global cholesterol efflux capacity (%)	10.3 (2.6)	8.2 (1.7)*	9.0 (1.7)†
cAMP-inducible efflux capacity (%)	4.0 (1.3)	2.6 (1.1)*	3.3±1.2
Non-ABCA1–mediated efflux capacity (%)	6.3 (1.4)	5.7 (1.3)‡	5.7 (0.9)§

ABCA1 indicates ATP-binding cassette transporter A1; BMI, body mass index; RYGB, Roux-en-Y gastric bypass; and SG, sleeve gastrectomy.

*P<0.05 vs Normal BMI.

†P=0.05 vs SG baseline.

‡P<0.01 vs RYGB baseline.

§P<0.001 vs SG baseline.

procedures on this outcome. We observed contrasting changes in CEC at 6 months after SG and RYGB, with superior improvements in Apo A1, HDL-C, and our primary end point of CEC—a measure predictive of prospective cardiovascular events—after SG. Our study makes a major contribution to the knowledge surrounding the metabolic effects of different bariatric surgical techniques. The changes in CEC and differences between procedures seem to be largely statistically explained by altered concentrations of Apo A1 or HDL particles after surgery. The relevance is profound as there is great need to better understand the metabolic effects of the ≈200 000 bariatric surgeries performed annually in the United States, particularly as almost half of bariatric surgery patients are <40 years old,[47] and may face unknown or unappreciated outcomes of the procedures[48] for decades. In addition, further study of the mechanisms underlying these changes may lead to improved understanding of the factors governing CEC and potential therapeutic interventions to improve CEC and reduce CVD risk in obese and nonobese patients.

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Disclosures

S.J. Adelman is CEO of Vascular Strategies LLC. H.L. Collins is an employee of Vascular Strategies LLC. The other authors report no conflicts.

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Highlights

- Sleeve gastrectomy and Roux-en-Y gastric bypass produce similar weight loss, but contrasting effects on cholesterol efflux capacity.
- The changes in cholesterol efflux capacity after bariatric surgery are largely, but incompletely, explained by changes in plasma concentrations of Apo A1 (apolipoprotein A1).
- Changes in cholesterol efflux capacity after bariatric surgery are not associated with reductions in inflammatory markers or measures of insulin resistance.
- Further clarification of the mechanisms underlying the procedure-specific changes may suggest therapeutic interventions for obese and non-obese patients at risk for cardiovascular disease.

Arteriosclerosis, Thrombosis, and Vascular Biology

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Changes in High-Density Lipoprotein Cholesterol Efflux Capacity After Bariatric Surgery Are Procedure Dependent

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Materials and methods

Premenopausal Hispanic women, at least 18 years of age, undergoing either RYGB or SG at Bellevue Hospital Center (New York, NY) were recruited for a prospective observational study approved by the NYU School of Medicine Institutional Review Board and the New York Health and Hospitals Corporation. The ethnicity and gender were chosen because of their preponderance in the patient population. Subjects met typical criteria for bariatric surgery (BMI ≥ 40 kg/m^2 or ≥ 35 kg/m^2 with at least one obesity-related comorbidity). The decision as to which procedure was performed was made by the patient after consultation with the attending surgeon.

Patients were excluded if they were active smokers, receiving lipid-lowering agents, diabetes medications, thyroid hormone, or oral contraceptives, had polycystic ovary syndrome, or if they became pregnant during the study.

Subjects providing informed consent presented to the NYU-HHC CTSI Clinical Research Center after an overnight fast, within one month prior to their surgery, in a state of weight maintenance prior to beginning pre-operative liquid diets (baseline visit), and at six and 12 months following surgery. At these visits, the following measurements were performed: weight, height, waist and hip circumferences, blood pressure, food frequency questionnaire, activity diary, and medication review. Subjects also underwent blood sampling for the collection of serum and plasma. Blood samples were immediately aliquoted and stored at -80C until analysis.

Subjects underwent laparoscopic RYGB or SG performed according to typical protocols.[1]

Normal BMI control subjects

Premenopausal Hispanic women, ≥18 years of age, presenting to the Bellevue Hospital Gynecology clinic, with normal BMI (18.5 – 24.9 kg/m^2), but otherwise meeting all inclusion and exclusion criteria, were recruited as control subjects. These subjects attended a single visit at the NYU-HHC CTSI Clinical Research Center.

Blood assays

Plasma was assessed for high density lipoprotein particle size and concentration by NMR (**Table**; LabCorp Inc., Raleigh, NC). Lipid profiles, apolipoprotein A1 (ApoA1), high-sensitivity CRP (hsCRP), and hemoglobin A1c were measured on a Beckman-Coulter AU5832 chemistry analyzer. Plasma glucose was measured using a colorimetric assay (Catalog number 10009582, Cayman Chemical, Ann Arbor, MI) and cholesterol ester transfer protein (CETP) activity using a commercially available, fluorometric assay (Catalog number MAK106, Sigma-Aldrich, St. Louis, MO). Plasma insulin and adiponectin were measured using multiplex immunoassays (Millipore, Darmstadt, Germany) in the Immune Monitoring Core Lab of NYU Langone Medical Center. HOMA-IR was calculated using the formula of Matthews et al.[2]

Cholesterol efflux capacity was quantified via a high-throughput method, as described by Khera et al.[3] at Vascular Strategies LLC (Plymouth Meeting, USA). Previously unthawed serum was depleted of apolipoprotein B-containing particles with the addition of 40 parts polyethylene glycol (Catalog number P2139, Sigma-Aldrich, St. Louis, MO) in glycine buffer (pH 7.4) to 100 parts serum. This mixture was incubated for 20 minutes at room temperature, centrifuged, and the supernatant removed (apolipoproteinB-depleted PEG serum). J774A.1 (ATCC TIB-67) cells were incubated with 2uCi/mL H^3-cholesterol and an ACAT inhibitor (Sandoz 58-035, Holzkirchen, Germany) overnight, but not loaded with cholesterol. J774A.1 cells were incubated with 0.3 mmol/L cAMP (Catalog number C3912, Sigma-Aldrich, St. Louis, MO) for 6

hours in order to upregulate ABCA1 expression and were then exposed to 2.8% PEG serum (equivalent to 2% serum) in media for 4 hours. At the completion of 4 hours, the 2.8% PEG serum in media was removed, macrophages lysed, and scintillation counting was used to quantify the amount of H^3-cholesterol in each compartment. The percent cholesterol efflux capacity was calculated using the formula: (microcuries H^3 in media containing PEG serum – microcuries H^3 in serum-free media/(total microcuries H^3 in media and cell lysate)x100. This value represents global CEC. The same protocol was employed using J774A.1 cells which had not been exposed to cAMP. This value represents nonABCA1-specific CEC. The difference between global and nonABCA1-mediated CEC is termed cAMP-inducible CEC. Assays were performed in triplicate. Pooled samples from healthy individuals were assayed in parallel with subject serum and data were normalized based on pooled sample results. Intra-assay and interassay coefficients of variation were 6% and 10% for global efflux, and 4% and 9% for non-ABCA1-specific efflux, respectively.

Statistical Analyses

Continuous data were assessed both visually and statistically (Kolmogorov-Smirnov) for normality. Non-normally distributed data were log-transformed for analyses. Baseline characteristics of surgical groups were compared using independent samples t-tests or Wilcoxon rank sum tests for continuous variables and chi-square analyses for categorical variables. Within group, post-operative changes over time were assessed via paired-samples t-tests.

The percent change in CEC (global, cAMP-inducible and nonABCA1-specific) was compared between surgical groups using independent samples t-tests. Pearson correlation testing was used to assess pairwise associations between CEC and clinical and blood variables,

as well as changes in CEC with changes in clinical characteristics and blood parameters. These measures were further used as independent variables in univariate linear regression analyses to predict post-operative changes in CEC. Variables associated with the outcome in univariate modeling ($p < 0.2$) were included in forward stepwise, multivariable linear regression analyses. Differences in correlations between procedures were assessed using Fisher's Z transformation.

Our *a priori* primary outcome measure was change in global CEC from baseline at six months after surgery, and enrollment was based upon the estimate that complete data on at least 26 subjects per surgical arm would be needed to detect a difference with 80% power using a two-sided $\alpha=0.05$. Statistical analyses were performed using SPSS (Version 23, Armonk, NY).

Sensitivity Analyses

We performed several sensitivity analyses, comparing the response in each of the above variables by procedure after, 1) excluding subjects in the top and bottom deciles of pre-operative global CEC, 2) excluding subjects in the top and bottom deciles of post-operative change in global CEC for each procedure, 3) matching 1:1 by pre-operative global CEC (± 0.15%), and 4) matching 1:1 by six month percent change in body weight (± 0.5%).

Table[4,5]

HDL particle	Size (nm)	Subfraction equivalent (mean diameter)
Small	7.3 – 8.2	HDL3c (7.6nm), HDL3b (8.0nm)
Medium	8.3 – 9.4	HDL3a (8.4nm), HDL2a (9.2nm)
Large	≥ 9.5	HDL2b

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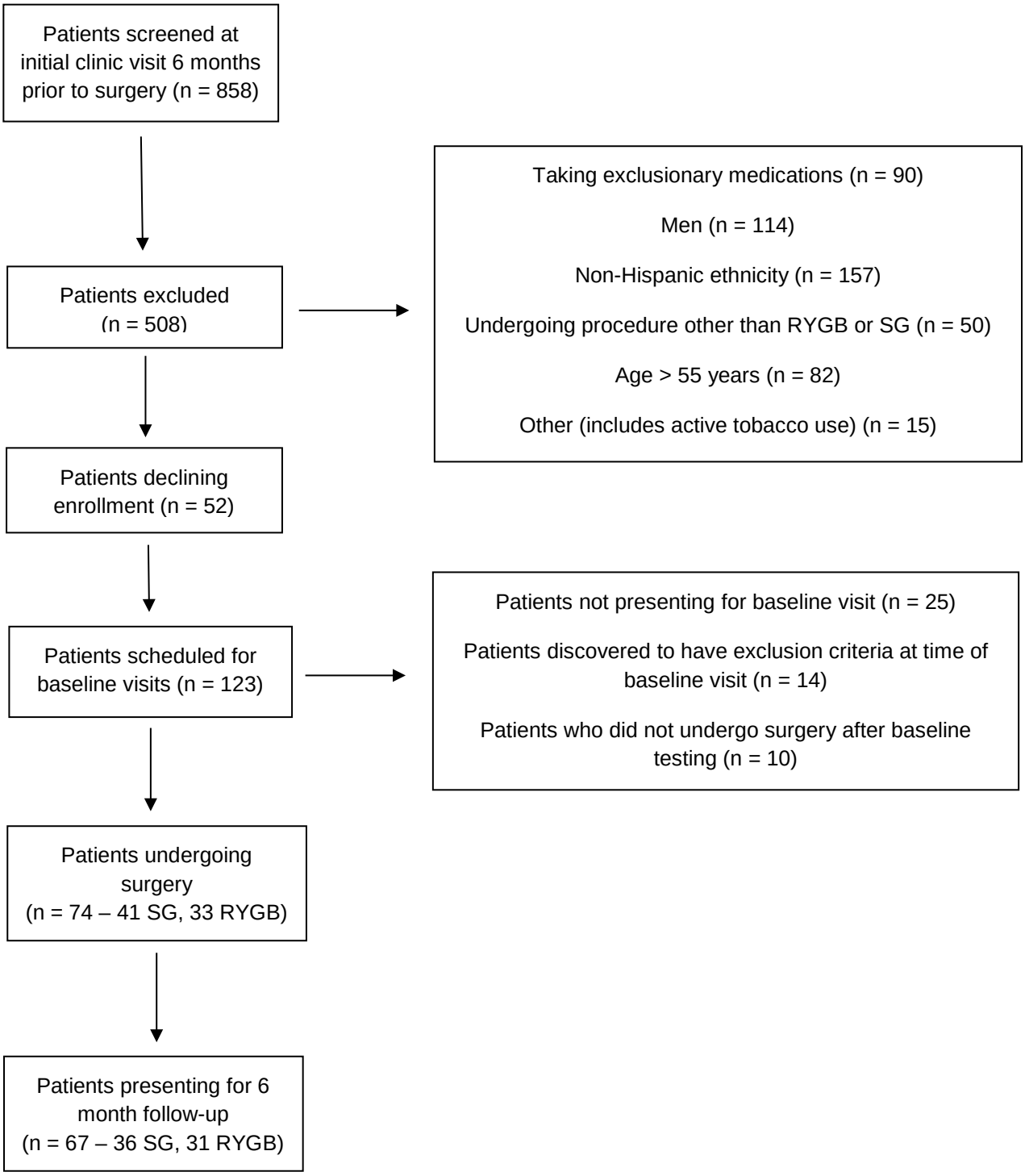
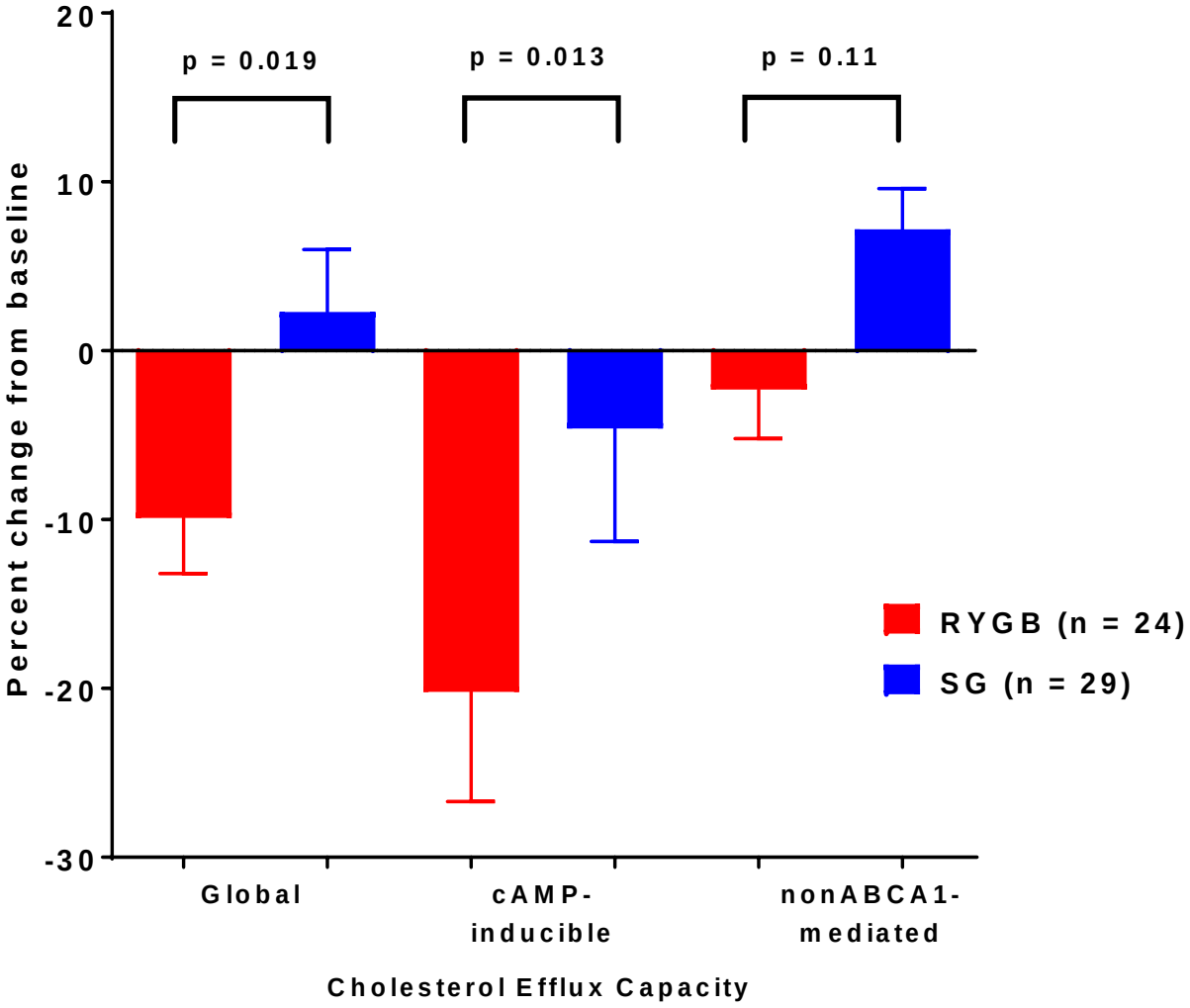
Supplemental Material

This appendix has been provided by the authors to give readers additional information about their work.

Contents



Supplemental Figure I. Study flow

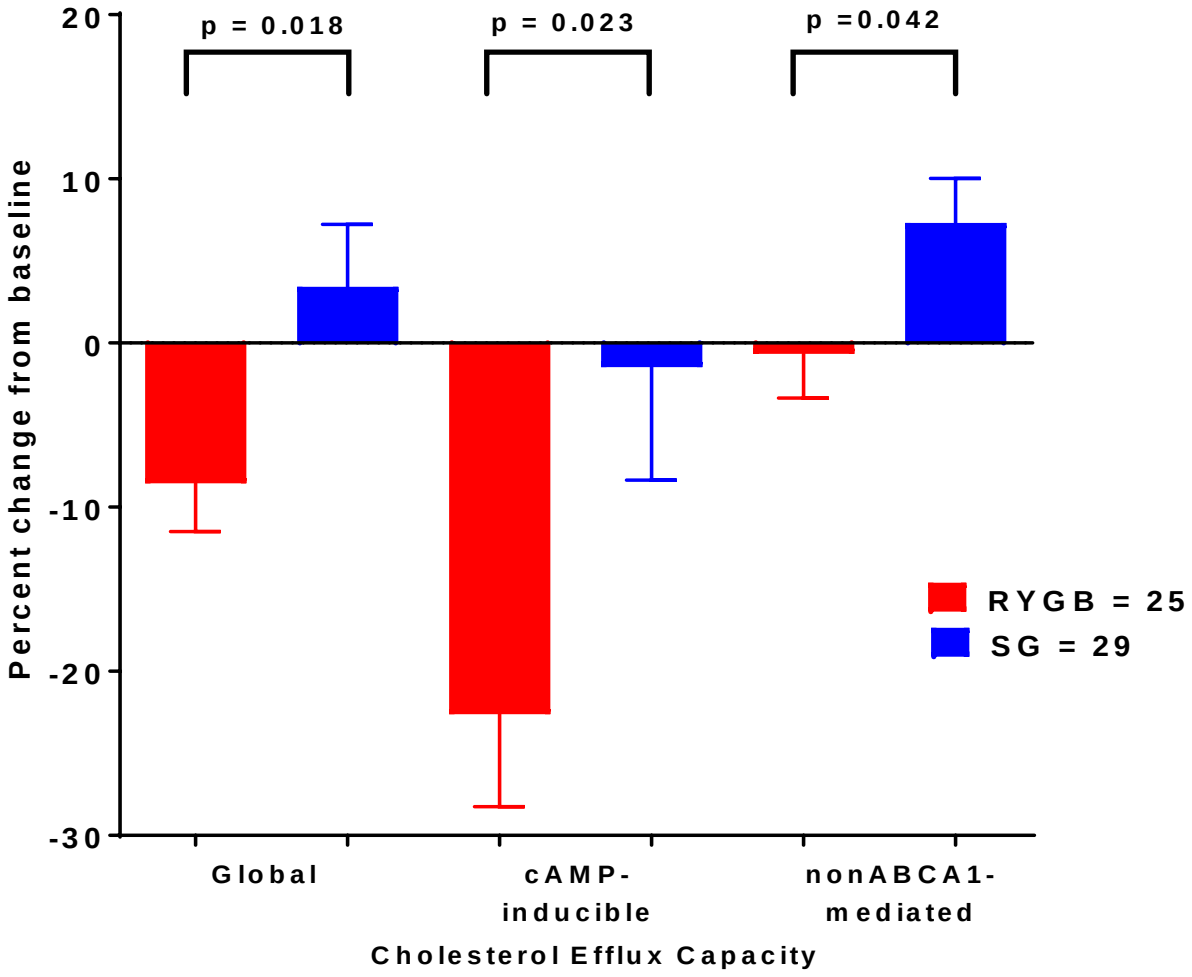


Supplemental Figure II. Percent change in cholesterol efflux capacity from before bariatric surgery at six months, excluding those subjects in the top and bottom deciles of pre-operative global cholesterol efflux capacity. Error bars indicate standard error of the mean.

ABCA1 = adenosine triphosphate-binding cassette transporter A1

RYGB = Roux-en-Y gastric bypass

SG = Sleeve gastrectomy

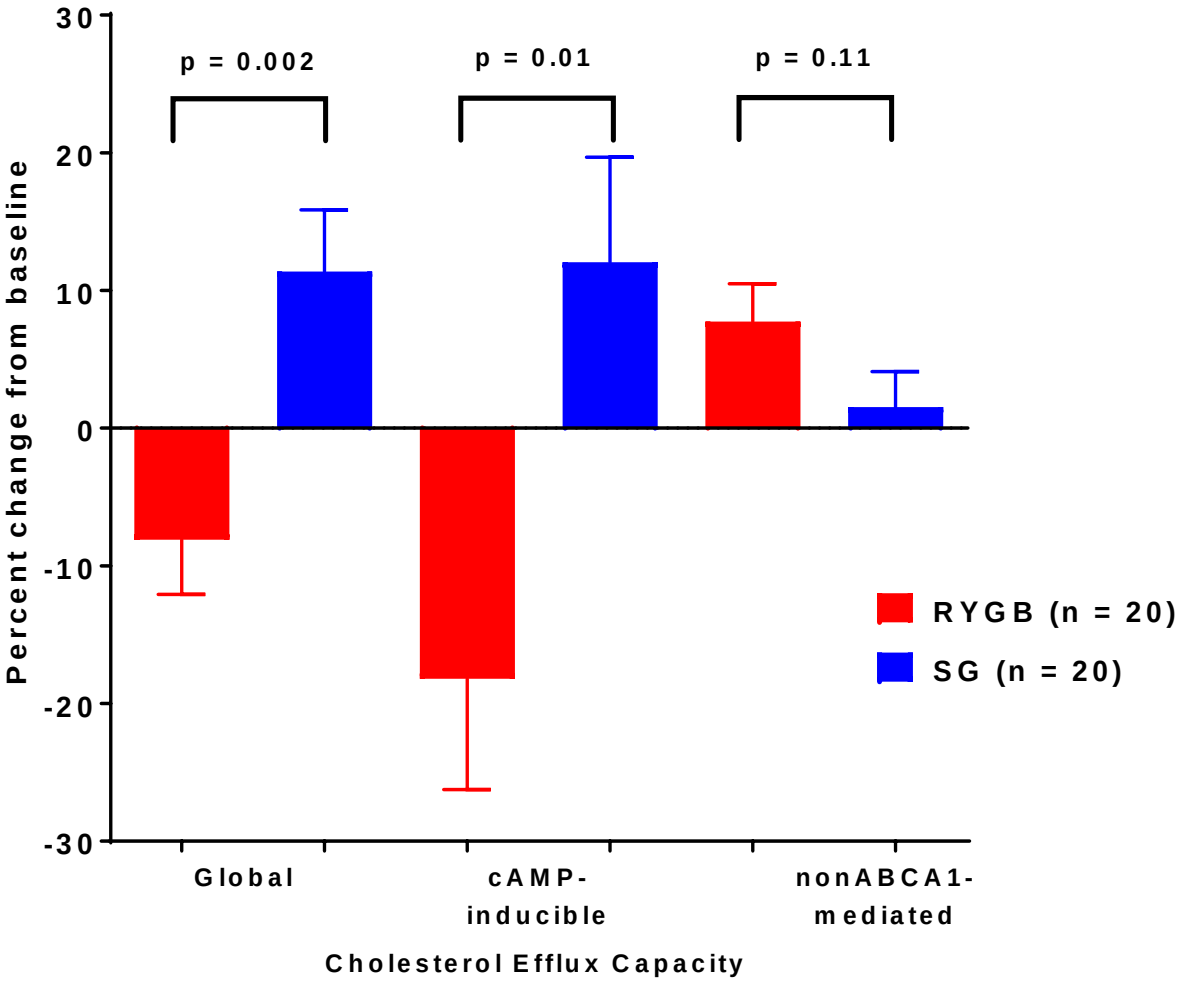


Supplemental Figure III. Percent change in cholesterol efflux capacity from before bariatric surgery at six months excluding those subjects in the top and bottom deciles of post-operative change in global cholesterol efflux capacity. Error bars indicate standard error of the mean.

ABCA1 = adenosine triphosphate-binding cassette transporter A1

RYGB = Roux-en-Y gastric bypass

SG = Sleeve gastrectomy

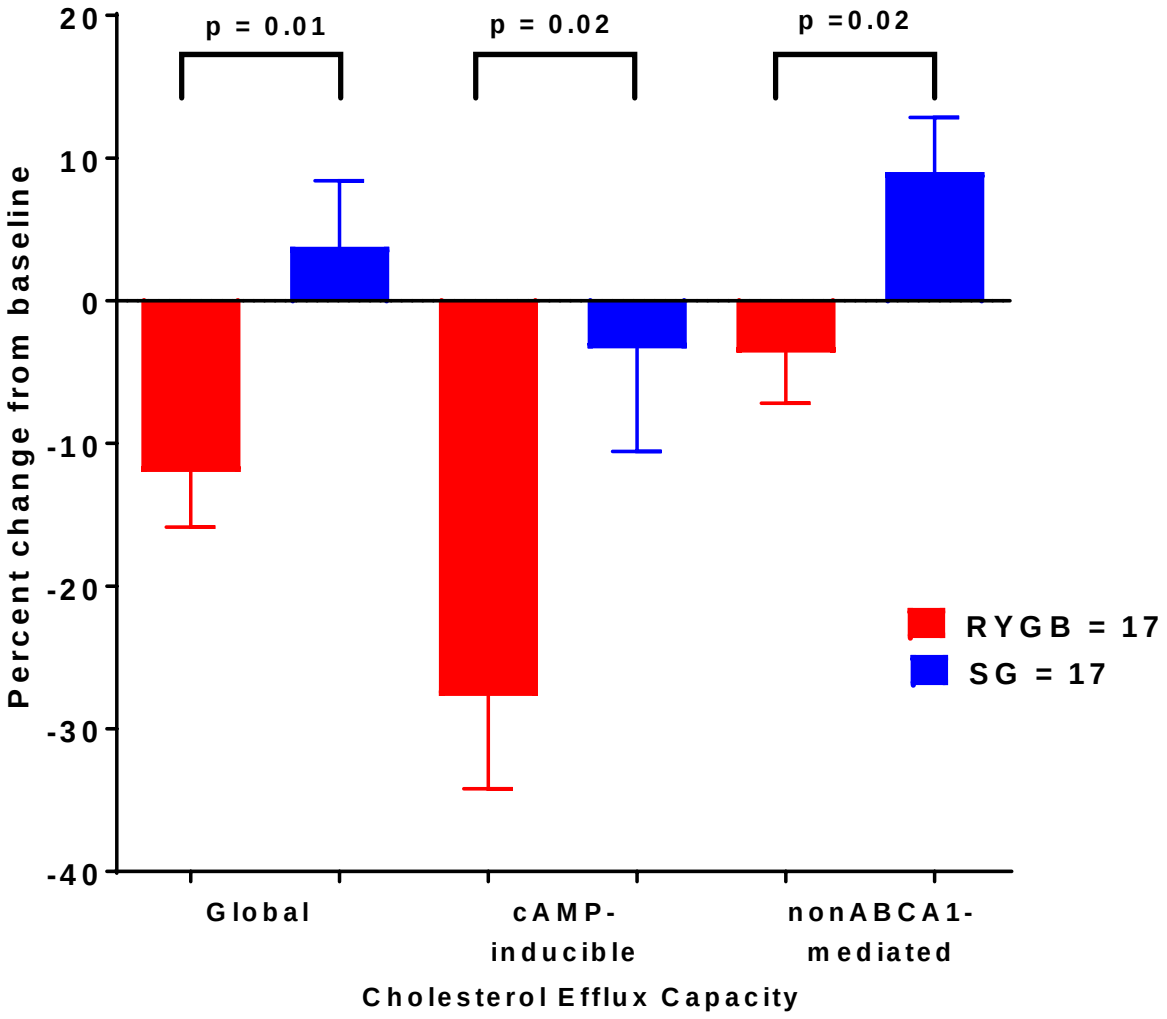


Supplemental Figure IV. Percent change in cholesterol efflux capacity from before bariatric surgery at six months in subjects undergoing RYGB and SG matched 1:1 by pre-operative global cholesterol efflux capacity. Error bars indicate standard error of the mean.

ABCA1 = adenosine triphosphate-binding cassette transporter A1

RYGB = Roux-en-Y gastric bypass

SG = Sleeve gastrectomy

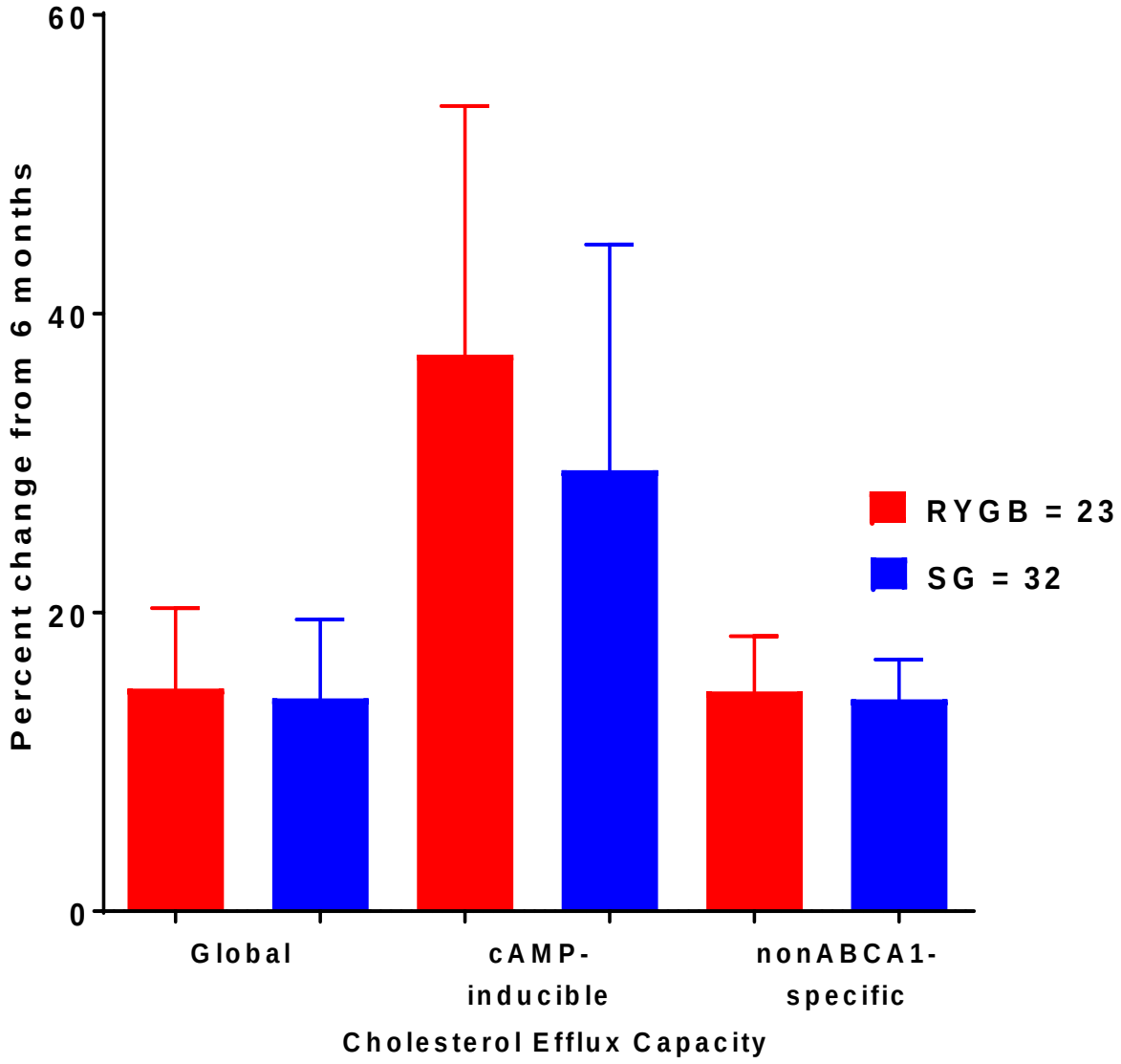


Supplemental Figure V. Percent change in cholesterol efflux capacity from before bariatric surgery at six months in subjects undergoing RYGB and SG matched 1:1 by percent body weight loss. Error bars indicate standard error of the mean.

ABCA1 = adenosine triphosphate-binding cassette transporter A1

RYGB = Roux-en-Y gastric bypass

SG = Sleeve gastrectomy



Supplemental Figure VI. Percent change in cholesterol efflux capacity from six to 12 months in subjects undergoing RYGB or SG. Error bars indicate standard error of the mean.

ABCA1 = adenosine triphosphate-binding cassette transporter A1

RYGB = Roux-en-Y gastric bypass

SG = Sleeve gastrectomy

Supplemental Table I. Characteristics of normal BMI control subjects (n = 8) [mean (SD), median [interquartile range]]

Age (years)	31.6 (2.4)
BMI (kg/m^2)	23.6 (2.0)‡
Weight (kg)	58.5 (2.9)‡
Waist circumference (cm)	79.2 (6.3)‡
Systolic blood pressure (mm Hg)	101 (7)‡
Diastolic blood pressure (mm Hg)	57 (5)‡
Total Cholesterol (mg/dL)	174 (32)
LDL-Cholesterol (mg/dL)	105 (34)
HDL-Cholesterol (mg/dL)	56.1 (11.0)*
ApoA1 (mg/dL)	146 (18.8)
HDL particles (umol/L)	31.7 (3.9)
Large HDL particles (umol/L)	7.6 (3.1)*
Small HDL particles (umol/L)	13.7 (5.0)
Triglycerides (mg/dL)	70 [62, 84]
HbA1c (%)	4.8 (0.2)†
CETP activity (pmol/uL/h)	18.2 (7.7)
Adiponectin (ug/mL)	34.1 (31.8)†
hsCRP (mg/L)	1.3 [0.7, 1.5]†

* $p < 0.05$, † $p < 0.01$, ‡ $p < 0.001$, obese vs normal-BMI participants
ABCA1 - adenosine triphosphate binding cassette transporter A1;
BMI - body mass index;
CETP - cholesterol ester transfer protein, HDL - high density lipoprotein;
hsCRP - high sensitivity C-reactive protein;
HOMA-IR - homeostatic model assessment - insulin resistance;
LDL - low density lipoprotein; SD – standard deviation

Supplemental Table II. Percent change in clinical and hematologic variables from baseline at 6 months following surgery (mean value (SD))

	All subjects (n = 67)	**RYGB (n = 31)**	**SG (n = 36)**
BMI (kg/m^2)	-27.7% (4.9)	-29.3% (4.1)*	-26.2% (5.2)
Weight (kg)	-27.7% (4.9)	-29.3% (4.1)*	-26.4% (5.2)
Waist circumference (cm)	-20.3 (6.2)	-20.6% (6.0)	-20.0% (6.5)
Systolic blood pressure (mm Hg)	-6.8% (8.5)	-6.2% (9.3)	-7.3% (7.9)
Diastolic blood pressure (mm Hg)	-6.2% (12.7)	-6.5% (14.0)	-6.0% (11.7)
Total Cholesterol (mg/dL)	-6.2% (16.1)	-14.2% (13.2)	0.5% (15.3)
LDL-Cholesterol (mg/dL)	-12.0 (18.0)	-23.2% (12.3)*	-2.9% (16.6)
HDL-Cholesterol (mg/dL)	7.3% (23.0)	-1.3% (15.8)*	14.2% (25.2)
ApoA1 (mg/dL)	2.5% (13.6)	-3.4% (10.6)*	7.2% (13.8)
HDL particles (umol/L)	-6.7% (12.6)	-10.4% (11.0)	-4.0% (13.1)
Large HDL particles (umol/L)	60.6% (73.9)	47.6% (60.3)	71.4% (81.4)
Small HDL particles (umol/L)	8.0% (52.8%)	12.6% (70.6)	3.6% (31.7)
CETP activity (pmol/uL/h)	-3.8% (33.1)	-17.4% (34.7)	6.8% (27.9)
Triglycerides (mg/dL)	-21.5% (25.0)	-23.0% (23.6)	-20.6% (26.2)
hsCRP (mg/L)	-72.5% (21.3)	-77.6% (18.0)	-68.2% (23.1)
HOMA-IR	-54.1% (32.0)	-47.8% (42.1)	-58.4% (22.8)
Hemoglobin A1c (%)	-8.9% (8.7)	-11.6% (9.7)	-6.7% (7.3)
Adiponectin (ug/mL)	151.1% (274)	129% (127)	167% (346)

* $p < 0.01$, RYGB vs SG

Abbreviations as in Supplemental Table I

Supplemental Table III. Pearson's correlation coefficients (r) for cholesterol efflux capacity with anthropometric measures and metabolic variables in normal-BMI subjects.

	Global	cAMP-inducible	nonABCA1
Age (years)	0.25	-0.17	0.05
BMI (kg/m^2)	-0.30	-0.26	-0.38
Body weight (kg)	0.38	0.06	0.23
Waist-to-hip ratio	0.06	0.31	-0.19
LDL-Cholesterol (mg/dL)	-0.27	0.15	-0.37
HDL-Cholesterol (mg/dL)	0.93†	0.77*	0.97†
ApoA1 (mg/dL)	0.89†	0.74*	0.95†
HDL particles (µmol/L)	0.64	0.41	0.79†
Large HDL particles (µmol/L)	0.93†	0.56	0.91†
Small HDL particles (µmol/L)	-0.60	-0.18	-0.33
CETP activity	0.44	0.19	0.18
Log Triglycerides (mg/dL)	-0.08	-0.03	-0.11
HOMA-IR	-0.11	-0.08	-0.13
Adiponectin	0.36	0.52	0.19
Log hsCRP (mg/L)	-0.48	-0.25	-0.65

* $p < 0.05$, † $p < 0.01$

Abbreviations as in Supplemental Table I

Supplemental Table IV. Multivariable linear regression model of baseline variables predicting change in global cholesterol efflux capacity at six months following surgery

	Univariate analysis		**Multivariable analysis**	
	B (SE)	**P-value**	**B (SE)**	**P-value**
Surgery type	9.10 (4.52)	0.05	8.87 (4.59)	0.05
Age	0.05 (0.04)	0.16		
Body weight	-0.20 (0.13)	0.15		
BMI	-0.36 (0.35)	0.31		
Waist circumference	-0.17 (0.19)	0.36		
Hip circumference	-0.25 (0.19)	0.18		
LDL-C	0.03 (0.08)	0.75		
HDL-C	-0.19 (0.23)	0.41		
ApoA1	-0.10 (0.10)	0.33		
HDL particles	-0.22 (0.44)	0.61		
Large HDL particles	-0.68 (0.83)	0.42		
Small HDL particles	-0.03 (0.49)	0.59		
CETP activity	-0.08 (0.09)	0.38		
Log Triglycerides	-1.69 (13.02)	0.90		
HOMA-IR	0.01 (0.09)	0.92		
Log Adiponectin	-3.12 (8.9)	0.73		
Log hsCRP	0.25 (6.28)	0.98		

Abbreviations as in Supplemental Table I

Supplemental Table V. Multivariable linear regression models of baseline variables predicting change in cAMP-inducible cholesterol efflux capacity at six months after surgery

	Univariate analysis		**Multivariable analysis**	
	B (SE)	**P-value**	**B (SE)**	**P-value**
Surgery type	12.40 (8.39)	0.15		
Age	0.04 (0.03)	0.13		
Body weight	-0.43 (0.24)	0.08		
BMI	-0.87 (0.64)	0.18		
Waist circumference	-0.27 (0.34)	0.44		
Hip circumference	-0.53 (0.34)	0.12		
LDL-C	0.07 (0.15)	0.63		
HDL-C	-0.09 (0.42)	0.83		
ApoA1	-0.09 (0.18)	0.64		
HDL particles	-0.16 (0.80)	0.84		
Large HDL particles	0.04 (1.5)	0.98		
Small HDL particles	-0.88 (0.88)	0.33		
CETP activity	-0.19 (0.17)	0.27		
Log Triglycerides	-2.54 (23.84)	0.92		
HOMA-IR	0.01 (0.06)	0.88		
Log Adiponectin	-1.81 (16.37)	0.92		
Log hsCRP	-0.13 (11.50)	0.99		

Abbreviations as in Supplemental Table I

Supplemental Table VI. Multivariable linear regression models of baseline variables predicting change in nonABCA1-mediated cholesterol efflux capacity at six months after surgery

	Univariate analysis		**Multivariable analysis**	
	B (SE)	**P-value**	**B (SE)**	**P-value**
Surgery type	8.24 (3.40)	0.02	8.08 (3.5)	0.02
Age	0.02 (0.02)	0.28		
Body weight	0.00 (0.10)	0.99		
BMI	0.10 (0.27)	0.73		
Waist circumference	-0.01 (0.15)	0.94		
Hip circumference	-0.02 (0.14)	0.92		
LDL-C	-0.02 (0.06)	0.72		
HDL-C	-0.22 (0.17)	0.21		
ApoA1	-0.03 (0.08)	0.22		
HDL particles	-0.25 (0.33)	0.44		
Large HDL particles	-1.02 (0.62)	0.11		
Small HDL particles	0.06 (0.37)	0.88		
CETP activity	<0.01 (0.07)	1.00		
Log Triglycerides	2.23 (10.02)	0.83		
HOMA-IR	-0.01 (0.04)	0.77		
Adiponectin	-7.63 (6.79)	0.27		
hsCRP	1.14 (4.83)	0.81		

Abbreviations as in Supplemental Table I