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Cholesterol absorption decreases after Roux-en-Y gastric bypass but not after gastric banding

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Abstract

The differences in cholesterol metabolism after the 2 most common forms of obesity surgery, Roux-en-Y gastric bypass (RYGB) and gastric banding (GB), have not been well characterized. In this study, effects of RYGB and GB on cholesterol absorption and synthesis were investigated. To this aim, 1-year follow-up of cholesterol metabolism in 2 nonrandomized cohorts undergoing either RYGB (n = 29; age, 45.2 ± 7.7 years; body mass index [BMI], 46.0 ± 6.1 kg/m^2) or GB (n = 26; age, 45.9 ± 8.6 years; BMI, 50.1 ± 7.7 kg/m^2) was performed in a university hospital center specializing in the treatment of morbid obesity. Serum markers of cholesterol synthesis (cholestenol, desmosterol, and lathosterol) and cholesterol absorption (campesterol, sitosterol, avenasterol, and cholestanol) were measured preoperatively and at follow-up and expressed as ratios to cholesterol. As expected based on observed weight loss (25% after RYGB and 17% after GB, $P < .001$ between groups), both operations decreased serum levels of cholesterol synthesis markers by 12% to 28% (all Ps $< .001$). A decrease in cholesterol absorption markers was only observed after RYGB (−26% for sitosterol) and not after GB (+16%, $P = 2 \times 10^{-6}$ for difference between the groups). The difference in sitosterol ratio between the groups remained significant after adjustment for age, BMI, fasting insulin levels, and nutritional status ($P = 2 \times 10^{-4}$), indicating a specific effect related to RYGB. We conclude that decrease in cholesterol absorption is a novel beneficial effect of RYGB. Together with an improved control of blood glucose, this may contribute to a better cardiovascular risk profile after RYGB.

1. Introduction

Cholesterol synthesis is increased and cholesterol absorption decreased in obese individuals. This balance can be reversed by weight loss [1,2]. It is difficult to estimate which of the pathways, cholesterol synthesis or absorption, is primarily affected in obesity and weight loss because, in both models, a change in one pathway will result in a compensatory change in the other to retain body cholesterol balance.

Obesity surgery has rapidly gained more interest because of its capability to induce sustained weight loss. Of the currently available options, the most widely used is Roux-en-Y gastric bypass (RYGB) that induces more weight loss than less invasive purely restrictive gastric banding (GB) [3,4]. Roux-en-Y gastric bypass seems also to have other metabolic benefits: glucose levels drop more rapidly and efficiently because of insulin secretion stimulated by increased release of gut peptides [5-7]. Nutrient absorption can also be changed by RYGB as demonstrated by the fact that nutritional deficiencies are more common after RYGB compared with GB [8].

Current consensus is that dyslipidemia resolution can be reached in approximately 60% of patients after RYGB and

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40% of patients after GB [9]. Several studies have suggested a decrease of 15% to 20% in serum total and low-density lipoprotein (LDL) cholesterol after RYGB [10-12]. In contrast, after GB, serum cholesterol levels have remained unchanged or less improved compared with other types of surgery [10,13,14]. Thus, it seems that RYGB may be more effective in the treatment of hypercholesterolemia than GB. Similarly, RYGB leads to a 40% to 60% decrease in serum triglycerides and to a 20% to 40% increase in high-density lipoprotein (HDL) cholesterol [10-12], whereas the effects of GB on triglycerides and HDL cholesterol are smaller [10,13].

We hypothesized that the more drastic decrease in serum total and LDL cholesterol after RYGB compared with GB could be related to changes in cholesterol absorption induced by intestinal bypass performed in RYGB. To this aim, we measured serum levels of cholesterol precursors cholestenol, desmosterol, and lathosterol (markers of whole-body cholesterol synthesis) and serum plant sterols campesterol, sitosterol, avenasterol, and cholestanol (markers of cholesterol absorption) preoperatively and at 1-year follow-up in 29 patients who underwent RYGB and in 26 patients who underwent GB.

2. Methods

2.1. Subjects and design

All subjects undergoing bariatric surgery at the Department of Surgery Kuopio University Hospital are recruited into our ongoing study investigating metabolic consequences of obesity surgery. In this study, we included first 29 subjects (group 1; male-female, 4:25; Table 1) who were operated by laparoscopic RYGB with alimentary limb of 100 cm in Kuopio University Hospital over the years 2005-2007. Criteria for surgery were (1) body mass index (BMI) greater than 40 kg/m^2, or greater than 35 kg/m^2 with significant comorbidity (type 2 diabetes mellitus in this study); (2) failure of dietary and drug treatments; and (3) no other contraindication for operation. Every participant had 1-day inpatient visit to the hospital for screening eligibility to bariatric surgery. Fasting blood samples were drawn after 12 hours of fasting, followed by an oral glucose tolerance test if type 2 diabetes mellitus had not been diagnosed earlier.

Group 2 included 26 subjects (male-female, 11:15) who had been operated with GB in Kuopio University Hospital over the years 1996-1997 with the same inclusion and exclusion criteria as with group 1 (Table 1), as described previously [15]. This group served as a control group for the effects observed after RYGB.

The study was approved by the Ethics Committee of the University of Kuopio and Kuopio University Hospital, and it was in accordance with the Helsinki Declaration.

2.2. Clinical measurements

Height and weight were measured to the nearest 0.5 cm and 0.1 kg, respectively. Body mass index was calculated as weight (in kilograms) divided by height (in meters) squared. Body composition was determined by bioelectrical impedance (RJL Systems, Clinton Township, MI) in subjects in the supine position after a 12-hour fast. Indirect calorimetry was performed with a computerized flow-through canopy gas analyzer system (Deltatrac; Datex, Helsinki, Finland) [16]. A 2-hour oral glucose tolerance test (75 g of glucose) was performed after overnight fasting; and samples for plasma glucose and insulin were drawn at 0, 30, and 120 minutes.

2.3. Laboratory determinations

Plasma glucose was measured by enzymatic hexokinase photometric assay (Konelab Systems Reagents; Thermo Fischer Scientific, Vantaa, Finland). Insulin was determined by immunoassay (ADVIA Centaur Insulin IRI, no. 02230141; Siemens Medical Solutions Diagnostics, Tarrytown, NY). Cholesterol and triglyceride levels from the

Table 1
Characteristics of study subjects

	RYGB			GB		
	Baseline	1 y	Change 1 y (%)	Baseline	1 y	Change 1 y (%)
Sex (male-female)	4:25			11:15*		
Age (y)	45.2 ± 7.7			45.9 ± 8.6		
Weight (kg)	130 ± 20	98 ± 20	**−25%**	145.0 ± 26*	123 ± 20‡	**−17%**†
BMI (kg/m^2)	46.0 ± 6.1	34.6 ± 6.3	**−25%**	50.1 ± 7.7*	42.6 ± 6.3‡	**−17%**†
Diabetes	8/29	2/29		19/26	1/26	
Fasting glucose (mmol/L)	6.7 ± 2.1	5.4 ± 0.7	**−15%**	5.9 ± 1.4	5.2 ± 0.9	**−10%**
Fasting insulin (mU/L)	20.6 ± 13.6	8.3 ± 8.3	**−59%**	36.4 ± 18.6†	21.9 ± 12.3‡	**−29%**†
Total cholesterol (mmol/L)	5.07 ± 0.80	4.55 ± 0.87	**−9%**	5.46 ± 0.91	5.20 ± 0.85†	−3%*
LDL cholesterol (mmol/L)	3.18 ± 0.84	2.66 ± 0.79	**−17%**	3.53 ± 0.78	3.29 ± 0.70†	+5%*
HDL cholesterol (mmol/L)	1.08 ± 0.25	1.36 ± 0.23	**+30%**	1.04 ± 0.19	1.08 ± 0.28‡	+4%‡
Total triglycerides (mmol/L)	1.68 ± 0.69	1.06 ± 0.30	**−31%**	1.96 ± 0.64	1.69 ± 0.78‡	−7%†

Bolded changes in response to RYGB or GB were statistically significant ($P < .01$ for all, paired t test).

* $P < .05$ vs RYGB.

† $P < .01$ vs RYGB.

‡ $P < .001$ vs RYGB (t test).

whole serum and from lipoprotein fractions were assayed by automated enzymatic methods (Roche Diagnostics, Mannheim, Germany).

2.4. Liver biopsies

Liver biopsies (n = 29, only in RYGB group) were performed using Trucut needle (Radiplast, Uppsala, Sweden) in the fasting state during elective gastric bypass. Histologic assessment of liver steatosis was performed according to Brunt et al [17].

2.5. Markers of cholesterol synthesis and absorption

Serum cholesterol precursors cholestenol, desmosterol, lathosterol ,and squalene, which reliably reflect whole-body cholesterol synthesis [18,19], and plant sterols campesterol, sitosterol, avenasterol, and cholestanol (a metabolite of cholesterol), sterols reliably reflecting cholesterol absorption efficiency [18,19], were quantitated with gas-liquid chromatography on a 50-m–long capillary column (Ultra 1; Agilent Technologies, Wilmington, DE) using 5α-cholestane as internal standard [20]. The squalene and noncholesterol sterol values were expressed in terms of 10^2 × millimoles per mole of cholesterol (called *ratio* in the text), dividing the squalene and sterol values by the cholesterol value of the same run to eliminate the effects of different cholesterol concentrations.

2.6. Statistical analysis

Data are presented as mean ± SD. Variables with nonnormal skewed distribution were logarithmically transformed before analysis. Categorical variables were examined by the χ^2 test. Pairwise *t* test was used when examining within-individual changes before and after obesity surgery. Differences between the study groups (RYGB vs GB) were examined using *t* test. Spearman rank correlation was used for correlation analysis. The analysis of variance for repeated measurements (general linear model) was used to analyze group by time interaction and changes over time in between-group comparisons. Analyses were conducted with the SPSS version 14 programs (SPSS, Chicago, IL). *P* value < .05 was considered statistically significant.

3. Results

Earlier RYGB has been shown to induce more weight loss and improve insulin action and serum glucose levels more than GB [9]. Accordingly, in this study, we observed more weight loss in subjects who underwent RYGB (25%, $P = 2 \times 10^{-17}$ for the weight loss, paired-samples *t* test) compared with subjects with GB (−17%, $P = 2 \times 10^{-6}$, $P = 3 \times 10^{-4}$, *t* test for the difference in percentage change between the groups), despite higher weight of GB patients at baseline (130 vs 145 kg, $P = .034$). Furthermore, fasting insulin levels dropped more after RYGB (−59%, $P = 9 \times 10^{-8}$) than GB (−29%, 9×10^{-3}, $P = 2 \times 10^{-3}$ for the difference), indicating more effect on insulin sensitivity by RYGB compared with GB. Fasting glucose decreased 15% after RYGB ($P = 2 \times 10^{-4}$) and 10% after GB ($P = 4 \times 10^{-2}$, $P = 2 \times 10^{-1}$ for the difference).

3.1. Cholesterol levels decrease more after RYGB than GB

Serum cholesterol, LDL cholesterol, and triglycerides levels decreased after RYGB by 9% ($P = 2 \times 10^{-3}$), 17% ($P = 3 \times 10^{-4}$), and 31 % ($P = 2 \times 10^{-7}$), respectively (Table 1). High-density lipoprotein cholesterol increased by 30% ($P = 6 \times 10^{-6}$). After GB, no significant changes in serum lipids were observed (Table 1). The decrease in serum triglycerides and increase in HDL cholesterol were expected based on improved insulin sensitivity in RYGB group and consistent with earlier publications [10-12]. However, clear reductions in total and LDL cholesterol after RYGB compared with GB, as also indicated before [10], implied a mechanism specifically related to RYGB.

3.2. Cholesterol absorption decreases after RYGB but not after GB

The possibilities to explain decreased cholesterol levels after RYGB included either decreased cholesterol synthesis or absorption. Similarly to dietary weight loss [1,2], ratios of serum cholesterol precursors cholestenol, desmosterol, and lathosterol to serum cholesterol decreased after RYGB by 12% to 28% (all Ps < 3×10^{-4}, Table 2). Because ratios of cholesterol precursors correlated positively with liver fat more than with BMI (Table 3), this decrease could be related to a known rapid decrease in liver fat after RYGB [21,22]. However, similar decrease by 16% to 27% (all Ps < 2×10^{-3}) was observed in these markers of cholesterol synthesis after GB (Table 1), indicating that differences in cholesterol synthesis cannot explain differential effects of RYGB and GB on serum cholesterol levels. Same changes at baseline and follow-up were observed in both groups using absolute levels of cholesterol precursors in the analysis (Fig. 1).

More strikingly, effects of RYGB and GB on cholesterol absorption clearly diverged. Ratios of serum plant sterols (sitosterol, campesterol, and avenasterol) to cholesterol decreased after RYGB by 16% to 28% (all Ps < 1×10^{-3}), whereas after GB, ratios increased (campesterol and sitosterol) or were not changed (for avenasterol, Table 2). These findings indicated that the normal compensatory increase in cholesterol absorption after weight loss and reduced cholesterol synthesis was absent after RYGB. In fact, the ratio of lathosterol to sitosterol, reflecting the balance between cholesterol synthesis and absorption, increased by 16% after RYGB groups and decreased by 33% after GB ($P = 4 \times 10^{-6}$ for difference between the groups, Table 2). Because there were some differences in baseline levels of BMI, insulin (Table 1), and serum absorption and synthesis markers between RYGB and GB

Table 2
Markers of cholesterol synthesis and absorption as ratios to cholesterol (10^2 × microgram per milligram of cholesterol) at baseline and at 1-year follow-up after RYGB and GB

	RYGB			GB		
	Baseline	1 y	Change 1 y (%)	Baseline	1 y	Change 1 y (%)
Cholesterol synthesis						
Cholestenol	26 ± 11	23 ± 16	**−12%**	32 ± 9*	25 ± 9	**−21%**
Desmosterol	97 ± 17	80 ± 15	**−18%**	133 ± 42‡	112 ± 34‡	**−16%**
Lathosterol	195 ± 60	140 ± 53	**−28%**	241 ± 66†	178 ± 60*	**−27%**
Squalene	14 ± 6	15 ± 11	+9%	16 ± 6	14 ± 6	−3%
Cholesterol absorption						
Sitosterol	87 ± 33	64 ± 26	**−26%**	63 ± 20†	73 ± 28	**+16%**‡
Campesterol	172 ± 66	124 ± 62	**−28%**	125 ± 47†	156 ± 63	**+25%**‡
Avenasterol	33 ± 8	28 ± 12	**−16%**	32 ± 6	31 ± 9	−3%
Cholestanol	132 ± 26	136 ± 27	+3%	136 ± 36	146 ± 36	**+9%**
Lathosterol/sitosterol	0.36 ± 27	0.42 ± 30	**+16%**	0.57 ± 0.25†	0.38 ± 0.27	**−33%**‡

Bolded changes in response to RYGB or GB were statistically significant ($P < .05$ for all, paired t test).
* $P < .05$ vs RYGB.
† $P < .01$ vs RYGB.
‡ $P < .001$ vs RYGB (t test).

groups (Table 2), and in responses to RYGB and GB (Table 2), we also analyzed results after adjusting for all these factors. In this analysis, changes in serum campesterol, sitosterol, and lathosterol to sitosterol ratio remained significant between RYGB and GB groups ($P < .01$ for all). In addition, we analyzed results separately in women that formed the major part of the study population, and could demonstrate similar results (Supplementary Tables 1 and 2). We also analyzed all data excluding patients using statins (n = 2 in RYGB group; none in GB group; no other lipid-lowering drug was used). All results were essentially the same than in the whole study group. Same changes baseline and follow-up were observed in both groups using absolute levels of cholesterol precursors in the analysis (Fig. 1). These changes were also independent of baseline cholesterol levels because they were observed both in subjects with serum total cholesterol less than 5 mmol/L and at least 5 mmol/L (shown for lathosterol and sitosterol in Fig. 2).

Table 3
Spearman nonparametric correlation between serum markers of cholesterol synthesis and absorption with BMI and liver steatosis grade in the RYGB group

	BMI baseline (n = 27)	Steatosis grade baseline (n = 24)
Serum total cholesterol	0.080	0.490*
Cholesterol synthesis		
Cholestenol	−0.043	**0.432***
Desmosterol	−0.269	**0.468***
Lathosterol	−0.154	**0.430***
Cholesterol absorption		
Sitosterol	−0.054	−0.018
Campesterol	−0.101	−0.004
Avenasterol	−0.071	0.097
Cholestanol	0.111	0.180

Ratios of markers to cholesterol were used in the analysis. Subjects using lipid-lowering drug have been excluded.
* $P < .05$ for the correlation.

Because our study was not a randomized study and matching between RYGB and GB groups at baseline was not optimal, we also searched for baseline regulators of cholesterol absorption in the whole data using multivariate analysis (Table 4). This analysis demonstrated that the type of operation was the strongest predictor of changes in cholesterol absorption markers sitosterol, campesterol, and avenasterol. In fact, operation type explained 35%, 36%, and 7% of changes in serum sitosterol, campesterol, and avenasterol ratios to cholesterol, respectively.

In both groups, the change in absolute serum sitosterol levels correlated positively with the change in serum cholesterol levels ($r = 0.464$ and 0.537, $P < .05$ in both groups), suggesting that cholesterol absorption has a role in the regulation of serum cholesterol levels after obesity surgery. In addition, the difference in reductions of serum cholesterol levels in response to RYGB vs GB disappeared if adjusted for the change in serum sitosterol ($P = .673$).

3.3. Decreased cholesterol absorption after RYGB is not linked with nutrient malabsorption

One explanation for reduced levels of plant sterols after RYGB could be reduced intake of cereals, margarine, vegetables, and vegetable oils, natural sources of plant sterols [23]. We did not have detailed dietary records to analyze intake of these nutrients. However, we evaluated the relationship between absorption of other nutrients and cholesterol absorption by analyzing the correlation of cholesterol absorption markers with blood hemoglobin, serum B12 and D25 vitamin, erythrocyte folate levels, and serum levels of magnesium and phosphate at 12 months after RYGB. This analysis revealed no significant association (scatter plots shown in Supplementary Figure 1), suggesting

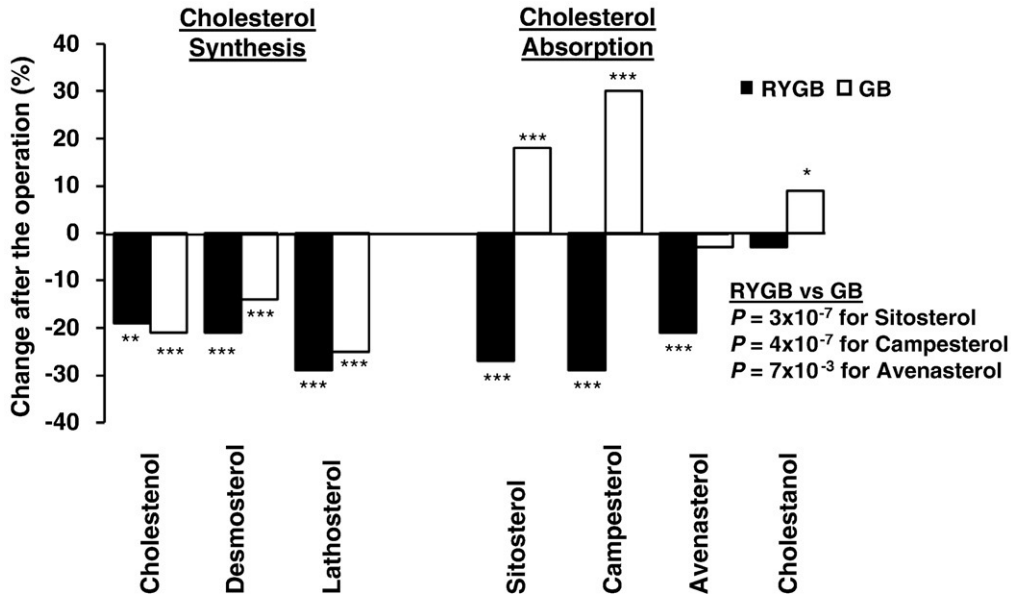

Fig. 1. Changes in serum absolute levels of cholesterol precursors and plant sterols during the first year after RYGB or GB. *$P < .05$, **$P < .01$, and ***$P < .001$ for the change between preoperative values and values at 1-year follow-up. P values for changes that were significantly different between RYGB and GB groups (sitosterol, campesterol, and avenasterol) are shown in a text box.

that the decrease in cholesterol absorption after RYGB is not associated with clinically significant nutritional deficiencies.

4. Discussion

In this study, we demonstrate using serum plant sterol levels as surrogate markers that cholesterol absorption is decreased after RYGB but not after GB (Table 2, Figs. 1 and 2). This potentially explains, at least partially, the reported more beneficial effects of RYGB on serum total and LDL cholesterol [9]. Because high levels of total and LDL cholesterol are the major risk factors for cardiovascular diseases, this effect could modify the risk of cardiovascular outcomes in morbidly obese patients.

The most important finding in our study was divergent findings in serum plant sterols after RYGB and GB: both absolute levels (Fig. 1) and ratios to cholesterol (Table 2) decreased by 16% to 28% after RYGB (all Ps $< 1 \times 10^{-3}$) and increased after GB. There are several possible explanations for this finding. First and most likely, absorption of plant sterols decreases after RYGB because of intestinal bypass. Whether this is because of reduced intestinal absorption area, impaired micelle formation, or alterations in enterohepatic circulation of bile acids and plant sterols remains to be

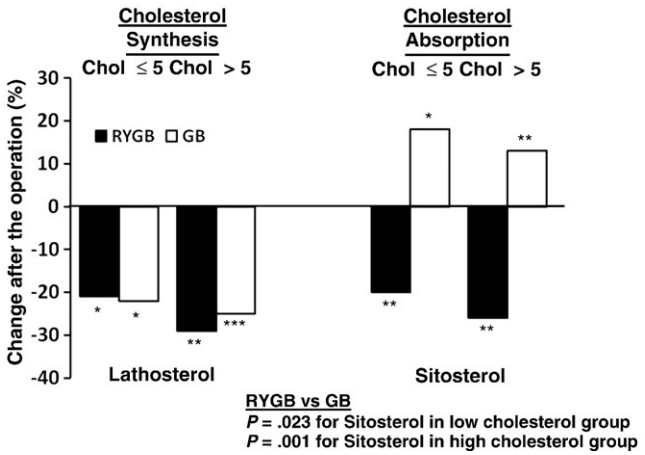

Fig. 2. Changes in serum absolute levels of lathosterol and sitosterol during the first year after RYGB or GB in subjects with low cholesterol at baseline (cholesterol <5 mmol/L) and in subjects with high cholesterol (cholesterol ≥5 mmol/L). *$P < .05$, **$P < .01$, and ***$P < .001$ for the change between preoperative values and values at 1-year follow-up. P values for changes in sitosterol that were significantly different between RYGB and GB groups are shown in a text box.

Table 4
Baseline predictors of changes in serum sitosterol, campesterol, and avenasterol (all used as ratios to total cholesterol)

Baseline data	Sitosterol change		Campesterol change		Avenasterol change	
	F	P	F	P	F	P
Sex (men/women)	0.471	NS	0.323	NS	0.847	NS
Age	2.203	NS	2.893	NS	5.675	.023
Weight	0.255	NS	0.404	NS	1.126	NS
BMI	0.030	NS	0.004	NS	0.077	NS
Fasting glucose	1.131	NS	1.267	NS	3.148	NS
Fasting insulin	0.529	NS	0.659	NS	3.098	NS
Total cholesterol	0.795	NS	0.043	NS	1.180	NS
HDL cholesterol	4.069	NS	1.598	NS	1.518	NS
Total triglycerides	0.061	NS	0.490	NS	3.325	NS
Study group (RYGB/GB)	16.178	.0007	13.676	.0004	6.291	.017

Multivariate general linear model. NS indicates $P > .05$.

answered. Reduced levels of plant sterols after RYGB could also be due to reduced intake of cereals, margarine, vegetables, and vegetable oils, natural sources of plant sterols [23]. We think this possibility is unlikely for 3 reasons. First, serum cholestanol, the cholesterol absorption marker practically unrelated to dietary intake [24], was only increased after GB and not after RYGB, indicating a difference also in cholestanol metabolism after RYGB (Fig. 1). Second, in earlier randomized trials, vegetable use was not avoided by patients who underwent RYGB compared with subjects operated with purely restrictive vertical banded gastroplasty [25]. Third, ratios of serum plant sterols and cholesterol precursors did alter significantly between RYGB and GB groups (lathosterol to sitosterol ratio, Table 1). Of course, we did not measure directly cholesterol absorption; and the possibility remains that levels of serum plant sterols would not reflect cholesterol absorption after bariatric surgery. It is currently unknown why the levels of sitosterol and campesterol seemed to be more differentially affected by operation type than the levels of avenasterol (Fig. 1, Table 4). Thus, more detailed studies, including studies with labeled isotopes and/or measurement of fecal plant sterol concentration after oral load, should be done to confirm differences in cholesterol absorption after different types of obesity surgery.

In line with observations from studies investigating effects of dietary caloric restriction on cholesterol metabolism [2], we observed an approximately 12% to 27% decrease in serum levels of cholesterol precursors, reflecting decreased cholesterol synthesis after RYGB and GB. This could be related to postsurgery decrease in liver fat content (Table 3), known to associate with liver cholesterol metabolism [26]. Together with impaired cholesterol absorption, decreased cholesterol synthesis is likely to lead to decreased whole-body cholesterol pool. This may be beneficial for cardiovascular risk as well as for the risk of obesity-related nonalcoholic steatohepatitis that has been linked with increased cholesterol synthesis [26,27]. Whether this observation has relevance for the treatment of hypercholesterolemia after bariatric surgery remains open.

We also considered the possibility that potential benefits due to reduced cholesterol absorption are related to impaired absorption of valuable nutrients. This analysis is somewhat compromised because of the fact that nutritional deficiencies are known to be relatively rare after RYGB and GB [8] and by routine supplementation of 1 g calcium, 800 IU D-25 vitamin, and a multivitamin tablet (including 400 μg folate) given to all patients in our institution after RYGB. We could not link the decline in cholesterol absorption with the prevalence of nutritional deficiencies. No correlation of cholesterol absorption with the levels of hemoglobin, serum D-25 vitamin, B12 vitamin, calcium, magnesium and phosphate, and erythrocyte folate levels was observed postoperatively. These findings confirmed that, at least with given supplementation, decreased cholesterol absorption post-RYGB is not related to clinically significant nutritional deficiencies.

Limitations of this study are related to the relatively small sample size and marked baseline differences in many variables. In addition, comparison of RYGB and GB was performed in a nonrandomized setting. However, the results regarding cholesterol absorption were effectively the opposite after RYGB and GB (Fig. 1) and remained after vigorous controlling of baseline differences between the groups (Table 3), making it unlikely that these limitations would compromise interpretation of our results. Evidently, larger long-term studies are needed to confirm the possible role of cholesterol absorption in the determination cardiovascular risk after obesity surgery.

In summary, this study demonstrated that RYGB limits cholesterol absorption, leading to negative cholesterol balance and a decrease in serum total cholesterol and LDL cholesterol. This potentially beneficial effect of RYGB does not seem to relate with nutritional deficiencies, at least when accompanied with appropriate dietary counseling and supplementations. We propose that the decrease in cholesterol absorption, together with the decrease in total body cholesterol synthesis, may contribute to improved cardiovascular risk profile after RYGB.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.metabol.2009.10.004.

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