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ORIGINAL CONTRIBUTIONS

Differential Effects of Roux-en-Y Gastric Bypass Surgery and Laparoscopic Sleeve Gastrectomy on Fatty Acid Levels

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Abstract

Background Bariatric surgery is associated with improved cardiovascular outcomes and also affects lipid levels, but few studies have compared the effects of Roux-en-Y gastric bypass (RYGB) surgery with those of laparoscopic sleeve gastrectomy (LSG) on serum fatty acid levels. The present study compares the effects of RYGB and LSG surgeries on serum fatty acid levels.

Methods The study participants were women who were undergoing either RYGB or LSG and body mass index (BMI)-matched controls. Fasting blood samples to measure glucose, insulin, and fatty acids were drawn at baseline and at 6 and 18 months from baseline.

Results Serum fatty acid data were available for 57 participants at baseline, of whom 56 had data at 6 months and 41 had data at 18 months from baseline. Compared with baseline, serum non-esterified fatty acids (NEFAs) levels were significantly higher at 6 and 18 months in the LSG group compared with the RYGB group. In the RYGB group, 2 saturated fatty acids (SFAs), 2 monounsaturated fatty acids (MUFAs), and 1 polyunsaturated fatty acid (PUFA) were significantly decreased after surgery, compared with those of the LSG group.

Conclusions A significant increase in NEFAs was seen after LSG, compared with RYGB. Compared with the LSG group, several serum fatty acids were significantly reduced after RYGB.

Trial Registration NCT01228097

Keywords Obesity · Gastric bypass surgery · Sleeve gastrectomy · Lipids · Fatty acids

Introduction

Obese individuals who undergo bariatric surgery compared with non-surgical treatment of obesity have improved cardiometabolic outcomes, including weight loss, greater insulin sensitivity, diabetes remission, and decreased rates of diabetes-associated microvascular and macrovascular complications [1–3]. Serum fatty acid levels, which affect inflammation and low-density lipoprotein oxidation, may influence cardiometabolic risk after bariatric surgery [4]. Studies have suggested that replacing saturated fatty acids (SFAs) with polyunsaturated fatty acids (PUFAs) in the diet decreases incident coronary heart disease risk [5] [6], and increased circulating plasma levels of certain PUFA species have been associated with lower risk of incident cardiovascular disease (CVD) [7].

Bariatric surgery alters serum fatty acid levels [8]. In addition to the effects of bariatric surgery on gastrointestinal hormones and neural pathways [9, 10], laparoscopic sleeve gastrectomy (LSG) decreases gastric size, whereas Roux-en-Y gastric bypass (RYGB) surgery both decreases gastric size and causes malabsorption of nutrients [11]. After RYGB, reduced fat absorption as a result of both decreased fat intake and malabsorption has been observed [12]. After LSG, Lin et al. found that serum eicosapentaenoic (EPA) levels and

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the ratio of EPA/arachidonic acid (AA) decreased 3 months after surgery but increased at 12 months, although not back to baseline [8]. In another study, plasma non-esterified fatty acids (NEFAs) were measured prior to either RYGB or LSG and 3 days after surgery, and reductions in all measured NEFAs were seen in the RYGB group [13]. However, the current literature comparing the effects of LSG and RYGB on serum fatty acid levels is limited [8, 13, 14].

The current study analyzed data from a previously published prospective observational study of obese female participants who underwent either RYGB or LSG and were compared with a body mass index (BMI)-matched control group [15, 16]. The primary aim of the current study was to compare changes in serum fatty acid levels after RYGB or LSG surgery.

Materials and Methods

Study Population

The details of the parent study have been published previously [15, 16] and are also described here. The study participants were patients from the Penn Metabolic and Bariatric Surgery Program at the University of Pennsylvania Health System. All study participants were women, age ≥ 18 years, with a BMI ≥ 40 kg/m^2 (or ≥ 35 kg/m^2 with significant co-morbid conditions). Individuals who were pregnant, lactating, or had a history of diabetes, recent substance abuse, weight loss medication use, or unstable psychiatric disease were excluded. The University of Pennsylvania Institutional Review Board approved the study (Clinical Trials registration number NCT01228097). Participants undergoing surgery decided with their surgeon whether to undergo RYGB or LSG. Weight-matched controls, who were not pursuing weight loss and were recruited by means of media advertisements, agreed to maintain their baseline weight (within 5%) over the course of 18 months.

Surgical Interventions

Participants in the treatment arms of the study underwent either RYGB or LSG. Both RYGB and LSG surgeries were performed laparoscopically. The RYGB surgeries involved the creation of a 30-mL gastric pouch that connected to a Roux limb, circumventing much of the stomach and also the duodenum and proximal jejunum. The Roux limb was between 100 and 150 cm long, the biliopancreatic limb was 50 cm long, and the average total small bowel length was 660 cm. The LSG surgeries consisted of removing the majority of the stomach, including the fundus [11, 16].

Assessments

Blood was obtained from participants at baseline (within 4 weeks before surgery) and at 6 months and 18 months post surgery. Serum NEFAs were measured using enzymatic colorimetric assay [17], and total fatty acid concentrations were measured at the Metabolic Tracer Resource at the University of Pennsylvania. Heptadecanoic acid was added to each plasma sample as an internal standard. Lipids were extracted on ice using chloroform:methanol (2:1). The lipid extract was dried, saponified using 0.3 N KOH-methanol and fatty acids derivatized to their fatty acid methyl esters (FAMEs). FAMEs were extracted into hexane and injected into an Agilent 7890A/5975 GC/MS run in electron ionization mode fitted with a DB-5MS column. Fatty acids were identified using known standards and normalized to the internal standard. The concentration of each fatty acid was determined using a standard curve. The following fatty acids were measured: NEFAs, SFAs (C14:0, C16:0, and C18:0), monounsaturated fatty acids (MUFAs) (C16:1, C18:1 n9, and C18:1 n7), and PUFAs (C18:2, C20:3, C20:4).

At each visit, BMI was calculated, as was HOMA-IR, using fasting serum glucose and insulin.

The control group participants underwent these assessments over the same time period as the bariatric surgery participants.

Statistical Analyses

Linear mixed models with residual maximum likelihood were used to determine whether the control, LSG, and RYGB groups differed in change in fatty acids from baseline at month 6 and month 18. Unconditional models were used to determine the appropriate model shape (e.g., linear, quadratic, piece-wise) and variance-covariance structure based on model fit criteria (e.g., − 2 log likelihood) [18]. Data modeled were changes in fatty acid levels controlling for baseline levels of the fatty acid. Estimated changes in fatty acids from baseline were compared between groups using least squared means. Linear mixed models also were used to study associations between changes in fatty acids and changes in BMI and HOMA-IR. An alpha of 0.05 was used in all analyses, which were conducted using the SPSS statistical software (version 25).

Results

Patient Characteristics

Table 1 presents baseline characteristics of the participants. In the parent study, 68 participants completed baseline assessments. Of these, 64 participants completed 6-month

Table 1 Baseline characteristics

Variable	Control ($N = 19$)	LSG ($N = 17$)	RYGB ($N = 21$)	Total ($N = 57$)
Age (years)	35.7 (8.4)	39.7 (8.4)	35.6 (10.1)	36.8 (9.1)
Race**				
Black	15 (78.9%)	12 (70.6%)	8 (38.1%)	35 (61.4%)
White	3 (15.8%)	4 (23.5%)	13 (61.9%)	21 (31.5%)
Other	1 (5.3%)	1 (5.9%)	0 (0%)	2 (3.6%)
Weight (kg)	116.0 (14.8)	117.8 (11.8)	119.5 (12.8)	117.8 (13.1)
BMI (kg/m^2)	43.3 (4.4)	43.7 (4.2)	44.6 (4.2)	43.9 (4.2)
Triglycerides (mg/dL)*	61.6 (24.2)[a]	85.9 (32.6)[ab]	90.3 (35.0)[b]	79.3 (33.1)
Total cholesterol (mg/dL)*	158.8 (21.3)	168.8 (37.9)	173.1 (41.7)	167.0 (34.8)
Fasting glucose (mg/dL)*	96.1 (10.0)	99.5 (12.4)	97.2 (8.4)	97.5 (10.3)
Fasting insulin (μU/mL)*	20.2 (2.8)	17.2 (5.5)	15.5 (6.7)	17.4 (7.7)
HOMA-IR*	5.0 (2.8)	4.3 (1.6)	3.7 (1.8)	4.3 (2.2)

Values shown are *N* (%) or means (standard deviation). *BMI*, body mass index; *HOMA-IR*, homeostatic model assessment of insulin resistance; *RYGB*, Roux-en-Y gastric bypass; *LSG*, laparoscopic sleeve gastrectomy. Significant differences ($P < 0.05$) between treatment groups are marked using superscripts. (Values with different superscripts (a vs. b) differ significantly from each other. Values that share a superscript do not differ significantly.) *Sample size is 56 for triglycerides and cholesterol ($n = 19$, $n = 16$, and $n = 21$, respectively), 55 for glucose and leptin ($n = 18$, $n = 16$, and $n = 21$, respectively), and 54 for insulin and HOMA-IR ($n = 17$, $n = 16$, and $n = 21$, respectively). **The distribution of Black/non-Black races differed significantly among the groups ($P = 0.019$)

assessments, and 51 participants completed the 18-month assessments. In the present study, baseline fatty acid levels were available for 57 of the participants, of which 19 were in the control group, 17 were in the LSG group, and 19 were in the RYGB group. Measurements were available at month 6 for 56 of these participants and at month 18 for 41 of these participants. All 57 participants were included in the statistical analyses. Because baseline differences between at least two groups were observed for six of the fatty acids (Table 2), baseline fatty acid levels were included as a covariate in all subsequent analyses.

NEFAs

Table 3 shows the mean changes in fatty acids from baseline at months 6 and 18 for each group. Significantly larger increases in NEFAs from baseline were observed at both month 6 ($P = 0.044$) and month 18 ($P = 0.005$) in the LSG group, compared with the RYGB group. The LSG group also had larger increases in NEFAs at month 6 relative to the control group ($p = 0.046$).

SFAs

At month 6, RYGB resulted in larger decreases in C16:0 from baseline, compared with the control group ($P = 0.011$) and the LSG group ($P = 0.011$), and in C18:0 compared with the control group ($P < 0.001$). At month 18, RYGB resulted in larger decreases in C18:0 from baseline, compared with both the control group ($P = 0.018$) and the LSG group ($P < 0.001$).

In the LSG group, at month 6, a larger decrease in C14:0 compared with the control group ($p = 0.003$) was observed, but this difference was not noted at month 18.

MUFAs

The LSG group demonstrated a different pattern of change in MUFAs compared with the RYGB group. At month 6, LSG resulted in decreased C16:1 ($P = 0.046$), increased C18:1 n7 ($P = 0.002$), and increased C18:1 n9 ($P = 0.013$) from baseline compared with the control group. However, after LSG, levels of C16:1, C18:1 n7 and C18:1 n9 were not significantly different from control at month 18.

Similarly, at month 6, LSG resulted in increased C18:1 n7 ($P = 0.002$) and C18:1 n9 ($P = 0.012$), compared with RYGB, but not at month 18.

PUFAs

The pattern of change in PUFAs differed between LSG and RYGB. At month 6, C18:2 was increased after LSG but decreased after RYGB, which was a significant difference ($P < 0.001$). At month 18, C18:2 continued to be increased after LSG and decreased after RYGB, which was also a significant difference ($P = 0.002$). In addition, at month 18, the increase in C18:2 after LSG was significantly different from the decrease in C18:2 in the control group ($P < 0.001$).

Table 2 Baseline serum fatty acid levels

Variable	Control ($N = 19$)	LSG ($N = 17$)	RYGB ($N = 21$)	Total ($N = 57$)
Non-esterified fatty acids				
Serum NEFA (mEq/L)	0.54 (0.17)	0.58 (0.17)	0.59 (0.16)	0.57 (0.17)
Saturated fatty acids				
C14:0 (μg/mL)	7.1 (3.4)[a]	7.5 (4.4)[ab]	11.2 (5.6)[b]	8.7 (4.9)
C16:0 (μg/mL)	261.8 (62.8)[a]	332.0 (58.7)[b]	283.1 (56.5)[a]	290.6 (64.9)
C18:0 (μg/mL)	107.6 (22.4)[a]	136.0 (24.5)[b]	108.2 (25.1)[a]	116.3 (26.9)
Monounsaturated fatty acids				
C16:1 (μg/mL)	16.9 (8.5)[a]	18.8 (6.4)[a]	29.6 (12.8)[b]	22.1 (11.3)
C18:1 n7 (μg/mL)	19.0 (8.5)	23.2 (9.6)	24.4 (7.0)	22.2 (8.5)
C18:1 n9 (μg/mL)	173.2 (53.0)[a]	220.6 (68.7)[ab]	227.32 (56.4)[b]	207.3 (63.1)
Polyunsaturated fatty acids				
C18:2 (μg/mL)	300.5 (84.0)	321.7 (97.2)	328.4 (86.2)	317.1 (88.1)
C20:3 (μg/mL)	9.8 (5.8)[a]	9.6 (6.5)[a]	15.7 (5.3)[b]	11.9 (6.4)
C20:4 (μg/mL)	66.4 (28.6)	66.0 (37.8)	85.3 (25.1)	73.3 (31.4)

Values shown are *N* (%) or means (standard deviation). *BMI*, body mass index; *HOMA-IR*, homeostatic model assessment of insulin resistance; *NEFA*, non-esterified fatty acids; *RYGB*, Roux-en-Y gastric bypass; *LSG*, laparoscopic sleeve gastrectomy. Significant differences ($P < 0.05$) between treatment groups are marked using superscripts. (Values with different superscripts (a vs. b) differ significantly from each other.) Values that share a superscript do not differ significantly)

Relation of Fatty Acids and BMI

No significant association was observed between change in NEFAs and change in BMI over 18 months (Table 4). Significant direct associations were seen between change in BMI and change in C16:0 ($P = 0.002$), change in C18:0 ($P < 0.001$), and change in C16:1 ($P < 0.001$).

Relation of Fatty Acids and HOMA-IR

No significant association was observed between change in NEFAs and change in HOMA-IR over 18 months (Table 4). Significant direct associations were seen between change in HOMA-IR and change in C14:0 ($P < 0.001$), change in C16:1 ($P = 0.001$), and change in C20:3 ($P = 0.036$).

Discussion

This study showed some significant differences in serum fatty acid levels after surgery between RYGB and LSG. One finding was that NEFAs increased significantly at both months 6 and 18 after LSG, compared with RYGB. In addition, at month 6, RYGB resulted in a significant decrease in the SFA C16:0, compared with LSG. At month 6, increases in MUFAs C18:1 n9 and C18:1 n7 and the PUFA C18:2 were seen after LSG, whereas decreases in these fatty acids were seen after RYGB. At month 18, the PUFA C18:2 and the SFA C18:0 were significantly decreased after RYGB compared with LSG. Some mechanisms that might explain these differences are outlined below.

Malabsorption is seen after RYGB, but not sleeve gastrectomy, which may explain the decreases in some fatty acids that were noted after RYGB in our study. In their study, Lin et al. found that EPA and EPA/AA were decreased at 3 months and 1 year after BPDDS, a procedure that, to a greater degree than RYGB, causes fat malabsorption [8, 19]. On the other hand, at 1 year after LSG, EPA and EPA/AA trended towards baseline levels [8]. In a study by Wijayatunga et al, C14:0 and C18:0 significantly increased and NEFAs significantly decreased at 6 months compared with baseline in patients who had undergone RYGB [20]. However, this study did not have a control group and had a sample size of 8 participants.

Decreased food consumption may also influence the changes in serum fatty acids seen after bariatric surgery. Decreases in macronutrient, including lipids, and micronutrient intake, as measured by food records, have been observed in the short term after RYBG [21]. However, in a study of long-term follow-up of dietary intake of individuals who underwent either RYGB or LSG, no difference in amount of energy intake from lipids at 6 and 12 months after surgery compared with baseline was noted between the two groups, and no differences were noted at 6 or 12 months compared with baseline in SFA, MUFA, and PUFA intake between the two groups [22].

Fatty acids have been implicated in regulating glucose homeostasis in obese individuals [23]. Specifically, NEFAs are elevated in obese patients and contribute to insulin resistance. However, malabsorptive bariatric surgery results in improved

Table 3 Estimated mean changes in baseline fatty acids at months 6 and 18 in the intention-to-treat population ($N = 57$)

Variable	Control ($N = 19$)	LSG ($N = 17$)	RYGB ($N = 21$)	*P* value		
				Control vs. LSG	Control vs. RYGB	LSG vs. RYGB
Non-esterified fatty acids						
Change in serum NEFA (mEq/L)						
Month 6	− 0.003 ± 0.04	+ 0.11 ± 0.04	+ 0.001 ± 0.04	0.046	0.951	0.044
Month 18	+ 0.06 ± 0.05	+ 0.19 ± 0.05	+ 0.01 ± 0.04	0.055	0.413	0.005
Saturated fatty acids						
Change in C14:0 (μg/mL)						
Month 6	− 0.7 ± 0.8	− 4.3 ± 0.8	− 2.5 ± 0.8	0.003	0.134	0.130
Month 18	− 0.1 ± 0.9	− 0.8 ± 0.9	− 0.3 ± 0.8	0.588	0.876	0.708
Change in C16:0 (μg/mL)						
Month 6	− 7.5 ± 12.5	− 4.8 ± 13.3	− 50.8 ± 11.2	0.890	0.011	0.011
Month 18	− 17.0 ± 13.7	− 4.0 ± 14.4	− 39.6 ± 12.2	0.538	0.225	0.062
Change in C18:0 (μg/mL)						
Month 6	− 0.4 ± 6.1	− 13.1 ± 6.7	− 30.8 ± 5.6	0.186	< 0.001	0.056
Month 18	− 0.7 ± 6.6	+ 14.6 ± 7.3	− 21.8 ± 6.0	0.142	0.018	< 0.001
Monounsaturated fatty acids						
Change in C16:1 (μg/mL)						
Month 6	− 1.3 ± 2.1	− 7.2 ± 2.1	− 6.3 ± 2.1	0.046	0.114	0.766
Month 18	− 0.1 ± 2.2	− 5.6 ± 2.2	− 3.6 ± 2.2	0.076	0.301	0.546
Change in C18:1 n7 (μg/mL)						
Month 6	− 2.5 ± 1.8	+ 5.5 ± 1.8	− 2.3 ± 1.6	0.002	0.930	0.002
Month 18	+ 0.7 ± 1.9	− 0.4 ± 1.9	− 4.3 ± 1.7	0.696	0.062	0.134
Change in C18:1 n9 (μg/mL)						
Month 6	− 19.2 ± 11.2	+ 21.9 ± 11.2	− 16.6 ± 10.2	0.013	0.872	0.012
Month 18	− 26.1 ± 12.1	+ 7.0 ± 11.9	+ 4.3 ± 11.2	0.060	0.081	0.867
Polyunsaturated fatty acids						
Change in C18:2 (μg/mL)						
Month 6	− 29.7 ± 13.9	+ 10.0 ± 14.2	− 63.9 ± 12.8	0.050	0.075	< 0.001
Month 18	− 39.3 ± 15.3	+ 47.9 ± 15.3	− 18.0 ± 14.4	< 0.001	0.325	0.002
Change in C20:3 (μg/mL)						
Month 6	− 1.5 ± 1.0	− 4.3 ± 1.1	− 4.4 ± 1.0	0.063	0.058	0.933
Month 18	− 1.1 ± 1.1	+ 1.7 ± 1.1	+ 0.6 ± 1.2	0.084	0.347	0.497
Change in C20:4 (μg/mL)						
Month 6	− 5.2 ± 5.0	+ 2.3 ± 5.1	− 10.7 ± 4.7	0.291	0.430	0.070
Month 18	− 9.7 ± 5.3	+ 7.9 ± 5.4	− 6.4 ± 5.1	0.022	0.655	0.062

Values shown are estimated marginal means (± SE) for the intention-to-treat population ($N = 57$), adjusted for baseline levels of the fatty acid. *NEFA*, non-esterified fatty acids; *RYGB*, Roux-en-Y gastric bypass; *LSG*, laparoscopic sleeve gastrectomy

insulin sensitivity, without a reduction in NEFAs [24]. We detected significant direct associations between change in BMI and 3 of the 10 measured fatty acids. Similarly, we found significant direct associations between change in HOMA-IR and 3 fatty acids, which did not, however, include NEFAs. In a study of Caucasian female participants, Honka et al found significant decreases in BMI, pancreatic fatty acid uptake, and fasting glucose and insulin levels at 6 months post RYGB surgery compared with baseline; however, there was no significant change in free fatty acid levels [25]. In contrast, Nemati et al. reported that of participants who underwent either RYGB, LSG, or a very low-calorie diet, there was a small but significant positive correlation between total insulin secretion during an oral glucose tolerance test and serum C18:2 levels, at baseline and 3 days post treatment. Moreover, C18:0 levels and the ratio of MUFA/PUFA and unsaturated/saturated fatty acids had a weak but significant positive correlation with HOMA-IR [14]. We did not find a significant association between change in HOMA-IR and change in C18:0 in our study. These differences in findings may be

Table 4 Associations between changes over time in BMI and HOMA-IR and changes in fatty acids in the intention-to-treat population

Change in variable	Change in BMI ($N = 57$)	Change in HOMA-IR ($N = 54$)
Non-esterified fatty acids		
Serum NEFA (mEq/L)	− 0.0002 ± 0.005	0.006 ± 0.01
Saturated fatty acids		
C14:0 (μg/mL)	0.13 ± 0.09	0.61 ± 0.16***
C16:0 (μg/mL)	3.89 ± 1.23**	5.20 ± 2.83°
C18:0 (μg/mL)	2.08 ± 0.57***	2.41 ± 1.33°
Monounsaturated fatty acids		
C16:1 (μg/mL)	0.71 ± 0.18***	1.16 ± 0.34**
C18:1 n7 (μg/mL)	0.33 ± 0.18°	− 0.09 ± 0.41
C18:1 n9 (μg/mL)	0.89 ± 1.18	2.18 ± 2.49
Polyunsaturated fatty acids		
C18:2 (μg/mL)	1.06 ± 1.62	− 0.89 ± 3.53
C20:3 (μg/mL)	0.12 ± 0.11	0.48 ± 0.23*
C20:4 (μg/mL)	0.60 ± 0.49	0.70 ± 1.09

Values shown are $b \pm$ standard error for the relationship between change in the variables over time during the 18-month follow-up period. *NEFA*, non-esterified fatty acids; BMI, body mass index; *HOMA-IR*, homeostatic model assessment of insulin resistance; °$p < 0.10$; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. Sample size for each analysis varies due to differences in available data at baseline

attributed to measurements being obtained at different times post surgery (i.e., days vs. months).

Bariatric surgery is associated with improvements in CVD risk factors such as obesity, hypertension, and type 2 diabetes, and some evidence shows that bariatric surgery is associated with decreased risk of myocardial infarction [26]. Alterations in serum fatty acids may play a role in the positive cardiovascular effects of bariatric surgery. Increased MUFA and PUFA intake and decreased SFA intake are associated with lower risk of CVD [27]. In our study, we observed significant decreases in 2 out of 3 measured SFAs after RYGB compared with LSG. Bariatric surgery is associated with improved cardiovascular outcomes [2, 28]. However, no randomized controlled trials have specifically compared the differences in cardiovascular outcomes among specific types of bariatric surgery. Potentially, the differing effects of RYGB and LSG on serum fatty acids could influence cardiovascular outcomes.

The findings of this study are important because studies to date in the literature on changes in fatty acids after bariatric surgery are limited by small study populations, lack of a control group, and short follow-up times. The strengths of the present study include a relatively long follow-up period of 18 months and comparison to a control group. Limitations of the present study include the following: the participants were not randomized to treatment groups and we did not have information about lipid-lowering medication use among the participants or comorbidities that could alter fat absorption.

Conclusion

Several fatty acids were significantly decreased after RYGB compared with LSG, and direct associations were found among some of these changes and improvements in BMI and HOMA-IR. Thus, relationships exist between decreased levels of some serum fatty acids and decreased BMI and HOMA-IR, although it is unclear whether decreases in some fatty acids contributed to lower weight and insulin resistance. Moreover, additional studies are needed to determine whether these fatty acid changes are associated with cardiovascular outcomes independent of changes in weight and insulin resistance.

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Compliance with Ethical Standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of Interest Author 1, Author 2, Author 3, Author 4, and Author 7 have nothing to declare. Author 5 reports receiving reimbursement for consulting for Novo Nordisk. Author 6 reports serving on advisory boards for Novo Nordisk and Weight Watchers International.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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