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Gastric Bypass vs Diet and Cardiovascular Risk Factors
A Nonrandomized Controlled Trial

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IMPORTANCE Roux-en-Y gastric bypass (RYGB) is associated with reduced cardiovascular (CV) risk factors, morbidity, and mortality. Whether these effects are specifically induced by the surgical procedure or the weight loss is unclear.

OBJECTIVE To compare 6-week changes in CV risk factors in patients with obesity undergoing matching caloric restriction and weight loss by RYGB or a very low-energy diet (VLED).

DESIGN, SETTING, AND PARTICIPANTS This nonrandomized controlled study (Impact of Body Weight, Low Calorie Diet, and Gastric Bypass on Drug Bioavailability, Cardiovascular Risk Factors, and Metabolic Biomarkers [COCKTAIL]) was conducted at a tertiary care obesity center in Norway. Participants were individuals with severe obesity preparing for RYGB or a VLED. Recruitment began February 26, 2015; the first patient visit was on March 18, 2015, and the last patient visit (9-week follow-up) was on August 9, 2017. Data were analyzed from April 30, 2021, through June 29, 2023.

INTERVENTIONS VLED alone for 6 weeks or VLED for 6 weeks after RYGB; both interventions were preceded by 3-week LED.

MAIN OUTCOMES AND MEASURES Between-group comparisons of 6-week changes in CV risk factors.

RESULTS Among 78 patients included in the analyses, the mean (SD) age was 47.5 (9.7) years; 51 (65%) were women, and 27 (35%) were men. Except for a slightly higher mean (SD) body mass index of 44.5 (6.2) in the RYGB group (n = 41) vs 41.9 (5.4) in the VLED group (n = 37), baseline demographic and clinical characteristics were similar between groups. Major atherogenic blood lipids (low-density lipoprotein cholesterol, non–high-density lipoprotein cholesterol, apolipoprotein B, lipoprotein[a]) were reduced after RYGB in comparison with VLED despite a similar fat mass loss. Mean between-group differences were −17.7 mg/dL (95% CI, −27.9 to −7.5), −17.4 mg/dL (95% CI, −29.8 to −5.0) mg/dL, −9.94 mg/dL (95% CI, −15.75 to −4.14), and geometric mean ratio was 0.55 U/L (95% CI, 0.42 to 0.72), respectively. Changes in glycemic control and blood pressure were similar between groups.

CONCLUSIONS AND RELEVANCE This study found that clinically meaningful reductions in major atherogenic blood lipids were demonstrated after RYGB, indicating that RYGB may reduce CV risk independent of weight loss.

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Supplemental content

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Bariatric surgery is more effective than nonsurgical treatment in reducing body weight[1] and cardiovascular risk factors such as type 2 diabetes,[2,3] hypertension,[4,5] and dyslipidemia in patients with severe obesity.[6,7] It is further associated with lower incidence of cardiovascular events[8-11] and lower all-cause mortality.[11-14] Whether the beneficial effects are specifically explained by the surgical procedure, caloric restriction, or weight loss is unclear, as most studies have displayed large weight loss differences between groups.[2,3,15] Some studies have reported similar weight loss between groups, but this was achieved over a longer time for the diet group with a main focus on glycemic control.[16,17] Results are conflicting, as 1 study[16] showed greater improvements in insulin sensitivity and disposition index after Roux-en-Y gastric bypass (RYGB), in contrast to another study[17] showing no differences between RYGB and diet in glucose parameters, insulin sensitivity, beta-cell function, and body composition. Another study reported the benefit of a composite end point of hemoglobin A_{1c} (HbA_{1c}), low-density lipoprotein (LDL) cholesterol, and systolic blood pressure to be primarily attributable to the weight loss.[15] Nonetheless, surgical procedures bypassing the upper gastrointestinal tract, including RYGB, have been shown to restore glycemic control within days after surgery, before any significant weight loss.[18] Further, RYGB has been associated with blood pressure reduction within 1 week before any significant weight loss in an observational study.[19] Examples of RYGB-specific effects are hormonal changes (eg, increases in the incretin hormones GLP-1 and PYY), increased circulating bile acids, decreased plasma branched-chain amino acids, and alterations in the gut microbiome.[20-24]

The principal aim of this nonrandomized controlled study was to compare the short-term (6 weeks) changes in glucose metabolism, blood pressure, blood lipids, metabolic biomarkers, and body composition in patients undergoing RYGB vs a very low-energy diet (VLED) with matching weight loss. We also evaluated changes in proteins/peptides, metabolites, and bile acids.

Key Points

Question Does Roux-en-Y gastric bypass (RYGB) affect cardiovascular risk factors independent of caloric restriction and weight loss?

Findings In this nonrandomized controlled study, patients with severe obesity undergoing RYGB demonstrated a clinically meaningful reduction in major atherogenic blood lipids, which was not seen in patients undergoing an isocaloric very low-energy diet with a matching weight loss.

Meaning Surgery-specific changes on major atherogenic blood lipids seem to be independent of weight loss and may explain at least part of the long-term cardiovascular benefits of RYGB.

Methods

Study Design and Participants

The study design has previously been described in detail.[25] Briefly, the Impact of Body Weight, Low Calorie Diet, and Gastric Bypass on Drug Bioavailability, Cardiovascular Risk Factors, and Metabolic Biomarkers (COCKTAIL) study was an open, nonrandomized, controlled, single-center study performed at Vestfold Hospital Trust, a tertiary care obesity center in Norway. Participants were treatment-seeking patients with severe obesity and a broad range of glucose tolerance levels. Consecutive adult patients (≥18 years) scheduled for weight loss treatment with RYGB or VLED with a stable body weight during the last 3 months were considered potentially eligible.[25] At screening, patients were assessed by a study physician according to the predetermined inclusion and exclusion criteria (eMethods in Supplement 1).

A comprehensive assessment of cardiovascular risk factors was conducted before, during, and at the end of matching weight loss induced by 6-week VLED alone or 6-week VLED after RYGB, with both interventions preceded by 3-week low-energy diet (LED). Race was determined as patient reported and/or assessed by an investigator.

The study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Council for Harmonization. Participants provided written informed consent before participating in the study, which was approved by the Regional Committee for Medical and Health Research Ethics (2013/2379/REK sørøst A) in Norway. The Transparent Reporting of Evaluations With Nonrandomized Designs (TREND) reporting guideline was followed.

Weight-Loss Interventions

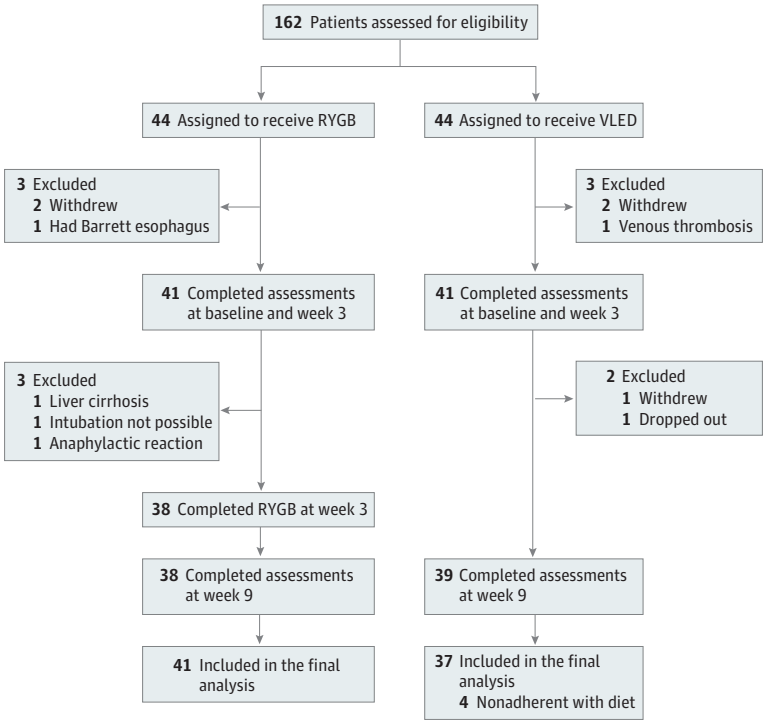
Both groups were prescribed an initial 3-week LED (<1200 kcal/d) followed by an additional 6-week VLED (<800 kcal/d) (eMethods in Supplement 1). To strengthen dietary adherence, a dietician consulted with patients weekly by telephone during the study. During the 6-week VLED, a 4-day diet diary at 3 time points (weeks 4, 6, and 9) was used to monitor dietary adherence. Routine laparoscopic RYGB was performed by hospital surgeons as described in the eMethods in Supplement 1.

Study Objectives, Outcomes, and Procedures

The study objectives were to compare the short-term (6-week) changes in cardiovascular risk factors such as HbA_{1c}, fasting glucose, insulin sensitivity, blood pressure, blood lipids, total body fat, body mass index (BMI), waist-hip circumference, and cardiometabolic biomarkers between the RYGB and VLED groups.[25] We also evaluated changes in proteins/peptides, metabolites, and bile acids.[25]

Measurable outcomes were changes in HbA_{1c}, fasting glucose, C-peptide, Homeostasis Model Assessment estimate of insulin sensitivity (HOMA2%S), blood pressure, heart rate, total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, apolipoprotein B, lipoprotein(a), fat mass, fat-free mass, BMI, waist circumference, waist-hip ratio, and various proteins/peptides, metabolites, and bile acids. Measures and samples were obtained at week 0 (before the start of the LED), at week 3 (end of LED; just before RYGB or start of VLED), at week 5 (2 weeks after RYGB/start of

Figure 1. Participant Flow Chart



Participant flow over the study period with a matching weight loss between Roux-en-Y gastric bypass (RYGB) and very low-energy diet (VLED).

VLED), and at week 9 (6 weeks after RYGB/start of VLED). Details of methods, sample analyses, and calculations are provided in the eMethods in Supplement 1.

Statistical Analysis

Baseline participant characteristics, medications, and dietary data were described using means (SD) for continuous variables and numbers and percentages for categorical variables. Participants reporting nonadherence with the VLED were excluded from the analysis because of the mechanistic nature of the study. The VLED group excluding nonadherent participants was compared with all VLED participants at baseline (eTable 1 in Supplement 1).

Potential effects of RYGB vs VLED on outcomes were assessed using a linear mixed-effects model for repeated measures. The outcome variables were entered into the model as the change from baseline (week 0). For each model, the covariates: treatment, time, age at baseline, sex and BMI at baseline (except when assessing BMI and weight); the treatment × time interaction term; and the baseline value of the outcome variable were entered into the model. To improve precision, a spatial power covariance matrix was specified. The estimation of the parameters was performed using restricted maximum likelihood. Because this was an exploratory study, no attempts were made at controlling the type I error, and missing data were not imputed. All analyses were performed using SAS version 9.4M5 (SAS Institute). Data were analyzed from April 30, 2021, through June 29, 2023.

This study had a number of exploratory objectives related to bioavailability and disposition of, for example, midazolam, as well as cardiovascular metabolism. The sample size calculation was based on comparisons of oral midazolam bioavailability requiring at least 25 patients in each group.[25] To ensure relevant assessments of the exploratory end points, inclusion of 40 patients in each group was planned. In addition, to prevent imbalance in the proportion of patients with normal glucose tolerance and type 2 diabetes between treatment groups, we aimed to include at least 15 patients with type 2 diabetes and at least 15 patients with normal glucose tolerance in each group (see the trial protocol in Supplement 2 and statistical analysis plan in Supplement 3).

Results

Participants

One hundred sixty-two patients preparing for RYGB or VLED were assessed for eligibility.[25] After exclusion of 74 ineligible patients, 88 were included in the RYGB (n = 44) and VLED groups (n = 44) (**Figure 1**). Three patients in each group withdrew or were excluded before the start of the study, and 4 reported nonadherence to VLED and were excluded from the analysis (eTable 1 in Supplement 1), leaving 41 RYGB and 37 VLED patients to be included in the statistical analysis.

Among the 78 patients included in the analyses, the mean (SD) age was 47.5 (9.7) years; 51 (65%) were women, and 27 (35%) were men. Participants in the RYGB group were slightly heavier, but there were no other substantial differences between groups (**Table 1**). The majority of participants were White (n = 77; 99%). Three did not complete the surgical procedure,

Table 1. Baseline Characteristics of the Study Participants

Characteristic	Mean (SD)	
	RYGB group (n = 41)	VLED group (n = 37)
Age, y	46.4 (9.4)	48.7 (10.0)
Sex, No. (%)		
Female	27 (65.9)	24 (64.9)
Male	14 (34.1)	13 (35.1)
Prediabetes, No. (%)[a]	14 (34.1)	10 (27.0)
Type 2 diabetes, No. (%)[a]	14 (34.1)	13 (35.1)
Body composition		
Body mass index[b]	44.5 (6.2)	41.9 (5.4)
Body weight, kg	131.7 (23.6)	124.7 (23.8)
Fat free mass, kg	68.2 (13.4)	67.0 (14.6)
Fat mass, kg	63.6 (14.1)	57.7 (12.7)
Waist circumference, cm	128.7 (13.1)	124.8 (13.3)
Waist-hip ratio	98.5 (10.9)	98.1 (10.5)
Glucose metabolism		
Glycated hemoglobin, %	6.1 (0.9)	6.2 (1.1)
Fasting glucose, mg/dL	116.7 (44.7)	116.2 (41.8)
Fasting insulin, μIU/mL[c]	27.6 (15.1)	23.6 (12.1)
Fasting C-peptide, pg/mL	4063.2 (1436.9)	3719.5 (1377.3)
HOMA2%S[d]	35.8 (13.5)	40.3 (17.5)
HOMA2%B[d]	146.5 (50.2)	138.1 (47.5)
Lipids		
Total cholesterol, mg/dL	187.4 (35.6)	183.7 (31.0)
LDL cholesterol, mg/dL	112.9 (28.5)	108.2 (28.2)
HDL cholesterol, mg/dL	43.1 (8.5)	43.4 (9.3)
Triglycerides, mg/dL	153.8 (91.1)	177.4 (156.7)
Non-HDL cholesterol, mg/dL	144.3 (37.8)	140.3 (31.4)
Apolipoprotein B, mg/dL	91.7 (23.7)	87.0 (23.1)
Lipoprotein(a), U/L	357.8 (414.8)	151.9 (273.6)
Vital signs, other measures		
Systolic BP, mm Hg	130.4 (16.2)	128.5 (15.7)
Diastolic BP, mm Hg	84.0 (8.0)	82.9 (9.5)
Pulse, beats/min	76.2 (9.6)	73.2 (8.5)
hs-C-reactive protein, mg/L	8.1 (6.2)	7.0 (6.8)
Leptin, pg/mL	47 725.7 (37 775.4)	40 460.2 (29 852.9)
Creatinine, mg/dL	0.7 (0.1)	0.7 (0.2)
Hemoglobin, g/100 mL	14.0 (1.2)	14.1 (1.1)
Current use of nicotine, No. (%)		
Present smoker	2 (4.9)	3 (8.1)
Former smoker	23 (56.1)	14 (37.8)
Never smoked	16 (39.0)	20 (54.1)

Abbreviations: BP, blood pressure; HDL, high-density lipoprotein; HOMA2%B, Homeostasis Model Assessment estimate of beta-cell function; HOMA2%S, Homeostasis Model Assessment estimate of insulin sensitivity; hs, high sensitivity; LDL, low-density lipoprotein; RYGB, Roux-en-Y gastric bypass; VLED, very low-energy diet.

SI conversion factors: To convert C-peptide to nmol/L, multiply by 0.331; creatinine to μmol/L, multiply by 88.4; glucose to mmol/L, multiply by 0.0555; HDL, LDL, non-HDL, and total cholesterol to mmol/L, multiply by 0.0259; insulin to pmol/L, multiply by 6.945; triglycerides to mmol/L, multiply by 0.0113.

[a] Prediabetes: hemoglobin A_{1c} ≥5.7% and ≤6.4%; type 2 diabetes: hemoglobin A_{1c} ≥6.5%, taking antidiabetic drug treatment, or previously diagnosed type 2 diabetes treated with lifestyle intervention.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Fasting insulin is the mean of 2 fasting insulin values taken 15 minutes apart.

[d] Calculations of HOMA2%S and HOMA2%B are C-peptide based.

while 1 participant withdrew and 1 dropped out between weeks 3 and 9 in the VLED group (Figure 1). No one withdrew consent.

Recruitment and Follow-Up Periods

The recruitment period took place from February 26, 2015, to May 8, 2017. The first patient signed informed consent and was included in the study at March 18, 2015, and attended the baseline visit at April 15, 2015. The last patient attended the 9-week follow-up visit at August 9, 2017.

Nutritional Data

Most participants recorded their dietary intake on at least 1 of the 3 diet registration periods (4-day periods in weeks 3-9). The mean (SD) daily energy intake (weeks 3-9) was similar in the VLED (800 [153] kcal) and RYGB groups (806 [393] kcal) (eTable 2 in Supplement 1). During week 9, the VLED and the RYGB groups reported similar intakes of saturated fat, unsaturated fat, and total cholesterol (eTable 3 in Supplement 1).

Changes in Cardiovascular Risk Factors and Biomarkers

LED (Week 0 to Week 3)

During the initial 3-week LED treatment, body weight declined by 5%, fat mass by 8%, HbA_{1c} by 4%, systolic blood pressure by 5%, and LDL cholesterol by 19%, with no clinically relevant differences between groups (**Table 2**, **Figure 2**, and **Figure 3**). Apolipoprotein B values decreased, while lipoprotein(a) and fibroblast growth factor 19 (FGF19) did not change.

RYGB vs VLED (Week 3 to Week 9)

The RYGB group lost more weight compared with the VLED group, with a mean between-group difference of −2.3 kg (95% CI, −3.4 to −1.2) (Table 2). The difference in change in body weight between groups occurred between week 3 and week 5 (−2.6 kg; 95% CI, −3.3 to −1.9), and change was parallel thereafter (Figure 2A and eTable 4 in Supplement 1). Body fat mass declined substantially in both groups with no difference in change between groups (Figure 2B, Table 2, and eTable 4 in Supplement 1). A larger reduction in fat-free mass occurred during the first 2 weeks after RYGB (week 3 to week 5), with a between-group difference of −2.4 kg (95% CI, −3.4 to −1.4), but did not maintain statistical significance at week 9 (Figure 2C, Table 2, and eTable 4 in Supplement 1). There were no differences in changes between groups in waist circumference, waist-hip ratio, or leptin levels (Table 2).

There were no differences in changes between groups in values for HbA_{1c}, fasting glucose, fasting insulin, C-peptide, or HOMA2%S. Both groups demonstrated an increase in hepatic insulin clearance with no difference between groups. There were no differences in changes between groups in systolic and diastolic blood pressure (Table 2).

Values for total cholesterol, LDL cholesterol, and non-HDL cholesterol declined during the first 6 weeks after RYGB but were stable or tended to increase during the 6 weeks in the VLED group; between-group differences were −18.0 mg/dL (95% CI, −31.4 to −4.6), −17.7 mg/dL (95% CI, −27.9 to −7.5), and −17.4 mg/dL (95% CI, −29.8 to −5.0), respectively (to convert cholesterol to mmol/L, multiply by 0.0259). During the same

Table 2. Within-Group Changes and Between-Group Differences During Matching Weight Loss Induced by RYGB or VLED[a]

Characteristic	LED (week 0 to 3)			RYGB or VLED (week 3 to 9)		
	RYGB group	VLED group	Difference between groups	RYGB group	VLED group	Difference between groups
Body mass index[b]	−2.07 (−2.36 to −1.78)	−2.05 (−2.35 to −1.75)	−0.01 (−0.43 to 0.40)	−3.62 (−3.88 to −3.37)	−2.77 (−3.03 to −2.51)	−0.85 (−1.22 to −0.49)
Body weight, kg	−6.28 (−7.18 to −5.38)	−6.28 (−7.19 to −5.37)	0.00 (−1.25 to 1.25)	−10.48 (−11.24 to −9.71)	−8.21 (−9.00 to −7.42)	−2.27 (−3.37 to −1.16)
Fat-free mass, kg	−1.24 (−2.10 to −0.39)	−1.22 (−2.13 to −0.30)	−0.03 (−1.19 to 1.14)	−3.02 (−3.99 to −2.06)	−1.73 (−2.73 to −0.72)	−1.30 (−2.69 to 0.09)
Fat mass, kg	−4.82 (−5.70 to −3.95)	−4.93 (−5.84 to −4.02)	0.11 (−1.14 to 1.36)	−7.52 (−8.44 to −6.60)	−6.37 (−7.32 to −5.42)	−1.15 (−2.47 to 0.17)
Waist circumference, cm	−4.34 (−5.58 to −3.09)	−4.54 (−5.84 to −3.25)	0.21 (−1.56 to 1.97)	−7.73 (−9.35 to −6.12)	−5.59 (−7.29 to −3.90)	−2.14 (−4.48 to 0.20)
Waist-hip ratio	−0.65 (−2.19 to 0.89)	−1.43 (−3.00 to 0.14)	0.78 (−1.37 to 2.93)	−0.21 (−2.11 to 1.69)	−0.61 (−2.59 to 1.37)	0.40 (−2.35 to 3.14)
Glycated hemoglobin, %	−0.25 (−0.32 to −0.17)	−0.31 (−0.39 to −0.23)	0.07 (−0.04 to 0.18)	−0.37 (−0.46 to −0.28)	−0.32 (−0.42 to −0.23)	−0.05 (−0.18 to 0.08)
Fasting glucose, mg/dL	−15.35 (−19.03 to −11.68)	−19.67 (−23.50 to −15.83)	4.31 (−0.97 to 9.60)	−8.20 (−12.69 to −3.71)	−1.89 (−6.57 to 2.79)	−6.31 (−12.80 to 0.18)
Fasting insulin, μU/mL	−7.61 (−9.49 to −5.73)	−10.43 (−12.38 to −8.48)	2.82 (0.12 to 5.52)	−4.40 (−6.96 to −1.83)	−1.27 (−3.95 to 1.42)	−3.13 (−6.84 to 0.58)
C-peptide, pg/mL	−486.11 (−701.83 to −270.39)	−807.32 (−1030.88 to −583.77)	321.21 (11.80 to 630.62)	−355.14 (−613.09 to −97.20)	−147.22 (−416.98 to 122.54)	−207.92 (−581.16 to 165.32)
HOMA2%S[c]	6.96 (3.39 to 10.53)	10.88 (7.17 to 14.58)	−3.92 (−9.06 to 1.23)	3.35 (−0.67 to 7.38)	3.97 (−0.25 to 8.18)	−0.61 (−6.44 to 5.22)
HOMA2%B[c]	14.70 (6.26 to 23.14)	11.38 (2.56 to 20.21)	3.32 (−8.77 to 15.41)	8.25 (−0.36 to 16.86)	−0.14 (−9.13 to 8.84)	8.39 (−4.05 to 20.84)
Hepatic insulin clearance	1.97 (1.21 to 2.74)	2.71 (1.91 to 3.51)	−0.74 (−1.84 to 0.37)	1.77 (0.89 to 2.65)	1.28 (0.36 to 2.19)	0.50 (−0.77 to 1.77)
Total cholesterol, mg/dL	−35.04 (−43.04 to −27.05)	−35.03 (−43.37 to −26.68)	−0.02 (−11.48 to 11.45)	−15.66 (−24.93 to −6.40)	2.37 (−7.29 to 12.03)	−18.03 (−31.41 to −4.64)
LDL cholesterol, mg/dL	−23.36 (−28.97 to −17.75)	−18.00 (−23.81 to −12.19)	−5.36 (−13.35 to 2.63)	−13.31 (−20.37 to −6.25)	4.37 (−2.98 to 11.71)	−17.68 (−27.87 to −7.49)
HDL cholesterol, mg/dL	−6.554 (−8.292 to −4.816)	−6.602 (−8.411 to −4.794)	0.049 (−2.435 to 2.532)	0.422 (−1.439 to 2.283)	1.121 (−0.818 to 3.059)	−0.699 (−3.386 to 1.988)
Triglycerides, mg/dL	−50.62 (−65.13 to −36.12)	−51.77 (−66.96 to −36.57)	1.14 (−19.68 to 21.97)	−4.12 (−22.18 to 13.93)	−12.88 (−31.73 to 5.97)	8.75 (−17.36 to 34.86)
Non-HDL cholesterol, mg/dL	−28.54 (−36.04 to −21.04)	−28.50 (−36.32 to −20.68)	−0.04 (−10.78 to 10.71)	−16.16 (−24.72 to −7.60)	1.22 (−7.70 to 10.15)	−17.38 (−29.75 to −5.02)
Apolipoprotein B, mg/dL	−13.08 (−17.79 to −8.37)	−14.17 (−19.07 to −9.27)	1.09 (−5.66 to 7.83)	−8.72 (−12.73 to −4.70)	1.23 (−2.97 to 5.42)	−9.94 (−15.75 to −4.14)
Lipoprotein(a), U/L[d]	1.15 (0.96 to 1.38)	1.10 (0.91 to 1.34)	1.04 (0.80 to 1.36)	0.67 (0.56 to 0.80)	1.21 (1.00 to 1.47)	0.55 (0.42 to 0.72)
LDL cholesterol/ apolipoprotein B	−0.08 (−0.14 to −0.02)	−0.04 (−0.10 to 0.03)	−0.04 (−0.13 to 0.04)	−0.07 (−0.14 to 0.00)	0.03 (−0.04 to 0.11)	−0.10 (−0.20 to −0.01)
Systolic BP, mm Hg	−8.5 (−11.5 to −5.6)	−6.8 (−9.8 to −3.7)	−1.8 (−6.0 to 2.4)	−1.9 (−6.0 to 2.2)	−4.5 (−8.8 to −0.2)	2.6 (−3.4 to 8.6)
Diastolic BP, mm Hg	−5.2 (−7.5 to −2.9)	−4.0 (−6.4 to −1.6)	−1.2 (−4.5 to 2.1)	−0.5 (−3.8 to 2.7)	−3.0 (−6.4 to 0.4)	2.5 (−2.2 to 7.2)
Pulse, beats/min	−6.3 (−8.9 to −3.6)	−5.5 (−8.4 to −2.7)	−0.7 (−4.6 to 3.1)	−2.0 (−5.5 to 1.5)	−2.6 (−6.4 to 1.1)	0.6 (−4.5 to 5.8)
hs-C-reactive protein, mg/L	−2.27 (−4.17 to −0.37)	−1.36 (−3.34 to 0.62)	−0.91 (−3.62 to 1.81)	1.60 (−0.83 to 4.04)	0.03 (−2.54 to 2.60)	1.57 (−1.97 to 5.11)
Leptin, pg/mL	−16 101.13 (−22 012.77 to −10 189.49)	−19 619.91 (−25 827.97 to −13 411.85)	3518.78 (−4955.76 to 11 993.31)	11 023.49 (−17 925.36 to −4121.62)	−5785.98 (−12 999.16 to 1427.19)	−5237.50 (−15 221.40 to 4746.39)
FGF19, pg/mL	23.46 (−5.73 to 52.65)	4.33 (−26.15 to 34.81)	19.13 (−22.94 to 61.20)	8.95 (−28.64 to 46.53)	−1.18 (−40.49 to 38.13)	10.13 (−44.26 to 64.51)
Creatinine, mg/dL	0.0 (0.0 to 0.1)	0.0 (0.0 to 0.1)	0.0 (−0.1 to 0.0)	0.0 (−0.1 to 0.0)	0.0 (−0.1 to 0.0)	0.0 (−0.1 to 0.0)
Hemoglobin, g/100 mL	−0.19 (−0.38 to 0.00)	−0.27 (−0.46 to −0.07)	0.08 (−0.19 to 0.34)	−0.47 (−0.72 to −0.22)	−0.10 (−0.36 to 0.16)	−0.37 (−0.73 to −0.02)

Abbreviations: BP, blood pressure; FGF19, fibroblast growth factor 19; HDL, high-density lipoprotein; HOMA2%B, Homeostasis Model Assessment estimate of beta-cell function; HOMA2%S, Homeostasis Model Assessment estimate of insulin sensitivity; hs, high sensitivity; LDL, low-density lipoprotein; LED, low-energy diet; RYGB, Roux-en-Y gastric bypass; VLED, very low-energy diet.

SI conversion factors: To convert C-peptide to nmol/L, multiply by 0.331; creatinine to μmol/L, multiply by 88.4; glucose to mmol/L, multiply by 0.0555; HDL, LDL, non-HDL, and total cholesterol to mmol/L, multiply by 0.0259; insulin to pmol/L, multiply by 6.945; triglycerides to mmol/L, multiply by 0.0113.

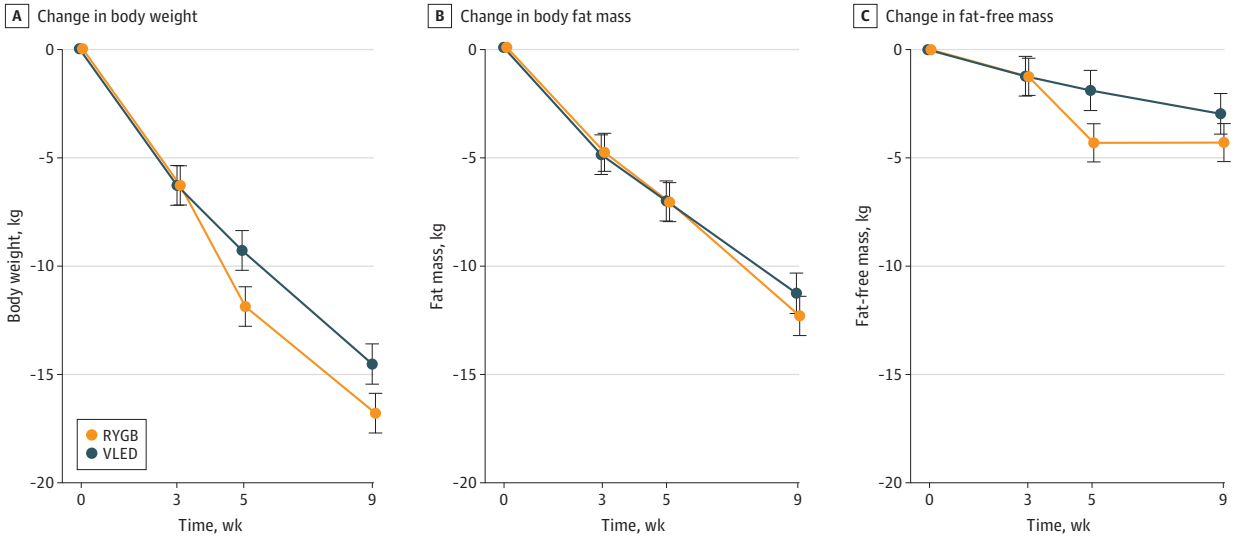
[a] Adjusted means and 95% CI from linear mixed-effects models for repeated measures with baseline covariates; factors for treatment, time, age at baseline, sex, and body mass index; and the treatment × time interaction term. Body mass index is not included for the body weight outcome model.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Calculations of HOMA2%S and HOMA2%B are C-peptide based.

[d] Log-transformed analysis with outputs being geometric mean ratios. For changes between visits, a geometric mean ratio above 1.0 indicates an increase from the previous visit. For comparisons between groups, a geometric mean ratio above 1.0 indicates a smaller value in the VLED group compared with the RYGB group.

Figure 2. Changes in Body Composition During Matching Weight Loss Between the Roux-en-Y Gastric Bypass (RYGB) and Very Low-Energy Diet (VLED) Groups



Mean changes and 95% CIs (error bars) estimated by linear mixed-effects models for repeated measures for study outcomes.

time period, concentrations of HDL cholesterol and fasting triglycerides did not change in either group (Figure 3 and Table 2). Apolipoprotein B values decreased during the 6 weeks after RYGB but were not altered by VLED. The LDL cholesterol/apolipoprotein B ratio was not altered by VLED while it was reduced following RYGB. Lipoprotein(a) decreased after RYGB but was unchanged during VLED. There was no difference in changes between groups in FGF19 values (Table 2).

Changes in Metabolomics (Omics Analysis)

LED (Week 0 to Week 3)

A total of 444 of 1119 plasma lipids identified using omics changed (change >1.5 fold) between week 0 and week 3 (eFigure 1A and eTable 5 in Supplement 1). Both groups showed similar decreases in the ratio of n6:n3 fatty acids (eFigure 2 in Supplement 1). Metabolite changes were similar in both groups with amino acid and xenobiotic-derived metabolites accounting for most of the changes (eFigure 1B and eTable 6 in Supplement 1).

RYGB vs VLED (Week 3 to Week 9)

RYGB led to further lipid and metabolite changes not seen in the VLED group (eFigure 1A-B and eTables 7 and 8 in Supplement 1). Twenty-one additional lipids (2%) decreased after RYGB compared with no further change after VLED (eFigure 1A and eTable 7 in Supplement 1). The ratio of n6:n3 fatty acids continued to decrease after RYGB but not during VLED (eFigure 2 in Supplement 1).

No metabolites reflecting changes in carbohydrate or energy metabolism were altered while changes in cofactor and vitamin metabolism likely reflected decreased absorption. Primary bile acids were significantly increased following RYGB while a number of secondary bile acids were decreased.

Metabolites of phenylalanine, tyrosine, and tryptophan metabolic pathways were altered. Branched chain amino acid metabolites and the lysine metabolite 2-aminoadipic acid were consistently reduced after RYGB but not after VLED (eFigure 1B and eTable 8 in Supplement 1).

Changes in Antihypertensive, Lipid-Lowering, and Antidiabetic Treatment

During the LED period (weeks 0-3), minor changes in antihypertensive, lipid- lowering, and antidiabetic treatments occurred (eTable 9 in Supplement 1). During weeks 3 to 9, there was a small numerical decrease in number of participants treated with antihypertensives, lipid-lowering, and antidiabetic medicines in the RYGB group, whereas no relevant changes were noticed in the VLED group (eTable 9 in Supplement 1).

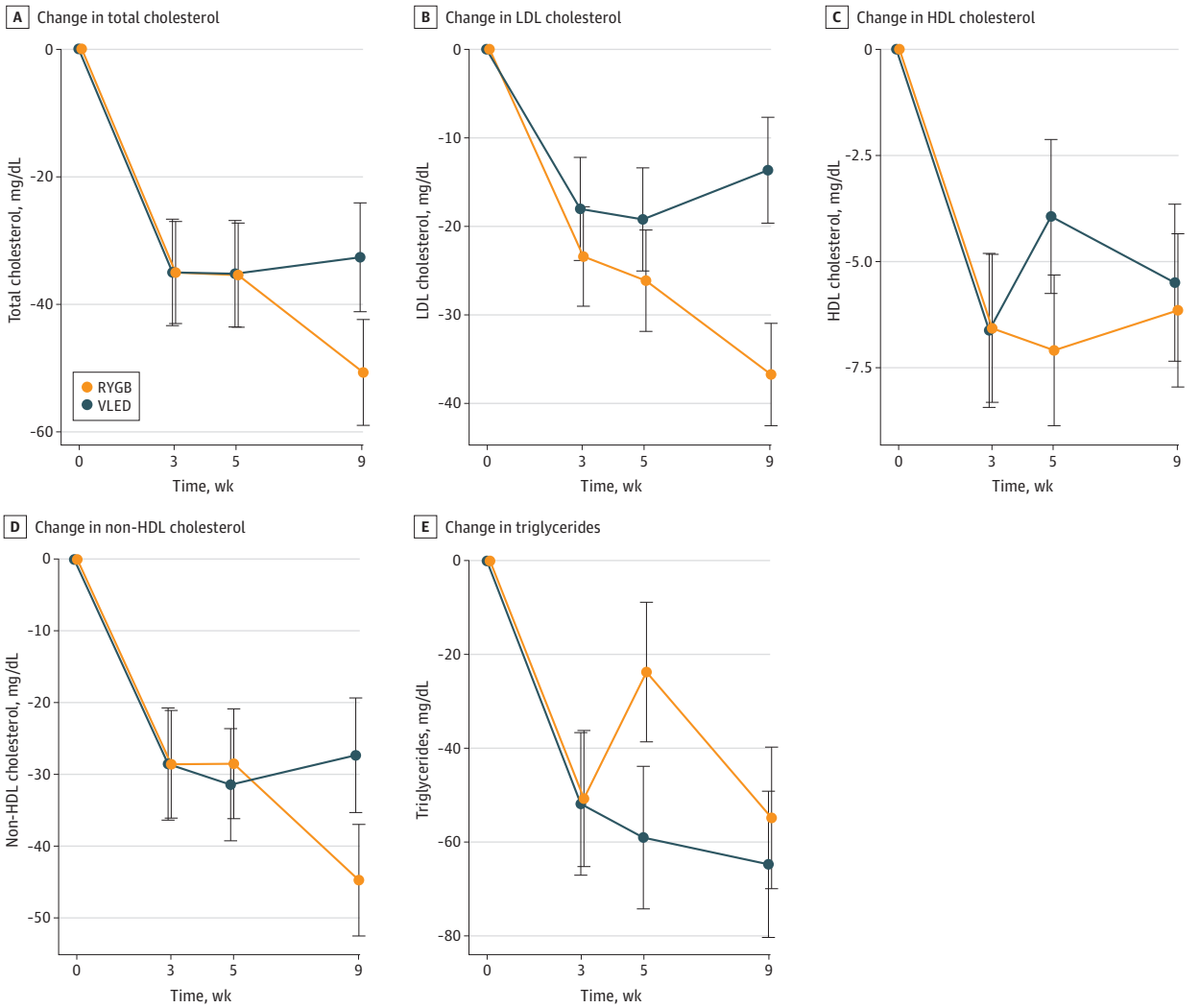
Adverse Events

In the intervention period from week 0 to 9, 12 adverse events occurred in the RYGB group (eTable 10 in Supplement 1).

Discussion

We evaluated whether RYGB had a beneficial impact on cardiovascular risk factors not explained by weight loss or caloric restriction. To reduce bias, all participants underwent an initial 3-week LED,[25] which as expected was associated with comparable improvements of most cardiovascular risk factors across groups. Our key novel findings demonstrated that major atherogenic blood lipids (LDL cholesterol, non-HDL cholesterol, apolipoprotein B, lipoprotein[a]) continued to decrease up to 6 weeks after RYGB in contrast to VLED, despite a

Figure 3. Changes in Blood Lipid Levels During Matching Weight Loss Between the Roux-en-Y Gastric Bypass (RYGB) and Very Low-Energy Diet (VLED) Groups



Mean changes and 95% CIs (error bars) estimated by linear mixed-effects models for repeated measures for study outcomes. HDL indicates high-density lipoprotein; LDL, low-density lipoprotein.

similar fat mass loss. By contrast, both groups improved their HbA_{1c}, with no differences in changes between groups in HbA_{1c}, insulin sensitivity (HOMA2%S), and blood pressure.

The additional LDL cholesterol reduction of approximately 18 mg/dL in the RYGB group is of a magnitude that may reduce the relative risk of cardiovascular disease (CVD) by 8% over 5 years.[26] Furthermore, the LDL cholesterol reduction after RYGB is similar with the effect of ezetimibe (10 mg/d), which may improve cardiovascular outcomes in people with preexisting CVD.[27] The absolute LDL cholesterol decrease in the RYGB group was 36.7 mg/dL, and about half of this effect was surgery specific (17.7 mg/dL). In low-risk populations, a meta-analysis demonstrated that each 1 mmol/L (38.7 mg/dL) reduction in LDL cholesterol produced an absolute reduction in major vascular events of about 11 per 1000 over 5 years.[28] Several studies have addressed the longer-term effects on lipid profile after bariatric surgery, indicating effects are not transient.[29]

Consistent with the RYGB-mediated changes in LDL cholesterol, we also observed concordant changes in apolipoprotein B reflecting the number of potential pro-atherogenic lipoprotein particles in circulation.[30] Another marker of cardiovascular risk is lipoprotein(a),[31] which was reduced by RYGB but not by VLED, indicating that these changes may also contribute to long-term cardiovascular benefit. By contrast, we did not observe any significant changes in HDL cholesterol or triglyceride levels during the 6-week period in either group, but the sample size was too low to observe any smaller changes.

The results of our study add evidence to the work by Yoshini et al,[17] which showed that in patients with obesity and type 2 diabetes, the glucometabolic benefits of RYGB were mainly explained by weight loss. While different study designs make it difficult to compare results, our 6-week matching weight loss study of patients with normal glucose tolerance, prediabetes, or type 2 diabetes did not show differences

between RYGB and VLED on various measures of insulin sensitivity and glucose metabolism. Similar caloric intake and rate of weight loss between groups in our study facilitates interpretation of results. Increased fasting hepatic insulin clearance was demonstrated in both groups,[32,33] and HOMA2%S and HOMA2%B, calculated with both insulin and C-peptide, had similar outcome.

Body fat loss was similar between groups, whereas a slightly larger weight loss occurred during the first 2 weeks after RYGB (week 3-5). The rate of weight loss was thereafter similar between groups (week 5-9). A larger loss of fat-free mass occurred during the first 2 weeks after surgery, numerically almost identical to the loss of body weight in the RYGB group during the same period. From the analyses conducted, it cannot be concluded which components of fat-free mass are affected, but there are reports on early effects on water and muscle loss after RYGB.[34,35] Decreased hydration has been reported after RYGB, and increased diuresis is commonly observed after severe calorie restriction.[36,37]

Metabolomics analysis demonstrated a broad reduction in the amount of circulating lipids during the initial 3-week LED period, while there were few further changes after RYGB. The n6:n3 omega fatty acid ratio has received attention as a marker of CVD. While the ratio was modestly decreased by LED, progression to VLED did not demonstrate a further reduction in contrast to RYGB, which further reduced the ratio. The change was not due to a change in diet, and we propose that the absorption of fatty acids may be affected as previously suggested after RYGB.[38] Decreased total and LDL cholesterol following RYGB was accompanied by increased circulating levels of primary bile acids and decreases in some secondary bile acids. In addition to their role in lipid absorption, bile acids regulate a number of processes via FXR and TGR5 receptors.[39] Bile acids are subject to feedback regulation between the gut and the liver via FGF19; however, no change was observed following RYGB. Other metabolic changes affected amino acid metabolism, in particular, aromatic amino acid metabolites that are believed to be predominantly microbiota derived. Increases in the phenylalanine metabolites phenylacetate and 4-hydroxyphenylacetate and the tyrosine metabolite phenol sulfate are likely microbiota derived. Serum tryptophan levels are reduced as are tryptophan metabolites indole-lactate, kynurenate, and xanthurenate. In contrast, microbiota derived 3-indoxylsulphate was increased. Whether these changes reflect changes in the gut microflora after RYGB remains to be determined. Reduction in the lysine metabolite aminoadipic acid is noteworthy because of its association with diabetes risk.[40] Future follow-up will allow assessment of long-term diabetes risk and progression.

Limitations

Our study has limitations. First, treatment allocation was not randomized, so confounding differences between groups cannot be excluded. However, the analyses were adjusted for baseline age, sex, and BMI. Second, the study was conducted at a single center, and the majority of patients were White, which may impact the generalizability of the study. Third, measures of glucose homeostasis did not include gold standard methods. Fourth, the matching weight loss was assessed over 6 weeks, and additional effects may be seen after a longer treatment period. Fifth, a large number of comparisons were performed without any adjustment for multiplicity, which leads to an increased risk of false-positive findings. Despite these limitations, to our knowledge, this study is the longest and largest study conducted with a matching weight loss between RYGB and diet over the same period of time and with similar energy intake between groups.

Conclusions

Key novel findings from our study demonstrate that major atherogenic blood lipids (LDL cholesterol, non-HDL cholesterol, apolipoprotein B, lipoprotein[a]) were reduced at 6 weeks after RYGB but remained stable after VLED despite a similar fat mass loss. By contrast, both groups improved in HbA_{1c}, with no differences in changes between groups in HbA_{1c}, insulin sensitivity (HOMA2%S), and blood pressure. Major metabolic improvements were seen in both groups already during the initial 3-week LED period.

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Acquisition, analysis, or interpretation of data: Karlsson, Johnson, Greasley, Retterstøl, Hedberg, Hall, Hawker, Robertsen, Havsol, Hertel, Skovlund, Olsen, Jansson-Löfmark, Åsberg, Hjelmesæth.
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Supervision: Karlsson, Johnson, Retterstøl, Hertel, Sandbu, Åsberg, Hjelmesæth.

Conflict of Interest Disclosures: Dr Karlsson reported holding stocks in AstraZeneca. Dr Greasley reported holding stocks in AstraZeneca. Dr Retterstøl reported personal fees from Amgen, Novo Nordisk, and Sanofi and grants from the Throne Holst Nutrition Research Foundation and South-Eastern Norway Regional Health Authority outside the submitted work. Dr Hedberg reported holding stocks in AstraZeneca. Dr Havsol reported holding stocks in AstraZeneca. Dr Jansson-Löfmark reported holding stocks in AstraZeneca. Dr Andersson reported holding stocks in AstraZeneca. Dr Åsberg reported grants from the Norwegian Research Council during the conduct of the study and payments to their institution from AstraZeneca and Orifarm for research activities in other therapeutic areas than relevant for the present publication. No other disclosures were reported.

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Invited Commentary

Gastric Bypass vs Diet—The Need for Contemporary Comparisons

Leah J. Schoel, MD; Dana A. Telem, MD, MPH

It is well demonstrated that weight loss surgery, such as Roux-en-Y gastric bypass (RYGB), has long-term benefits for hypertension, type 2 diabetes, and dyslipidemia.[1-4] Whether these benefits are secondary to the surgical procedure itself, weight loss alone, or some combination of both, remains unclear.[5,6] To answer this question, Karlsson et al[7] performed a nonrandomized controlled study at a tertiary care obesity center to determine whether the cardiovascular benefits following RYGB were independent of caloric restriction and weight loss.

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The study consisted of 2 nonrandomized cohorts: RYGB followed by very low-energy diet (VLED) vs VLED alone. Study duration was 9 weeks total: 3 weeks of low-energy diet (LED), with the intervention occurring at week 3 and following to week 9. LED was defined as less than 1200 kcal/d, and VLED was less than 800 kcal/d. Cardiovascular risk factors were assessed at week 0, week 3 (after completing 3 weeks of LED), week 5 (2 weeks after RYGB/start of VLED), and week 9 (6 weeks after RYGB/start of VLED). Demographics and clinical characteristics were comparable, except for a slightly higher body mass index in the RYGB cohort.

Despite similar fat mass loss, major atherogenic blood lipids (low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, apolipoprotein B, lipoprotein[a]) were reduced after RYGB and were stable or increased after VLED alone. Interestingly, greatest between-group differences occurred in the first 2 weeks following RYGB, with the cohorts demonstrating parallel improvements in the subsequent 4 weeks. While there was a small decrease in participants treated with medications for hypertension and diabetes in the RYGB cohort, no medication changes were made in the VLED cohort. This is notable because no clinical differences in blood pressure or glycemic control were observed between cohorts; thus, the medication changes may result from the study's nonrandomized and nonblinded design.

Overall, this study compared RYGB to a restrictive diet to evaluate cardiovascular benefits following RYGB. While impressive, one is left wondering about the relevance of