Physical Activity Improves Lipid and Weight-Loss Outcomes After Metabolic Bariatric Surgery in Adolescents with Severe Obesity

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Objective: This study tested the hypothesis that physical activity improves cardiovascular disease–related lipids beyond that associated with weight loss in adolescents with severe obesity after metabolic/bariatric surgery (MBS).

Methods: Objective activity monitor data from 108 participants of the Teen Longitudinal Assessment of Bariatric Surgery (Teen-LABS) study from baseline to 3 years post MBS were used. Primary outcomes included absolute change in LDL cholesterol (LDL-C) and non-HDL cholesterol (non-HDL-C) from baseline. Baseline measurement, visit, surgical procedure, and percent change in iliac waist circumference or BMI from baseline in linear regression models were adjusted for use of generalized estimating equations. PROC TRAJ in SAS generated optimal activity trajectories based on individual step count.

Results: Despite low step counts and slow cadence, differences by activity trajectory were found. Greater absolute decreases in LDL-C and non-HDL-C (−15 mg/dL [95% CI: −28 to −2], \( P = 0.026 \); and −15 mg/dL [95% CI: −28 to −1], \( P = 0.035 \)), respectively, were associated with more activity. More activity was associated with greater resolution of triglycerides, LDL-C, and non-HDL-C dyslipidemia and with greater weight loss 3 years post MBS.

Conclusions: More activity in adolescents was associated with improvements in cardiovascular disease–related lipid measures and weight loss after MBS.

Introduction

Severe obesity has long been recognized to increase cardiovascular disease (CVD) risk in adults and adolescents (1-3). Poor cardiovascular health is strongly associated with obesity (4), and cardiovascular health has been demonstrated to decrease with obesity severity (4,5). The prevalence of severe obesity in childhood and adolescence, defined as ≥ 120% of the 95th percentile of BMI for sex and age, continues to rise and now impacts millions of youth (6). Obesity in adolescence tracks into adulthood, increasing the risk of cardiometabolic morbidity 15-fold (7). Dyslipidemia in adolescence also predicts CVD risk in adulthood, particularly high LDL cholesterol (LDL-C) and non-HDL cholesterol (non-HDL-C) (3). Both obesity and dyslipidemia have been identified as important treatment targets in childhood and adolescence for the reduction of lifelong CVD risk, and metabolic/bariatric surgery (MBS) has been demonstrated to effectively treat severe obesity and improve dyslipidemia in adolescents (3,8).

Physical activity (PA) also improves lipid levels, reduces CVD risk, and supports weight-loss maintenance. However, PA participation wanes in adolescence (9,10). At age 18, daily step counts of 8,000 to 9,000 steps per day at a moderate cadence of > 87 steps per minute have been reported in adolescents with a healthy weight (11,12). Severe obesity is associated with approximately 50% fewer steps per day, slower cadence, and more sedentary time (13,14). Assessments of PA in adolescents with severe obesity, before and after MBS, are sparse and

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largely based on self-report, which has been repeatedly shown to poorly estimate actual PA (15,16). PA participation and its potential to further improve lipid measures after MBS have been examined in adults but not in adolescents (17).

This evaluation examined the influence of PA on lipid changes in adolescents with severe obesity from baseline to 3 years after MBS. We hypothesized that objectively measured PA would be positively associated with improvement in lipid measures. Study participants were enrolled in the Teen Longitudinal Assessment of Bariatric Surgery (Teen-LABS) study, which collected longitudinal, prospective, and observational clinical and laboratory data in adolescents undergoing MBS at five centers in the United States.

Methods

Design
This analysis was designed to examine associations between objectively measured PA and changes in lipid measures before and after MBS (Roux-en-Y gastric bypass [RYGB], n = 92, and vertical sleeve gastrectomy [VSG], n = 16) in adolescents. PA was defined by daily step counts and cadence (steps per minute). Moderate activity was defined as a cadence > 80 steps per minute, as described by King et al. (18). The methods used for data collection have been previously described (19). The original protocol and data and safety monitoring plans were approved by the institutional review board at each of the five participating institutions and by a data and safety monitoring board. All participants and/or their legally authorized representatives provided written informed consent. The analysis plan was also reviewed and approved by the Institutional Review Board at the University of Colorado, Anschutz Medical Campus.

Participants
Adolescents with severe obesity who participated in the Teen-LABS study, received MBS (VSG or RYGB), and completed objective measurements of PA were included (19). More specifically, for inclusion in the analyses, participants had (1) StepWatch (CYMA Corp., Mountlake Terrace, Washington) activity data for a minimum of 3 days (two weekdays and one weekend day), (2) at least 6 hours with at least 10 steps per hour per day of recorded data, (3) data collection at baseline and at least one postoperative time point (6 months, 1 year, 2 years, or 3 years), (4) time-point–matched laboratory and anthropometric data, and (5) no lipid-lowering medications. Original, objectively measured Teen-LABS data were used for all analyses. No significant differences were noted in demographics or baseline outcomes between the included and the excluded participant groups.

Outcomes of interest
The primary outcome of interest was change in lipid measures of cardiovascular risk, primarily non-HDL-C and LDL-C (calculated using the Friedewald equation) and, secondarily, HDL-C, plasma total cholesterol, and triglycerides (TG). The clinical significance of the changes in lipid measures was also examined as percent resolution of dyslipidemia, defined as a change in individual lipid measures from outside of the acceptable range at baseline to acceptable range at 1 and 2 years based on 2011 guidelines from the National Heart, Lung, and Blood Institute (20). Additional secondary outcomes included weight change as iliac waist circumference (IWC) and BMI.

Activity trajectory membership was the independent variable of interest, and covariates chosen a priori included sex, race, visit, and surgical procedure.

Statistical analysis
The SAS version 9.4 PROC TRAJ (SAS Institute Inc., Cary, North Carolina) procedure was used for latent class modeling to separate participants by categorical activity trajectories using the average step count data for a visit. The optimal model was identified based on the process described by Andruff et al. (21) to select the number of categorical activity trajectories and their respective shape (e.g., linear vs. quadratic). Based on this optimal model, two categories were identified that we labeled as “less active” (LA) and “more active” (MA), which were linear and quadratic in shape, respectively. The probability of group trajectory membership for each individual was determined from the individual’s trajectory of average step counts across all available time points. The analyses examined lipid and anthropometric outcomes by time periods of clinical relevance, including baseline to 1 year as a period of active weight loss and baseline to 2 years and 3 years as periods of relative weight-loss maintenance.

Descriptive summaries included mean and SD for continuous measures and count and percent of total for discrete measures. Baseline comparisons between activity categories were made using two-sample t tests for continuous outcomes and two-sample tests of proportions for dichotomous outcomes. TG values were log-transformed.

Analysis of change in outcomes by trajectory categories used linear regression with generalized estimating equations, assuming an exchangeable working correlation structure to account for the longitudinal, correlated nature of our data to estimate the change from baseline to a measured period of time or visit. Change in lipid outcomes from baseline were fit, adjusting for percent change from baseline to a given visit for both IWC and BMI as independent covariates of weight loss to examine the impact of general obesity as BMI and central obesity as IWC. The model also potentially included covariates for baseline lipid values, sex, surgical procedure type, race and/or ethnicity (white, non-Hispanic vs. all others), PA trajectory group, study visit indicator, and the interaction between trajectory and visit indicator. To improve interpretability, reduced models were created by iteratively removing sex or race if the adjusted $P > 0.1$, and the model was refit before evaluating significance of the remaining covariate. Additionally, the interaction was removed if the adjusted $P > 0.05$. Similar models were fit for change in central adiposity measure but with percent change in the covariate excluded from the model. Graphs were created to illustrate individual and activity category trajectories, plotting average step count over time from baseline to specified visits and changes in lipid and anthropometric measures of interest over time as well. SAS version 9.4 was used for identifying trajectories, and R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria) was used for all other analyses and figures.

Results

Participants
Of the 242 adolescents enrolled in the Teen-LABS study, 125 provided PA data generated from wearing a StepWatch activity monitor. Of the 125 participants with objective PA data, 108 met criteria for inclusion in these analyses, with 14 classified as MA (mean probability of
97.8%) and 94 as LA (mean probability 99.2%). The baseline characteristics of the study participants are presented in Table 1. In this analysis of 108 participants, 77% were female, 75% were white, and 11% were Hispanic. The baseline mean (SD) age was 17.0 (1.6) years. The baseline mean (SD) BMI was 54.3 (9.9) kg/m², and mean IWC by horizontal iliac crest measurement was 149.6 (17.3) cm. Baseline mean plasma total cholesterol was 161 (31) mg/dL, LDL-C was 95 (28) mg/dL, non-HDL-C was 122 (31) mg/dL, logTG was 5 (1) mg/dL, and HDL-C was 39 (9.5) mg/dL. When the cohort was examined by activity trajectory, MA versus LA, there were no significant differences in baseline lipid values, race and/or ethnicity, or surgical procedure (Table 2).

The MA trajectory average daily step count was >6,000 average steps at baseline and increased to >9,000 at 2 years. The LA trajectory was characterized by a stable daily step count of <4,000 steps from baseline to 3 years (Figure 1). Although average daily step counts of all participants increased steadily over time, there were differences noted by sex (Table 3). Cadence was consistent at all time points, with no participant recording more than 4 minutes of moderate activity cadence per day (>80 steps/minute).

### Primary outcome

The MA trajectory was associated with a significantly greater absolute decrease in non-HDL-C (−15 mg/dL, 95% CI: −28 to −1; \( P=0.035 \)), adjusting for baseline non-HDL-C, time, percent change in IWC, and procedure (Table 4). Similarly, a greater absolute decrease in LDL-C was associated with the MA trajectory, adjusting for baseline LDL-C, time, procedure, and for either percent change in IWC (−15 mg/dL, 95% CI: −28 to −2; \( P=0.026 \)) or percent change in BMI (−13 mg/dL, 95% CI: −26 to 0; \( P=0.044 \)). In the same models, RYGB surgical procedure was associated with an additional absolute change of −19 mg/dL in measured non-HDL-C (95% CI: −5 to −33; \( P=0.007 \)) and a change of −15 mg/dL in calculated LDL-C (95% CI: −2 to −28; \( P=0.019 \)) over the VSG procedure (Table 4).
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Trajectories illustrating individual and activity trajectory mean longitudinal change in non-HDL-C and LDL-C by procedure are shown in Figure 2.

Secondary outcomes

HDL-C increased in association with both activity trajectories throughout active weight loss, from baseline to 1 year, and throughout weight-loss maintenance to 3 years ($P<0.001$ for both models) in association with time and percent change in BMI. Female sex was associated with an additional mean absolute HDL-C increase of 3.9 mg/dL (95% CI: 0.3-7.5; $P=0.033$) or 4.4 mg/dL (95% CI: 0.7-8.1; $P=0.021$) after adjusting for percent change in IWC or percent change in BMI, respectively. Surgical procedure (RYGB vs. VSG) did not appear to influence improvement in HDL-C ($P>0.6$ for both models).

Trajectories illustrating individual and activity trajectory mean longitudinal change in HDL-C and TG by procedure are also shown in Figure 2. Improvement in TG was not associated with activity trajectory ($P>0.2$ for all models) but was strongly associated with the active weight-loss period from baseline to 1 year ($P<0.001$ for both models), indicating that the predicted additional decrease of 0.22 to 0.25 in log TG value in year 1 was largely influenced by
weight loss. The influence of change in BMI on log TG was significant ($P = 0.041$), as indicated by a decrease of 0.01 in log TG value for every 1% decrease in BMI.

Of clinical significance, a greater percentage of elevated measures of non-HDL-C, LDL-C, and TG converted to acceptable values in association with the MA trajectory over time compared with the LA trajectory. This was based on the 2011 Integrated Guidelines (20) (Table 5). Overall, the conversion of elevated lipid measures to acceptable lipid values occurred more often with MA trajectory membership compared with the LA trajectory membership.

Importantly, the MA trajectory was also associated with an 11% greater reduction in BMI at 3 years compared with the LA trajectory (95% CI: 0.2% to 22%; $P = 0.046$). White, non-Hispanic race was also more likely to experience weight loss, with an average 7% greater reduction in BMI (95% CI: 4% to 11%; $P < 0.001$; BMI and central adiposity regression tables not shown).

### TABLE 4 Absolute change in lipid outcomes from baseline regression output with percent change in IWC or BMI as adiposity measure

| IWC | Coefficient (95% CI) | $P$ value | BMI | Coefficient (95% CI) | $P$ value |
|-----|----------------------|-----------|-----|----------------------|-----------|
| **Outcome: log (TG)** | | | **Outcome: log (TG)** | | |
| Intercept | $1.91 (1.22 to 2.59)$ | $<0.001$ | Intercept | $2.09 (1.41 to 2.78)$ | $<0.001$ |
| Baseline log (TG) | $-0.48 (-0.62 to -0.34)$ | $<0.001$ | Baseline log (TG) | $-0.50 (-0.64 to -0.35)$ | $<0.001$ |
| White, non-Hispanic (vs. “Other”) | $0.16 (0.04 to 0.27)$ | 0.007 | White, non-Hispanic (vs. “Other”) | $0.20 (0.08 to 0.32)$ | $<0.001$ |
| %Ad change from baseline | $0.01 (0.00 to 0.01)$ | 0.255 | %Ad change from baseline | $0.01 (0.00 to 0.02)$ | 0.041 |
| MA (vs. LA) | $-0.10 (-0.27 to 0.06)$ | 0.224 | MA (vs. LA) | $-0.09 (-0.25 to 0.07)$ | 0.282 |
| Baseline to 1 year | $-0.25 (-0.34 to -0.16)$ | $<0.001$ | Baseline to 1 year | $-0.22 (-0.31 to -0.14)$ | $<0.001$ |
| Baseline to 2 years | $-0.07 (-0.21 to 0.07)$ | 0.327 | Baseline to 2 years | $-0.09 (-0.22 to 0.05)$ | 0.222 |
| Baseline to 3 years | $-0.12 (-0.37 to 0.13)$ | 0.343 | Baseline to 3 years | $-0.15 (-0.39 to 0.10)$ | 0.237 |
| VSG procedure (vs. RYGB) | $0.11 (-0.08 to 0.30)$ | 0.266 | VSG procedure (vs. RYGB) | $0.09 (-0.10 to 0.29)$ | 0.337 |
| **Outcome: HDL-C (mg/dL)** | | | **Outcome: HDL-C (mg/dL)** | | |
| Intercept | $16.51 (5.88 to 27.14)$ | 0.002 | Intercept | $12.55 (3.01 to 22.09)$ | 0.010 |
| Baseline HDL-C | $-0.28 (-0.54 to -0.03)$ | 0.026 | Baseline HDL-C | $-0.23 (-0.47 to 0.01)$ | 0.056 |
| White, non-Hispanic (vs. “Other”) | $-3.93 (-7.54 to -0.31)$ | 0.033 | White, non-Hispanic (vs. “Other”) | $-4.37 (-8.10 to -0.65)$ | 0.021 |
| Male | $-3.14 (-6.45 to 0.16)$ | 0.062 | Male | $-3.21 (-6.43 to 0.01)$ | 0.050 |
| %Ad change from baseline | $-0.17 (-0.39 to 0.06)$ | 0.152 | %Ad change from baseline | $-0.22 (-0.38 to -0.06)$ | 0.009 |
| MA (vs. LA) | $1.51 (-3.63 to 6.64)$ | 0.565 | MA (vs. LA) | $0.39 (-4.71 to 5.49)$ | 0.881 |
| Baseline to 1 year | $6.17 (4.24 to 8.11)$ | $<0.001$ | Baseline to 1 year | $5.10 (2.97 to 7.22)$ | $<0.001$ |
| Baseline to 2 years | $9.83 (7.06 to 12.60)$ | $<0.001$ | Baseline to 2 years | $9.45 (6.64 to 12.25)$ | $<0.001$ |
| Baseline to 3 years | $7.31 (5.53 to 11.08)$ | $<0.001$ | Baseline to 3 years | $7.34 (3.67 to 11.01)$ | $<0.001$ |
| VSG procedure (vs. RYGB) | $-0.64 (-4.84 to 3.56)$ | 0.765 | VSG procedure (vs. RYGB) | $-1.00 (-5.26 to 3.26)$ | 0.645 |
| **Outcome: non-HDL-C (mg/dL)** | | | **Outcome: non-HDL-C (mg/dL)** | | |
| Intercept | $44.39 (22.52 to 66.26)$ | $<0.001$ | Intercept | $51.78 (29.42 to 74.13)$ | $<0.001$ |
| Baseline non-HDL-C | $-0.43 (-0.57 to -0.29)$ | $<0.001$ | Baseline non-HDL-C | $-0.42 (-0.56 to -0.28)$ | $<0.001$ |
| %Ad change from baseline | $0.52 (-0.08 to 1.12)$ | 0.092 | %Ad change from baseline | $0.69 (0.21 to 1.18)$ | 0.005 |
| MA (vs. LA) | $-14.62 (-28.18 to -1.06)$ | 0.035 | MA (vs. LA) | $-12.78 (-26.07 to 0.51)$ | 0.059 |
| Baseline to 1 year | $-7.76 (-12.78 to -2.75)$ | 0.002 | Baseline to 1 year | $-6.19 (-11.19 to -1.18)$ | 0.015 |
| Baseline to 2 years | $-4.02 (-12.01 to 3.96)$ | 0.323 | Baseline to 2 years | $-3.44 (-10.77 to 3.89)$ | 0.358 |
| Baseline to 3 years | $-3.45 (-17.05 to 10.15)$ | 0.619 | Baseline to 3 years | $-3.98 (-17.90 to 9.95)$ | 0.576 |
| VSG procedure (vs. RYGB) | $19.36 (5.30 to 33.42)$ | 0.007 | VSG procedure (vs. RYGB) | $19.33 (5.13 to 33.54)$ | 0.008 |
| **Outcome: LDL-C (mg/dL)** | | | **Outcome: LDL-C (mg/dL)** | | |
| Intercept | $41.37 (23.48 to 59.26)$ | $<0.001$ | Intercept | $47.24 (29.21 to 65.26)$ | $<0.001$ |
| Baseline LDL-C | $-0.43 (-0.59 to -0.27)$ | $<0.001$ | Baseline LDL-C | $-0.42 (-0.56 to -0.28)$ | $<0.001$ |
| %Ad change from baseline | $0.53 (-0.08 to 1.12)$ | 0.092 | %Ad change from baseline | $0.69 (0.21 to 1.18)$ | 0.005 |
| MA (vs. LA) | $-14.83 (-27.88 to -1.78)$ | 0.026 | MA (vs. LA) | $-13.26 (-26.14 to -0.38)$ | 0.044 |
| Baseline to 1 year | $-3.32 (-8.18 to 1.53)$ | 0.180 | Baseline to 1 year | $-2.04 (-6.80 to 2.72)$ | 0.401 |
| Baseline to 2 years | $-2.46 (-9.30 to 4.38)$ | 0.481 | Baseline to 2 years | $-1.34 (-7.69 to 5.00)$ | 0.679 |
| Baseline to 3 years | $-3.76 (-14.64 to 7.12)$ | 0.498 | Baseline to 3 years | $-4.10 (-15.40 to 7.19)$ | 0.476 |
| VSG procedure (vs. RYGB) | $15.12 (2.39 to 27.86)$ | 0.020 | VSG procedure (vs. RYGB) | $15.27 (2.48 to 28.05)$ | 0.019 |

%Ad, percent change in adiposity measure.
Discussion

These results demonstrate that, using objectively measured PA, a relationship between PA and improvement in lipid status beyond weight loss after MBS in adolescents with severe obesity was demonstrated. As has been previously reported after MBS in adults, PA was low (22); it was well below the equivalent of the recommended 60 min/d of moderate to vigorous PA in adolescence (23), 30 minutes of moderate to vigorous PA on at least 5 d/wk for adults, or the typical 8,000 to 9,000 steps per day at a moderate cadence (11,23). Additionally, cadence was too low to be considered moderate activity, with fewer than 4 minutes of high step counts recorded by all participants. Yet despite overall low step counts and slow cadence, objectively measured PA after MBS was associated with greater improvement in absolute change in LDL-C, adjusting for baseline lipid values, percent BMI change, and procedure. PA was also associated with greater improvement in non-HDL-C, accounting for baseline lipid values, surgical procedure, and either percent BMI change or percent IWC change. Also, membership in the MA trajectory effectively doubled the percentage of participants with resolution of dyslipidemia at 2 years, as indicated by the return to acceptable values of LDL-C, non-HDL-C, and TG (20). In contrast, <9% of LDL-C, non-HDL-C, and TG dyslipidemia resolved from baseline to 2 years in association with the LA trajectory. Importantly, by 36 months post MBS, these results demonstrated a normalization of dyslipidemia in participants within the MA trajectory category. Of particular interest, our study did not find that activity was associated with longitudinal increases in HDL-C or clinical remission of HDL-C dyslipidemia, as has been previously reported in adults (22). We found that HDL-C increased from baseline to 2 years post MBS in association with time, suggesting the improvement in HDL-C at each time point was related to the impact of MBS rather than PA. Additionally, the association of increased PA with greater weight loss and improved weight-loss maintenance post MBS suggests the possibility of an expected causal relationship. Although supported by previously published reports in adults (24), this cannot be confirmed without future studies designed to measure these effects in adolescents. The MA trajectory was associated with an 11% greater decrease in BMI at 3 years, extending well beyond the period of active weight loss from baseline to 12 months. The unexpected finding that RYGB may influence a larger reduction in non-HDL-C and LDL-C over VSG is worthy of further examination and confirmation, as the VSG participants were few. PA-associated improvements in lipid outcomes persisted even when adjusted for percent change in BMI.

An augmented activity-associated decrease in CVD-related lipid values and greater long-term weight loss after MBS in adolescents likely predict better long-term outcomes and improved cardiometabolic status.
This is important because CVD is strongly associated with dyslipidemia and BMI (7,25). Improved lipid measures and clinical remission of dyslipidemia in association with weight loss after MBS have previously been reported in adults and adolescents (8,24,26-28). Although percent BMI change was the primary contributor to improvements in LDL-C, non-HDL-C, HDL-C, and TG after MBS, PA was associated with further decrease in CVD-related lipids, LDL-C, and non-HDL-C. Likewise, clinical dyslipidemia was reported to resolve in 66% of adolescents post MBS (29). In this analysis, more activity was associated with almost complete resolution of dyslipidemia. While both PA and MBS were reported to increase HDL-C (30), our study found that PA was not associated with an increase in HDL-C. It may be that the low step counts and slow cadence of the population were insufficient to increase HDL-C. This is worthy of future exploration in adolescents with severe obesity.

PA has also been previously shown to support weight loss and weight-loss maintenance resulting from both lifestyle modification and MBS in adults (31); however, self-reported PA did not distinguish maintainers from those who failed to maintain weight loss in adolescents after MBS (15). By examining objectively measured activity data, our study demonstrated that more objectively measured PA was associated with greater weight loss in the weight-maintenance period from 1 to 3 years, well beyond the period of active weight loss at year 1.

These results are unique and highlight the value of PA to modify cardiometabolic risk and improve individual long-term outcomes as an adjunct therapy to MBS in adolescents with severe obesity. These study results are strengthened by the longitudinal study design, the use of an objective PA measure, and the analysis of individual longitudinal activity trajectories rather than medians or group means, accounting for sex, race, procedure, baseline data, and percent change in BMI or IWC. There are limitations to be considered as well, including limited PA participation among the population of adolescents with severe obesity, fewer VSG participants, limited StepWatch data available from the Teen-LABS participants, and limitation of recording steps and cadence with StepWatch. Participant self-selection may have influenced the participation with step data collection and continued participation over time. Also, individual dietary intake was not available in the Teen-LABS data set, although dietary instructions before and after MBS were consistent for all of the participants.

In summary, in adolescents with severe obesity, PA appears to further reduce lipid-related CVD risk and support long-term weight-loss maintenance after MBS. As such, PA support should be included as an integral part of the chronic care plan for all adolescents undergoing MBS. Further research is needed to determine best practices and strategies to modify PA behavior among adolescents with severe obesity. Additionally, a better understanding of the frequency, intensity, and duration of PA needed before and after MBS is needed to modify specific lipid and weight-maintenance outcomes longitudinally in adolescents and adults. Additional study is needed to confirm the potential influence of surgical procedure type in the reduction of CVD-related LDL-C and non-HDL-C and weight maintenance.

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