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Clinical Practice Guideline Systematic Review

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Weight Loss and Serum Lipids in Overweight and Obese Adults: A Systematic Review and Meta-Analysis

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Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; BPD, biliopancreatic diversion; CVD, cardiovascular disease; FDA, US Food and Drug Administration; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RCT, randomized controlled trial; RYGB, Roux-en-Y gastric bypass; TC, total cholesterol; TGs, triglycerides; T2DM, type 2 diabetes mellitus.

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Abstract

Background: Excess adipose tissue is associated with an abnormal lipid profile that may improve with weight reduction. In this meta-analysis, we aimed to estimate the magnitude of change in lipid parameters associated with weight loss in adults who are overweight or obese.

Methods: We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Scopus from 2013 to September, 2018. We included randomized controlled trials (RCTs) that evaluated interventions to treat adult obesity (lifestyle, pharmacologic and surgical) with follow-up of 6 months or more.

Results: We included 73 RCTs with moderate-to-low risk of bias, enrolling 32 496 patients (mean age, 48.1 years; weight, 101.6 kg; and body mass index [BMI], 36.3 kg/m^2). Lifestyle interventions (diet, exercise, or both), pharmacotherapy, and bariatric surgery were associated with reduced triglyceride (TG) and low-density lipoprotein cholesterol (LDL-C) concentrations and increased high-density lipoprotein cholesterol (HDL-C) at 6 and 12 months. The following data are for changes in lipid parameters after 12 months of the intervention with 95% CI. Following lifestyle interventions, per 1 kg of weight lost, TGs were reduced by –4.0 mg/dL (95% CI, –5.24 to –2.77 mg/dL), LDL-C was reduced by –1.28 mg/dL (95% CI, –2.19 to –0.37 mg/dL), and HDL-C increased by 0.46 mg/dL (95%

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CI, 0.20 to 0.71 mg/dL). Following pharmacologic interventions, per 1 kg of weight lost, TGs were reduced by –1.25 mg/dL (95% CI, –2.94 to 0.43 mg/dL), LDL-C was reduced by –1.67 mg/dL (95% CI, –2.28 to –1.06 mg/dL), and HDL-C increased by 0.37 mg/dL (95% CI, 0.23 to 0.52 mg/dL). Following bariatric surgery, per 1 kg of weight lost, TGs were reduced by –2.47 mg/dL (95% CI, –3.14 to –1.80 mg/dL), LDL-C was reduced by –0.33 mg/dL (95% CI, –0.77 to 0.10 mg/dL), and HDL-C increased by 0.42 mg/dL (95% CI, 0.37 to 0.47 mg/dL). Low-carbohydrate diets resulted in reductions in TGs and increases in HDL-C, whereas low-fat diets resulted in reductions in TGs and LDL-C and increases in HDL-C. Results were consistent across malabsorptive and restrictive surgery.

Conclusions: Weight loss in adults is associated with statistically significant changes in serum lipids. The reported magnitude of improvement can help in setting expectations, inform shared decision making, and facilitate counseling.

Freeform/Key Words: weight loss, serum lipids, obesity, systematic review, meta-analysis

The incidence of obesity among men and women in the United States and globally continues to rise (1) and is associated with various health comorbidities (2, 3), including cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), and dyslipidemia (4-6). In people with obesity, the lipid profile is atherogenic, characterized by elevated triglycerides (TGs), low high-density lipoprotein cholesterol (HDL-C), and small, dense low-density lipoprotein cholesterol (LDL-C). Increased visceral fat is associated with insulin resistance, and many patients fit the criteria for metabolic syndrome (7).

Various guidelines recommend weight loss in people with obesity as a means of reducing CVD risk and dyslipidemia. The 2019 Report of the American College of Cardiology/American Heart Association (ACC/AHA) on the management of blood cholesterol recommends lifestyle therapy as a means of preventing atherosclerotic cardiovascular disease (ASCVD), including a healthy diet, with reduced calories for those who are overweight or have obesity (8).

The US Preventive Services Task Force recommends screening all adults for obesity and offering and referring patients with a body mass index (BMI) of 30 kg/m^2 or higher, to intensive, multicomponent behavioral interventions (9). Strong evidence supports effectiveness in weight loss and CVD prevention from several types of diets (low fat and low carbohydrate) (10-12), exercise (aerobic, resistance) (13, 14), and multiple antiobesity medications (15) as well as bariatric surgery for those suffering from severe obesity (BMI > 40) (16, 17).

Weight loss has been proposed as a means to improve serum lipids, insulin resistance, and blood pressure (18-22). However, it is unclear when these changes take place and the magnitude of these changes. The 2013 ACC/AHA guidelines on weight loss in primary care suggested a dose-response relationship between the amount of weight loss achieved by lifestyle interventions and the improvement in lipid profile (LDL-C, TGs, and HDL-C) (23).

Furthermore, the amount of weight loss recommended to achieve clinically meaningful outcomes may vary depending on the intervention (eg, lifestyle, pharmacotherapy, bariatric surgery) and the coexisting comorbidities such as hypertension and T2DM.

A taskforce from the Endocrine Society was charged with developing guidelines for the management of lipids in endocrine disorders. To aid in the development of these recommendations, we performed a systematic review of the literature and a meta-analysis to estimate the magnitude of change in lipid parameters in people with obesity associated with weight loss through different interventions such as diet, exercise, pharmacotherapy, and bariatric surgery.

Materials and Methods

This systematic review was performed following a protocol approved by taskforce members of the Endocrine Society. We followed the standards set in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (24). Supplemental materials are publicly shared online (25).

Search strategy

Considering the availability of many adult obesity intervention trials and systematic reviews, we conducted an overview of systematic reviews (umbrella systematic review) (26, 27) to identify eligible randomized controlled trials (RCTs) that compared weight-loss interventions with placebo or usual care in adults and evaluated serum lipid change. A comprehensive search of several databases from 2013 to September 26, 2018, was conducted for studies published in the English language. The databases included Ovid MEDLINE(R), Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily, Ovid EMBASE, Ovid Cochrane Database of Systematic Reviews, and Scopus. The search strategy was

designed and conducted by an experienced librarian with input from the study's principal investigator. Controlled vocabulary supplemented with keywords was used to search for systematic reviews and meta-analyses of interventions for adult obesity. The actual search strategy is available in the Supplementary Appendix (25). For each comparison and outcome, we chose the most recent and comprehensive review and retrieved and compiled a list of eligible RCTs.

Eligibility criteria

We included RCTs that enrolled adult patients who were overweight or obese (BMI ≥ 25 kg/m^2, age ≥ 18 years) and evaluated interventions for weight loss (lifestyle interventions, pharmacotherapy, and bariatric surgery) and changes in serum lipids (total cholesterol [TC], TGs, LDL-C, and HDL-C). We included RCTs that compared an intervention arm to a placebo or usual care arm. We excluded studies that were nonrandomized. Studies on children were also excluded. We excluded studies with a follow-up duration of less than 6 months and studies that did not report both weight outcome changes and serum lipid changes. Foreign-language studies were excluded. Eligible pharmacotherapy included were US Food and Drug Administration (FDA)-approved medications for weight loss (orlistat, liraglutide, lorcaserin, combination phentermine-extended release/topiramate, combination bupropion/naltrexone, and phentermine) and metformin. Lifestyle interventions were diet, exercise, and diet and exercise combined, each supplemented with behavioral modifications.

Study selection, data extraction, and appraisal

Two reviewers independently screened references (systematic reviews and individual trials) for eligibility. Conflicts were resolved by a third reviewer. We selected the most recent systematic review, and, if more than one was available, we selected the most comprehensive among them using AMSTAR2 (A Measurement Tool to Assess Systematic Reviews) as a tool for evaluating their credibility (28, 29). At least one systematic review per intervention was included. Data extracted were description of participants, details of interventions, and measures of outcomes of interest. We used the Cochrane risk of bias tool to assess the methodologic quality of the included RCTs.

Statistical analysis

We used a random-effects meta-analysis model to assess the association between BMI or weight changes and lipid profile changes. All analyses were conducted using STATA, version 15.1 (StataCorp LP).

Results

Search results and study description

A total of 2094 systematic reviews were identified by the electronic search strategy, of which 20 were eligible. From these reviews, we identified and included in the analysis 73 RCTs enrolling 32 496 patients (mean age, 48.1 years; weight, 101.6 kg; and BMI, 36.3 kg/m^2). Fig. 1 depicts the process of study selection. The characteristics of the included studies are summarized in Supplemental Table 1 (25).

Main results

Estimated serum lipids change per 1-unit weight and BMI decrease are summarized in Fig. 2. Panels 2A and 2B depict the changes in lipid parameters per 1-unit decrease in weight and BMI, respectively, in lifestyle interventions (diet, exercise, or combined) studies. Panels 2C and 2D depict the changes in serum lipids per 1-unit decrease in weight and BMI, respectively, in studies that used any pharmacologic

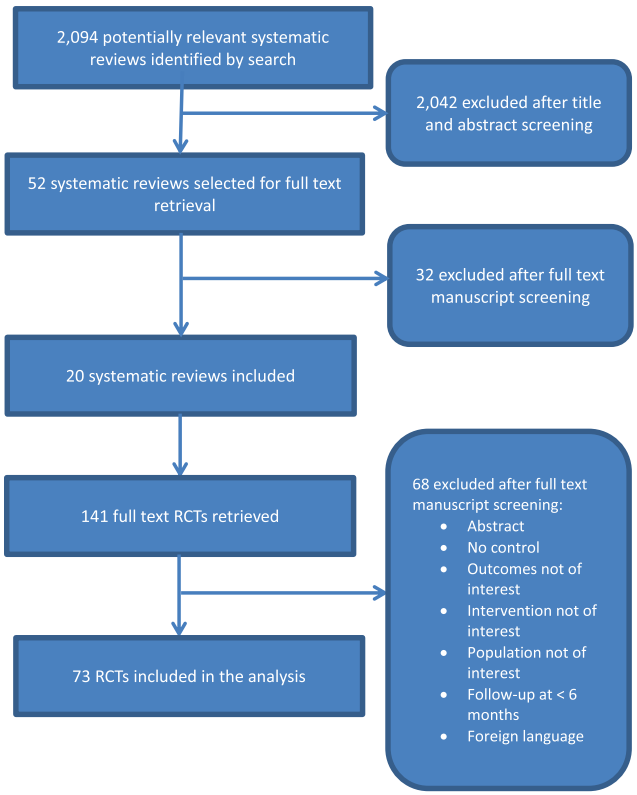

Figure 1. Flowchart depicting the study selection process.

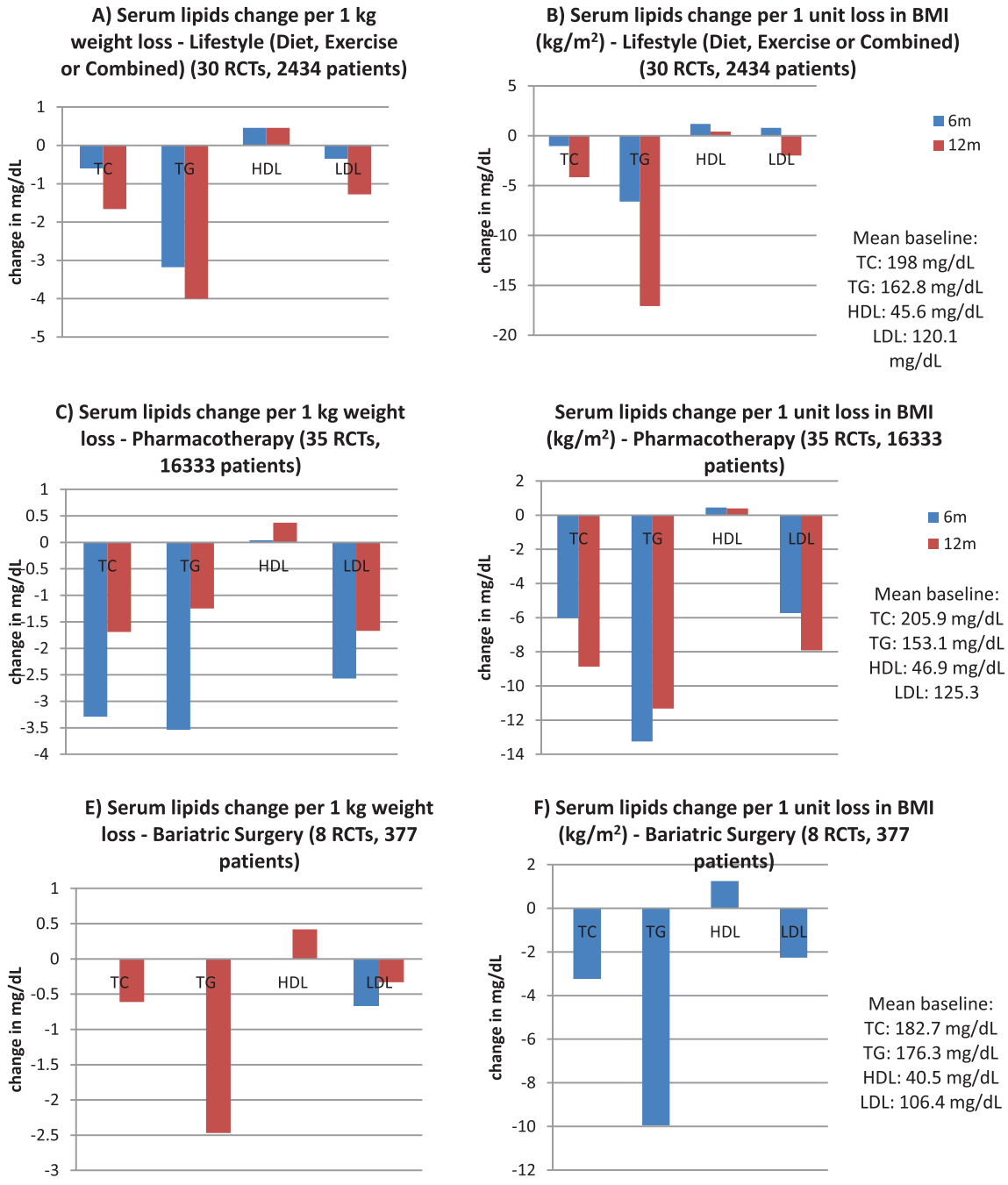

Figure 2. Serum lipids change per 1-unit weight or body mass index (BMI) decrease. A, Serum lipids change per 1-kg weight loss following lifestyle interventions. B, Serum lipids change per 1-kg/m^2 decrease in BMI following lifestyle interventions. C, Serum lipids change per 1-kg weight loss following pharmacologic interventions. D, Serum lipids change per 1-kg/m^2 decrease in BMI following pharmacologic interventions. E, Serum lipids change per 1-kg weight loss following bariatric surgical interventions. F, Serum lipids change per 1-kg/m^2 decrease in BMI following bariatric surgical interventions.

intervention. Panels 2E and 2F depict the changes in lipid parameters per 1-unit decrease in weight and BMI, respectively, in studies that used bariatric surgical interventions. Mean baseline lipid values at which these interventions were tested are also shown in Fig. 2.

Table 1 shows detailed results of the change in serum lipids per 1-kg weight lost for each type of intervention (lifestyle, pharmacotherapy, and bariatric surgery). In 30 RCTs with 2434 participants, lifestyle changes reduced TGs, TC, and LDL-C and increased HDL-C both at 6 and 12 months. The mean reduction in TGs per 1-kg weight lost at 12 months was 4.0 mg/dL, and the mean decrease in LDL-C per 1-kg weight lost was 1.28 mg/dL, whereas HDL-C increased by 0.46 mg/dL. Pharmacotherapy, in

Table 1. Change in lipids at 6 and 12 months per 1-kg weight loss

Group, mo	TC	95% CI	I^2, %	TGs	95% CI	I^2, %	HDL	95% CI	I^2, %	LDL	95% CI	I^2, %
Lifestyle (diet, exercise, or combined)												
6	**–0.60**	**–1.17 to –0.02**	**84.8**	**–3.18**	**–2.19 to –4.17**	**93.1**	**0.46**	**0.29 to 0.63**	**89.3**	–0.35	–0.83 to 0.13	93.1
12	**–1.66**	**–2.83 to –0.50**	**97.4**	**–4.00**	**–5.24 to –2.77**	**95.3**	**0.46**	**0.20 to 0.71**	**91.7**	**–1.28**	**–2.19 to –0.37**	**95.5**
Pharmacotherapy												
6	**–3.29**	**–3.86 to –2.73**	**44.1**	**–3.54**	**–4.84 to –2.25**	**99.5**	0.04	–0.19 to 0.28	99.4	**–2.57**	**–3.73 to –1.41**	**99.8**
12	**–1.69**	**–2.77 to –0.61**	**95.1**	–1.25	–2.94 to 0.43	83.5	**0.37**	**0.23 to 0.52**	**92.9**	**–1.67**	**–2.28 to –1.06**	**97.3**
Bariatric surgery												
6	NA	NA	NA	NA	NA	NA	NA	NA	NA	–0.66[a]	NA	N/
12	**–0.61**	**–1.04 to –0.19**	**76.2**	**–2.47**	**–3.14 to –1.80**	**70.9**	**0.42**	**0.37 to 0.47**	**0.0**	–0.33	–0.77 to 0.10	81.3

Bold: statistically significant association.

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; NA, not available; TC, total cholesterol; TGs, triglycerides.

[a]Insufficient data for meta-analysis.

35 trials with 16 333 participants, was also effective in improving the lipid profile at 6 and 12 months. In 35 trials with 16 333 participants treated for 12 months, pharmacotherapy reduced TGs by 1.25 mg/dL, reduced LDL-C by 1.67 mg/dL, and increased HDL-C by 0.42 mg/dL per 1-kg weight lost.

Most studies of bariatric surgical interventions reported lipid changes after 12-month follow-up, and there are insufficient data for meta-analysis at the 6-month time point. However, we calculated a reduction in LDL-C at 6 months of 0.66 mg/dL per 1-kg weight lost. In 8 trials evaluating bariatric surgery in 377 patients, at 12 months, mean reduction in TGs per 1-kg weight lost was 2.47 mg/dL, mean reduction in LDL-C was 0.33 mg/dL, and HDL-C increased by 0.42 mg/dL. Table 2 shows the change in serum lipids per 1-kg/m^2 decrease in BMI for each intervention. The results are consistent.

Subgroup analyses

As shown in Supplemental Tables 4 to 13 (25), heterogeneity was further explored by conducting subgroup analyses based on type of intervention (type of lifestyle interventions, type of diet, type of pharmacologic intervention, and type of bariatric surgery). Supplemental Tables 4 and 5 (25) depict meta-analyses for type of diet (low-carbohydrate and low-fat diets). Supplemental Tables 6 and 7 (25) show meta-analyses for lifestyle interventions (diet, exercise, and diet with exercise). Supplemental Tables 8 and 9 (25) show meta-analyses for pharmacologic therapeutic agents (liraglutide, bupropion-naltrexone, lorcaserin, orlistat, phentermine topiramate, and metformin). Supplemental Tables 10 and 11 (25) depict meta-analyses for different types of bariatric surgery, including malabsorptive bariatric surgery (Roux-en-Y gastric bypass [RYGB] and biliopancreatic diversion [BPD]), banding, sleeve, RYGB, and BPD). Supplemental Tables 12 and 13 (25) show meta-analysis performed to show the changes in lipid after weight or BMI decrease in patients with T2DM and those without T2DM. Some comparisons were not feasible because of the low number of included studies in that subgroup.

All of these subgroups have also been depicted in supplemental figures (25) that show the magnitude of serum lipid changes alongside the mean baseline lipid values at which these interventions were tested.

Methodological quality

Quality assessment for systematic reviews is depicted in Supplemental Table 14 (25). The chosen reviews had credible searches and approaches. The included RCTs had an

Table 2. Change in lipids at 6 and 12 months per 1-unit loss in body mass index (kg/m^2)

Group, mo	TC	95% CI	I^2, %	TGs	95% CI	I^2, %	HDL	95% CI	I^2, %	LDL	95% CI	I^2, %
Lifestyle (diet, exercise, or combined)												
6	–1.02	–2.34 to 0.29	0.0%	–6.59	–13.60 to 0.43	82.2%	1.19	–0.58 to 2.95	92.9%	0.80	0.51 to 1.08	0.0%
12	–4.15	–10.34 to 2.04	98.1%	–17.07	–25.08 to –9.07	91.0%	0.42	–1.27 to 2.10	96.2%	–1.98	–7.79 to 3.83	94.0%
Pharmacotherapy												
6	**–6.02**	**–9.32 to–2.73**	**41.1%**	**–13.25**	**–16.18 to–10.33**	**0.0%**	0.45	–0.32 to 1.22	67.1%	**–5.73**	**–7.2 to –4.22**	**44.8%**
12	**–8.87**	**–11.7 to–5.94**	**68.2%**	**–11.33**	**–14.38 to –8.28**	**0.0%**	**0.39**	**0.013 to 0.76**	**54.8%**	**–7.92**	**–9.80 to–6.04**	**51.7%**
Bariatric surgery												
12	**–3.24**	**–5.95 to–0.52**	**96.4%**	**–9.95**	**–12.78 to –7.11**	**87.3%**	**1.25**	**0.98 to 1.53**	**78.6%**	**–2.26**	**–4.49 to 0.03**	**95.6%**

Bold: statistically significant association.

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; NA, not available; TC, total cholesterol; TGs, triglycerides.

overall moderate-to-low risk of bias. Supplemental Table 15 (25) shows details about the risk of bias assessment for individual RCTs.

Discussion

Dyslipidemia is a comorbidity of obesity and contributes to increased CVD risk and, in selected patients, to increased risk of pancreatitis, when TGs approach 1000 mg/dL. Typically, a reduction in body weight of 5% has a significant impact on comorbidities of obesity (30). However, the degree of weight loss needed to affect the lipid profile is not well established, thus making it difficult for the practitioner to predict whether weight loss alone will be sufficient to improve dyslipidemia. This meta-analysis combines data from multiple studies using lifestyle therapies, pharmacotherapy, or bariatric surgery to provide estimates for each intervention of the change in TC, LDL-C, TGs, and HDL-C associated with every kilogram reduction in weight or every unit reduction in BMI.

Arguably, sustainability of weight loss is the cornerstone for many improvements in CVD risk factors (31); however, the scope of this study was to evaluate the effects of weight loss achieved via different interventions and, at the smallest considerable amounts, on changes in different components of lipid panel. In their 2013 ACC/AHA/The Obesity Society guideline for weight loss in primary care, Jensen and colleagues considered the evidence for a weight-loss benefit on CVD risk factors, including lipids. They noted a significant 15-mg/dL reduction in TGs at 3-kg weight loss and, at higher levels of weight loss of 5 to 8 kg, 2 to 3-mg/dL increases in HDL-C and 5-mg/dL decreases in LDL-C (23). These changes, however, were mainly achieved via lifestyle weight-loss interventions. The guidelines pointed out that addition of the weight-loss medication orlistat, a lipase inhibitor that prevents fat absorption, and the only pharmacotherapy approved for long-term weight reduction when the guidelines were written, had been associated with a 3-kg greater weight loss and an 8 to 12-mg/dL LDL reduction but also with a 1-mg/dL HDL reduction. Using a 1-kg weight reduction unit, we report generally consistent results with a 0.46-mg/dL increase in HDL and 0.6-, 3.18-, and 0.35-(nonsignificant) mg/dL decreases in TC, TGs, and LDL, respectively, at 6-month follow-up through lifestyle interventions. Results continued to be significant (except for LDL) at the 12-month follow-up mark. The lack of a significant effect of weight loss by lifestyle changes on LDL-C has been previously observed in the Look Ahead clinical trial in patients with diabetes and either overweight or obesity (32). Although a 5% to less than 10% weight loss at 1 year was associated with a significant reduction

in TGs of 40 mg/dL and increase in HDL-C of 5 mg/dL, the reduction in LDL-C was modest and not statistically significant. In an analysis of data from this trial after 4 years of follow-up, TGs remained reduced, and HDL-C increased at year 4 compared to baseline in those who maintained the weight lost at year 1 (33). However, the change in LDL-C was not significant, including in those with greater weight loss of 8% to 20%.

Similar but larger observations in the present study were noted with pharmacotherapy interventions consistent with a previous meta-analysis (34). Although the increases in HDL were significant only at 12-month follow-up (+0.37 mg/dL; 95% CI, 0.23 to 0.52 mg/dL), the significant decreases in LDL were noted both at the 6- and 12-month marks (–2.57 mg/dL; 95% CI, –3.73 to –1.41 mg/dL) and (–1.67mg/dL; 95% CI, –2.28 to –1.06 mg/dL), respectively. These data on bariatric surgery interventions were mostly limited to 12-month follow-up but showed similar trends in lipid improvement with 1-kg weight loss. When studying the association between 1-kg/m^2 BMI unit change with different outcomes, the estimates were generally larger (especially with pharmacotherapy) and less heterogeneous.

As noted, our subgroup analyses were based on the type of interventions, from different type of diets to all FDA-approved medications for weight reduction, metformin, and several bariatric surgery procedures. We found that low-carbohydrate weight-loss diets resulted in significant reductions in TGs and increases in HDL-C, whereas effects from low-fat weight-loss diets were seen across the lipid panel, including HDL-C. Although the latest Dietary Guidelines for Americans 2015 to 2020 still primarily focus on limiting fat intake in general (35), recent evidence from 2 meta-analyses with follow-up intervals similar to this study drew similar conclusions and proposed low-carbohydrate diets as a comparable intervention for weight loss and cardiometabolic risk reduction (36, 37).

Analyzing data from exercise-only interventions, we did not observe any significant improvements in serum lipids. In a 2018 systematic review and network meta-analysis, Pan et al observed significant reductions in all components of the CVD risk profile, including HDL-C, with different types of exercise including supervised aerobic, resistance, or combined exercise (38).

Data on different kinds of FDA-approved weight-loss medications were limited and came mostly from trials of orlistat showing improvement in TC, TGs, and LDL-C but not HDL-C at 6- and 12-month follow-up when using both weight and BMI for weight-loss estimates. These findings are consistent with previous evidence on the benefits of orlistat on both weight loss and cardiometabolic outcomes (39).

Data from RCTs studying different types of bariatric surgical procedures were generally limited to 12-month follow-up but showed improvements in all lipid profile components per 1-kg weight loss both in malabsorptive and restrictive procedures (with the exception of gastric banding). Several previous meta-analyses of RCTs have demonstrated the effectiveness of different bariatric surgeries on long-term weight loss and resolution of concurrent comorbidities like T2DM and hyperlipidemia (40-42).

Furthermore, we evaluated the association of weight loss and lipid changes in patients with and without T2DM. At the 6-month follow-up mark, patients with T2DM experienced positive changes in all components of the lipid panel that, in comparison to patients without T2DM, were also sustained at 12-month follow-up. Last, whereas other guidelines have observed clinically meaningful weight-loss cutoffs ranging from 3 to 8 kg (23), we note that our associations were based on much smaller units of weight loss (1-kg or 1-kg/m^2 weight reduction), likely resulting in considerable variations in some of the findings. Nonetheless, we report statistically significant improvements in lipids associated with the smallest amount of weight reduction, with the magnitude of reduction greatest in TGs. The variable and small effect on LDL-C suggests that, in addition to weight reduction, patients with T2DM or high risk of ASCVD will require statin treatment to achieve the percentage reduction in LDL-C recommended by guidelines. These results should aid practitioners in guiding and encouraging their patients to lose excess body weight and reduce their CVD risk.

Limitations and strengths

The certainty of evidence is limited by heterogeneity of the enrolled patients and the interventions used for weight loss. The associations observed are also subject to: 1) the ecological fallacy that stems from identifying changes at a study level, rather than an individual patient level; 2) confounding (ie, lipid changes may be due to other aspects of the intervention than weight loss); 3) effect saturation or nonlinear association (eg, lipids changes may be most associated with the early weight loss rather than subsequent long-term weight loss); 4) imprecision (ie, associations not found to be statistically significant may actually be true if tested in larger trials); and 5) data range (ie, the associations found in this analysis may hold true only in patients within the age and weight range of patients enrolled in the included RCTs).

The strengths of this systematic review lie in following a priori established protocol; the comprehensive search that spanned multiple databases; screening and appraising

RCTs by pairs of independent reviewers; and the multidisciplinary nature of the research team involved, which included expert input from the Endocrine Society as well as expertise in preventive medicine, public health, clinical epidemiology, statistics, research methodology, and library science.

Conclusion

Weight loss in adults is associated with statistically significant changes in TC, TGs, and HDL-C, with more modest changes in LDL-C. The magnitude of improvement is helpful in informing shared decision making and patient counseling as well as in setting expectations about improvements in the lipid profile associated with the method chosen to achieve weight loss.

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Additional Information

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Disclosure Summary: The authors have nothing to disclose.

Data Availability: Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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