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Mini-Review

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Long-Term Weight Loss Strategies for Obesity

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Abbreviations: T2D, type 2 diabetes; AOMs, anti-obesity medications; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy; RCT, randomized controlled trial; Look AHEAD, the Action for Health in Diabetes; ILM, intensive lifestyle modification; CVD, cardiovascular disease; HbA1c, hemoglobin A1c; CI, confidence interval; BMI, body mass index; HPDs, high-protein diets; LCDs, low-carbohydrate diets; LFDs, low-fat diets; VLKDs, very-low kilocalorie diets; LKDs, low-kilocalorie diets; BMD, bone mineral density; OA, osteoarthritis; CEC, cholesterol efflux capacity.

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Abstract

Context: Obesity is a chronic disease that is difficult to manage without holistic therapy. The therapeutic armamentarium for obesity primarily consists of 4 forms of therapy: lifestyle modification (ie, diet and exercise), cognitive behavioral therapy, pharmacotherapy, and bariatric surgery.

Evidence acquisition: Evidence was consolidated from randomized controlled trials, observational studies, and meta-analyses.

Evidence synthesis: After 2 years, lifestyle interventions can facilitate weight loss that equates to ~5%. Even though lifestyle interventions are plagued by weight regain, they can have substantial effects on type 2 diabetes and cardiovascular disease risk. Although 10-year percentage excess weight loss can surpass 50% after bariatric surgery, weight regain is likely.To mitigate weight regain, instituting a multifactorial maintenance program is imperative. Such a program can integrate diet, exercise, and pharmacotherapy. Moreover, behavioral therapy can complement a maintenance program well.

Conclusions: Obesity is best managed by a multidisciplinary clinical team that integrates diet, exercise, and pharmacotherapy. Bariatric surgery is needed to manage type 2 diabetes and obesity in select patients.

Key Words: obesity, diet, exercise, bariatric surgery, pharmacotherapy

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Obesity, a cancer-causing disease, increases the risk for metabolic, cardiovascular, and musculoskeletal diseases (1). Patients who are diagnosed with obesity are predisposed to comorbidities such as osteoarthritis (OA) and type 2 diabetes (T2D). The Center for Disease Control and Prevention states that when patients are afflicted by OA and T2D, physical activity level is further diminished (2). Given that functional capacity is reduced by obesity alone and by diseases that can manifest secondary to obesity (3), it is difficult to achieve durable weight loss success with exercise-based interventions (4).

By contrast, bariatric surgery is capable of fostering clinically meaningful weight loss (5). When therapy is successful in fostering at least a 10% weight loss deficit, significant effects on morbidity and mortality risk may be seen (6). Bariatric surgery represents 1 medical stride in response to the obesity epidemic. However, bariatric surgery is limited by its therapeutic scope, as only 1.1% of patients who qualified for surgery underwent surgery in 2018 (7).

Bariatric surgery, lifestyle modification, and pharmacotherapy share 1 commonality: efficacy is limited by weight loss variability. However, the fact that weight loss variability exists between human races and diseases underscores that there are underlying demographic and hereditary characteristics that also influence weight loss outcomes (8). Obesity, in particular, is well-known to have strong demographic and hereditary roots (1).

Given that obesity has a complex etiology, long-term weight loss success is less commonly achieved with a diet- or exercise-only intervention (9,10). Even the treatment of T2D has proven to be a challenge with more contemporary therapies (11). Indeed, after an initial improvement, glycemic control can deteriorate over a 10-year period when patients primarily rely on pharmacotherapy to manage their T2D (12). For this reason, treating obesity and T2D necessitate multifaceted therapeutic interventions that integrate lifestyle modification, cognitive behavioral therapy (CBT), pharmacotherapy, and/or bariatric surgery.

The purpose of this narrative review is to provide an overview of the long-term therapeutic impact of lifestyle modification, CBT, pharmacotherapy, and bariatric surgery. In addition, insights into the effectiveness of coupled interventions such as bariatric surgery and exercise, diet and exercise, and pharmacotherapy and bariatric surgery are provided.

Methodology

We identified pertinent work related to this review by extracting studies from PubMed. The majority of the studies had at least 12-month follow-ups. Long- and short-term evidence were mainly synthesized from randomized controlled trials (RCTs) and meta-analyses. Unfortunately, there is a risk of attrition bias with long-term studies due to study dropouts. Nonadherence is common in the clinical setting. Therefore, to reduce reporting bias, preference was given to RCTs that analyzed their data via intention-to-treat analyses; in doing so, the statistical findings can best be extrapolated to the real word.

Dietary Modification

There are 2 reason why diets are lauded and marketed for short-term (eg, 3-6 months) use: weight loss and weight regain tend to be substantial and negligible, respectively (13). The goal of a low-kilocalorie diet (LKD) is to reduce caloric intake to 1200 or 1800 kcals/day for men or women, respectively (14). Among weight loss studies, an analysis of 53 RCTs indicated that LKDs elicited a mean weight loss of 3.75 ± 2.7 kgs after 12 months (9).

Comparatively, very-low kilocalorie diets (VLKDs), diets that are guided by clinical personnel (15), target a caloric intake of <800 kcals/day (14). Short-term weight loss is more substantial with VLKDs than with LKDs (16.1 ± 1.6% *vs* 9.7 ± 2.4%) (16). As a result, VLKDs can facilitate obesity remission after 12 months; further, VLKD's short-term effects on obesity-associated comorbidities are substantial (17).

However, VLKDs can increase the risk for gallstones (18). Ketogenic VLKDs can also have a plethora of side effects: fatigue, headache, constipation, diarrhea, etc. (15). Given the low energy intake, menstruating women may be prone to cycle irregularities (19).

Diets can also be subcategorized by their macronutrient composition. Two short-term meta-analyses indicated that weight loss outcomes favored low-carbohydrate diets (LCDs) and high-protein diets (HPDs) in relation to low-fat diets (LFDs): 1.15-kg difference [95% confidence interval (CI) 0.52-1.79) and 0.79-kg difference (95% CI 0.08-1.50), respectively (9,20). Even if such differences hold true, they are not clinically meaningful. The subtle difference between LCDs and LFDs is likely attributed to differences in adherence.

Long-term impact of dietary modification

Generally, there is no major difference between protein-, fat-, and carbohydrate-based diets (13). Whether a LFD, HPD, or LCD is prescribed, volunteers can lose ~5% of their baseline weight after 2 years (16). However, a large (n = 48 835 postmenopausal women) 8.1-year RCT questioned the efficacy of LFDs (21). Relative to the control group, the RCT demonstrated that there was a 1.9-kg difference in weight ($P < 0.001$), but the incidence of diabetes

was nonsignificantly lower in the LFD group (7.1% *vs* 7.4%) (21). Indeed, even with HPDs, diet's impact on weight loss over the long-term can wane (22).

When compared to a LFD, an isocaloric LCD—a diet characterized by higher fat (eg, unsaturated fat) and protein intake—had the most beneficial impact on serum high-density lipoprotein (HDL) and triglyceride levels (23). However, the positive results are counterbalanced by insignificant decreases or increases in low-density lipoprotein (LDL) levels (24).

LCD's short-term effects on hemoglobin A1c (HbA1c) and blood glucose are generally not maintained over the long-term (25). However, due to reductions in glycemic variability, LCDs reduce the dependency on antihyperglycemic medications more so than LFDs (25). Albeit a non-RCT, one 2-year study noted a 61% reduction in insulin dose; 17.6% of volunteers achieved complete or partial T2D remission (26).

Given that short-term weight loss is more pronounced with VLKDs, these diets have some utility. For instance, shortly before bariatric surgery, VLKDs are sometimes prescribed for 2 weeks to reduce intrahepatic fat content (27). In such instances, weight regain is minimized. However, over the long-term, a meta-analysis indicates that weight loss outcomes tend to equalize in comparison to LKDs (16). As such, whether there is a long-term differential effect on cardiovascular disease (CVD) risk factors is unclear (16). Additional study is needed to investigate whether VLKDs induce greater long-term reductions in fat-free mass in relation to LKDs (28).

The evidence indicates that long-term success is hindered by weight regain (13). Volunteers [body mass index (BMI) = 35kg/m^2] who were randomized to a LKD or VLKD had a similar weight regain trajectory after 144 weeks (29); thus, absolute and relative weight regain were similar between the 2 groups (29). However, a meta-analysis contradicts the aforementioned results by indicating that a greater proportion of lost weight is regained after a VLKD than after a LKD (62% *vs* 41%, respectively) (16,29). The 6 RCTs that were included in the meta-analysis had an average follow-up of 1.9 ± 1.6 years; also, the studies recruited volunteers with class 2 or 3 obesity (16).

The long-term efficacy of VLKDs and LKDs is dependent upon the ability of maintenance programs to attenuate weight regain (30). More aggressive weight maintenance programs—monthly multidisciplinary interventions that help patients adopt a healthier lifestyle (ie, diet and exercise)—are capable of mitigating weight regain (31). Specifically, given that meal replacements are effective at preventing weight regain, they can constitute the dietary portion of the intervention (32). Multidimensional maintenance programs can also include CBT (33). Volunteers who more actively partake in maintenance programs tend to achieve better results (31).

Supplementing a maintenance program with anti-obesity medications (AOMs) can further attenuate weight regain (34). Although AOM's (eg, orlistat) effects on weight regain may deteriorate with time, they are effective at mitigating weight regain over a 3-year period (35). As a result, the prevalence of new-onset T2D can be lessened (35). Additional evidence is needed for other AOMs.

When exercise is prescribed after peak weight loss is achieved, low-volume exercise-only interventions are unable to attenuate weight regain (36). One 3-year RCT noted that a moderate-intensity walking program had a nonsignificant (P = 0.06) effect on weight regain, but there were favorable effects on the incidence of metabolic syndrome (37). Another study documented that a walking program (150 min/week) was statistically inferior to CBT in preventing weight regain (+5.2 kgs *vs* +3.1 kgs, respectively) (38). The impact of aerobic exercise on weight regain is likely dependent upon exercise volume (39). Poor adherence limits the effectiveness of exercise-only interventions (36).

There are 2 postulated mechanisms by which HPDs influence weight regain. First, by preserving lean mass, HPDs may attenuate reductions in resting energy expenditure (20,23). Second, HPDs may impact satiation (40), but it is unclear if this is mediated by gastrointestinal hormone secretion (41). To derive benefit, protein intake may need to amount to 25% to 30% of daily energy intake, while most of the remaining kcals can be obtained from low glycemic index and/or low energy-dense foods (42). While 1 meta-analysis indicated that HPD's effect on weight regain is statistically significant, the effect size is modest: −1.02 kgs (95% CI −1.77 to −0.28) (43). Such a modest effect may not manifest statistically, which would explain the lack of disparity between diets (13).

While weight regain can beset LKDs and VLKDs, positive effects on CVD and diabetes risk factors can be gleaned when weight loss is low. For example, the incidence of metabolic syndrome may be lessened when weight loss totals −3.5 kgs (13). Moreover, lipid, glucose, and insulin levels can be improved with modest weight loss (32). Even when weight loss was negligible, 2 studies noted positive effects on CVD risk factors: (i) a low-salt diet reduced systolic and diastolic blood pressure by −5.5 mmHG and −3 mmHG, respectively (44); 2) a vegetarian-based diet reduced LDL-cholesterol and total cholesterol levels by 26 mgs/dL and 27 mgs/dL, respectively (45). Most important, a 4.8-year RCT that allocated volunteers who were at high risk for CVD (n = 7447) into a control or Mediterranean diet group indicated that CVD and T2D risk can be reduced when weight loss is modest (46,47).

Although adherence deteriorates with time, more favorable outcomes can be attained if patients adhere to a diet that aligns with their food preferences (13). Patients who lose the most weight over the first few months (ie, responders) tend to have better short- and long-term success (48). Even if clinically meaningful weight loss is not achieved, adopting healthier eating habits helps mitigate weight gain over a 7-year period (49).

Diet and Exercise

Short-term results

When implemented for weight loss, coupling diet with exercise is advantageous. A meta-analysis indicates that patients who adhere to a diet and exercise program can achieve clinically meaningful weight loss: −6.29 kg (95% CI −7.33 to −5.25) after 12 to 18 months (50). The additive effects of exercise on weight loss can be numerically modest, but statistically significant [+1.14 kgs lost (95% CI 0.21-2.07)] (51). Meaningful weight loss that is achieved within the first 2 months after an intervention portends long-term success (52).

Reducing visceral and hepatic fat content is an area of clinical importance given their relationship with cardiovascular and hepatic diseases, respectively (53,54). Diet and exercise interventions significantly reduce subcutaneous, visceral, and hepatic fat content (55). For example, in 1 RCT, hepatic, visceral, and subcutaneous fat content were reduced by 47.9%, 19%, and 7%, respectively, when volunteers diagnosed with nonalcoholic fatty liver disease reduced their weight by <5% (55).

Two 18-month studies noted that pain and mobility were improved when weight loss surpassed 5.7%; further, there were reductions in knee compressive forces, but OA progression was unmitigated (56-59). Low-grade inflammation, an underlying manifestation of obesity, was also improved (57). Importantly, the more substantial the weight loss is, the greater the benefit are (57).

Moderate weight loss can also have beneficial effects on an obesity-related comorbidity that is associated with OA: T2D (60). After surpassing the 10% weight loss threshold, one 12-month RCT noted that 61% of volunteers (n = 70) who were diagnosed with T2D (BMI = 34.9 kg/m^2) achieved T2D remission (61). Reductions in weight were accompanied by reductions in blood pressure and insulin resistance (62). As a consequence, volunteers were less dependent on antihypertensive and antihyperglycemic medications (61). Even if weight loss is not extensive, volunteers diagnosed with metabolic syndrome, prediabetes, or acute-onset T2D can derive benefit (63-66).

Long-term results

A diet and exercise program is superior to a diet-only intervention over the long-term [mean difference: −1.38 kgs (95% CI −1.98 to −0.79)]; in turn, blood pressure and blood lipids are more substantially improved (67). There is a positive relationship between exercise volume and weight loss outcomes (68). Although adhering to a high-volume exercise program is difficult (69), observational and RCT data indicate that patients who sustain their weight loss success tend to expend ≥1800 kcals/week (275 minutes/week) (70). Even though the caloric expenditure in the aforementioned study was likely overestimated by questionnaires (71), the study's recommendation aligns with physical activity guidelines that suggest higher volumes of exercise for weight loss (225-420 minutes/week) (72).

Although long-term weight loss outcomes can be confounded by age-related reductions in muscle mass (73), the Action for Health in Diabetes (Look AHEAD, BMI = 36 kgs/m^2) and Diabetes Prevention Program (DPP) demonstrated that meaningful weight loss can be achieved with lifestyle modification; specifically, they found that volunteers who were randomized to a diet and exercise regimen reduced their body weight by 6% and 5.6 kgs after a median of 9.6 years and a mean of 2.8 years, respectively (74,75). Even though it can be a difficult undertaking for patients diagnosed with obesity, these 2 studies demonstrated that volunteers can adhere to a diet and exercise program.

However, the positive 2.8-year weight loss results noted by the DPP study were tempered by follow-up data from the Diabetes Prevention Program Outcomes Study; after 15 years, weight loss totaled −3.48 kgs, −3.23 kgs, and −2.32 kgs in the metformin, intensive lifestyle modification (ILM), and placebo groups, respectively (76). The −3.23 kgs were 53% lower than the 12-month weight loss outcomes: −6.82 kgs (76). Similarly, a 3.5-year analysis of a community-based and pragmatic RCT (n = 488, BMI = 35.4 kg/m^2) indicated that men lost a net of 2.9 kgs (95% CI 1.78-4.02) (77), but the volunteers regained about half [+2.59 kgs (95% CI 1.61-3.58)] of the weight that they had lost at 12 months (77). As another 24-month RCT noted, regaining 50% of lost weight is common (70).

Even though lifestyle modification is affected by weight regain, 4 RCTs that were 2, 3, 6, and 9 years in duration indicated that diet and exercise interventions can delay or prevent the onset of T2D (78-81). Notably, the DPP study demonstrated that ILM reduced the risk for developing T2D by 58% *vs* 31% with metformin after a mean of 2.8 years (74). After 15 years, the incidence of diabetes was 62%, 56%, and 55% in the placebo, metformin, and ILM groups, respectively (76). Each 1-kg of weight lost conferred a 16% reduction in the risk for developing diabetes

(82). The durable effect on diabetes incidence in the DPP study is likely related to the fact that volunteers remained more active at 10 years than at baseline (83).

The positive effects on diabetes risk are partly mediated by improvements in insulin sensitivity and glucose metabolism (62,63). For instance, the Look Ahead study demonstrated that lifestyle interventions had a positive impact on HbA1c levels after 9.6 years [−0.22% 95% CI −0.28 to −0.16)] (84). Lifestyle interventions can, in turn, reduce the 20-year risk for retinopathy (85).

Even though 1-dimensional interventions can improve CVD risk factors (eg, exercise and HDLs) when weight loss is negligible (86), CVD risk factors are generally more greatly impacted by weight loss (87). CVD risk is similarly reduced by weight loss; indeed, a post-hoc analysis of the Look AHEAD study indicated that the risk of death from the primary cardiovascular composite outcome was reduced by 21% when volunteers lost ≥10% of their body weight (6).

Likewise, exercise is associated with reductions in CVD risk (88,89). As 1 study demonstrated, lifestyle modification, an amalgamation of diet and exercise groups, decreased the 6-year risk for CVD and all-cause mortality in patients diagnosed with impaired fasting glucose (90). However, 2 other studies reported nonsignificant effects on CVD and all-cause mortality risk (84,91). The latter 2 studies recruited elderly volunteers who were overweight or middle-aged volunteers who were obese.

Future research will need to elucidate whether diet-induced weight loss exacerbates T2D-related defects in bone strength and quality (92). If true, fracture risk may be compounded in a population that is at a heightened risk for falls and fractures (93,94). Regardless, coupling a resistance training program with a dietary intervention may be needed, as resistance training attenuates reductions in lean mass; moreover, resistance training increases muscle strength and reduces fall risk (95). Additional benefits can be derived (eg, fitness and frailty) by synergizing an aerobic and resistance training program with a dietary program (96). Coupling diet with exercise can also attenuate disability risk (97).

Cognitive Behavioral Therapy

For a multidisciplinary therapeutic regimen to succeed, implementing CBT with lifestyle modification is needed. The central focus of CBT is to help patients manage their goals and treat maladaptive behaviors (eg, binge eating disorders) (98). In doing so, patients can improve their eating and exercise habits. Inevitably, there will be some behavioral relapse with lifestyle modification; therefore, CBT can also help patients with any perceived setbacks (33).

Although CBT has a modest effect on weight loss [−1.7 kgs (95% CI −2.52 to −0.86)] (99), instituting CBT with lifestyle modification amplifies weight loss results [−4.9 kgs (95% CI −7.3 to −2.4)] (100). In part, improvements in cognitive restraint and emotional eating underlie the weight loss effects of CBT (99). The number and duration of sessions needed to elicit positive weight loss results is not definitively known. However, instituting an individualized format is best.

Anti-obesity Pharmacotherapy

Optimally, AOMs are prescribed in adjunct to lifestyle modification. AOMs are clinically indicated for patients who are overweight (BMI ≥ 27 kg/m^2) or obese (BMI ≥ 30 kg/m^2); if a patient is overweight (BMI ≥ 27 kg/m^2), they must also be diagnosed with at least 1 weight-related comorbidity (14). Excluding Lorcaserin, which was discontinued in early 2020 after a large postmarketing trial demonstrated a higher incidence of cancer in relation to placebo (101), there are 5 approved AOMs: phentermine, phentermine/topiramate extended-release, orlistat, liraglutide (3.0 mg), and naltrexone/bupropion sustained-release. The latter 4 are approved for long-term use.

Phentermine was initially approved in 1959 (102). Guidelines indicate that phentermine should be prescribed for 12 weeks. Given that no RCTs have investigated the long-term safety and efficacy of phentermine as monotherapy, concerns remain about its potential deleterious long-term effects on CVD; furthermore, phentermine induces psychotic symptoms.

Initially, in 1968, a study (n = 108) touted phentermine's effectiveness in conjunction with a 1000-kcal diet (103). In comparison to the placebo group that lost 4.8 kgs, the results indicated that volunteers who used phentermine intermittently or continuously lost 13 kgs or 12.2 kgs, respectively, after 36 weeks (103). Additionally, a retrospective observational study investigated whether phentermine potentiated CVD and mortality risk (n = 13 972) (104). There were 3 principal findings: (i) 3 months after phentermine discontinuation, on-label patients lost 2.7% of their body weight, but this was effectively nullified by weight regain over the long term; (ii) at 12 and 24 months, patients who were prescribed phentermine over the long-term (off-label use) lost 5.6% and 7.4% more weight than the on-label participants, respectively; and (iii) phentermine did not significantly increase CVD or mortality risk 3 years after it was dispensed (104).

Additional data regarding the long-term safety of phentermine is scarce; however, in 2012, US Food and Drug Administration approval was granted for phentermine/topiramate extended-release. One RCT provided long-term

data regarding low-dose phentermine (105). After 108 weeks, subjects in the placebo, 7.5-milligram (mg) phentermine/46-mg controlled-release topiramate, and 15-mg phentermine/92-mg controlled-release topiramate groups decreased their body weight by −1.8%, −9.3%, and −10.5%, respectively (105). In the treatment arms, blood pressure decreased by 3 to 5 mmHg. Lipid and glycemic parameters also improved, and progression to T2D was reduced by at least 70.5% (106).

Orlistat was studied for up to 4 years in the XENical in the Prevention of Diabetes in Obese Subjects study (107). As an adjunct to lifestyle modification, this RCT supplied orlistat or placebo to 3305 volunteers who were diagnosed with obesity; patients also had normal (79%) or impaired glucose tolerance (21%) (107). After 4 years, weight loss in the orlistat and placebo groups totaled 5.8 and 3.0 kgs, respectively. In the subset of volunteers who were diagnosed with impaired glucose tolerance, orlistat conferred a T2D risk reduction of 37.3% ($P = 0.0032$), as the incidence of T2D was lower in the orlistat group (6.2%) compared to the placebo group (9.0%) (107).

Liraglutide, a commonly prescribed medication for T2D, is also approved for weight loss; while up to 1.8 mgs/day can be prescribed for T2D, 3.0 mgs/day can be prescribed for weight loss. As indicated by 2 RCTs that were 56 weeks in duration, 54.3% and 63.2% of volunteers who received liraglutide (3.0 mgs) lost 5% of their baseline body weight; moreover, 25.2% and 33.1% of volunteers lost 10% of their baseline body weight (108,109). A 3-year RCT corroborated the findings of the 2 aforementioned studies, as 49.6% and 24.8% of volunteers lost 5% and 10% of their body weight, respectively (110).

Naltrexone/bupropion sustained release was approved by the US Food and Drug Administration in 2014. The combination medications' effect on weight loss compare favorably to other AOMs. Specifically, a 78-week RCT (naltrexone [32 mgs]/bupropion [360 mgs]) noted a reduction in percentage body weight of roughly 10% (111). At similar doses, 2 additional RCTs noted percentage body weight reductions of 6.1% and 9.3% after 56 weeks (112,113).

Despite the widespread availability of AOMs, they are infrequently prescribed; in a cohort of over 2.2 million adults who met eligibility criteria for AOMs, only 1.3% were prescribed at least 1 AOM; moreover, of the 3919 providers who wrote at least 1 filled prescription, 23.8% were considered frequent prescribers as they wrote nearly 90% of all prescriptions (102). Oftentimes, when AOMs are prescribed, the targeted demographic is white females (102).

Given that AOMs are associated with multiple side effects, barriers to AOM's widespread adoption persist; liraglutide, in particular, is more commonly discontinued due to its side effects (relative to placebo, odds ratio is 2.95) (114). Even once clinicians are certified in obesity medicine, they may still be reluctant to prescribe AOMs, as insurance providers may not cover their high cost (115).

Responders versus nonresponders

Patients who respond to pharmacotherapy within the first 3 months tend to have a better chance of sustaining their weight loss success over the long-term (8,104). Clinicians may need to consider halting a prescribed weight loss agent if adequate weight loss is not attained (104). As a general guideline, if patients do not achieve 5% weight loss by 16 weeks, they may be considered nonresponders (111). Clinicians must also consider disease status; for instance, in 1 study, a lower percentage of volunteers who were diagnosed with T2D than without T2D were characterized as being early responders (62.7% *vs* 77.3%) (8).

Bariatric Surgery

Patients who are diagnosed with long-standing T2D and obesity are commonly referred to bariatric surgeons even though patients with more preserved beta-cell function may more aptly respond to surgery (116). There are 2 popular bariatric surgical techniques that can treat T2D and obesity: Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG).

As demonstrated by 4 RCTs (5,117-119), the majority of volunteers who undergo bariatric surgery achieve clinically meaningful weight loss results. Specifically, 3 RCTs reported that the 5-year weight loss results for RYGB were −23.2 ± 9.6 kgs, −24.9 ± 2.12 kgs, and −37.0 ± 13.8 kgs (5,118,119); Ikramuddin et al (117) elected to summarize their results via percentage weight loss (−21.8%). Comparatively, a meta-analysis indicated that 10-year percentage excess weight loss values for RYGB and SG were 57% and 55.4%, respectively (120). Additional evidence is needed for SG.

Even after 12 years, a prospective observational study found that patients who underwent RYGB lost an average of 35 kgs (27% reduction in weight); peak weight loss (−45 kgs) was achieved at 2 years (121). After 20 years, the Swedish Obese Subjects study noted an 18% reduction in body weight even though the majority of patients underwent a dated surgical procedure: vertical banded gastroplasty (122). The volunteers in the Swedish Obese Subjects study reaped the benefits of bariatric surgery as their life expectancy improved by 3 years relative to the control group (123).

Weight loss is accompanied by improvements in blood lipids, blood pressure, and blood glucose (5,117-119). With

respect to the latter, 4 RCTs indicated that HbA1c was reduced by 1.5 to 2.5%; as a result, 16% to 37% of patients maintained partial remission (HbA1c ≤ 6.5%) of their T2D up to 5 years after surgery (5,117-119). Improvements in glycemic control are paralleled by reductions in microvascular disease risk (12).

Unfortunately, there are weight loss-related negative effects on bone mineral density (BMD) and bone turnover (124,125). As a result, fracture risk may be increased after RYGB, but additional evidence is needed (126). Assessing BMD and/or bone microarchitecture on an annual basis is recommended (127); the latter can be assessed by a more sophisticated method: high-resolution peripheral quantitative computed tomography.

Cardiovascular disease risk after bariatric surgery

HDL's negative relationship with CVD risk is thought to be primarily mediated by their cholesterol efflux capacity (CEC), an essential step of reverse cholesterol transport (128). Although improvements in CEC can be confounded by increases in apolipoprotein-A1 and HDL levels, bariatric surgery may improve HDL's ability to efflux cholesterol (129). Such a postulated effect is beneficial given that CEC may be compromised in patients with T2D (130).

Long-term observational studies indicate that bariatric surgery likely reduces CVD risk (131). For example, in a cohort that was comprised of patients diagnosed with T2D, 1 study observed a risk reduction of about one half after 5 years (131). Similarly, inpatient mortality risk after a cerebrovascular accident or myocardial infarction was attenuated by bariatric surgery (odds ratio, 0.54 or 0.61, respectively) (132). Additional evidence from long-term RCTs is needed to substantiate the extent of risk reduction.

Weight regain and dietary modification after bariatric surgery

At least for the first 1 to 2 years after bariatric surgery, there usually is sustained weight loss (5). Afterward, weight regain is possible. The implications of this weight regain, however, are not as dire because net weight loss is still substantial. Adherence to a LKD may offset weight regain. For example, 1 RCT found that a dietary modification program 1 year after RYGB surgery helped patients lose additional weight (–4.07%) relative to controls whose weight loss outcomes plateaued (–0.14%) (133); additional research in this area is needed.

Exercise After Bariatric Surgery

Although a walking-based exercise program can improve glucose homeostasis (134), weight loss is not amplified by exercise in the postsurgical setting (4). However, the postsurgical exercise interventions improved cardiovascular fitness and insulin sensitivity (135); these exercise-mediated adaptations are pertinent because some patients with obesity exhibit low functional fitness and high insulin resistance (136).

Exercise duration and intensity must surpass patient-specific thresholds before noticeable changes in body composition manifest (72). Indeed, high-intensity training significantly reduces total fat mass (137), but if an aerobic exercise regimen is too intense, it may preclude patients from wanting to adhere to a long-term exercise regimen (10). It may behoove patients to initiate a low-intensity and moderate-duration (150 minutes/week) exercise regimen; afterward, they can gradually modify the intensity or duration upward to help manage glycemic- and weight-related endpoints (138).

There is 1 common question among clinicians: is it feasible for patients to substantially increase their physical activity levels because they are equally as sedentary postsurgery (139)? Fortunately, a 12-month RCT indicated that patients diagnosed with severe obesity can adhere to lifestyle modification (62). Whether it is via home- or gym-based exercise, patients and clinicians will need to find creative ways to meet the 225 to 420-minute/week duration threshold for weight loss (72).

Pharmacotherapy after bariatric surgery

Although a 10-year study noted that >70% of RYGB patients (BMI = 47.5 kg/m^2) were less dependent on medications for hypertension, dyslipidemia, and diabetes (140), a subset of patients will require pharmacotherapy to attenuate weight regain and manage hyperglycemia (141). Treating hyperglycemia with pharmacotherapy can reduce all-cause mortality and CVD risk (142). Currently, evidence exists for 3 medications: liraglutide, canagliflozin, and sitagliptin. CVD risk reduction may be derived from treatment with canagliflozin or liraglutide (143,144).

The canagliflozin RCT (300 mg/day) enrolled volunteers who experienced T2D relapse after bariatric surgery; there were 2 notable findings after 6 months: weight and HbA1c were reduced by 3.77 kgs (95% CI 6.33-1.22) and 0.31% (95% CI 0.72-0.10), respectively (145). Canagliflozin causes modest weight (–2.23% to –3.0%) loss in patients with elevated blood glucose (146). Similarly, the sitagliptin RCT recruited volunteers who were diagnosed with T2D; the results indicated that fasting and postprandial blood

glucose levels were reduced in the volunteers who were randomized to 100 mgs/day of sitagliptin (147).

The 3 remaining non-RCTs studied the safety and efficacy of liraglutide. In 1 retrospective study, weight and HbA1c were reduced by 3.4 kgs and 0.39%, respectively (148). After 28 weeks, the second retrospective study reported that the change in BMI was –4.7 kg/m^2; however, the patients were also enrolled in a dietary modification program (149). Lastly, a prospective study that enrolled volunteers who underwent RYGB or SG found that liraglutide (3.0 mgs) facilitated weight reductions of 5.6% or 3.3%, respectively (150). Liraglutide was well-tolerated in this patient population.

Conclusion

The treatment of obesity necessitates a multifaceted therapeutic intervention that is guided by multiple clinical personnel. There is no one-size-fits-all approach. Indeed, while some patients may succeed in managing their weight with diet and exercise, the majority of patients will likely require more aggressive therapy. For example, AOMs can be prescribed as adjuvant therapy; for patients who are diagnosed with obesity and T2D, bariatric surgery may be needed to help them lose a significant amount of their excess weight. Even then, however, the clinician will likely need to integrate pharmacotherapy, lifestyle modification, and CBT with bariatric surgery. Ultimately, the clinician or endocrinologist may exhaust all therapeutic options before deciding on which combination treatment is best. Monitoring for reductions in BMD is advised especially when weight loss is substantial.

Additional Information

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