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Treatment of obesity in mitigating metabolic risk

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Abstract

Through diverse mechanisms, obesity contributes to worsened cardiometabolic health and increases rates of cardiovascular events. Effective treatment of obesity is necessary to reduce the associated burdens of diabetes, cardiovascular disease, and death. Despite increasing cardiovascular outcome data on obesity interventions, only a small fraction of the population with obesity are optimally treated. This is a primary impetus for this article in which we describe the typical weight loss, as well as the associated impact on both traditional and novel cardiovascular disease risk factors, provided by the four primary modalities for obtaining weight loss in obesity – dietary modification, increasing physical activity, pharmacotherapy, and surgery. We also attempt to highlight instances where changes in metabolic risk are relatively specific to particular interventions and appear at least somewhat independent of weight loss. Finally, we suggest important areas for further research to reduce and prevent adverse cardiovascular consequences due to obesity.

Keywords

obesity; risk factors; lifestyle; treatment; weight loss medication; bariatric surgery

Weight loss has been studied in millions of people with results consistently suggesting that the severity of all common obesity-related metabolic comorbidities can be lessened to some extent with different interventions. However, evidence of these changes translating to improved cardiovascular outcomes has been elusive. Prominently, the Look AHEAD trial, which compared intensive lifestyle intervention to diabetes support and education in overweight and obese patients, failed to reduce cardiovascular events over nearly 10 years follow-up. Recently, however, the hard cardiovascular benefits of substantial weight loss

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Disclosures

None

have come to bear with several groups demonstrating improved outcomes following bariatric surgery,[1–4] although these data are observational and not from randomized controlled trials. Further, GLP-1 agonist medications – agents that are now approved for treatment of overweight and obesity absent diabetes – have repeatedly improved cardiovascular outcomes in diabetic populations.[5]

These emerging data are reflected in treatment guidelines produced by the American Heart Association, American College of Cardiology, The Obesity Society and the Endocrine Society which recommend augmenting a foundation of lifestyle intervention and individualized support with pharmacotherapy or bariatric surgery focused on goals of ≥10% body weight loss.[6,7] Even with ideal support and improvements in lifestyle, achieving and maintaining substantial weight loss, such as ≥10% of starting weight, is uncommon, and most individuals find it difficult. Yet there is reason to think that many individuals with obesity could benefit from weight loss in this range. For instance, while the overall Look AHEAD trial was negative, post-hoc analysis demonstrated that subjects who lost ≥10% of their pre-study body weight had a >20% reduction in risk for cardiovascular events.[8] Additionally, based on strong-to-intermediate evidence, American Association of Clinical Endocrinology guidelines encourage ≥10% body weight loss for the specific prevention of diabetes in obesity.[9] Despite guideline recommendations and growing numbers and varieties of approaches to treating obesity and mitigating its associated risk (Figure 1), the epidemic continues largely unabated with only approximately 1% of eligible patients undergoing bariatric surgery or filling an antiobesity medication prescription annually.[10,11] These are motivating factors behind this comprehensive review.

In this article, we discuss the effects of the four primary modalities for obtaining weight loss in obesity (dietary modification, increasing physical activity, pharmacotherapy, and surgery). We focus first on the typical amount of weight loss achieved via each intervention and then on the effects on both traditional and novel cardiovascular disease risk factors. We have attempted to highlight changes in metabolic risk that appear to be modality-independent, relating primarily to weight loss itself, and changes that appear to be modality-dependent and relatively independent of weight change.

Energy Restriction and Dietary Modification

Effects on metabolic risk via energy restriction

In obesity, many markers of cardiovascular risk tend to improve in response to dietary weight reduction from energy restriction, some earlier or more impressively than others. Studies to date frequently have involved restricting fat, in addition to total, calories, and many interventions have also often included exercise.[6]

Systolic and diastolic blood pressure (SBP/DBP) tend to show the most sensitive response to weight changes. For example, an observational study showed a 0.43mm Hg rise or fall in 24-hour SBP associated with every 1% change in body weight in overweight individuals instructed to follow a “weight-reducing diet.”[12] Meta-analyses have supported similar relationships in various contexts,[13,14] with one finding a 0.36mmHg/kg association between

SBP and weight.[14] Flow-mediated dilation (FMD) also improves with diet-induced weight loss, although more (~10 kg) is required for a notable effect.[15]

Dysglycemia has tended to improve fairly early in the course of lifestyle-based weight loss in large landmark studies including the Diabetes Prevention Program and Look AHEAD, [16,17] with further benefit seen with additional weight loss. Even when HbA1c, a relatively crude measure of dysglycemia, was examined in a small study of individuals with obesity and prediabetes, a dose-response was detected between lifestyle-based weight loss and HbA1c decrease.[18] There is evidence from a recent, elegant study using radiolabeled tracers in obese humans that glycemic improvement can be attributed to improved insulin sensitivity at multiple target organs as well as improved beta cell function.[19] The results of this study suggest that liver and adipose insulin sensitivity show maximal improvement at 5% weight loss, while muscle insulin sensitivity continues to improve with additional weight loss. A composite measure of beta cell function also continued to improve as weight loss increased, up to the maximum of 16% evaluated in this study.

Favorable changes in lipid profile result from weight loss by lifestyle modification in individuals with BMI >25kg/m^2. These alterations suggest partial resolution of pathology within the “adiposopathic dyslipidemia” framework, which posits that insufficient lipoprotein lipase (LPL) activity and adipogenesis at peripheral subcutaneous adipose tissue during positive energy balance results in increased visceral adiposity and increased free fatty acid (FFA) delivery to non-adipose tissues, notably the liver. This results in increased production of VLDL and a trend toward smaller and denser LDL (which holds greater atherogenic potential) and HDL (which is more rapidly cleared, resulting in decreased total HDL). Excess FFA delivery to the liver further contributes to hepatosteatosis, insulin insensitivity, and additional downstream pathophysiologic changes.[20]

Based on a comprehensive evidence review, the most recent American consensus guidelines on obesity management conclude that substantial triglyceride reduction (≥15mg/dL) is seen with relatively modest weight loss (~3 kg), while larger amounts of weight loss (5-8 kg) are needed to see consistent improvements in LDL-C (~5 mg/dL) and HDL-C (~2-3 mg/dL).[21] The only major meta-analysis to specifically focus on changes in lipoproteins after dietary weight loss was published in 1992.[22] While including only small studies and <2000 subjects total, this analysis estimated that each kg of weight loss is associated with: LDL-C, −0.8mg/dL; HDL-C,−0.3mg/dL during active weight loss, but +0.3mg/dL once weight stabilizes; triglycerides, −1.3 mg/dL.[22] These changes appear driven by increased apoB100 clearance without an increase in production, in addition to increased rates of VLDL to LDL conversion.[23] Further, while apoA1 production decreases, it is offset by decreased clearance, at least early on.

As reviewed elsewhere in this Compendium, obesity is associated with multiple inflammatory and immune changes in adipose tissue, which appear to contribute to cardiometabolic risk. These changes, and their reversibility by weight loss, appear to depend on individual context, particularly baseline inflammatory status. In one study of low-fat diet-based weight loss, clinically well individuals with severe obesity and moderately elevated levels of C-reactive protein (CRP) (median ~3.65mg/L) required loss of 16% of starting

weight to significantly reduce CRP.[19] Contrastingly, in another study, when individuals with psoriatic arthritis and BMI >25 lost weight mostly via low-calorie/fat/sugar high-fiber diet, decrease in CRP was detected when only 5-10% of starting weight had been lost, which also correlated with an improved clinical response to TNF-α blockade.[24]

In mice, adipose tissue macrophage content has shown an intriguing temporal response to caloric restriction, increasing at first but later decreasing to below the pre-weight-loss levels, in synchrony with markers of adipose tissue lipolysis.[25] This has also been reported in humans, specifically in the subcutaneous adipose tissue of a small group of women with obesity who undertook very-low-calorie diets to achieve >10% weight loss.[26] Their adipose tissue macrophage markers peaked at the end of the initial 4-week weight loss period, but fell below baseline levels following a period of stability at the reduced weight. Studies in mice and humans find that insulin insensitivity improves in association with reduced inflammatory cell content of adipose with weight loss.[27] However, whether reduced adipose inflammation contributes to improved insulin sensitivity or the inverse, is unclear.[28] Progression of adipose tissue pathology to fibrosis has been associated with hepatic fibrosis and diabetes, but also to poor weight loss response.[29]

Effects on metabolic risk from altered dietary composition

Patient-specific factors (genetics, gut microbiota, activity/exercise patterns, comorbidities, etc.), probably interact in important ways with dietary content in affecting cardiometabolic risk, so one single dietary pattern recommendation is unlikely to be optimal for all individuals. Nonetheless, dietary patterns can mediate cardiometabolic risk beyond their caloric content. The clearest examples perhaps are the low sodium and Dietary Approaches to Stop Hypertension (DASH) dietary patterns, which lowered SBP and DBP in a clinical trial while participants maintained stable weights.[30] More complex effects of dietary patterns are plausible – for instance, degree of adherence to a “Mediterranean” pattern as assessed by determination of nutrient indices from diet diaries,[31] or by a scoring system,[32] has been associated with lower levels of multiple markers of inflammation and with improved endothelial function, even after adjusting for body weight or body mass index and other likely confounders – but these effects require further delineation and corroboration.

At the level of defined macronutrients as dietary components, there is a reasonable consensus that saturated fatty acids confer cardiometabolic risk out of proportion to their caloric content,[33,34] and that lower-carbohydrate weight-reducing diets tend to reduce triglycerides, increase HDL-C, and transiently increase LDL-C, compared to higher-carbohydrate ones.[20]

Sugar-sweetened beverages, and perhaps “free” sugars generally, appear to confer cardiometabolic risk beyond their caloric content, perhaps in part because of relatively high fructose content.[33] One small human study compared isocaloric high glucose and fructose consumption finding that while glucose increased post-prandial glucose and insulin, fructose led to greater visceral adipose gain in the context of greater de novo lipogenesis, decreased fat oxidation, and increased triglycerides, apoB, small dense LDL, and oxidized LDL.[35,36] A plausible basis for these differences is that hepatic uptake of glucose, but not fructose, is regulated by hepatic energy status. Moreover, glucose and fructose consumed together may

synergize, raising LDL-C and apoB further than either alone.[37] As studies consistently associate consumption of whole fruits, which are high in fructose, with improved cardiovascular outcomes and all-cause mortality even when controlled for BMI and other confounders, monosaccharide content alone is not the only factor mediating the metabolic impact of the food.

Connections between dietary composition and the innate immune system have recently been reported. In one recent study, non-obese mice were fed a high-sucrose/saturated fat diet for four weeks, but were returned to a control diet before weight gain was noted. Multiple inflammatory markers increased on the experimental diet and reverted on return to control diet, but enhanced toll-like receptor responses also developed and did not revert, indicative of a phenotype of epigenetically trained innate immunity phenotype in monocytes, expected to persist for months.[38]

A more dramatic change in macronutrient balance, currently the subject of substantial scientific and popular interest, involves very-low carbohydrate consumption, sometimes designed to promote ketosis. Such diets could plausibly have cardiometabolic effects separate from those of the associated weight change, particularly if prolonged ketosis is achieved, but data is lacking in humans in the presence of an appropriate control diet. A National Lipid Association scientific statement recently comprehensively reviewed effects of very low carbohydrate diets on energy metabolism, weight loss, cardiometabolic risk, as well as safety concerns, concluding that “there is a physiological basis for potential metabolic benefits of carbohydrate-restriction compared with dietary strategies with a higher carbohydrate content in some individuals” and that multiple risk markers improve in the short term on these diets, but that “by approximately 2 years, there are no differences for most cardiometabolic risk markers.”[39]

Regulating the timing of caloric intake has also been of recent interest, generally with the hypothesis that frequency and duration of exposure to fasting can be clinically significant. These approaches can involve avoiding, or markedly limiting, energy intake over times ranging from about half a day to one or more days.[40] At long enough fasting durations intermittent fasting probably has some physiologic overlap with ketogenic diets. Multiple cardiovascular benefits have been reported, including on BP, lipid profile, glycemic response, and inflammation, as has been reviewed,[40] but whether these differ from the effects seen with equivalent energy restriction from a non-restricted feeding pattern, is unclear. One notable study of a small group of men with BMI >25 succeeded in maintaining approximately stable weights between a 5-week period of early time-restricted feeding and a 5-week period of control feeding schedule.[41] Insulin levels and insulin responsiveness improved, with large reductions in SBP and DBP, but fasting triglycerides worsened (+57±13 mg/dL) and no change was noted in inflammatory markers.

Looking forward, personalizing dietary recommendations based on objective as well as subjective data seems likely to become increasingly possible and powerful. For instance, there has been some evidence that baseline glycemic status helps predict successful weight loss with low-carbohydrate/high-fat diets.[42] A wide variety of mechanisms may link the microbiome, particularly gut microbiota, to cardiometabolic risk, through effects on energy

balance as well as through weight-independent effects. Moreover, the composition of the microbiome responds, sometimes rapidly, to changes in diet.[43] Manipulation of the microbiome, or compensating for metabolite deficiencies related to it, through dietary optimization, probiotic/prebiotic supplementation, or perhaps other means, could potentially have a role in preventing or mitigating obesity or its cardiometabolic risks. Some specific considerations with respect to changes in energy intake have been reviewed.[43]

Exercise

Exercise represents volitional energy expenditure, and as discussed below, improvements in cardiometabolic risk markers appear similar when equivalent weight loss is achieved by increased sustained aerobic activity or dietary modification. Exercise is a valuable adjunct to weight loss (and especially weight maintenance[44,45]) efforts and also offers myriad cardiovascular benefits independent of weight loss as will be discussed below.

Effects on body weight

The American College of Sports Medicine (ACSM) has suggested that 225-420 minutes of aerobic training per week is needed for 5-7.5 kg weight loss[45] – modest weight loss for many individuals with obesity – whereas just over half of all Americans achieve even 150 minutes per week of moderate-intensity physical activity.[46] Thus, the American Heart Association statement that “physical activity is not an effective approach for achieving initial weight loss”[47] is understandable. An analysis by Shaw and colleagues suggested that combining exercise with diet led to an additional 1.1kg body weight loss vs diet alone, with high-intensity exercise associated with 1.5kg greater weight loss than lower-intensity exercise.[48] Further, incorporation of exercise into a weight loss plan promotes beneficial changes in body composition – preservation of lean body mass and greater fat loss.[49–52]

Effects on metabolic risk in obesity

Several large studies and a meta-analysis suggest that weight loss, whether due to diet or exercise, has comparably beneficial effects on apoB concentration,[52,53] triglycerides,[53] HbA1c,[54] and BP.[54] Although greater weight loss offers greater benefit in most situations, there is evidence that cardiometabolic risk in obesity can improve with modest, or even no weight loss, in conjunction with exercise.[45,55,56] Data suggest that while increasing BMI is associated with worse outcomes, excess risk is attenuated in obesity individuals who are non-sedentary or cardiovascularly fit.[57] In part, this is probably due to improved vascular health resulting from exercise. For example, BP was one of the first measures noted to improve with exercise independent of weight loss.[58] Moreover, experiments in obese rodents demonstrate improved endothelium-dependent and -independent dilatation in response to aerobic training,[59] as well as increased endothelial prostacyclin production. With respect to exercise-induced improvements in endothelial function, certainly reductions in circulating glucose, cholesterol, and triglycerides contribute, but FMD has been shown to improve in obese humans following either aerobic or resistance training in the absence of change in body weight, lipids, or glucose.[60,61] These vasodilatory effects are understood to be largely mediated by shear stress-induced increases in nitric oxide synthase expression occurring with exercise (Figure 2).[62] This is mediated through KLF2 signaling in endothelial cells,

which also affects adhesion molecule expression, improving endothelial function in subjects with obesity, diabetes and the metabolic syndrome.[63,64]

Aerobic exercise training may modestly reduce LDL-C in obesity.[65] In the STRRIDE study, Kraus and colleagues reported reduced LDL-C with training, but further observed that aerobic exercise specifically reduced the concentrations of small LDL particles in those performing large amounts of high-intensity exercise.[66] The subjects in the high amount and intensity group exhibited a degree of reduction in visceral adipose tissue not seen in the other groups[67] – in line with resolution of adiposopathic dyslipidemia discussed above. Although limited, some data suggest that resistance training may produce greater reductions in LDL-C than aerobic training.[34]

A single bout of exercise may be adequate to observe reduced post-prandial triglyceridemia. This is seen after endurance exercise,[68] but high intensity interval training (HIIT), an exercise protocol consisting of several repeated episodes of brief, maximal sprint-type exercises followed by a slightly longer recovery periods,[69] seems particularly effective at acutely improving postprandial lipemia via increased LPL activity and reduced VLDL synthesis.[70] Chronic exercise-induced reductions in triglycerides probably result from improved insulin sensitivity,[65, 66] increased LPL activity, and increases in muscle mitochondrial number and activity that result in greater FFA oxidation.[71] Increased skeletal muscle mitochrondria and fat oxidation capacity do not occur with weight loss by other means[72,73] - results of aerobic exercise's activity in stimulation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) activity.[74] Exercise-mediated increases in skeletal muscle PGC1α also improve glucose and lipid homeostasis,[75,76] may act to reduce inflammation, and induce skeletal muscle angiogenesis (Figure 2).[7778]

Aerobic exercise may increase HDL-C, and specifically large HDL particles,[66] in a dose-dependent manner.[79] However, how duration, frequency, or intensity relate to these changes remains unclear.[71,80,81] Moreover, this response to exercise exhibits particularly large inter-individual variation,[79] is impaired in obesity,[80,82] and is even more uncertain in the setting of active weight loss.[22,53] Additional data suggest exercise may improve HDL function. Similar to observations regarding HDL-C, it appears that large amounts of high intensity exercise may be required to improve HDL cholesterol efflux capacity in obesity.[83]

Improvements in insulin sensitivity are consistently seen in studies of aerobic exercise despite weight loss of <3%.[84,85] Exercise alone translated to a 46% reduction in incident diabetes over six years in individuals with impaired glucose tolerance in the Da Qing IGT and Diabetes Study.[86] Further, some data support additive effects of diet and exercise on insulin sensitivity.[87] Acutely, exercise induces an improvement in insulin sensitivity[88,89] which, impressively, persists for up to 2 days.[90] Aerobic exercise increases skeletal muscle GLUT4 protein expression.[91] Skeletal muscle contractions cause translocation of GLUT4 transporters to the muscle cell surface independent of insulin, improving glucose transport and insulin sensitivity.[92,52,93] Inhibition of the NF-κB pathway with exercise may further contribute to improved insulin sensitivity in obesity.[94,95] Finally, while some evidence suggests HIIT may produce greater improvements in insulin sensitivity than continuous

aerobic training,[96] even just interrupting prolonged sitting may improve insulin sensitivity in obese children[97] and adults.[98]

Aerobic-exercise-induced visceral adipose tissue reduction, in the absence of weight loss, is associated with reduced circulating inflammatory cytokines.[99,100] Exercise in obese mice is adequate to normalize visceral adipose inflammation as indicated by number of macrophages, amount of crown-like structures, and TNFα and IL-6 expression.[85,101,102] Exercise also appears to reduce hepatic and skeletal muscle fat, although the findings are less consistent than with visceral adipose tissue.[103–105] Endurance exercise in the absence of body weight loss has also been shown to reduce epicardial fat mass.[106,107]

Exercise has anti-inflammatory effects separate from reduced adipose tissue mass in obesity. Muscle contraction provokes the release of numerous myokines.[108] IL-6 release, specifically, occurs in response to acute muscle contraction in a dose-response manner and is felt to be beneficial through its induction of anti-inflammatory cytokines, including IL-10, and IL-1Rα, a competitive inhibitor of IL-1 signaling.[90,99,109] Muscle-released IL-6 also stimulates adipocyte lipolysis[110] and may increase GLP-1 production,[111] further improving glycemia as well as other metabolic risk factors, as discussed below (Figure 3). In fact, administration of an IL-6 receptor antibody has been reported to suppress the epicardial fat loss observed with exercise in obese humans.[112]

Aerobic exercise also elicits an intensity-dependent increase in skeletal muscle extracellular vesicle release, and obesity may influence vesicle characteristics.[113] These microparticles and exosomes contain proteins, lipids, mRNA and non-coding RNAs,[114] the last of which have been reported to differ by exercise type and amount.[63] For example, circulating amounts of MiR 27a, 27b and 126 are reduced in obesity, but increase in response to exercise.[115] Their relevance to cardiometabolic risk in obesity has yet to be adequately described.

As described in detail in this compendium,[116] obesity is characterized by increased numbers of leukocytes, as well as pro-inflammatory leukocyte phenotype. Exercise absent changes in body weight may increase regulatory T cells[117] and reduce numbers of inflammatory monocytes,[118] with a dose-response to increasing intensity of exercise.[99,119] One group recently demonstrated that visceral adipose-derived leptin regulates bone marrow precursor proliferation and contributes to leukocytosis.[120] They further showed that aerobic exercise prevents leukocytosis via a reduction in leptin production in non-obese mice. Both chronic and acute exercise seem to increase specialized pro-resolving mediators in mice, and accordingly, improve macrophage efferocytosis activity in *in vitro* assays, although the effects in humans and in obesity are unclear.[121–123]

Finally, changes are observed in the intestinal microbiota with exercise in obesity, but given the diversity of studies and interventions it is not currently possible to describe a generalized effect and any impact on metabolic risk remains speculative.[124–126] Further, exercise-induced changes in the microbiome appear to not be durable with the cessation of exercise, and possibly impaired in obesity.[126]

Pharmacotherapy

Major guidelines recommend pharmacotherapy for weight loss as an adjunct to diet, exercise, and behavioral modification in patients with BMI >27kg/m² with obesity related comorbidities or those with BMI >30kg/m².[6,7] Five* medications are currently approved by the US Food and Drug Administration (FDA) for long-term use for obesity. They act through both peripheral and central mechanisms, with effects on satiety, energy expenditure, reward pathways, and caloric absorption. While all are efficacious to some degree for weight loss, one single medication class, the GLP-1 agonists, offers particularly notable metabolic risk reduction that appears independent of the associated weight loss.

* This article was completed and accepted prior to the recommended removal of locaserin from the US market by the Food and Drug Administration on February 13, 2020.

Pancreatic lipase inhibitors:

Orlistat is unique among current agents in that it acts completely through a peripheral mechanism of action – reversibly inhibiting lipases in the lumen of the stomach and small intestine, inhibiting dietary fat hydrolysis and thus absorption. The resulting caloric deficit of unabsorbed dietary fat facilitates weight loss. At its recommended therapeutic dose, orlistat inhibits dietary fat absorption by 30%.[127]

Effects on body weight

Trials over 1-2 years demonstrate average weight loss of ~3% with orlistat relative to placebo.[128,129]

Effects on metabolic risk in obesity

Multiple studies have demonstrated modest improvement in metabolic parameters with orlistat use, including reductions in SBP, DBP, and HbA1c, comparable to those seen with caloric restriction.[12,19] Orlistat reduces LDL-C more than expected with similar weight loss via caloric restriction, likely through the particular reduction in fat absorption.[130,131] Orlistat has also been reported to increase levels of adiponectin, thus potentially reducing inflammation and improving insulin sensitivity.[132]

Phentermine/extended-release topiramate:

Phentermine, a sympathomimetic amine pharmacologically similar to amphetamines, functions as a central nervous system stimulant. Its exact mechanism of action for weight loss remains uncertain, but it is believed to stimulate catecholamine release in the hypothalamus, inhibiting norepinephrine reuptake and decreasing appetite and food consumption.[133,134] Topiramate is a traditional anti-epileptic agent. Its mechanism of action on weight loss is also uncertain, but may be due to appetite suppression and satiety enhancement, induced by a combination of effects including: increased activity of the neurotransmitter gamma-aminobutyrate (GABA), inhibition of AMPA/kainite excitatory glutamate receptors, modulation of voltage-gated ion channels, and inhibition of carbonic anhydrase.[133] It may also alter neuropeptide Y levels, which may affect satiety.[134]

Effects on body weight

Placebo-adjusted weight loss from several phase 3 clinical trials of phentermine/topiramate was 7.5-9.3% at the target dose.[135–137]

Effects on metabolic risk in obesity

In the above trials, phentermine/topiramate improved glycemic control, increased HDL-C, and decreased triglycerides, with a neutral effect on LDL-C, similar to expected changes with weight loss from calorie restriction. SBP generally decreased with phentermine/topiramate, but less than would be expected from a similar amount of weight loss through other means, and DBP changes were neutral. Topiramate has demonstrated inhibition of fat deposition while reducing LPL activity in adipose tissue, but increasing LPL activity in skeletal muscle.[138] Given the sympathomimetic action of phentermine, there is concern for potential adverse cardiovascular outcomes. While a single retrospective cohort study examining a database of users suggested no excess cardiovascular risk,[139] no prospective trials powered for cardiovascular endpoints have been performed.

Bupropion-naltrexone:

Bupropion inhibits neuronal reuptake of dopamine and norepinephrine, while naltrexone is an opioid antagonist. It is believed that bupropion-naltrexone affects two separate areas of the brain involved in food intake: the mesolimbic dopamine circuit, which is involved in reward pathways, and the hypothalamus, which regulates satiety.[140]

Effects on body weight

In multiple phase 3 trials, bupropion-naltrexone demonstrated placebo-adjusted weight loss of 2.5-5.2% at target doses.[141–143]

Effects on metabolic risk in obesity

In the same trials, bupropion/naltrexone was associated with small increases in HDL-C and decreases in LDL-C and triglycerides. Changes in HbA1c ranged from neutral to slightly favorable dependent on weight loss. The effect of bupropion-naltrexone on BP appears to be unfavorable, with increases in SBP during phase 3 testing.[141–143] The initial phase 3 trials did not demonstrate any significant change in cardiovascular events, but they were not powered to assess cardiovascular outcomes. Finally, bupropion/naltrexone may have additional considerations for use given its impact on addiction-reward pathways. Of note, bupropion/naltrexone has helped with tobacco cessation and mitigated some of the resulting weight gain typically seen with smoking cessation.[144]

Serotonin agonists*:

Lorcaserin selectively activates 5-HT2c receptors on anorexigenic pro-opiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus, promoting satiety.[45]

Effects on body weight

Several trials have demonstrated a placebo-subtracted weight loss of 3-3.6% with lorcaserin at 1 year.[145,146]

Effects on metabolic risk in obesity

In the CAMELLIA-TIMI 61 study, lorcaserin demonstrated slight improvements in SBP, DBP, triglycerides, LDL-C, and non-HDL-C consistent with improvements expected with the same amount of weight loss via other methods.[147] Over a median of 3.3 years, lorcaserin reduced the risk of incident diabetes by 19% in patients with prediabetes and by 23% in patients without prediabetes.[148] Improvement in glycemia has been greater than expected for the associated weight loss.[145,146] Post-hoc analysis of the BLOOM-DM trial demonstrated improvement in fasting plasma glucose within 2 weeks of lorcaserin initiation, and subjects that achieved <5% weight loss on lorcaserin still demonstrated significant improvement in HbA1c and HOMA-IR.[149] The early improvement in fasting glucose suggests improvement in peripheral insulin sensitivity. However it is unclear if these early benefits are from caloric restriction via increased satiety or some other mechanism, in particular, related to lorcaserin's main effect, 5-HT2c receptor activation. 5-HT2c receptor knockout mice exhibit insulin insensitivity which can be improved with reactivation of receptor function in POMC neurons.[150] In POMC neurons, 5-HT2c receptor activation causes second-order signaling via melanocortin 4 (MC4) receptors.[151,152] MC4 activation may improve insulin sensitivity, reduce hepatic glucose production and increase GLUT4 expression.[153–155]

GLP-1 agonists:

Liraglutide, an acylated human glucagon-like peptide-1 (GLP-1) receptor agonist, is a subcutaneously administered medication originally developed for type 2 diabetes, now FDA-approved for treatment of obesity at an increased 3.0 mg daily dose.[156] GLP-1 is an incretin hormone secreted by intestinal epithelial L-cells in response to meals. Liraglutide has 97% amino acid sequence homology to endogenous human GLP-1, but liraglutide has a longer half-life because it is stable against metabolic degradation by dipeptidyl-peptidase 4 (DPP-4) and neutral endopeptidase. Liraglutide binds to GLP-1 receptors on pancreatic beta and alpha cells, increasing their sensitivity to glucose, and suppressing glucagon production. GLP-1 agonists also reduce hepatic gluconeogenesis and slow gastric transit, promoting satiety and reducing energy intake (Figure 3A). In addition, GLP-1 receptors are present in several areas of the brain involved in appetite regulation including mesolimbic neurons and the arcuate nucleus of the hypothalamus, suggesting a possible central role (Figure 3A).[157] Semaglutide, a newer GLP-1 agonist, has demonstrated even greater weight loss compared to liraglutide, and an oral formulation of semaglutide was recently approved by the FDA.[158,159] Semaglutide is not currently FDA-approved specifically for weight loss, but trials are underway for this indication.[160]

Effects on body weight

Liraglutide has demonstrated efficacy in both weight loss and weight maintenance. In clinical trials, liraglutide has demonstrated a 4.0-5.4% placebo-subtracted weight loss at 1 year.[161,162] The SCALE trials, which included obese or overweight subjects with

hypertension or dyslipidemia, but excluded patients with diabetes, demonstrated an additional 6.2% weight reduction when liraglutide was administered to obese subjects who had already achieved an average of 6% weight loss on a low-calorie diet.[163] The weight loss seen with liraglutide is mediated by reduced energy intake, with no effect on 24-hour energy expenditure.[156]

Effects on metabolic risk in obesity

In addition to weight loss, the GLP-1 agonists have demonstrated improvement in many traditional cardiovascular risk factors, including SBP, LDL-C, HDL-C, triglycerides and glycemic control, with liraglutide and semaglutide demonstrating the largest reduction in HbA1c.[164–167] As expected, given the mechanism of action, the improvement in glycemic control and triglyceride reduction are greater than typically seen in weight loss due to lifestyle alone.[168] Importantly, liraglutide and semaglutide use in patients with diabetes has been shown to reduce adverse cardiovascular events and mortality[166,167] – effects notably absent from any prior trials of glucose-lowering medications.[169]

There is evidence to suggest that GLP-1 agonists benefit vascular function – enhancing endothelium-dependent relaxation,[170] increasing nitric oxide synthase activity,[171,172] improving coronary flow velocity reserve,[171] and decreasing production of soluble ICAM-1 and VCAM-1.[171] Inhibitor experiments suggested that the actions of exenatide (another GLP-1 agonist) on endothelial function may be mediated by AMPK and PI3K/serine-threonine kinase (Akt)/eNOS pathways in a GLP-1R/cAMP-dependent manner.[171] Another study demonstrated that liraglutide decreased endothelin-1, a vasoconstriction-inducing protein produced by endothelial cells, via GLP-1 inhibition of NFκB signaling.[172]

The anti-inflammatory potential of GLP-1 has also been studied. In humans, the GLP-1 agonist, exenatide, reduced NFkB signaling in monocytes, and decreased the production of TNFα, IL-6, IL-1β, and CRP independent of any weight loss.[173,174] Invariant natural killer T (iNKT) cells also express GLP-1 receptors, and in at least one study, a GLP-1 agonist inhibited iNKT cell cytokine secretion.[175]

Multiple studies have demonstrated improvement in post-myocardial infarction necrotic area[176,177] and left ventricular ejection fraction[178] in mice treated with GLP-1 agonists, suggesting activity in ischemic conditioning. Rat models have demonstrated GLP-1-mediated improvements in myocardial glucose uptake,[179] which may help reduce oxygen demand during ischemia. Additionally, liraglutide has been associated with better systolic function in human patients with myocardial infarction.[177]As mentioned above, GLP-1 promotes activation of multiple protein kinases, such as PI3K, Akt, mitogen-activated protein kinase (MEK1/2), and extracellular signal–regulated kinase (ERK1/2).[180] PI3K increases nitric oxide production and inhibits the proapoptotic protein Bcl-xL/Bcl-2-associated death promoter.[181] Furthermore, activation of these signaling pathways stimulates opening of the mitochondrial K_{ATP} channels[181, 182] and prevents the opening of mitochondrial permeability transition pores,[181] which are critical steps in both apoptosis and necrosis.[181] These factors may all contribute to the cardioprotective effects of GLP-1 and are summarized in Figure 3B.

Finally, in addition to their effect on glycemic control, the GLP-1 agonists have been shown to reduce post-prandial increases in apoB-48 and apoCIII, independent of weight loss.[183] Rat models infused with recombinant GLP-1 demonstrated decreased intestinal lymph flow, decreased triglyceride absorption and decreased production of apoB and apoAIV, potentially due to effects on microcirculation and gastric lipase inhibition.[184] Epicardial fat in patients with diabetes was found to be reduced as early as 3 months after initiating treatment with liraglutide.[185]

Metabolic surgery

Metabolic surgery was one of the first interventions demonstrated to reduce cardiovascular morbidity and mortality.[186] However, the partial ileal bypass procedure employed in the POSCH trial was not a treatment for obesity, but rather for hyperlipidemia in the pre-statin era. While lipid management is now nearly wholly a pharmacologic enterprise, metabolic/bariatric surgery has proven to be the most effective way to achieve significant durable weight loss in obesity.[187] Long-term data now support that the improvements in metabolic risk in association with weight loss following bariatric surgery translate to reductions in adverse cardiovascular outcomes and mortality.[1–4] Consideration of bariatric surgery is recommended for patients with BMI ≥40kg/m^2; or ≥35kg/m^2; with obesity related comorbidities.[6]

The varying metabolic benefits of bariatric surgery were originally postulated to be related to a procedure's restrictive and/or malabsorptive effects.[188] However, enhanced incretin and bile acid signaling (and possibly an altered intestinal microbiota) are now recognized to contribute to both weight loss and cardiometabolic risk improvement with some procedures (Figure 4).[189] However, the mechanisms underlying metabolic improvements and marked weight loss following metabolic surgery remain far from thoroughly understood and require much more investigation. As a case in point, despite the performance of hundreds of thousands of procedures worldwide annually, the absence of well-controlled studies in this area allowed for the inclusion of data from <1500 subjects in a 2014 Cochrane review.[190]

Gastric Banding

Laparoscopic adjustable gastric banding (LAGB) involves placing an adjustable ring or band at the pylorus. The band is connected to a subcutaneous port at which saline can be injected or removed to adjust pyloric pressure. LAGB is intrinsically a restrictive procedure that limits the volume of food entering the pylorus with any given meal. Beyond restriction of the gastric pouch size, the band pressure increases peristaltic activity of the lower esophagus and upper stomach, leading to vagal nerve stimulation and enhanced satiety with smaller meals.[191, 192]

Effects on body weight

LAGB, in combination with a calorie-restricted diet and exercise intervention, generally produces ~15% weight loss from baseline at 52 weeks.[193,194]

Effects on metabolic risk in obesity

The effects of LAGB on cardiovascular risk factors are largely comparable to equivalent weight loss via caloric restriction.[19] For example, in patients with grade 1 obesity, we observed significant reductions in SBP, DBP, and triglycerides along with increased HDL-C.[195] Larger studies and a meta-analysis demonstrate improvements in glycemia[196,197] and modest reductions in LDL-C,[198] respectively. Longitudinal data suggest that improvements in dyslipidemia may be more durable than reductions in BP and blood glucose.[194] The procedure has largely fallen out of favor despite its potential in specific populations, such as adolescents, [199] that would benefit from reversible procedures.

Sleeve Gastrectomy

Sleeve gastrectomy has recently become the most commonly performed metabolic surgical procedure in both the United States and South America.[200] This procedure evolved as a hybrid of other procedures and consists of removal of the fundal and antral portion of the stomach through a plication procedure, leaving the patient with a remnant stomach “sleeve” through which nutrients flow into the small intestine.

Effects on body weight

Sleeve gastrectomy leads to 25-30% mean weight loss from baseline at 1 year, with weight loss being quite durable at 5 years.[201,202] The degree of weight loss achieved with sleeve gastrectomy is larger than can be attributed to the restrictive and malabsorptive effects of removal of 75% stomach volume alone.[203] Accordingly, it is felt that other mechanisms mediate additional satiety and decreased caloric consumption following sleeve gastrectomy, and may further contribute to reduced metabolic risk. The probable mediators of such hypocaloric effects include the anorectic hormones GLP-1 and Peptide-YY (PYY),[204,192,205] as well as ghrelin, an orexogenic hormone that decreases with removal of ghrelin-secreting P-D1 cells in the gastric fundus.[192] Sleeve gastrectomy also perturbs the gut microbiota in ways that may facilitate additional weight loss through reduced energy absorption.[206]

Effects on metabolic risk in obesity

In concert with the substantial weight loss that occurs with sleeve gastrectomy come greater improvements in metabolic risk than any intervention thus far discussed within this review.[198,201,202,207] These include sizable reductions in BP, HbA1c, triglycerides, and inflammatory markers, with significant increases in HDL-C. Notably, sleeve gastrectomy has not consistently demonstrated reductions in LDL-C, even in cohorts not taking lipid-lowering medications prior to surgery.[208] Notably, increases in GLP-1 and PYY at least partly mediate improvements in glycemia beyond that seen with equivalent non-surgical weight loss.[209] Other effects on metabolic risk of this relatively new, yet dominant, procedure are uncertain.

Roux-en-Y Gastric Bypass

Roux-en-Y gastric bypass (RYGB) has the longest history of bariatric procedures and the best evidence for sustained maintenance of weight loss and improvement in cardiovascular risk.[207,210,211] This procedure involves connecting a small gastric pouch to the proximal jejunum allowing for transit of nutrients directly to the small intestine, while a biliary limb connects the bypassed stomach and duodenum to the more distal jejunum.

Effects on body weight

Roux-en-Y bariatric procedures have been simplified over the years to be performed laparoscopically or with a single anastomosis, and lead to ≥30% mean weight loss from baseline at 1 year with weight loss largely durable at ≥5 years.[1,194,207,212,213] The substantial weight loss is due to a combination of superior reductions in appetite and caloric intake mediated through GLP-1 and PYY action, increased nutrient transit, and gut microenvironment changes, resulting from the unique gastrointestinal tract rearrangement.[192]

Effects on metabolic risk in obesity

RYGB produces the greatest improvements in BP, glycemia and dyslipidemia of any weight loss modality. Similar to the procedure's effects on body weight, the associated improvements in metabolic risk are largely durable.[1,194,207,212,213] Further, weight loss-independent cardiometabolic improvements with RYGB have long been recognized – the procedure being renowned for improving diabetes while patients are still recovering in the hospital. Altered nutrient transit is one mechanism underlying the benefits. Rapid carbohydrate transit from the pylorus to the small intestine augments GLP-1 secretion beyond that seen with sleeve gastrectomy. Greater increases in post-prandial GLP-1 (possibly in addition to reduced glucose-dependent insulinotropic peptide (GIP) unique to RYGB) contribute to the superior improvements in insulin resistance, beta-cell function, and glycemic variation seen with RYGB.[214,215] The absence of nutrient contact with the duodenum specifically, has been additionally implicated in improved glucose control, independent of weight loss,[216] although the mechanism has not been elucidated.

Exposure of the small intestine to undigested proteins and lipids that are not as readily absorbed contributes to greater reductions in LDL-C[198] than expected with equivalent weight loss through other means. In addition to improvements in triglycerides and HDL are durable and superior to other weight loss methods,[194,198] beneficial HDL remodeling[217,218] has been reported following RYGB. Increases in GLP-1 following RYGB are believed to mediate cardiovascular benefit similarly to GLP-1 receptor agonists, as outlined in Figure 3. Specifically in the context of RYGB, increases in GLP-1 have also been implicated in improved HDL function, independent of weight loss.[219] However, data on the effects on HDL cholesterol efflux following RYGB are mixed.[208,218]

The rapid transit of less digested nutrients perturbs the intestinal microbiome following RYGB, similar to sleeve gastrectomy. Some work suggests that increased microbial diversity post-RYGB results in reduced bacterial energy harvest from food, decreasing caloric

absorption and facilitating weight loss.[220–222] The altered microbiota, combined with augmented rates of absorption secondary to small bowel rearrangement, contributes to increased circulating bile acid concentrations following RYGB.[223] As farnesoid-X receptor agonists, bile acids act to reduce triglycerides,[224] and as TGR5 agonists, they further stimulate GLP-1 secretion.[225] Interestingly, a gall bladder-to-ileum anastomosis (which greatly increases circulating bile acids), without intervention on the stomach or small bowel, was able to reproduce many of the metabolic improvements of RYGB, in murine diet-induced obesity.[226] While some data suggest a cost of worsening lipoprotein profiles from increased circulating bile acids,[227] these appear to be more than mitigated by overall weight loss and competing pathways stimulated by RYGB outlined above.[198]

As mentioned earlier, bariatric surgery is the only weight loss modality demonstrated to improve cardiovascular outcomes in obesity. This is likely due to a combination of the substantial weight loss induced by procedures, in addition to mechanisms by which metabolic surgery, specifically sleeve gastrectomy and RYGB, mitigate cardiovascular risk beyond that of matched, non-surgical weight loss. We outline these mechanisms in Figure 4. The mechanisms highlighted in this figure have largely been uncovered over the past decade and remain under intense investigation. We are confident that this figure is incomplete and that additional basic and translational research will further elucidate the mechanisms and identify potentially novel outcomes affected by these procedures. Should these mechanisms be extricated from the procedures themselves, this could provide new therapeutic strategies in the treatment of obesity, diabetes, and consequent cardiovascular disease.

Perspective

To comprehensively review all proven and promising weight loss/management approaches would be impossible, particularly in the space available. We have only touched on a small subset of the countless diet and exercise variations that have been studied, much less all that could be conceived of. New and novel pharmacologic agents, surgical and minimally invasive techniques continue to be developed as basic and translational research suggest promising targets for achieving weight loss and reduction of metabolic risk.

For example, oxyntomodulin is a peptide hormone secreted in the gut with GLP-1 after nutrient ingestion. It activates both the GLP-1 receptor and the glucagon receptor (GCGR).[228,229] Trials of oxyntomodulin have demonstrated weight loss in humans and evidence of both increased satiety and increased energy expenditure.[230,231] The impact on metabolic risk in obesity remains to be seen, but a dual GLP-1/GCGR agonist for the treatment of diabetes and obesity is currently in development and a triple GLP-1/GCGR and GIP co-agonist is currently being developed with early promising results in both obesity and hepatosteatosis.[232] Further, preliminary studies of novel hormonal multiagonists of existing incretins, including GLP-1-estrogen, GLP-1-triiodothyronine and glucagon-dexamethasone, indicated that they may provide the metabolic benefit of each individual hormone without the adverse effects common in hormonal supplementation.[233–235]

In addition to research on variations in sleeve gastrectomy and RYGB, there is growing interest in endoscopic bariatric procedures. Endoscopic gastroplasty involves reduction of

gastric volume via creation of a mucosa-to-mucosa tissue apposition, similar to a sleeve gastrectomy.[236] Early trials of duodenal resurfacing, which involved catheter-based thermal ablation of the duodenal mucosa, has demonstrated durable efficacy in diabetes management in humans, despite minimal weight loss.[237] Basic research into the biology underlying the benefits of these procedures may suggest molecules and pathways that can be targeted to further optimize metabolic risk reduction in obesity.

We have also largely omitted the topic of consolidating a healthier weight when it is achieved and preventing weight regain, a frustrating problem to which no intervention is immune. Research into ways that successfully maintain reduced weight and metabolic risk is needed. Given the genetic, molecular and behavior pathways that contribute to obesity, an integrated, personalized approach seems necessary.[238]

Finally, while we have discussed how diverse obesity treatments can reduce cardiometabolic risk markers, several points warrant emphasis. Only significant weight loss via bariatric surgery has proven sufficient to reduce cardiovascular events. Even in this setting, current approaches may not fully reverse the risk in all individuals, particularly after advanced changes such as adipose tissue fibrosis have set in.[29] Further, accumulating data support immune memory as mitigating persistently elevated metabolic risk in obesity despite weight loss.[239,240] This is suggestive of a concept of, “once obese, always at risk,” and is an area of intense investigation by many groups, including our own. While these observations suggest that targeting immune cell metabolism may hold benefit for cardiovascular risk reduction in obesity, they should also highlight the importance of prevention. In 2009, the ACSM made the following apropos statement – “the prevention of weight gain may be the easiest way to prevent the development of undesirable changes in cardiovascular disease risk factors.”[45] While preventing obesity has proven far from easy, it is likely the most effective way to reduce metabolic risk. Considering this, effectively preventing obesity and its progression are paramount goals at the individual and population level, and deserve substantial research and policy attention.

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Abbreviations

ACSM	American College of Sports Medicine
BMI	Body Mass Index
CRP	C-reactive protein
DASH	Dietary Approaches to Stop Hypertension

DBP	diastolic blood pressure
DPP4	dipeptidyl-peptidase 4
ERK	extracellular signal–regulated kinase
FDA	Food and Drug Administration
FFA	free fatty acids
FMD	flow-mediated dilation
FXR	farnesyl X receptor
GABA	gamma-aminobutyrate
GIP	glucose-dependent insulinotropic peptide
GLP-1	glucagon-like peptide 1
GLUT4	glucose transporter type 4
HbA1c	Hemoglobin A1c
HIIT	high intensity interval training
ICAM1	intercellular adhesion molecule 1
IL-1	interleukin 1
IL-1Rα	interleukin 1 receptor antagonist
IL-10	interleukin 10
iNKT	Invariant natural killer T cells
KLF2	kruppel-like factor 2
LAGB	laparoscopic adjustable gastric banding
LPL	lipoprotein lipase
MC4	melanocortin 4
MAPK	mitogen-activated protein kinase
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
PGC-1α	peroxisome proliferator-activated receptor gamma coactivator 1-alpha
POMC	pro-opiomelanocortin
PYY	Peptide-YY
RYGB	Roux-en-Y Gastric Bypass

SBP	systolic blood pressure
TNF-α	Tumor Necrosis factor alpha
VCAM1	vascular cell adhesion molecule 1
VLDL	very low density lipoprotein

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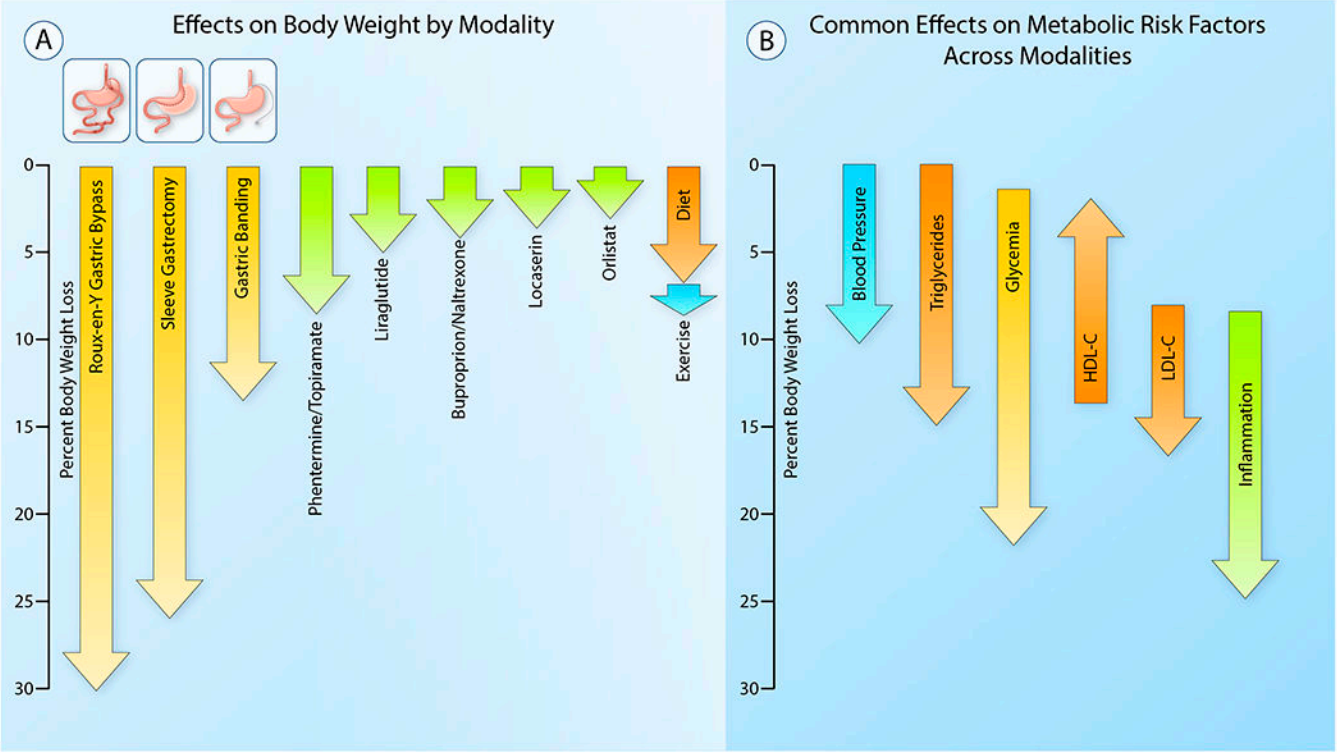

Figure 1. Typical changes in body weight and traditional cardiovascular disease risk factors via weight loss in obesity.

(A) This diagram represents average observed weight loss in clinical studies with lifestyle interventions (dietary modification and increased physical activity), pharmacotherapy and metabolic surgery.

(B) This figure demonstrates the range of weight loss over which changes in traditional cardiovascular risk factors typically occur. Improvements in blood pressure, triglycerides and glycemia become noticeable with modest weight loss. Reductions in LDL-cholesterol and inflammatory markers require more substantial weight loss. Reductions in triglycerides, glycemia and inflammation particularly, continue to improve as weight loss increases and have the potential to be significantly impacted with substantial weight loss, whereas LDL-C and HDL-C generally improve only modestly. (Illustration Credit: Ben Smith)

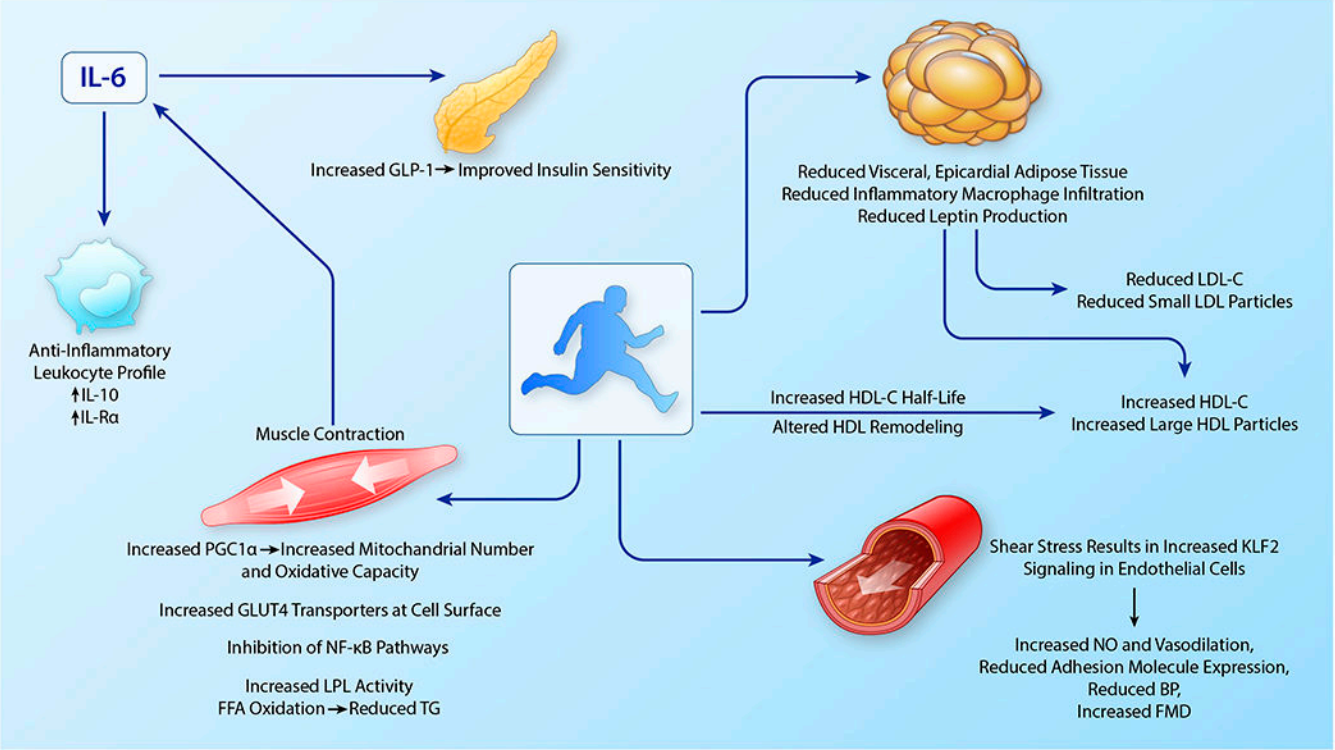

Figure 2. Weight loss-independent effects of exercise on cardiovascular disease risk in obesity.

Exercise improves multiple aspects of metabolic risk in obesity. Many of these happen at the level of the skeletal muscle and are mediated with skeletal muscle contraction which increases GLUT4 transporters at the cell surface, PGC1α expression, LPL activity, and induces IL-6 release. IL-6 increases circulating GLP-1 and has anti-inflammatory effects. Increased shear stress in the vasculature with exercise improves endothelial function and reduces blood pressure. Exercise is associated with reductions in visceral and epicardial adipose and adipose inflammation independent of weight loss. Loss of adipose tissue and reduced adipose inflammation contributes to a less atherogenic lipid profile characterized by increased HDL-C and larger HDL particles and reduced LDL-C and small LDL particles. Exercise-mediated changes in the activity of enzymes necessarily for HDL metabolism also play roles in increasing HDL size and HDL-C half-life in the circulation. (Illustration credit: Ben Smith)

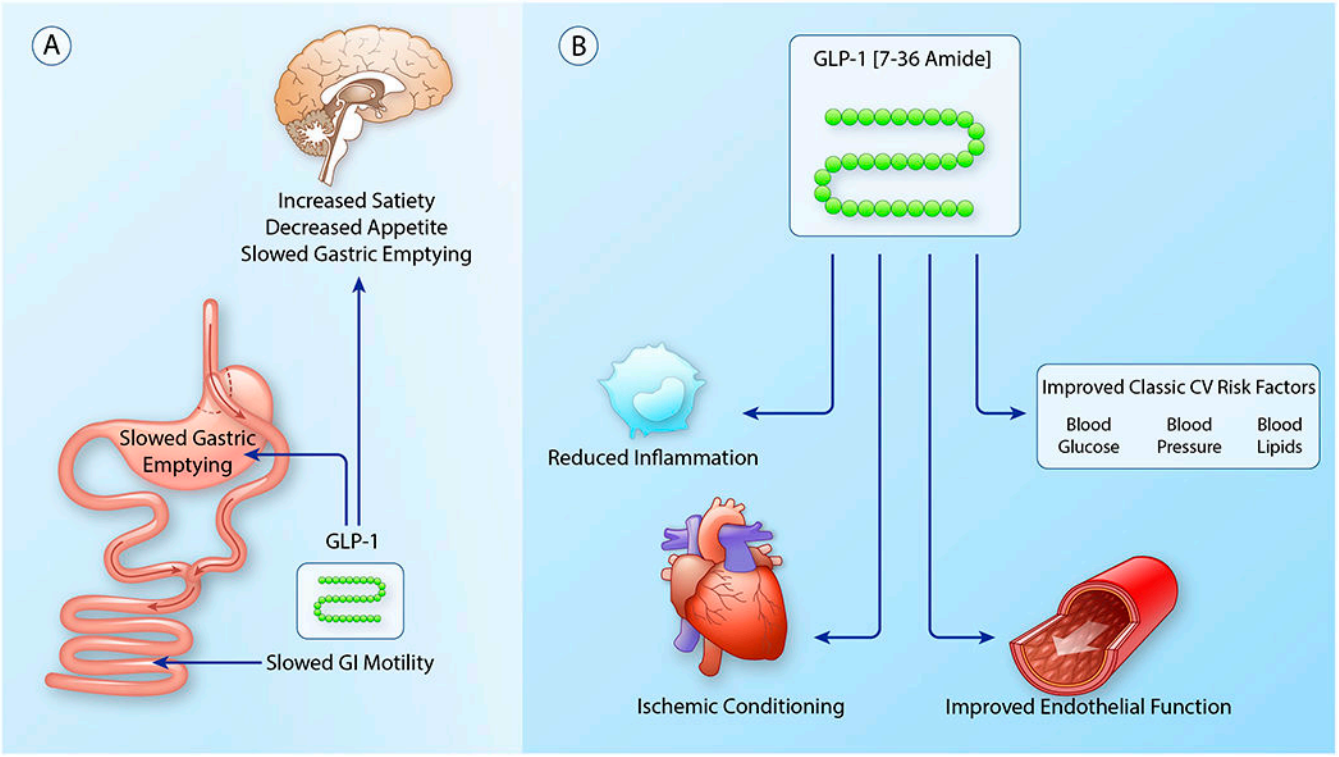

Figure 3.

(A) Pathways mediating weight loss via either pharmacologic- or metabolic surgery-induced increases in GLP-1. Metabolic surgery and GLP-1 agonists increase signaling through central and peripheral GLP-1 receptors enhancing satiety and facilitating weight loss. Central receptor activation in the hyppothalamus increases satiety, decreases appetite and slows gastric emptying. Peripheral receptors slow gastric emptying and GI motility, enhancing satiety.

(B) Weight loss-independent activity of GLP-1 in reduction of cardiovascular risk in obesity. As described in detail in the text, increased GLP-1 signaling improves traditional cardiovascular risk factors, reduces systemic inflammation, extensively benefits the vasculature and stimulates myocardial ischemic conditioning. (Illustration credit: Ben Smith)

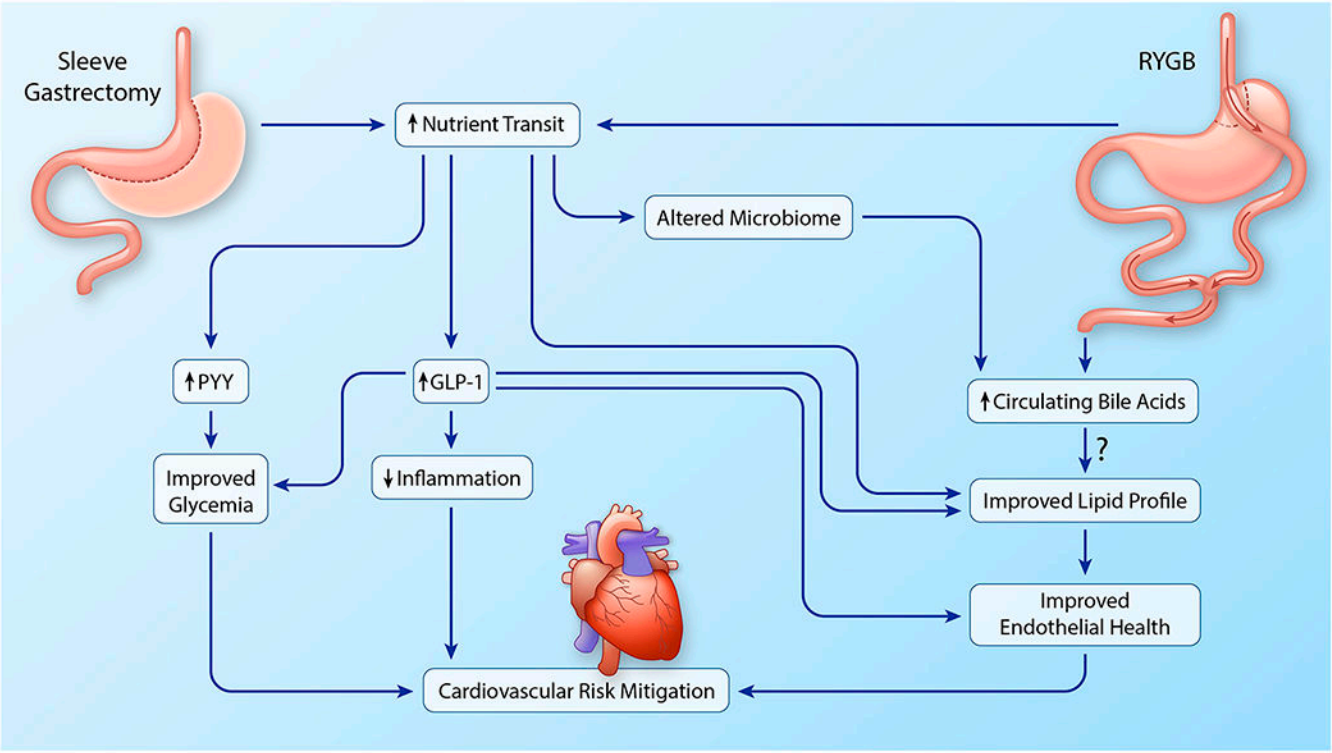

Figure 4. Weight loss-independent mechanisms of cardiovascular risk reduction in metabolic surgery.

Both RYGB and sleeve gastrectomy increase nutrient transit which results in increases in circulating PYY and GLP-1 which, in turn, improve glycemia, reduce inflammation and improve endothelial function. These activities contribute to cardiovascular risk mitigation following metabolic surgery. RYGB further increases levels of circulating bile acids which further stimulates GLP-1 release and may have additional positive effects on lipid profile (predominantly triglyceride lowering). Changes in the gut microbiome may also contribute to increased circulating bile acids after RYGB. (Illustration credit: Ben Smith)