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Medical and Surgical Obesity Treatments and Atherosclerosis: Mechanisms Beyond Typical Risk Factors

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Abstract

Purpose of review: To discuss the mechanisms by which GLP-1 agonists and bariatric surgery improve cardiovascular outcomes in severely obese patients.

Recent findings: Recent studies have demonstrated that both GLP-1 agonist use and bariatric surgery reduce adverse cardiovascular outcomes. Improvements in traditional atherosclerosis risk factors in association with weight loss likely contribute, but weight loss-independent mechanisms are also suggested to have roles.

Summary: We review the clinical and preclinical evidence base for cardiovascular benefit of LP-1 agonists and bariatric surgery beyond traditional risk factors, including improvements in endothelial function, direct impacts on atherosclerotic plaques and anti-inflammatory effects.

Keywords

Obesity; GLP-1 agonists; bariatric surgery; atherosclerosis; cardiovascular outcomes

Introduction

Obesity, officially designated as a chronic disease by the American Medical Association in 2013, is a global epidemic with steadily rising prevalence.[1,2] Over 40% of American adults

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Conflict of Interest

Dr. Heffron reports grants from Novo Nordisk (he is a site Co-Investigator of the SELECT trial and receive research support for a study of the effects of liraglutide on weight loss after RYGB). The other authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

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are obese,[1] and in 2016, approximately 13% of the world's population was obese – three times the prevalence in 1975.[3] Obesity is an independent risk factor for atherosclerosis, and the World Health Organization estimates that nearly 25% of the worldwide cardiovascular disease (CVD) burden is attributable to obesity.[4] Obesity is associated with greater prevalence and incidence of multiple causative atherosclerosis risk factors, such as diabetes, hypertension and dyslipidemia.[5-8] Obesity may also directly contribute to atherogenesis and atherosclerosis progression independent of these comorbidities. [9,10]

Lifestyle interventions – including dietary modification – are regarded as the cornerstones of obesity management, but are generally associated with only modest weight reduction and are often difficult for patients to maintain.[11] Their utility in the prevention of major cardiovascular events (death from cardiovascular causes, myocardial infarction, or stroke) in high-risk individuals (i.e., obese adults with diabetes) is also unproven: to date, no randomized trials evaluating intense lifestyle interventions have demonstrated reductions in cardiovascular events in patients with obesity.[12] Current multi-society guidelines recommend adjunctive pharmacotherapy in addition to lifestyle modification for patients with BMI ≥ 30 kg/m^2 or ≥ 27 kg/m^2 with adiposity-associated comorbidities.[13,14] Surgical therapies are recommended in addition to diet and lifestyle modification in adults with BMI ≥ 40mg/kg^2 or BMI ≥ 35mg/kg^2 with associated obesity-related comorbid conditions.[13] Despite these guidelines, only about 1% of eligible patients fill an anti-obesity prescription or undergo bariatric surgery.[15,16] This may reflect a missed opportunity for reduction of CVD risk. Although each has limitations due to their observational nature, multiple large studies strongly suggest that bariatric surgery significantly lowers risk of adverse cardiovascular events,[17-19] and multiple randomized trials evaluating cardiovascular outcomes in patients using glucagon-like peptide 1 (GLP-1) agonist agents have shown reduction in cardiovascular events.[20] Both surgery and GLP-1 receptor agonists produce significant weight loss which is associated with improvements in many typical CVD risk factors. However there is emerging evidence that additional mechanisms - including effects on vascular function, plaque composition, and platelet activity - also contribute to favorably impact cardiovascular outcomes. In this focused review, we will highlight how these effective weight loss modalities (GLP-1 agonists and bariatric surgery), beyond their well-known favorable effects on the modification of traditional risk factors, may directly alter the pathophysiologic processes underlying atherosclerosis and lead to improved outcomes.

Obesity pharmacotherapy

While not for lack of effort, the armamentarium of weight loss pharmacotherapy remains quite limited.[21] Until 2014, the United States' Food and Drug Administration (FDA) had approved only three agents: orlistat (a pancreatic lipase inhibitor), phentermine/topiramate (a combination sympathomimetic and antiepileptic agent), and naltrexone/bupropion (a combination opioid antagonist and dopamine/norepinephrine reuptake inhibitor) for the treatment of obesity. These agents - while associated with weight loss of ~6% (naltrexone/bupropion) to ~10% (phentermine/topiramate) – have not been shown to improve cardiovascular outcomes.[2,22,23] Further, several previously approved weight loss agents have been withdrawn due to significant adverse effects: sibutramine increased myocardial infarction and stroke,[24] fenfluramine was found to induce acute pulmonary hypertension

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and valvular heart disease,[25] and more recently, lorcaserin (a selective 5-hydroxytyramine 2c serotonin receptor agonist) was removed from the market after long-term safety data revealed increased rates of malignancy.[26]

GLP-1 agonists

The past decade, however, has witnessed a sea change within the medical weight loss field, namely with the development of the GLP-1 agonists. These agents, initially developed for management of diabetes, have emerged as very useful for the management of obesity. They are also the first glucose-lowering or weight loss facilitating medications to be consistently associated with improved cardiovascular outcomes – an effect that appears to be at least partly independent from their impact on body weight and reduction in blood glucose.[20,27] Importantly, at the time of this article, trials showing improved CVD outcomes with GLP-1 agonists have exclusively been performed in patients with diabetes and at doses lower than those used specifically for weight loss (though weight loss has been consistently seen in the GLP-1 agonist arm of the major cardiovascular outcomes trials).[20] Cardiovascular outcomes trials involving weight-loss dosing for GLP-1 agonists are currently ongoing.[28]

There is currently one GLP-1 agonist approved for weight loss: liraglutide (at 3.0mg daily subcutaneous dosing), largely based on the results of the SCALE (Satiety and Clinical Adiposity – Liraglutide Evidence) trial.[29] In SCALE, 3,371 adults with overweight or obesity (and without diabetes) were randomized to liraglutide (3.0mg daily subcutaneous dosing) vs. placebo. After 56 weeks, patients randomized to liraglutide had lost a mean 8.0% of their baseline weight, compared to 2.6% in the placebo arm.[29] Another GLP-1 agonist approved for the management of diabetes, semaglutide, is currently under evaluation as a weight loss treatment, and evidence suggests it may be more effective than liraglutide. The recent STEP-1 trial (Semaglutide Treatment Effect in People with Obesity) randomized 1,961 adults with overweight or obesity (like SCALE, also without diabetes) to weekly semaglutide (2.4mg subcutaneous dosing). After 68 weeks, 50.5% of patients randomized to semaglutide had lost ≥15% of their baseline weight. The mean reduction in weight from baseline in the semaglutide arm was 14.9%, a degree of weight loss only previously seen in bariatric surgery.[30]

Potential Mechanisms of Benefit in Atherosclerosis

Native GLP-1 is an incretin hormone secreted by intestinal epithelial cells in response to feeding. It binds to GLP-1 receptors in the pancreas, potentiating insulin secretion, suppressing glucagon production, and enhancing glycemic control. GLP-1 receptors are also found in the arcuate nucleus of the hypothalamus where activation is thought to increase satiety and suppress appetite.[2] As mentioned previously, there has been consistent randomized trial data showing that the use of GLP-1 agonists is associated with improved cardiovascular outcomes in patients with diabetes.[20] Beyond lowering blood glucose, GLP-1 agonists are associated with improvement of other traditional atherosclerosis risk factors in obese patients with diabetes, including improvements in blood pressure[31,32] and possibly low-density-lipoprotein cholesterol.[33] Emerging evidence suggests these benefits are observed in obese patients without diabetes, as well.[29,30] The beneficial impact on

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cardiovascular outcomes, absent in most weight loss or diabetes medications, appears unique to the GLP-1 agonist medication class as liraglutide elicits similar (or less) reduction in blood glucose compared to other diabetes agents and less weight loss than phentermine/topiramate[34,35] – suggesting weight-loss (and blood glucose-lowering) independent mechanisms of benefit. Thus, mechanisms outside of the modification of "traditional" atherosclerosis risk factors are hypothesized to play a role in the improved outcomes associated with these agents. We outline several of these mechanisms below.

Vascular Effects—GLP-1 has been shown to have direct effects on the endothelium, possibly through a nitric oxide (NO)-dependent mechanism. NO, synthesized by endothelial nitric oxide synthase (eNOS) in endothelial cells, has potent vasodilatory, anti-inflammatory, and anti-thrombotic effects.[36] Early studies showed that recombinant GLP-1 promoted endothelial vasodilation in rat pulmonary arteries, an effect that was abolished after administration of a nitric oxide (NO) inhibitor, suggesting the response may be NO-dependent.[37] The impact of GLP-1 on NO activity has been demonstrated in other in vitro studies. For example, application of exendin-4 (a form of exenatide, a GLP-1 agonist) to human coronary artery endothelial cells produced dose-dependent increases in eNOS[38] and exposure of human umbilical vein endothelial cells to either recombinant GLP-1 or exendin-4 resulted in dose-dependent increases in nitric oxide (NO) production and eNOS phosphorylation, respectively.[36,39] In a study evaluating the metabolic effects of bariatric surgery, rats that received a sham bariatric surgery but were subsequently treated with liraglutide for 8 days demonstrated improved NO bioavailability and improved endothelium-dependent relaxation.[40]

GLP-1 agonists may also improve vascular health and function via direct effects on the extracellular matrix. Matrix metalloproteinases (MMPs) are thought to promote atherosclerosis through the degradation of the extracellular matrix and by stimulating proliferation of vascular smooth muscle cells.[41] Multiple recent in vitro studies have shown that incubation of human coronary artery smooth muscle cells and coronary artery endothelial cells with GLP-1 (or exendin-4) inhibits the expression of pro-atherosclerotic MMPs in the extracellular matrix.[41,42] GLP-1 may even promote the proliferation of endothelial cells. In the above study by Erdogdu et al.,[38] incubation of human coronary artery endothelial cells with GLP-1 agonists caused an increase in cell number, hypothesized to be mediated through cAMP-dependent protein kinase (PKA) and phosphoinositide 3-kinase (PI3K) pathways. Another study demonstrated that incubation of endothelial cells with GLP-1 reduced advanced glycation end product-induced apoptosis.[43] Reduction of oxidative stress in hyperglycemia by GLP-1 may mediate this inhibition of apoptosis.[44]

Perhaps through these mechanisms, use of GLP-1 agonists has been shown to be associated with improved vascular function *in vivo*. Patients with diabetes administered recombinant GLP-1 exhibit increased flow-mediated vasodilation after brachial artery reactivity testing,[45] while another study using exenatide in diabetic patients demonstrated improved coronary flow velocity reserve in conjunction with decreased serum levels of soluble intercellular adhesion molecule-1 (ICAM-1) and soluble vascular cell adhesion molecule-1 (VCAM-1).[39] As mentioned above, a modest reduction in blood pressure has been seen in GLP-1 agonist trials;[20] although it is difficult to separate this reduction in blood pressure from the expected

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impact from weight loss achieved, it is plausible that the above mechanisms may contribute to this clinical outcome.

Additional work suggests that GLP-1 agonists may also reduce vascular stiffening and calcification. Exenatide has been shown to reduce the expression of receptor activator of nuclear factor-κB ligand (RANKL) in a dose-dependent manner, subsequently reducing the calcification of human vascular smooth muscle cells.[46] Similar findings were seen after incubating human vascular smooth muscle cells with liraglutide, inhibiting osteoblastic differentiation and calcification through activation of the PI3K/Akt/mTOR/S6K1 signaling.[47]

Direct Plaque Effects—GLP-1 agonists may stabilize atherosclerotic plaques, possibly via direct anti-inflammatory effects. In an animal model, rabbits treated with GLP-1 agonists exhibited slowed plaque progression compared to placebo, with histologic evidence of reduced macrophage infiltration, despite higher LDL-cholesterol levels than the control animals.[48] Similar findings have been seen in ApoE knockout mice treated with native GLP-1 and its split products[49] or liraglutide,[50] and in ApoE/Irs2 knockout mice (a murine model of metabolic syndrome and atherosclerosis) treated with lixisenatide or liragltuide.[51] There is also limited evidence to suggest that this effect may extend to humans. In a study evaluating patients who recently underwent carotid endarterectomies, the plaques of patients taking GLP-1 agonists, when compared to the plaques of patients not taking GLP-agonists, were of similar absolute size but exhibited less evidence of inflammation and oxidative stress along with a lower proportion of macrophage-rich areas and lower concentration of T-cells.[52] The mechanism of suppressed macrophage activation may be from a GLP-1-associated increase in adiponectin (which is thought to suppress macrophage activation)[53] or sirtuin (SIRT) expression (the exact role of SIRT in the pathophysiology atherosclerosis is still being elucidated, though several studies have suggested it has anti-inflammatory properties).[52]

Platelet Function—Obesity is associated with increased platelet activation, which may contribute to adverse atherothrombotic outcomes in the condition.[54-56] GLP-1 agonists may impact platelet function, contributing to the reduction in cardiovascular events over relatively short study periods. This may be a direct effect, as human platelets exhibit GLP-1 receptors.[57,58] An in vitro study using human platelets found that incubation with exenatide resulted in inhibition of agonist-induced platelet aggregation.[57] The same study showed that administration of a single dose of exenatide inhibited thrombus formation in vivo in a murine artery injury model. The antithrombotic effect was lost in mice without functional GLP-1 receptors.[57] In murine models of sepsis, injection of liraglutide resulted in decreased microvascular thrombosis and improved endothelial function, effects that were attenuated in GLP-1-receptor-deficient mice.[59] In the same study, incubation of human platelets and cultured monocytes with exendin or liraglutide inhibited platelet activation, presumably through a cAMP/PLA-dependent mechanism.[59] Finally, in a rat model of chronic kidney disease, administration of exendin-4 improved the function of newly created arteriovenous fistula function, reducing ADP-stimulated platelet adhesion.[60]

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Bariatric surgery

A metabolic surgical procedure was actually one of the first interventions proven to improve cardiovascular outcomes. The results of the POSCH (Program on the Surgical Control of the Hyperlipidemias) trial demonstrated that lipid lowering via partial-ileal bypass surgery reduced adverse events in individuals with coronary artery disease in the pre-statin era.[61] It is critical to note, however, that patients with obesity were excluded from this trial. In the intervening decades, metabolic surgery for obesity treatment (bariatric surgery) has grown exponentially. During this time, a number of surgeries have risen and fallen from prominence. Currently, two techniques are used in more than 95% of all bariatric surgical procedures. Sleeve gastrectomy, a procedure developed approximately 15 years ago, is the predominant procedure performed in the United States.[62] Roux-en-Y gastric bypass (RYGB), one of the earliest developed procedures, and still considered the gold-standard for diabetes treatment in the setting of obesity,[63] accounts for most of the rest.

Bariatric surgery is far more effective at achieving marked, sustained weight loss in severe obesity than either lifestyle or pharmacologic interventions,[64] and through this profound weight loss can result in complete resolution, or at least improvement, in diabetes, hyperlipidemia, and hypertension in the majority of obese patients.[65] The effects of bariatric surgery – particularly sleeve gastrectomy and RYGB – on traditional atherosclerosis risk factors are well described.[23,66] This risk factor modification is thought to contribute to reductions in major adverse cardiovascular events and mortality in those who have undergone a bariatric procedure,[17,18] including those with previous ischemic heart disease or heart failure.[19,67] However, accumulating data suggest that additional effects of bariatric surgery, beyond improvement in traditional risk factors, may suppress atherogenesis and atherosclerosis progression. These include changes in incretin and bile acid signaling, modulation of the gut microbiome, improved vascular function, altered adipokine profile, and reduced inflammation. These mechanisms will be addressed below.

Incretin and Bile Acid Signaling

As discussed above, the incretin hormone GLP-1 may improve atherosclerotic risk through diverse mechanisms beyond its role in insulin sensitization and weight loss. Several studies have demonstrated increased postprandial levels of GLP-1 following bariatric surgery, specifically following RYGB.[68,69] The unique anatomic gut arrangement following RYGB leads to rapid carbohydrate transit from the pylorus to the small intestine.[70] Additionally, the modified enterohepatic circulation of bile acids created following RYGB increases intraluminal and systemic concentrations of these compounds, which modifies the release of gut hormones such as GLP-1[71] via binding to farnesoid-X (FXR) and Takeda G-protein-coupled receptor 5 (TGR5).[72] Combined, postprandial GLP-1 secretion following RYGB is enhanced. Notably, the increases following RYGB are greater than those seen with sleeve gastrectomy,[70] suggestive of a specific role for the anatomical alterations in RYGB in inducing this response.

The increased concentrations of bile acids following RYGB may have beneficial effects on atherosclerosis via mechanisms independent from GLP-1 as well. Absence of FXR has been shown to be associated with worse lipid profiles and results in more

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extensive atherosclerotic lesions in several mouse models of hypercholesterolemia and atherosclerosis.[73,74] Additionally, administration of synthetic FXR agonists in APOE$^{-/-}$ and LDLR$^{-/-}$ mice prevents plaque formation.[75] Administration of TGR5 agonists in LDLR$^{-/-}$ mice has also been shown to attenuate atherosclerosis via dampened intraplaque inflammation.[76] Taken together, increased concentrations of bile acids following RYGB could plausibly have direct anti-atherogenic effects via FXR and TGR5 agonism.

The increases in GLP-1 and bile acids after RYGB may mediate the rapid and surgery-specific metabolic improvement achieved within days of the procedure, before any substantial weight loss occurs.[40] For example, a study by Osto et al. showed that eight days after RYGB in rats, higher plasma levels of bile acids and GLP-1 were associated with improved endothelium-dependent vascular relaxation ex vivo, as measured by percent of pre-contraction to norepinephrine in isolated aortic rings.[40] The beneficial effect of bariatric surgery on vascular function outside of GLP-1- and bile acid-mediated effects is discussed further below.

Gut Microbiome

Obesity is associated with gut dysbiosis, which encompasses both modifications in gut microbiota composition as well as reduced microbial gene richness and diversity.[77] Bariatric surgery has been shown to alter the gut microbiota composition in both short-term[78,79] and long-term studies.[80] Tremaroli et al. analyzed the gut microbiota of weight-stable women nine years after randomization to either RYGB or vertical banded gastroplasty (VBG). They found significant differences in microbiota composition for RYGB versus non-operated women with BMI matched to each patient's pre-surgical BMI (OBS), but not for VBG versus OBS, again highlighting the unique metabolic effects of RYGB – in this case, even nine years after the procedure.[80] Importantly, the microbiomes of OBS and non-operated women with BMI matched to the patient's post-surgical BMI were similar, strongly suggesting that differences in gut microbiota occur due to bariatric surgery specifically and not from weight loss itself.

Bariatric surgery leads to significantly increased gut microbiota richness.[79] This increase in microbial diversity is associated with reduced insulin resistance, adiposity, dyslipidemia, and systemic inflammation.[81] Increased microbial diversity may also reduce bacterial energy harvest from food and decrease caloric absorption, thus facilitating weight loss.[82] Additionally, the altered microbiota likely contributes to increased circulating bile acid concentrations and associated increases in GLP-1,[23,72] as the gut microbiota is an important regulator of bile acid pool composition.[83,84]

It is important to mention that, in contrast to the wholly beneficial impacts of medical and surgical weight loss therapies discussed so far, several studies in both animals and humans have demonstrated that circulating trimethylamine-N-oxide (TMAO) is increased following bariatric surgery.[68,69,80,85] TMAO, a metabolite exclusively generated by the gut microbiota from dietary phosphatidylcholine and carnitine, is mechanistically linked to both atherosclerosis and thrombosis.[86,87] Interestingly, Tremaroli et al. found that TMAO was increased following RYGB but not VBG.[80] In another study, Trøseid and colleagues reported equivalently increased TMAO levels following RYGB and duodenal

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switch procedures, whereas TMAO levels were unchanged following weight loss induced by lifestyle interventions.[85] Finally, there are minimal data on the effect of SG on TMAO, despite its status as the dominant bariatric surgical procedure for more than a half-decade. These observations highlight the persistent uncertainty surrounding the role of the gut microbiome in atherogenesis and progression. The relevance of the changes following bariatric surgery remains unclear and highlight the need for further study of the myriad metabolic impacts of different bariatric procedures.

Vascular Function and Subclinical Atherosclerosis

Several surrogate markers of endothelial function and subclinical atherosclerosis have been used to evaluate the cardiovascular effects of bariatric surgery, such as carotid intima-media thickness, flow-mediated dilation, and nitrate-mediated dilation.[88,89] These markers have been shown to be strong predictors of CV events,[90-93] and are suboptimal in obese subjects.[94,95]

A meta-analysis of studies evaluating changes in in the above measures of vascular function and plaque burden in obese patients undergoing bariatric surgery found that surgery resulted in a significant reduction of intima-media thickness and increase in brachial artery flow-mediated dilation.[88] These effects were enhanced when restricted to subjects who underwent RYGB specifically. While there was no significant increase of nitrate-mediated dilation after bariatric surgery when all surgical procedures were included, significant improvements were again seen when restricted to subjects undergoing RYGB. One study included in the meta-analysis also included a group treated with medical therapy alone and demonstrated that bariatric surgery resulted in a greater improvement in endothelial function than medical treatment alone, although the non-surgical weight loss group experienced far less weight loss.[96] Nonetheless, these data suggest a cardioprotective effect of bariatric surgery, specifically RYGB, through beneficial effects on endothelial function and among patients with established subclinical atherosclerosis,[88] beyond that expected with the improvement of traditional atherosclerosis risk factors associated with weight loss.

One potential mechanism by which bariatric surgery has vascular protective effects is via GLP-1. As discussed above, postprandial levels of GLP-1 are elevated following bariatric surgery.[68,69] Additional mechanisms by which bariatric surgery may enhance vascular function include improvement in the hypercoagulable state of obesity via modulation of the hemostatic and fibrinolytic balance,[97] and reduction in obesity-associated systemic inflammation,[98] which will be further discussed in the next section.

Adipokine normalization

Obesity is characterized by dysfunctional adipose tissue, which is implicated in atherosclerosis development and progression partly through increased secretion of leptin and deficient adiponectin.[99] Leptin concentrations similar to those found in obesity have been shown to impair NO-dependent coronary artery vasorelaxation induced by acetylcholine in dogs both in vitro and in vivo,[100] and leptin has been shown to augment ADP-induced platelet aggregation in vitro in studies of human platelets when applied at concentrations found in obese subjects.[101,102] Furthermore, in vivo studies suggest that

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leptin is directly involved in atherogenesis. *Ob/ob* mice—mice lacking the gene responsible for the production of leptin—are resistant to atherosclerosis,[103] and exogenous leptin administration has been shown to aggravate spontaneous atherosclerotic lesions in ApoE$^{-/-}$ mic.[104] Hyperleptinemia has also been associated with several additional proatherogenic mechanisms including increased oxidative stress, vascular smooth muscle cell (VSMC) proliferation, and vascular inflammation.[105] Therefore, it is unsurprising that increased leptin levels are associated with increased intima-media thickness, atheroma formation, and myocardial infarction.[106]

Adiponectin has anti-atherosclerotic properties via enhanced endothelium-dependent vasodilation, reduced VSCM proliferation, reduced scavenger receptors in macrophages, and increased cholesterol efflux from atherosclerotic plaques.[107] Adiponectin has also been shown to reduce atherosclerosis burden in ApoE-knockout mice.[108] This study implicated reduced endothelial activation and increased plaque inflammation. This could possibly be mediated by adiponectin-elicited increases in NO production through eNOS activation which has been shown to improve endothelial cell function in vitro.[109] Increased adiponectin may also reduce atherosclerosis and improve cardiovascular outcomes by inducing increased cholesterol efflux from plaques.[107] Adiponectin is a strong predictor of high-density lipoprotein cholesterol efflux capacity, a functional marker inversely associated with incidence of cardiovascular events,[110] irrespective of BMI and fat distribution.[111]

A recent meta-analysis by Askarpour et al. demonstrated that leptin levels are substantially decreased, and adiponectin levels increased following bariatric surgery.[112] Furthermore, investigators comparing cardiovascular risk markers following intensive medical therapy and bariatric surgery found that RYGB results in relatively larger decreases in leptin was significantly and increases in adiponectin.[113] By correcting these abnormalities in circulating adipokines, the benefits described are suggested to play a role in improved cardiovascular outcomes following bariatric surgery. For example, bariatric surgery has been shown to restore CEC in both rats and humans.[40,114-116] Aron-Wisnewsky et al. showed that while ABCA1-independent CEC increased significantly following RYGB, it was not significantly affected by intensive medical therapy.[114] Interestingly, Heffron et al. showed that SG, but not RYGB, improved ABCA1-independent CEC at 6-month follow-up. While both procedures improved ABCA1-independent CEC at 12-month follow-up, SG produced overall superior improvement.[115] Further studies are needed to further elucidate these surgery-specific effects on CEC.

Conclusions

The worldwide prevalence of obesity continues to rise, and through a variety of mechanisms, contributes to the global burden of cardiovascular disease. The prevention of obesity - through the foundation of a healthy lifestyle - remains paramount, but is increasingly failing. With the development of the GLP-1 agonists and increasing use of bariatric surgery, we now have pharmacologic and surgical options to not only augment weight loss but to improve cardiovascular outcomes in patients with severe obesity. While we have outlined many potential mechanisms by which GLP-1 agonists and bariatric surgery may reduce atherosclerotic cardiovascular disease, few have been rigorously tested. Further study and

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improved understanding of the weight-loss independent mechanisms underlying reduced atherosclerotic cardiovascular disease in obese patients treated with surgical management or GLP-1 agonists is sorely needed. The expanded knowledge may lead to the development of novel therapies to reduce atherosclerotic cardiovascular disease risk in patients with or without obesity.

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