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Bariatric Surgery: Remission of Inflammation, Cardiometabolic Benefits, and Common Adverse Effects

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Obesity is associated with increased mortality as a result of several comorbidities which occur in tandem with the obese state. Chronic inflammation is well documented in obesity, and evidence from numerous studies support the notion that the increased inflammation in individuals with obesity accentuates the comorbidities seen in this condition. The remission of comorbidities such as metabolic, cardiovascular, and neurological complications occurs following bariatric procedures. Bariatric surgery significantly reduces mortality and results in remarkable weight loss and reversal in several obesity-related comorbidities. There is indisputable evidence that the resolution of inflammation that occurs after bariatric surgery mitigates some of these comorbidities. With the increasing use of bariatric surgery for the treatment of severe obesity, it is pivotal to elucidate the underlying mechanisms responsible for the notable improvements seen after the procedure. This review summarizes underlying mechanisms responsible for the remission of obesity-related abnormalities and discusses the common adverse effects of bariatric surgery. Well-stratified, large-scale studies are still needed for a proper evaluation of these underlying mechanisms.

Key Words: bariatric surgery, obesity, inflammation, insulin resistance, hypertension, hypogonadism

The cardinal foundation of the link between obesity and inflammation was laid by Hotamisligil et al. [1], who demonstrated that in the insulin-resistant ob/ob mouse the expression of tumor necrosis factor alpha (TNFα) in adipose tissue and the concentration of TNFα in serum were increased. In addition, the infusion of soluble TNFα receptor into these animals to bind and neutralize TNFα led to the restoration of insulin sensitivity. Hence, TNFα, an inflammatory cytokine, may be a mediator of insulin resistance.

These observations led to an explosion of work in this area. Adipose tissue in obese humans was shown to express increased levels of TNFα and other inflammatory mediators. Increased plasma concentrations of TNFα were also demonstrated in obese humans and these were shown to fall following caloric restriction and weight loss [2, 3]. Oxidative stress, related to inflammation, was also shown to be increased in obese humans and it diminished

Abbreviations: ACE, angiotensin-converting enzyme; ADAM, A Disintegrin and Metalloproteinase; BNP, brain natriuretic peptide; BPD/DS, biliopancreatic diversion/duodenal switch; CRP, C-reactive protein; GLP, glucagon-like peptide; GSK, Glycogen Synthase Kinase; IGF, insulin-like growth factor; IL, interleukin; IRS, insulin receptor substrate; LIGHT, tumor necrosis factor superfamily member 14; MCP-1, monocyte chemoattractant protein-1; MMP, matrix metallopeptidase; PPAR γ, peroxisome proliferator activated receptor γ; PYY, peptide YY; RYGB, Roux-en-Y gastric bypass; SFCA, short-chain fatty acid; SOCS-3, suppressor of cytokine signaling 3; TNFα, tumor necrosis factor alpha.

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after caloric restriction and weight loss [4]. Further investigations revealed that obesity-related insulin resistance could result from a diminution in insulin receptor substrate-1 (IRS-1) in animals, secondary to an increase in suppressor of cytokine signaling 3 (SOCS-3), which binds to IRS-1 and leads to its ubiquitylation and proteolysis in experimental animals [5]. SOCS-3 protein also interferes with leptin signaling, thus causing leptin resistance [6]. Several other inflammatory mediators such as protein kinase Cβ, Jun N-terminal kinases, IκB kinase, S6 Protein Kinase, and mammalian target of rapamycin have also been causally implicated in the development of insulin resistance in human obesity as they can interfere with insulin signal transduction at the IRS-1 level [7-9].

Several comorbidities such as diabetes, hypertension, cardiovascular/renal/hepatic complications, hypogonadotropic hypogonadism, bronchial asthma, and Alzheimer's disease are associated with obesity [10-13]. The mechanisms underlying these associations are not fully understood. In view of the marked increase in the association of severe obesity with prediabetes, type 2 diabetes, and hypertension, it is important to get a better understanding of the underlying mechanisms involved. The marked weight loss that follows bariatric surgery provides us with an effective opportunity to investigate some of these mechanisms and their relevance to the pathogenesis of insulin resistance, hypertension, hypogonadism, and other obesity-related comorbidities. This review highlights pertinent benefits and adverse effects of bariatric surgery; however, a comprehensive overview of all the benefits or deleterious effects of bariatric surgery is beyond the scope of this review.

1. Obesity and Inflammation: Reversal with Weight Loss

Following bariatric surgery, inflammatory mediators and cytokines closely associated with obesity and insulin resistance are expected to gradually decline. In a study published in 2006 [14], monocyte chemoattractant protein-1 (MCP-1) fell remarkably (by over 50%) following bariatric surgery. This observation was also noted in 2012, 6 months after a Roux-en-Y gastric bypass (RYGB) procedure [15], where a reduction in plasma concentrations of endotoxin was observed. Substantial decreases in the expression of toll-like receptors, TLR-4 and TLR-2 (the respective receptors for endotoxin and Gram-positive bacterial products), occurred in mononuclear cells. In addition, intranuclear binding of nuclear factor kappa B, a major proinflammatory transcription factor, also fell. Concomitant reductions in plasma concentrations of matrix metallopeptidase (MMP)-9 and C-reactive protein (CRP) were seen and there was also a reduction in the expression of CD14, the marker of activated monocytes. This clearly shows a comprehensive reduction in inflammation systemically. In addition, there was a parallel reduction in fasting glucose and insulin concentrations, reflected in reduced Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), an index of insulin resistance. In a number of studies, however, a reduction in CRP appears to be the only marker of inflammation shown to consistently decline after bariatric surgery. Marked decreases in CRP are seen within 1 month following bariatric procedures, with more prominent reductions seen in insulin-sensitive patients [16]. Also, insulin-sensitive patients show earlier and more marked decreases in markers of inflammation than patients who are insulin resistant following bariatric surgery. In a study, weight loss from metabolic surgery resulted in reductions in CRP in the third, sixth, and twelfth month after the procedure in nondiabetic patients whereas significant reductions in CRP were observed in patients with diabetes only 12 months after bariatric surgery [17]. Similar observations were noted for concentrations of serum tartrate-resistant acid phosphatase 5a and interleukin (IL)-6 in the study [17].

Although it is well established that the obese state is associated with chronic, low-grade inflammation [18, 19], the slower and reduced decline in inflammatory mediators/cytokines in obese patients with diabetes compared with their nondiabetic counterparts following bariatric surgery requires further investigation. One possible explanation is the greater intensity of inflammation due to hyperglycemia and increased free fatty acid concentrations in obese patients with diabetes [20]. Also, higher expression of markers of inflammation

before bariatric surgery may also predict lower weight loss in the first 3 months after the procedure [21]. Studies on the concentrations of TNFα, IL-6, MCP-1, and other inflammatory cytokines/markers following bariatric surgery have been inconsistent. While some studies have observed reductions in the levels of these inflammatory markers following metabolic surgery, others have reported no such decline. Nevertheless, the universal decline in the baseline levels of CRP across studies gives credence to the fact that substantial attenuation of inflammation occurs following metabolic surgery-induced weight loss. Factors influencing the discrepancies seen across the studies may include the differences in the baseline severity of insulin resistance in the study populations and variability in the expression of inflammatory mediators. The limited study sizes, study design/laboratory techniques, timing of evaluation of postoperative outcomes, and inherent differences in study populations are some factors that may have considerably increased the heterogeneity across the studies. Anti-inflammatory mediators such as adiponectin and IL-10 are reduced in the obese state and most studies report an increase in these mediators (especially those of adiponectin) after bariatric surgery. Adiponectin is an antiatherogenic adipokine that also protects against metabolic disorders through improvements in insulin secretion and sensitivity [22]. Table 1 summarizes observed changes in inflammation and endothelial function following bariatric surgery in some studies.

2. The Effect of Bariatric Surgery on Insulin Resistance and Type 2 Diabetes

A remarkable improvement in glycemia is seen in obese patients with diabetes who undergo bariatric surgery, even before clinically significant weight loss occurs. The improvement in glycemia manifests within a few days following the procedure. A decrease of 50% in HOMA-IR is seen within 1 week following procedures such as RYGB [39]. Partial or total remission rates in type 2 diabetes as high as 80% to 90% have been observed to occur following bariatric surgery [40-45].

It is known that postoperative complete remission of type 2 diabetes is mostly dependent on the duration and severity of the diabetes. Patients with shorter duration of diabetes and/or less severity (not requiring insulin) are more likely to undergo complete remission following bariatric surgery [42]. Also, patients with diabetes who have complications such as albuminuria and neuropathy have also been noted to show significant improvement following bariatric surgery [42, 46]. In addition, 50% of patients with diabetic neuropathy have reported symptomatic improvement [42].

Although the mechanisms underlying the postoperative improvement in glycemic control and clinical outcomes are dependent on a constellation of factors including the type of anatomic procedure, it is important to note that the acute caloric restriction and the immediate dramatic increase in the levels of the gut peptide glucagon-like peptide (GLP)-1 after surgery largely contribute to the immense improvement in glycemia seen within days of the procedure [39, 47]. This enhanced GLP-1 response, shown to persist in the long term, improves insulin action and β-cell function [48]. Strikingly elevated postprandial GLP-1 levels are seen more commonly with biliopancreatic diversion/duodenal switch (BPD/DS) procedures and RYGB, followed by vertical sleeve gastrectomy, and then gastric banding [48]. Similarly, resolution of diabetes and weight loss are greater with BPD/DS procedures followed by gastric bypass, sleeve gastrectomy, and then gastric banding [44]. It appears that the procedures which alter the normal anatomy of the gastrointestinal tract (such as BPD/DS and gastric bypass) are more effective for weight loss and amelioration of diabetes than restrictive procedures like sleeve gastrectomy and gastric banding. Early exposure of the distal intestinal epithelium to nutrients via anatomic alteration (BPD, gastric bypass) and expedited gastric and small bowel transit (sleeve gastrectomy) are seen following bariatric procedures and these seem to be the underlying factors responsible for the marked enhancement in GLP-1 response [49]. Peptide YY (PYY) levels also increase, and a fall in ghrelin levels is seen after most bariatric procedures. Since GLP-1 and PYY are appetite

Table 1. Inflammatory outcomes after bariatric surgery

Surgical procedure	Postoperative period	Inflammatory outcome
RYGB [15]	6 months	↓CRP; ↓MMP-9; ↓MCP-1 ↓NF-κB binding; ↓LPS; ↓CD14; ↓TLR-2; ↓TLR-4
RYGB [23]	12 months	↓CRP; ↑Adiponectin ↓sTNFR2; ↔sTNFR1; ↓IL-18
RYGB [23]	6 months	↓CRP; ↓Leptin; ↓Resistin; ↓ICAM-1; ↓TNFα ↓PAI-1; ↑Adiponectin; ↑IL-10; ↔IL-6
RYGB [24]	6 and 12 months	↓CRP; ↓Leptin; IL-6 gene expression in subcutaneous adipose tissue; ↔ TNFα
RYGB [25]	3, 6 and 12 months	↓CRP; ↓IL-6; ↑Adiponectin
	3 months	↑TNFα
RYGB [26]	3 weeks and 3 months	↓sTNFR1 ↑Adiponectin
	3 weeks, 3 months and 6 months	↓Leptin
	6 months	↓CRP; ↔TNFα; ↔IL-6
RYGB [27]	Average of 13 months	↓CRP; ↑Adiponectin; ↓Leptin ↓SAA; ↓sialic acid ↔TNFα; MCP-1(tendency to ↓)
RYGB [16]	6 months and 12 months	↓CRP; ↓SAA; ↓IL-6
RYGB [28]	3 months	↓Expression of chemoattractant genes (MCP-1, CSF-3, and PLAUR)
RYGB [29]	12 months	↓IL-1; ↓IL-6; ↓TNFα; ↓Ghrelin; ↓Resistin; ↑Adiponectin
	6 months and 12 months	↓TBARS
	3 months, 6 months, and 12 months	↑Catalase; ↑Superoxide dismutase
RYGB [30]	1 year	↓CRP; ↓IL-6; ↓PAI-1 ↓Protein C and activated protein C ↓Soluble thrombomodulin; ↓soluble E-selectin
RYGB, SG, and AGB [31]	12 months	↓MCP-1; ↓MIF; ↓CCL-18
RYGB and SG [32]	1 year	↓CRP; ↓Endogenous thrombin potential; ↓Fibrinogen
RYGB and SG [33]	1 year	↓CRP; ↓TNFα; ↓IL-6
RYGB and SG [34]	6-12 months	↓CRP; ↑Adiponectin
SG [35]	2 months and 8 months	↓CRP; ↓Serum ferritin
	8 months	↓IL-6; ↓Leptin; ↓Hepcidin
SG [36]	1 month and 6 months	↓CRP; ↓Leptin
	6 months	↓IL-6; ↔Adiponectin; ↔IL-10
VBG and BPD [37]	Average of 4 months (4.2 ± 0.8 months)	↓CRP; ↓sialic acid; ↓E-selectin; ↓P-selectin; ↓PAI-1; ↓VWF ↔VCAM-1; ↔ICAM-1; ↔ACE; ↔thrombomodulin ↔TNFα; ↔sTNFR1, ↔sTNFR2; ↔IL-6
AGB [38]	1 year	↓CRP; ↔TNFα; ↔ IL-6

↔, no change; CSF-3, colony stimulating factor-3; PLAUR, plasminogen activator urokinase receptor; MCP-1, monocyte chemotactic protein-1; MIF, macrophage migration inhibitory factor; CCL-18, chemokine ligand-18; PAI-1, plasminogen activator inhibitor-1; VCAM-1, vascular cell adhesion molecule-1; ICAM-1, intercellular adhesion molecule-1; ACE, angiotensin-converting enzyme; MMP-9, Matrix metallopeptidase 9; LPS, lipopolysaccharide, NF-κB, nuclear factor kappa B; sTNFR1, soluble tumor necrosis factor alpha receptor 1; sTNFR2, soluble tumor necrosis factor alpha receptor 2; TLR, toll-like receptor; SAA, serum amyloid A; VWF, von Willebrand factor; TBARS, Thiobarbituric acid reactive substances; VBG, vertical banded gastroplasty; BPD, biliopancreatic diversion; AGB, adjustable gastric banding; SG, sleeve gastrectomy, RYGB, Roux-en-Y gastric bypass.

suppressants and ghrelin stimulates appetite, these changes reduce caloric intake and induce weight loss [47].

Modifications in the gut hormones coupled with appropriate alterations in neural signaling and appetite suppression, and the associated impressive weight loss following bariatric procedures result in improved glucose homeostasis and amelioration or complete resolution of diabetes [47]. In addition, alterations in bile acid signaling and the gut microbiome play a role. Increments in serum bile acids are well documented following

procedures such as RYGB [50]. Bile acids activate the G protein-coupled receptor TGR5, stimulating intestinal L-cell secretion of GLP-1 and PYY [47-50]. Bile acids also regulate gut microbiota composition via binding to the nuclear Farnesoid X Receptor in the intestine [50]. The bile acid-activated Farnesoid X Receptor is pivotal in regulating bile acids, lipids, glucose homeostasis, inflammatory responses, and intestinal barrier function. The gut microbiota have bile salt hydroxylase activity and are also key modulators of bile acids [51]. Thus, the bile acid–microbiota interaction after bariatric surgery influences the metabolic effects observed.

3. The Effect of Bariatric Surgery on the Gut Microbiome

The postsurgical alterations in gut microbiome that occur after bariatric surgery do not appear to have long-term effects on weight loss because the changes seen in the gut microbiome after surgery often reverse to the presurgical baseline levels within 1 year [52]. Factors contributing to gut microbiome alteration after metabolic surgery include dietary changes, anatomic rearrangement, nutrient flow, luminal pH changes, alterations in bile acid metabolism [52]. Gut microbial diversity is seen to increase after metabolic surgery, although inconsistent observations are reported in the literature especially for changes that occur in Bacteroidetes and Firmicutes phyla. On the other hand, postsurgical increase in the phyla Proteobacteria and Verrucomicrobia (*Akkermansia muciniphila*) are often reported [52, 53]. *Akkermansia muciniphila* is well documented to confer protective effects against metabolic disorders including obesity [54, 55]. *Akkermansia muciniphila* generates mucin, which provides a protective lining for the gut mucosa, and this may prevent absorption of endotoxin and other toxins from the gut.

Increase in short-chain fatty acids (SCFAs) such as butyrate and propionate from fermentation of polysaccharides by these gut microbiota also has immense metabolic and anti-inflammatory benefits. SCFAs activate the nuclear receptor peroxisome proliferator activated receptor γ (PPARγ) without inducing PPARγ-mediated adipogenesis [56], and PPARγ ligands suppress inflammatory gene expression via the suppression of nuclear factor kappa B [57].

SCFAs enhance intestinal barrier function. They inhibit the degradation of primary bile acids to the carcinogenic secondary bile acids, and decrease the solubility of free bile acids, thus rendering the bile acids less carcinogenic. SCFAs lower intracolonic pH, hence preventing the growth of pH-sensitive pathogenic bacteria, and they also promote satiety by modulating secretion of satiety peptides from the gut [58].

4. Reversal of Hypertension and Cardiometabolic Risk after Bariatric Surgery: Underlying Mechanisms

Amelioration or resolution of hypertension in obese individuals occurs after bariatric surgery (Fig. 1). We have shown that the levels of vasoconstrictors such as angiotensinogen, angiotensin II, renin, and endothelin-1 fall with bariatric surgery-induced weight loss while vasodilators such as atrial natriuretic peptide significantly increase after the surgery procedure [59]. A marked fall in neprilysin, which is known to catalyze the degradation of natriuretic peptides, was also seen in our study [59], while no changes were seen in brain natriuretic peptide (BNP), cyclic guanosine monophosphate, and angiotensin-converting enzyme (ACE) levels. In addition, there is a marked reduction in insulin and leptin resistance, reduction in adiposity, decreased activation of the renin–angiotensin–aldosterone system, and improved endothelial function following bariatric surgery, all of which contribute to the decrease in blood pressure [31].

These decreases in vasoconstrictors, increases in vasodilators, and natriuresis (through atrial natriuretic peptide) are key underlying factors mediating reduction in blood pressure after bariatric surgery. The lack of changes in the levels of cyclic guanosine monophosphate

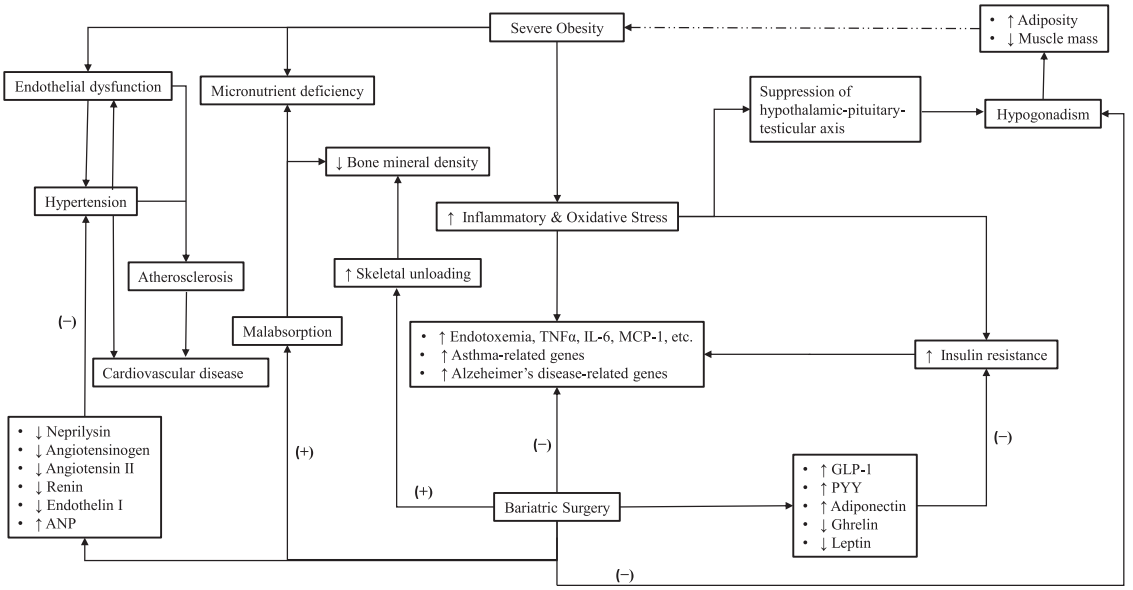

Figure 1. Schematic representation of some of the effects of bariatric surgery on obesity-related comorbidities and inflammation. The increased inflammatory and oxidative stress seen in severe obesity fosters endotoxemia and insulin resistance. Increased predisposition to asthma and Alzheimer's disease is seen (with notable increases in genes related to these conditions observed). Multifactorial factors in severe obesity such as insulin resistance and systemic inflammation augment the risks for these conditions. Endothelial dysfunction and insulin resistance in obesity also potentiate hypertension and atherosclerotic cardiovascular disease. Hypogonadotropic hypogonadism is seen in severe obesity which further augments adiposity. Bariatric surgery results in the remission of oxidative stress, endotoxemia, insulin resistance, hypertension, and hypogonadism, but also accelerates skeletal unloading and micronutrient deficiencies.

and ACE in our study [59] is consistent with the observations of Vázquez et al. [37]. However, our observations on BNP is in sharp contrast with the study by Changchien et al. [60], where significant increases in BNP were seen after bariatric surgery which correlated with weight loss. Obstructive sleep apnea in obese people is also a significant contributor to the hypertension seen in these patients. Increased activation of the sympathetic nervous system and inflammatory/oxidative stress are observed with obstructive sleep apnea. The intermittent hypoxia activates the renin–angiotensin–aldosterone system. Nocturnal hypertension then ensues and this elevation in blood pressure persists during the day.

Resolution of obstructive sleep apnea and dyslipidemia (reductions in triglycerides, low-density lipoprotein, and total cholesterol, and increment in high-density lipoprotein cholesterol) occur following bariatric surgery-induced weight loss. Also, amelioration of other obesity-related comorbidities including metabolic syndrome, chronic kidney disease, left ventricular hypertrophy, and nonalcoholic fatty liver disease are seen after bariatric surgery [61]. In a recently published retrospective cohort study, a substantial reduction in all-cause mortality and incident cases of major adverse cardiovascular events such as coronary artery events, cerebrovascular events, nephropathy, heart failure and atrial fibrillation was noted in those who had bariatric surgery [62]. The marked reductions in obesity-related comorbidities after bariatric procedures significantly contribute to the decrease in cardiovascular disease mortality.

5. Low Testosterone in Male Obesity: Reversal with Bariatric Surgery

Hypogonadism is highly prevalent (25%) in the obese, male population [63]. In obese, adolescent males, testosterone concentrations are approximately 50% lower than those of normal males [11, 63]. The low testosterone levels in the obese adult or adolescent males

further potentiates excess accumulation of fat mass [64]. The mechanisms underlying testosterone deficiency in the obese state have not been fully elucidated. Elevated levels of saturated fatty acids are seen in obesity and are strongly linked to insulin resistance, leptin resistance, and inflammation [65-67]. The increased proinflammatory cytokines and leptin in the obese state induce hypothalamic endoplasmic reticulum stress, suppress the hypothalamic–pituitary–testicular axis, and inhibit testicular steroid production [68, 69]. High-dose palmitate and hypothalamic endoplasmic reticulum stress have been shown to repress GnRH gene expression by upregulating the expression of cFos, which is a subunit of the proinflammatory transcription factor activator protein 1 [70]. Following metabolic surgery, significant reductions in saturated fatty acids are seen, which is mainly due to a decrease in the proportion of palmitic acid [71].

RYGB-induced weight loss leads to the suppression of cFos/activator protein 1 transcription activity [72]. Decreased sex hormone binding globulin is also seen in the obese due to insulin resistance and this contributes to the reduction in total testosterone but not free testosterone levels. Interestingly, the neuronal insulin receptor knockout in mice leads to neuronal and systemic insulin resistance, which is also associated with hypogonadotropic hypogonadism [73]. Clearly, there is a parallelism between insulin resistance and hypogonadism in diabetes and obesity and the neuronal insulin receptor knockout animal model. Total and free testosterone concentrations significantly increase after bariatric procedures [74, 75]. Also, reversal of obesity-related low testosterone levels occur with substantial weight loss after bariatric surgery and an approximately 50% increment in free testosterone concentration is seen [75].

6. Effect of Bariatric Surgery on Asthma Control

The proinflammatory state of obesity is associated with increased prevalence of asthma (Fig. 1). A linear relationship exists between the 2 entities such that with increases in body weight, the risk of asthma increases [76, 77]. Obesity increases the odds of having asthma by over 2.5-fold when compared with those with normal body mass indices [77]. The underlying mechanisms responsible for the link between asthma and obesity is not fully understood, but some factors such as obesity-related mechanical changes in the airways, increased gastroesophageal reflux, and increased inflammatory/oxidative stress with obesity have been implicated.

Declines in expiratory reserve volume, vital capacity, total lung capacity, residual volume, and functional residual capacity have been documented with increasing body mass index [78]. The elevated levels of inflammatory cytokines seen in the obese state such as TNFα may also play a substantial role in the obesity–asthma link. Increased expression of TNFα messenger ribonucleic acid is seen in the airway of subjects with asthma [79]. Even in normal subjects, inhaled recombinant human TNFα has been shown to increase airway responsiveness with neutrophilic infiltration [80]. Bariatric surgery results in substantial improvements in the symptoms of asthma. Reductions in markers of airway hyper-responsiveness and asthma-related inflammation occur after the procedure [81]. The expression of asthma-related genes and cytokines, such as IL-4, tumor necrosis factor superfamily member 14 (LIGHT), MMP-9, MCP-1, and its chemokine receptor type 2 receptor, are increased in patients with obesity and insulin resistance [12]. The role of IL-4 in asthma pathogenesis is well established [82, 83]. IL-4 stimulates the production of immunoglobulin E. The binding of immunoglobulin E to its receptor activates mast cells and basophils, inducing the release of histamine and prostaglandins that trigger bronchoconstriction.

Remodeling of the bronchial architecture in asthma is mediated by cytokines such as LIGHT (via binding to the lymphotoxin-β receptor) and MMP-9 [84]. MCP-1 and other cytokines also mediate chemotaxis of inflammatory cells into the bronchi [85]. Significant reductions in these asthma-related factors are seen following bariatric surgery-induced weight loss [12]. We noted reductions in the expression of IL-4 by 49%, LIGHT by 29%, lymphotoxin-β receptor by 33%, A Disintegrin and Metalloproteinase (ADAM)-33 by 20%,

MMP-9 by 59%, MCP-1 by 23%, and chemokine receptor type 2 by 27%. Plasma nitric oxide metabolites also fell by 22%. Consistent with this observation is the fact that intravenous infusion of insulin acutely suppresses the expression of IL-4, lymphotoxin-β receptor, and ADAM-33, while reducing the plasma concentrations of LIGHT, TGFβ, MCP-1, and MMP-9 [86]. Thus, bariatric surgery and weight loss result in changes similar to those exerted by insulin acutely. Undoubtedly, the overall reduction in inflammation and the restoration of insulin sensitivity following bariatric surgery has a beneficial effect on the expression of asthma-related genes and the risk of bronchial asthma.

7. Possible Reversal of the Risk for Alzheimer's Disease with Bariatric Surgery

Obesity and insulin resistance are significant risk factors for Alzheimer's disease [13] (Fig. 1). The major factors implicated in the increased risk for Alzheimer's disease in the obese, insulin-resistant state are decreased action of insulin, chronic inflammatory/oxidative stress, amyloid-β protein accumulation, and mitochondrial dysfunction [87]. Insulin has neuroprotective properties, and brain insulin signaling has been implicated in promoting neuroplasticity and modulation of memory and learning [87]. Increased dementia is seen in the insulin-resistant state and, not surprisingly, there is a strong link between global brain atrophy and insulin resistance [88]. Improvement in cognition has also been observed with significant weight loss following bariatric surgery. In a novel study investigating the effect of bariatric surgery on the genes related to Alzheimer's disease, the expression of amyloid precursor protein and other Alzheimer's disease-related genes such as presenilin-2, ADAM-9, Glycogen Synthase Kinase (GSK)-3β, Phosphatidylinositol-binding clathrin assembly protein (PICALM), Sortilin Related Receptor 1 (SORL-1), and clusterin fell significantly after RYGB-induced weight loss [72]. Also, an intravenous infusion of insulin has been shown to acutely reduce the expression of amyloid precursor protein, presenilins, and GSK-3β. GSK-3β is responsible for the phosphorylation of tau protein, which forms tangles characteristic of Alzheimer's disease [89].

Furthermore, intranasal administration of insulin, which transports insulin directly into the brain without inducing systemic effects, has been shown to improve cognitive function in patients with mild to moderate Alzheimer's disease and to improve glucose uptake in the affected brain regions [90, 91]. Thus, the benefits of bariatric surgery in the reduction of Alzheimer's disease and improvements in cognition may be related to the reduction in inflammation and improvements in insulin sensitivity and action in the brain.

8. Reduction in Mortality after Bariatric Surgery

Compelling studies show that both short- and long-term mortality are reduced in morbidly obese patients who undergo bariatric surgery. A prospective surgical intervention trial in 4047 obese patients with a follow-up period ranging from 4 to 18 years revealed that significantly higher long-term weight loss in the bariatric surgical intervention group led to marked, overall reductions in mortality compared with controls [41]. This was despite the higher body weight in the intervention group prior to the metabolic surgical intervention. The most common causes of mortality were cardiovascular events (myocardial infarction, heart failure, sudden death) and cancer. Long-term weight loss was also significantly higher in the surgical intervention group. Similar reductions in mortality have been documented in notable, retrospective studies [40, 92, 93].

9. Bariatric Surgery and Incidence of Cancer

Consistent with the data on reduced cancer mortality following bariatric surgery is the prospective cohort study by Schauer et al., which revealed a marked reduction in the incident cases of cancer in obese subjects who underwent bariatric surgery compared with their

nonsurgical counterparts [94]. The reductions in incident cancer cases were most notable for obesity-associated cancers such as postmenopausal breast and endometrial cancer, and colon cancer. The weight loss-induced reduction in circulating estrogen levels is believed to be partly responsible for the marked decline in the risk of breast and endometrial cancers in the bariatric group. Also, the chronic inflammatory state in subjects with obesity may elevate their risk of cancer [95], and the decline in inflammation with bariatric surgery reduces this risk.

The marked reduction in hyperinsulinemia that occurs with bariatric surgery may also be protective against carcinogenesis. Hyperinsulinemic states such as obesity result in increased production of insulin-like growth factor (IGF)-1 by the liver, and this has a positive correlation with several malignancies including breast cancer, colorectal, and prostate cancer [96, 97]. The IGF-1 receptor is a tyrosine kinase receptor that mediates the proliferative and antiapoptotic effects of IGF-1, and it is often overexpressed in breast cancer [97]. The overexpression of some of the binding proteins to IGF-1 such as IGFBP-2 has also been observed in breast cancer cell lines [98].

10. Adverse Effects of Bariatric Surgery on Bone and Muscle

Despite the more favorable clinical outcomes seen with the malabsorption-inducing bariatric procedures, it is noteworthy that these procedures are more strongly associated with decreased bone mineral density and increased fracture risk (Fig. 1). This is largely because they induce more pronounced abnormalities in calciotropic hormones. These procedures affect calcium and vitamin D metabolism, mostly through malabsorption, and patients often require regular calcium and vitamin D supplementation postoperatively. Severe vitamin D deficiency is associated with secondary hyperparathyroidism, which could contribute to bone loss. This coupled with the accompanying rapid weight loss from bariatric procedures results in skeletal unloading [99, 100]. Loss of body fat and fat-free mass are seen with bariatric surgery-induced weight loss. This results in mechanical unloading of bones, favoring bone resorption.

An elevation in plasma concentrations of C-terminal telopeptides of collagen indicating an increase in bone breakdown and turnover is seen after bariatric surgery. Also, the postoperative alterations in adipokines (especially leptin and adiponectin) may negatively affect bone health [101-104]. Biliopancreatic diversion procedures have the greatest detrimental impact on bone density followed by gastric bypass [99]. While the type of bariatric surgery and extent of weight loss considerably impacts the loss of free-fat mass including muscle [105], the associated hypogonadal state in obese men may also be a contributing factor [106]. Although testosterone concentrations increase after bariatric surgery, this increase may take several months and there is potentially an initial loss of lean body mass and muscle.

11. Bariatric Surgery and Micronutrient Deficiency

Micronutrient deficiency is very rampant following bariatric surgery and highly dependent on the type of bariatric procedure. The common micronutrient deficiencies include deficiencies in fat-soluble vitamins (vitamins A, D, E, and K), B vitamins (folate, thiamine, B12, biotin), iron, copper, zinc, and selenium [107-109]. Although the levels of these micronutrients are frequently decreased at baseline in the obese state, metabolic surgery often results in marked reductions in their levels necessitating replacement therapy. Unfortunately, dietary supplements may not optimally correct some of the postoperative micronutrient deficiencies as a result of the surgically induced malabsorption. Factors contributing to postoperative micronutrient deficiency are multifactorial and include decreased absorption of nutrients and dumping syndrome, bacterial overgrowth in the small bowel, maladaptive eating behaviors, and recurrent vomiting.

Biliopancreatic diversion procedures induce more significant declines in fat-soluble vitamins, copper, and zinc when compared with gastric bypass, whereas vitamin B12

deficiency (ensuing from decreased intrinsic factor) is more commonly seen with gastric bypass than the other procedures [109]. Because the greatest micronutrient deficiency occurs with the BPB/DS procedure, maximal need for dietary supplementation is seen with this procedure, followed by gastric bypass.

12. Operative Mortality and Weight Regain after Bariatric Surgery

Relative to other major surgical procedures, the operative mortality rate after bariatric surgery is low and it ranges from 0.28% to 0.4% [110-113]. Restrictive procedures such as adjustable gastric banding have the lowest mortality rate (0.04%) and the lowest rate of serious complications (0.9%), while BPD/DS has the highest rate of serious complications (8%), although the weight loss response is quite impressive [113].

It is noteworthy that the favorable, dramatic weight loss and metabolic responses to bariatric surgery are not achieved in all patients. As many as 15% to 20% fail to lose weight or regain the lost weight [114, 115]. There is no consensus on the mechanism of poor weight loss or weight regain following bariatric procedures. However, the intuitive cause is a failure to comply with behavioral recommendations that induce negative energy balance. Evidence from the study by Knuth et al. demonstrates that dietary intervention combined with rigorous physical activity (The Biggest Loser weight loss competition) results in a greater reduction in resting metabolic rate than RYGB, despite the reduced loss of free fat mass in the former [116]. Data from short- and long-term studies corroborate the superiority of bariatric surgery compared with medical/lifestyle interventions in the maintenance of weight loss and the remission of diabetes and dyslipidemia [117, 118]. The 6-year follow-up data of participants in the biggest loser competition demonstrated an average weight regain of approximately 70%, with a subset of the participants regaining weight above their baseline weight before the competition [119, 120]. These observations are striking and highlight 2 salient points: (1) Inducing weight loss through traditional negative energy balance approaches may predispose to long-term recidivism by creating a persistent erosion of resting metabolic rate below the original baseline, thus leading to a net weight increase over time; and (2) weight loss from bariatric procedures such as RYGB may be distinct from traditional negative energy balance approaches because the former is accompanied by substantial weight loss without disproportionately eroding resting metabolic rate. Indeed, this may be a central reason for the wide difference seen in long-term weight loss response rates between negative energy balance approaches and bariatric surgery procedures [117, 118].

While it is clear that beneficial effects of bariatric surgery are not achieved through caloric restriction or malabsorption alone [121, 122], incompletely understood multifactorial mechanisms underlie successful weight loss maintenance. Gastrointestinal derived signals play a key role in weight loss maintenance. As previously stated, reductions in ghrelin levels are seen, with increments in cholecystokinin and bile acids. Proglucagon-derived hormones such as GLP-1, GLP-2, glicentin/oxyntomodulin, and nonproglucagon-derived peptides such as PYY and neurotensin, have also been demonstrated to increase in bariatric studies [123-125]. The net effects of these changes are significantly altered feeding behavior (decreased appetite/increased satiety) and enhanced energy expenditure through signaling at hypothalamic nuclei.

Furthermore, it has been shown that patients with poor postoperative weight loss have greater concentrations of ghrelin and lower concentrations of GLP-1 and PYY than those with good weight loss [126]. Also, surgical revision to a more distal RYGB induces weight loss and increases postprandial GLP-1 and PYY secretion in those with poor weight loss response [127]. Conversely, inducing weight loss through very low calorie dietary intervention increases ghrelin, decreases GLP-1 and PYY, and increases perceptions of hunger [128].

Beyond gastrointestinal derived signals and feeding behavior alteration, contributing factors include the reductions in endotoxemia/inflammation and insulin resistance after bariatric surgery [15]. The reasons why the surgery induces these changes are likely multiple. Exclusion of high-fat, high-carbohydrate foods known to induce endotoxemia and

inflammation may be a primary factor [129]. A second factor may be the altered gut barrier function through either reduced bowel permeability from chronically increased secretion of GLP-2 or shifts in the intestinal microflora after surgery [130-132].

Irrespective of the reasons (lack of behavioral compliance, incomplete physiologic response, or both) attributed to weight loss failure after surgery, it may be of greater importance to ascertain that the surgery induced the primary intended effect. Nuclear imaging studies tracking the transit of a mixed meal have shown that sleeve gastrectomy aids expedition of nutrients out of the stomach and through the proximal small bowel to quickly reach the ileum [133]. On the other hand, RYGB passively transits nutrients through the stomach pouch and deposits them directly into the mid-jejunum, reaching the ileum faster [134]. The commonality between these procedures is that the residence time of food is profoundly reduced in the stomach and the proximal small bowel. This changes the nutrient load and composition, and the concentrations of gastrointestinal secretions exposed to the distal ileum.

To the best of our knowledge, there are no published studies that compare segmented transit times through the stomach, the proximal (duodenum/jejunum) and the distal small bowel (ileum) between successful and failed bariatric procedures. This is a notable gap because duration of food passage through the stomach and small bowel would be expected to directly impact the time profile and concentrations of the aforementioned gastrointestinal secretions. Intestinal microflora and immunoinflammatory response to meals are also expected to have significant impact on weight. To bridge these voids in knowledge, there is a need for increased research focused on the minority of patients that do not favorably respond to surgery. This will help to properly identify and differentiate mechanisms responsible for weight loss and maintenance.

13. Conclusion

Apart from the marked weight loss that occurs with bariatric surgery, immense benefits such as significant remission in diabetes, hypertension, hypogonadism, asthma, and the risk of Alzheimer's disease are seen. The amelioration of insulin resistance, inflammation, and changes in vasoactive factors following bariatric surgery are key factors responsible for a number of these notable improvements. Further studies that are focused on the elucidation of the underlying mechanisms involved are required for a better understanding of the benefits of bariatric surgery.

Additional Information

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