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Molecular Insights from Bariatric Surgery

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Obesity Epidemic Fuels Demand for Bariatric Surgery

It is estimated by the Centers for Disease Control that more than a third of all adults and approximately 20% of all adolescents in the United States are now obese (Body Mass Index >30) [1,2]. As far back as 1991 the National Institutes of Health (NIH) organized a "Consensus Development Panel" which proposed guidelines for consideration of bariatric surgery as part of the solution to this growing national problem. These guidelines suggested to include well-informed, motivated patients with BMI of ≥40 kg/m^2 or BMI >35 kg/m^2 and with documented high-risk comorbid conditions to be as candidates for bariatric surgery [3]. We now understand even better how these co-morbidities of obesity such as glucose intolerance, type 2 diabetes (T2DM), metabolic syndrome, steatohepatitis, hyperlipidemia and cardiovascular disease have significant impacts on the overall quality of life of the individual and our society at large [4]. Roux-en-Y gastric bypass (RYGB) and the relatively newer procedures of gastric banding (GB) and vertical sleeve gastrectomy (VSG) have proven to be efficacious in achieving rapid weight loss and reversing the comorbidities of obesity[5]. Thus, bariatric surgical procedures have become important therapeutic options for treatment of morbid obesity in both adults and adolescents [5] [6]. Unfortunately, bariatric procedures are not without risks including micronutrient deficiency, failure to maintain lost weight, and mortality [7]. Additionally, these procedures are inherently not scalable to a large population. In order to design more effective, safe, and widely available therapeutics for obesity, important and highly relevant questions need to be addressed regarding mechanisms behind the weight-loss-independent benefits of bariatric surgical

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procedures. This review will provide an overview of the molecular changes occurring across all biological systems after bariatric surgery.

Weight-Loss-Independent Metabolic Benefits of Bariatric Surgery

Bariatric surgical procedures are associated with rapid metabolic improvements. Most notably, diabetes remission has been reported within days to weeks after surgery, even before substantial weight loss occurred. These improvements are sustained for long periods of time after surgery. A meta-analysis reported resolution of type 2 diabetes mellitus (84% post- RYGB, and 98% post-BPD) and reduction in hypercholesterolemia (95% post-RYGB and 87% post-BPD). These improvements were sustained and led to long-term reduction in mortality when patients were followed up to 12 years postoperatively [8].

Dramatic, rapid metabolic improvements observed in bariatric surgery patients have led to several theories proposing that altered gut hormone secretion or action may underlie these changes. Cummings et al. outline two hypotheses for metabolic improvement following foregut exclusion. These are the “upper intestinal hypothesis” and the “lower intestinal hypothesis,” which propose that the beneficial metabolic effects of bariatric surgery are related to altered proximal intestinal or reduced distal intestinal function, respectively [9]. Although these hypotheses are focused on mechanisms for improvements after gastric bypass surgery, it is increasingly evident that some non-bypass weight-loss surgeries may also elicit hormonal changes which confer metabolic improvement. A relatively small randomized study comparing RYGB and VSG recently reported similar improvements to glucose homeostasis after either procedure [10]. Remarkably, the time course of improvements to glucose homeostasis was comparable for the two procedures.

Growing evidence highlights the involvement of multiple endocrine and paracrine signals in both the early and long-term metabolic changes observed after bariatric surgery [11,12]. The importance of an individual change cannot be assessed outside of a systems biology approach, but current literature suggests that relevant components should include pancreatic signals impacting whole body and hepatic insulin resistance (insulin), adipokines regulating energy balance (leptin, adiponectin, resistin), intestinal signals influencing satiety and hunger (glucagon like peptide-1, peptide YY, ghrelin, FGF 19/21), hepatic signals influencing lipid absorption and energy expenditure (bile acids, farnesoid X receptor and liver X receptor ligands), and ultimately integration of these signals in the central nervous system (CNS) [13].

Changes in Insulin Secretion and Insulin Resistance

Hyperinsulinemia and insulin resistance have been commonly noted in morbidly obese patients presenting for bariatric surgery. Insulin resistance is associated with numerous comorbid conditions, most particularly T2DM, PCOS, NASH, and even obstructive sleep apnea. Studies have shown that adipose tissue derived T cells contribute to obesity induced inflammation [14][15]. Specifically regulatory T cells in the adipose tissue of lean mice provide protective anti-inflammatory signals to block adipose tissue driven inflammation. Thus it has been speculated that T cell receptors and the innate immune system with adipose tissue macrophages may communicate with the adaptive immune system to regulate weight

gain (Lumeng et al Nat Med 15 2009). Improvements in insulin resistance and resolution of T2DM have both been major benefits seen after successful bariatric surgical procedures [11]. One study comparing VSG with RYGB found that post-prandial plasma insulin levels were markedly increased in patients after either VSG or RYGB [10]. Interestingly, this exaggerated post-prandial response in insulin secretion was also seen in individuals after non-surgical weight loss [16] and therefore may not be exclusive to the bariatric weight loss population. When studies have looked into fasting insulin and glucose levels in RYGB patients, these levels were comparable to lean controls even 3 years after surgery [17]. These benefits were sustained only as long as the weight loss was maintained, however.

Improvements in insulin resistance and T2DM after bariatric surgery could be related to numerous antecedent events along a short or more protracted time course: acute fasting, changes in gastrointestinal hormone expression patterns following surgical manipulations of the gastrointestinal tract, changes in glycemic load due to changes in dietary preference following RYGP, changes in systemic inflammation, or decreased intracellular lipid content in peripheral cells leading to more normal insulin action. The relationship and the nature of interacting factors are not clear at present. The resolution of T2DM has long been understood to precede weight loss, and this finding provides important clues about the physiologic underpinnings of the observation. In a series of patients who underwent bilio-pancreatic bypass the most significant decrease in insulin resistance occurred within 15 days of the operation. At this point, the lipid profile and inflammatory and oxidative stress parameters had not improved. Four weeks after surgery, insulin resistance had a parallel evolution to weight loss [18]. These data raise the possibility of two different mechanisms at work for improvement in insulin resistance post-bariatric surgery: 1) an early, weight-independent mechanism and 2) a later mechanism which is related to weight loss

There have been numerous reports of postprandial neuroglycopenia following RYGB. This condition is believed to be caused by an exaggerated insulin response to ingested nutrients, leading to severe hypoglycemia. Authors have questioned the role of enhanced islet cell insulin production and indeed, pancreatectomy specimens from RYGB patients with this condition have revealed a nesidioblastosis-like hyperplasia of islets [19]. However, other authors have found conflicting results in patients with post-RYGB hypoglycemia, where β-cell area was not found to be increased compared with either obese or lean control subjects [20]. Due to the lack of comparison pancreatic specimens from post-RYGB patients without symptoms, it is not clear whether the islets histology in RYGB patients with hyperinsulinemic neuroglycopenia are similar to or different than would be expected based on the dynamic enteroendocrine changes following RYGB. Interestingly, a single case of postprandial hyperinsulinemic neuroglycopenic has been reported 14 years following fundoplication, suggesting that this condition may not be a unique complication only of RYGB surgery.

Changes in Adipocyte Derived Cytokines

In 1994 Friedman and colleagues made an important contribution to obesity research. They reported that the product of the obesity (ob) gene, leptin, was responsible for the development of profound obesity and T2DM [21]. This excitement was taken to an even

higher level when the first child with congenital leptin deficiency was provided leptin replacement therapy with resulting reversal of his obesity [22]. We now understand that excessive levels of leptin do not suppress appetite in obese individuals and that this is due to leptin resistance [23]. On the other hand, altered sensitivity to leptin might promote weight loss. Additionally, it is now known that many other adipose tissue derived cytokines and products affect energy homeostasis and glucose metabolism. These include adiponectin, resistin, chemerin, interleukin-6 (IL-6), plasminogen activator inhibitor-1 (PAI-1), retinol binding protein 4 (RBP4), tumor necrosis factor-alpha (TNFα) and visfatin. We focus on a few of these cytokines in more detail below.

Several studies have investigated the potential role for adipokines to contribute to a newly defended body weight after bariatric surgery. For the most part, however, adipose-derived factors have been shown to parallel the amount of adipose tissue mass and therefore decrease in proportion to the weight loss achieved by bariatric surgical procedures [24,25]. The exception is adiponectin, which increases after RYGB [26] [27] and VSG [28], but unlike other adipokines which circulate in high levels in obese patients, adiponectin concentrations are lower in obese patients [25]. Plasma leptin levels are reduced after RYGB [17,29] [30], VSG [31], and AGB [32] [33] [29].

Resistin is an adipokine which has been thought to directly correlate with adiposity and therefore contribute to the development of insulin resistance [34]. In a study of patients undergoing RYGB, weight loss was accompanied by increased resistin serum levels after 6 months but resistin levels below baseline values after 12 months [35]. These data highlight the controversy with regard to a potential correlation between body weight and plasma resistin levels. Some data also suggest an inverse correlation similar to that of adiponectin, but this remains to be replicated.

Resident macrophages within adipose tissue are an important source of inflammatory cytokines, such as TNFα, PAI-1 and IL-6 [34]. Although a link between altered inflammatory signaling and metabolic improvement after bariatric surgery has not yet been completely explored, these inflammatory cytokines seem to mirror weight loss and so bariatric surgery would be expected to decrease adipose tissue inflammation. Collectively, data have relegated these adipose derived factors and hormones to correlate with weight loss but not to play a causative or mechanistic role to induce or sustain weight loss. Thus, despite the early excitement regarding the central role of leptin in control of appetite we now realize that these adiposity signals maybe more realistically categorized as signifying the amount of fat deposits rather than central appetite control [36].

Changes in Gut Derived Factors

The impact of RYGB and other bariatric surgeries on the gastrointestinal tract has been diligently investigated based on hypotheses either that reduced action of upper intestinal or that enhanced action of lower intestinal hormones may mediate the effects of these surgeries. Peptide YY (PYY), glucagon like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) are intestinally derived, while ghrelin is produced primarily in the stomach. As incretin hormones, PYY, GIP, and GLP-1 elicit exaggerated insulin secretion in

response to enteral versus parenteral glucose. These incretin hormones are also anorectic. Ghrelin, on the other hand, is a putative hunger hormone.

PYY and GLP-1 are key elements of the “hind-gut” hypothesis for weight loss and metabolic improvement after bariatric surgery. According to this hypothesis, proximal small intestinal bypass accelerates nutrient delivery to the distal small intestine, enhancing PYY and/or GLP-1 secretion. Both PYY and GLP-1 act to reduce food intake and to improve glucose homeostasis. The mechanism of action of PYY is understood to be through the interaction of its active form PYY_{3-36} on the NPY neurons in the arcuate nucleus of the central nervous system [37]. In a recent prospective double blind study comparing RYGB against VSG outcomes, post-prandial PYY levels were found to be equally increased after both procedures [38]. It is yet unclear what role, if any, PYY may play to mediate the effects of surgery, but these data support the hypothesis that enhanced postprandial PYY release may contribute to a reduction in body weight and improved glucose homeostasis after either surgery.

GLP-1 release occurs 40-60 min after a meal [16] and elicits incretin and anorexic effects. GLP-1 is limited as a pharmacologic therapy for obesity and diabetes due to its rapid inactivation by the enzyme dipeptidyl peptidase-4 (DPP4) produced by vascular epithelia[39]. RYGB has also been demonstrated to enhance postprandial GLP-1 release [40] [29]. GIP is another incretin hormone whose postprandial release is enhanced by RYGB [40]. An understanding of the mechanisms for the enhancement of these incretin hormones may lead the way to future therapies aimed at boosting endogenous incretin (GLP-1, GIP, PYY) release.

Increased incretin hormone secretion may also provide insight into potential mechanisms for changes to insulin levels observed after bariatric surgery. Insulin secretion in morbidly obese T2DM patients who underwent RYGB was normalized to the level of non diabetic controls, a change which was concomitant with increased levels of circulating incretin hormones. Additionally there is now exciting pre-clinical data that suggest that RYGB increases the expression of the gene pancreatic duodenal homeobox-1; that induces the regeneration of beta-cells paralleling an increase in incretin hormone secretion [41]. Such increase in incretin hormone secretion was not seen after an equivalent weight loss by diet in this series of patients [40], highlighting the need to further use an understanding of mechanisms behind post-surgical improvements to drive the development of novel diabetes therapies.

Ghrelin, its forms, its assays and changes in its plasma levels post-surgery have been a matter of continuous debate and development. VSG significantly reduced fasting ghrelin levels in one recent study [38]. Similar decreases in ghrelin levels post-RYGB have been reported by multiple investigators [42] though there have also been contrasting reports with observations of an either equivocal [32] or increases in ghrelin levels post-RYGB [43]. This apparent discrepancy in results has been speculated to be due to a difference in procedural technique with respect to vagotomies [44]. Recently, we have come to understand that the gastric ghrelin O-acyl transferase (GOAT) enzyme is critical for the octanoylation and activation of Ghrelin and that this is dependent on dietary lipid availability and sensing[45]. Korner et al reported further that RYGB reduces fasting ghrelin levels but does not alter the

ratio of octanoyl to total ghrelin [17]. Clearly this area currently requires more intense and in depth investigation to further clarify this controversies in the literature.

Changes in Hepatic Signals

Cholelithiasis and cholecystitis have been recognized as co-morbidities of obesity but only recently have bile acids (BA) been brought to the attention of the bariatric surgical community. Nakatani et al reported that, in 34 patients who underwent malabsorptive or restrictive bariatric surgery, total plasma BA level increased from 3.1 +/− 3.5 to 7.2 +/− 5.3 μmol/L and from 3.2 +/− 2.6 to 9.4 +/− 10.0 μmol/L, respectively. Presurgical serum concentrations of primary BA were positively correlated with plasma GIP levels, and post-surgical changes in primary BA levels were positively correlated both with changes in GIP ($r = 0.626$, $P = .001$) and with changes in serum insulin levels ($r = 0.592$, $P = .002$). These changes in BA may reflect the “hormonal” effects of BA and allude to roles for BA in improving glucose tolerance after bariatric surgery [46]. Similar data was also presented by Patiti et al from their cohort of RYGB patients wherein the BA subfractions taurochenodeoxycholic, taurodeoxycholic, glycocholic, glycochenodeoxycholic, and glycodeoxycholic acids were all significantly higher in RYGB compared to weight-matched controls and total BA levels correlated inversely with thyroid stimulating hormone [47]. These data have together led to recent interest in the G protein-coupled bile acid receptor, TGR5, to which BA bind as ligands to activate deiodinases that increase energy expenditure via conversion of the prohormone thyroxine to the active hormone triiodothyronine[47-50].

Weight loss after bariatric surgery is much more durable than after dieting

Body weight is strongly defended and features of obesity such as leptin resistance can make weight loss very difficult to maintain. Consistent with anecdotal evidence describing rebound weight gain after dieting in humans, calorically-restricted rodents will overeat to quickly regain lost body weight [51]. Importantly, this rebound weight gain effect does not appear to occur after bariatric surgeries. Caloric restriction following sleeve gastrectomy drives hyperphagic behavior eliciting gain of body weight to achieve pre-restriction, but not pre-surgical, levels [52]. Reduced motivation, rather than ability, to overeat is thought to underlie this effect. Human studies documenting long-term weight loss suggest that reduced hyperphagic drive is an effect of several bariatric procedures including RYGB [8]. To understand the mechanisms by which a new, lower level of body weight might be defended after bariatric surgery is an important area of emerging research. While it is yet unclear what role changes to energy expenditure, if any, may play to regulate body weight after bariatric surgery, reduced ingestive motivation appears to be a common theme related to most bariatric procedures. Several hypotheses, discussed above, focus on hormonal changes elicited by these procedures and on their potential impact on ingestive behavior.

Role of CNS Integration

The defense of body weight is dependent on the brain’s ability to respond to internal cues relaying information about both long-term and short-term energy availability. The arcuate nucleus of the hypothalamus is an important control center, but other brain areas are also important integration and control centers for coordinating whole-body energy homeostasis.

These include, among other regions, the paraventricular nucleus of the hypothalamus and in the brainstem, the dorsal motor nucleus and nucleus of the solitary tract. Melanocortin signaling in these regions elicits changes to food intake, energy expenditure, and glucose homeostasis in response to hormonal, nervous, and nutrient cues from the periphery [51]. These cues include PYY, GLP-1 [53], leptin [23], and ghrelin [54] among many other intestinally- and adipose-derived factors. After bariatric surgery, changes to any of these factors may inevitably affect central melanocortin signaling, thereby effecting changes to energy homeostasis. Melanocortin signaling also converges on the brain's reward circuitry, raising questions about how the CNS may mediate changes to taste and food preference which have been documented following bariatric surgery [55] [56] [57] [58]. Very little is currently known about changes which may occur in the CNS after bariatric surgery, but this is likely to be a widely expanding field as it is increasingly clear that signals such as GLP-1 may play a role to mediate the effects of these surgeries.

Summary and Discussion

The surgical procedures used today to produce weight loss are varied. In addition, the obligatorily steep learning curve for surgeons further produces "era" effects within data pools. All together it makes for complicated statistical analyses and leaves much open room for personal interpretation of the literature. Fortunately, animal models of bariatric procedures that allow investigators to control and manipulate critical anatomic, physiologic, and genetic factors are now underway. Isolating component parts of the complex operations and studying them in detail will be critical to understanding the combined effects of the gastrointestinal manipulations leading to weight loss, weight maintenance, and metabolic improvement. In addition, prospective data from large cohorts of patients are being collected with robust funding made possible by professional societies, industry partners, and governmental sources worldwide. For instance, the National Institutes of Health is funding numerous randomized trials examining various questions about bariatric surgery. In addition, large consortia have been established to conduct the Longitudinal Assessment of Bariatric Surgery for adults and the Teen-LABS study for adolescents. These efforts should help to evaluate safety and efficacy of multiple procedures. Data and specimens that are being collected from such studies will hopefully lead to mechanistic insights [59] [60].

The number of bariatric procedures been performed are still woefully short of meeting the immense demand in our general population. Also, the answer to the co-morbidities and challenges of obesity lies in a much more scalable modality. Therefore, understanding the molecular mechanisms behind the "magic" of bariatric surgery is definitely the ultimate goal. Small animal bariatric surgery models are helping us better understand the mechanisms behind human bariatric surgeries in a much more controlled and standardized experimental environment [52,61]. A prime example of such success has been the pharmacological compounds called DPP4 inhibitors; that increase the half life of GLP-1 and therefore have efficacy against T2DM seen post-RYGB; that are already in trials and some under production [62,63]. Similarly the recent pre-clinical and human BA data together led to selective transcription factor TGR5 agonist development that are already in human trials for T2DM and fatty liver disease [47-50]. Thus, moving forward we should continue to collate

and use existing pre-clinical and clinical data to test hypothesis and interventions on small animal surgical models that may help uncover future novel therapeutic targets.

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