Obesity and Addiction:
Can a Complication of Surgery Help Us Understand the Connection?

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Abbreviations

RYGB = Roux-en-Y gastric bypass
WLS = Weight Loss Surgery
LAGB = Laparoscopic Adjustable Gastric Banding
LSG = Laparoscopic Sleeve Gastrectomy
AUD = Alcohol Use Disorder
EAI = Excessive Alcohol Intake
SUD = Substance Use Disorder
LABS-2 = Longitudinal Assessment of Bariatric Surgery -2
AUDIT = Alcohol Use Disorders Identification Test
GAD = Gastric Alcohol Dehydrogenase
AUC = Area-Under-the-Plasma Concentration Curve
YFAS = Yale Food Addiction Scale
DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders IV-TR
BED = Binge Eating Disorder
DA = Dopamine
ACh = Acetylcholine
DD = Delay Discounting
Abstract

Obesity is a multifactorial, chronic disease that has proven difficult to treat. An increased understanding of etiological mechanisms is critical to the development of more effective obesity prevention and treatment strategies. A growing body of empirical evidence has demonstrated parallels between obesity, overeating, and substance abuse, including shared behavioral, psychological, and neurophysiological factors implicated in the excessive intake of both food and substances of abuse. Several different lines of research have recently emerged that hold the potential to shed light on the connection between obesity, food reward, and addiction, with studies examining changes in alcohol use/misuse after weight loss surgery providing a particularly interesting perspective on these interrelationships. However, these lines of investigation have proceeded in relative isolation, and relevant research findings have yet to be integrated in a synthesized, comprehensive manner. To provide an opportunity to achieve such a synthesis, a scientific symposium was convened at the Radcliffe Institute in Cambridge, Massachusetts. Invited participants were researchers working in diverse domains related to the intersection between obesity and addiction. Extensive discussion was generated suggesting novel research directions. Below, we summarize and synthesize the symposium participants’ ongoing research
in this area, incorporating additional relevant research holding potential clues regarding the connections between obesity, weight loss surgery, and addiction.

Introduction

Obesity is a multifactorial, chronic disease, with comorbidities that impair quality of life and decrease longevity, including cardiovascular disease, various cancers, and type II diabetes\textsuperscript{1,2}. The prevalence of severe obesity continues to rise rapidly\textsuperscript{3}, posing significant economic and social burdens for our society\textsuperscript{4,5}. Obesity has proven to be extremely difficult to treat, likely because there are numerous contributing factors, including genetic, environmental, and behavioral forces that not only lead to higher body weights\textsuperscript{6}, but also serve to defend elevated body weights when weight is reduced\textsuperscript{7,8}. An increased understanding of etiological mechanisms is critical to the development of more effective obesity prevention and treatment strategies.

Roux-en-Y gastric bypass (RYGB) is one of several types of weight loss surgery (WLS) procedures used to treat obesity and its comorbidities. WLS is currently the most effective and durable treatment for severe obesity, yielding lasting weight loss and the improvement or resolution of a number of co-morbidities\textsuperscript{9}. However, RYGB has also been reported to alter intake, craving and misuse of alcohol, with increases in alcohol use, and misuse, being observed in some individuals or populations. However decreases have been noted in others\textsuperscript{10-22}. These changes are either not seen, or have not yet been examined, with the two other predominant WLS procedures, laparoscopic adjustable gastric banding (LAGB) and laparoscopic sleeve gastrectomy (LSG)\textsuperscript{23,24}.

A growing body of empirical evidence has demonstrated parallels between obesity, overeating, and substance abuse, including shared brain reward pathways implicated in the excessive intake of both
food and substances of abuse. In addition, obesity and substance use disorders share psychological risk factors, such as impulsivity and other deficits in executive function. A number of different lines of research have recently emerged that hold the potential to shed light on the connection between obesity, food reward, and addiction, with studies examining changes in alcohol use and misuse after WLS providing a particularly interesting perspective on these interrelationships. However, these lines of investigation have proceeded in relative isolation, and relevant research findings have yet to be integrated in a synthesized, comprehensive manner.

To provide an opportunity to achieve such a synthesis, a scientific symposium entitled “Obesity and Addiction: Can a Complication of Bariatric Surgery Help Us Understand the Connection?” was convened at the Radcliffe Institute in Cambridge, Massachusetts. Invited participants were researchers working in diverse domains that all relate to the intersection between obesity and addiction. The symposium focused on three major domains. The first concerned clinical research in humans, including work in the domain of ‘food addiction’ and studies of the prevalence of addictions arising after WLS, and after RYGB in particular. The second focused on rodent models of ‘food addiction’, the intake of alcohol in rodents after RYGB, and changes in the pharmacokinetics of alcohol after WLS. The third focused on research on neurobiological aspects of obesity, addiction, and neural changes after WLS. Extensive discussion was generated by the presentations, suggesting novel research directions. Below, we summarize and synthesize the findings of the symposium participants’ ongoing research in this area. Selected additional relevant research is discussed to further demonstrate current investigation in these areas; however, a systematic review of all of the relevant literature is beyond the scope of this article.

Alcohol misuse after WLS in humans
A number of cross-sectional studies have shown that RYGB patients appear to be at risk for alcohol misuse or alcohol use disorder (AUD) after surgery\textsuperscript{19, 22, 28-31}. For instance, Sogg and colleagues\textsuperscript{32}, using a retrospective, semi-structured interview, found that 9.4% of post-RYGB patients reported a period of excessive alcohol intake (EAI) at some time after surgery, more commonly among those who had had surgery longer ago (which was possibly an artifact of a longer observation period), and those with a younger age and/or higher BMI at the time of surgery. Though EAI in the six months preceding surgery was strongly associated with reporting a period of post-operative EAI, a remote history of EAI was not related to post-RYGB alcohol intake. Strikingly, 7% of those with no pre-surgical history of alcohol problems developed new-onset EAI after RYGB, and more than half of all cases of post-operative EAI were of new onset. Similarly, when examining substance misuse more broadly, as defined by the Michigan Assessment Screening Tool for Alcohol and Drugs, Saules and colleagues\textsuperscript{29, 30} found that 14.2-19.6% of a post-RYGB sample reported problems with drugs or alcohol after surgery, with more than half of the total cases of post-operative substance misuse reporting new onset misuse. Conversely, most who endorsed pre-surgical substance use disorder (SUD) did not relapse after surgery.

Prospective studies have also identified a risk for onset of alcohol problems after RYGB, with prevalence increasing, in one study, over a period of up to ten years after surgery\textsuperscript{18}. In a large, prospective study, King et al.\textsuperscript{16} reported findings from 2-year follow-up data from the Longitudinal Assessment of Bariatric Surgery-2 (LABS-2) study, including participants who had undergone RYGB and LAGB. The authors used total scores and specific items from the Alcohol Use Disorders Identification Test (AUDIT)\textsuperscript{33} to assess AUD symptoms and alcohol-related harm. In this sample 1,945 patients completed the AUDIT before and at both one and two years after surgery. During post-operative year one, there was no significant change from the pre-operative assessment in the percentage of participants who were
positive for AUD (7.2% at preoperative assessment, 7.9% at year 1). However, in year 2 there was a significant increase in the prevalence of AUD (9.6%), compared to pre-surgery rates. In some cases, preoperative AUD symptoms predicted post-RYGB increases in alcohol consumption. Of great concern, however, over half (60.5%) of the post-operative AUDs were new-onset cases, in participants who did not report pre-operative alcohol use problems. Endorsement of post-operative AUD was associated with a number of variables including male sex, younger age, pre-operative smoking, pre-operative regular alcohol consumption, and pre-operative recreational drug use. Importantly, when participants were examined separately by type of surgical procedure, risk of post-operative AUD appeared to be solely associated with having undergone RYGB; there was no change in AUD prevalence from pre-surgery to either post-operative time point among participants who had undergone LAGB. Other prospective studies have similarly highlighted higher risk for onset of post-WLS AUD or SUD after RYGB than after LAGB\textsuperscript{18,22}. For instance, one study that investigated changes in alcohol, cigarette, and drug use following surgery revealed increasing rates of substance use from pre-surgery to 24 months following surgery, with these increases driven largely by increased alcohol use in RYGB (vs. LAGB) patients\textsuperscript{10}. Converging findings that post-WLS alcohol misuse is much more common after RYGB than LAGB suggests that the etiology is likely physiological. While it might be possible that the difference in prevalence of post-WLS alcohol misuse could be due to systematic differences between those patients who choose or are recommended to undergo RYGB versus LAGB, to our knowledge there is no published empirical data suggesting that such differences exist. An RCT comparing RYGB to LAGB would provide an opportunity to control for this possibility; however, a number of barriers exist to conducting such trials, and thus such data are lacking\textsuperscript{34}.
Another approach to understanding how WLS impacts alcohol misuse is through examining the proportion of patients seeking addiction treatment who have undergone WLS. Saules et al. found that 2-6% of admissions over a two-year period to an inpatient addiction treatment facility were positive for a history of having undergone WLS. Approximately 70% of participants were seeking treatment for AUD, either solely, or in combination with another SUD. Notably, 93% of those patients had undergone the RYGB procedure. More recently, these authors conducted a similar examination of the prevalence of bariatric surgery history documented in the electronic medical records of a newer cohort of inpatient SUD patients (N=4,658), and found that 2.8% of this sample had undergone WLS, with 93% having had the RYGB procedure. Both studies suggest that bariatric surgery patients are overrepresented in inpatient SUD treatment settings and, given that the use of an inpatient SUD treatment sample likely captures the extreme end of the SUD severity spectrum, it is likely that many more bariatric patients are struggling with substance misuse but have not yet been identified or treated.

Potential Etiological Mechanisms

Studies examining post-WLS changes in substance use and misuse share a few common findings that may shed some light on the etiology of these changes. Firstly, existing research, including a number of the studies presented here, collectively suggests that post-WLS addiction problems seem to be fairly specific to alcohol, as relapse to or new-onset misuse of other substances have not been observed nearly as frequently as issues with alcohol. In addition, as noted above, findings that changes in alcohol consumption and misuse appear to be particularly related to the RYGB procedure suggest a physiological (e.g. anatomical, metabolic) mechanism; it is not yet known whether LSG has an impact on alcohol use or misuse.
It is notable that the characteristics of patients who develop problems with alcohol after RYGB stand in significant contrast to epidemiological data regarding the prevalence and incidence of AUD in the general population. Typically, individuals with obesity are found to exhibit lower rates of SUD’s\textsuperscript{36-39}. While epidemiologic data that report SUD incidence separately by age, gender, and BMI category are not available, in the general population as a whole, 50\% of AUD’s develop in the early 20’s, and 90\% of AUD’s develop before the ages of 39 to 41\textsuperscript{40,41}, and are more prevalent in men than in women\textsuperscript{40}. However, the onset of new AUD’s within bariatric samples is being observed among largely middle-aged, female patients\textsuperscript{16}, providing more support for the possibility that the surgery itself plays an etiological role in this phenomenon.

It should be noted, however, that more than one study has found that there are also subgroups of patients whose alcohol use decreases after WLS, and even some patients for whom pre-existing AUD’s or alcohol misuse improve or remit\textsuperscript{12,22}. Findings suggesting that WLS may effect different types of changes in differing subgroups of individuals has interesting parallels to findings obtained in rodent studies, which are reviewed below, and suggest a potential etiological role for genetics and other biological mechanisms.

\textit{Changes in the pharmacokinetics of alcohol after WLS}

In the presence of multiple anatomical and physiological changes post-RYGB, reports have consistently shown alterations in the pharmacokinetic characteristics of alcohol post-surgery, though the studies have produced slightly varied results\textsuperscript{42-46}. Among the most noteworthy of the pharmacokinetic findings regarding post-RYGB patients, relative to their own pre-surgery values or to those of nonsurgical comparison groups, are: 1) a rapid rise to maximum blood alcohol concentration\textsuperscript{43,45}, occurring as early as five minutes following ingestion of alcohol\textsuperscript{45}; 2) significantly higher maximum blood or breath alcohol
concentration\textsuperscript{42, 43, 46}; and 3) longer time required for alcohol elimination\textsuperscript{42, 44, 46}. Taken together, these findings suggest that alcohol absorption (and/or metabolism) is altered after RYGB, potentially contributing to the alcohol misuse that has been observed in a subset of post-RYGB patients. It should be noted that, with one exception\textsuperscript{47}, post-operative pharmacokinetic changes in alcohol absorption/metabolism have not been observed in LSG\textsuperscript{48, 49}, or LAGB patients\textsuperscript{48}. This may explain, at least in part, why changes in alcohol use or misuse have been observed almost solely in RYGB patients.

Several anatomical and physiological changes effected by RYGB may contribute to these pharmacokinetic changes. First, there is a reduction in the presence of the enzyme gastric alcohol dehydrogenase (GAD), given the decrease in the surface area of the stomach that comes into contact with alcohol. This enzyme is responsible for a portion of the first-pass metabolism of alcohol, which normally accounts for a ~6-8\% reduction in eventual absorption\textsuperscript{50}. The significance of attenuating the role of GAD in the metabolism of alcohol was demonstrated by Caballeria and colleagues\textsuperscript{51} in a study of patients who had undergone a gastrectomy for non-weight-related indications. Findings from this study showed much higher absorption of alcohol; indeed, there was little difference in the area-under-the-plasma concentration time curve (AUC) between conditions of oral and intravenous alcohol administration.

Another change effected by RYGB is that the emptying of liquids into the small bowel is reported to be accelerated after surgery\textsuperscript{52, 53}, allowing alcohol to move rapidly after ingestion to the jejunum for absorption. This may contribute to the rapid time to reach peak alcohol concentrations observed following RYGB. Finally, there are significant changes in total body weight and body composition following RYGB, potentially leading to changes in the distribution of alcohol. All of these changes may contribute to the alterations in alcohol pharmacokinetics after surgery, which in turn may play a significant role in the development of AUD’s following surgery. As noted, patients often report enhanced sensitivity to
alcohol following RYGB\textsuperscript{14, 54}, and this subjective evaluation is generally supported by pharmacokinetic data. It should be noted, however, that post-WLS changes in the GI tract are likely not the sole contributor to changes in alcohol use/misuse after surgery, as changes in alcohol preference and self-administration of intravenous alcohol, as well as self-administration of intravenous opiates, have been observed after RYGB in rodent models\textsuperscript{55, 56}. This suggests a role for changes within neural reward pathways, discussed below.

\textit{Food as an addictive substance}

One recurrent theme in the research examining parallels between obesity and addiction is the concept that food itself might be considered an addictive substance. Evidence is building that an addictive process may play a role in growing obesity rates\textsuperscript{57, 58}. Although addictive-like eating may contribute to obesity in some people, it is important to highlight that obesity and “food addiction” are not equivalent constructs\textsuperscript{59}. To most precisely evaluate how addiction to highly palatable foods might play a role in obesity, and in the outcomes of obesity treatments such as WLS, it is necessary to identify a phenotype of patients who exhibit signs of addictive eating, which is often measured by the Yale Food Addiction Scale (YFAS)\textsuperscript{60}. The YFAS operationalized the construct of food addiction by translating the Diagnostic and Statistical Manual of Mental Disorders IV-TR (DSM-IV-TR)\textsuperscript{61} diagnostic criteria for substance dependence to parallel items relating to the overconsumption of highly palatable foods (and has since been revised to reflect the DSM-5\textsuperscript{62} criteria for substance use disorders)\textsuperscript{63}.

In a preliminary validation of the YFAS in a non-clinical sample, the measure showed good internal consistency and reliability, as well as convergent validity with theoretically related constructs (e.g., binge eating, emotional eating) and discriminant validity from dissimilar constructs (e.g., drinking frequency). The YFAS also correlated with binge eating behavior above and beyond existing measures of
eating pathology, providing evidence of incremental validity\textsuperscript{60}. A clinical study of those with obesity found the YFAS to be psychometrically sound, and that approximately half of the patients with binge eating disorder (BED) met the YFAS food addiction threshold\textsuperscript{64}. In a separate study, elevated YFAS scores were linked with patterns of neural activation typically seen in other addictions, such as greater cue-related activation in the medial orbitofrontal cortex, caudate, amygdala, anterior cingulate cortex, and dorsolateral prefrontal cortex\textsuperscript{65}.

Studies using animal models have also investigated whether hedonically-driven food intake can lead to addiction-like behaviors and brain changes that may explain why some individuals develop obesity. Although foods are natural reinforcers, certain foods (and particularly those engineered to be hyper-palatable), consumed in excess, may result in an addiction-like state. Research by Avena and colleagues provides strong evidence of the impact of the consumption of certain foods, and in certain patterns, on behaviors and brain circuitry, and shows that several of the key hallmarks of DSM-IV-TR-defined substance dependence have been observed in rats that overeat highly-palatable foods, such as fats and sugars, in a binge-like manner\textsuperscript{66, 67}. For instance, binge eating on sugar can be induced when rats are maintained on a daily regimen of 12-hour food restriction and then granted access to a sugar solution in addition to standard chow. Rats maintained on this paradigm increase their sugar intake over the course of 21 days, providing evidence of both binge consumption and increased tolerance\textsuperscript{67}. After administration of the opioid antagonist naloxone, or food deprivation for 24 or 36 hours, these rats also show signs of withdrawal, such as physiological and behavioral distress, as well as increased anxiety\textsuperscript{68, 69}. Additional preclinical evidence of food addiction comes from evidence that rats that are genetically prone to overeat (compared to those that are resistant to such behavior) tolerated significantly higher levels of a shock grid
to obtain palatable food rich in sugar and fat, which could be seen as a behavioral proxy for the substance
dependence criterion of continued use of the substance despite aversive consequences70.

Pointing to a neural substrate underlying these behavioral observations, overconsumption of
certain macronutrients, in certain patterns, has also been shown to elicit neurochemical changes similar to
those that result from addiction to drugs and alcohol71. Whereas the magnitude of food-induced dopamine
(DA) release generally attenuates after repeated access to a food, this is not seen with sugar intake when
rats are given repeated but intermittent access to sugar72, which is similar to the pattern of DA release
seen with drugs of abuse73. Reduced levels of striatal D2 receptors have also been found in rats that
overeat sugar74, and in rats that developed obesity through prolonged access to a cafeteria-style diet75.
This mirrors findings of reduced levels of D2 receptors in the striata of individuals addicted to drugs of
abuse76 and in the striata of people with obesity76, 77. Corresponding to the behavioral signs of withdrawal
described earlier, rats that overeat sugar and are then deprived of sugar exhibit a DA and acetylcholine
(ACh) imbalance in the nucleus accumbens that resembles the DA/ACh imbalance present during
withdrawal from drugs of abuse68. Further, overeating sugar has been found to result in behavioral cross-
sensitization to drugs of abuse, such as alcohol and amphetamine78, 79, in diet-induced obese rats,
manifested as an enhanced increase in the release of accumbens DA in response to palatable food, and a
blunted DA response to lab chow, the latter being rectified with administration of palatable food80.

The role of neurophysiological reward circuitry in obesity and substance abuse

One potential contributor to obesity, particularly a phenotype with “addictive-like”
eating, could be individual differences in brain reward circuitry, stronger cue-responsivity, and reduced
inhibitory control, which may confer vulnerability to both overeating and substance abuse. The rewarding
effects of addictive drugs and natural reinforcers such as foods - especially highly palatable foods - are
driven by common neural systems\textsuperscript{81}. Exaggerated reactivity to cues for high-calorie foods may lead to
hyperphagia and excessive weight gain. The increased motivational potency of foods and food cues
driving relatively greater food intake in individuals with obesity appears to be mediated in part by a
hyperactive brain reward system, which includes the nucleus accumbens/ventral striatum, amygdala, and
orbitofrontal cortex\textsuperscript{82, 83}. In addition to hyperactivity within the reward circuit, there also appears to be
disrupted network connectivity among the brain regions in this circuit, which may not adequately
modulate reward-related activation in response to food cues, further promoting hyperphagia and obesity\textsuperscript{83, 84}. Repeated intake of high-calorie palatable foods results in an elevated responsivity of regions involved in incentive valuation to cues that are associated with palatable food intake via conditioning, which prompts craving and overeating when these cues are encountered\textsuperscript{85}. Similar phenomena are observed in response to alcohol use disorders\textsuperscript{86}. Obesity and substance-related addiction, including alcohol use disorders, can also be accompanied by other neurocognitive abnormalities in domains such as reward learning, decision-making, and executive function, and the neural circuity that support these functions\textsuperscript{27, 87}.

Neurophysiological changes after WLS

Given that elevated responsivity of reward regions and deficits in executive function and
decision-making increases risk for both overeating and substance use onset may explain why individuals who have undergone WLS are at increased risk for the emergence of other appetitive behavior problems, such as AUD's, as emerging research has identified some changes in various neural systems after RYGB, and that these changes may be associated with the magnitude of weight loss outcomes. For instance, a
cross-sectional pilot study used fMRI to examine the association of functional neuroanatomical characteristics and the magnitude of post-RYGB weight loss. Brain activation patterns in response to food cues were observed in post-RYGB patients under two different conditions. In one condition, participants were instructed to allow themselves to crave the pictured highly-palatable foods; in the other, they were instructed to try to resist those cravings. Differing neural activity was seen in the two conditions, consistent with other studies examining the relationship between appetitive motivation and cognitive control, and the effects of cognitive reappraisal strategies on neural responses to palatable food. Specifically, in this study, when participants allowed themselves to experience cravings, they exhibited significantly more activity in the limbic-related neural regions, and when instructed to resist cravings, they exhibited significantly more activity throughout the dorsolateral prefrontal cortex (DLPFC), replicating previous studies comparing individuals with and without obesity. Notably, when participants were instructed to resist cravings, those who had experienced greater weight loss after RYGB demonstrated significantly more activation in the left DLPFC. These findings suggest that, at least post-operatively, the ability to recruit executive control circuitry in the face of food cues or cravings was related to better weight loss after surgery, and that those who were less successful in losing weight may have a relative dissociation between their limbic drive and executive control circuitry. This phenomenon is commonly cited in the addiction literature as being implicated in both substance use and relapse.

Post-WLS changes in gut peptides

Significant postoperative changes in postprandial gut peptides (e.g., GLP-1, PYY) have been well documented after WLS, and these changes may contribute to the changes observed in brain reward systems.
circuity after surgery. A series of studies investigated the impact of RYGB on ethanol intake in high-fat-diet-induced obese vs chow-fed lean Long-Evans (LE) rats, a species that typically refrains from voluntary ethanol consumption. RYGB increased post-surgical ethanol consumption in LE rats with high-fat-diet-induced obesity. The authors next determined that RYGB led to increased ethanol consumption in LE rats maintained on standard rodent chow prior to surgery. These findings suggest that the ability of RYGB to stimulate ethanol intake cannot be explained solely by post-surgical weight loss, and that it is independent of pre-surgical body weight or dietary composition. The authors also examined the impact of RYGB on the ghrelin-orexin signaling pathway, a system known to regulate ethanol consumption in rodents. Plasma ghrelin levels were also evaluated in LE rats at 110 days following surgery, the timeframe during which increased ethanol intake was observed, plasma ghrelin levels were significantly decreased. Blood alcohol concentration (BAC) levels were also investigated 30 minutes following oral gavage of ethanol in LE rats after RYGB. RYGB rats displayed elevated BAC’s compared to sham control or weight loss control rats; though this effect did not reach statistical significance, this may have been due to the fact that 30 minutes after ethanol exposure is likely too long a time frame in which to detect meaningful changes in BAC.

In contrast to findings that some rats (and some humans) increase alcohol use after RYGB, preclinical and clinical data also indicate that individuals with high alcohol intake at baseline experience decreases in alcohol intake following surgery, an effect likely associated with decreased alcohol reward in this subgroup. Davis and Benoit investigated self-report of ethanol intake in a large cohort of human bariatric patients before and after undergoing RYGB. Patients who reported frequent consumption of ethanol preoperatively reported decreased frequency of alcohol consumption following RYGB, a phenomenon also observed in a different large cohort in which 50% of RYGB patients with high alcohol
intake at baseline decreased their intakes following surgery\textsuperscript{22}. In parallel, a rodent model of RYGB was utilized to examine ethanol consumption and ethanol reward in male ethanol preferring (P) rats, which are selectively bred to consume large volumes of ethanol. The RYGB procedure decreased ethanol intake and ethanol-induced conditioned place preference in P rats\textsuperscript{12}.

A clue to the mechanisms behind this observation was that the attenuation of ethanol consumption after RYGB was associated with increases in ethanol-induced secretion of the gut hormone glucagon like peptide-1 (GLP-1). Specifically, oral gavage of a 10% ethanol solution increased active GLP-1 in RYGB, but not sham operated, P rats. Moreover, pharmacological administration of the GLP-1 agonist exendin-4 attenuated ethanol consumption in sham-operated P rats, who, unlike the RYGB rats, had maintained elevated levels of ethanol consumption. GLP-1 has previously been demonstrated to be an important mediator of visceral illness and early reports of the effect of GLP-1 on food intake assumed reductions were principally driven by nausea\textsuperscript{94}. If higher GLP-1 levels, such as what has been observed after RYGB, increases sensations of visceral illness, then increases in that hormone after ethanol consumption would be expected to act as an endogenous conditioned taste aversion mechanism. Overall, these findings suggest that post-surgical increases in GLP-1 may decrease ethanol intake in ethanol preferring rodents, and possibly heavy-drinking humans, following RYGB.

The gut hormone ghrelin may also be implicated in the observed changes in ethanol intake after RYGB. Ghrelin has been reported to regulate ethanol self-administration, ethanol intake and ethanol-induced dopamine release in rodents\textsuperscript{95}. In addition, studies using rodent models have found that ghrelin levels are suppressed following RYGB\textsuperscript{96}. Davis and colleagues\textsuperscript{12} found that pharmacological replacement of the active form of ghrelin (acyl-ghrelin) restored drinking behavior in P rats, in whom RYGB had previously attenuated ethanol consumption. Conversely, antagonism of the ghrelin receptor attenuated...
ethanol consumption in sham-operated P rats, whose alcohol consumption had not decreased after surgery. Collectively, these findings help to illuminate the observed effect of RYGB surgery of attenuating ethanol consumption in some humans who, before surgery, were frequent consumers of ethanol\textsuperscript{12}, and in rats that are genetically bred to prefer ethanol\textsuperscript{12}. Further, these data indicate that this effect is achieved in part through reduction of ethanol reward, via changes in the gut hormones GLP-1 and ghrelin.

The observed changes in both subgroups of rats and humans may be attributed to an increased sensitivity to the pharmacological properties of alcohol. According to this conceptualization, experienced drinkers may voluntarily consume less alcohol following surgery because they have become more sensitive to the pharmacological effects of the alcohol, whereas ethanol naïve individuals may begin to drink more, due to the increased potency of alcohol. However, these contentions require further experimental validation.

Potential psychosocial contributors to post-WLS changes in alcohol use/misuse

While, as reviewed above, a number of findings support a physiological explanation for the observed increase in substance use after RYGB, psychosocial factors may interact with physiological factors to confer particular vulnerability. While physiological changes after RYGB would be expected to be largely similar across patients, it is possible that a particular subset of post-RYGB patients, due to psychosocial or behavioral factors, could be particularly vulnerable to the impact of the physiological changes in alcohol metabolism and reward processing after RYGB, conferring an increased risk of post-WLS addiction.
Few studies have examined psychosocial predictors of post-WLS changes in alcohol use or misuse. The King et al. study cited above did examine a number of potential psychosocial correlates of post-WLS AUD. Pre-surgical depression scores were not related to the risk of developing post-WLS AUD, nor were socioeconomic factors such as race, marital status, education, employment, or household income. Interestingly, a history of having treatment for psychiatric or emotional problems before surgery was found to be related to a lower risk of AUD after surgery, while psychiatric treatment after surgery was positively correlated with risk of post-WLS AUD. These authors did find that lower scores on a measure of feeling of “belonging” before surgery predicted higher likelihood of post-WLS AUD; the reason for this relationship is not clear. Though one possibility might be that such individuals may have seen an increase in social connection after surgery, possibly leading to more frequent socialization in contexts where alcohol is consumed, no studies have examined this hypothesis directly. In a smaller, but longer-term study of a subset of the same patients who underwent RYGB, pre-operative lifetime history of mood and anxiety disorders were found to be associated with post-operative AUD, though a distinction was not made between new-onset cases and individuals with a lifetime pre-surgical history of AUD. In one small cross-sectional, retrospective study, WLS patients with new-onset AUD had greater number of life stressors than both the no-use and relapsed/continued groups, and had significantly higher scores on coping with substances than those who reported never having problems with substances and those reporting pre-surgical, but not post-surgical, struggles with substance use. These quantitative findings mirror findings from a qualitative study which examined patient perceptions of the etiology of AUD/SUD among individuals with a history of RYGB surgery who were in inpatient addiction programs. The majority of patients described unresolved psychological problems as a contributor to the development of AUD/SUD post-RYGB.
One model popular in the lay media is the “addiction transfer” model\textsuperscript{30}, which posits that individuals who had an “addiction to food” before surgery simply “traded one addiction for another” and developed problems with alcohol or other substances. Indeed, in one qualitative study of post-WLS patients who were receiving inpatient substance abuse treatment, this explanation was cited by 83\% of the participants\textsuperscript{97}. Though there is little research examining this model directly, in one preliminary study, the YFAS was used to retrospectively assess pre-surgical “food addiction”\textsuperscript{30}. The authors found a significant association between higher pre-surgical YFAS scores and SUD after RYGB. In a similar study, participants were more likely to endorse new-onset post-RYGB SUD if they endorsed having had problematic pre-surgical intake of high-sugar/low-fat and high glycemic index foods, even after controlling for variables found in previous work to predict new-onset post-surgical SUD\textsuperscript{98}. On the other hand, the King et al.\textsuperscript{16} study found that pre-operative binge eating disorder was not related to the onset of AUD after WLS; other studies have also failed to show such an association\textsuperscript{19}, though the Mitchell et al.\textsuperscript{17} study cited above did find evidence of a relationship between lifetime preoperative BED and post-WLS AUD – again, a distinction was not made between new-onset and non-new-onset cases in these analyses. Findings in rodent models also provide some evidence against the “addiction transfer” model; for instance, the post-RYGB increase in alcohol consumption/preference was observed in rats even when those rats had not been previously maintained on the type of diet or feeding schedule that have been shown to lead to addiction-like changes in brain circuitry or behavior\textsuperscript{13}.

Future Directions

This symposium was designed to ‘assemble all of the pieces of the puzzle’ of the relationship between obesity and addiction. Doing so demonstrated quite clearly that a number of important ‘puzzle
pieces’ are still missing, and there are a number of ways in which future research will be informative. Refinement in operationalization of the constructs being studied is also important. At a very basic level, research on post-WLS SUD is hampered by inconsistent definitions of SUD, and standardization of operational definitions will improve the quality of information obtained from future studies. Additionally, most studies of post-WLS SUD do not make distinction between new-onset vs. continued or relapsed substance use, obscuring our ability to examine phenotypic differences between these groups, and potentially differing correlates and risk factors. As yet, protective factors preventing some WLS patients from continuing or relapsing to previous SUD have not been identified. There is also a dearth of research on the misuse of substances other than alcohol in the post-WLS population, and no research examining the prevalence of post-WLS SUD among individuals who have undergone LSG, which is currently the most-utilized WLS procedure in the US99.

Very little is known about predictors or correlates of post-WLS SUDs and the chronology of their onset, including when the highest-risk period is for the development of these problems and whether patient characteristics are associated with outcomes. Most of the research on post-WLS SUD is limited by small samples and cross-sectional designs; definitive study of the processes involved in the onset of these problems will require prospective research with large samples, frequent assessments, and a long follow-up duration, which renders this proposition both expensive and time consuming. Some clues in this domain may be gleaned from rodent studies; for instance, it would be helpful to determine how soon LE rats begin to drink significant amounts of alcohol after RYGB. Additionally, studies with longer follow-up duration are needed to determine if P rats begin to drink pharmacological levels of alcohol following surgery.
There is much still to be learned about the physiological underpinnings of post-WLS SUD. Findings that bariatric surgery alters the absorption of alcohol\textsuperscript{42, 43, 45, 46} also suggests that there would be value in prospective studies that investigate how WLS affects responsivity of reward, gustatory, and oral somatosensory brain regions in response to high-sweet food, high-fat foods, as well as alcohol, and whether responsivity in these regions changes in the longer-term post-surgery, which is when substance use problems tend to emerge. Future research should investigate whether individuals who show abnormally strong or weak reward region responsivity at baseline are at increased risk for the onset of a substance use disorder and/or weight regain following surgery. Research examining potential links between deficits in executive function and decision-making to post-WLS SUD will be informative, including an investigation of whether individuals who show a greater increase in executive function and decision-making are more resistant to developing substance use problems after surgery.

In light of the connection between WLS and substance misuse, it is critical to consider practical treatment implications. At minimum, it appears that enough is known about the potential risk of post-WLS SUD to advocate long-term monitoring of substance use and changes in sensitivity to substance-based reward in post-WLS patients, particularly in populations at high risk for SUD, including adolescents and individuals with a family history of SUD, and patients with characteristics found in previous studies to be associated with post-WLS SUD\textsuperscript{16, 29}. Further, because no published research has examined treatment of individuals with post-WLS SUD, it is not known whether they would benefit from standard SUD treatment options, or whether specialized care is needed.

Conclusion
In summary, compelling evidence from human and rodent models provides preliminary support for an increased risk of AUDs following RYGB surgery; however, the literature is limited by few prospective studies, inconsistent measurement/operational definitions, and small samples. Prospective research designs with large samples are needed to examine risk factors and associated psychosocial and physiological features of post-WLS AUDs. Finally, there is a pressing need to utilize an interdisciplinary approach to help advance our understanding of the intersection among obesity, addictive-type eating, and substance use.
Conflicts of Interest

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