CORRELATIONS BETWEEN OBESITY, BARIATRIC SURGERY, AND DEPRESSION: A ROLE FOR THE GUT MICROBIOME

by

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As the prevalence of both obesity and mental disorders continues to rise, researchers aim to determine the physiological mechanisms of these conditions. Many people with obesity have medical comorbidities such as hypertension and cardiovascular disease, but there are often many psychological comorbidities to obesity as well. The newly developing idea of the gut-brain axis has been theorized to play a role in linking many conditions via the gut microbiome, which exhibits distinct differences in obese and depressed individuals when compared to lean/healthy controls. Bariatric surgery, the frontier treatment method for sustained weight loss and improved metabolic functioning in morbidly obese patients, drastically changes the anatomy of the gastrointestinal tract along with the composition of the gut microbiome. Depression is also associated with distinct changes to the gut microbiome. The purpose of this review is to compare changes in the gut microbiome caused by bariatric surgery to the alterations of the gut microbiome in depressed individuals. When obesity and depression co-occur following bariatric surgery, the role of the gut microbiome may be amplified, and further researching the mechanisms by which obesity, depression, and the gut microbiome interact will allow for more personalized treatments for both obesity and depression in the future.

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Introduction

All systems that require a balance can be modeled using the concept of homeostasis, the use of feedback loops to maintain a set equilibrium point when a system changes in response to changing stimuli. Overall physiological and psychological health is regulated by thousands of homeostatic feedback loops, and the disruption to any one of these loops can cause many pathways to sway from equilibrium. Oftentimes in the treatment of clinical conditions, patients are asked to consciously alter the state of their psychological homeostasis to maintain or improve one's physical and mental health. As the prevalence of both obesity and depression continue to rise, researchers are looking into the imbalances that are associated with these conditions and how various treatments affect the reinstatement of patients' homeostatic equilibrium. Although it would be incorrect to point out a single reason as to why a person has obesity or depression, developing understanding of how all variables may cause or prevent against said conditions will make way for individualizing treatment and improving population health.

There is an abundance of theories which attempt to explain how any condition comes to fruition. One such theory which utilizes the basic concept of homeostasis has been presented by David Marks. Marks proposes that health is maintained through four main categories: physical health, life satisfaction (measured via subjective well-being), consumption (measured via restraint), and affect (positive or negative). An imbalance in any of these categories will alter the outcoming affect. Marks applies the relationships between these four attributes to obesity, introducing the idea that general homeostasis is out of balance in obese individuals. He claims that obesity is induced by

the Circle of Discontent, a collection of feedback loops between these four main points in which any disequilibria are hard to control (Figure 1).

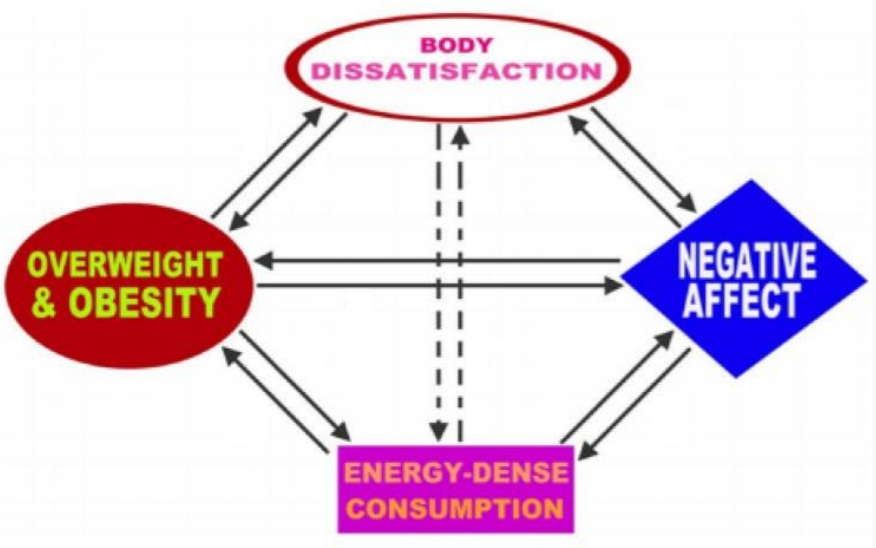

Figure 1: The Circle of Discontent

The application of homeostatic health as a cause of obesity. Imbalance of any one pathway connecting any two of the variables can induce poor homeostatic health. Disequilibrium of multiple pathways may result in a more severe affect. Arrows connecting body dissatisfaction and energy-dense consumption are dashed due to inconsistent evidence (Marks, 2015).

There are many ways this chart can be viewed. For one, as weight gain changes physical health, food is overconsumed, body dissatisfaction increases, and the result is negative affect. The cycle could also begin with other categories such as energy-dense consumption which causes weight gain, leading to body dissatisfaction and negative affect. Due to the dual nature of these homeostatic relationships, it may not even be

necessary for all factors to be out of alignment to result in negative affect. Considering body positivity, body dissatisfaction may not play a large role for some individuals. This could possibly reduce the overall negative affect established by the remaining impact of overweight/obesity and energy dense consumption in Marks' Circle of Discontent (Marks, 2015). This theory describes obesity as a disruptive feedback loop that requires conscious intervention to return to equilibrium. Marks considers a very broad view of the causes of health and disease. Research is now narrowing the scope to understand how smaller internal systems impact the overall state of the host.

Conforming to the idea of homeostasis, a person's ideal body weight can be viewed as the set equilibrium weight. This equilibrium, which seeks to maintain overall body composition at any weight, is carried out via many hormonal pathways that aim to physiologically control body weight via the control of food intake (Harris, 1990). Among these regulatory hormones are anorexigenic (appetite suppressing) glucagon-like peptide 1, cholecystokinin, leptin, and peptide YY along with orexigenic (appetite stimulating) ghrelin and pancreatic polypeptide. A summary of body weight regulatory hormones and their physiological roles can be seen in Table 1. These hormones often work by targeting either the vagus nerve, enteric nervous system, and/or the immune system to communicate with the central nervous system (Lean & Malkova, 2016). The hypothalamus works as a relay station for neural and hormonal signals from the body. After processing, the hypothalamus propagates appropriate signals to bring about desired changes in the autonomic nervous system and behavior (Toni et al., 2004).

Hormone	Physiological Role
Ghrelin	Increase appetite, lipogenesis, glucose output from the liver, and gastric motility.
Pancreatic Polypeptide	Increase appetite, lipogenesis, glucose output from the liver, and gastric motility.
Leptin	Decrease appetite, energy balance.
Oxyntomodulin	Decrease appetite, energy balance.
Cholecystokinin	Decrease appetite, glucose output from the liver, and intestinal motility.
Glucagon-like Peptide 1	Decrease appetite, glucose output from the liver, and intestinal motility.
Peptide YY	Decrease appetite, intestinal motility, and secretion of pancreatic enzymes.
Serotonin	Increase lipolysis, gastric motility, pancreatic enzyme secretion, and bile fluid turnover. Decrease uptake of glucose by the liver.

Table 1: Common Gut Hormones and their Corresponding Physiological Roles

These hormones bring about the mentioned physiological affects upon secretion. The hormones cause affect via homeostatic loops which aim to maintain a set equilibrium point for appetite, gastric motility, energy expenditure, etc. (Martin et al., 2019).

Definition and Prevalence of Obesity and Depression

According to the World Health Organization, obesity rates have nearly tripled since 1975. Obesity is often defined using the Body Mass Index (BMI), calculated by dividing one's weight (in kilograms) by the square of their height (in meters). Those with a BMI of 25 or above are considered overweight and those with a BMI of 30 or above are considered obese. BMI, while an indicator, is not a perfect tool to predict body composition and health risk. Having an elevated BMI, like seen in many highly trained athletes, does not definitively mean someone is at risk for comorbid diseases associated with obesity such as type two diabetes, hypertension, non-alcoholic fatty liver disease, and cardiovascular disease to name a few (Apovian, 2016; Chooi et al., 2019). Discussing obesity is made complicated because the condition differs based on gender, race, ethnicity, sex, and age. For example, men tend to accumulate more fat

within the abdominal cavity (i.e., visceral fat) than women which is more highly associated with risk for cardiovascular disease than subcutaneous fat (Tchernof & Després, 2013). Obesity often results from complex relationships between genetic factors, socioeconomic status, and cultural influences. Overall obesity prevalence is impacted by lifestyle habits, consumption patterns, and urban development (Apovian, 2016).

The World Health Organization identifies depression as a major contributor to global disease and disability that affects more than 264 million people worldwide. There are many types of depressive disorders that differ in severity but generalized moderate depression can be described as having a "sad, empty, or irritable mood, accompanied by somatic and cognitive changes that significantly affect the individual's ability to function" (*Diagnostic and Statistical Manual of Mental Disorders*, 2013). People with depression often experience symptoms of dissatisfaction and loneliness that affect a person's homeostatic category of subjective well-being. Many studies have determined that obesity is a risk factor for depression and vice versa, although it may be impossible to determine if one causes the other. A common component of both obesity and depression is loss of self-esteem, and it is theorized that this loss may often be a result of distorted body image in obese patients (Gutiérrez-Rojas et al., 2020). Simon et al. (2008) interviewed thousands of middle-aged women. The study showed that prevalence of depression increased from 6.5% in women with a BMI below 25 to 26% in women with a BMI above 35. Further, they determined that obesity prevalence increased from 25% in women who did not claim to have depression to 58% in women with depressive symptoms. Together this data suggests a positive correlation between

obesity and depression and determining the mechanisms of this bi-directional relationship has become increasingly popular among researchers over the last decade.

Treatments for Depression

Depressive disorders are often treated using selective serotonin reuptake inhibitors (SSRIs), increase the amount of free serotonin available to bind to serotonin receptors (Harmer et al., 2017). The neurotransmitter serotonin regulates behavioral and neuropsychological processes of mood, perception, reward, aggression, appetite, memory, sexuality, and attention (Berger et al., 2009). Serotonin can carry out such an array of effects due to the complex system of peripheral and neural serotonergic neurons accompanied by approximately 14 subtypes of serotonin receptors located throughout the body. The 14 receptor types are categorized into five families based on receptor structure, and each type is associated with its own physiological functions (Stahl, 1998).

Central serotonin is produced primarily by the raphe nuclei, located in the midline of the brain stem. Neuronal projections from the raphe nuclei innervate the rest of central nervous system to create the neuronal serotonergic system (Berger et al., 2009). The serotonin produced by the raphe nuclei is the population of serotonin capable of binding behavior-modulating serotonin receptor types located in the central nervous system. The majority of the body's serotonin is produced and released from enterochromaffin cells (also known as enteroendocrine cells) that line the digestive tract. This population of serotonin can then travel throughout the body, binding to many subtypes of peripheral serotonin receptors to induce its effects (Mawe & Hoffman, 2013). Enterochromaffin cells are activated by and respond to the presence

of carbohydrates, short chain fatty acids (lipids), and bile acids (Martin et al., 2019). Peripheral serotonin has been found to regulate glucose homeostasis, lipolysis, bone density, and metabolic disorders such as Type 2 diabetes (Martin et al., 2017). However, peripheral serotonin does not easily cross the blood brain barrier, meaning peripheral serotonin cannot directly target mood regulating central serotonin receptors.

Some studies have shown that supplementation with 5-Hydroxytryptophan, an intermediate of serotonin synthesis, may help increase central serotonin concentration. The rate limiting step of serotonin synthesis takes place when L-tryptophan is converted into 5-Hydroxytryptophan via the enzyme tryptophan hydroxylase. By supplementing 5-Hydroxytryptophan, this slow step is surpassed. The blood brain barrier is permeable to 5-Hydroxytryptophan, meaning the molecule can supplement serotonin synthesis in the raphe nuclei after crossing, resulting in greater production of serotonin capable of modulating mood (Birdsall, 1998). Supplementation of tryptophan, an essential amino acid as well as a precursor to serotonin, has also shown this same ability to cross the blood brain barrier where it can be synthesized into serotonin to induce positive behavioral outcomes (Steenbergen et al., 2016). Although many see improved mood and social behavior with supplementation of tryptophan, tryptophan is also a precursor to other molecules such as melatonin which plays a role in regulating the sleep-wake cycle. This may impact efficacy of tryptophan supplementation on serotonin synthesis based on the variability of the supplementing individual's metabolic needs (Bartlett, 2017).

Bariatric Surgery as a Treatment for Obesity

Aside from lifestyle changes to diet and physical activity levels recommended for losing weight, bariatric surgery has been shown to be the most effective for long-term weight loss and metabolic improvement in morbidly obese patients (Buchwald et al., 2004). There are many types of bariatric surgical procedures (Figure 2), the two most common being the sleeve gastrectomy (SG) and the Roux-en-Y gastric bypass (RYGB).

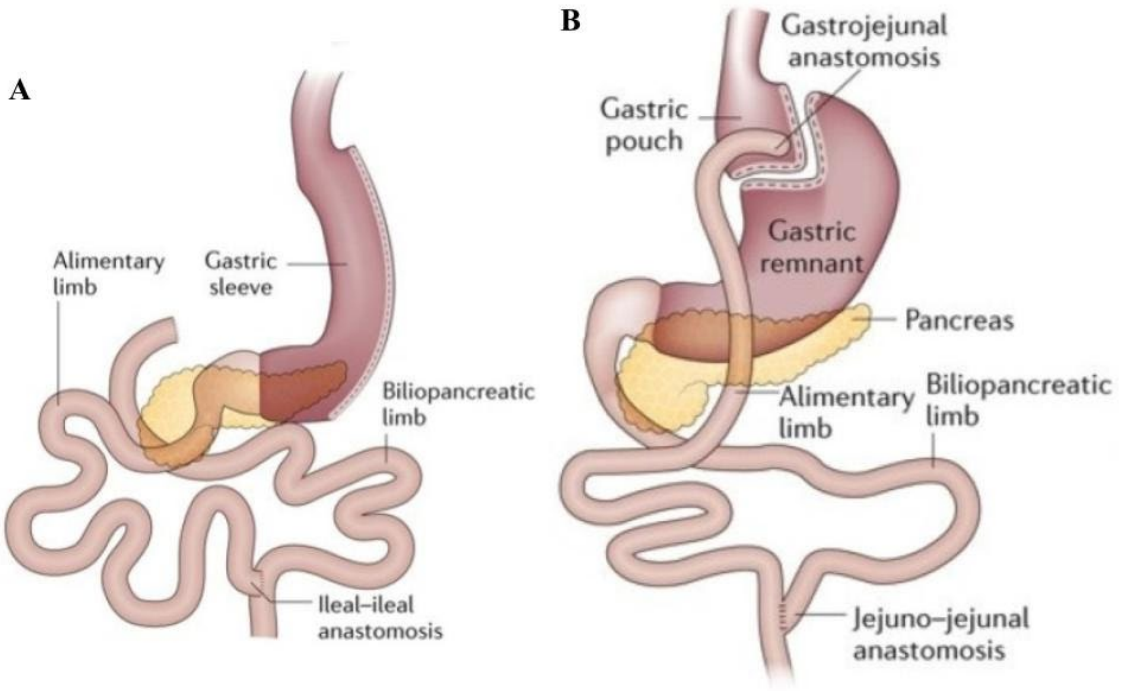

Figure 2: Anatomy of Bariatric Surgery Procedures

Sleeve gastrectomy (A) and Roux-en-Y gastric bypass (B) (Ulker & Yildiran, 2019).

In SG, approximately 70 percent of the stomach is removed with an incision, leaving behind a smaller pouch that resembles a banana. This procedure does not affect the absorption of nutrients because it does not alter the anatomy of the intestines where absorption takes place. In the RYGB procedure, the top of the stomach is separated

from the rest to create a small pouch capable of holding only approximately 30 milliliters in volume. This pouch is then connected directly to the jejunum, so the bypassed remaining stomach and the duodenum attached to the small intestine create a Y-shape. The bypassed stomach and duodenum continue to secrete gastric acid and hormones, but the patient's nutrient absorption is greatly reduced because food no longer travels through the bypassed organs. In general, these procedures work to limit the amount of food that can be consumed, leading to lesser caloric intake and weight loss which often allows for the betterment of comorbidities while also affecting the production and usage of gastrointestinal hormones that control hunger and satiety, as well as the composition of the gut microbiome (Cătoi et al., 2019).

Crosstalk Between Obesity, Bariatric Surgery, and Depression

Given the prevalence of coexisting obesity and depression discussed earlier, many patients seeking esthetically enhancing surgery, bariatric or others such as liposuction, show moderate to severe symptoms of depressive disorders and body image dysmorphia (Brito et al., 2016). Every bariatric surgery candidate must undergo extensive psychological evaluations before bariatric surgery. It is required that bariatric surgery patients be given increased access to resources like support groups, mentor programs, and nutritional support post-surgery in an attempt to lessen pre-existing and/or prevent the worsening of depressive symptoms during the period of rapid change following bariatric surgery. However, these interventions cannot always be utilized or maintained by the patient, and body image dissatisfaction often increases after surgery as the rapid surgically induced weight loss can cause patients to seek unrealistic body shapes (Munoz et al., 2010; Sarwer & Fabricatore, 2008). One study indicates that

bariatric surgery results in improved long-term depressive symptoms when measured two years after surgery (Gill et al., 2019). However, other studies provide evidence of immediate decreases in depression levels following bariatric surgery, but these are not maintained as in the years following surgery symptoms of decreased mood and body dissatisfaction increase once again (Canetti et al., 2016). When following a group of adolescence that underwent bariatric surgery over a span of five years, Järvholm et al. (2020) found that, while self-esteem and binge eating were improved, general mood did not. Despite substantially greater weight loss compared to control, patients often report the same or worse overall mood, which then also positively correlates with decreased weight loss and/or increased weight regain following surgery (Monpellier et al., 2018).

As part of the surgical process, patients are expected to attend follow up appointments for both physical and psychological care, but long-term attendance at these appointments is not reliable due to financial requirements, time availability, and geographic location limitations (Bradley et al., 2018). Remote care has been on the rise and is proving beneficial thus far, particularly in the time of the Covid-19 pandemic and may be a useful tool to fight attendance issues in the long-term future (Rubino et al., 2020). Literature emphasizes the need for active intervention that targets mental health via life coaching to prolong weight loss, but the problem of patient attendance has yet to be solved (Belligoli et al., 2020; Rudolph & Hilbert, 2013).

Cognitive Behavioral Therapy (CBT) has been associated with improved eating patterns, psychological symptoms, and decreased weight regain. The current question being asked about CBT is when it should begin. Some suggest that participation before and/or after surgery (Cheroutre et al., 2020), but some report that pre-surgery CBT

alone does not result in any significant benefits. When postoperative benefits of a normal treatment group are compared to that of a group that received CBT emphasizing nutritional and activity management, cognitive restructuring, and relapse prevention, there was no significant improvement in long-term eating behavior or depression post-surgery (Paul et al., 2020). However, CBT taking place briefly before and for at least three months following surgery, before any weight regain or problematic eating behaviors develop, positively correlates with improved postoperative psychological wellbeing (Beaulac & Sandre, 2015; David et al., 2020).

Maintenance of pharmacotherapy for comorbidities such as hypertension and diabetes following bariatric surgery is vital to survival, and psychological findings suggest that pharmacotherapy regarding antidepressants should be no different (Bland et al., 2016). With the high prevalence of psychiatric disorders in those who seek out bariatric surgery, approximately 35% of patients already take antidepressants before surgery (Hawkins et al., 2020). The rate of antidepressant drug discontinuation is significantly lower than that of drugs that treat physical symptoms like hypertension, indicating a need for further research on how bariatric surgery affects the effectiveness of antidepressants (Kennedy et al., 2014). Antidepressant medications normally come in the form of selective serotonin reuptake inhibitors SSRIs or selective serotonin-norepinephrine reuptake inhibitors (SNRIs). Patients taking SNRIs rather than SSRIs one year after surgery have a statistically higher percent total weight loss (Hawkins et al., 2020). Sources of tryptophan can deplete when an enzyme involved in immune activation is overactivated. This overactivation via chronic inflammation in obese patients and resulting tryptophan depletion are highly present in morbidly obese

individuals and persist even after surgical weight loss (Brandacher et al., 2006). The decreased amount of serotonin available likely contributes to depressive symptoms after bariatric surgery and SSRI/SNRI drugs may not be enough to efficiently correct the concentration of serotonin.

Serotonin type 2C receptor signaling is essential for weight loss, but it has been shown that this receptor's signaling is not what causes post-surgical weight loss. It may be possible that serotonergic drug activation of these receptors could cause weight loss therapeutically (Carmody et al., 2015). Neuronal serotonin differs in obese individuals in that there is a much higher rate of serotonin binding to type 2A receptors, binding of which positively correlates with weight regulation (Haahr et al., 2015). Significant decreases in the availability of SSRIs one month after bariatric surgery correlates with increased depressive symptoms that get better as drug availability, an indicator of serotonin levels, normalizes over time (Hamad et al., 2012). This indicates that simply prescribing SSRIs to every bariatric surgery patient will not efficiently treat drooping serotonin levels, and therefore depressive symptoms, post-surgery. A large amount of current research focuses on the pharmaceutical and behavioral aspects of treating depressive symptoms following bariatric surgery, but these are not the only possible targets. Given the sheer alteration to the anatomy of the gastrointestinal tract in bariatric surgery, perhaps there are alterations in how the gut and the brain are communicating.

The Gut-Brain Axis

The collection of enterochromaffin cells that line the gut, the largest endocrine organ in the body, form the enteroendocrine system. This system works to secrete over

20 known hormones that play a major role in bodily homeostasis (Martin et al., 2019). These hormones interact with the enteric nervous system which propagates signals to the brain for processing. After processing, the brain responds with signals to the gut as needed. But these enterochromaffin cells function at the hand of the supporting gut microbiome (GM), the highly diverse and variable collection of bacteria (mostly anaerobes), fungi, viruses, and protozoa that reside in the intestines. The GM differs slightly in each person and has been found to regulate vital physiological and neurological processes vital for homeostasis. The GM greatly influences hormone production, and therefore neurological response. The circular communication between the GM and central nervous system, deemed the gut-brain axis, often occurs via the vagus nerve, immune system, and the enteric nervous system. Many neuronal pathways connecting the gastrointestinal tract to the brain travel along the vagus nerve. Secretion of enteroendocrine hormones, discussed earlier, activates receptors of afferent pathways, sending various signals to the brain for processing. Each hormone, receptor, and neural pathway will bring about a specific response, such as changing appetite and/or energy expenditure to maintain homeostasis (Lyte & Cryan, 2014).

The makeup of the GM in lean, healthy individuals has been extensively studied for use as a baseline when analyzing changes to the GM in any specific circumstance. The compositions are more broadly categorized into main phyla, and further analysis can determine species presence and concentration. The main phyla that make up the GM are Firmicutes (genera such as *Clostridium, Ruminococcus, Lactobacillus*, and *Faecalibacterium*), Bacteroidetes (genera such as *Bacteroides, Porphyromonas*, and *Prevotella*), Proteobacteria (examples include *Helicobacter* and *Escherichia*),

Actinobacteria (mainly *Bifidobacterium*), and less of the phyla Verrucomicrobiota (species *Akkermansia muciniphila* in particular). Fungi and archaea compose less than 1% of the GM (Ruan et al., 2020). It is also important to note that the composition of the GM varies by location (Figure 3). Utilizing location-specific populations of microbes in congruence with disorder anatomy can aid in treatment development.

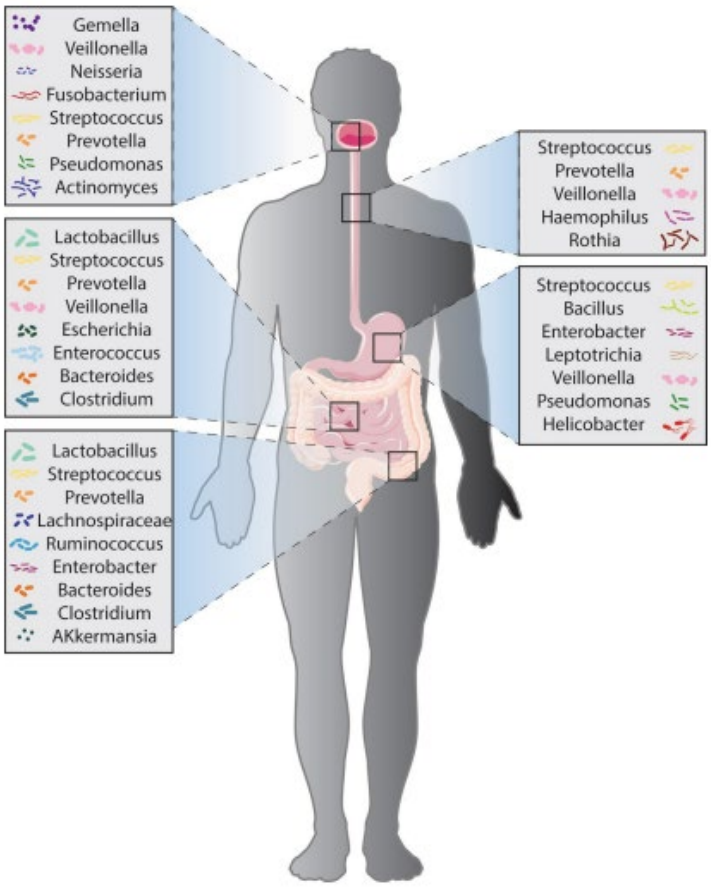

Figure 3: Gut Microbiome Composition based on Location

The composition of microbes in the gastrointestinal tract varies depending on location. Dominant genera of bacteria in the oral cavity, esophagus, stomach, small intestine, and colon are depicted (Ruan et al., 2020).

Dysbiosis of the Gut Microbiome

When an individual possesses a healthy GM, there is a symbiotic (i.e., mutually beneficial) relationship between the GM and the host. For example, mice models have demonstrated that a healthy GM plays a vital role in the development of the central nervous system. With dysbiosis of the GM, there is an imbalance of microorganisms that can result in an innumerable number of symptoms. The GM actively communicates via pathways that utilize the immune system, vagus nerve, enteric

nervous system, and neuroactive compounds. For example, some bacteria in the GM can produce neurotransmitters, such as serotonin and dopamine, which are capable of activating pathways associated with the gut-brain axis (Foster & McVey Neufeld, 2013; Strandwitz, 2018). Changing the GM in turn alters the signaling to and from the brain. Dysbiosis of the GM has been linked to many diseases, many of which are neuropsychological, such as irritable bowel disease, cardiovascular disease, Alzheimer's disease, Parkinson's disease, schizophrenia, as well as obesity, depression, or even daily stress (Barko et al., 2018). When the microbiota of depressed patients is transferred to a microbiota-deficient (i.e., germ free) rat, the transplanted rat begins to show behavioral and psychological features that are associated with depression, indicating a causal role for the GM in the gut-brain axis (Kelly et al., 2016). Similarly, transplantation of microbiota from obese to germ free mice results in a significantly larger increase in adiposity than when transplanted with microbiota from lean mice (Turnbaugh et al., 2008). Transplantation of obese gut microbiota into germ free mice also induced neurobehavioral disruptions even in the absence of increased adiposity, further indicating that the GM plays a role in neurological functioning (Bruce-Keller et al., 2015). As the importance of the GM in regulating brain function comes to light, researchers are investigating the physiological basis for the GM's modulation of neurological function (Cryan et al., 2019).

Changing a subject's diet is the primary method of altering the GM. Dietary changes have been shown to cause large adjustments to microbial concentration within a 24-hour period, but these changes are temporary if the healthy GM promoting diet is not maintained. Various diet components affect the GM in a specific manner. Eating a

high fat diet correlates with decreased GM diversity, while increasing animal protein intake helps increase microbial diversity (Singh et al., 2017). The recent development of microbiota transfer therapy is being used as a method to alter the GM of patients with conditions such as autism spectrum disorders, which often presents with gastrointestinal symptoms as symptom severity increases. In an extended clinical trial using microbiota transfer therapy, symptoms of constipation, diarrhea, indigestion, abdominal pain, and behavioral symptoms of autism spectrum disorders all improved eight weeks after the completion of microbiota transfer therapy. Increases in *Bifidobacterium*, *Prevotella*, and *Desulfovibrio* were noted as the main changes to GM composition (Kang et al., 2017). Continuing to develop the understanding of functions modulated by the GM for the treatment of disorders is a promising field of study.

The Obese Microbiome

Human studies demonstrate that obese individuals present with a decreasingly diverse community of microbes in the GM. Specifically, obese individuals have a higher *Firmicute* to *Bacteroidetes* ratio and functional disturbances to metabolic pathways affected by the GM (Cătoi et al., 2019). Bacteria involved in weight gain are thought to induce increases in the expression of genes involved with carbohydrate and lipid metabolism, resulting in greater energy absorption from dietary foods. As obesity is already associated with greater energy intake than energy expenditure, increased absorption due to the GM only further complicates the development and treatment of obesity (John & Mullin, 2016). Short chain fatty acids produced by the GM can become concentrated enough to harm lipid metabolism, possibly contributing to the development of non-alcoholic fatty liver disease and hyperlipidemia. Gene expression

of proteins involved in essential and nonessential amino acid metabolic pathways are significantly reduced in obese individuals (Sanmiguel et al., 2015). One major aim of bariatric surgery is to restore metabolic functions in obese individuals, and some may argue that improving one's state of mind is a secondary goal as it is a major component of overall health. The mechanisms by which GM bacteria regulate metabolic and neural functions are actively being examined by current researchers.

Methods

Using the PubMed database, a systematic review of the literature regarding how bariatric surgery and depression individually change the profile of the GM will be formed. Further, studies that evaluate the gut microbiota in individuals who undergo bariatric surgery and individuals with depression will be analyzed in search of precise changes in composition corresponding to each condition (phyla, genus, etc.). The relative trends in taxa were then compared to one another in search of common directional changes in GM abundance. Common shifts in GM composition may indicate mechanisms/pathways that contribute to the continued presence of depressive symptoms after bariatric surgery.

The selected term(s) for GM changes caused by bariatric surgery were "bariatric surgery" AND "gut microbiome." For analyzing GM changes with depression, the terms "bariatric surgery" AND "depression," and "gut microbiome dysbiosis" AND "depression" were used. All searches were filtered to require a publication date on or after January 1, 2015. All articles were screened based on title and abstract. Prospective cohort studies, pilot studies, reviews, and systematic reviews were selected.

Results

For GM alteration caused by bariatric surgery, 3606 articles were retrieved and 41 were selected for further analysis based on title. For GM alteration influenced by depression, 930 articles were retrieved and 32 were selected for further review based on title. Article abstracts were the evaluated in search of reporting species-specific changes in the GM. Nine studies researching the GM after bariatric surgery and eight studies researching the GM in depression (17 total) were selected for demographic and GM content analysis. Study demographics are described in Tables 2 and 3 and include citation, study description, participant number (n), population descriptions, and findings/outcomes. Tables 4 and 5 reports changes in GM population expression for bariatric surgery and depression, respectively. Table 6 identifies similarities in GM changes associated with both bariatric surgery and depression.

In general, the analysis revealed that both post-bariatric surgery and depressed GMs showed an increased relative abundance of *Streptococcus*, Proteobacteria, *Citrobacter*, *Enterobacter*, *Klebsiella pneumoniae*, Bacteroidetes, *Alistipes*, Fusobacteria, *Akkermansia*, and Actinobacteria, and decreased levels of Firmicutes, *Lactobacillus*, *Faecalbacterium*, *Ruminococcus*, and *Bifidobacterium*. Trends in *Anaerostipes*, *Clostridium*, *Blautia*, *Veillonella*, *Roseburia*, *Escherichia*, *Escherichia coli*, *Bacteroides*, *Prevotella*, and Verrucomicrobiota were divergent. Table 7 indicates where bacterial genera that show the same trend are located throughout the gastrointestinal tract.

Author and Publication Year	Study Design	Sample Population (n)	Topic(s) Examined	Main Findings
Cook et al., 2020	SR	n=20 human studies n=21 invertebrate studies	GM changes in humans compared to invertebrate sham bariatric surgery controls. Probiotic usage, psychological states and behaviors.	Could not determine a direct linkage to psychological conditions due to insufficient data in the context of bariatric surgery, increases in Proteobacteria and the *Akkermansia* species of the Verrucomicrobiota phylum follow bariatric surgery.
Davies et al., 2019	SR	n=14 clinical studies n=222 participants	Metabolic benefits of BS	Diet, medication, and Type 2 Diabetes are discussed in the context of bariatric surgery and future research. Bariatric surgery results in increased micriobial diversity in the gut.
Guo et al., 2018	SR	12 human studies, 9 animal studies	Metabolic benefits of BS	Increases of four main phyla (Bacteroidetes, Fusobacteria, Verrucomicriobiota, and Proteobacteria) follow baraitric surgery, mentioning of specific species follows. More research is needed to determine causal and mechanistic metabolic affects caused by changing GM in bariatric surgery patients.
Lee et al., 2019	P	n=4 medical weight loss n=4 adjustable gastric band n=4 RYGB	GM changes in bariatric surgery vs. medical weight loss patients	Bariatric surgery increases GM diversity more than medical weight loss. More research is needed to determine how different GM changes affects remission of Type 2 Diabetes.
Luijten et al., 2019	SR	n=21 studies	GM changes in association with improving comorbidities that follow bariatric surgery	Changes in GM composition positively correlate with weight loss and Type 2 Diabetes remission, but an exact causal relationship has yet to be determined.
Mabey et al., 2020	PC	n=16 bariatric surgery n=19 medical weight loss	GM composition after a decade in patients that had bariatric surgery compared to obese individuals that did not have surgery.	Long term differences in GM composition were reported for the surgical group, but not for the control group. Subjects that underwent surgery had increased amounts of the families Verrucomicrobiaceae and Streptococcaceae, but decreased levels of the Bacteroidaceae family 10.6 years after surgery compared to the non-surgical group. Increased in the *Akkermansia* species may be linked to Type 2 Diabetes remission.
Magouliotis et al., 2017	SR	n=22 studies	Metabolic functioning and microbe contents following bariatric surgery	Postoperative GM compisition is more similar to lean and less obese patients. Decreased branched chain amino acids (BCAA's) along with increased GLP-1 and PYY were observed after surgery.
Pajecki et al., 2019	PC	n=9 RYGB subjects	Post surgical GM composition compared to before surgery.	Higher levels of Firmicutes and decreased levels Bacteroidetes after surgery were associated with less weight loss. A general decrease in Proteobacteria was observed.
Steinert et al., 2020	P	n=16 RYGB n=9 control	Bacterial and fungal GM composition before and 3 months post bariatric surgery compared to healthy controls.	Bacterial GM diveristy significantly increased after surgery, but was still significantly different from healthy controls. Changes in fungal microbiota were significant before and after surgery but dependent on the individual.

Table 2: Selected Studies that Report Changes to the Gut Microbiome After Bariatric Surgery

General demographics and findings of selected studies that examine changes in the GM after bariatric surgery. Abbreviations are SR (systematic review), P (pilot study), and PC (prospective cohort study).

Author and Publication Year	Study Design	Sample Population (n)	Topic(s) Examined	Main Findings
Aizawa et al., 2016	PC	n=43 depressed n=57 control	Association between *Bifidobacterium* and *Lactobacillus* in the gut of patients with MDD compared to control.	Significantly lower *Bifidobacterium* and trending lower L*actobacillus* counts were observed in MDD patients. Consumption of fermented milk was associated with higher *Bifidobacterium* counts.
Cheung et al., 2019	SR	n=6 case-control studies	Relationship between GM composition and MDD compared to contols.	No clear outline of GM changes in MDD patients was determined. Reports genera of microbiota that increased, decreased, or were divergent with MDD.
Du et al., 2020	R	N/A	Methods by which the GM alters the HPA axis and induces depressive symptoms.	Alterations to the HPA axis by the GM can decrease levels of brain-derived neurotropic factor (BDNF), leading to depression. Much more research is needed to determine causative mechanisms of the GM relating to depression.
Heym et al., 2019	PC	n=40 subjects	Comparing GM composition of faecal samples to depression via self-report questionnaires	Increased *Lactobaccilus* content positively correlated with positive self judgement, but further research is needed to determine the role of *Lactobacillus* in depression.
Jiang et al., 2015	PC	n=46 depressed n=30 control	Comparing GM composition in patients with active and recovered MDD to controls.	Active MDD patients had increased bacterial diversity compared to healthy controls. Active MDD was associated with increased Proteobacteria, Actinobacteria, and Bacteroides but decreased Firmucutes. Higher *Faecilibacterium* levels positively correlated with severity of MDD symptoms. Temporal and causal relationships still need to be determined in further studies.
Naseribafrouei et al., 2014	PC	n=37 depressed n=18 control	GM composition of depressed compared to healthy controls	Significant differences in GM were seen at the order taxonomic level. The *Alistipes* species significantly related to depression severity.
Macedo et al., 2017	SR	n=120 studies	GM associated with depression and treating an altered GM with SSRIs and antimicrobials	Depression associated GM phenotype reported. Explains the possible neuroprotective effects of antidepressants and antimicrobials which may act by altering GM composition.
Slyepchenko et al., 2017	R	N/A	Relationship between GM and diet on the pathophsyiology of MDD	Dysbiosis of the GM and a leaky gut my greatly influence MDD via immune activation and neuroplasticity. More research is needed to determine exact causal relationships between microbiota and MDD.

Table 3: Selected Articles that Report the Altered Gut Microbiome in Depressed Individuals

General demographics and findings of selected studies that examine changes in the GM relating to depression. Abbreviations are SR (systematic review), R (review), and PC (prospective cohort study).

Microbe	Taxonomic Level	Cook et al., 2020	Davies et al., 2019	Guo et al., 2018	Lee et al., 2019	Luijten et al., 2019	Mabey et al., 2020	Magouliotis et al., 2017	Pajecki et al., 2019	Steinert et al., 2020
Firmicutes	Phylum	↓	↓	↓	↓	↓	NR	↑/↓	↑/↓	↓
Anaerostipes	Genus	NR	↓	↓	NR	NR	NR	↓	NR	NR
Lactobacillus	Genus	NR	↓	NR	NR	↓	NR	↓	↓	NR
Clostridium	Genus	NR	NR	↓	NR	↑/↓	NR	↓	↓	NR
Blautia	Genus	NR	NR	↓	NR	NR	NR	↓	NR	↓
Faecalibacterium	Genus	NR	↓	↓	↑	NR	NR	↓	NR	↓
Streptococcus	Genus	NR	NR	NR	↑	↑	↑	↑	NR	↑
Ruminococcus	Genus	NR	NR	↓	NR	NR	NR	↓	NR	NR
Veillonella	Genus	NR	NR	↑	↑	↑	NR	↑	NR	NR
Roseburia	Genus	NR	↓	NR	↓	↑	NR	↓	NR	↓
Proteobacteria	Phylum	↑	↑	↑	↑	↑	NR	↑	↓	↑
Citrobacter	Genus	NR	NR	↑	↑	NR	NR	↑	NR	NR
Enterobacter	Genus	NR	NR	↑	↑	↑	NR	↑	NR	NR
Escherichia	Genus	↑	↑	↑	NR	↑/↓	NR	↑	NR	↑
Eschericha coli	Species	↑	↑	↑	↑	↑	NR	↑	NR	↑
Klebsiella pneumoniae	Species	NR	↑	↑	NR	↑	NR	↑	NR	↑
Bacteroidetes	Phylum	↑/↓	↑	↑	↑/↓	↑/↓	↑/↓	↑	↑/↓	↑/↓
Parabacteroides	Genus	NR	NR	↑	NR	NR	NR	NR	NR	NR
Bacteroides	Genus	NR	NR	NR	NR	↑	NR	↑	↑/↓	NR
Prevotella	Genus	NR	NR	NR	NR	↑	NR	↑	NR	↑/↓
Alistipes	Genus	NR	NR	↑	NR	NR	NR	↑	NR	NR
Fusobacteria	Phylum	NR	NR	↑	↑	↑	NR	NR	NR	NR
Verrucomicrobiota	Phylum	↑/↓	NR	↑	↑	NR	↑	NR	NR	↑/↓
Akkermansia	Genus	↑	↑	↑	↑	↑	↑	↑	NR	NR
Actinobacteria	Phylum	↑/↓	↓	NR	↑	↑	NR	↑	NR	↓
Bifidobacterium	Genus	NR	↓	↓	NR	↓	NR	↓	↓	↓

Table 4: Trends in Gut Microbiome Dysbiosis Associated with Bariatric Surgery

Trend data extracted from selected articles relating bariatric surgery to changes in the gut microbiome. Microbiota are categorized by phyla, with genus or species listed below belonging to the above phylum. Trends were increase (↑, pink), decrease (↓, blue), or reports of increased and decreased prevalence (↑/↓, yellow), or not reported (NR, grey).

Microbe	Taxonomic Level	Aizawa et al., 2016	Cheung et al., 2019	Du et al., 2020	Heym et al., 2019	Jiang et al., 2015	Naseribafrouei et al., 2014	Macedo et al., 2017	Slyepchenko et al., 2017
Firmicutes	Phylum	NR	↑/↓	↓	NR	↓	↑	↓	↑
Anaerostipes	Genus	NR	↑	NR	NR	NR	NR	NR	NR
Lactobacillus	Genus	↓	↓	↓	↓	NR	NR	NR	↓
Clostridium	Genus	NR	↑	NR	NR	↑	NR	↑	↑
Blautia	Genus	NR	↑	NR	NR	↑	NR	NR	NR
Faecalibacterium	Genus	NR	↓	↓	NR	↓	NR	↓	↓
Streptococcus	Genus	NR	↑	NR	NR	NR	NR	NR	NR
Ruminococcus	Genus	NR	↓	↓	NR	↓	NR	NR	↑
Veillonella	Genus	NR	NR	NR	NR	NR	NR	NR	NR
Roseburia	Genus	NR	↑/↓	NR	NR	↑	NR	NR	NR
Proteobacteria	Phylum	NR	↑/↓	↑	NR	↑	NR	↑	NR
Citrobacter	Genus	NR	NR	NR	NR	NR	NR	↑	↑
Enterobacter	Genus	NR	NR	NR	NR	↑	NR	↑	NR
Escherchia	Genus	NR	↓	NR	NR	NR	NR	NR	NR
Escherchia coli	Species	NR	↓	NR	NR	NR	NR	↑	NR
Klebsiella pneumoniae	Species	NR	↑	NR	NR	NR	NR	↑	↑
Bacteroidetes	Phylum	NR	↑/↓	↑	NR	↓	↑	↑	↑
Parabacteroides	Genus	NR	↑	NR	NR	↑	NR	NR	↑
Bacteroides	Genus	NR	↑/↓	NR	NR	↓	↑	NR	NR
Prevotella	Genus	NR	↑/↓	NR	NR	↓	NR	NR	NR
Alistipes	Genus	NR	↑/↓	↑	NR	↑	↑	↑	↑
Fusobacteria	Phylum	NR	↑/↓	NR	NR	↑	NR	NR	NR
Verrucomicrobiota	Phylum	NR	NR	NR	NR	NR	NR	NR	NR
Akkermansia	Genus	NR	↑	NR	NR	NR	NR	NR	NR
Actinobacteria	Phylum	NR	↑	↑	NR	↓	NR	↑	↑
Bifidobacterium	Genus	↓	↓	↓	↓	NR	NR	NR	↓

Table 5: Trends in Gut Microbiome Dysbiosis Associated with Depression

Trend data extracted from selected articles relating the gut microbiome to depression. Microbiota are categorized by phyla, with genus or species listed below belonging to the above phylum. Trends were increase (↑, pink), decrease (↓, blue), or reports of increased and decreased prevalence (↑/↓, yellow), or not reported (NR, grey).

Microbe	Taxonomic Level	Bariatric Surgery	Depression
Firmicutes*	Phylum	↓	↓
Anaerostipes	Genus	↓	↑
*Lactobacillus**	Genus	↓	↓
Clostridium	Genus	↓	↑
Blautia	Genus	↓	↑
*Faecalibacterium**	Genus	↓	↓
*Streptococcus **	Genus	↑	↑
*Ruminococcus**	Genus	↓	↓
Veillonella	Genus	↑	CD
Roseburia	Genus	↓	↑
Proteobacteria*	Phylum	↑	↑
*Citrobacter**	Genus	↑	↑
*Enterobacter**	Genus	↑	↑
Escherichia	Genus	↑	↓
Eschericha coli	Species	↑	CD
*Klebsiella pneumoniae**	Species	↑	↑
Bacteroidetes*	Phylum	↑	↑
*Parabacteroides**	Genus	↑	↑
Bacteroides	Genus	↑	CD
Prevotella	Genus	↑	CD
*Alistipes**	Genus	↑	↑
Fusobacteria*	Phylum	↑	↑
Verrucomicrobiota	Phylum	↑	CD
*Akkermansia**	Genus	↑	↑
Actinobacteria*	Phylum	↑	↑
*Bifidobacterium**	Genus	↓	↓

Table 6: Overall Trends in Gut Microbiome Dysbiosis from Tables 4 and 5

Overall trends of each microbiota for changes associated with bariatric surgery and depression. The * symbol represents similar trends, indicating a positive correlation between bariatric surgery and depressive GM phenotypes. Trends were increase (↑, pink), decrease (↓, blue), or cannot determine (CD).

Location	Increased Abundance	Decreased Abundance
Oral Cavity	Proteobacteria Actinobacteria Fusobacteria *Streptococcus*	Firmicutes *Lactobacillus* *Bifidobacterium*
Esophagus	*Fusobacteria* *Streptococcus*	N/A
Stomach	*Streptococcus* *Enterobacter*	N/A
Small Intestine	*Streptococcus* *Enterobacter* *Akkermansia* Fusobacteria *Klebsiella*	*Lactobacillus* *Ruminococcus* *Bifidobacterium*
Colon	Proteobacteria Actinobacteria Bacteroidetes Fusobacteria *Ruminococcus* *Alistipes* *Enterobacter*	Firmicutes *Lactobacillus* *Faecalibacterium* *Ruminococcus* *Bifidobacterium*

Table 7: Location of Bacteria with Similar Trends of Abundance in the Gut Microbiome of Depressed and Bariatric Surgery Patients

Known locations of bacteria along the gastrointestinal tract for identified bacterial taxa that mutually change in depressed and bariatric surgery gut microbiomes (Ruan et al., 2020; Shigwedha & Ji, 2013)

Discussion

Although bariatric surgery has generally been shown to alter microbial diversity in the GM, the surgery does not restore a lean/control GM and beneficial changes may begin digressing as soon as six months after surgery (Shen et al., 2019). GM composition is often still compared to lean/healthy individuals so that relative changes can be compared between patient/intervention and control groups. By comparing changes in the GM in depressed and bariatric surgery populations to that of lean individuals, similar trends indicate similar markers of GM dysbiosis. Some studies indicate that the changes to the GM caused by both surgical and medical/dietary weight loss may be harmful. In medical weight loss, the nutrient absorbing abilities of the GM increase, making it difficult for people to continue losing weight in this manner (Damms-Machado et al., 2015). Even though surgical intervention has been shown to increase the abundance of some beneficial bacteria, such as *Faecalibacterium*, these changes are not large enough to restore a lean phenotype. There are also some alterations in potentially harmful bacterial populations following bariatric surgery, such as the phyla Proteobacteria which impacts intestinal absorption and pH, possibly resulting in long-term detriments in colonic function, preventing weight loss and contributing to neurobehavioral deficits (Seganfredo et al., 2017). The lack of lean GM restoration indicates the need for other treatment targets, such as plant fibers that feed beneficial bacteria known as prebiotics, which aim to restore the composition of a lean GM phenotype in obese and depressed individuals.

Other than diet, a common method used to alter GM composition is probiotic treatment, the oral administration of live bacteria and yeast. Taking prebiotics and

probiotics together could increase the efficacy of lean GM restoration (Damms-Machado et al., 2015). Studies looking into how administration of microbe specific probiotics may be able to alleviate a variety of symptoms is actively underway, particularly for the use of bacteria belonging to the *Lactobacillus* and *Bifidobacterium* genera. The species tested to treat depressive symptoms are often the same as those that have obesity fighting affects (Dinan et al., 2013). Administration of *Bifidobacterium longum* and *Lactobacillus helveticus*, both from genuera that decrease in both bariatric surgery and depressed GM phenotypes, has been shown to improve symptoms of depression and decrease levels of cortisol by inhibiting activation of the hypothalamic-pituitary-adrenal axis, important for immune activation, stress response, digestion, and mood (Ait-Belgnaoui et al., 2014; Messaoudi et al., 2011). Alterations in pro-inflammatory cytokine release have been restored to normal along with the resolution of separation-induced depressive behavior by administering *Bifidobacterium infantis* (Desbonnet et al., 2010). Treatment with *Bifidobacterium infantis* is also correlated with greater levels of peripheral tryptophan available for serotonin synthesis, perhaps leading to increased neural serotonin production and improved mood (O'Mahony et al., 2015). The effect caused by the probiotic depends on its specific formula of bacterial taxa, and the roles of many species have yet to be determined.

Some species within the GM have been found to produce precursors to neurotransmitters, such as tryptophan, or even some neurotransmitters themselves including serotonin, dopamine, and gamma (γ) aminobutyric acid (GABA), all of which are associated with the neurochemical aspects of depression. Both *Lactobacillus brevis* and *Bifidobacterium dentium* are efficient at producing GABA, the main inhibitory

neurotransmitter of the central nervous system, and probiotic supplementation with several species from the *Bifidobacterium* genus have been seen to produce elevated levels of dopamine and serotonin (Du et al., 2020). A higher abundance of *Alistipes*, a bacterium capable of utilizing tryptophan, may also decrease serotonin production by limiting tryptophan availability (Slyepchenko et al., 2017). Many studies are focusing on how the GM modulates production of brain derived neurotrophic factor, a factor involved in neuroplasticity that is often reduced in patients with depression and/or obesity (Naseribafrouei et al., 2014). High fat diet induced dysbiosis of the GM in mice results in decreased levels of brain derived neurotrophic factor and reduced cognitive ability, indicating a role for the GM in the regulation of neuroplasticity and mood symptoms via regulation of brain derived neurotrophic factor levels (Schachter et al., 2018).

Obesity is associated with chronic, low-grade inflammation in peripheral tissues, first examined when the pro-inflammatory cytokine known as tumor necrosis-factor alpha (TNF-α) was found to be significantly elevated in the blood and adipose tissue of obese individuals (Hotamisligil et al., 1995). Obesity related inflammation is often linked to metabolic syndrome, the coexistence of hypertension, hyperglycemia, altered cholesterol (dyslipidemia), and visceral fat accumulation which together increases one's risk for cardiovascular disease, diabetes, and stroke (Alberti et al., 2005). Adipose tissue possesses immune cells that secrete inflammatory factors (cytokines, adipokines), and increased adiposity in obese individuals results in higher levels of circulating inflammatory factors which results in what is known as chronic low-grade inflammation. The release of adipokines such as TNF-α and interleukin-6 (IL-6)

recruits macrophages to adipose tissue in an inflammatory response, contributing to comorbidities such as insulin resistance that are associated with obesity (Ouchi et al., 2011).

Similarly, inflammatory response has been shown to play a cyclical and dose-dependent role in depression. Individuals with major depressive disorder often respond to stressors with a greater inflammatory response compared to controls, and increased inflammatory immune activation can induce depressive symptoms. Higher levels of pro-inflammatory factors TNF-α, IL-6, and C-reactive protein have been found in depressed individuals (Kiecolt-Glaser et al., 2015). Cytokines released during sickness can cross and/or disrupt the functioning of the blood brain barrier, causing inflammation within the central nervous system which may contribute to symptoms of depression. Hyperactivation of the hypothalamic-pituitary-adrenal axis by cytokines IL-6 and TNF-α activates a cascade that induces a greater stress response via release of cortisol, the stress hormone also associated with conditions like obesity and anxiety, from the adrenal gland. These cytokines also inhibit the homeostatic loop that tells the hypothalamic-pituitary-adrenal axis to slow and decrease cortisol release (Dantzer et al., 2008). Cytokines have also been found responsible for increasing the activity of the enzyme that converts the amino acid tryptophan into kynurenine, decreasing available tryptophan molecules and slowing serotonin production. In addition, IL-6 and TNF-α are associated with the increased breakdown of serotonin molecules, further depleting serotonin levels necessary for mood regulation (Rosenblat et al., 2014).

The mechanisms by which the microbiota in the gut contribute to inflammatory responses are still being determined. Many studies are working to link populations of

microbiota to inflammatory diseases. For example, decreases in the phyla Firmicutes and increases in the phyla Proteobacteria, essential for regulating intestinal absorption, pH, and digestion speed, have been documented in patients with irritable bowel disease, of which 49% also have depression, characterized by chronic inflammation of the gastrointestinal tract (Rosenblat et al., 2014). Studies show that the presence of an inflammation-promoting GM, such as that seen in obese individuals, increases intestinal permeability and subsequently peripheral and central inflammation, encouraging neurological dysfunction (Bruce-Keller et al., 2015; Seganfredo et al., 2017). Depressed and obese subjects have been seen to have a decreased abundance of anti-inflammatory *Faecalibacterium* along with an increased abundance of pro-inflammatory *Alistipes* (Du et al., 2020). One possible mechanism for an increased inflammatory response comes from the GM's production of lipopolysaccharides which activate TNF-α synthesis and increase gut permeability. When injected with lipopolysaccharides, human subjects had higher levels of cytokines in the blood and demonstrated increased anxiety and negative mood (Cani et al., 2008; Grigoleit et al., 2011). Increased gut permeability may allow for greater translocation of pathogenic bacteria across the intestinal membrane, further contributing to levels of inflammation.

Altered GM states may also alter the ability of bacteria to produce short chain fatty acids (SCFAs) in the gut. However, the mechanisms as to how SCFAs affect obesity and/or depression are up still up for debate. SCFAs are produced when bacteria ferment dietary fibers, starches, unabsorbed sugars, and undigested proteins within the large intestine. These SCFAs can be used as energy by epithelial cells and may also activate intestinal gluconeogenesis, both of which add to the pool of energy substrates

available for host use, making the host susceptible to energy substrate accumulation and fat deposition at higher concentrations. Communication via the gut-brain axis also occurs via SCFAs which stimulate the release of anorexigenic hormones peptide YY and glucagon-like peptide 1 upon binding to enterochromaffin cell receptors (Cătoi et al., 2019). Some suggest that increased SCFA production is protective against obesity and associated with improved host metabolism, glucose homeostasis, and energy balance. For example, increased levels of the SCFA butyrate in the gut, primarily produced by Firmicutes, *Lactobacillus*, and *Bifidobacterium* which are all decreased in depressed and obese individuals after bariatric surgery, has been associated with higher insulin sensitivity, whereas subjects with lower levels of butyrate are at greater risk for Type 2 Diabetes (Sanna et al., 2019; Seganfredo et al., 2017). It has also been suggested that SCFAs regulate the host's immune response by decreasing the secretion of pro-inflammatory cytokines. While the mechanism is unclear, decreased production of SCFAs may be a cause of chronic inflammation which may cause neural inflammation that impacts neurological functioning (Sun et al., 2017). The mechanisms by which gut derived SCFAs and other bacteria within the GM impact host physiology and psychology are largely yet to be determined, but ongoing research proves promising for developing treatments for GM modulated disorders in the future.

Conclusion

As can be inferred from the results, changes in the GM are quite dependent on the individual. While there are clearly trending similarities between the general GM makeup of bariatric surgery and depressed patients, recognizing relative changes in composition is only the beginning. The GM can be altered by nearly anything. Whether it be diet, surgery, stress levels, medication, etc., variances in GM composition are expected whether they are permanent or not. This makes studying dysbiosis of the GM difficult and indicates a requirement for the determination of exact species-host response mechanisms for successful personalized treatment via the GM. Ongoing research aims to determine said mechanisms that relate specific phyla and species to host physiology in accordance with all types of physiological and psychological conditions, and much more research must be performed to determine how a seemingly infinite number of systems are homeostatically regulated according to the state of the GM.

As demonstrated, the interplay between the gut and the brain is extremely complex and depends on a wide variety of factors. As the search for which species play a role in modulating host response, it is important that the mechanism of action by which a species induces said affect is also examined. Dysbiosis of the GM is associated with many conditions and regulating the composition of the GM has become a very popular method of treating physical and psychological symptoms. Ongoing symptoms of depression following bariatric surgery may be associated with a lingering pro-inflammatory GM phenotype capable of inducing neurobehavioral deficits via a variety of possible mechanisms, as discussed above, such as neurotransmitter production or

immune response. Fecal sample analysis and transplantation will continue to play a key role in determining both the correlation and causation between the GM and host physiology as the taxonomical characterization of GM dysbiosis according to diagnosable conditions could prove an invaluable tool for personalizing treatments for obesity, depression, and countless other conditions in the future.

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