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Gut-Brain Axis and Behavioral Health in Metabolic Syndrome: A Perspective

Swarup K. Chakrabarti[1]*, Dhrubajyoti Chattopadhyay[1,2]

[1]*H. P. Ghosh Research Center, New Town, Kolkata, West Bengal 700161, India.*

[2]*Sister Nivedita University, New Town, West Bengal 700156, India.*

**Corresponding author: Swarup K. Chakrabarti.*

Abstract

Metabolic Syndrome (MS) is a cluster of conditions—including central obesity, insulin resistance, hypertension, and dyslipidemia—that significantly increase the risk of cardiovascular disease (CVD) and type 2 diabetes (T2D). Recent evidence highlights MS's role in exacerbating cognitive decline and behavioral health issues, particularly through the Gut-Brain Axis (GBA), a complex communication network linking the gut microbiota with the central nervous system (CNS). Central obesity, a key component of MS, leads to elevated free fatty acids and inflammatory cytokines, aggravating insulin resistance and endothelial dysfunction, which accelerates atherosclerosis and impacts cognitive function. The GBA, involving the gut microbiota, enteric nervous system, vagus nerve, and CNS, mediates these effects by influencing neurotransmitter systems and immune responses. Recent research indicates that glucagon-like peptide-1 receptor agonists (GLP-1RAs), originally developed for glucose control and weight management, may also offer therapeutic benefits for behavioral health issues. GLP-1RAs have demonstrated potential in alleviating depressive symptoms and modulating addiction behaviors, possibly through their effects on dopamine release in the brain's reward system. This dual benefit underscores the promising role of GLP-1RAs in managing both metabolic and behavioral health aspects of MS. Future research should delve into the mechanisms by which GLP-1RAs interact with the GBA and their long-term effects on cognitive and emotional health. Additionally, exploring their combined use with other therapeutic strategies could enhance comprehensive treatment approaches for MS and its associated behavioral health challenges.

Keywords: metabolic syndrome; emotional health; inflammatory cytokines; fatty acids; hypertension; insulin resistance

Introduction

Metabolic syndrome (MS), characterized by a constellation of metabolic aberrations—including central adiposity, insulin resistance, hypertension, and dyslipidemia—significantly amplifies the risk of developing atherosclerotic cardiovascular disease (CVD) and type II diabetes (T2D). The diagnosis of MS requires the presence of at least three of these metabolic derangements, highlighting the critical need for early identification and targeted intervention [1-5]. Central obesity contributes to elevated levels of free fatty acids (FFAs) and inflammatory cytokines, which exacerbate insulin resistance and endothelial dysfunction [6, 7]. Insulin resistance, a hallmark of MS, impairs glucose uptake and promotes hyperglycemia [8]. This, in turn, accelerates the progression of atherosclerosis by fostering chronic inflammation and endothelial damage. Hypertension further aggravates endothelial injury and promotes arterial stiffness, while dyslipidemia—characterized by elevated triglycerides and low HDL (high-density lipoprotein) cholesterol—facilitates plaque formation in the arteries [9-12]. Collectively, these interconnected abnormalities create an environment conducive to the progression of CVDs and T2D, making MS a critical target for both preventive and therapeutic strategies. The prevalence of MS has escalated substantially in recent decades, paralleling the global rise in obesity rates. Currently, approximately 25–30% of the adult population worldwide is affected by this syndrome, highlighting its prominence as a significant public health concern [13, 14].

MS, widely recognized for its role in increasing the risk of CVDs, is also gaining attention as a potential contributor to cognitive decline, especially among older adults. Especially, as individuals age, these metabolic disturbances can exacerbate age-related cognitive decline and heighten the risk of neurodegenerative conditions like Alzheimer's disease and vascular dementia [15, 16]. More importantly, addressing MS not only aims to reduce cardiovascular risks but also has significant implications for behavioral health due to its connection with cognitive

function. Behavioral health, which encompasses mental well-being, lifestyle choices, and daily functioning, is intricately tied to cognitive health. Cognitive dysfunction can profoundly impact behavioral health by impairing memory, decision-making, and daily activities, which often leads to increased stress, frustration, and a decline in overall mental well-being. This decline can exacerbate symptoms of depression and anxiety, creating a vicious cycle where cognitive impairment and behavioral issues reinforce each other [17-20]. The gut-brain axis (GBA) represents a complex and essential communication network that intricately links the gut microbiota with the central nervous system (CNS). Functioning as a dynamic feedback loop, the GBA facilitates constant interaction between gut and brain signals, influencing each other's functions and playing a crucial role in maintaining homeostasis [21, 22]. Central to this system, the gut microbiota—a diverse consortium of microorganisms residing within the gastrointestinal (GI) tract—plays a fundamental role in mediating these interactions [23].

Beyond its critical role in sustaining physiological equilibrium, the GBA profoundly impacts brain function and behavioral health. The vagus nerve, a primary communication conduit within this axis, transmits signals from the gut that directly affect the brain's neural circuits and neurotransmitter systems. Consequently, alterations in gut microbiota composition can significantly influence mental health, potentially contributing to the development or exacerbation of conditions such as anxiety, depression, and cognitive disorders. This bidirectional communication highlights the intricate interplay between gut health and mental well-being, underscoring the importance of understanding the GBA for addressing both physiological and psychological health challenges [24-26]. Against this backdrop, this review examines how MS impacts cognitive and behavioral health through the GBA. Additionally, it evaluates the influence of GLP-1 (glucagon-like peptide 1) receptor agonists (GLP-1RAs) on these aspects. GLP-1, a hormone produced in the gut, is known for its roles in weight management and glucose regulation [27, 28]. However, GLP-1RAs are emerging as potential modulators of behavioral health, with implications for conditions like addiction and depression. By targeting the GBA, these agents may provide novel approaches to enhancing both metabolic and behavioral health outcomes in individuals with MS.

Components and Functions of the Gut-Brain Axis (GBA)

The GBA is a multifaceted system connecting the gut microbiota, intestinal mucosa, enteric nervous system (ENS), vagus nerve, and central nervous system (CNS). The gut microbiota, a rich ensemble of microorganisms, is essential for digestion, nutrient production, and immune regulation [21-24]. These microbes produce neurotransmitters such as serotonin and GABA (gamma-aminobutyric acid), which can affect mood and behavior, underscoring their pivotal role in the GBA [29, 30]. The gut mucosa, which lines the innermost part of the GI tract, serves as a critical barrier between the gut's interior and the bloodstream. It plays a key role in absorbing nutrients and blocking harmful pathogens and toxins from entering the body. Additionally, this mucosal layer houses immune cells that react to both the microbiota and external factors, influencing immune responses both locally and throughout the body. Any disturbances to this barrier can potentially lead to health problems that might impact brain function and mood [21-24, 29, 30]. The intricate network of neurons that make up the ENS, sometimes called the "second brain," is embedded in the gut wall and controls various aspects of digestion, including motility and secretion. The ENS consists of two primary networks: the myenteric and submucosal plexuses, with 400–600 million neurons. It runs the length of the GI tract, from the esophagus to the anal canal, and is the biggest and most complex segment of the peripheral nervous system (PNS). The vagus nerve and a variety of neurotransmitters allow the ENS to connect with the CNS even though it is capable of functioning independently. Through this relationship, the ENS can interact with the brain to affect emotional and cognitive states in addition to regulating digestive activities [31, 32].

One important channel of communication between the CNS and the gut is the vagus nerve, commonly referred to as cranial nerve X. It runs from the brainstem to the abdomen, carrying motor commands from the brain to the gut and sensory data about the condition of the stomach to the brain. It consists of motor and sensory fibers, allowing these systems to communicate in both directions. Sensory fibers provide data about fullness, nutritional status, and GI discomfort from the gut to the brain [24, 33]. On the other hand, motor fibers carry out signal transmission from the brain to control several aspects of the stomach, such as motility and gastric secretion. This

bidirectional communication allows for continuous feedback and modification, guaranteeing proper synchronization between the gut and the brain. This nerve regulates digestion, heart rate, and immune responses, and its signaling influences both physical and emotional health [24, 31- 33]. The CNS, encompassing the brain and spinal cord, plays a pivotal role in the intricate communication network with the gut, known as the GBA. This bidirectional communication pathway allows the CNS to interpret sensory information from the gut, influencing both physiological and psychological states. The brain's regulatory functions extend to modulating digestive processes, reflecting the deep interconnection between mental health and gut function. For instance, stress and emotional states can alter gut motility and microbial balance, while GI signals can affect mood and cognitive processes. This dynamic interaction highlights the CNS's central role in integrating gut health with mental and emotional well-being, emphasizing that optimal health involves a balanced interplay between our physiological and psychological systems [22-24, 33-35].

The GBA relies on a complex network of neurotransmitters to promote communication between the gut and the brain, which affects a variety of physiological processes. This mechanism relies heavily on neurotransmitters like adrenaline, norepinephrine, dopamine, serotonin, and GABA. Serotonin, which is mostly produced in the gut, is critical for regulating mood, cognition, and digestive function. GABA, an inhibitory neurotransmitter, regulates stress reactions and GI motility. The GBA's homeostasis depends on maintaining a perfect balance of these neurotransmitters [21-26, 35-38]. In addition to neurotransmitters, hormones are crucial for the GBA's function, significantly influencing both gut and brain activities. Cortisol, known as the stress hormone, is pivotal in regulating stress responses and can affect gut permeability and mucosal health when elevated [39]. Ghrelin, the hunger hormone, and leptin, which regulates appetite and energy balance, also play significant roles in the GBA. These hormones relay information about nutritional status to the brain, affecting food intake and energy expenditure. The dynamic interaction between these hormones is fundamental to maintaining overall homeostasis within the GBA [40, 41]. Additionally, the gut microbiota, a sophisticated consortium of microorganisms within the GI tract, exerts profound influence on brain function via the GBA. This microbiota regulates brain activity through several mechanisms: it synthesizes key neurotransmitters such as serotonin and GABA, which are integral to mood regulation and emotional stability [35, 36, 42]. Moreover, it modulates the immune system, impacting systemic inflammation and its subsequent effects on neurophysiological processes, which are implicated in mood disorders such as depression and anxiety. Crucially, the microbiota maintains the integrity of the gut barrier, preventing excessive permeability ("leaky gut") and mitigating systemic inflammation that could disrupt neurocognitive functions [35, 36, 43, 44]. Dysbiosis, or microbial imbalance, can therefore precipitate mood disorders and cognitive dysfunction, highlighting the pivotal role of gut microbiota in mental health and indicating promising therapeutic strategies for addressing neuropsychiatric conditions [43, 44].

The Intersection of Behavioral Health and Metabolic Syndrome (MS)

MS profoundly affects mental health and cognitive abilities, extending well beyond mere contributions to depression and anxiety. This effect is partly due to the chronic stress involved in managing multiple health conditions like obesity and hypertension, which can result in feelings of hopelessness or frustration [15, 16, 45, 46]

Chronic inflammation plays a central role in linking these psychological impacts to MS. Elevated levels of inflammatory cytokines in MS can cross the blood-brain barrier (BBB) and disrupt neurobiological processes, leading to alterations in mood and cognitive functions [47- 49]. Studies show that persistent inflammation can impact neurotransmitter systems, including serotonin and dopamine, which play a crucial role in mood regulation. Elevated levels of inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6) are linked to a higher risk of developing depression, indicating a biological relationship between inflammation and mood disorders [50, 51]. In patients with MS, anxiety is frequently influenced by the dual pressures of dealing with a chronic condition and the physiological impact of the illness itself. Recent research indicates a strong association between anxiety symptoms and the degree of metabolic disturbances, like insulin resistance, in MS patients. These metabolic issues can lead to increased fatigue, which in turn may worsen anxiety and amplify worries about worsening health [52, 53]. Cognitive challenges in MS patients, such as difficulties with attention, memory, and executive functions, are becoming more acknowledged.

Research shows that these cognitive problems are linked to how insulin resistance and metabolic inflammation affect the brain. Insulin resistance can disrupt neuronal activity and brain adaptability, whereas inflammation can cause oxidative stress, which further hampers cognitive abilities [54, 55]. Moreover, addiction behaviors, such as increased substance use, may emerge as individuals attempt to cope with the emotional strain and lifestyle changes imposed by MS. These behaviors can worsen health outcomes, creating a vicious cycle that is difficult to break [56, 57]. Addressing these psychological and behavioral aspects is crucial for comprehensive management of MS, underscoring the need for a holistic approach that integrates mental health support with physical health care.

Case Studies Connecting Behavioral Health with Metabolic Syndrome

Recent research into the GBA has revealed significant insights into how gut health affects behavioral health in individuals with MS. For instance, a critical study investigates the association between MS and maternal mental illness during the perinatal period, examining the time to incident mental disorder diagnosis in postpartum women.

The authors of this study conclude that the risk of mental disorder, both prenatal and incident, significantly correlates with MS. They find an incremental relationship between the number of MS conditions and the incidence of mental illness diagnosis, noting a significant association with younger mothers and a relatively long period before diagnosis [58]. This highlights the need for enhanced screening and treatment during pregnancy and postpartum to address the mental health challenges associated with MS. Obesity, marked by hormonal imbalances and ongoing inflammation, significantly contributes to the onset of depressive symptoms. Studies indicate that children and teenagers who are overweight or obese frequently experience negative body image, social stigma, and lowered self-esteem, which greatly increases their susceptibility to depressive disorders [59, 60].

Sutaria and colleagues conducted an extensive meta-analysis, integrating findings from twenty-two studies that utilized prospective, retrospective, and cross-sectional designs. Their review covered a total of 143,603 children aged 18 years or younger from general population and community settings [61]. The results indicate that obese female children have a 44% higher risk of developing depression compared to their peers with normal weight. However, the analysis did not find a notable link between overweight status and depression in children, nor did it uncover any significant relationship between either obesity or overweight status and depression in male children or specific subgroups. While their findings are pivotal, additional research linking metabolic syndrome to behavioral health exists, extending beyond the scope of this study.

The Role of the Gut-Brain Axis (GBA) in Behavioral Health

The GBA is a revolutionary concept that redefines our understanding of the interplay between the digestive system and behavioral health. This intricate and dynamic communication network is not a simple, linear pathway but a complex, bi-directional system where the gut and brain continuously influence one another. At its core lies the gut microbiome, residing in our GI tract. These microorganisms are not passive inhabitants; they actively participate in a myriad of biochemical processes that affect our overall health [35-37]. The gut microbiome engages with the brain through several intricate mechanisms. As previously stated, one significant pathway involves the regulation of neurotransmitters and neuromodulators. For example, gut bacteria play a role in the production of serotonin, a neurotransmitter essential for managing mood and associated with conditions like depression [25, 29, 30]. Furthermore, the gut microbiota affects immune responses and inflammation, factors that are increasingly linked to mental health. Emerging evidence also suggests that gut imbalances may influence addiction by affecting the brain's reward and craving systems. A key player in this interaction is the vagus nerve, which connects the gut to the brain and helps relay signals that impact both mood and potentially addictive behaviors [23, 24, 44, 62, 63].

On the flip side, the brain communicates with the gut, influencing gut motility, permeability, and microbial composition. Stress, for instance, can alter gut function and microbial balance, creating a feedback loop that can exacerbate or even trigger GI and psychological issues. This bidirectional relationship illustrates that our mental and digestive health are inextricably linked, challenging traditional notions that these systems operate independently [64, 65]. Hence, grasping the complex interaction between the gut and brain enhances our understanding of behavioral health and unveils novel treatment and prevention opportunities. Recognizing the profound effects of the GBA reveals how factors like diet,

lifestyle, and microbial balance are crucial to emotional and cognitive health. This broader view promotes a comprehensive approach to well-being, integrating gut health into behavioral health strategies. More importantly, given the critical role of GLP-1 in regulating metabolic processes, gut motility, inflammation, gut barrier function, and microbial ecosystems, GLP-1 receptor agonists (GLP-1RAs)—which offer more stable pharmacological effects compared to the naturally transient GLP-1 hormone—may represent a promising therapeutic option [66-68]. Thus, the following section delves into the potential role of GLP-1RAs in enhancing behavioral health in MS patients. By addressing the complex interplay between metabolism and behavior, GLP-1RAs might offer new insights and interventions that could improve overall well-being and cognitive function in this patient population.

Metabolic Syndrome Meets Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RAs)

Implications for Behavioral Health Body weight regulation is chiefly controlled by the interaction between the brain and adipose tissue, which coordinate signals to manage food intake, satiety, and energy balance. Key hormones in this gut-brain-fat axis include adipokines like adiponectin and leptin, ghrelin, glucagon from pancreatic alpha cells, and GLP-1 [69-71]. Notably, GLP-1, produced by enteroendocrine L cells in the ileum and colonic mucosa, plays a crucial role in maintaining glucose homeostasis by enhancing insulin secretion and suppressing glucagon release [72]. Additionally, GLP-1 offers significant cardiovascular and neurological protection, reduces cellular apoptosis and inflammation, and influences reward and taste perception. Most importantly, GLP-1 impacts body weight by effectively reducing food consumption [72, 73]. However, the pharmacological application of native bioactive GLP-1 is limited due to its short half-life of 2-3 minutes, caused by rapid renal clearance and degradation by dipeptidyl peptidase-4 (DPP-4). To overcome this, several GLP-1RAs, such as lixisenatide, liraglutide, exenatide, dulaglutide, albiglutide, and semaglutide, have been approved for managing weight loss and blood glucose levels [28]. Recent research suggests that GLP-1RAs might provide therapeutic benefits for individuals with depression. A comprehensive review was performed using a wide array of electronic databases, such as CENTRAL, PubMed, EMBASE, PsycINFO, the World Health Organization International Clinical Trials Registry Platform, ClinicalTrials.gov, China Network Knowledge Infrastructure, China Biomedical Database, Wan Fang Data, and the Chinese Scientific Journals Database, encompassing studies up to February 16, 2023. This review concentrated on randomized controlled trials and prospective cohort studies that evaluated the impact of GLP-1RAs compared to placebo or other antidiabetic treatments on depressive symptoms [74]. The results of this extensive search suggest that GLP-1RAs may be more than just glucose-lowering agents; they show promise as potential treatments for depression. This highlights the dual therapeutic potential of GLP-1RAs, offering possible advantages not only in managing blood glucose but also in improving mood disorders. These findings open new avenues for exploring the role of GLP-1RAs in comprehensive mental health care, potentially enhancing the quality of life for patients with both diabetes and depression. Preclinical studies in rodents and non-human primates have highlighted that GLP-1RAs significantly affect compulsive and reward-related behaviors associated with substance abuse [75, 76]. At the central nervous system level, GLP-1 RAs can influence dopamine release in the nucleus accumbens, a key brain region involved in the reward system. This modulation of dopamine activity impacts the rewarding effects of various addictive substances, such as alcohol, nicotine, opioids, and cocaine [77, 78]. By altering dopamine signaling, GLP-1RAs may not only influence drug-seeking behavior and reduce responsiveness to drug cues but also potentially alleviate withdrawal symptoms [79, 80]. These insights underscore the potential of GLP-1 RAs to address substance use disorders more effectively. This ability to modulate both the seeking and consumption aspects of addiction, coupled with their potential for broader therapeutic applications, positions GLP-1 RAs as promising candidates for advancing treatment strategies for addiction and behavioral health challenges.

At the CNS level, GLP-1 RAs have been shown to influence dopamine release in the nucleus accumbens, a crucial region for reward processing. This interaction can modulate the pleasurable effects associated with substance abuse, thereby affecting drug-seeking behavior and reducing sensitivity to drug-related cues [81]. Furthermore, GLP-1 RAs may also help alleviate symptoms of withdrawal. These effects suggest that GLP-1 RAs could play a significant role in managing addiction and substance use disorders by altering the brain's reward circuitry and

improving overall treatment outcomes [82]. In summary, GLP-1RAs not only aid in glucose control and weight management but also exhibit significant effects on reward-related behaviors. They modulate dopamine release in the nucleus accumbens, impacting addiction-related reward pathways. This suggests that GLP-1RAs have potential as therapeutic agents for managing depression and substance use disorders, highlighting their broad and promising therapeutic applications.

Conclusions & Future Directions

In conclusion, the intersection of metabolic syndrome (MS) and behavioral health presents a complex and multifaceted challenge, impacting both cognitive and emotional well-being. The gut-brain axis (GBA) plays a critical role in this interplay, influencing how metabolic disturbances in MS can affect mental health. GLP-1 receptor agonists (GLP-1RAs) have emerged as promising tools not only for managing metabolic abnormalities but also for addressing behavioral health issues. Their potential benefits in improving mood disorders and influencing addictive behaviors offer a dual therapeutic advantage, which could significantly enhance patient care. Future research should delve deeper into the mechanisms by which GLP-1RAs affect the GBA and behavioral health. Specifically, studies should aim to elucidate the precise pathways through which GLP-1RAs impact cognitive function, mood regulation, and addiction. Understanding these mechanisms could reveal new therapeutic targets for managing conditions linked to these processes. Longitudinal trials assessing the long-term efficacy and safety of GLP-1RAs in diverse populations, including those with varying degrees of MS, are essential for establishing their broader applicability and effectiveness. These trials should consider both the benefits and potential risks of prolonged GLP-1RA use.

Moreover, exploring the synergistic effects of GLP-1RAs alongside other therapeutic strategies could provide a more comprehensive approach to managing MS and its related behavioral health challenges. Combining GLP-1RAs with therapies that address physical aspects, like lifestyle interventions or medications targeting cardiovascular risk factors, could enhance overall metabolic control. For example, while GLP-1RAs may help regulate appetite and improve insulin sensitivity, psychological therapies could support emotional resilience and stress management, addressing the interconnected nature of MS and its behavioral effects. Lastly, could GLP-1RAs offer benefits for individuals without MS, particularly in managing behavioral issues like depression and other psychiatric conditions? Research into their effects on cognitive function and overall brain health might uncover new ways to integrate GLP-1RAs into broader behavioral health strategies. This could also potentially help prevent the future development of MS in these individuals.

Conflict of Interest

The authors declare that they have no conflicts of interest to disclose.

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