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Original Article

MicroRNAs in Neurocognitive and Neuroprotective Outcomes of Bariatric Surgery: Decoding Pathways to Precision Medicine

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Abstract

Bariatric surgery has demonstrated significant benefits in reversing obesity-induced cognitive decline and promoting neuroprotection, yet the molecular mechanisms underlying these effects remain poorly understood. Among the critical regulators of these processes are microRNAs (miRNAs), which orchestrate inflammatory, metabolic, and neuroplastic pathways central to systemic and neural recovery. This review aims to synthesize current evidence on the role of miRNAs in mediating the neurocognitive and neuroprotective benefits of bariatric surgery, focusing on their involvement in modulating neuroinflammation, oxidative stress, and synaptic plasticity. A systematic analysis of studies across multiple databases was conducted to explore the impact of bariatric surgery on miRNA expression and its correlation with neurocognitive outcomes. Findings reveal that specific miRNAs, such as miR-122 and miR-92a, play pivotal roles in reducing systemic inflammation and enhancing mitochondrial function, contributing to improved cognitive performance and resilience against neurodegenerative stressors. The potential of miRNAs as biomarkers for predicting surgical outcomes and guiding personalized therapeutic strategies is highlighted, emphasizing their relevance in precision medicine. Despite these advancements, significant gaps remain in understanding long-term miRNA dynamics, their tissue-specific roles, and their interactions with other regulatory RNAs. Research should prioritize multi-omics approaches and longitudinal studies to elucidate these complexities and optimize miRNA-targeted interventions. This review comprehensively overviews the emerging intersection between miRNAs, bariatric surgery, and neurocognitive health. It offers valuable insights for advancing therapeutic strategies and addressing obesity-related neurological complications.

Keywords: ***microRNAs, bariatric surgery, neurocognitive disorders, neuroprotective effect.***

Introduction

Obesity, a global health crisis, represents one of the most pressing challenges of modern medicine due to its increasing prevalence and associated complications. Characterized by excessive adiposity and dysregulated energy metabolism, it significantly increases the risk of metabolic syndrome, type 2 diabetes, cardiovascular diseases, and systemic inflammation [1-3].

Beyond these well-documented physical impacts, obesity exerts profound effects on brain structure and function, contributing to cognitive deficits and heightened susceptibility to neurodegenerative diseases [2-4].

These cognitive impairments, which often include reduced memory, executive dysfunction, and diminished attention, have been linked to chronic low-grade inflammation, oxidative stress, and metabolic dysregulation within the central nervous system. Given their implications for individual well-being and public health, addressing these neurological consequences has become a critical focus [3-5].

Bariatric surgery, the most effective intervention for severe obesity, provides durable weight loss and significant metabolic benefits. Procedures such as Roux-en-Y gastric bypass and sleeve gastrectomy address obesity-related comorbidities and have far-reaching effects on systemic inflammation, hormonal balance, and glucose regulation [6-8].

Recent findings highlight the profound neurocognitive benefits associated with bariatric surgery, including improvements in memory, executive function, and overall mental clarity. These changes are attributed to reduced neuroinflammation, enhanced neuroplasticity, and improved cerebral metabolism [10-12].

Despite these promising findings, the precise molecular mechanisms underpinning these cognitive improvements remain poorly understood, highlighting the need for a deeper exploration of the biological pathways involved [13].

MicroRNAs (miRNAs), small non-coding RNA molecules that regulate gene expression, have emerged as critical modulators of cellular and systemic processes. By binding to messenger RNAs,

miRNAs influence protein synthesis, impacting inflammation, metabolism, and neural function pathways [14-16].

In the context of obesity, miRNAs play key roles in regulating adipogenesis, insulin signaling, and immune responses. Bariatric surgery induces significant alterations in miRNA expression profiles in both circulating blood and tissue-specific contexts, suggesting their involvement in mediating the multifaceted effects of surgical weight loss [17]. While much research has focused on miRNAs in metabolic pathways, their role in neurocognitive and neuroprotective outcomes following bariatric surgery remains an area of nascent investigation [18-20].

The neuroprotective potential of miRNAs is substantial, with evidence pointing to their ability to modulate pathways integral to brain health. Specific miRNAs influence neuroinflammation, oxidative stress, and synaptic plasticity key processes underlying cognitive function and resilience to neurodegeneration [21-23].

Alterations in miRNA expression post-surgery have been linked to improved glucose metabolism, reduced systemic inflammation, and enhanced endothelial function, all contributing to brain health [11]. These findings underscore miRNAs' potential as biomarkers and therapeutic targets for addressing obesity-induced neurological impairments [24-26]. However, systematic research connecting miRNA dynamics to neurocognitive recovery is lacking, leaving critical gaps in understanding the mechanistic underpinnings of these processes [27].

Emerging studies have identified miRNAs such as miR-122 and miR-92a as key regulators of pathways linked to metabolic and inflammatory processes. Their modulation following bariatric surgery highlights their dual role in systemic and central effects. Additionally, miRNAs like miR-448 and miR-215 have shown promise in influencing insulin sensitivity and neurovascular function[28-30].

Despite these advancements, the landscape of miRNA research in neurocognitive outcomes is fragmented, with limited longitudinal data and inconsistent findings across patient populations. This underscores the need for integrative approaches that combine molecular biology, clinical research, and neurocognitive assessments to unravel the complex interplay between miRNAs and brain health [31-33].

This field's state-of-the-art reveals a critical need for innovation and collaboration. Advances in RNA-based therapeutics, high-throughput sequencing technologies, and biomarker discovery have opened new avenues for exploring the role of miRNAs in obesity and its systemic effects [34].

Integrating these tools into bariatric surgery research could yield transformative insights, enabling precision medicine approaches tailored to individual patients. Furthermore, the potential to use miRNA profiles as predictive markers for cognitive recovery post-surgery could revolutionize preoperative assessments and postoperative care strategies [35-37].

This review seeks to bridge these gaps by synthesizing current evidence on the role of miRNAs in the neurocognitive and neuroprotective effects of bariatric surgery. It explores the molecular pathways modulated by miRNAs, identifies key regulatory targets, and evaluates their potential as biomarkers and therapeutic agents [29]. By highlighting the intersection of obesity, molecular biology, and cognitive health, this study aims to advance precision medicine approaches in addressing the multifaceted challenges of obesity [38-40].

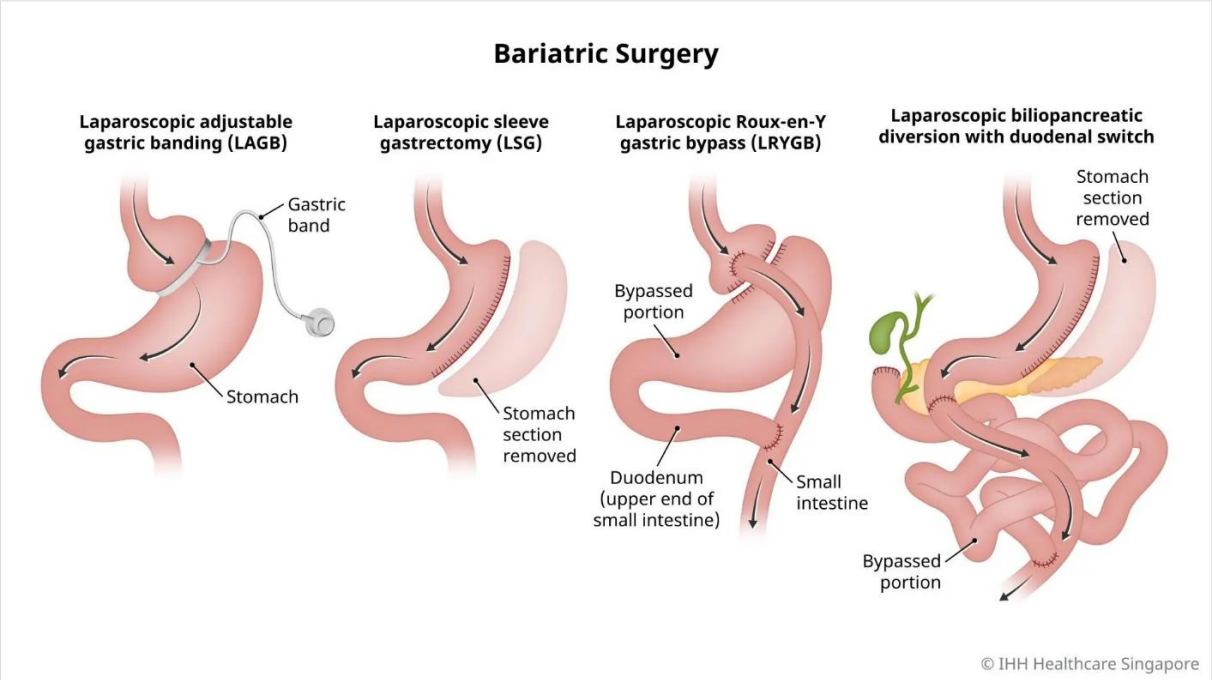
This review aims to elucidate the role of microRNAs in mediating the neurocognitive and neuroprotective outcomes of bariatric surgery. By decoding the molecular pathways influenced by miRNAs, this study seeks to identify their potential as biomarkers and therapeutic targets, paving the way for innovative strategies in precision medicine for obesity and its neurological complications.

Methods

This review aimed to explore the role of microRNAs (miRNAs) in the neurocognitive and neuroprotective effects observed following bariatric surgery, focusing on the molecular, metabolic, and neurological mechanisms involved. To ensure the inclusion of gray literature, a systematic and comprehensive search was conducted across multiple scientific databases, including PubMed, Embase, Scopus, Web of Science, and SciELO, supplemented by Google Scholar, gray literature. The search encompassed studies published up to the present date. The search strategy was developed using keywords and medical subject headings (MeSH) terms related to the central themes of the review. These included terms such as "MicroRNAs," "Bariatric Surgery," "Neurocognitive Disorders," "Neuroprotection," "Inflammation," "Metabolism," and "Neuroplasticity." Boolean operators (AND, OR) were used to refine the search, allowing for the retrieval of a broad range of studies while maintaining relevance to the review's objectives. Studies were included based on predefined eligibility criteria, encompassing various study designs such as randomized controlled trials, cohort studies, case-control studies, cross-sectional studies, systematic reviews, and meta-analyses. Inclusion was limited to studies that provided insights into the relationship between miRNAs, bariatric surgery, and neurocognitive outcomes, including neuroprotection mechanisms, inflammation modulation, and metabolic changes. Articles focusing on patient populations undergoing different bariatric procedures were also considered, provided they included data relevant to miRNA expression and its impact on neurological outcomes. The selection process involved two independent reviewers screening titles and abstracts. Subsequently, full-text articles were assessed for eligibility based on inclusion and exclusion criteria. Any disagreements with the reviewer were resolved through discussion, with arbitration by a third reviewer when necessary. To eliminate potential bias, reviewers were blinded to the authorship and institutional affiliations of the studies during the screening process. Data extraction was performed systematically using a standardized protocol. Extracted information included study design, sample size, characteristics of the study population, miRNA profiles investigated, primary findings, and outcomes related to neurocognitive and neuroprotective effects post-bariatric surgery. Thematic analysis was applied to organize findings into core categories. Key themes addressed in the review included the modulation of neuroinflammation and oxidative stress by miRNAs, their role in enhancing neuroplasticity and mitochondrial function, and their potential as biomarkers for predicting cognitive recovery and neuroprotection. Special attention was given to gaps in the current literature, such as the lack of longitudinal studies on miRNA dynamics post-surgery and the variability in miRNA profiles across different bariatric procedures. The review also evaluated methodological limitations in existing research and proposed future directions for investigating the role of miRNAs in bariatric surgery outcomes. This review synthesizes current knowledge to provide a detailed understanding of the interplay between miRNAs, bariatric surgery, and neurocognitive health. By identifying research gaps and emphasizing areas for future investigation, this study seeks to contribute to optimizing bariatric interventions and developing miRNA-based therapeutic strategies.

Results and Discussion

Types of bariatric surgery:



Source: https://www.gleneagles.com.sg/tests-treatments/bariatric-surgery.

There are four types of minimally invasive bariatric surgery:
The bariatric surgical techniques described below represent key interventions in managing severe obesity. Each offers distinct mechanisms to promote weight loss and metabolic improvements. These procedures aim to induce significant and sustained weight reduction and profoundly affect metabolic regulation, including hormonal changes and gut microbiota modulation, which may influence neurocognitive outcomes and miRNA profiles [41-43].

- ***Laparoscopic Adjustable Gastric Banding (LAGB):***

This technique involves the placement of a silicone band around the upper portion of the stomach, creating a small gastric pouch. By restricting the stomach's capacity, LAGB enhances satiety signals, reducing food intake. Although reversible and minimally invasive, its impact on hormonal regulation and miRNA expression may be less pronounced than other bariatric procedures, warranting further exploration of its long-term metabolic and neurocognitive effects.

- ***Laparoscopic Sleeve Gastrectomy (LSG):***

In LSG, approximately 75% of the stomach is resected, resulting in a tubular gastric remnant that limits food intake and accelerates gastric emptying. Beyond physical restriction, LSG induces significant hormonal changes, including alterations in ghrelin and other appetite-regulating hormones. These changes potentially affect neurocognitive functions and systemic inflammation. The procedure's influence on miRNA expression patterns and its role in neuroprotection deserves further investigation.

- ***Laparoscopic Roux-en-Y Gastric Bypass (LRYGB):***

This procedure creates a small gastric pouch directly anastomosed to the jejunum, bypassing a significant portion of the stomach and proximal small intestine. LRYGB is associated with profound metabolic changes, including enhanced insulin sensitivity and altered gut hormone secretion. These effects extend to systemic inflammation and potential neuroprotective pathways, likely mediated by miRNA modulation. The procedure's multifaceted impact on cognitive and neurodegenerative outcomes represents an area of active research.

- ***Laparoscopic Biliopancreatic Diversion with Duodenal Switch (BPD-DS):***

BPD-DS combines restrictive and malabsorptive components, reducing the stomach's volume to a tubular structure while rerouting the small intestine to minimize nutrient absorption. This procedure dramatically changes gut hormone profiles and bile acid metabolism, potentially influencing systemic inflammation and cognitive functions. The unique interplay between these changes and miRNA expression presents a compelling area for further study, particularly in understanding its neuroprotective potential.

Each surgical approach facilitates weight loss and initiates complex physiological changes that extend beyond the gastrointestinal system. Investigating their specific impacts on miRNA profiles and neurocognitive outcomes will enhance our understanding of their therapeutic potential.

Cognitive and Neuroprotective Effects of Bariatric Surgery

Bariatric surgery represents a transformative intervention for cognitive dysfunction associated with obesity, impacting systemic inflammation, neuroplasticity, and metabolic regulation [44].

Chronic obesity induces a pro-inflammatory state characterized by elevated levels of cytokines such as IL-6, TNF-α, and CRP. These cytokines disrupt neural integrity by impairing synaptic plasticity, promoting oxidative stress, and accelerating neurodegeneration [45].

Post-surgical reductions in adipose tissue mass significantly decrease these inflammatory mediators, facilitating neural recovery. Enhanced memory, executive function, and attention span are frequently reported following bariatric surgery, highlighting its potential for restoring cognitive health [46].

Neuroplasticity plays a pivotal role in these cognitive improvements. Increased brain-derived neurotrophic factor (BDNF) after surgery promotes synaptic remodeling, dendritic growth, and neuronal survival, particularly in the hippocampus and prefrontal cortex regions essential for memory and decision-making [22]. Concurrent improvements in mitochondrial function provide the energy required for sustaining these adaptive changes. These synergistic effects underscore the profound impact of bariatric surgery on brain structure and function [47-49].

The gut-brain axis emerges as another critical pathway mediating the cognitive benefits of bariatric surgery. Alterations in gut microbiota composition lead to increased production of

neuroactive metabolites such as short-chain fatty acids (SCFAs), which enhance blood-brain barrier integrity, regulate neurotransmitter systems, and reduce neuroinflammation. Gut-derived hormones such as GLP-1 and PYY exhibit neuroprotective effects by modulating synaptic activity and promoting neural resilience [50-52].

Despite these advances, variability in cognitive outcomes remains a challenge. Baseline cognitive reserve, genetic predispositions, age, and comorbid conditions influence recovery trajectories. For instance, older individuals or those with severe comorbidities may experience slower or less pronounced cognitive benefits. Addressing these differences requires personalized approaches integrating genetic, metabolic, and neuroimaging data [53-55].

Future research should adopt longitudinal designs to assess the durability of cognitive improvements over decades. Integrating molecular biomarkers with advanced imaging and neuropsychological testing will provide a comprehensive understanding of systemic and neural recovery interplay. Such studies will also inform therapeutic strategies to maximize the cognitive benefits of bariatric surgery [54-56].

Role of miRNAs in Modulating Inflammatory and Metabolic Processes

MicroRNAs (miRNAs) are pivotal regulators of the inflammatory and metabolic pathways disrupted in obesity and restored post-bariatric surgery. miRNAs such as miR-122 and miR-92a are central to these processes, influencing cytokine production, lipid metabolism, and insulin sensitivity. For example, miR-122 downregulation following bariatric surgery correlates with reduced hepatic inflammation and improved lipid profiles. Similarly, miR-92a modulation is associated with improved endothelial function, contributing to systemic vascular health [55-57].

Oxidative stress, a key driver of obesity-related cognitive decline, is also regulated by miRNAs. Dysregulated pathways generate excessive reactive oxygen species (ROS), damaging mitochondria and impairing synaptic function. miRNAs such as miR-448 and miR-215 play protective roles by enhancing mitochondrial biogenesis and regulating antioxidant responses. These miRNAs mitigate oxidative stress, preserving neuronal health and cognitive performance [56-58].

Exosomal miRNAs serve as intercellular messengers, adding a layer of regulation. Released by adipose tissue, the liver and other organs circulate systemically, coordinating recovery processes across multiple tissues, including the brain. This inter-organ communication highlights the integrative role of miRNAs in bridging peripheral metabolic changes with central neural recovery [57-59].

Despite their potential, significant gaps remain in understanding the tissue-specific roles of miRNAs. Most studies focus on circulating miRNAs, neglecting their localized expression and function in key tissues such as the brain, liver, and adipose tissue. The temporal dynamics of miRNA changes post-surgery remain underexplored. Future studies should employ multi-tissue profiling and longitudinal analyses to uncover the full regulatory potential of miRNAs [58-60].

Therapeutically, miRNA-based interventions hold immense promise. miRNA mimics and inhibitors could target specific pathways involved in metabolic and inflammatory regulation, accelerating recovery and enhancing long-term outcomes. However, translating these findings into clinical practice will require robust validation across diverse populations and standardization of miRNA quantification protocols [59-61].

Perspectives on miRNAs as Neurocognitive Biomarkers

One of the most exciting advancements in bariatric surgery research is the potential of miRNAs as biomarkers for neurocognitive recovery. Panels of miRNAs, including miR-122, miR-92a, and miR-448, have demonstrated strong associations with metabolic recovery, reduced neuroinflammation, and improved cognitive outcomes. These biomarkers provide a noninvasive tool for stratifying patients preoperatively, predicting recovery trajectories, and tailoring interventions to individual needs [60-62].

MiRNAs offer a unique opportunity to address obesity-related cognitive decline. miR-215 mimics could enhance mitochondrial function and resilience, while inhibitors targeting pro-inflammatory miRNAs like miR-92a could expedite the resolution of neuroinflammation. These therapeutic strategies align with the goals of precision medicine, offering personalized interventions based on molecular profiles [61-63].

Implementing miRNA biomarkers and therapies in clinical practice presents substantial challenges. Variability in miRNA expressions due to demographic factors, environmental influences, and comorbid conditions complicates standardization. Additionally, the lack of robust, reproducible protocols for miRNA quantification limits their scalability for widespread clinical use. Addressing these challenges will require collaborative research efforts and multi-center validation studies [62-64].

Longitudinal studies are crucial to establish miRNAs as reliable biomarkers for sustained cognitive improvements. These studies should investigate the temporal stability of miRNA profiles and their predictive value for long-term outcomes. Integrating miRNA data with imaging and neuropsychological assessments could provide a comprehensive framework for understanding neurocognitive recovery [63-65].

By overcoming these challenges, miRNA-based diagnostics and therapeutics have the potential to revolutionize the management of obesity-related cognitive dysfunction. Their integration into clinical practice could bridge the gap between molecular discoveries and patient care, advancing the field of precision medicine [64-66].

Long-Term Impact on miRNA Profiles

While the short-term effects of bariatric surgery on miRNA expression have been well-documented, the long-term dynamics of these changes remain poorly understood. Understanding whether miRNA profiles stabilize, fluctuate, or revert to pre-surgical states is critical for evaluating the sustainability of recovery. Persistent changes in miRNAs, such as miR-122 and miR-448, may reflect durable benefits, while transient alterations could indicate the need for ongoing interventions [65-67].

Environmental factors such as diet, physical activity, and psychological well-being likely influence the long-term modulation of miRNAs. For example, adherence to post-surgical dietary recommendations may sustain favorable miRNA profiles, while sedentary behavior could negate these benefits. Investigating these interactions could provide insights into optimizing long-term recovery [66-68].

Advanced technologies, including next-generation sequencing and machine learning, offer new opportunities to study miRNA dynamics. These tools can capture high-resolution expression patterns, providing insights into the molecular pathways driving sustained recovery. Combining these approaches with clinical and behavioral data could uncover novel therapeutic targets [67-69].

Long-term studies should also explore the relationship between miRNA dynamics and preventing obesity-related comorbidities, such as diabetes and cardiovascular disease. These

investigations could establish miRNAs as predictive markers for broader health outcomes beyond neurocognitive recovery [68-70].

Expanding research into the long-term effects of miRNA modulation will provide a comprehensive understanding of their role in recovery. This knowledge could inform the development of sustained therapeutic interventions, maximizing the benefits of bariatric surgery for diverse patient populations [69-71].

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Influence of Demographic Variables on miRNA Modulation

Demographic factors such as age, sex, ethnicity, and genetic predispositions significantly influence miRNA expression and its modulation after bariatric surgery. These variables can alter the effectiveness of miRNA-driven recovery, including their roles in inflammation resolution, metabolic regulation, and neurocognitive improvements. Older patients may exhibit reduced miRNA plasticity, potentially leading to slower recovery of cognitive functions compared to younger individuals [73-75].

Sex-based differences in miRNA profiles have also been observed, with specific miRNAs exhibiting distinct expression patterns in males and females. These differences could result from variations in hormonal regulation, particularly the effects of estrogen and testosterone on inflammatory and metabolic pathways. Understanding these sex-specific miRNA dynamics could improve the personalization of therapeutic interventions, ensuring both genders benefit equally from surgery [74-76].

Ethnicity introduces additional complexity, as genetic and environmental factors linked to different populations can influence baseline miRNA expression and modulate it post-surgery. Variations in diet, lifestyle, and access to healthcare further exacerbate these differences, highlighting the need for research that includes diverse populations. Multi-center studies that account for these variables are essential to improving the generalizability of findings [75-77].

Genetic predispositions, including single nucleotide polymorphisms (SNPs) in miRNA genes or their target sites, can further modulate miRNA function. These genetic variations may affect how specific miRNAs regulate inflammatory, metabolic, and neurocognitive pathways, influencing recovery outcomes. Identifying such genetic markers could help stratify patients based on their likelihood of achieving optimal results [76-78].

Addressing these demographic influences will require integrating miRNA profiling with genomic, proteomic, and epigenomic data. Such multi-omics approaches will provide a holistic understanding of how individual differences shape miRNA-driven recovery, enabling the development of genuinely personalized bariatric interventions [79].

Synergy between miRNAs and Other Non-Coding RNAs

MicroRNAs operate within a broader regulatory network that includes long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs). These non-coding RNAs interact synergistically to modulate inflammation, metabolism, and neural plasticity, processes central to recovery after bariatric surgery. lncRNAs can act as sponges for miRNAs, preventing them from binding to their target mRNAs and influencing gene expression [80-82].

The interaction between miRNAs and lncRNAs in post-surgical recovery is particularly evident in metabolic regulation. Specific lncRNAs, such as MALAT1, modulate miRNA activity in insulin sensitivity pathways and lipid metabolism pathways. Similarly, circRNAs have been implicated in regulating oxidative stress and mitochondrial function by sequestering miRNAs like miR-215, amplifying their protective effects on neuronal health [81-83].

These interactions are not limited to metabolic processes; they extend to neuroinflammatory pathways. Non-coding RNAs regulate cytokine production and ROS generation, mediating systemic and neural recovery. Understanding how these RNA molecules collaborate could uncover novel therapeutic targets for enhancing recovery outcomes [82-84].

Despite their importance, the study of non-coding RNA interactions remains nascent. Most research focuses on individual miRNAs, neglecting the broader regulatory networks they operate. Future studies should employ integrative approaches to elucidate these networks, leveraging advanced sequencing technologies and bioinformatics tools to map their interactions comprehensively [83-85].

Incorporating lncRNAs and circRNAs into therapeutic strategies could enhance the efficacy of miRNA-based interventions. For example, targeting specific lncRNAs that modulate key miRNAs could amplify their beneficial effects, providing a multi-layered approach to recovery. These strategies hold promises for optimizing bariatric surgery outcomes and addressing obesity-related cognitive decline [84-86].

miRNAs in the Prevention of Neurodegenerative Diseases

The modulation of miRNAs post-bariatric surgery offers potential neuroprotective benefits beyond immediate recovery, potentially reducing the risk of neurodegenerative diseases such as Alzheimer's and Parkinson's. Obesity is a known risk factor for these conditions, primarily due to chronic inflammation, oxidative stress, and disrupted insulin signaling. By restoring miRNA balance, bariatric surgery may counteract these mechanisms, offering long-term protection against neurodegeneration [85-87].

Specific miRNAs, such as miR-34a and miR-146a, have been implicated in regulating pathways associated with amyloid-beta clearance and tau phosphorylation, which are central to Alzheimer's disease pathology. Downregulating these miRNAs post-surgery could reduce the accumulation of neurotoxic proteins, mitigating the progression of cognitive decline. Similarly, miR-132 and miR-124 play protective roles in dopaminergic neurons, suggesting their relevance in Parkinson's disease [86-88].

Oxidative stress and mitochondrial dysfunction are common pathways in both obesity and neurodegeneration. miRNAs such as miR-448, which regulate mitochondrial biogenesis and antioxidant defenses, could be therapeutic targets for protecting neuronal health. Their modulation post-surgery may enhance mitochondrial resilience, reducing neuronal vulnerability to degenerative processes [87-89].

Longitudinal studies are essential to confirm the neuroprotective effects of miRNAs in post-bariatric populations. These studies should investigate whether sustained miRNA changes correlate with reduced incidence or delayed onset of neurodegenerative diseases. Multi-omics approaches integrating miRNA profiling with proteomic and metabolomic data could provide deeper insights into these protective mechanisms [88-90].

The potential to use miRNA-based therapies for preventing neurodegeneration is an exciting avenue for future research. By targeting miRNAs involved in neuroinflammatory and oxidative pathways, these therapies could complement the benefits of bariatric surgery, offering a proactive approach to long-term brain health [91].

Variations Among Bariatric Procedures

Different types of bariatric surgery, including Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG), and adjustable gastric banding (AGB), exhibit distinct effects on miRNA expression and

subsequent recovery outcomes. These variations arise from differences in hormonal changes, gut microbiota modulation, and systemic metabolic shifts induced by each procedure [92,93].

RYGB, for example, has been shown to produce significant alterations in gut hormones such as GLP-1 and PYY, which influence miRNA expression linked to inflammation and neuroprotection. In contrast, SG primarily impacts gastric emptying rates and ghrelin levels, leading to unique miRNA profiles associated with appetite regulation and energy balance. Being less invasive, AGB induces milder hormonal and metabolic changes, which may result in more modest miRNA modulation [8,16].

The effects of these procedures on neurocognitive recovery also differ. RYGB has been associated with more pronounced cognitive improvements, potentially due to its extensive impact on gut-brain communication and systemic inflammation. SG, while effective, may yield less dramatic neurocognitive benefits, reflecting its more localized physiological effects. Understanding these differences is critical for tailoring surgical approaches to individual patient needs [94-96].

Comparative studies are needed to delineate the miRNA profiles associated with each procedure and their implications for recovery. These studies should incorporate multi-omics approaches to capture the complex interactions between hormonal, metabolic, and neural pathways. Identifying procedure-specific miRNA markers could guide surgical decision-making and optimize patient outcomes [95-97].

Future assays should also explore the long-term effects of different bariatric procedures on miRNA dynamics and recovery trajectories. By understanding how each surgery modulates miRNA expression over time, clinicians can develop targeted follow-up strategies to sustain the benefits of the chosen intervention [98].

miRNAs and Mental Health

The relationship between obesity and mental health conditions such as depression and anxiety are well-documented, with chronic inflammation, metabolic dysregulation, and altered neurocircuitry serving as key mediators [99].

Bariatric surgery has shown significant benefits in alleviating these psychological comorbidities, and miRNAs likely play a pivotal role in this process. miRNAs influence the expression of genes involved in serotonin signaling, neuroinflammation, and hypothalamic-pituitary-adrenal (HPA) axis regulation, which are critical in mood regulation. For example, miRNAs such as miR-16 and miR-132 regulate serotonin transporter levels and synaptic activity, affecting mood stability and stress resilience [98-100].

Post-surgical modulation of these miRNAs correlates with improvements in depressive symptoms, suggesting their involvement in restoring neurochemical balance. Additionally, miRNAs that downregulate pro-inflammatory cytokines, such as miR-146a and miR-155, may alleviate the chronic neuroinflammatory state associated with anxiety disorders [87-89].

Bariatric surgery also alters the gut-brain axis, indirectly impacting mental health via miRNA-mediated mechanisms. Changes in gut microbiota composition influence the production of neuroactive metabolites, such as gamma-aminobutyric acid (GABA) and serotonin precursors, which are regulated by miRNA activity. This interaction underscores the importance of miRNAs in linking metabolic and psychological recovery [74-76].

Despite these findings, significant gaps remain in understanding the specific roles of miRNAs in mental health recovery post-surgery. Most studies focus on broad psychological outcomes without exploring the molecular mechanisms underlying these changes. Future research should prioritize identifying miRNAs directly associated with mood regulation and their temporal dynamics during recovery [28,64].

Integrating miRNA profiling with psychological assessments and neuroimaging could provide a comprehensive understanding of the molecular underpinnings of mental health improvements. This approach would also facilitate the development of miRNA-based interventions targeting specific pathways involved in depression and anxiety, offering a novel therapeutic avenue for bariatric patients [32,87].

Interaction Between Microbiota and miRNAs

The gut microbiota plays a central role in mediating bariatric surgery's systemic and neural benefits, and miRNAs act as key modulators of this interaction. Alterations in microbial diversity and abundance following surgery lead to changes in the production of metabolites such as short-chain fatty acids (SCFAs), which influence miRNA expression in tissues, including the brain, liver, and adipose tissue. These metabolites regulate inflammation, oxidative stress, and neuronal health pathways [35,52].

SCFAs produced by beneficial gut bacteria modulate the expression of miRNAs such as miR-223 and miR-146a, which are implicated in anti-inflammatory and neuroprotective pathways. Post-surgery, reduced levels of lipopolysaccharides (LPS), a pro-inflammatory endotoxin, further enhance the systemic anti-inflammatory state by suppressing miRNAs that promote cytokine production [64,79].

Gut-derived hormones, including GLP-1 and PYY, also interact with miRNAs to regulate appetite, metabolism, and neural activity. These hormones influence miRNA expression in the hypothalamus, a key brain region controlling energy homeostasis and stress responses. The synergistic effects of these hormones and miRNAs underscore their importance in linking gut health with systemic recovery [86-89].

Despite the growing recognition of the microbiota-miRNA axis, its specific mechanisms remain poorly characterized. Most research has focused on individual miRNAs or microbial species, neglecting the complex networks underlying these interactions. Multi-omics approaches integrating metagenomics, transcriptomics, and metabolomics could provide a more comprehensive understanding of this axis [98-100].

It is necessary explore the potential for manipulating the microbiota-miRNA axis through probiotics, prebiotics, or dietary interventions. Such strategies could enhance recovery outcomes by modulating key miRNA pathways, offering a personalized approach to optimizing the benefits of bariatric surgery [83,94].

Challenges in Translational Applications

While miRNAs are promising biomarkers and therapeutic targets, translating them into clinical practice presents significant challenges. Variability in miRNA expression due to demographic factors, environmental influences, and surgical techniques complicates their standardization. Developing robust miRNA quantification and normalization protocols is critical for ensuring reproducibility and reliability across studies [15,63-66].

The high cost of advanced technologies such as RNA sequencing and miRNA-based therapeutics presents another barrier to clinical implementation. To make these tools accessible to broader patient populations, scalable and cost-effective methods must be developed. Additionally, the regulatory landscape for RNA-based therapies remains complex, requiring rigorous safety and efficacy evaluations [28-32,88].

Ethical considerations also influence the translation of miRNA research into practice. Genetic and epigenetic data use concerns privacy, consent, and potential misuse. Addressing these

issues through clear guidelines and patient education will be essential for fostering public trust in miRNA-based interventions [44,91].

Despite these challenges, significant progress has been made in overcoming technical and logistical barriers. Advances in nanoparticle-based delivery systems and CRISPR-Cas9 technologies have improved the precision and efficiency of miRNA-targeting therapies. Collaborative efforts between academic, clinical, and industry stakeholders will further accelerate the translation of miRNA research into practical applications [7-10,68].

These challenges through interdisciplinary collaboration and technological innovation will unlock the full potential of miRNAs in obesity management and neurocognitive recovery. This effort will ensure that the benefits of miRNA-based approaches reach all patients, advancing the field of precision medicine [16,79-82].

Comparison with Non-Surgical Interventions

The effects of bariatric surgery on miRNA modulation and neurocognitive recovery are unique compared to non-surgical interventions such as pharmacotherapy or intensive lifestyle modifications. While these alternatives can achieve modest weight loss and metabolic improvements, they often fail to induce the systemic and neural benefits observed with surgery. This difference highlights the distinct mechanisms underlying surgical and non-surgical approaches [53-56,94].

Pharmacological interventions primarily target specific metabolic pathways, offering limited effects on inflammation and oxidative stress. In contrast, bariatric surgery induces global changes in hormonal and metabolic profiles, resulting in broader miRNA modulation. For example, the downregulation of pro-inflammatory miRNAs such as miR-146a is more pronounced following surgery, contributing to its superior anti-inflammatory effects [40-42,85].

Lifestyle modifications, including diet and exercise, can improve miRNA expression, but adherence challenges and individual variability often limit their impact. Bariatric surgery, particularly in patients with severe obesity or metabolic syndrome, provides a more consistent and sustained stimulus for miRNA-mediated recovery [51-53,92].

Comparative studies are needed to delineate the specific miRNA profiles associated with surgical and non-surgical interventions. These studies should also explore the potential for combining these approaches to maximize recovery outcomes. For instance, integrating post-surgical lifestyle modifications with miRNA-targeting therapies could enhance the benefits of both strategies [68-70,100].

Understanding these interventions' relative advantages and limitations will inform the development of comprehensive treatment plans that optimize patient outcomes. Such plans could leverage the strengths of each approach, ensuring that all patients receive personalized and effective care [74,88-90].

Advances in miRNA Research Technologies

Emerging technologies are revolutionizing miRNA research, enabling more profound insights into their metabolic and neurocognitive recovery roles. RNA sequencing (RNA-seq) has significantly improved the resolution and accuracy of miRNA profiling, allowing researchers to identify novel miRNAs and their target pathways. These advancements have uncovered previously unrecognized regulatory networks, expanding our understanding of miRNA biology [16,55-57].

Nanoparticle-based delivery systems have emerged as a promising tool for miRNA-based therapies. These systems enhance the stability and bioavailability of miRNA mimics or inhibitors, ensuring efficient delivery to target tissues. For example, lipid nanoparticles have been successfully used to deliver miRNA therapeutics in preclinical models, demonstrating their potential for clinical applications [40-43,77].

CRISPR-Cas9 technology offers another innovative approach to studying and manipulating miRNAs. By enabling precise editing of miRNA genes, CRISPR allows researchers to investigate their specific functions and develop targeted interventions. This technology could be beneficial for identifying and correcting dysregulated miRNA pathways in obesity-related conditions [34-36,58].

Artificial intelligence (AI) and machine learning are increasingly being applied to analyze complex miRNA datasets. These tools can identify patterns and correlations that may be overlooked using traditional methods, facilitating the discovery of predictive biomarkers and therapeutic targets. Integrating AI with omics technologies will accelerate the pace of miRNA research and its translation into clinical practice [18-20,66].

These technologies' continued development and application will transform miRNA research, opening new avenues for understanding and treating obesity-related cognitive decline. Collaborative efforts between researchers, clinicians, and industry stakeholders will be essential for harnessing these innovations to improve patient outcomes [58-60,85].

Economic and Clinical Feasibility of miRNAs as Biomarkers

Implementing miRNA-based biomarkers and therapies in clinical practice raises critical questions about cost-effectiveness and scalability. Current technologies for miRNA quantification, such as RNA sequencing and real-time PCR, are highly sensitive and accurate but remain prohibitively expensive for widespread clinical use. Developing cost-effective and scalable methods for miRNA detection is essential to ensure accessibility for diverse healthcare systems and patient populations [10-13,22].

Despite these challenges, the economic benefits of miRNA-based approaches could outweigh their initial costs. By enabling early detection of neurocognitive and metabolic complications, miRNA biomarkers could reduce the need for expensive diagnostic tests and prolonged treatments. Additionally, miRNA-guided interventions could improve recovery trajectories, reducing the long-term burden of obesity-related comorbidities on healthcare systems [73-75,99].

Standardization of miRNA profiling protocols is another critical step for clinical feasibility. Variability in sample collection, processing, and analysis currently limits the reproducibility and comparability of miRNA studies. Establishing standardized workflows and quality control measures will enhance the reliability of miRNA-based diagnostics and therapeutics, fostering their adoption in routine clinical practice [90-92].

Integrating miRNA technologies into existing healthcare frameworks also requires considering ethical and logistical challenges. Ensuring patient privacy and data security in the collection and use of miRNA profiles is paramount. Additionally, education and training programs for healthcare providers will be essential to facilitate the effective implementation of miRNA-based tools [44,52,60].

Investing in infrastructure and interdisciplinary collaboration will accelerate the transition of miRNA research from bench to bedside. Public and private partnerships can drive innovation while addressing economic and logistical barriers. As these efforts progress, miRNA-based approaches can potentially transform obesity management and neurocognitive recovery globally [37,45,100].

Conclusion

The comprehensive role of microRNAs in the neurocognitive and neuroprotective benefits of bariatric surgery underscores their potential as biomarkers and therapeutic targets. MiRNAs bridge systemic recovery with cognitive and emotional well-being by modulating inflammatory, metabolic, and neural pathways. This dual impact positions miRNAs at the forefront of precision medicine, offering novel opportunities to optimize patient outcomes and address the broader health implications of obesity.

Despite significant advancements, critical knowledge gaps remain. The long-term dynamics of miRNA expression, the influence of demographic variables, and the interplay between miRNAs and other non-coding RNAs require further exploration. The variability in miRNA responses across different bariatric procedures highlights the need for personalized approaches considering individual genetic and environmental factors.

Robust research in this area should prioritize multi-omics integration, combining miRNA profiling with transcriptomics, proteomics, and metabolomics to construct comprehensive regulatory networks. Longitudinal studies and collaborative multi-center trials will be essential to validate miRNA biomarkers and therapeutic strategies and ensure their reliability and applicability across diverse populations.

Translating miRNA research into clinical practice will depend on overcoming economic, technical, and ethical challenges. Technological advances, such as nanoparticle-based delivery systems and artificial intelligence, offer promising solutions to these barriers, paving the way for scalable and cost-effective miRNA-based diagnostics and treatments.

Lastly, harnessing the full potential of miRNAs will revolutionize the management of obesity-related cognitive dysfunction and metabolic disorders. By addressing these challenges and opportunities, integrating miRNAs into bariatric surgery frameworks will set a new standard for personalized and effective healthcare.

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Conflict of interest

The authors declare that there is no conflict of interest.

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