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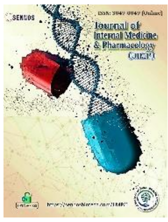

Review Article

Glial Metabolism in Neurodegenerative Disorders: Bridging Pathophysiology and Therapeutics

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ARTICLEINFO ABSTRACT

Glial cells, including astrocytes, microglia, and oligodendrocytes, are crucial for maintaining homeostasis in the central nervous system (CNS). Recent research highlights the significant role of glial metabolism in the pathophysiology of neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (MS). These disorders are associated with metabolic dysregulation within glial cells, leading to impaired neuroprotection, increased inflammation, and oxidative stress, which worsen neuronal damage. Astrocytic glycolysis, microglial metabolic reprogramming, and oligodendrocytic energy deficits have emerged as key contributors to disease progression. This review examines the complex relationship between glial metabolism and neurodegeneration, focusing on how metabolic changes in glial cells affect synaptic integrity, neuronal survival, and immune responses. Advances in metabolomics and imaging technologies have provided valuable insights into these metabolic disruptions at both cellular and molecular levels. Furthermore, novel therapeutic strategies targeting glial metabolism are gaining attention, offering potential avenues for neuroprotection and disease modulation. Interventions such as boosting astrocytic lactate production, modulating microglial polarization through metabolic approaches, and restoring mitochondrial function in oligodendrocytes are discussed. By linking glial metabolic dysfunction with neurodegenerative diseases, this review emphasizes the therapeutic potential of targeting glial metabolism to improve patient outcomes and reduce disease burden.

Keywords: Glial Cells, Neurodegenerative Disorders, Metabolism, Pathophysiology, Therapeutics

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1. Introduction

The central nervous system (CNS) relies on a delicate interplay between neurons and glial cells for its proper function and maintenance [1]. While neurons have long been considered the primary mediators of brain activity, glial cells, including astrocytes, microglia, and oligodendrocytes, play equally critical roles in maintaining CNS homeostasis. These roles extend beyond support functions, encompassing active contributions to metabolic processes essential for neuronal survival, synaptic transmission, and overall brain health. Glial cells are central to brain metabolism, orchestrating nutrient delivery, energy production, and waste removal. Astrocytes, for instance, regulate glucose uptake, lactate production, and neurotransmitter recycling, ensuring an uninterrupted energy supply to neurons [2]. Microglia, the resident immune cells of the brain, modulate inflammatory responses and adapt their metabolism during immune challenges [3]. Oligodendrocytes contribute by maintaining the structural and metabolic integrity of myelin, which is crucial for efficient nerve conduction. The importance of glial metabolism becomes particularly evident in the context of neurodegenerative disorders [4]. Conditions such as Alzheimer’s disease, Parkinson’s disease, and multiple sclerosis are characterized not only by neuronal dysfunction but also by glial metabolic dysregulation. Emerging evidence suggests that disruptions in glial metabolism contribute to oxidative stress, neuroinflammation, and energy deficits, exacerbating disease progression [5]. This recognition has placed glial metabolism at the forefront of neurodegenerative disease research, presenting novel opportunities for therapeutic intervention. As the prevalence of neurodegenerative disorders continues to rise globally, understanding the metabolic roles of glial cells is more crucial than ever. This review explores the intricate relationship between glial metabolism and neurodegenerative diseases, emphasizing the potential of targeting glial metabolic pathways to mitigate pathophysiology and develop innovative therapeutic strategies [6,7].

2. Types of Glial Cells and Their Metabolic Functions

Glial cells are non-neuronal cells in the central nervous system that perform a wide range of functions essential for brain homeostasis. Among them, astrocytes, microglia, and oligodendrocytes are particularly significant for their distinct metabolic contributions. Each cell type exhibits specialized roles in maintaining neuronal function and adapting to the brain's dynamic metabolic needs [8-10].

2.1 Astrocytes: Energy Supply and Neurotransmitter Cycling

Astrocytes are the most abundant glial cells in the brain and serve as the primary regulators of metabolic support for neurons. They play a critical role in glucose uptake from the bloodstream, converting it into lactate through glycolysis. This lactate is shuttled to neurons as a key energy source, particularly during periods of high synaptic activity, a process known as the astrocyte-neuron lactate shuttle (ANLS) [11-13].

In addition to energy metabolism, astrocytes are pivotal in neurotransmitter cycling. They uptake glutamate from synaptic clefts via excitatory amino acid transporters (EAATs) and convert it into glutamine through the action of glutamine synthetase. This glutamine is then supplied back to neurons, where it is used to synthesize glutamate or gamma-aminobutyric acid (GABA). This recycling process ensures excitatory and inhibitory neurotransmitter balance, preventing excitotoxicity and maintaining synaptic function [14].

2.2 Microglia: Immune Response and Metabolic Adaptation

Microglia are the resident immune cells of the CNS, responsible for monitoring the brain's microenvironment and responding to injury or infection. Their metabolic state is closely linked to their functional roles. In a resting state, microglia rely on oxidative phosphorylation (OXPHOS) for energy, which supports their surveillance activities. Upon activation during injury or disease, they shift to glycolysis to meet the increased energy demands of phagocytosis and pro-inflammatory cytokine production [15].

This metabolic plasticity allows microglia to adapt to the brain's needs during stress or injury. However, in neurodegenerative disorders, prolonged activation of microglia can lead to chronic neuroinflammation and oxidative stress, exacerbating neuronal damage. Understanding and modulating microglial metabolism offers a promising avenue for mitigating inflammatory processes in these diseases [16].

2.3 Oligodendrocytes: Myelination and Lipid Metabolism

Oligodendrocytes are responsible for producing and maintaining the myelin sheath, a lipid-rich structure that insulates axons and facilitates rapid nerve impulse conduction. Myelination is a metabolically demanding process that requires the synthesis of substantial amounts of lipids and proteins. Oligodendrocytes derive energy primarily from glucose metabolism but also rely on fatty acid oxidation to meet their high energy demands [17].

Beyond their role in myelination, oligodendrocytes contribute to neuronal metabolic support by supplying lactate through monocarboxylate transporters (MCTs). This lactate serves as an energy substrate for axons, particularly in long-range neurons where energy demands are high. Dysregulation of oligodendrocyte metabolism can impair myelination and axonal function, contributing to neurodegenerative conditions such as multiple sclerosis and leukodystrophies [18].

3. Glial Metabolism in Neurodegenerative Disorders

Neurodegenerative disorders are characterized by progressive loss of neuronal structure and function, often accompanied by glial cell dysfunction. Metabolic disruptions in astrocytes, microglia, and oligodendrocytes play a significant role in the pathogenesis and progression of these diseases. Understanding the unique metabolic alterations in glial cells across different disorders provides insight into potential therapeutic targets [19].

3.1 Alzheimer’s Disease: Amyloid Metabolism and Astrocyte Dysfunction

Alzheimer's disease (AD) is marked by the accumulation of amyloid-beta (Aβ) plaques and neurofibrillary tangles, accompanied by glial cell dysfunction. Astrocytes play a dual role in AD, attempting to clear Aβ through phagocytosis but often failing due to metabolic impairments. Dysregulation of glucose metabolism in astrocytes reduces the production of lactate, leading to insufficient energy supply to neurons. Furthermore, astrocytes in AD exhibit altered glutamate uptake, contributing to excitotoxicity and neuronal damage [20]. Amyloid deposits also induce a pro-inflammatory state in microglia and astrocytes, exacerbating oxidative stress. These metabolic disruptions collectively accelerate neuronal degeneration, highlighting the need to target astrocytic metabolic pathways in AD therapies [21].

3.2 Parkinson's Disease: Mitochondrial Impairments in Microglia

Parkinson's disease (PD) is associated with dopaminergic neuron loss in the substantia nigra and the accumulation of alpha-synuclein aggregates. Microglia in PD exhibit mitochondrial dysfunction, leading to impaired oxidative phosphorylation and increased reliance on glycolysis. This metabolic shift promotes the production of pro-inflammatory cytokines and reactive oxygen species (ROS), perpetuating a cycle of neuroinflammation and oxidative damage.

Astrocytes in PD also show reduced efficiency in glutamate clearance and energy metabolism, further contributing to neuronal vulnerability. Targeting microglial mitochondrial function and restoring metabolic balance in glial cells could offer novel approaches for PD treatment.

3.3 Amyotrophic Lateral Sclerosis (ALS): Glial Lactate Shuttle Disruption

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by motor neuron degeneration. Astrocytes in ALS exhibit impaired lactate production and transfer, disrupting the astrocyte-neuron lactate shuttle that provides neurons with essential energy substrates. This energy deficit exacerbates motor neuron degeneration.

Microglia in ALS also show metabolic dysfunction, switching to a pro-inflammatory glycolytic state. This chronic activation leads to persistent neuroinflammation and contributes to the progression of motor neuron damage. Enhancing astrocytic lactate production and modulating microglial metabolic states are potential therapeutic strategies for ALS [22].

3.4 Huntington's Disease: Energetic Deficits in Astrocytes and Microglia

Huntington's disease (HD) is caused by an expanded CAG repeat in the huntingtin gene, leading to protein aggregation and neuronal dysfunction. Astrocytes in HD show reduced glucose uptake and altered glycolytic activity, resulting in inadequate energy support for neurons. Impaired glutamate clearance by astrocytes also contributes to excitotoxicity.

Microglia in HD display hyperactive inflammatory states fueled by metabolic imbalances, producing excessive ROS and cytokines. These metabolic deficits in astrocytes and microglia synergistically worsen neuronal damage, emphasizing the importance of targeting glial metabolic pathways in HD therapies.

3.5 *Multiple Sclerosis (MS): Glial Lipid Metabolism and Demyelination*

Multiple sclerosis (MS) is an autoimmune disease characterized by demyelination and axonal degeneration. Oligodendrocytes in MS exhibit disrupted lipid metabolism, impairing myelin synthesis and repair. The chronic inflammatory environment in MS, driven by activated microglia and astrocytes, further exacerbates demyelination and prevents remyelination.

Metabolic disruptions in oligodendrocytes reduce their ability to provide lactate and energy substrates to axons, leading to energy deficits in neurons. Therapeutic approaches aimed at restoring lipid metabolism in oligodendrocytes and modulating inflammatory responses in microglia and astrocytes hold promise for MS management.

4. Mechanisms Linking Glial Metabolism to Disease Pathophysiology

The progression of neurodegenerative disorders is closely linked to disruptions in glial metabolism. These disruptions manifest through several interconnected mechanisms, including oxidative stress, neuroinflammation, impaired astrocytic-neuronal interactions, and lipid metabolism imbalances. Together, these pathways contribute to neuronal dysfunction and cell death [23].

4.1 Oxidative Stress and Mitochondrial Dysfunction

Mitochondrial dysfunction in glial cells leads to impaired oxidative phosphorylation, resulting in the accumulation of reactive oxygen species (ROS). In astrocytes, mitochondrial deficits reduce their capacity to buffer ROS, exacerbating oxidative damage to neurons. Similarly, microglia with compromised mitochondrial function produce excessive ROS during inflammatory responses, further amplifying oxidative stress in the brain.

In disorders like Alzheimer’s disease and Parkinson’s disease, mitochondrial dysfunction in glial cells not only reduces their energy efficiency but also triggers apoptotic pathways, contributing to both glial and neuronal cell death. Targeting mitochondrial integrity in glial cells may mitigate oxidative stress and protect neuronal populations.

4.2 Neuroinflammation Driven by Microglial Metabolism

Microglia are central mediators of neuroinflammation, with their metabolic states dictating their functional roles. Under normal conditions, microglia rely on oxidative phosphorylation for surveillance activities. However, during activation, they shift to glycolysis, producing pro-inflammatory cytokines and ROS.

This glycolytic state is often sustained in chronic neurodegenerative conditions, resulting in persistent neuroinflammation. Such inflammation exacerbates neuronal injury and creates a toxic environment that disrupts brain homeostasis. Modulating microglial metabolism to balance pro-inflammatory and anti-inflammatory states holds potential for mitigating inflammation-driven pathophysiology.

4.3 Dysregulation of Astrocytic-Neuronal Metabolic Coupling

Astrocytes play a pivotal role in supplying energy to neurons via the astrocyte-neuron lactate shuttle (ANLS). Disruption of this metabolic coupling, as observed in amyotrophic lateral sclerosis (ALS) and

Huntington's disease, leads to energy deficits in neurons. Impaired glucose uptake and lactate production in astrocytes result in decreased energy availability, contributing to neuronal degeneration.

Additionally, astrocytic dysfunction affects neurotransmitter cycling, particularly glutamate uptake. Excess glutamate in the synaptic cleft causes excitotoxicity, damaging neurons and exacerbating neurodegenerative processes. Restoring astrocytic metabolic function could re-establish metabolic coupling and reduce neuronal vulnerability.

4.4 Altered Lipid Metabolism and Energy Balance

Lipid metabolism in glial cells, particularly oligodendrocytes, is critical for maintaining myelin integrity and energy balance in the CNS. Disruptions in lipid synthesis and storage impair myelination, as seen in multiple sclerosis (MS). Additionally, astrocytes and microglia rely on lipid metabolism for energy production and inflammatory modulation. Alterations in lipid homeostasis can lead to the accumulation of toxic lipid intermediates, further exacerbating neuronal damage [24].

In neurodegenerative diseases, such as Alzheimer's disease, astrocytic lipid metabolism is disrupted, leading to the accumulation of lipid droplets and impaired energy storage. Therapeutic strategies aimed at normalizing lipid metabolism in glial cells may help restore energy balance and reduce disease progression.

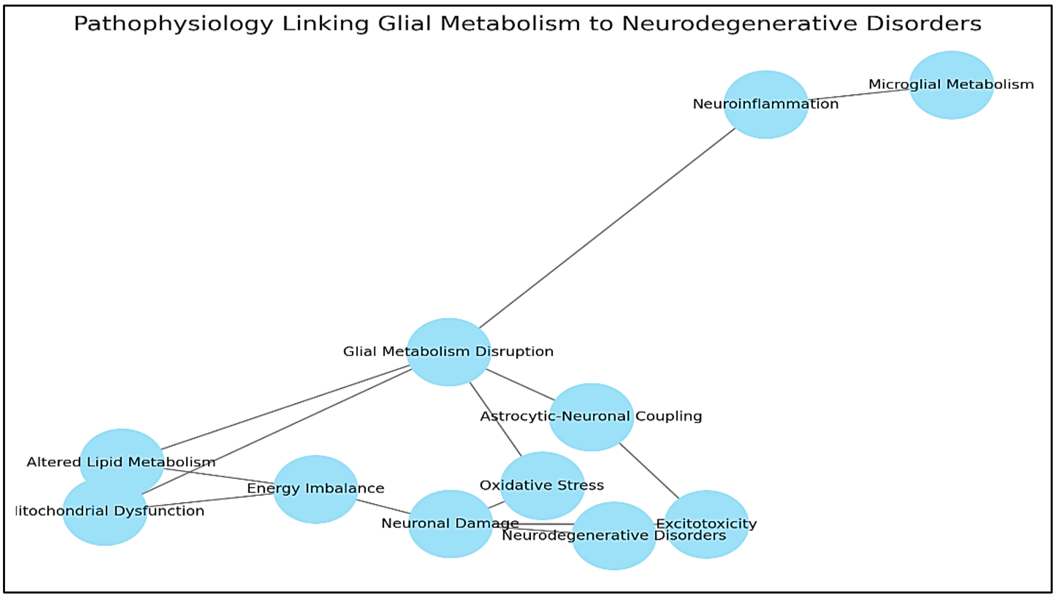

Figure 1: Pathophysiology of Glial Metabolism in Neurodegenerative Disorders5. Therapeutic Approaches Targeting Glial Metabolism

Targeting glial metabolism offers a promising avenue for developing therapies for neurodegenerative disorders. Therapeutic strategies can focus on restoring energy balance, controlling neuroinflammation, protecting neuronal function, and regenerating glial cells. Here, we discuss emerging and established approaches to address glial metabolic dysfunction.

5.1 Metabolic Modulators: Restoring Energy Homeostasis

Metabolic modulators aim to restore energy production in glial cells by targeting key metabolic pathways. Agents such as pyruvate and lactate precursors have shown potential in boosting astrocytic energy metabolism and supporting the astrocyte-neuron lactate shuttle. Similarly, compounds that enhance mitochondrial function, such as coenzyme Q10 and nicotinamide riboside, can improve oxidative phosphorylation in glial cells.

In diseases like Alzheimer's and Parkinson's, metabolic modulators may reverse the energy deficits caused by mitochondrial dysfunction, reducing oxidative stress and improving neuronal support. Developing drugs that fine-tune glycolysis and oxidative phosphorylation in astrocytes and microglia represents a critical focus for therapeutic innovation.

5.2 Anti-inflammatory Strategies: Controlling Glial Activation

Chronic activation of microglia and astrocytes drives neuroinflammation in many neurodegenerative disorders. Anti-inflammatory strategies targeting glial metabolism can help balance their inflammatory states. For instance, compounds like resveratrol and curcumin inhibit microglial pro-inflammatory pathways by modulating metabolic shifts toward glycolysis. Additionally, immunomodulatory drugs such as minocycline and NLRP3 inflammasome inhibitors can suppress excessive glial activation, reducing the production of pro-inflammatory cytokines and reactive oxygen species. By restoring metabolic equilibrium, these therapies can mitigate neuroinflammation and protect neuronal integrity [25].

5.3 Neuroprotective Agents: Supporting Glial-Neuronal Interactions

Neuroprotective therapies aim to enhance glial support for neurons by targeting metabolic coupling. Astrocytic lactate supplementation or drugs that enhance glucose uptake and utilization can strengthen the astrocyte-neuron lactate shuttle, ensuring consistent energy supply to neurons. Similarly, agents like riluzole, used in amyotrophic lateral sclerosis (ALS), improve glutamate clearance by astrocytes, preventing excitotoxicity.

Oligodendrocyte-targeted therapies, such as clemastine, promote remyelination by restoring lipid metabolism and improving glial-neuronal communication. These approaches highlight the importance of preserving glial-neuronal interactions for maintaining brain homeostasis.

5.4 Gene Therapy: Targeting Metabolic Dysfunction in Glial Cells

Gene therapy offers a targeted approach to address specific metabolic dysfunctions in glial cells. Techniques such as adeno-associated virus (AAV) delivery can introduce genes that restore mitochondrial function or enhance metabolic pathways. For example, gene editing tools like CRISPR-Cas9 have been used to correct mutations associated with mitochondrial disorders in glial cells.

In Huntington's disease and ALS, gene therapy targeting astrocytic and microglial metabolism has shown promise in preclinical models. By directly modifying the genetic and metabolic underpinnings of glial dysfunction, gene therapy provides a personalized treatment option for neurodegenerative diseases.

5.5 Stem Cell-Based Therapies: Regenerating Glial Functionality

Stem cell-based therapies focus on replenishing damaged glial cells and restoring their metabolic functions. Transplantation of glial progenitor cells, such as astrocyte-like or oligodendrocyte precursor cells, has demonstrated the potential to replace dysfunctional cells and improve brain metabolism. Induced pluripotent stem cells (iPSCs) can be differentiated into glial cells and used to restore myelination or metabolic support. For multiple sclerosis, stem cell therapies have shown success in promoting remyelination by regenerating oligodendrocytes. These approaches hold promise for reversing glial cell loss and metabolic imbalances, offering a regenerative solution for neurodegenerative conditions.

6. Emerging Technologies in Glial Metabolism Research

Recent advancements in technology have significantly enhanced our understanding of glial metabolism and its role in neurodegenerative diseases. Cutting-edge tools such as metabolomics, in vivo imaging, and advanced disease models are enabling detailed investigations into the metabolic functions of glial cells and their interactions with neurons. These technologies pave the way for novel therapeutic strategies targeting glial metabolism.

6.1 Metabolomics and Single-Cell Analysis

Metabolomics, the comprehensive study of metabolites in biological systems, has revolutionized the analysis of glial cell metabolism. By profiling metabolic changes in glial cells under various conditions, researchers can identify key pathways involved in neurodegenerative diseases. Advanced metabolomic techniques, such as mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopy, provide high-resolution insights into cellular metabolic states.

Single-cell analysis further refines this approach by enabling the study of individual glial cells, revealing cell-specific metabolic variations. Techniques like single-cell RNA sequencing (scRNA-seq) and single-cell proteomics are uncovering the heterogeneity of glial cell populations, providing critical information about their distinct roles in health and disease.

6.2 In Vivo Imaging of Glial Metabolic Processes

In vivo imaging techniques have become indispensable for studying glial metabolism within the intact brain. Positron emission tomography (PET) and magnetic resonance spectroscopy (MRS) are widely used to monitor metabolic processes in real time. These methods allow researchers to visualize glucose uptake, lactate production, and mitochondrial activity in astrocytes, microglia, and oligodendrocytes.

Recent advancements, such as genetically encoded metabolic sensors, provide even greater specificity. For example, fluorescent biosensors can track lactate dynamics in astrocytes or mitochondrial activity in microglia, offering precise data on metabolic fluxes. In vivo imaging not only enhances our understanding of glial function but also facilitates the evaluation of therapeutic interventions targeting metabolism.

6.3 Advanced Models of Neurodegenerative Diseases

To study glial metabolism in the context of neurodegenerative diseases, researchers are increasingly utilizing advanced experimental models. These include three-dimensional brain organoids derived from human induced pluripotent stem cells (iPSCs) and genetically modified animal models. Brain organoids replicate key features of the human brain, including glial cell development and metabolism, providing a unique platform for studying disease-specific metabolic changes.

Genetically engineered mice and zebrafish models allow precise manipulation of glial metabolic pathways to observe their effects on disease progression. These models enable researchers to mimic conditions such as mitochondrial dysfunction, lipid metabolism dysregulation, and neuroinflammation in glial cells, providing invaluable insights into disease mechanisms and potential therapeutic targets.

7. Challenges and Future Directions

The study of glial metabolism faces several challenges that must be addressed to advance therapeutic strategies for neurodegenerative disorders. One significant hurdle is the metabolic heterogeneity in glial cells, as astrocytes, microglia, and oligodendrocytes exhibit diverse and context-specific metabolic profiles influenced by factors such as brain region, developmental stage, and functional state. This complexity necessitates advanced techniques, such as single-cell metabolomics and spatial transcriptomics, to elucidate cell-specific metabolic pathways. Another challenge is integrating glial metabolism into therapeutic frameworks, as current treatments predominantly target neuronal dysfunction while often neglecting the critical metabolic interactions between glial cells and neurons. Developing therapies that restore metabolic balance in glial cells, such as enhancing lactate production or modulating mitochondrial function, is essential for comprehensive neuroprotection. Lastly, bridging basic research with clinical applications remains difficult due to limitations in preclinical models and a lack of biomarkers to monitor glial metabolic dysfunction in patients. Advances in patient-derived models, imaging technologies, and biomarker discovery will be critical to translating glial metabolism research into effective and personalized therapeutic interventions. Overcoming these challenges will pave the way for innovative approaches to treat neurodegenerative diseases by targeting the underlying metabolic dysfunctions in glial cells.

8. Conclusion

In conclusion, the intricate roles of glial cells in maintaining brain homeostasis and their critical contributions to neurodegenerative disease pathophysiology underscore the importance of glial metabolism as a research focus. Current knowledge reveals that metabolic dysfunctions in astrocytes, microglia, and oligodendrocytes contribute to oxidative stress, neuroinflammation, energy imbalances, and disrupted neuronal-glial interactions, exacerbating disease progression. Targeting these metabolic pathways holds immense therapeutic potential, offering opportunities to restore energy homeostasis, mitigate inflammation, and protect neuronal integrity in conditions such as Alzheimer’s disease, Parkinson’s disease, and multiple sclerosis. Despite these promising insights, the field faces significant challenges, including the need to unravel the metabolic heterogeneity of glial cells, develop integrative therapeutic frameworks, and bridge basic research with clinical applications. To fully realize the potential of targeting glial metabolism, further interdisciplinary research is essential. Collaborative efforts between neuroscientists, bioengineers, and clinicians, supported by advancements in technologies such as metabolomics, imaging, and patient-derived models, will be pivotal in translating these findings into innovative and effective treatments for neurodegenerative disorders.

Conflict of Interest

The authors declare no competing interests.

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Data Availability

The authors confirm that the data supporting the findings of this study are available within the article

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