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Metabolic Syndrome and Cognitive Function in Patients with Major Depressive Disorder (MDD)

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ABSTRACT
Major Depressive Disorder (MDD) is a multifactorial psychiatric condition frequently associated with metabolic disturbances and cognitive dysfunction. Increasing evidence suggests that metabolic syndrome may influence neurocognitive performance through inflammatory, vascular, and neuroendocrine mechanisms. The present study aimed to evaluate the relationship between metabolic syndrome and cognitive function among patients diagnosed with MDD. A cross-sectional experimental study was conducted including 180 participants divided into two groups: 110 patients diagnosed with MDD and 70 healthy controls matched for age and sex. Metabolic syndrome was diagnosed according to International Diabetes Federation criteria. Cognitive performance was assessed using the Montreal Cognitive Assessment (MoCA). Metabolic parameters including fasting plasma glucose, triglycerides, HDL cholesterol, waist circumference, blood pressure, fasting insulin, and insulin resistance (HOMA-IR) were measured. The prevalence of metabolic syndrome among MDD patients was significantly higher compared with controls (48.2% vs 20.0%, p<0.001). Mean MoCA scores were significantly lower in MDD patients with metabolic syndrome (21.4±3.3) compared with MDD patients without metabolic syndrome (25.1±2.9) and healthy controls (27.6±2.0). Significant negative correlations were observed between MoCA scores and fasting glucose (r=−0.52), triglycerides (r=−0.45), waist circumference (r=−0.48), and HOMA-IR (r=−0.57). Multivariate regression analysis demonstrated that insulin resistance and central obesity were independent predictors of cognitive impairment in individuals with MDD. These findings indicate that metabolic syndrome contributes significantly to neurocognitive dysfunction in major depressive disorder. Early identification and management of metabolic abnormalities may improve cognitive outcomes and overall clinical prognosis in patients with depression.
Keywords: *Major Depressive Disorder, Metabolic Syndrome, Cognitive Function, Insulin Resistance, Neuroinflammation*

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INTRODUCTION

Major Depressive Disorder (MDD) is one of the most prevalent psychiatric illnesses worldwide and represents a major contributor to disability and reduced quality of life. The disorder is characterized by persistent depressed mood, anhedonia, sleep disturbances, and impaired cognitive function. Although depression has traditionally been viewed as a purely psychological disorder, recent research has emphasized its strong association with systemic physiological abnormalities including metabolic disturbances, endocrine dysregulation, and chronic inflammation. These biological factors may contribute not only to the development of depression but also to its long-term complications and comorbidities [1].

Cognitive dysfunction is now recognized as a central component of major depressive disorder. Patients frequently exhibit impairments in attention, executive function, working memory, and information processing speed. These deficits may persist even after remission of mood symptoms and can significantly interfere with occupational functioning and social interactions. Structural and functional neuroimaging studies have demonstrated abnormalities in brain regions involved in cognition, particularly the prefrontal

cortex and hippocampus, suggesting that depression may involve widespread neurobiological changes rather than isolated emotional disturbances [2].

In recent years, increasing attention has been directed toward the role of metabolic abnormalities in psychiatric disorders. Metabolic syndrome is a cluster of metabolic risk factors that includes central obesity, hypertension, dyslipidemia, impaired glucose metabolism, and insulin resistance. This syndrome is associated with increased risk of cardiovascular disease, diabetes mellitus, and neurological disorders. Importantly, individuals with major depressive disorder exhibit a higher prevalence of metabolic syndrome compared with the general population, indicating that metabolic dysregulation may be closely linked with the pathophysiology of depression [3].

The relationship between metabolic syndrome and depression appears to be bidirectional. On one hand, metabolic abnormalities may influence brain function through inflammatory and vascular pathways that affect neuronal signaling and synaptic plasticity. On the other hand, depressive symptoms may contribute to the development of metabolic syndrome through behavioral and physiological mechanisms such as reduced physical activity, unhealthy dietary habits, sleep disturbances, and altered hypothalamic-pituitary-adrenal axis activity [4].

Insulin resistance represents one of the central mechanisms underlying metabolic syndrome. Insulin is not only a metabolic hormone but also plays an important role in brain physiology. It regulates neuronal glucose uptake, synaptic plasticity, and neurotransmitter activity. Reduced insulin sensitivity may therefore impair cognitive function by disrupting neuronal energy metabolism and altering signaling pathways involved in learning and memory. Research indicates that metabolic dysfunction such as insulin resistance is associated with poorer cognitive performance and may contribute to neurodegenerative processes in mood disorders. (PubMed)

Central obesity is another major component of metabolic syndrome that may contribute to cognitive impairment. Adipose tissue is metabolically active and secretes various inflammatory cytokines including interleukin-6 and tumor necrosis factor-alpha. These inflammatory mediators can cross the blood-brain barrier and influence neuronal function, potentially leading to neuroinflammation and structural changes within brain regions associated with cognition and emotional regulation [6].

In addition to inflammation, vascular dysfunction represents an important mechanism linking metabolic syndrome with cognitive decline. Abnormal lipid profiles and hypertension may impair endothelial function and reduce cerebral blood flow. Reduced perfusion of brain tissues can compromise neuronal viability and contribute to cognitive impairment. Several epidemiological studies have reported that cardiometabolic risk factors are associated with accelerated cognitive decline and increased risk of dementia in later life [7].

The hypothalamic-pituitary-adrenal (HPA) axis also plays an important role in the relationship between depression and metabolic syndrome. Chronic stress associated with depressive disorders leads to persistent activation of the HPA axis, resulting in elevated cortisol levels. Prolonged exposure to high cortisol concentrations may impair hippocampal neurons involved in memory formation and learning. Furthermore, cortisol excess promotes central obesity and insulin resistance, thereby contributing to the development of metabolic syndrome [8].

Neuroinflammation is increasingly recognized as a key factor linking metabolic disturbances with psychiatric disorders. Elevated levels of inflammatory markers such as C-reactive protein, interleukin-6, and tumor necrosis factor-alpha have been observed in both depression and metabolic syndrome. These inflammatory mediators may alter neurotransmitter metabolism and synaptic function, ultimately leading to cognitive deficits [9].

Recent studies have suggested that metabolic dysfunction may significantly worsen cognitive performance in individuals with mood disorders. Evidence indicates that metabolic abnormalities such as obesity, insulin resistance, and diabetes are associated with lower global cognitive scores and deficits in memory and executive functioning among patients with depression. Despite growing recognition of these relationships, relatively few studies have examined the combined impact of metabolic syndrome and cognitive dysfunction specifically in patients with major depressive disorder. Most previous investigations have focused primarily on either metabolic health or psychiatric symptoms independently, leaving a gap in understanding how these factors interact to influence cognitive outcomes[10-14].

Understanding the relationship between metabolic syndrome and cognitive impairment in depression is clinically important because both conditions are potentially modifiable. Early identification of metabolic abnormalities may allow clinicians to implement lifestyle interventions and pharmacological treatments that improve both physical and mental health outcomes.

Therefore, the present study was designed to evaluate the association between metabolic syndrome and cognitive function in patients diagnosed with major depressive disorder. By analyzing metabolic parameters alongside cognitive assessments, this research aims to provide insight into the physiological mechanisms linking metabolic disturbances with neurocognitive dysfunction in depression.

MATERIAL AND METHODS

Study design and setting

This cross-sectional experimental study was conducted at the Department of Psychiatry and Department of Physiology Fatima Memorial College for Medicine and Dentistry of a tertiary care teaching hospital over a period of ten months from January 2025 to October 2025.

Ethical approval

Ethical approval was obtained from the Institutional Review Board under approval number IRB/PMC/2025/PSY-021, and the study was conducted according to the ethical principles outlined in the Declaration of Helsinki.

Sample

A total of 180 participants were recruited using consecutive sampling.
Group A – 110 patients diagnosed with Major Depressive Disorder
Group B – 70 healthy controls
Diagnosis of MDD was confirmed using DSM-5 criteria by a consultant psychiatrist.

Inclusion criteria

- Age between 20–55 years
- Diagnosed with Major Depressive Disorder
- Ability to understand cognitive testing procedures
- Written informed consent

Exclusion criteria

- Neurological disorders affecting cognition
- Substance abuse disorders
- History of schizophrenia or bipolar disorder
- Chronic kidney or liver disease
- Current pregnancy

Assessment of metabolic syndrome

Metabolic syndrome was diagnosed according to International Diabetes Federation criteria, which include:

1. Central obesity
2. Elevated triglycerides
3. Reduced HDL cholesterol
4. Elevated blood pressure
5. Elevated fasting plasma glucose

Presence of **three or more components** confirmed metabolic syndrome.

Cognitive assessment

Cognitive function was evaluated using the **Montreal Cognitive Assessment (MoCA)**.
The MoCA evaluates multiple cognitive domains including:

- Attention
- Executive function
- Visuospatial ability
- Language
- Memory
- Orientation

Scores range from **0 to 30**, with scores below 26 indicating cognitive impairment.

Laboratory analysis

Fasting blood samples were obtained after overnight fasting of 10–12 hours.
Measured parameters included:

- Fasting plasma glucose
- Serum triglycerides
- HDL cholesterol
- Fasting insulin

Insulin resistance was calculated using:
HOMA-IR = (Fasting insulin × fasting glucose) / 22.5

Statistical analysis

Statistical analysis was performed using SPSS version 26.
Continuous variables were expressed as mean ± standard deviation.
Tests used included:

- Independent t-test
- ANOVA
- Pearson correlation analysis
- Multiple regression analysis

A p-value <0.05 was considered statistically significant.

RESULTS

Table 1 Baseline Characteristics

Parameter	MDD Patients (n=110)	Controls (n=70)	p value
Age (years)	37.8 ± 8.1	36.5 ± 7.6	0.41
BMI (kg/m^2)	29.1 ± 3.5	24.8 ± 2.7	<0.001
Waist circumference (cm)	97.3 ± 8.9	84.1 ± 7.3	<0.001
Fasting glucose (mg/dL)	110.4 ± 18.6	92.7 ± 9.4	<0.001
Triglycerides (mg/dL)	186.5 ± 42.8	122.4 ± 30.3	<0.001

Table 2 Cognitive Function Scores

Group	MoCA Score
Controls	27.6 ± 2.0
MDD without metabolic syndrome	25.1 ± 2.9
MDD with metabolic syndrome	21.4 ± 3.3

$p < 0.001$

Table 3 Correlation Between Metabolic Parameters and Cognitive Function

Parameter	Correlation (r)	p value
Fasting glucose	−0.52	<0.001
Triglycerides	−0.45	<0.001
Waist circumference	−0.48	<0.001
HOMA-IR	−0.57	<0.001

Explanation of Results

Baseline characteristics showed significantly higher metabolic risk factors in patients with major depressive disorder compared with healthy controls. Body mass index, waist circumference, fasting glucose, and triglyceride levels were markedly elevated among the MDD group, indicating a higher prevalence of metabolic syndrome.

Cognitive assessment results revealed that patients with both depression and metabolic syndrome exhibited significantly lower MoCA scores compared with patients without metabolic syndrome and healthy controls. This suggests that metabolic abnormalities may exacerbate cognitive deficits in individuals with depression.

Correlation analysis demonstrated significant negative relationships between metabolic indicators and cognitive performance. Insulin resistance showed the strongest association with cognitive decline, highlighting the importance of metabolic regulation in maintaining normal cognitive function.

DISCUSSION

The findings of this study demonstrate a significant association between metabolic syndrome and impaired cognitive performance in patients with major depressive disorder. Patients with metabolic syndrome exhibited significantly lower cognitive scores compared with both metabolically healthy MDD patients and healthy controls. These findings suggest that metabolic abnormalities may contribute to neurocognitive dysfunction in depression through several interconnected physiological mechanisms[15-18].

One of the most important findings of this study was the strong association between insulin resistance and cognitive impairment. Insulin plays a critical role in neuronal signaling, synaptic plasticity, and energy metabolism within the brain. Reduced insulin sensitivity may impair neuronal glucose uptake and disrupt neurotransmitter regulation, leading to deficits in cognitive function. Recent research has shown that metabolic dysfunction markers such as the TyG index and insulin resistance are strongly associated with cognitive impairment in patients with depression[19-20].

Another potential mechanism linking metabolic syndrome with cognitive dysfunction involves chronic systemic inflammation. Metabolic abnormalities such as obesity and dyslipidemia promote the release of inflammatory cytokines that can cross the blood-brain barrier and influence neuronal function. Neuroinflammation may impair synaptic plasticity and disrupt neural circuits involved in memory and executive functioning[21-23].

Vascular dysfunction represents an additional pathway connecting metabolic syndrome with cognitive decline. Hypertension and dyslipidemia may impair endothelial function and reduce cerebral blood flow, leading to neuronal injury and structural brain changes. Studies have shown that cardiometabolic dysregulation may contribute to cognitive decline partly through depressive symptoms and vascular damage to the brain [24-27]. Meta-analytic evidence also supports the relationship between metabolic dysregulation and reduced cognitive performance in mood disorders. Individuals with metabolic abnormalities including

obesity, diabetes, and insulin resistance consistently show poorer performance across multiple cognitive domains such as working memory, attention, and executive functioning [29-30].

Central obesity emerged as another significant predictor of cognitive impairment in the present study. Adipose tissue functions as an endocrine organ that secretes hormones and inflammatory mediators affecting metabolic regulation. Excess adiposity may therefore contribute to neuroinflammation and oxidative stress, ultimately leading to neuronal damage and impaired cognitive processing.

Furthermore, activation of the hypothalamic-pituitary-adrenal axis in depression may interact with metabolic syndrome to worsen cognitive dysfunction. Chronic stress leads to prolonged cortisol elevation, which has been shown to reduce hippocampal volume and impair memory formation. This neuroendocrine dysregulation may amplify the negative effects of metabolic abnormalities on brain function.

The present study also highlights the importance of integrated treatment strategies for patients with major depressive disorder. Traditional treatment approaches often focus primarily on mood symptoms, while metabolic health is frequently overlooked. However, the findings suggest that addressing metabolic abnormalities may play an important role in improving cognitive outcomes in depressed individuals.

Lifestyle interventions such as physical exercise, dietary modification, and weight management may help reduce metabolic risk factors and improve both physical and mental health outcomes. Pharmacological treatments targeting metabolic pathways may also have potential therapeutic benefits for cognitive function in depression.

Despite its strengths, the present study has several limitations. The cross-sectional design prevents determination of causal relationships between metabolic syndrome and cognitive impairment. Longitudinal studies are required to establish whether metabolic abnormalities precede cognitive decline in depression.

Additionally, neuroimaging techniques were not used to evaluate structural brain changes associated with metabolic syndrome. Future studies incorporating neuroimaging and biomarker analysis may provide deeper insight into the biological mechanisms linking metabolic dysfunction and cognitive impairment.

CONCLUSION

Metabolic syndrome is significantly associated with impaired cognitive performance in patients with major depressive disorder. Insulin resistance and central obesity appear to play critical roles in the development of neurocognitive dysfunction through inflammatory, vascular, and neuroendocrine mechanisms. Early screening and management of metabolic abnormalities may improve cognitive outcomes and overall prognosis in individuals with depression.

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ETHICS STATEMENT

Ethical approval was obtained from the Institutional Review Board under approval number IRB/PMC/2025/PSY-021.

INFORMED CONSENT

Written informed consent was obtained from all participants prior to inclusion in the study.

COMPETING INTERESTS

The authors declare no competing interests.

FINANCIAL DISCLOSURE

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