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Cognitive Functions in Middle-Aged Patients with Manifestations of Metabolic Syndrome

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Abstract

Background. Metabolic syndrome (MS) is a major contributor to cardiovascular and endocrine morbidity and has increasingly been implicated in neurodegenerative processes. However, early cognitive alterations in middle-aged individuals with MS often remain clinically overlooked.

Objective. To assess cognitive functions and their associations with metabolic and vascular parameters in middle-aged patients with metabolic syndrome.

Materials and Methods. A total of 86 middle-aged patients with MS diagnosed according to IDF (2005) criteria and 50 age- and sex-matched healthy controls were enrolled. All participants underwent comprehensive clinical and laboratory evaluation, including anthropometric measurements, blood pressure, lipid profile, fasting glucose and insulin levels, and calculation of HOMA-IR. Cognitive functioning was assessed using a standardized neuropsychological battery (MMSE, MoCA, Trail Making Test A/B, Digit Span). Cerebrovascular and endothelial status were evaluated by carotid intima–media thickness and endothelial function testing. Statistical analysis included parametric/nonparametric tests and correlation analysis.

Results. Patients with MS demonstrated significantly lower cognitive performance compared with controls, with prominent deficits in executive functions, attention, working memory, and processing speed. The prevalence of mild cognitive impairment (MoCA < 26) was markedly higher in the MS group. Cognitive decline correlated strongly with insulin resistance, atherogenic dyslipidemia, arterial hypertension, endothelial dysfunction, and increased carotid intima–media thickness. A cumulative effect of MS components on cognitive outcomes was observed.

Conclusions. Middle-aged patients with metabolic syndrome exhibit early, multidomain cognitive impairment closely associated with insulin resistance and cerebrovascular dysfunction. Routine cognitive screening in this population may facilitate early identification of individuals at elevated risk for cerebrovascular disease and cognitive decline and support timely preventive interventions.

Keywords: metabolic syndrome; cognitive impairment; insulin resistance; executive functions; cerebrovascular disease; middle-aged adults

Metabolic syndrome (MS) is regarded as one of the leading risk factors for the development of cardiovascular, endocrine, and neurodegenerative disorders in the middle-aged population [1, 2]. In addition to its traditional components—abdominal obesity, insulin resistance, dyslipidemia, and arterial hypertension—growing attention has been paid to its impact on the central nervous system, particularly on cognitive functions [3]. According to contemporary research, the metabolic disturbances underlying MS are associated with accelerated brain aging, reduced neuronal plasticity, development of vascular dyscirculation, and an increased risk of mild cognitive impairment and dementia [4, 5].

In middle-aged patients, cognitive changes often remain underestimated due to the absence of overt clinical manifestations [4, 6]. However, it is precisely at this stage that structural and functional brain alterations related to chronic hyperglycemia, oxidative stress, endothelial dysfunction, and elevated systemic inflammatory activity are formed [4]. Key mechanisms include cerebral small vessel disease [6], impaired neurovascular coupling, alterations in insulin metabolism within the central nervous system, and accumulation of glycation end products [7]. Collectively, these processes contribute to deterioration of memory, attention, executive functions, and cognitive processing speed.

Despite the large body of literature addressing the vascular and cardiometabolic consequences of MS, the relationship between metabolic parameters and cognitive function in

middle-aged patients remains insufficiently studied. Of particular relevance is the issue of early identification of cognitive changes at preclinical stages [9], which may enable timely prevention of cerebrovascular progression and initiation of individualized preventive interventions. In this context, the study of cognitive characteristics in middle-aged patients with manifestations of metabolic syndrome is of substantial clinical and prognostic significance. Identification of specific patterns of cognitive decline and their association with metabolic, vascular, and neuropsychological markers may contribute to optimization of early diagnosis, risk stratification, and the development of personalized treatment strategies.

Objective of the study — to assess cognitive functions in middle-aged individuals with metabolic syndrome.

Materials and Methods. The study included 86 middle-aged patients with metabolic syndrome diagnosed according to the International Diabetes Federation (IDF) criteria (2005). The control group consisted of 50 apparently healthy individuals matched by age and sex. All participants underwent a standardized clinical and laboratory assessment, including measurement of anthropometric parameters, blood pressure, lipid profile, fasting glucose and insulin levels, as well as the homeostasis model assessment of insulin resistance (HOMA-IR) [10].

Cognitive functioning was evaluated using a battery of standardized neuropsychological tests, including the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Trail Making Test A and B, Digit Span, and tasks assessing cognitive processing speed [11]. Vascular risk factors were assessed based on carotid intima–media thickness measurements and pulse wave velocity indices [12], as well as evaluation of endothelial function [13].

Statistical analysis was performed using parametric and nonparametric methods depending on the data distribution. Intergroup differences were assessed using Student’s t-test or the Mann–Whitney U test, while correlation analysis was conducted using Pearson or Spearman methods [14]. Results were considered statistically significant at $p < 0.05$.

The study was conducted in accordance with the principles of the Declaration of Helsinki (2024), Good Clinical Practice (GCP), and current national legislation [15, 16]. The study protocol was approved by the Local Bioethics Committee of Petro Mohyla Black Sea National University (protocol number to be added). All participants provided written informed consent after receiving a detailed explanation of the study objectives, methods, and potential risks. Confidentiality of personal data was ensured in compliance with GDPR requirements and national standards of medical ethics.

Results. The mean age of the MS group was 52.7 ± 6.4 years, while that of the control group was 51.9 ± 5.8 years ($p > 0.05$). The gender distribution was comparable: in the MS group, 46 patients (53.5%) were women and 40 (46.5%) were men; in the control group, there were 28 women (56.0%) and 22 men (44.0%) ($p > 0.05$). Despite similar age and sex profiles, patients with MS demonstrated significantly higher anthropometric indices. Body mass index was 31.4 ± 3.8 kg/m² in the MS group versus 25.2 ± 2.6 kg/m² in controls ($p < 0.001$), and waist circumference was 104.3 ± 9.1 cm compared with 86.2 ± 7.8 cm. Systolic blood pressure was elevated in the MS group (137 ± 12 mmHg), whereas in controls it was 121 ± 10 mmHg ($p < 0.001$).

Metabolic parameters also differed markedly between groups. Fasting glucose levels in MS patients were 6.4 ± 0.7 mmol/L, insulin levels were 17.2 ± 3.1 μIU/mL, resulting in a significantly increased HOMA-IR index (4.87 ± 0.9) compared with the control group (2.1 ± 0.5; $p < 0.001$). The lipid profile revealed pronounced atherogenic changes: triglyceride levels in the MS group were 2.31 ± 0.4 mmol/L versus 1.18 ± 0.3 mmol/L ($p < 0.001$); LDL cholesterol was 4.22 ± 0.6 mmol/L versus 2.91 ± 0.5 mmol/L; HDL cholesterol was 1.01 ± 0.14 mmol/L compared with 1.46 ± 0.18 mmol/L in controls ($p < 0.001$). These findings confirmed substantial disturbances of carbohydrate and lipid metabolism, which may adversely affect cognitive functioning.

Against this metabolic background, patients with MS exhibited significantly lower cognitive performance. The mean MMSE score in the MS group was 27.1 ± 0.3, compared with 28.6 ± 0.2 in the control group ($p < 0.01$). Although both values formally fell within the normal range, they indicated early signs of cognitive decline. The more sensitive MoCA test demonstrated clearer differences: MS patients scored 23.4 ± 0.4, whereas controls scored 26.9 ± 0.3 ($p < 0.001$). The prevalence of mild cognitive impairment (MoCA < 26) was 57.0% among MS patients and only 16.0% in the control group ($p < 0.001$). The most pronounced deficits were observed in executive functions, visuospatial organization, attention, and cognitive processing speed. In the Trail Making Test, completion time in MS patients was longer by 28% in Part A ($p < 0.001$) and by 41% in Part B ($p < 0.001$), reflecting impaired cognitive flexibility and reduced processing speed. In the Digit Span test, both forward and backward recall were reduced ($p < 0.01$), indicating deterioration of working memory and executive control. Overall, these findings demonstrate a multidomain cognitive impairment profile in middle-aged patients with MS.

Vascular indices also differed significantly between groups. Carotid intima–media thickness (IMT) in MS patients was 0.79 ± 0.02 mm compared with 0.62 ± 0.01 mm in

controls ($p < 0.001$), indicating early manifestations of subclinical atherosclerosis. Endothelial dysfunction, assessed by the reactive hyperemia test, was detected in 68% of MS patients and in 22% of controls ($p < 0.001$). Both parameters showed significant correlations with MoCA scores, Trail Making Test performance, and working memory measures (r ranging from –0.32 to –0.51; $p < 0.01$), underscoring the role of the cerebrovascular component in cognitive decline. HOMA-IR, triglycerides, and LDL cholesterol demonstrated the strongest linear associations with executive functions and cognitive processing speed.

Stratified analysis revealed that the greater the number of MS components present, the more pronounced the cognitive decline ($p < 0.001$). Insulin resistance, arterial hypertension, and abdominal obesity exerted the most deleterious effects. Thus, the results indicate that already in middle age, patients with metabolic syndrome exhibit complex, multifactorial cognitive impairment closely linked to neurometabolic and vascular changes, as well as to components of systemic metabolic dysregulation.

The obtained data demonstrate that middle-aged patients with metabolic syndrome already show significant cognitive deficits of a multifactorial nature affecting several key neuropsychological domains, including global cognition, executive functions, attention, working memory, and processing speed. These alterations have a common pathophysiological basis that integrates insulin resistance, endothelial dysfunction, early cerebrovascular damage, and chronic low-grade inflammation.

Comparison with the control group showed that even modest deviations in MMSE and MoCA scores—often underestimated in routine clinical practice—may serve as markers of systemic metabolic and vascular effects on the brain. A nearly 3.5-point reduction in MoCA scores and the high prevalence of cognitive dysfunction (57.0%) among MS patients confirm that this population is at substantially increased risk of developing mild cognitive impairment. Given that MoCA is a sensitive tool for detecting early vascular-related cognitive deficits, the present findings are consistent with contemporary recommendations emphasizing the importance of early cognitive screening in MS.

Impairment of executive functions and slowing of cognitive processing, as evidenced by Trail Making Test A/B performance, support involvement of prefrontal regions and attentional networks, which are particularly vulnerable to vascular insufficiency and disturbances in insulin metabolism. Insulin in the central nervous system acts as a neuromodulator, regulating memory, attention, synaptic plasticity, and neurotrophic processes. Elevated HOMA-IR, which in our study correlated with worse MoCA and Trail Making Test results, suggests that insulin resistance may represent one of the leading mechanisms

underlying early cognitive impairment. Disrupted insulin signaling in the hippocampus and prefrontal cortex is known to promote neuroinflammation, oxidative stress, amyloid accumulation, and reduced neuronal plasticity.

Endothelial dysfunction emerged as another key factor, with a prevalence in the MS group more than three times higher than in controls. Contemporary evidence indicates that endothelial dysfunction represents an early pathogenic stage of cerebral small vessel disease, leading to impaired neurovascular coupling and chronic brain hypoperfusion. Increased IMT (0.79 mm in MS vs 0.62 mm in controls) is likewise a marker of systemic atherosclerotic remodeling. Population studies have shown that every 0.1-mm increase in IMT is associated with a 15–20% higher risk of cognitive decline. Our results therefore support the hypothesis that early vascular alterations largely account for the cognitive vulnerability observed in middle-aged patients with MS.

Importantly, not all components of metabolic syndrome exert equal effects on cognitive function. Insulin resistance, arterial hypertension, and abdominal obesity were the most influential factors—each directly affecting cerebral microcirculation. Hypertension contributes to small-vessel remodeling, reduced arteriolar compliance, and impaired cerebral autoregulation. Insulin resistance disrupts PI3K/Akt signaling, leading to diminished vasodilatory responses. Abdominal obesity initiates chronic low-grade inflammation, contributing to blood–brain barrier dysfunction.

Together, these processes create conditions for early cognitive impairment even in the absence of overt clinical symptoms. The detection of cognitive changes in middle-aged individuals highlights the importance of early identification and preventive intervention. Unlike older patients, in whom cognitive decline is often multifactorial and irreversible, substantial regression may still be achievable in this population through optimization of metabolic parameters, weight reduction, glycemic control, and blood pressure management.

It is noteworthy that differences in MMSE scores between groups were modest, whereas MoCA and executive function tests were considerably more sensitive. This aligns with the concept that MMSE is less suitable for early detection of vascular-related cognitive impairment, whereas MoCA and Trail Making Tests more accurately capture prefrontal network dysfunction and processing-speed deficits characteristic of the cerebrovascular cognitive phenotype.

Finally, cognitive deficits in the present study were not isolated phenomena but closely correlated with clinical and metabolic parameters. Increased HOMA-IR, higher IMT, reduced HDL, and elevated LDL all showed significant negative associations with cognitive domains.

This pattern reinforces the systemic nature of the pathological process and indicates that cognitive decline is an integral component of metabolic syndrome rather than an incidental comorbidity.

In light of these findings, cognitive dysfunction in MS may be regarded as an early predictor of cerebral small vessel disease and future cardiovascular events. The presence of executive and processing-speed deficits may signal incipient cerebral microangiopathy and warrants not only systematic screening but also proactive risk-factor modification.

Conclusion:

1. In middle-aged patients with metabolic syndrome (MS), a significant multidomain decline in cognitive function was identified. The mean MoCA score in the MS group was 23.4 ± 0.4 versus 26.9 ± 0.3 in controls ($t = 7.21$; $p < 0.001$), and the proportion of individuals with MoCA < 26 reached 57.0% compared with 16.0% in the control group ($\chi^2 = 21.5$; $p < 0.001$). The Trail Making Test A/B confirmed a slowing of cognitive processing: completion time was increased by 28% and 41%, respectively (t ranging from 4.9 to 6.2; $p < 0.001$).

2. Insulin resistance emerged as a key metabolic predictor of cognitive decline. HOMA-IR values in MS patients were 4.87 ± 0.9 versus 2.1 ± 0.5 in controls ($t = 15.6$; $p < 0.001$). HOMA-IR showed the strongest correlations with MoCA scores ($r = –0.48$; $p < 0.001$), Trail Making Test B ($r = 0.51$; $p < 0.001$), and Digit Span backward ($r = –0.39$; $p < 0.01$), indicating a direct impact of impaired insulin signaling on executive functions, attention, and working memory.

3. Atherogenic dyslipidemia and abdominal obesity were associated with reduced cognitive performance. Levels of triglycerides (2.31 ± 0.4 mmol/L), LDL-C (4.22 ± 0.6 mmol/L), and low HDL-C (1.01 ± 0.14 mmol/L) demonstrated significant correlations with MoCA scores (r from –0.28 to –0.41; $p < 0.01$), Trail A/B performance (r from 0.31 to 0.44; $p < 0.01$), and working memory (r from –0.25 to –0.38). Waist circumference also correlated with cognitive decline ($r = –0.34$; $p < 0.01$).

4. Arterial hypertension and vascular stiffness had a substantial impact on the cognitive profile. Systolic blood pressure in the MS group was 137 ± 12 mmHg versus 121 ± 10 mmHg in controls ($p < 0.001$). Carotid intima–media thickness (CIMT) was increased to 0.79 ± 0.02 mm versus 0.62 ± 0.01 mm ($t = 6.45$; $p < 0.001$). CIMT correlated with MoCA ($r = –0.36$; $p < 0.01$) and Trail B performance ($r = 0.42$; $p < 0.001$). Endothelial dysfunction was detected in 68% of MS patients compared with 22% of controls ($\chi^2 = 28.9$; $p < 0.001$), confirming the involvement of cerebral small vessel disease mechanisms.

5. The number of metabolic syndrome components exerted a cumulative effect. Patients with 4–5 MS components had MoCA scores lower by 3.8 points ($p < 0.001$) and 36% longer completion time on Trail Making Test B than those with 3 components. The number of MS components correlated linearly with the severity of cognitive deficit ($r = –0.44$; $p < 0.001$).

6. The findings indicate that cognitive decline in metabolic syndrome represents an integrated reflection of insulin resistance, systemic inflammation, cerebrovascular dysfunction, and early microangiopathy. The observed correlations between metabolic, vascular, and cognitive parameters underscore the systemic nature of the pathological process and its pathogenetic coherence.

7. The results support the need for the implementation of routine cognitive screening in middle-aged patients with MS. Given the high correlation coefficients (up to $r = –0.51$), significant between-group differences (t ranging from 4.0 to 7.2; χ^2 up to 29.0; $p < 0.001$), cognitive tests should be regarded as an early tool for risk stratification of cerebrovascular complications.

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