Cerebrometabolic Health

Marine M. Tanashyan, Ksenia V. Antonova

Russian Center of Neurology and Neurosciences, Moscow, Russia

Abstract

The article addresses the global challenge of nervous system damage and cerebral consequences in metabolic disorders. It introduces the concept of impaired cerebral metabolic health as a progredient progression of cerebral dysfunction. Delineating the sequence of changes at all stages underscores the importance of targeted timely interventions to ensure preventive measures and treatment of cerebral vascular diseases.

Keywords: *stroke; cerebrovascular disease; cognitive impairment; obesity; diabetes mellitus; cerebrometabolic health*

Source of funding. The study was not supported by any external sources of funding.

Conflict of interest. The authors declare no apparent or potential conflicts of interest related to the publication of this article.

For correspondence: 80, Volokolamskoye shosse, Moscow, Russia, 125367. Russian Center of Neurology and Neurosciences. E-mail: kseniya.antonova@mail.ru. Ksenia V. Antonova

For citation: Tanashyan M.M., Antonova K.V. Cerebrometabolic health. *Annals of Clinical and Experimental Neurology*. 2025;19(2):62–73
DOI: https://doi.org/10.17816/ACEN.1359
EDN: https://elibrary.ru/TJXFNR

Received 07.05.2025 / Accepted 16.05.2025 / Published 30.06.2025

Цереброметаболическое здоровье

М.М. Танашян, К.В. Антонова

Российский центр неврологии и нейронаук, Москва, Россия

Аннотация

В статье освещена глобальная проблема поражения нервной системы и церебральных последствий при метаболических расстройствах. Представлена концепция нарушения цереброметаболического здоровья как прогредиентное прогрессирование мозговой дисфункции. Выделение последовательности изменений на всех этапах определяет важность и таргетность своевременного вмешательства для обеспечения мер профилактики и лечения сосудистых заболеваний головного мозга.

Ключевые слова: *инсульт; цереброваскулярные заболевания; когнитивные нарушения; ожирение; сахарный диабет; цереброметаболическое здоровье*

Источник финансирования. Авторы заявляют об отсутствии внешних источников финансирования при проведении исследования.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Адрес для корреспонденции: 125367, Россия, Москва, Волоколамское шоссе, д. 80. Российский центр неврологии и нейронаук. E-mail: kseniya.antonova@mail.ru. Антонова К.В.

Для цитирования: Танашян М.М., Антонова К.В. Цереброметаболическое здоровье. *Анналы клинической и экспериментальной неврологии*. 2025;19(2):62–73.
DOI: https://doi.org/10.17816/ACEN.1359
EDN: https://elibrary.ru/TJXFNR

Поступила 07.05.2025 / Принята в печать 16.05.2025 / Опубликована 30.06.2025

Introduction

Preserving the population, strengthening public health, and enhancing people's well-being are strategic national priorities. A key objective is to increase the healthy and active life expectancy of Russia's population. To achieve these critical goals amid rapidly changing modern conditions, it is imperative to promptly implement effective healthcare measures. Advances in medical science, emerging next-generation devices and platforms, and biomedical and cognitive technologies are essential for addressing population preservation challenges in line with contemporary demands.

Combating the global leading cause of death — cardiovascular diseases, among which cerebrovascular disorders (CVD) hold significant and distinct prominence — is a priority task for preserving public health. CVDs are characterized not only by high rates of disability and mortality but also by neurocognitive disorders that can lead to loss of independence. Cognitive impairments and dementia have emerged as public health priorities requiring national-level action.

CVDs represent a group of conditions that constitute not only a major medical but also a socioeconomic issue. Preventive measures for CVD, implemented at both population and individual levels, should target key metabolic risk factors — drivers of vascular disease progression, including acute stroke, chronic CVDs, cerebral microangiopathy, and associated cognitive disorders [1–4].

The link between metabolic and cerebral disorders is well-established; however, the systemic integration of the broad spectrum of brain diseases (primarily vascular) and metabolic disturbances remains unresolved. The high incidence and mortality rates of CVDs, coupled with the burden of stroke and cognitive impairment (CI), raise numerous unresolved questions. The developed ***concept of cerebrometabolic health*** reflects the interplay of metabolic risk factors, vascular system integrity, and the structural and functional state of the brain. In cases of impaired cerebrometabolic health, particularly among individuals with adverse lifestyle factors, there is a pressing need to understand developmental mechanisms and define preventive and therapeutic strategies tailored to the stage of disease progression.

Spectrum of cerebral metabolic disorders

There are a number of factors or underlying causes influencing chronic diseases. These factors reflect the primary driving forces behind social, economic, and cultural changes, primarily globalization, whose effects on human health are mediated through disruptions in homeostasis. Thus, the complex interplay of socioeconomic, demographic, and environmental changes affecting nations underpins the observed syndemia of cerebrometabolic disorders, directly impacting quality and longevity of life.

Global consequences of syndemic cerebral and metabolic disorders

Findings from epidemiological studies and trends in absolute stroke rates over the past three decades underscore the escalating significance of cerebrometabolic health concerns. According to the Global Burden of Diseases, Injuries, and Risk Factors[1] Study (GBD), in 2021, stroke ranked as the third leading cause of death — 7.3 million cases (95% confidence interval 6.6–7.8; 10.7% (9.8–11.3) of all deaths) — after ischemic heart disease and COVID-19, and the fourth leading cause of disability-adjusted life-years (DALYs) (160.5 million (147.8–171.6) DALYs; 5.6% (5.0–6.1) of all DALYs). A substantial rise in DALY values was linked to metabolic factors. Among stroke risk factors, high body mass index (BMI) exhibited the most marked increase — 88.2% (53.4–117.7). Stroke burden correlated with elevated fasting plasma glucose levels — 32.1% (26.7–38.1), diets rich in sugar-sweetened beverages — 23.4% (12.7–35.7), physical inactivity — 11.3% (1.8–34.9), high systolic blood pressure — 6.7% (2.5–11.6), and environmental contributors. Metabolic risk-associated strokes accounted for 68.8% (57.6–77.5) of all stroke cases [1]. These risk factors are modifiable and potentially preventable, highlighting the critical need for their stratification and management to mitigate stroke burden.

Cognitive impairment. The domain of national strategic interests has clearly defined objectives for reducing the burden of age-associated disorders: preventing and treating CI and sensory disorders, advancing preventive medicine, and promoting healthy and active longevity. The primary causes of CI in older age include various neurodegenerative diseases, CVDs, and dysmetabolic disorders. The number of people with dementia is projected to increase globally from 57.4 million (50.4–65.1) cases in 2019 to 152.8 million (130.8–175.9) by 2050. Compelling evidence has been identified supporting the importance of potentially modifiable risk factors for dementia. Characterizing the distribution and magnitude of the projected growth is critical for planning countermeasures. The predicted rise in dementia prevalence (2019–2050) is attributed to three risk factors included in the GBD Study: high body mass index, elevated fasting plasma glucose levels, and smoking. The growing number of people living with dementia underscores the need for public health planning efforts, including multifaceted approaches and scaled-up interventions to address modifiable risk factors.

Elucidating the pivotal role of metabolic disorders in cerebral dysfunction provides a foundation for developing novel approaches to combat neurocognitive disorders associated with impaired cerebrometabolic health.

Metabolic disorders such as diabetes mellitus (DM), arterial hypertension (AH), and obesity represent significant and growing challenges for global healthcare systems [6, 7]. The pathophysiological foundations of these metabolic diseases are interconnected and serve as major risk factors for circulatory system diseases — the leading cause of death worldwide [8, 9]. The global burden of five common metabolic diseases has been revealed [6, 10]: type 2 diabetes mellitus (T2DM), AH, hypercholesterolemia, obesity, and non-alcoholic fatty liver disease (NAFLD) [11–13]. These metabolic disorders often coexist and exert cumulative health impacts [7,13]. In 2021, among the five prevalent metabolic diseases, AH carried the greatest

[1]Global burden of disease, injuries, and risk factors study.
URL: https://www.healthdata.org/research-analysis/about-gbd

burden (226 (259–9190) million DALY), while T2DM (75 (63–90) million DALY) caused substantially greater disability than NAFLD (3.67 (2.90–4.61) million). The significance of these metabolic diseases has increased over the past three decades, with the global consequences of T2DM and obesity predominating, while the burden impact of AH and hypercholesterolemia has diminished. Despite medical treatment and preventive interventions, there has been a sharp rise in fatal outcomes and mortality associated with metabolic diseases, underscoring the need for coordinated measures [5].

Changes in diet and physical activity often result from environmental and social transformations driven by shifts in sectors such as healthcare, agriculture, transportation, urban planning, food production and distribution, marketing, and industrial technologies. Weight gain and obesity driven by these changes lead to global disruptions to public health.

Obesity is a pandemic of the early 21st century. It affects 39–49% of the global population and is associated with CVD. The prevalence of obesity has tripled since 1975, with 30% of the world's population currently having obesity or overweight [1]. Russia follows global trends: the population-average BMI is 27.6 kg/m^2, obesity is more common in women, its prevalence increases with age, and abdominal obesity is becoming more prominent [14]. According to a screening of the working-age population (40–59 years) conducted by the Russian Center of Neurology and Neurosciences, obesity was observed in one-third of participants, reaching 67% when combined with overweight [15].

Overweight and obesity are associated with higher rates of overall acute stroke and ischemic stroke (IS) in particular, in both men and women. In our study group of IS patients, 7% had normal BMI, 40% were overweight (25.0–29.9 kg/m^2), and 53% had obesity: 34% with grade 1 (BMI 30.0–34.9 kg/m^2), 13% with grade 2 (BMI 35.0–39.9 kg/m^2), and 6% with grade 3 (BMI $\geqslant$ 40 kg/m^2). The BMI values in IS patients with T2DM were 32.7 (29–36) kg/m^2 versus 29 (27–31) kg/m^2 in non-diabetic patients.

Furthermore, overweight and obesity are associated with increased risk of hemorrhagic stroke in men [16]. The prevalence of obesity in stroke patients ranges from 18% to 50% [17, 18]. Notably, obese patients who survive their first stroke show lower long-term post-stroke mortality rates — the obesity paradox [19, 20]. However, the obesity paradox effect in stroke outcomes may vary depending on the pathogenetic subtype of IS [21]. This paradox was observed when using BMI as a criterion but not detected with indices such as waist-to-hip ratio and body fat percentage [22], highlighting the importance of considering obesity phenotype in stroke prognosis.

Excess adipose tissue (both general and visceral) is associated with reduced cognitive performance after adjustment for cardiovascular risk factors, education level, and cerebral vascular lesions [23]. In evaluating the impact of adipose tissue on microangiopathy through a cross-sectional study of over 6,000 volunteers, it was found that elevated BMI itself is not associated with a higher burden of cerebral microangiopathy; however, markers of metabolic dysregulation (particularly elevated blood pressure and hyperglycemia) are significant risk factors for microangiopathy [24], confirming the importance of a comprehensive approach to cerebral metabolic health.

It is abdominal obesity, associated with metabolic alterations, that increases the CVD risk. Current research findings suggest that BMI is insufficiently effective in assessing the risk of comorbid conditions, including CVD. Several alternative approaches to evaluating body fat mass in patients have been proposed [25]. The detrimental effects of abdominal obesity are linked to dysfunction of visceral adipose tissue, which correlates with vascular disease risk factors such as insulin resistance, systemic inflammation, dyslipidemia, and AH [18].

Our own study using bioimpedance analysis revealed that patients with CVD differ in body composition from individuals without CVD [26]. In those patients, both anthropometric measurements and instrumental studies demonstrated an increase in markers of visceral fat redistribution. Specifically, increased abdominal fat area (163.4 ± 63.5 *vs.* 136.34 ± 53.4 cm^2; $p = 0.039$), waist circumference (106.7 ± 18.0 *vs.* 98.2 ± 13.3 cm; $p = 0.017$), and waist-to-hip ratio (1.02 ± 0.1 *vs.* 0.95 ± 0.08; $p < 0.001$) were observed, indicating abdominal obesity despite no significant differences in BMI assessment. Visceral fat redistribution, which contributes to metabolic disorders, was associated with a higher prevalence of AH, T2DM, and blood lipid profile abnormalities in CVD patients [26].

The increased prevalence of metabolic disorders elevates the likelihood of cerebrovascular events. A meta-analysis of 87 studies demonstrated an elevated risk of stroke (RR = 2.27 [1.80–2.85]) [27] and stroke recurrence (RR = 1.46 [1.07–1.97]; $p = 0.02$) [28]. Individuals with $\geqslant$ 3 components of metabolic syndrome have an increased overall stroke risk (RR = 1.29 [1.09–1.52]) and ischemic stroke risk (RR = 1.31 [1.05–1.63]) [29]. A heightened risk of cognitive impairment progression — from mild deficits to dementia — has also been noted [30].

Our multiyear research cycle investigating clinical features of both acute and chronic forms of CVD with various metabolic syndrome manifestations revealed their more pronounced and accentuated severity. Furthermore, not only more profound neurological impairments were observed, but also insufficient functional recovery with poorer outcomes in sensory and speech disorders, which may affect patients' rehabilitation potential [31–38].

Diabetes mellitus (DM) is a major global healthcare challenge due to its epidemic growth rates and the associated medical and social burden caused by severe diabetic complications, risks of disability, and premature mortality in patients [39]. According to the International Diabetes Federation[2], DM is one of the fastest-growing global health emergencies of the 21st century. By 2024, the global number of patients with DM aged 20–79 years reached 588.7 million, exceeding earlier projected growth rates, with an anticipated near-doubling to 852.5 million (a 45% increase) by 2050. Russian national statistics report a 74.5% rise in DM cases between 2009 and

[2] IDF Diabetes Atlas 2025. URL: https://diabetesatlas.org/resources/idf-diabetes-atlas-2025/

2023 [40]. Clinical and epidemiological monitoring of DM in Russia revealed that the target glycated hemoglobin (HbA1c < 7%) level is achieved in only 42% patients with T2DM, while effective blood pressure control is attained in 60% [41].

Numerous large-scale epidemiological studies have established DM as a significant independent risk factor for stroke [42]. A multidimensional palette model conceptualizes DM as the cumulative effect of multiple factors and identifies DM subcategories. Within cluster analyses, the risk of circulatory system diseases and stroke is linked to mild, age-related diabetes [45]. Stratification of heterogeneous DM patient groups may help identify high-risk cohorts requiring enhanced monitoring and pharmacological interventions to prevent stroke.

Among patients with IS, those with DM account for up to 33%. These patients are generally younger and have more comorbidities [44, 45]. Even after controlling for all risk factors, DM increases stroke risk by 22% in patients under 55 years; having more risk factors outside target ranges further elevates stroke likelihood, peaking at 6.23-fold in individuals under 55 years. The strongest predictors of stroke include elevated glycated hemoglobin (HbA_{1c}), systolic blood pressure, longer DM duration, low physical activity, and atrial fibrillation. Elevated HbA_{1c} is the most potent predictor of stroke [46]. Post-stroke CI rate is 5.8 times higher in T2DM patients (OR = 5.83 [2.07–16.41]) [47]. Concurrent DM increases the risk of recurrent stroke (OR = 1.50 [1.36–1.65]) [48]. The likelihood of recurrent events is equally high in prediabetes and DM, suggesting vascular involvement even at early stages of carbohydrate metabolism disorders [49].

DM affects not only the risk but also the course and outcome of stroke. Studies conducted at the Russian Center of Neurology and Neurosciences demonstrated significantly worse hospital-stage outcomes in stroke patients with DM compared to those without DM: higher NIH Stroke Scale scores (6 [4–10] *vs.* 4 [1–8]; $p = 0.03$), more frequent lack of improvement or progression of neurological deficits (21.6% *vs.* 7%; $p = 0.02$), and less frequent minor improvement (13.7% *vs.* 4.7%; $p = 0.004$). Functional independence recovery outcomes were also poorer in patients with T2DM, as evidenced by higher modified Rankin Scale scores (3 [1–4] *vs.* 2 [0–3]; $p = 0.02$) and a lower proportion achieving 0–2 points (46% *vs.* 72%), underscoring the social significance of metabolic comorbidity in stroke management [34, 50].

Our data indicate that acute stroke in patients with T2DM is accompanied by hyperglycemia (9.1 [7.1–12.0] mmol/L) and elevated HbA_{1c} levels (7.8% [6.8–9.6]), with 34% of patients showing values ⩾8%, highlighting the role of poor glycemic control in CVD pathogenesis and emphasizing the importance of its correction for prevention [51].

Both hyper- and hypoglycemia, as well as advanced glycation end product (AGE) accumulation, have been shown to negatively affect prognosis and recovery in stroke patients. Parameters such as diabetes duration, HbA_{1c} levels, and glycemia were statistically significant predictors of greater disability. The likelihood of unfavorable stroke outcomes (mRS ⩽ 3) increased with HbA_{1c} ⩾ 7%, confirming the importance of achieving glycemic control targets. An algorithm for assessing carbohydrate metabolism and predicting outcomes in patients during the hyperacute stroke phase has been developed [32, 50].

Metabolic disorders influence CI. Risk factors for CI in DM include the following groups (including genetic ones):
- conventional (advanced age, low education level, depression, sedentary lifestyle, smoking, family history);
- diabetes-associated (hypo- and hyperglycemia, hyperinsulinemia, retinopathy, nephropathy, longer DM duration);

vascular (AH, dyslipidemia, stroke, coronary artery disease, atherosclerotic lower extremity artery disease);
- genetic (ApoE ε4 allele, haptoglobin genotype 1-1, and Gly/Ser genotype of the receptor for advanced glycation end products) [52].

Our study revealed a pattern of changes in CVD and T2DM, characterized by concurrent disturbances in carbohydrate metabolism and neurocognitive dysfunction accompanied by neurophysiological and neuroimaging changes. This comorbidity is associated not only with memory and attention impairments but also with significant executive brain function deficits, while regulatory deficits primarily manifest as mental rigidity and emotional disturbances and volitional disorders. The quality of glycemic control influences cognitive function assessment outcomes. We identified not only an interrelationship between clinical, neurophysiological, and metabolic characteristics but also the potential for diagnosing subclinical manifestations of impaired CNS function in patients with both chronic CVD and DM. The particular importance of early detection and therapy of cognitive impairment in this patient group is underscored by the fact that DM, more than any other disease, requires active patient participation in disease control and treatment [53].

Treatment adherence issues are critical for achieving clinical outcomes, particularly in patients with chronic diseases. Patients with cerebroal metabolic disorders demonstrated incomplete or low adherence across various aspects of therapeutic interventions. Specifically, low treatment adherence was observed in 10.3% of patients without DM and 34.4% of those with T2DM ($p = 0.001$). Obesity parameters, assessed not only by BMI but also by waist circumference, showed significant inverse associations with adherence to lifestyle modifications and overall treatment adherence. According to the developed model for identifying low compliance, the concurrent T2DM and AH are expected to reduce adherence to medical management in over 20% of patients. A multifactorial relationship was identified between treatment adherence aspects, the clinical course of vascular disease, and the presence of metabolic risk markers, forming a vicious cycle: inadequate metabolic control → CVD → CI → low adherence [54].

In the context of age-related brain disorders, it should be emphasized that DM represents a model of accelerated cerebral aging, further increasing the risk of age-related degenerative and vascular diseases of the nervous system. One surrogate biomarker of aging may be the white matter age gap, defined as the difference between instrumentally assessed white

matter age (based on diffusion-weighted MRI) and real age. Among all risk factors, T2DM showed the strongest association with an increased gap (1.39 years; $p < 0.001$), followed by AH and smoking. T2DM may be associated with diffuse brain atrophy, altered functional connectivity, and reduced cerebral perfusion.

Cerebral artery atherosclerosis represents the leading pathological process within the spectrum of CVD subtypes. Findings from a series of studies conducted at the Russian Center of Neurology and Neurosciences confirmed a higher frequency of cerebral atherosclerosis progression in patients with T2DM. Ultrasonographic evaluation of the brachiocephalic arteries demonstrated that the prevalence of multiple vascular territories involvement is significantly higher in patients with combined cerebral metabolic disorders [35]. Progression of atherosclerosis in the internal carotid artery system is further associated with marked changes in vascular wall inflammatory biomarkers and neoangiogenesis – including lipoprotein-associated phospholipase A2, tumor necrosis factor-α, and vascular endothelial growth factor – as well as elevated blood glucose levels. In turn, progression of atherosclerotic lesions in the carotid system was accompanied by new or worsening pre-existing neurological symptoms in 50% of cases [36].

Metabolic disorders correlate with an aggressive atherosclerotic process, evidenced by a predominance of atherothrombotic stroke subtypes and high-grade cerebral artery stenoses. Combined assessment of carbohydrate and lipid metabolism using the triglyceride-glucose index in patients with acute/chronic stroke revealed not only reduced insulin sensitivity in this cohort but also highlighted the role of glucolipotoxicity in hemodynamically significant stenosis formation, CVD progression, and prognosis [35, 37, 50]. A prospective study of CVD patients, focusing on cases with > 50% stenosis in one internal carotid artery, found metabolic syndrome to be more frequently associated with high-grade stenoses (70–99%). Among patients with T2DM and symptomatic stenoses, 87.5% exhibited high-grade stenoses. Ultrasound characteristics in T2DM-comorbid patients predominantly revealed hyperechoic atherosclerotic plaques, including those with calcified areas.

A series of studies on cerebral atherosclerosis has proposeda biomarker-based model for assessing atherogenic potential in patients with ischemic cerebrovascular events and comorbid T2DM. This model incorporates lipid profile markers, endothelial dysfunction indicators, inflammatory markers, hemostasis parameters, and adipokines [55, 56]. Proatherogenic markers include levels of highly sensitive hyperatherogenic small dense low-density lipoprotein (LDL) subfractions, total cholesterol, plasminogen activator inhibitor-1, NO_2-, NO_3-, endothelin-1, monocyte chemoattractant protein-1, vascular endothelial growth factor A, platelet-derived growth factor BB, tumor necrosis factor-α, interleukin (IL)-1β, C-reactive protein, and IL-6. The anti-atherogenic category comprises lipoprotein(a), high-density lipoprotein, nitric oxide, tissue plasminogen activator, and adiponectin. This biomarker-based technology for evaluating cerebral atherosclerosis progression is used to optimize diagnostic approaches and therapeutic strategies in patients with cerebral metabolic disorders [55, 56]. The ongoing search for novel biomarkers amid the epidemic rise of metabolic diseases aims to stratify high-risk patients and holds clinical potential.

Morphological studies of atherosclerotic plaque biopsy specimens obtained during prophylactic carotid endarterectomy provided critical evidence of the adverse effects of comorbid metabolic factors on cerebral atherosclerosis progression. Histopathological analyses frequently reveal critical atherosclerotic stenosis, active atherogenesis, predominant large atheromatous foci with abundant lipophages in plaque composition, and focal fibrosis with calcification in the arterial tunica media [57].

Underlying Mechanisms of Cerebral Metabolic Disorders

The concurrent epidemic increase in the prevalence of metabolic disorders, obesity, and DM inevitably undermines global efforts to combat CVD.

Current evidence suggests that brain is a multifunctional endocrine organ that regulates neuroendocrine processes, coordinating systemic development and maintaining body homeostasis. Obesity represents a continuum of initially adaptive changes that transition to pathological alterations as the disease progresses, triggered by disrupted signaling cascades in the setting of excessive caloric intake. Insulin plays a pivotal role in these processes. Cerebral insulin signaling mediates complex interorgan crosstalk, orchestrating nutrient distribution through regulation of appetite, lipolysis, triglyceride secretion and uptake, amino acid metabolism, thermogenesis, and hepatic glucose production. Ultimately, this system protects against ectopic lipid deposition, lipotoxicity, and hyperglycemia [58–60].

Hypoglycemia prevention is key to survival. Brain insulin resistance can be understood as a physiological adaptation to maintain euglycemia by enhancing lipolysis and increasing hepatic glucose production—a process critical for survival under nutrient-deficient conditions. Overeating rapidly induces brain insulin resistance, which acts as a key driver of metabolic diseases and T2DM [60].

Insulin resistance, chronic hyperglycemia, and dyslipidemia trigger a cascade of changes, including the formation of atherogenic low-density lipoproteins, advanced glycation end products, and activation of proinflammatory signals that affect the arterial wall, initiating and promoting atherosclerotic lesions. Numerous components characterizing metabolic dysfunction lead to a wide range of consequences, including blood-brain barrier disruption, neuroinflammation, vascular pathology, neurodegeneration, and CI [61, 62]. Brain damage is associated with inflammatory processes, including meta-inflammation – a chronic systemic disorder caused by obesity. This pathway serves as the primary pathophysiological mechanism leading to the development, progression, and thrombotic complications of atherosclerosis and vascular disorders [63]. In meta-inflammation, external or endogenous factors may act by stimulating membrane or cytoplasmic receptors of monocytes, macrophages, neutrophils, or dendritic cells. These

factors can induce inflammasome oligomerization and activate the NLRP3 [64]. IL-1β and IL-18, generated through NLRP3-caspase activation, enter a self-amplifying loop and also induce macrophage production of IL-6. IL-6 stimulates hepatocytes to produce C-reactive protein, fibrinogen, and plasminogen activator inhibitor-1, releasing them systemically and mediating thrombotic propensity. IL-6 directly potentiates another prothrombotic pathway mediated by the JAK1/TYK2 membrane receptor, leading to thrombocytosis and procoagulant changes [65].

The primary functional load of the hemostatic system lies in the microvascular bed, including cerebral vessels. The critical role of prothrombotic changes in CVD has been demonstrated in fundamental studies from the Russian Center of Neurology and Neurosciences [66–71]. In patients with acute/chronic CVD accompanied by metabolic syndrome, significant disturbances are observed in platelet and plasma hemostasis components, altered blood microrheological parameters (both baseline and dynamic), elevated blood viscosity, fibrinogen, hematocrit, platelet aggregation activity, and reduced erythrocyte deformability [31, 72].

Hyperglycemia significantly contributes to these hemorheological and hemostatic changes [73, 74]. Increased advanced glycation end product formation activates platelet hemostasis, suppresses fibrinolysis, and promotes prothrombogenic blood potential. AGE levels correlate positively with ADP-induced platelet aggregation (r = 0.4176) and negatively with fibrinolytic activity (r = –0.426117) and fibrinolytic index (r = –0.36) [73].

We confirmed the significance of excessive intra-abdominal fat deposition, which is pathogenetically linked to meta-inflammation, in shaping hemorheological and hemostatic system changes in patients with CVD [26]. Increased visceral fat volume not only negatively impacts metabolic parameters but is also associated with prothrombogenic blood changes. Visceral fat area showed significant correlations with fibrinogen levels (r = 0.83), von Willebrand factor (r = 0.250), factor VIII (r = 0.321), epinephrine-induced platelet aggregation (r = 0.780), and protein S (r = 0.532), while demonstrating inverse correlations with tissue plasminogen activator levels (r = –0.370) and the tissue plasminogen activator/plasminogen activator inhibitor ratio (r = –0.3). The obtained data on hemorheological and hemostatic changes in CVD associated with body composition alterations highlight the role of abdominal obesity in prothrombotic and procoagulant changes in CVD patients [26]. The identified correlations between hemostasis parameters and adipose tissue characteristics reveal mechanisms through which risk factors contribute to the CVD.

Functional and structural cerebral impairments under metabolic load

When damaging stimuli become chronic, as seen in obesity, metabolic syndrome, and T2DM, a persistent reparative process with tissue remodeling occurs. The brain undergoes astrogliosis [61]. Metabolic neuroinflammation is a chronic aseptic inflammatory process characterized by systemic changes involving elevated proinflammatory cytokines (IL-1β and IL-18), microglial activation, and dysregulated NLRP3 inflammasome formation [75]. Hypothalamic neuroinflammation causing gliosis and neuronal death [75] may stem from leptin and insulin effects, as well as factors acting through the pro-opiomelanocortin system [76]. In turn, hypothalamic neuroinflammation modulates satiety regulation, thereby promoting obesity [77], creating a vicious cycle of cerebral and metabolic disturbances. Prolonged neuroinflammation disrupts existing protective barriers, leading to neurodegenerative changes. Individuals with obesity face increased risks of CI, vascular dementia, Alzheimer's disease, as well as Parkinson's and Huntington's diseases [78].

The results of studies conducted at the Russian Center of Neurology and Neurosciences demonstrate the negative impact of chronic hyperglycemia on the white matter of the cerebral hemispheres, mediated through mechanisms of direct damage to brain tissue and microcirculatory vessels [79]. The contribution of insulin resistance and glucolipotoxicity to the clinical manifestation of structural brain changes in chronic CVD has been established, and the concept of an adverse cerebral metabolic profile has been developed, encompassing clinical, neuroimaging, and laboratory characteristics of patients.

Cerebral metabolic health

A series of studies, collectively involving over 5,500 observations of CVD patients, has provided a detailed investigation of its various aspects in the context of metabolic disorders. The study revealed and examined interconnections between obesity, T2DM, metabolic syndrome, and cerebral macro- and microvascular damage, prothrombotic changes, clinical course, and prognosis of acute stroke and chronic CVD, identifying a set of biomarkers for vascular and cerebral injury. Analysis of the current state of neuroscience and the findings of our own research enabled the synthesis of a unified conceptual approach to the issue of cerebral metabolic health.

In cerebral metabolic disorders, the development and progression of brain lesions are associated with the involvement of vessels of various calibers, alterations in hemorheology and hemostasis systems, meta-inflammation and neuroinflammation, and neurodegeneration, which are linked to excessive adipogenesis, dyslipidemia, dysglycemia, and impaired permeability of the blood-brain and blood-nerve barriers, ultimately resulting in the CVDs, cerebral microangiopathy, and CI, with potential involvement of the peripheral nervous system.

A concept of a bidirectional relationship between cerebral and metabolic disorders has been established. Brain functioning is inextricably linked to metabolism; signaling pathways associated with the supply and accumulation of energy substrates influence both the nervous and vascular systems, whereas mechanisms underlying metabolic and neurological disorders are closely intertwined. Therefore, instead of viewing CVD and metabolic diseases as separate processes, it is essential to assess their mutual influence within a unified paradigm. The development of methods for

preventing and treating CVD requires adopting a new strategic concept of cerebral metabolic health, within which the association between metabolic disorders and CVD is examined. The significance of cerebral metabolic health impairment consequences for the healthcare system and society necessitates comprehensive strategies encompassing both population-wide and personalized prevention at different stages of human life.

The concept of cerebral metabolic health defines the interaction of a complex of metabolic risk factors, functional and organic changes in cerebral macro- and microvasculature, and brain structures, which influences the incidence of acute and chronic cerebrovascular events and cognitive disorders, determines worse outcomes and mortality. The implementation of this term reflects the strong interrelationship between the mechanisms of metabolic and cerebral disorders and serves to adjust both population-level and patient-centered treatment strategies for brain diseases, as well as primary and secondary prevention measures.

Disorders of cerebral metabolic health represent a progressive impairment of central nervous system activity, initiated by adverse environmental influences under conditions of genetic predisposition, excessive intake of energy substrates, and disruption of central energy balance regulation, leading to excessive adipose tissue deposition with increased systemic and cerebral insulin resistance, neuroinflammation, and oxidative stress. The synergistic damaging effects of metabolic risk factors (AH, dyslipidemia, and hyperglycemia) have a unidirectional pathway and manifest through combined damage to cerebral arteries of various calibers alongside increased thrombogenic potential. Progression of the process leads to acute and chronic cerebrovascular events, cerebral microangiopathy, neurocognitive disorders, and ultimately to disability and/or death. The concept of staged disturbances in cerebral metabolic health reflects the phasic nature of the pathophysiological process, the progressive advancement of disorders leading to cerebral dysfunction, and underscores the importance of targeted interventions at all stages for CVD prevention and treatment (Fig. 1, Table 1).

The concept of cerebral metabolic health serves to form a comprehensive picture of diverse metabolic processes associated with the nervous system dysfunction. Primarily, this applies to CVDs due to their higher prevalence and severe consequences. At the same time, the methodological advantages of this approach – including integrative strategies, multidisciplinarity, diversification of preventive measures, stepwise diagnostics, and therapy personalization – inevitably extend to other socially significant disorders of the nervous system (i.e., neurodegenerative, demyelinating, autoimmune, etc.).

Conclusion

The syndemia of obesity and DM underlies the progressive rise in CVD, impacting key mechanisms of CVD pathogenesis. The lack of significant success in preventing the spectrum of CVD amid an aggressive increase in metabolic disorders necessitates a revision of approaches to this issue at the national level. Both high-risk strategies and population-wide preventive medicine strategies should complement each other [80].

Promising directions for studying cerebral metabolic health include:
- prevention of CVDs in individuals with disorders of hemostasis, and carbohydrate and lipid metabolism;
- multisystem interrelationships between cerebral metabolic disorders and other endocrine organs: effects of oral contraceptives and menopausal hormone therapy on stroke development, hypogonadism, thyroid diseases, dysregulation of the hypothalamus-pituitary-adrenal axis, etc.;
- development of measures to preserve cognitive health (studies of innovative agents with proposed metabolic and neuroprotective mechanisms of action).

Approaches to overcoming the objective complexity of cerebral metabolic disorders include:
- development of algorithms for multidisciplinary collaboration to preserve cerebral metabolic health in the Russian population;

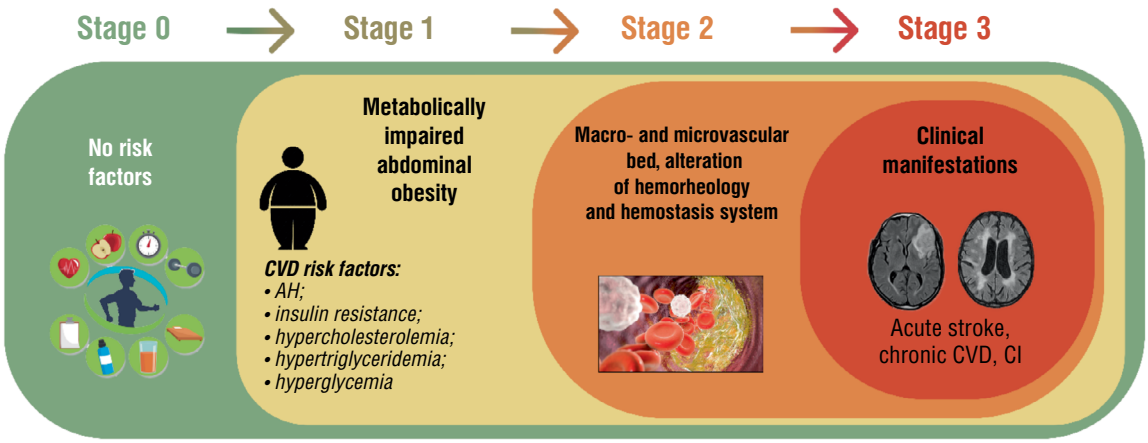

Fig. 1. Sequence of CVD development.

Table 1. Cerebral metabolic disorders

Stage	Description	Characteristic
Stage 0	No metabolic disorders or CVD symptoms	No risk factors: • normal waist circumference (considering race and sex); • BMI < 25 kg/m^2; • no carbohydrate metabolism disturbances (no DM or pre-diabetes) • no dyslipidemia; • no AH
Stage 1	CVD risk factors stage	Stage of metabolically impaired obesity — obesity + risk factors: • abdominal obesity: waist circumference ⩾ 88/102 cm in women/men (for Asians ⩾ 80/90 cm in women/men) plus 2 or more criteria: - AH; - insulin resistance; - hypercholesterolemia; - hypertriglyceridemia; - hyperglycemia: DM or prediabetes (impaired fasting glycemia/impaired glucose tolerance)
Stage 2	Macro- and microangiopathy stage	Brachiocephalic artery atherosclerosis, intracranial atherosclerosis, cerebral microangiopathy, changes in the hemorheology and hemostasis system
Stage 3	Symptomatic CVD	Acute stroke, chronic CVD, CI

- exploration of innovative approaches to cerebroprotection through advancements in brain metabolism research, including artificial intelligence, neuromodulation, and other cutting-edge technologies.

The challenge of preserving cerebral metabolic health and quality of life in society is acquiring a population-wide significance, necessitating the integration of population-based and personalized measures for the prevention and treatment of brain diseases.

References | Список источников

1. GBD 2021 Stroke Risk Factor Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet Neurol.* 2024;23(10):973–1003. doi: 10.1016/S1474-4422(24)00369-7
2. GBD 2016 Dementia Collaborators. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* 2019;18(1):88–106. doi: 10.1016/S1474-4422(18)30403-4
3. Li X, Feng X, Sun X, Hou N, et al. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990–2019. *Front Aging Neurosci.* 2022;14:937486. doi: 10.3389/fnagi.2022.937486
4. Zhang H, Zhou XD, Shapiro MD, et al. Global burden of metabolic diseases, 1990-2021. *Metabolism.* 2024;160:155999. doi: 10.1016/j.metabol.2024.155999
5. GBD 2019 Dementia Forecasting Collaborators. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. *Lancet Public Health.* 2022;7(2):e105–e125. doi: 10.1016/S2468-2667(21)00249-8
6. Chew NWS, Ng CH, Tan DJH, et al. The global burden of metabolic disease: Data from 2000 to 2019. *Cell Metab.* 2023;35(3):414.e3–428.e3. doi: 10.1016/j.cmet.2023.02.003
7. Chong B, Kong G, Shankar K, et al. The global syndemic of metabolic diseases in the young adult population: a consortium of trends and projections from the Global Burden of Disease 2000–2019. *Metabolism.* 2023;141:155402. doi: 10.1016/j.metabol.2023
8. Jin Y, Liang J, Hong C, et al. Cardiometabolic multimorbidity, lifestyle behaviours, and cognitive function: a multicohort study. *Lancet Healthy Longev.* 2023;4(6):e265–e273. doi: 10.1016/S2666-7568(23)00054-5
9. GBD 2021 Risk Factors Collaborators. Global burden and strength of evidence for 88 risk factors in 204 countries and 811 subnational locations, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet.* 2024; 403(10440):2162–2203. doi: 10.1016/S0140-6736(24)00933-4
10. Swinburn BA, Kraak VI, Allender S, et al. The global syndemic of obesity, undernutrition, and climate change: the Lancet Commission report. *Lancet.* 2019;393(10173):791–846. doi: 10.1016/S0140-6736(18)32822-8
11. GBD 2021 Diabetes Collaborators. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet.* 2023;402(10397):203–234. doi: 10.1016/S0140-6736(23)01301-6
12. Mills KT, Bundy JD, Kelly TN, et al. Global disparities of hypertension prevalence and control: a systematic analysis of population-based studies from 90 countries. *Circulation.* 2016; 134(6):441–450. doi: 10.1161/CIRCULATIONAHA.115.018912
13. Cariou B, Byrne CD, Loomba R, Sanyal AJ. Nonalcoholic fatty liver disease as a metabolic disease in humans: A literature review. *Diabetes Obes Metab.* 2021;23(5):1069–1083. doi: 10.1111/dom.14322
14. Алфёрова В.И., Мустафина С.В. Распространенность ожирения во взрослой популяции Российской Федерации (обзор литературы). *Ожирение и метаболизм.* 2022;19(1):96–105.
Alferova VI, Mustafina SV. The prevalence of obesity in the adult population of the Russian Federation (literature review). *Obesity and metabolism.* 2022;19(1):96–105. doi: 10.14341/omet12809
15. Гнедовская Е.В., Кравченко М.А., Прокопович М.Е. и др. Распространенность факторов риска цереброваскулярных заболеваний у жителей мегаполиса в возрасте 40–59 лет (клинико-эпидемиологическое исследование). *Анналы клинической и экспериментальной неврологии.* 2016;10(4):11–19.

Gnedovskaya EV, Kravchenko MA, Prokopovich ME, et al. Prevalence of the risk factors of cerebrovascular disorders in the capital city residents aged 40–59: a clinical and epidemiological study. *Annals of Clinical and Experimental Neurology*. 2016;10(4):11–19. doi: 10.17816/psaic13

16. Shiozawa M, Kaneko H, Itoh H, et al. Association of body mass index with ischemic and hemorrhagic stroke. *Nutrients*. 2021;13(7):2343. doi: 10.3390/nu13072343
17. Marini S, Merino J, Montgomery BE, et al. Mendelian randomization study of obesity and cerebrovascular disease. *Ann Neurol*. 2020. 87(4):516–524. doi: 10.1002/ana.25686
18. Letra L, Sena C. Cerebrovascular disease: consequences of obesity-induced endothelial dysfunction. *Adv Neurobiol*. 2017;19:163–189. doi: 10.1007/978-3-319-63260-5_7
19. Huang K, Liu F, Han X, et al. Association of BMI with total mortality and recurrent stroke among stroke patients: A meta-analysis of cohort studies. *Atherosclerosis*. 2016;253:94–101. doi: 10.1016/j.atherosclerosis.2016.08.042
20. Wang Z, Wang J, Wang J, et al. The obesity paradox in intracerebral hemorrhage: a systematic review and meta-analysis. *Front Endocrinol (Lausanne)*. 2023;14:1255538. doi: 10.3389/fendo.2023.1255538
21. Lee SH, Jung JM, Park MH. Obesity paradox and stroke outcomes according to stroke subtype: a propensity score-matched analysis. *Int J Obes (Lond)*. 2023;47(8):669–676. doi: 10.1038/s41366-023-01318-0
22. Padwal R, Leslie WD, Lix LM, Majumdar SR. Relationship among body fat percentage, body mass index, and all-cause mortality: a cohort study. *Ann Intern Med*. 2016;164(8):532–541. doi: 10.7326/M15-1181
23. Anand SS, Friedrich MG, Lee DS, et al. Evaluation of adiposity and cognitive function in adults. *JAMA Netw Open*. 2022;5(2):e2146324. doi: 10.1001/jamanetworkopen.2021.46324
24. Ishida A, Nakanishi R, Miyagi T, et al. Association of obesity and metabolic health status with cerebral small-vessel disease in stroke-free individuals. *J Atheroscler Thromb*. 2025;32. doi: 10.5551/jat.65649
25. Hebebrand J, Holm JC, Woodward E, et al. A proposal of the European Association for the Study of Obesity to improve the ICD-11 diagnostic criteria for obesity based on the three dimensions etiology, degree of adiposity and health risk. *Obes Facts*. 2017;10(4):284–307. doi: 10.1159/000479208
26. Танашян М.М., Антонова К.В., Лагода О.В. и др. Ожирение и протромбогенное состояние крови у пациентов с цереброваскулярными заболеваниями. *Тромбоз, гемостаз и реология*. 2023;(3):53–62.
Tanashyan MM, Antonova KV, Lagoda OV, et al. Obesity and prothrombotic state in patients with cerebrovascular diseases. *Thrombosis, Hemostasis and Rheology*. 2023;(3):53–62. doi: 10.25555/THR.2023.3.1069
27. Mottillo S, Filion KB, Genest J, et al. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. *J Am Coll Cardiol*. 2010;56(14):1113–1132. doi: 10.1016/j.jacc.2010.05.034
28. Zhang F, Liu L, Zhang C, Ji S, Mei Z, Li T. Association of metabolic syndrome and its components with risk of stroke recurrence and mortality: a meta-analysis. *Neurology*. 2021;97(7):e695–e705. doi: 10.1212/WNL.0000000000012415
29. Liu Q, Wu S, Shao J, et al. Metabolic syndrome parameters' variability and stroke incidence in hypertensive patients: evidence from a functional community cohort. *Cardiovasc Diabetol*. 2024;23(1):203. doi: 10.1186/s12933-024-02282-3
30. Atti AR, Valente S, Iodice A, et al. Metabolic syndrome, mild cognitive impairment, and dementia: a meta-analysis of longitudinal studies. *Am J Geriatr Psychiatry*. 2019;27(6):625–637. doi: 10.1016/j.jagp.2019.01.214
31. Танашян М.М., Орлов С.В., Домашенко М.А., Ионова В.Г. Метаболический синдром и ишемический инсульт. *Анналы клинической и экспериментальной неврологии*. 2007;1(3):5–11.
Tanashyan MM, Orlov SV, Domashenko MA, Ionova VG. Metabolic syndrome and ischemic stroke. *Annals of Clinical and Experimental Neurology*. 2007;1(3):5–11. doi: 10.17816/psaic432
32. Танашян М.М., Антонова К.В., Лагода О.В. и др. Острые нарушения мозгового кровообращения и сахарный диабет 2 типа. *Анналы клинической и экспериментальной неврологии*. 2014;8(3):4–8.
Tanashyan MM, Antonova KV, Lagoda O.V., et al. Acute stroke and type 2 diabetes. *Annals of Clinical and Experimental Neurology*. 2014;8(3):4–8. doi: 10.17816/psaic178
33. Танашян М.М., Лагода О.В., Орлов С.В. и др. Сосудистые заболевания головного мозга и метаболический синдром. *Терапевтический архив*. 2013;85(10):34–42.
Tanashyan MM, Lagoda OV, Orlov SV, et al. Cerebrovascular diseases and metabolic syndrome. *Therapeutic Archive*. 2013;85(10):34–42.
34. Антонова К.В., Танашян М.М., Романцова Т.И., Максимова М.Ю. Острые нарушения мозгового кровообращения: клиническое течение и прогноз у больных сахарным диабетом 2 типа. *Ожирение и метаболизм*. 2016;13(2):20–24.
Antonova KV, Tanashyan MM, Romantsova TI, Maksimova MY. Type 2 diabetes mellitus and the clinical course of acute stroke. *Obesity and metabolism*. 2016;13(2):20–24. doi: 10.14341/omet2016220-24
35. Антонова К.В., Медведев Р.Б., Шабалина А.А. и др. Нарушения углеводного обмена и церебральный атеросклероз у больных с ишемическими нарушениями мозгового кровообращения. *Анналы клинической и экспериментальной неврологии*. 2016;10(1):20–26.
Antonova KV, Medvedev RB, Shabalina AA, et al. Carbohydrate metabolism disorders and cerebral atherosclerosis in patients with ischemic cerebrovascular diseases. *Annals of Clinical and Experimental Neurology*. 2016;10(1):20–26. doi: 10.17816/psaic74
36. Танашян М.М., Лагода О.В., Гулевская Т.С. и др. Прогрессирующий церебральный атеросклероз: клинические, биохимические и морфологические аспекты. *Анналы клинической и экспериментальной неврологии*. 2013;7(4):4–9. doi: 10.17816/psaic224.
Tanashyan MM, Lagoda OV, Gulevskaya TS et al. Progressing cerebral atherosclerosis: clinical, biochemical and morphological aspects. *Annals of Clinical and Experimental Neurology*. 2013;7(4):4–9. doi: 10.17816/psaic224
37. Танашян М.М., Антонова К.В., Раскуражев А.А. и др. Цереброваскулярные заболевания и глюколипотоксичность. *Анналы клинической и экспериментальной неврологии*. 2020;14(1);17–24.
Tanashyan MM, Antonova KV, Raskurazhev AA, et al. Cerebrovascular disorders and glucolipotoxicity. *Annals of Clinical and Experimental Neurology*. 2020;14(1);17–24. doi: 10.25692/ACEN.2020.1.2
38. Танашян М.М., Щепанкевич Л.А., Орлов С.В. и др. Гемореология и гемостаз у больных с ишемическим инсультом на фоне сахарного диабета 2 типа и метаболического синдрома. *Анналы клинической и экспериментальной неврологии*. 2014;8(3):14–20.
Tanashyan MM, Shchepankevich LA, Orlov SV, et al. Hemorheology and hemostasis in stroke patients with type 2 diabetes and metabolic syndrome. *Annals of Clinical and Experimental Neurology*. 2017;8(3):14–20. doi: 10.17816/psaic176
39. The Lancet. Diabetes: a defining disease of the 21st century. *Lancet*. 2023;401(10394):2087. doi: 10.1016/S0140-6736(23)01296-5
40. Деев И.А., Кобякова О.С., Стародубов В.И. и др. Заболеваемость всего населения России в 2023 году: статистические материалы. М.; 2024.
Deev IA, Kobyakova OS, Starodubov VI, et al. Morbidity of the entire population of Russia in 2023: statistical materials. Moscow; 2024. doi: 10.21045/978-5-94116-160-7-2024 (In Russ.)
41. Дедов И.И., Шестакова М.В., Викулова О.К. и др. Эпидемиология и ключевые клинико-терапевтические показатели сахарного диабета в Российской Федерации в разрезе стратегических целей Всемирной организации здравоохранения. *Сахарный диабет*. 2025;28(1):4–17.
Dedov II, Shestakova MV, Vikulova OK, et al. Epidemiology and key clinical and therapeutic indicators of diabetes mellitus in Russian Federation according to the World Health Organization's strategy goals. *Diabetes mellitus*. 2025;28(1):4–17. doi: 10.14341/DM13292

42. Mosenzon O, Cheng AY, Rabinstein AA, Sacco S. Diabetes and stroke: what are the connections? *J Stroke*. 2023;25(1):26–38. doi: 10.5853/jos.2022.02306
43. Дедов И.И., Шестакова М.В. Сахарный диабет: «история болезни». Сквозь призму научных открытий. М.; 2025;1.
Dedov II, Shestakova MV. Diabetes mellitus: "case history". Through the prism of scientific discoveries. Moscow; 2025;1. (In Russ.)
44. Lau LH, Lew J, Borschmann K., et al. Prevalence of diabetes and its effects on stroke outcomes: a meta-analysis and literature review. *J Diabetes Investig*. 2019;10(3):780–792. doi: 10.1111/jdi.12932
45. Echouffo-Tcheugui JB, Xu H, Matsouaka RA, et al. Diabetes and long-term outcomes of ischaemic stroke: findings from get with the guidelines-stroke. *Eur Heart J*. 2018;39(25):2376–2386. doi: 10.1093/eurheartj/ehy036
46. Rawshani A, Rawshani A, Franzén S, et al. Risk factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2018;379(7):633–644. doi: 10.1056/NEJMoa1800256
47. Ding MY, Xu Y, Wang YZ, et al. Predictors of cognitive impairment after stroke: a prospective stroke cohort study. *J Alzheimers Dis*. 2019;71(4):1139–1151. doi: 10.3233/JAD-190382
48 Zhang L, Li X, Wolfe CDA, et al. Diabetes as an independent risk factor for stroke recurrence in ischemic stroke patients: an updated meta-analysis. *Neuroepidemiology*. 2021;55(6):427–435. doi: 10.1159/000519327
49. Kaynak N, Kennel V, Rackoll T, et al. Impaired glucose metabolism and the risk of vascular events and mortality after ischemic stroke: a systematic review and meta-analysis. *Cardiovasc Diabetol*. 2024;23(1):323. doi: 10.1186/s12933-024-02413-w
50. Танашян М.М., Антонова К.В., Лагода О.В., Шабалина А.А. Решённые и нерешённые вопросы цереброваскулярной патологии при сахарном диабете. *Анналы клинической и экспериментальной неврологии*. 2021;15(3):5–14.
Tanashyan MM, Antonova KV, Lagoda OV, Shabalina AA. Resolved and unresolved issues of cerebrovascular disease in diabetes mellitus. *Annals of Clinical and Experimental Neurology*. 2021;15(3):5–14. doi: 10.54101/ACEN.2021.3.1
51. Антонова К.В., Танашян М.М., Раскуражев А.А. и др. Ожирение и нервная система. *Ожирение и метаболизм*. 2024;21(1):68–78.
Antonova KV, Tanashyan MM, Raskurazhev AA, et al. Obesity and the nervous system. *Obesity and metabolism*. 2024;21(1):68–78. doi: 10.14341/omet13019
52. Ehtewish H, Arredouani A, El-Agnaf O. Diagnostic, prognostic, and mechanistic biomarkers of diabetes mellitus-associated cognitive decline. *Int J Mol Sci*. 2022;23(11):6144. doi: 10.3390/ijms23116144
53. Суркова Е.В., Майоров А.Ю., Мельникова О.Г. Сахарный диабет 2 типа. Руководство для пациентов. М.; 2021.
Surkova EV, Majorov AY, Mel'nikova OG. Type 2 diabetes mellitus: a guide for patients. Moscow; 2021. doi: 10.33029/9704-6250-8-DMT2-2021-1-160 (In Russ.)
54. Танашян М.М., Антонова К.В., Лагода О.В. и др. Приверженность лечению у пациентов с цереброваскулярными заболеваниями как мультифакториальная проблема. *Неврология, нейропсихиатрия, психосоматика*. 2023;15(1):18–27.
Tanashyan MM, Antonova KV, Lagoda OV, et al. Adherence to treatment in patients with cerebrovascular disease as a multifactorial problem. *Neurology, Neuropsychiatry, Psychosomatics*. 2023;15(1):18–27. doi: 10.14412/2074-2711-2023-1-18-27
55. Быковская М.А., Раскуражев А.А., Шабалина А.А. и др. Биомаркеры повреждения сосудистой стенки у пациентов с цереброваскулярными заболеваниями и сахарным диабетом 2-го типа. *Тромбоз, гемостаз и реология*. 2021;2:80–86.
Bykovskaya MA, Raskurazhev AA, Shabalina AA, et al. Biomarkers of vascular wall damage in patients with cerebrovascular diseases and type 2 diabetes mellitus. *Thrombosis, hemostasis and rheology*. 2021;2:80–86. doi: 10.25555/THR.2021
56. Tanashyan MM, Antonova KV, Shabalina AA, et al. Proatherogenic changes in the blood lipid profile in patients with cerebrovascular disease and type 2 diabetes. *Hum Physiol*. 2020;46(8):840–844. doi: 10.1134/S0362119720080125
57. Ануфриев П.Л., Танашян М.М., Гулевская Т.С. и др. Особенности атеросклероза церебральных артерий и патоморфологии инфарктов головного мозга при сахарном диабете 2-го типа. *Анналы клинической и экспериментальной неврологии*. 2015;9(3):4–9. doi: 10.17816/psaic143
Anufriev PL, Tanashyan MM, Gulevskaya TS, et al. Features of atherosclerosis of the cerebral arteries and pathomorphology of cerebral infarctions in patients with type 2 diabetes mellitus. *Annals of Clinical and Experimental Neurology*. 2015;9(3):4–9. doi: 10.17816/psaic143
58. Scherer T, Lindtner C, O'Hare J, et al. Insulin regulates hepatic triglyceride secretion and lipid content via signaling in the brain. *Diabetes*. 2016;65(6):1511–1520. doi: 10.2337/db15-1552
59. Dodd GT, Decherf S, Loh K, et al. Leptin and insulin act on POMC neurons to promote the browning of white fat. *Cell*. 2015;160(1-2):88–104. doi: 10.1016/j.cell.2014.12.022
60. Scherer T, Sakamoto K, Buettner C. Brain insulin signalling in metabolic homeostasis and disease. *Nat Rev Endocrinol*. 2021;17(8):468–483. doi: 10.1038/s41574-021-00498-x
61. Hayden M.R. Brain injury: response to injury wound-healing mechanisms and enlarged perivascular spaces in obesity, metabolic syndrome, and type 2 diabetes mellitus. *Medicina*. 2023;59(7):1337. doi: 10.3390/medicina59071337
62. Van Dyken P, Lacoste B. Impact of metabolic syndrome on neuroinflammation and the blood-brain barrier. *Front Neurosci*. 2018;12:930. doi: 10.3389/fnins.2018.00930
63. Schleh MW, Caslin HL, Garcia JN, et al. Metaflammation in obesity and its therapeutic targeting. *Sci Transl Med*. 2023;15(723):eadf9382. doi: 10.1126/scitranslmed.adf9382
64. Chen Y, Ye X, Escames G, et al. The NLRP3 inflammasome: contributions to inflammation-related diseases. *Cell Mol Biol Lett*. 2023;28(1):51. doi: 10.1186/s11658-023-00462-9
65. Kotyla PJ, Engelmann M, Giemza-Stokłosa J, et al. Thromboembolic adverse drug reactions in janus kinase (jak) inhibitors: does the inhibitor specificity play a role? *Int. J. Mol. Sci*. 2021;22(5):2449. doi: 10.3390/ijms22052449
66. Суслина З.А., Танашян М.М., Ерофеева А.В., Ионова В.Г. Особенности гемостатической активности и факторы церебральной эмболии при кардиоэмболическом инсульте. *Журнал неврологии и психиатрии им. С.С. Корсакова*. 2003;103(9):138–138.
Suslina ZA, Tanashyan MM, Erofeeva AV, Ionova VG. Features of hemostatic activity and factors of cerebral embolism in cardioembolic stroke. *S.S. Korsakov Journal of Neurology and Psychiatry*. 2003;103(9):138–138. (In Russ.)
67. Суслина З.А., Ерофеева А.В., Танашян М.М., Ионова В.Г. Ишемические инсульты: состояние гемостаза и факторы церебральной эмболии. *Журнал неврологии и психиатрии им. С.С. Корсакова*. 2006;106(S16):3–9.
Suslina ZA, Erofeeva AV, Tanashyan MM, Ionova VG. Ischemic stroke: hemostasis and factors of cerebral embolism. *S.S. Korsakov Journal of Neurology and Psychiatry*. 2006;106(S16):3–9.
68. Танашян М.М, Суслина З.А., Ионова В.Г. и др. Гемореология и гемостаз у больных с ишемическим инсультом при различной степени поражения магистральных артерий головы. *Неврологический журнал*. 2001;6(6):17–21.
Tanashyan MM, Suslina ZA, Ionova VG, et al. Hemorheology and hemostasis in patients with ischemic stroke with varying degrees of damage to the main arteries of the head. *Neurological Journal*. 2001;6(6):17–21. (In Russ.)
69. Танашян М.М, Суслина З.А., Ионова В.Г. Антиагрегационная активность сосудистой стенки в остром периоде ишемического инсульта. *Ангиология и сосудистая хирургия*. 2001;7(1):10–16.

Tanashyan MM, Suslina ZA, Ionova VG. Antiaggregational activity of the vascular wall in the acute period of ischemic stroke. *Angiology and Vascular Surgery*. 2001;7(1):10–16. (In Russ.)

70. Максимова М.Ю., Суслина З.А., Ионова В.Г. Гемореология и гемостаз в острейшем периоде лакунарного инсульта. *Журнал неврологии и психиатрии им. С.С. Корсакова*. 2007;107(12):4–7.
Maksimova MYu, Suslina ZA, Ionova VG. Hemorheology and homeostasis in the most acute stage of lacunar stroke. *S.S. Korsakov Journal of Neurology and Psychiatry*. 2007;(12):4–7.
71. Суслина З.А, Танашян М.М., Ионова В.Г. Ишемический инсульт: кровь, сосудистая стенка, антитромботическая терапия. М.; 2005.
Suslina ZA, Tanashyan MM, Ionova VG. Ischemic stroke: blood, vascular wall, antithrombotic therapy. Moscow; 2005. (In Russ.)
72. Танашян М.М., Орлов С.В., Домашенко М.А., Ионова В.Г. Метаболический синдром и ишемический инсульт. *Анналы клинической и экспериментальной неврологии*. 2007;1(3):5–11.
Tanashyan MM, Orlov SV, Domashenko M, Ionova VG. Metabolic syndrome and ischemic stroke. *Annals of Clinical and Experimental Neurology*. 2007;1(3):5–11. doi: 10.17816/psaic432
73. Танашян М.М., Антонова К.В., Шабалина А.А. и др. Состояние гемостаза и углеводного обмена у пациентов с сахарным диабетом 2-го типа и цереброваскулярными заболеваниями. *Тромбоз, гемостаз и реология*. 2018;(4):16–23.
Tanashyan MM, Antonova KV, Shabalina AA, et al. Hemostasis and carbohydrate metabolism in patients with diabetes mellitus type 2 and cerebrovascular diseases. *Thrombosis, Hemostasis and Rheology*. 2018;(4):16–23. doi: 10.25555/THR.2018.4.0858
74. Антонова К.В., Танашян М.М., Шабалина А.А. и др. Гемостаз у лиц с сахарным диабетом 2-го типа и ожирением при острой и хронической цереброваскулярной патологии. *Тромбоз, гемостаз и реология*. 2020;82(2):60–67.
Antonova KV, Tanashyan MM, Shabalina AA, et al. Hemostasis in patients with type 2 diabetes mellitus and obesity in acute and chronic cerebrovascular pathology. *Thrombosis, Hemostasis and Rheology*. 2020;82(2):60–67. doi: 10.25555/THR.2020.2.0919
75. Marcos JL, Olivares-Barraza R, Ceballo K, et al. Obesogenic diet-induced neuroinflammation: a pathological link between hedonic and homeostatic control of food intake. *Int J Mol Sci*. 2023;24(2):1468. doi: 10.3390/ijms24021468
76. Yang D, Hou X, Yang G, et al. Effects of the POMC system on glucose homeostasis and potential therapeutic targets for obesity and diabetes. *Diabetes Metab Syndr Obes*. 2022;15:2939–2950. doi: 10.2147/DMSO.S380577
77. Sinha R. Role of addiction and stress neurobiology on food intake and obesity. *Biol Psychol*. 2018;131:5–13. doi: 10.1016/j.biopsycho.2017.05.001
78. Flores-Cordero JA, Pérez-Pérez A, Jiménez-Cortegana C, et al. Obesity as a risk factor for dementia and Alzheimer's disease: the role of leptin. *Int J Mol Sci*. 2022;23(9):5202. doi: 10.3390/ijms23095202
79. Танашян М.М., Суркова Е.В., Антонова К.В. и др. Сахарный диабет 2-го типа и когнитивные функции у пациентов с хроническими цереброваскулярными заболеваниями. *Терапевтический архив*. 2021;93(10):1179–1185.
Tanashyan MM, Surkova EV, Antonova KV, et al. Type 2 diabetes and cognitive functions in patients with chronic cerebrovascular diseases. *Terapevticheskii Arkhiv*. 2021;93(10):1179–1185. doi: 10.26442/00403660.2021.10.201108
80. Owolabi MO, Thrift AG, Mahal A, et al. Primary stroke prevention worldwide: translating evidence into action. *Lancet Public Health*. 2022;7(1):e74–e85. doi: 10.1016/S2468-2667(21)00230-9

Information about the authors

Marine M. Tanashyan – Dr. Sci. (Med.), Professor, Full Member of the Russian Academy of Sciences, Deputy Director for research, Head, 1st Neurological department, Institute of Clinical and Preventive Neurology, Russian Center of Neurology and Neurosciences, Moscow, Russia,
https://orcid.org/0000-0002-5883-8119
Ksenia V. Antonova – Dr. Sci. (Med.), leading researcher, 1st Neurological department, Russian Center of Neurology and Neurosciences, Moscow, Russia,
https://orcid.org/0000-0003-2373-2231

Author contribution: *Tanashyan M.M.* – development of the concept, planning and elaboration of the research, expert assessment, final correction of the text of the manuscript; *Antonova K.V.* – development of the concept, planning and elaboration of the research, writing and scientific editing of the text of the manuscript.

Информация об авторах

Танашян Маринэ Мовсесовна – д-р мед. наук, профессор, акад. РАН, зам. директора по научной работе, рук. 1-го неврологического отд. Института клинической и профилактической неврологии Российского центра неврологии и нейронаук, Москва, Россия,
https://orcid.org/0000-0002-5883-8119
Антонова Ксения Валентиновна – д-р мед. наук, в. н. с. 1-го неврологического отд. Института клинической и профилактической неврологии Российского центра неврологии и нейронаук, Москва, Россия,
https://orcid.org/0000-0003-2373-2231

Вклад авторов: *Танашян М.М.* – разработка концепции, планирование и проработка исследования, экспертная оценка, финальная корректировка текста рукописи; *Антонова К.В.* – разработка концепции, планирование и проработка исследования, написание и научное редактирование текста рукописи.