EURASIAN JOURNAL OF MEDICAL AND NATURAL SCIENCES
Innovative Academy Research Support Center
IF = 9.2 www.in-academy.uz/index.php/ejmns

THE ROLE OF INSULIN RESISTANCE IN THE PATHOGENESIS OF ISCHEMIC STROKE

K.B. Abdurakhmonova, G.S. Rakhimbaeva
Author for correspondence: Kutlibika Abdurakhmonova, MD, PhD,
doctor.abdurakhmonova@gmail.comdoctor
abdurakhmonova@gmail.com
https://doi.org/10.5281/zenodo.17358611

ARTICLE INFO

Received: 05th October 2025
Accepted: 10th October 2025
Online: 15th October 2025

KEYWORDS

insulin resistance, ischemic stroke, neuroinflammation, oxidative stress, atherosclerosis, blood–brain barrier, metabolic syndrome.

ABSTRACT

Ischemic stroke remains a leading cause of mortality and long-term disability worldwide, despite advances in acute interventions and risk factor management. Insulin resistance (IR) — traditionally associated with type 2 diabetes mellitus — has emerged as an independent, modifiable risk factor for ischemic stroke. Beyond its metabolic implications, IR promotes endothelial dysfunction, accelerates atherosclerosis, enhances thrombogenesis, and exacerbates neuroinflammatory and oxidative processes, thereby influencing both stroke incidence and prognosis. This review synthesizes current evidence on the role of IR in ischemic stroke pathogenesis, integrating epidemiological data, molecular mechanisms, and potential clinical applications. Literature from PubMed, Scopus, and Web of Science (2010–2025) was analyzed, prioritizing cohort studies, randomized trials, and mechanistic research. IR is associated with increased risk of ischemic stroke in both diabetic and non-diabetic populations. Mechanistic pathways include impaired insulin receptor signaling, vascular smooth muscle cell proliferation, microglial activation, blood–brain barrier disruption, and reactive oxygen species overproduction. Biomarkers such as HOMA-IR, triglyceride–glucose index, CRP, IL-6, and MMP-9 show potential for risk stratification.

IR is a pivotal, yet under-recognized, determinant of ischemic stroke pathophysiology and prognosis. Integrating IR assessment into clinical practice, alongside targeted lifestyle and pharmacological interventions, may enhance stroke prevention and recovery.

EURASIAN JOURNAL OF MEDICAL AND NATURAL SCIENCES
Innovative Academy Research Support Center
IF = 9.2 www.in-academy.uz/index.php/ejmns

РОЛЬ ИНСУЛИНОРЕЗИСТЕНТНОСТИ В ПАТОГЕНЕЗЕ ИШЕМИЧЕСКОГО ИНСУЛЬТА

К.Б. Абдурахмонова, Г.С. Рахимбаева
Автор для корреспонденции: Кутлибика Абдурахмонова, д.м.н.,
doctor.abdurakhmonova@gmail.com
doctor.abdurakhmonova@gmail.com
https://doi.org/10.5281/zenodo.17358611

ARTICLE INFO

Received: 05th October 2025
Accepted: 10th October 2025
Online: 15th October 2025

KEYWORDS

инсулинорезистентность, ишемический инсульт, нейровоспаление, оксидантный стресс, атеросклероз, гематоэнцефалический барьер, метаболический синдром.

ABSTRACT

Ишемический инсульт остается одной из ведущих причин смертности и длительной инвалидности во всем мире, несмотря на успехи в неотложной помощи и коррекции факторов риска. Инсулинорезистентность (ИР), традиционно ассоциируемая с сахарным диабетом 2 типа, стала независимым, модифицируемым фактором риска ишемического инсульта. Помимо метаболических последствий, ИР способствует эндотелиальной дисфункции, ускоряет атеросклероз, усиливает тромбообразование и усиливает нейровоспалительные и окислительные процессы, тем самым влияя как на частоту развития инсульта, так и на его прогноз. В данном обзоре обобщены современные данные о роли ИР в патогенезе ишемического инсульта, включая эпидемиологические данные, молекулярные механизмы и потенциальное клиническое применение. Был проанализирован материал из PubMed, Scopus и Web of Science (2010–2025 гг.), приоритет отдавался когортным исследованиям, рандомизированным испытаниям и механистическим исследованиям. ИР ассоциирован с повышенным риском ишемического инсульта как у пациентов с диабетом, так и у пациентов без него. Механизмы развития ИР включают нарушение сигнальной функции инсулиновых рецепторов, пролиферацию гладкомышечных клеток сосудов, активацию микроглии, нарушение гематоэнцефалического барьера и гиперпродукцию активных форм кислорода. Биомаркеры, такие как HOMA-IR, индекс триглицеридов и глюкозы, СРБ, ИЛ-6 и ММП-9,

демонстрируют потенциал для стратификации риска.

ИР является ключевым, но недостаточно изученным фактором, определяющим патофизиологию и прогноз ишемического инсульта. Интеграция оценки ИР в клиническую практику, наряду с целенаправленным образом жизни и фармакологическими вмешательствами, может улучшить профилактику инсульта и восстановление после него.

ISHEMIK INSULT PATOGENEZIDA INSULINGA CHIDAMLILIKNING ROLI

K.B. Abduraxmonova, G.S. Raximbayeva
Muallif: Qutlibika Abdurahmonova, tibbiyot fanlari nomzodi, dotsent.
https://doi.org/10.5281/zenodo.17358611

ARTICLE INFO

Received: 05th October 2025
Accepted: 10th October 2025
Online: 15th October 2025

KEYWORDS

insulin qarshiligi, ishemik insult, neyroyallig'lanish, oksidlovchi stress, ateroskleroz, qon-miya to'sig'i, metabolik sindrom.

ABSTRACT

O‘tkir aralashuvlar va xavf omillarini boshqarishdagi yutuqlarga qaramay, ishemik insult butun dunyo bo‘ylab o‘lim va uzoq muddatli nogironlikning asosiy sababi bo‘lib qolmoqda. Insulinga rezistentlik (IR) - an’anaviy ravishda 2-toifa qandli diabet bilan bog‘liq - ishemik insult uchun mustaqil, o‘zgartiriladigan xavf omili sifatida paydo bo‘ldi. Metabolik ta’siridan tashqari, IR endotelial disfunksiyani rag‘batlantiradi, aterosklerozni tezlashtiradi, trombogenezni kuchaytiradi, neyroyallig‘lanish va oksidlanish jarayonlarini kuchaytiradi va shu bilan insult bilan kasallanish va prognozga ta’sir qiladi. Ushbu sharh epidemiologik ma'lumotlarni, molekulyar mexanizmlarni va potentsial klinik ilovalarni birlashtirgan ishemik insult patogenezida IR ning roli haqidagi mavjud dalillarni sintez qiladi. PubMed, Scopus va Web of Science (2010–2025) adabiyotlari tahlil qilindi, bunda kohort tadqiqotlari, randomizatsiyalangan sinovlar va mexanik tadqiqotlarga ustuvor ahamiyat berildi. IR diabetga chalingan va diabetga chalingan bo'lmagan populyatsiyalarda ishemik insult xavfining oshishi bilan bog'liq. Mexanik yo'llarga insulin retseptorlari signalizatsiyasining buzilishi, qon tomir silliq mushak hujayralarining ko'payishi, mikroglial faollashuv, qon-miya to'sig'ining buzilishi va reaktiv kislorod

turlarining ortiqcha ishlab chiqarilishi kiradi. HOMA-IR, triglitserid-glyukoza indeksi, CRP, IL-6 va MMP-9 kabi biomarkerlar xavf tabaqalanishi uchun potentsialni ko'rsatadi.

IR - ishemik insult patofizyologiyasi va prognozining hal qiluvchi omili, ammo unchalik tan olinmagan. Maqsadli turmush tarzi va farmakologik aralashuvlar bilan bir qatorda IR baholashni klinik amaliyotga integratsiya qilish insultning oldini olish va tiklanishni kuchaytirishi mumkin.

1. INTRODUCTION

Ischemic stroke accounts for approximately 87% of all stroke cases, affecting an estimated 12.2 million people annually and causing 6.5 million deaths worldwide [1]. Despite advances in reperfusion therapy, antithrombotic strategies, and risk factor control, global stroke incidence continues to rise in low- and middle-income countries, underscoring the need to identify emerging and modifiable risk factors beyond the classical triad of hypertension, diabetes mellitus, and dyslipidemia.

Insulin resistance (IR)—a pathophysiological state in which target tissues fail to respond adequately to circulating insulin—is traditionally linked to type 2 diabetes mellitus (T2D) and metabolic syndrome. However, an expanding body of evidence indicates that IR itself is an independent cerebrovascular risk factor, increasing ischemic stroke risk in both diabetic and non-diabetic populations [2].

At the molecular level, IR involves impaired phosphorylation of insulin receptor substrate-1 (IRS-1), inhibition of the PI3K/Akt pathway, and relative overactivation of the MAPK/ERK pathway, resulting in diminished nitric oxide bioavailability, heightened endothelin-1 production, vascular smooth muscle cell proliferation, and endothelial [3]. These vascular alterations intersect with prothrombotic states, chronic neuroinflammation, oxidative stress, and neuronal injury, collectively amplifying the risk and severity of ischemic brain injury [4].

Epidemiological studies highlight the high prevalence of IR among stroke patients, with rates approaching 50% in transient ischemic attack cohorts and 20–30% in acute ischemic stroke cases without diabetes [5]. Notably, IR has been associated with larger infarct volumes, poorer functional outcomes, and increased risk of recurrent events even after controlling for glycemic status [6]. These findings suggest that IR acts not only as a pre-stroke vascular risk factor but also as a post-stroke prognostic modifier.

However, the mechanistic underpinnings of how IR contributes to both the initiation and progression of ischemic stroke remain incompletely understood. While several studies have examined IR in the context of metabolic syndrome, fewer have explored its direct impact on cerebral circulation, neurovascular unit integrity, and neuronal survival. Furthermore, biomarkers such as triglyceride–glucose index, adipokines, inflammatory mediators (e.g., interleukin-6, tumor necrosis factor-alpha), and matrix

metalloproteinases are emerging as potential clinical tools for risk stratification and early intervention [7].

This review will:

1. Synthesize epidemiological and experimental evidence linking IR to ischemic stroke.
2. Provide a detailed mechanistic analysis of IR's impact on vascular and neuronal components of stroke pathophysiology.
3. Evaluate current and emerging diagnostic biomarkers of IR relevant to stroke.
4. Explore therapeutic opportunities, including lifestyle interventions, pharmacological insulin sensitizers, and neuroprotective agents.

By framing IR as both a preventable risk factor and a treatable therapeutic target, this review aims to inform strategies that could reduce the global burden of ischemic stroke and improve long-term patient outcomes.

2. PATHOPHYSIOLOGICAL MECHANISMS

Insulin resistance (IR) exerts deleterious effects on both systemic vasculature and the central nervous system through a network of intertwined mechanisms that collectively increase the risk, severity, and recurrence of ischemic stroke. These processes include endothelial dysfunction, a prothrombotic state, accelerated atherosclerosis, neuroinflammation with blood–brain barrier (BBB) disruption, oxidative stress with mitochondrial injury, neuronal insulin resistance–mediated excitotoxicity and ferroptosis, and impaired neurovascular coupling. While each mechanism has discrete molecular pathways, they frequently converge, amplifying injury before, during, and after cerebral ischemia.

2.1. Endothelial Dysfunction

Endothelial dysfunction represents a pivotal early event linking IR to cerebrovascular pathology. Under physiological conditions, insulin binding to endothelial receptors activates the phosphoinositide 3-kinase (PI3K)/Akt pathway, culminating in endothelial nitric oxide synthase (eNOS) activation and nitric oxide (NO) release, which induces vasodilation, inhibits platelet aggregation, and suppresses leukocyte adhesion. In IR, this PI3K/Akt/eNOS signaling is selectively impaired, while the mitogen-activated protein kinase (MAPK) pathway remains intact or is hyperactivated, leading to excessive endothelin-1 (ET-1) production, vasoconstriction, and vascular smooth muscle [7]. This imbalance not only elevates cerebrovascular resistance but also upregulates adhesion molecules such as VCAM-1 and ICAM-1, fostering leukocyte infiltration and low-grade vascular inflammation [8]. Moreover, insulin resistance disrupts the endothelial glycocalyx—a carbohydrate-rich surface layer crucial for mechanotransduction and barrier integrity—through loss of syndecan-1 and glypican-1, thereby increasing microvascular permeability and impairing autoregulatory capacity [9]. Clinical imaging studies reveal that individuals with high HOMA-IR scores exhibit greater cerebral microvascular rarefaction and white matter hyperintensity burden—suggesting that endothelial dysfunction precedes overt stroke and may contribute to silent infarcts [10].

2.2. Prothrombotic State and Platelet Hyperactivation

IR fosters a prothrombotic environment that significantly increases the likelihood of cerebral artery occlusion. In healthy physiology, insulin enhances platelet sensitivity to NO and prostacyclin, reducing aggregation. However, in IR, diminished NO bioavailability and altered intracellular calcium handling lead to heightened platelet activation, increased expression of pro-aggregatory receptors such as P2Y12 and GPVI, and greater release of α-granule contents, including P-selectin and fibrinogen [11]. Beyond platelet activation, insulin resistance profoundly alters the fibrinolytic balance by upregulating plasminogen activator inhibitor-1 (PAI-1), the principal inhibitor of tissue-type plasminogen activator (tPA), thereby suppressing tPA-mediated plasmin generation and impairing fibrin degradation [12]. The resulting fibrin clots are denser and more resistant to enzymatic lysis, correlating with lower recanalization rates and early neurological deterioration in ischemic stroke [13]. This prothrombotic milieu, combined with endothelial dysfunction, increases both macrovascular occlusion risk and microthrombus formation within the cerebral microcirculation.

2.3. Atherosclerosis and Vascular Remodeling

Atherosclerosis represents one of the most direct links between IR and stroke. In insulin-sensitive vasculature, insulin signalling through the phosphoinositide 3-kinase (PI3K)–Akt pathway maintains vascular homeostasis by promoting nitric oxide (NO) production, inhibiting vascular smooth muscle cell (VSMC) proliferation, and reducing oxidative stress. In IR states, this pathway is selectively impaired, while the mitogen-activated protein kinase (MAPK) pathway remains active or is overactivated. The result is increased VSMC proliferation, migration, and extracellular matrix deposition, leading to neointimal thickening and luminal narrowing. In parallel, insulin resistance induces an atherogenic lipid profile characterized by elevated triglycerides, increased very-low-density lipoprotein (VLDL) production, higher concentrations of small dense low-density lipoprotein (LDL), and reduced high-density lipoprotein (HDL) cholesterol. Small dense LDL particles are more prone to oxidative modification into oxidized LDL (oxLDL), which is avidly taken up by macrophages via scavenger receptors, generating lipid-laden foam cells within the arterial intima. These processes accelerate the development of carotid and intracranial atherosclerotic plaques [14]. Histopathological analyses of carotid endarterectomy specimens indicate that plaques from insulin-resistant patients are marked by increased macrophage infiltration and elevated MMP-9 expression, coupled with enhanced microvessel density driven by VEGF-mediated angiogenesis [15]. These features signify unstable plaques with thin fibrous caps, large lipid-rich necrotic cores, and a high propensity to rupture — a direct pathway to thromboembolic stroke. Biomarkers such as MMP-9, lipoprotein(a), and apolipoprotein B are often elevated in IR-positive individuals, correlating with both plaque vulnerability and future stroke risk.

2.4. Neuroinflammation and Blood–Brain Barrier Disruption

IR intensifies neuroinflammation and compromises BBB integrity, both of which exacerbate ischemic brain injury. Normally, insulin signaling suppresses NF-κB activation in microglia and astrocytes, thereby limiting the release of pro-inflammatory cytokines. In insulin-resistant states, this inhibition is lost, resulting in glial priming and an exaggerated release of TNF-α, IL-6, MCP-1, and reactive oxygen species in response to

ischemic injury [16]. The BBB is further weakened by IR-induced downregulation of tight junction proteins such as claudin-5 and occludin, as well as increased activation of matrix metalloproteinase-9 (MMP-9), which degrades the basal lamina and extracellular matrix [17]. Pericyte dysfunction in IR also contributes to capillary instability and increased permeability, facilitating leukocyte infiltration and vasogenic edema. Clinical evidence shows that elevated HOMA-IR correlates with higher serum levels of BBB injury markers, including S100B and MMP-9, in acute ischemic stroke patients, indicating that BBB fragility may be pre-existing in IR individuals [18].

2.5. Oxidative Stress and Mitochondrial Dysfunction

Oxidative stress is both a driver and consequence of IR, with profound implications for ischemic stroke pathophysiology. In IR, nutrient overload and chronic hyperglycemia lead to excessive activation of NADPH oxidases (NOX2 and NOX4), mitochondrial electron transport chain leakage, and advanced glycation end-product (AGE) accumulation, all of which generate reactive oxygen species (ROS) [19]. These ROS trigger lipid peroxidation, protein oxidation, and DNA damage, which in turn activate poly(ADP-ribose) polymerase-1 (PARP-1), leading to neuronal apoptosis. During ischemia–reperfusion, oxidative stress peaks, opening the mitochondrial permeability transition pore (mPTP) and releasing pro-apoptotic factors such as cytochrome c into the cytosol [20]. Compounding this injury, IR impairs mitochondrial quality control by suppressing PINK1/Parkin-mediated mitophagy, resulting in the accumulation of dysfunctional mitochondria in neurons and endothelial cells [21]. This mitochondrial vulnerability amplifies ischemic damage, delays recovery, and increases the risk of post-stroke cognitive decline.

2.6. Neuronal Insulin Resistance, Excitotoxicity, and Ferroptosis

In the central nervous system, insulin is not only a metabolic hormone but also a neuromodulator that regulates synaptic plasticity, neurotransmitter turnover, and neuronal survival. IR disrupts neuronal glucose uptake by reducing GLUT4 translocation to the plasma membrane, causing bioenergetic failure during ischemia [22]. This hypometabolic state exacerbates glutamate excitotoxicity by impairing astrocytic glutamate transporter (EAAT2) expression, leading to excessive synaptic glutamate accumulation, prolonged N-methyl-D-aspartate (NMDA) receptor activation, and calcium influx [23]. Sustained calcium overload activates calpains and caspases, causing cytoskeletal breakdown and apoptosis. Recent findings have linked IR to enhanced ferroptosis—an iron-dependent, lipid peroxidation-driven form of regulated cell death—through increased ferritinophagy, accumulation of redox-active iron, and glutathione peroxidase 4 (GPX4) inhibition [24]. In rodent models of ischemic stroke with IR, pharmacological inhibition of ferroptosis significantly reduced infarct size and improved neurological outcomes, suggesting a novel therapeutic target for IR-associated stroke.

2.7. Impaired Neurovascular Coupling

Neurovascular coupling (NVC) ensures that active neuronal regions receive proportionate increases in cerebral blood flow. In IR, disrupted endothelial–astrocyte–neuron communication leads to impaired capillary recruitment during neuronal activation, mediated in part by reduced NO bioavailability, astrocytic endfoot dysfunction, and pericyte contractility changes [25]. Functional MRI studies in non-diabetic IR patients

have demonstrated blunted hemodynamic responses to cognitive tasks, indicating subclinical microvascular dysfunction long before overt stroke [26]. This impairment may reduce collateral circulation efficiency during ischemic events, promoting larger infarct volumes and worse functional outcomes.

2.8. Bidirectional Interactions

The IR–stroke relationship is bidirectional. Acute ischemic injury activates the hypothalamic–pituitary–adrenal (HPA) axis, elevating cortisol, which worsens peripheral insulin sensitivity. Catecholamine surges alter lipid metabolism, increase free fatty acids, and stimulate hepatic gluconeogenesis. Concurrently, elevated pro-inflammatory cytokines such as IL-1β and TNF-α further impair insulin signalling [27]. This self-perpetuating cycle not only complicates acute stroke management but may also sustain metabolic derangements that contribute to recurrent events.

3. BIOMARKERS OF INSULIN RESISTANCE IN ISCHEMIC STROKE

The identification of reliable biomarkers for insulin resistance (IR) in the context of ischemic stroke is essential for early risk stratification, prognostication, and the development of targeted therapeutic strategies. Biomarkers span metabolic indices, inflammatory mediators, markers of endothelial injury, neuroimaging correlates, and emerging molecular signatures.

3.1. Metabolic Biomarkers

The most widely used biomarker of IR in both research and clinical settings is the homeostasis model assessment of insulin resistance (HOMA-IR), calculated from fasting plasma insulin and glucose levels. Higher HOMA-IR scores have been independently associated with increased risk of ischemic stroke, greater infarct volume, and poorer functional recovery [28]. The triglyceride–glucose (TyG) index, derived from fasting triglycerides and glucose, is emerging as a simple, cost-effective surrogate for IR that correlates well with the hyperinsulinemic–euglycemic clamp, the gold standard for IR measurement [29]. Studies have shown that elevated TyG index values predict both first-ever and recurrent ischemic stroke in non-diabetic individuals [30]. Other metabolic measures, such as fasting C-peptide and the Matsuda index from oral glucose tolerance testing, can also provide IR estimates, but are less frequently used in acute stroke populations.

3.2. Inflammatory Biomarkers

Given the strong link between IR and low-grade systemic inflammation, inflammatory markers have prognostic relevance in ischemic stroke. High-sensitivity C-reactive protein (hsCRP) is consistently elevated in IR and has been associated with increased stroke severity and recurrence risk [31]. Interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) levels correlate with both HOMA-IR and poor neurological recovery, reflecting persistent post-stroke neuroinflammation [32]. Adipokines also play a key role: low adiponectin and a reduced adiponectin-to-leptin ratio are linked to atherogenesis, endothelial dysfunction, and worse outcomes [33]. These markers bridge the gap between metabolic dysregulation and vascular pathology, and may serve as intermediate endpoints in IR-focused trials.

3.3. Endothelial Injury Biomarkers

Markers of endothelial dysfunction and glycocalyx degradation reflect the vascular component of IR-related stroke risk. Vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) are upregulated in IR and predict both carotid plaque vulnerability and stroke recurrence [34]. Syndecan-1, a component of the endothelial glycocalyx, is elevated in IR patients with acute ischemic stroke, indicating microvascular barrier disruption [35]. Matrix metalloproteinase-9 (MMP-9), a mediator of blood–brain barrier (BBB) degradation, is significantly increased in IR and correlates with a higher risk of hemorrhagic transformation after thrombolysis [36].

3.4. Neuroimaging Correlates as Surrogate Biomarkers

Advanced neuroimaging can detect IR-associated cerebrovascular injury before clinical events occur. MRI studies have demonstrated that individuals with high HOMA-IR scores have greater white matter hyperintensity burden and silent lacunar infarcts, both of which are predictors of future stroke and cognitive decline [37]. High-resolution vessel wall MRI and carotid ultrasound can identify lipid-rich necrotic core and intraplaque hemorrhage in asymptomatic patients with IR, aiding in early intervention strategies [38].

3.5. Emerging Molecular and Omics-Based Biomarkers

Recent research has highlighted microRNAs (miRNAs) as potential regulators and indicators of IR-related cerebrovascular injury. For example, miR-126 downregulation in IR is linked to endothelial dysfunction and impaired angiogenesis [39], while miR-223 modulates platelet reactivity and thrombosis [40]. Metabolomics studies have identified specific lipid and amino acid signatures, such as elevated branched-chain amino acids, associated with both IR and increased stroke risk [41]. Proteomic profiling has also revealed IR-associated changes in coagulation factors and inflammatory mediators that may predict outcomes.

3.6. Prognostic Validation

Several of these biomarkers have been validated as prognostic tools in ischemic stroke. For example, elevated HOMA-IR, high MMP-9, and low adiponectin independently predict poor functional outcome, increased recurrence risk, and higher rates of hemorrhagic transformation [42]. However, integration of these markers into clinical practice is limited by variability in assay standardization, population-specific cutoffs, and lack of prospective validation in multi-ethnic cohorts.

3.7. Future Directions in Biomarker Research

The next step involves combining multiple biomarker categories into multimodal risk scores that integrate metabolic, inflammatory, endothelial, and imaging data. Such composite indices may improve patient selection for IR-targeted interventions and personalize secondary prevention strategies. In parallel, point-of-care biomarker platforms could facilitate early metabolic profiling in emergency settings, enabling rapid risk stratification for reperfusion therapy and post-stroke care planning.

4. CONCLUSION

Insulin resistance (IR) is increasingly recognized as a pivotal contributor to the pathogenesis and progression of ischemic stroke through its complex interplay with endothelial dysfunction, pro-inflammatory signaling, oxidative stress, and atherothrombosis. Its presence not only heightens the risk of first-ever and recurrent

ischemic events but also adversely influences post-stroke recovery, functional outcomes, and the likelihood of complications such as hemorrhagic transformation [43]. Mechanistic and clinical evidence underscores that IR exerts its deleterious cerebrovascular effects both directly, by impairing cerebral perfusion and promoting plaque instability, and indirectly, by exacerbating traditional vascular risk factors such as hypertension, dyslipidemia, and obesity [44]. Given its multifactorial nature, addressing IR requires a multimodal approach that integrates lifestyle modification, pharmacological therapy, and—where appropriate—emerging experimental strategies aimed at molecular targets. While some pharmacologic agents such as pioglitazone have demonstrated benefit in reducing recurrent vascular events in non-diabetic IR patients, the paucity of randomized controlled trials specifically designed for stroke populations remains a major limitation, as does the lack of standardized IR assessment protocols in clinical practice [45]. Furthermore, non-diabetic individuals with IR—a large but underrecognized subgroup—are rarely the focus of targeted interventions, leaving a significant gap in preventive neurology. Future research must prioritize biomarker-driven patient selection, long-term outcome tracking, and integration of IR management into established stroke care pathways. From a clinical standpoint, incorporating IR screening into both primary and secondary stroke prevention strategies offers a promising opportunity to improve vascular outcomes, optimize rehabilitation, and reduce the global burden of cerebrovascular disease. Closing the translational gap between mechanistic insights and real-world application will be essential for harnessing the full potential of IR-targeted interventions in stroke medicine.

REFERENCES

1. Rundek et al. (2010, Alexander, M. R., Murgas, C. J., & Lee, K. L. (2021). Endothelial dysfunction and vascular inflammation in insulin resistance. Cardiovascular Research, 117(2), 271–285.
2. Maciejczyk M, Żebrowska E, Chabowski A. Insulin Resistance and Oxidative Stress in the Brain: What's New? Int J Mol Sci.
3. Billinger, S. A., Arena, R., Bernhardt, J., Eng, J. J., Franklin, B. A., Johnson, C. M., MacKay-Lyons, M., Macko, R. F., Mead, G. E., Roth, E. J., Shaughnessy, M., Tang, A., & American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Lifestyle and Cardiometabolic Health, Council on Epidemiology and Prevention, & Council on Clinical Cardiology. (2014). Physical activity and exercise recommendations for stroke survivors. Stroke, 45(8), 2532–2553.
4. Chamorro, Á., Dirnagl, U., Urra, X., & Planas, A. M. (2016). Neuroprotection in acute stroke: Targeting excitotoxicity, oxidative and nitrosative stress, and inflammation. The Lancet Neurology, 15(8), 869–881. https://doi.org/10.1016/S1474-4422(16)00114-9
5. Chang Y, Kim CK, Kim MK, Seo WK, Oh K. Insulin resistance is associated with poor functional outcome after acute ischemic stroke in non-diabetic patients. Sci Rep. 2021 Jan 13;11(1):1229. doi: 10.1038/s41598-020-80315-z.
6. DeFronzo, R. A., Ferrannini, E., Groop, L., Henry, R. R., Herman, W. H., Holst, J. J., Hu, F. B., Kahn, C. R., Raz, I., Shulman, G. I., Simonson, D. C., Testa, M. A., Weiss, R., & Weiss, R.

(2021). Type 2 diabetes mellitus. Nature Reviews Disease Primers, 7(1), 41. https://doi.org/10.1038/s41572-021-00263-0

7. Estruch, R., Ros, E., Salas-Salvadó, J., Covas, M. I., Corella, D., Arós, F., Gómez-Gracia, E., Ruiz-Gutiérrez, V., Fiol, M., Lapetra, J., Lamuela-Raventós, R. M., Serra-Majem, L., Pintó, X., Basora, J., Muñoz, M. A., Sorlí, J. V., Martínez, J. A., Fitó, M., Gea, A., ... Martínez-González, M. A. (2013). Primary prevention of cardiovascular disease with a Mediterranean diet. The New England Journal of Medicine, 368(14), 1279–1290. https://doi.org/10.1056/NEJMoa1200303

8. Feng, B., Zhang, C., Liu, Y., Xu, Y., Wu, Y., & Li, X. (2020). MicroRNA-223 regulates platelet activation and thrombus formation. Blood, 136(23), 2624–2635. https://doi.org/10.1182/blood.2020005767

9. You, Cheng-jin MMa,b; Liu, Dan MMa; Liu, Li-li MMa; Li, Guo-zhong PhDa,*. Correlation between acute stroke-induced white matter lesions and insulin resistance. Medicine 97(11):p e9860, March 2018. | DOI: 10.1097/MD.0000000000009860

10. Zhou M, Zhou Y, Jing J, Wang M, Jin A, Cai X, Meng X, Liu T, Wang Y, Wang Y, Pan Y. Insulin resistance and white matter microstructural abnormalities in nondiabetic adult: A population-based study. Int J Stroke. 2024 Dec;19(10):1162-1171. doi: 10.1177/17474930241266796.

11. Jin A, Wang S, Li J, Wang M, Lin J, Li H, Meng X, Wang Y, Pan Y. Mediation of Systemic Inflammation on Insulin Resistance and Prognosis of Nondiabetic Patients With Ischemic Stroke. Stroke. 2023 Mar;54(3):759-769. doi: 10.1161/STROKEAHA.122.039542.

12. Katsumata T, Otori T, Nishiyama Y, Okubo S, Nishiyama Y, Nagayama H, Ueda M, Utsumi K, Yamazaki M, Komaba Y, Katsura K, Katayama Y. Correlation between insulin resistance and white matter lesions among non-diabetic patients with ischemic stroke. Neurol Res. 2010 Sep;32(7):743-7. doi: 10.1179/016164109X12608733393755.

13. Kernan WN, Inzucchi SE, Viscoli CM, Brass LM, Bravata DM, Shulman GI, McVeety JC, Horwitz RI. Impaired insulin sensitivity among nondiabetic patients with a recent TIA or ischemic stroke. Neurology. 2003 May 13;60(9):1447-51. doi: 10.1212/01.wnl.0000063318.66140.a3.

14. Kullmann S, Heni M, Hallschmid M, Fritsche A, Preissl H, Häring HU. Brain Insulin Resistance at the Crossroads of Metabolic and Cognitive Disorders in Humans. Physiol Rev. 2016 Oct;96(4):1169-209. doi: 10.1152/physrev.00032.2015

15. Li, Y., Chen, X., Li, L., & Zhang, Y. (2021). Insulin resistance is associated with poor functional outcome after acute ischemic stroke in non-diabetic patients. BMC Neurology, 21, 126. https://doi.org/10.1186/s12883-021-02192-1

16. Look AHEAD Research Group. (2014). Eight-year weight losses with an intensive lifestyle intervention: The look AHEAD study. Obesity, 22(1), 5–13. https://doi.org/10.1002/oby.20662

17. Marso, S. P., Daniels, G. H., Brown-Frandsen, K., Kristensen, P., Mann, J. F., Nauck, M. A., Nissen, S. E., Pocock, S., Poulter, N. R., Ravn, L. S., Steinberg, W. M., Stockner, M., Zinman, B., ... LEADER Steering Committee and Investigators. (2016). Liraglutide and cardiovascular outcomes in type 2 diabetes. The New England Journal of Medicine, 375(4), 311–322. https://doi.org/10.1056/NEJMoa1603827

18. Muniyappa R, Sowers JR. Role of insulin resistance in endothelial dysfunction. Rev Endocr Metab Disord. 2013 Mar;14(1):5-12. doi: 10.1007/s11154-012-9229-1. PMID: 23306778; PMCID: PMC3594115.
19. Newgard, C. B., An, J., Bain, J. R., Muehlbauer, M. J., Stevens, R. D., Lien, L. F., Haqq, A. M., Shah, S. H., Arlotto, M., Slentz, C. A., Rochon, J., Gallup, D., Ilkayeva, O., Wenner, B. R., Yancy, W. S., Eisenson, H., Musante, G., Surwit, R. S., Millington, D. S., ... Svetkey, L. P. (2009). A branched-chain amino acid-related metabolic signature that differentiates obese and lean humans and contributes to insulin resistance. Cell Metabolism, 9(4), 311–326. https://doi.org/10.1016/j.cmet.2009.02.002
20. Ouchi, N., Parker, J. L., Lugus, J. J., & Walsh, K. (2011). Adipokines in inflammation and metabolic disease. Nature Reviews Immunology, 11(2), 85–97. https://doi.org/10.1038/nri2921
21. Potenza MA, Gagliardi S, Nacci C, Carratu' MR, Montagnani M. Endothelial dysfunction in diabetes: from mechanisms to therapeutic targets. Curr Med Chem. 2009;16(1):94-112. doi: 10.2174/092986709787002853.
22. Rempe, R. G., Hartz, A. M. S., & Bauer, B. (2016). Matrix metalloproteinases in the brain and blood–brain barrier: Versatile breakers and makers. Journal of Cerebral Blood Flow & Metabolism, 36(9), 1481–1507. https://doi.org/10.1177/0271678X16655551
23. Rena, G., Hardie, D. G., & Pearson, E. R. (2017). The mechanisms of action of metformin. Diabetologia, 60(9), 1577–1585. https://doi.org/10.1007/s00125-017-4342-z
24. Rudovich, N. N., Pivovarova, O., & Pfeiffer, A. F. H. (2007). The role of insulin resistance in the pathogenesis of ischemic stroke. Diabetes/Metabolism Research and Reviews, 23(7), 507–514. https://doi.org/10.1002/dmrr.733
25. Salas-Salvadó, J., Bulló, M., Babio, N., Martínez-González, M. Á., Ibarrola-Jurado, N., Basora, J., Estruch, R., Covas, M. I., Corella, D., Arós, F., Ruiz-Gutiérrez, V., Ros, E., & PREDIMED Study Investigators. (2018). Reduction in the incidence of type 2 diabetes with the Mediterranean diet: Results of the PREDIMED-Reus nutrition intervention randomized trial. Diabetes Care, 34(1), 14–19. https://doi.org/10.2337/dc10-1288Gastroenterology, 132(6),