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OXIDATIVE STRESS AND ANTIOXIDANT IMBALANCE IN METABOLIC SYNDROME

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Abstract: Metabolic syndrome (MetS) is a multifactorial disorder characterized by central obesity, insulin resistance, dyslipidemia, elevated blood pressure, and chronic low-grade inflammation. Oxidative stress is considered an important mechanism linking these metabolic abnormalities to cardiovascular disease and type 2 diabetes mellitus. It occurs when reactive oxygen species (ROS) production exceeds the capacity of endogenous antioxidant defenses. In MetS, excessive nutrient availability, adipose tissue dysfunction, hyperglycemia, elevated free fatty acids, mitochondrial dysfunction, and activation of ROS-producing enzymes contribute to increased oxidative burden. Persistent oxidative stress promotes lipid, protein, and DNA damage, endothelial dysfunction, inflammation, and impaired insulin signaling. At the same time, disruption of enzymatic and non-enzymatic antioxidant defenses further compromises redox homeostasis. This review summarizes the major mechanisms of oxidative stress and antioxidant imbalance in MetS, focusing on mitochondrial ROS production, inflammation, insulin resistance, endothelial dysfunction, and oxidative stress biomarkers. The potential role of antioxidant defenses and lifestyle-based interventions in restoring redox balance is also discussed..

Key words: Metabolic syndrome; oxidative stress; reactive oxygen species; antioxidant defense; insulin resistance; mitochondrial dysfunction; inflammation; endothelial dysfunction; lipid peroxidation; cardiovascular disease.

АННОТАЦИЯ: Метаболический синдром (МС) представляет собой сложное метаболическое состояние, характеризующееся сочетанием центрального ожирения, инсулинорезистентности, дислипидемии, повышенного артериального давления и хронического воспаления низкой степени активности. Накопленные научные данные показывают, что окислительный стресс является одним из важных механизмов, связывающих данные метаболические нарушения и способствующих развитию сердечно-сосудистых заболеваний и сахарного диабета 2-го типа. Окислительный стресс возникает тогда, когда образование активных форм кислорода (АФК) превышает возможности эндогенных антиоксидантных систем по поддержанию клеточного редокс-гомеостаза. При метаболическом синдроме избыточное поступление питательных веществ, дисфункция жировой ткани, гипергликемия, повышение уровня свободных жирных кислот, митохондриальная дисфункция и активация ферментов, продуцирующих АФК, могут приводить к увеличению окислительной нагрузки. Персистирующий окислительный стресс может способствовать перекисному окислению липидов, повреждению белков и ДНК, эндотелиальной дисфункции и активации воспалительных сигнальных путей, одновременно нарушая клеточные реакции на инсулин. Нарушения ферментативной и неферментативной антиоксидантной защиты могут дополнительно снижать способность тканей нейтрализовать избыток активных форм кислорода. В данном обзоре рассматриваются основные механизмы окислительного стресса и дисбаланса антиоксидантной защиты при метаболическом синдроме, включая митохондриальную продукцию АФК, воспаление, инсулинорезистентность, эндотелиальную дисфункцию и биомаркеры окислительного стресса. Также обсуждается потенциальное значение антиоксидантных механизмов защиты и подходов, основанных на изменении образа жизни, в восстановлении редокс-баланса. Понимание взаимодействия

окислительных и антиоксидантных процессов может способствовать более глубокому пониманию патофизиологии и профилактики метаболического синдрома и связанных с ним осложнений.

Ключевые слова: метаболический синдром; окислительный стресс; активные формы кислорода; антиоксидантная защита; инсулинорезистентность; митохондриальная дисфункция; воспаление; эндотелиальная дисфункция; перекисное окисление липидов; сердечно-сосудистые заболевания.

ANNOTATSIYA: Metabolik sindrom (MS) abdominal semirish, insulin rezistentligi, dislipidemiya, arterial bosimning oshishi va surunkali past darajadagi yallig‘lanish bilan tavsiflanadigan ko‘p omilli metabolik buzilishdir. Oksidlovchi stress ushbu metabolik o‘zgarishlarni yurak-qon tomir kasalliklari va 2-tur qandli diabet rivojlanishi bilan bog‘lovchi muhim mexanizmlardan biri hisoblanadi. U reaktiv kislorod turlari (ROS) hosil bo‘lishi endogen antioksidant himoya tizimlarining imkoniyatlaridan oshib ketganda yuzaga keladi. Metabolik sindromda oziq moddalarning ortiqcha ta’minlanishi, yog‘ to‘qimasi disfunksiyasi, giperglikemiya, erkin yog‘ kislotalari miqdorining oshishi, mitoxondrial disfunksiya va ROS hosil qiluvchi fermentlarning faollashuvi oksidlovchi yuklamaning kuchayishiga olib keladi. Uzoq davom etuvchi oksidlovchi stress lipidlar, oqsillar va DNKning shikastlanishi, endotelial disfunksiya, yallig‘lanish hamda insulin signalizatsiyasining buzilishiga sabab bo‘ladi. Shu bilan birga, fermentativ va nofermentativ antioksidant himoya tizimlarining buzilishi redoks-gomeostazni yanada izdan chiqaradi. Ushbu sharhda metabolik sindromda oksidlovchi stress va antioksidant muvozanat buzilishining asosiy mexanizmlari, xususan, mitoxondrial ROS hosil bo‘lishi, yallig‘lanish, insulin rezistentligi, endotelial disfunksiya va oksidlovchi stress biomarkerlari ko‘rib chiqiladi. Shuningdek, antioksidant himoya mexanizmlari hamda turmush tarzini o‘zgartirishning redoks muvozanatini tiklashdagi potensial roli yoritiladi.

Kalit so‘zlar: metabolik sindrom; oksidlovchi stress; reaktiv kislorod turlari; antioksidant himoya; insulin rezistentligi; mitoxondrial disfunksiya; yallig‘lanish; endotelial disfunksiya; lipidlarning peroksidlanishi; yurak-qon tomir kasalliklari.

Introduction: Metabolic syndrome (MetS) is a multifactorial condition characterized by central obesity, impaired glucose regulation, dyslipidemia, and elevated blood pressure. The coexistence of these abnormalities increases the risk of type 2 diabetes mellitus and cardiovascular disease. Its pathophysiology involves complex interactions among adipose tissue dysfunction, insulin resistance, chronic inflammation, abnormal lipid metabolism, and disturbed cellular redox homeostasis [1,2].Oxidative stress is an important component of MetS and develops when reactive oxygen species (ROS) production exceeds antioxidant capacity. Although ROS are involved in normal cellular signaling, their excessive accumulation can damage lipids, proteins, and nucleic acids. In MetS, hyperglycemia, elevated free fatty acids, mitochondrial dysfunction, NADPH oxidase activity, and chronic inflammation may increase ROS generation while weakening antioxidant defenses [2–4].Oxidative stress is closely linked to insulin resistance, as excessive ROS can disrupt insulin signaling, while metabolic overload may further enhance ROS production. Antioxidant protection is provided by enzymatic systems, including superoxide dismutase, catalase, and glutathione peroxidase, as well as non-enzymatic antioxidants such as glutathione and vitamins C and E. Persistent oxidative stress may overwhelm these defenses, resulting in antioxidant imbalance [3,5].Furthermore, oxidative stress may contribute to endothelial dysfunction, lipid oxidation, inflammation, and vascular injury, thereby promoting atherosclerotic and cardiovascular complications of MetS [4,6]. Therefore, oxidative stress represents an important link between metabolic dysfunction and cardiovascular pathology.This review examines the major sources of oxidative stress, alterations in antioxidant defense, and their relationships with insulin resistance, inflammation, endothelial dysfunction, and cardiovascular complications. The potential clinical relevance of

oxidative stress biomarkers and strategies for maintaining redox balance are also discussed.

Oxidative Stress in Metabolic Syndrome

Oxidative stress occurs when reactive oxygen species (ROS) and reactive nitrogen species exceed the capacity of antioxidant systems to maintain redox homeostasis. In metabolic syndrome (MetS), obesity, hyperglycemia, elevated free fatty acids, insulin resistance, and chronic inflammation can increase ROS production and promote oxidative damage [3,7].Mitochondria and NADPH oxidases (NOX) are major sources of ROS. Mitochondrial dysfunction and increased NOX activity can enhance oxidative stress in adipose tissue, vascular cells, and other metabolic tissues. Other contributors include xanthine oxidase, myeloperoxidase, and dysfunctional endothelial nitric oxide synthase [1,7,11].Excessive ROS can cause lipid, protein, and DNA oxidation. Important products include malondialdehyde (MDA), 4-hydroxynonenal (4-HNE), and 8-hydroxy-2′-deoxyguanosine (8-OHdG). ROS can also activate NF-κB and other signaling pathways, promoting chronic inflammation [3,11].

Antioxidant Defense and Imbalance

Antioxidant protection involves enzymatic systems such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx), together with non-enzymatic antioxidants including glutathione, vitamins C and E, uric acid, and bilirubin [5,8]. The Nrf2 pathway further regulates the expression of antioxidant and detoxification genes [12].In MetS, increased ROS production may exceed antioxidant capacity, resulting in redox imbalance. Oxidative stress can also damage antioxidant systems, creating a cycle in which oxidative injury and impaired antioxidant defense reinforce each other [3,5].

Oxidative Stress and Insulin Resistance

Oxidative stress contributes to insulin resistance by disrupting the IRS–PI3K/Akt signaling pathway and activating stress-sensitive kinases such as JNK and

IKK. Mitochondrial dysfunction, adipose tissue expansion, elevated free fatty acids, and inflammation may further increase ROS production [4,13].Thus, metabolic overload can increase oxidative stress, while excessive ROS can aggravate insulin resistance, creating a reciprocal cycle that contributes to the progression of MetS and type 2 diabetes [2,4].

Inflammation and Endothelial Dysfunction

Oxidative stress and inflammation are closely interconnected. ROS can activate NF-κB and increase inflammatory mediators such as TNF-α and IL-6, while inflammatory processes can further stimulate ROS production [9,14].In the vascular endothelium, superoxide can react with nitric oxide (NO), reducing its availability and forming peroxynitrite. Oxidative stress may also promote endothelial nitric oxide synthase (eNOS) dysfunction. Reduced NO availability contributes to impaired vasodilation and endothelial dysfunction [15,16].

Cardiovascular Complications

Oxidative stress may contribute to cardiovascular complications of MetS through endothelial dysfunction, LDL oxidation, inflammation, and vascular remodeling. Oxidized LDL can promote macrophage lipid accumulation and foam-cell formation, contributing to atherosclerotic plaque development [6,14,17].Therefore, oxidative stress represents an important link between metabolic abnormalities and cardiovascular pathology, although it acts together with dyslipidemia, hypertension, inflammation, and insulin resistance rather than as an isolated cause.

Oxidative Stress Biomarkers

No single biomarker completely reflects systemic oxidative stress. Common markers include MDA, 4-HNE, F2-isoprostanes, 8-OHdG, and oxidized LDL. Antioxidant status can be assessed using SOD, catalase, GPx, glutathione, and total antioxidant capacity [3,5,19–21].Because these biomarkers are influenced by nutritional status, lifestyle, medications, age, and analytical methods, a combination

of oxidative-damage and antioxidant markers provides a more informative assessment of redox imbalance.

Antioxidant and Lifestyle Strategies

Lifestyle modification is an important approach to improving metabolic and oxidative balance. Regular physical activity can improve insulin sensitivity, lipid metabolism, body composition, and endogenous antioxidant defenses [22,24]. Diets rich in vegetables, fruits, whole grains, legumes, nuts, and unsaturated fatty acids may also support antioxidant and anti-inflammatory processes [23,25].Weight management is particularly important because excessive adipose tissue promotes inflammation and ROS production. Although antioxidant supplements such as vitamins C and E, selenium, and coenzyme Q10 have been investigated, clinical evidence remains inconsistent. Therefore, antioxidant supplementation should not replace comprehensive lifestyle modification and treatment of the underlying metabolic abnormalities [22,26].Overall, oxidative stress in MetS results from excessive ROS production combined with inadequate antioxidant protection. This imbalance contributes to insulin resistance, inflammation, endothelial dysfunction, and cardiovascular complications. Understanding these interactions may help identify useful biomarkers and support strategies aimed at restoring redox balance.

Conclusion: Oxidative stress is an important component of the pathophysiology of metabolic syndrome. Excessive reactive oxygen species production and insufficient antioxidant protection can disrupt insulin signaling, mitochondrial function, lipid metabolism, inflammation, and vascular homeostasis. These processes interact bidirectionally, creating a cycle in which metabolic abnormalities further increase oxidative stress, while oxidative damage aggravates metabolic dysfunction.Mitochondrial dysfunction, increased NADPH oxidase activity, and impaired antioxidant defenses may promote lipid peroxidation, DNA damage, inflammation, and endothelial dysfunction, contributing to cardiovascular complications. Biomarkers such as malondialdehyde, F2-isoprostanes, 8-OHdG,

oxidized LDL, and antioxidant-related parameters may help assess different aspects of redox imbalance; however, no single biomarker fully reflects oxidative stress.Lifestyle modification, including regular physical activity, weight management, and a balanced diet, remains important for improving metabolic and antioxidant status. Although antioxidant supplementation has shown potential effects on oxidative stress markers, clinical evidence remains inconsistent.Overall, oxidative stress represents an important link between metabolic, inflammatory, mitochondrial, and vascular abnormalities in metabolic syndrome. Further research should focus on standardized biomarker assessment and individualized strategies for improving redox balance and reducing metabolic and cardiovascular complications.

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