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ЗМІСТ

FERROPTOSIS AS A NOVEL PATHOGENETIC TARGET IN INSULIN RESISTANCE AND METABOLIC SYNDROME

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Introduction. Insulin resistance and metabolic syndrome are among the key components of contemporary endocrine pathology, as they underlie the progression of prediabetes, type 2 diabetes mellitus, metabolic dysfunction-associated steatotic liver disease, arterial hypertension, and atherosclerotic complications. Their pathogenesis is centred on chronic low-grade inflammation, oxidative stress, lipotoxicity, and mitochondrial dysfunction. Increasing attention is being paid to ferroptosis, an iron-dependent form of regulated cell death characterised by lipid hydroperoxide accumulation and impairment of the cellular antioxidant defence. Contemporary reviews consider ferroptosis a potentially important pathogenetic link in obesity-associated comorbid metabolic and endocrine disorders. This is particularly important in insulin resistance and prediabetes at early stages, when molecular abnormalities have already developed, whereas clinical consequences can still be prevented or attenuated. For this reason, ferroptosis is of particular interest as a potential target for pathogenetically oriented therapy, since it integrates mechanisms of oxidative damage, disturbed iron homeostasis, and redox-dependent cellular dysfunction, which may, in theory, be influenced by both novel and already known drugs.

Aim. To summarise the data of contemporary studies represented in PubMed, Scopus, and Web of Science on the role of ferroptosis in the development of insulin resistance and metabolic syndrome and to assess the prospects for using ferroptosis-associated mechanisms as novel therapeutic targets in endocrinology, as well as the pharmacological possibilities for their modulation.

Materials and methods. An analytical review of current publications on ferroptosis in obesity, insulin resistance, type 2 diabetes mellitus, and their complications was conducted, with a focus on the pathogenetic significance of ferroptosis, potential pharmacological targets, and clinically relevant therapeutic approaches.

Results. Ferroptosis develops at the intersection of several pathogenetically significant processes: disruption of iron homeostasis, excessive generation of reactive oxygen species, depletion of the glutathione/glutathione peroxidase 4 (GPX4) system, and intensification of lipid peroxidation of polyunsaturated fatty acids. In the context of insulin resistance, ferroptosis is particularly important, as it links metabolic stress to damage to cellular structures that maintain insulin sensitivity and insulin secretion. In obesity, chronic inflammation and dysregulation of adipokines contribute to iron overload in β-cells through hepcidin-mediated suppression of ferroportin. Excess Fe^{2+} enhances Fenton reactions, mitochondrial reactive oxygen species generation, and damage to the insulin-secretory apparatus of β-cells. Importantly, contemporary reviews consider ferroptosis a pathogenetic hub in which iron-dependent damage, lipid peroxidation, mitochondrial dysfunction, inflammation, and β-cell insufficiency

converge. This provides grounds for considering several directions of potential anti-ferroptotic intervention: limiting cellular iron overload, suppressing lipid peroxidation, supporting the glutathione/GPX4 system, and modifying redox-dependent signalling pathways. In preclinical studies, iron chelators, lipid peroxidation inhibitors, and compounds that support cellular antioxidant defence are being investigated as agents to suppress ferroptosis. However, most of these approaches have not yet moved beyond experimental pharmacology. Therefore, practical interest lies not only in the study of new molecules, but also in the search for already used drugs capable of indirectly modulating ferroptosis as one of the links in metabolic injury. At the same time, contemporary data indicate that the role of ferroptosis in obesity and metabolic disorders is not purely linear. A 2025 study in Cell Metabolism showed that ferroptotic signalling in adipocytes may, conversely, limit obesity, reduce lipid accumulation, and enhance thermogenesis. This demonstrates that ferroptosis should not be oversimplified as an unequivocally damaging process, and that its pathogenetic and therapeutic significance may be tissue-specific and stage-dependent, that is, determined by cell type, the affected tissue, and the characteristics of the pathological process. A 2025 narrative review presented experimental data suggesting that glucagon-like peptide-1 receptor agonists (GLP-1) may reduce the severity of ferroptosis and pyroptosis in diabetic kidney disease and metabolic dysfunction-associated fatty liver disease: ferroptosis-associated markers decreased, whereas indicators of ferroptosis inhibition increased. At the same time, the authors emphasise that these conclusions are based primarily on experimental models; therefore, clinical verification remains pending. This suggests that the anti-ferroptotic effect may be one of the pleiotropic mechanisms of action of contemporary glucose-lowering agents, primarily GLP-1 receptor agonists. Thus, ferroptosis emerges not only as a pathogenetic phenomenon but also as a possible pharmacodynamic reference point for assessing the additional nephroprotective and hepatoprotective effects of antidiabetic drugs. According to the 2025 International Diabetes Federation (IDF Diabetes Atlas), approximately 2.3 million adults in Ukraine are living with diabetes. Given the challenges to continuity of patient care under wartime conditions in Ukraine, there is a particularly high demand for early pathogenetic targets relevant to insulin resistance, prediabetes, and the comorbid course of metabolic diseases. The 2025 report of the WHO Regional Office for Europe emphasises the need for further integration of prevention and management of noncommunicable diseases into the response of the Ukrainian healthcare system, and a domestic study among patients with type 2 diabetes mellitus demonstrated a substantial negative impact of war-related factors on glycemic control. In this context, ferroptosis deserves attention as a potential basis for future risk stratification and personalisation of adjunctive therapy.

Conclusions. Ferroptosis is a promising novel pathogenetic target in insulin resistance and metabolic syndrome. Its significance is determined by its involvement in the development of β-cell dysfunction, intensification of metabolic inflammation, lipid peroxidation, and mitochondrial damage. At the same time, its role may be tissue-specific and functionally ambiguous. Further study of ferroptosis-associated mechanisms may provide a basis for more precise, pathogenetically oriented, and individualised therapy of metabolic disorders in patients with prediabetes, insulin

resistance, and metabolic syndrome. From a pharmacological perspective, the greatest interest lies in identifying drugs and molecular approaches that selectively modulate ferroptosis without disrupting adaptive cellular responses, as well as in determining whether the anti-ferroptotic effect is part of the clinically significant pleiotropic action of contemporary antidiabetic agents. For Ukraine, this topic is particularly relevant given the need to improve endocrine care, cardiometabolic prevention, and the management of patients with chronic noncommunicable diseases under wartime conditions.

Keywords: Ferroptosis, insulin resistance, metabolic syndrome, pharmacological targets, GLP-1RA.