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REVIEWS

Oxidative Stress: Pathogenetic Role in Diabetes Mellitus and Its Complications and Therapeutic Approaches to Correction

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The review presents modern views about the role of oxidative stress reactions in the pathogenesis of types 1 and 2 diabetes mellitus and their complications based on the analysis of experimental and clinical studies. The sources of increased ROS generation in diabetes are specified, including the main pathways of altered glucose metabolism, oxidative damage to pancreatic β-cells, and endothelial dysfunction. The relationship between oxidative stress, carbonyl stress, and inflammation is described. The significance of oxidative stress reactions associated with hyperglycemia is considered in the context of the "metabolic memory" phenomenon. The results of our studies demonstrated significant ethnic and age-related variability of the LPO—antioxidant defense system parameters in patients with diabetes mellitus, which should be considered during complex therapy of the disease. Numerous studies of the effectiveness of antioxidants in diabetes mellitus of both types convincingly proved that antioxidants should be a part of the therapeutic process. Modern therapeutic strategies in the treatment of diabetes mellitus are aimed at developing new methods of personalized antioxidant therapy, including ROS sources targeting combined with new ways of antioxidant delivery.

Key words: *diabetes mellitus; oxidative stress; antioxidants; experiment; patients*

Diabetes mellitus (DM) is a group of metabolic diseases characterized by chronic hyperglycemia that results from disturbed insulin secretion or function or both [1]. Currently, many countries are on the verge of a global diabetes "epidemic", which is rapidly spreading across the planet [90]. Chronic hyperglycemia in DM is accompanied by damage, dysfunction, and failure of various organs and tissues, development of micro- (retinopathy, nephropathy, and neuropathy) and macrovascular (cardiovascular disorders) complications [48]. According to the WHO classification (1999, with amendments), two types of DM are distinguished: type 1 DM (DM1) resulting from destruction of pancreatic β-cells usually leading to absolute insulin insufficiency and type 2 (DM2) mainly related to insulin resistance and relative insulin insufficiency or mainly violation of insulin secretion with or without insulin resistances [1].

ROS are chemically active oxygen-containing molecules generated in living systems. They are oxygen metabolism natural by-products in all aerobic organisms [75]. The main ROS types include superoxide, hydroperoxyl radical, singlet radical, hydroxyl radical, nitric oxide, peroxynitrite, *etc*. [93]. ROS are primarily generated in mitochondria, but there are also alternative mechanisms that contribute to their formation: NADPH-oxidase (NOX), immune reactions, xanthine oxidase, arachidonic acid metabolism, *etc*. [41]. ROS are widely involved in the processes of intracellular signaling and regulation of cell activity — apoptosis induction, adaptation to the effects of

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various factors, and immune response [92]. Moreover, ROS can stimulate inflammatory responses through protein kinases, transcription factors, and proinflammatory factors genomic expression [69]. Increased ROS accumulation leads to oxidative stress (OS), which contributes to major cellular components damage, including lipids, proteins, and DNA [94]. The antioxidant defense (AOD) system provides critical defense for the biological system by limiting the damaging effects of ROS. There are many antioxidant enzymes, including superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR), catalase, paraoxanase (PON), *etc*. [76]. In addition to enzymatic antioxidants, non-enzymatic antioxidant defense (ascorbate, tocopherols, retinol, carotenoids, reduced glutathione (GSH), melatonin, polyphenols, ceruloplasmin, carnosine, *etc*.) also plays an important role in maintaining normal ROS levels [70]. Under different pathological conditions, including DM, the redox balance can be disturbed that leads to negative consequences for the cell [75].

Molecular mechanisms of OS development in DM. At present, there is strong evidence of direct involvement of hyperglycemia in the initiation of vascular complications of DM, while OS associated with enhanced ROS generation plays a crucial role in their pathogenesis [31]. The main molecular mechanisms associated with OS in DM have been determined and they are associated with glucose and lipid metabolism [52]. Thus, several metabolic pathways that stimulate OS development under glycemic conditions are considered: glycolytic pathway, enhanced formation of advanced glycation end products (AGE), hexosamine pathway, activation of protein kinase C (PKC), polyol pathway, and deactivation of the insulin signaling pathway [20]. Under hyperglycemia conditions, excessive production of ROS during glycolysis reactions is observed. It leads to DNA damage and subsequent activation of poly-ADP-ribose polymerase 1 (PARP1), a DNA repair enzyme [82,85]. PARP1 inhibits glyceraldehyde-3-phosphate dehydrogenase (GA3PDG) activity, which leads to accumulation of glyceraldehyde-3-phosphate (GA3P) and other glycolysis intermediates, such as fructose-6-phosphate (F6P) and glucose-6-phosphate (G6P) [45]. The increase in the content of GA3P activates other prooxidant pathways, including polyol, hexosamine pathways, *etc*. [85]. In addition, GA3P accumulation can cause glucose autoxidation, which leads to the hydrogen peroxide formation that contributes to OS. Glucose autoxidation can occur due to its accumulation in cells. This leads usually to the formation of glyoxal, an AGE precursor, and definitely promotes cellular OS [39].

Formation of AGE-products (carbonyl stress). Under hyperglycemia conditions, glucose autoxidation occurs and carbonyl compound glyoxal, an AGE-precursor is forming. Also, glucose metabolites, such as GA3P and dihydroxyacetone-3-phosphate, non-enzymatic dephosphorylation gives methylglyoxal, another precursor of AGE. Glyoxal and methylglyoxal bind to different receptors of AGE (AGE-R1, AGE-R2, AGE-R3 and receptor for advanced glycation end products) or interact with different biomolecules, causing OS directly or indirectly through PKC activation [28]. 3-Deoxyglucosone is the third precursor of AGE, it is formed by the cleavage of the glucose-derived adduct of lysine 1-amino-1-deoxyfructose, commonly referred to as the Amadori product [67]. It was found that other extracellular matrix components, lipids and nucleic acids, can also be converted into AGE [66]. Modern concept of OS provides its relationship with carbonyl stress, as a result of which an active synthesis of carbonyl compounds occurs. This relationship is evident also for DM.

Hexosamine pathway of glucose oxidation. Under glycemia conditions, the F6P level increases and the molecule is metabolized by glucosamine-fructose aminotransferase to glucosamine-6-phosphate, which subsequently turns into uridine phosphate-N-acetylglucosamine (UDP-GlcNAc) through activity of UDP-N-acetylglucosamine-1-phosphate uridyltransferase?. Accumulation of UDP-GlcNAc triggers activation of O-glucosamine-N-acetyltransferase, which is associated with the prooxidant role of the hexosamine pathway in DM. Activity of this enzyme and hexosamine pathway is associated with changes in gene expression and increased expression of transcription factors TGF-α and TGF-β that inhibit mitogenesis of mesangial cells, activate the proliferation of the collagen matrix and thickening of the basement membrane [36].

PKC activation pathway. PARP1 that is activated as a result of DNA damage caused by OS, inhibits GA3PDG activity, which leads to GA3P and its isomer, dihydroxyacetone-3-phosphate (DHA3P) accumulation. DHA3P, which in the presence of free fatty acids, is oxidized to glycerol-3-phosphate by the glycerol-3-phosphate dehydrogenase, forms diacylglycerol, which interacts with the AGE receptor, stimulating OS reactions through PKC activation [52].

Polyol pathway of glucose oxidation. In hyperglycemia, aldose reductase is activated that leads to an increase in the level of sorbitol that is converted by sorbitol dehydrogenase to fructose. High levels of fructose cause accumulation of GA3P and DHAP that leads to OS due to methylglyoxal formation and PKC activation [45]. In addition, increased activity of aldose reductase causes a decrease in NADPH levels, which subsequently leads to GPx activity and glutathione levels decrease. This situation causes the AOD suppression, which leads to OS.

Deactivation of the insulin signaling pathway. Hyperglycemia leads to activation of uncoupling protein-2 (UCP-2), which results in a decrease in ATP/ADP ratio and inhibition of the ATP-dependent pathways leading to secretion, release, and action insulin [49]. OS causes deactivation of the main signaling pathways that are usually activated during the action of insulin (Cb1, PI3K, and p38 MARK) by stimulating activity of phosphatases such as protein tyrosine phosphatase 1B and SH_2-containing tyrosine protein phosphatase, resulting in termination of insulin action [63]. OS also activates several stress-sensitive signaling pathways that contain components such as NF-κB, inflammatory molecules such as inducible NO synthase, and a class II histocompatibility complex [29]. These processes greatly and generally contribute to impairment of insulin secretion and action.

Oxidative damage to β-cells caused by ROS as a result of hyperglycemia affects the quantity and quality of secreted insulin [88]. There are data that β-cell dysfunction (impaired secretory ability and increased insulin resistance) caused by OS plays an important role in the DM1 and DM2pathogenesis [34]. Excessive ROS production in β-cells can cause changes in the shape, volume, and function of mitochondria, which contributes to disintegration of ATP-dependent K^+-channels and impaired insulin secretion [34,35,88]. These processes can be due to the fact that the content of antioxidant enzymes in β-cells is 10-20-fold lower than in cells of the liver, kidneys, heart, brain, and other organs [98]. It was found that the expression of mitochondrial Mn-dependent SOD2 and cytoplasmic Cu/Zn-dependent SOD1 genes does not exceed 50% of the level of their synthesis in the liver, the content of GPx and catalase is 5% [30,98]. As a result, islet cells are most sensitive to the attack of ROS and other diabetogenic agents. Nitric oxide (NO), an unstable radical whose oxidation products are nitrates and nitrites, also takes an active part in the destruction and death of β-cells mechanisms [34]. NO, cytokines, and other forms of ROS can affect the process of genetically programmed cell death, apoptosis, which is based on the endonuclease activation leading to fragmentation of genetic material and death of β-cells [66].

OS in relation to DM can play a dual role, contributing not only to its manifestation, but also to escalation of the disease and related complications [31,45,95]. ROS can activate several other pathways, which, in turn, cause one of the main complications of DM — endothelial dysfunction [34]. Endothelial dysfunction is an independent risk factor for cardiovascular complications of DM, contributes to the leukocytes and platelets adhesion, thrombosis and inflammatory reactions development, which are the most important factors of atherosclerosis [79]. It was found that even short-term exposure to hyperglycemia leads to a selective increase in the expression of *iNOS* gene, followed by an increase in NO. Simultaneous elevation of NO and superoxide radicals increases the formation of peroxynitrite, which is a strong oxidant with a toxic effect on the vascular network, which can contribute to the disease progression and myocardium damage [33,44]. Various isoforms of NOX are expressed in monocytes, macrophages, and vascular cells, and both perform a protective role and contribute to the development of endothelial dysfunction and inflammation [44]. Activation of PKC, AP-2 and AGE generation, increase the expression of NOX isoforms in monocytes and macrophages, stimulate ROS increase, as well as the synthesis of proinflammatory proteins such as IL-6, monocyte chemoattractant protein 1 (MCP-1), and intercellular adhesion molecules 1 (ICAM-1) [55,89].

OS plays a major role in progression of other serious complications of DM: neuropathy, nephropathy, and retinopathy. The main ROS sources in the kidneys are NOX enzymes, in particular NOX4 and NOX5 homologues. Various factors affect the expression and activity of these enzymes, which leads to the proinflammatory and profibrotic markers growth, including NF-κB p65 subunit, TNFα, TGF-β, and fibronectin [47,79]. At the molecular level, the initial driver of diabetic retinopathy is glucose, which affects the same metabolic pathways, including the polyol, hexosamine pathway, PKC, and the AGE/RAGE axis. In endothelial cells of retinal microvessels, OS leads to a decrease in the expression of hypoxia-induced factor alpha (HIF1α), which, in turn, activates vascular endothelial growth factor (VEGF), which stimulates angiogenesis [54]. OS increases retinal inflammation by increasing the expression of proinflammatory proteins (NF-κB-factor, MCP-1, and ICAM-1). In addition, Müller cells promote OS-induced inflammation by glial fibrillar protein activation (GFAP) [79]. In diabetic neuropathy, OS induced by hyperglycemia stimulates damage to nerve cell through LPO, DNA damage, with pathological activation of repair pathways, exhaustion of cell antioxidants, and induction of proinflammatory transcription factors [96].

High intensity of free processes promotes the expression of redox-sensitive genes of AOD enzymes. Their promoters have binding sites with transcription factors — NF-κB, AP-1, Nrf2, FoxO, PPARS, and Bach 1, NF-κB/ARE system, regulating the development of inflammation and AOD activity [84]. Insulin is involved in the regulation of antioxidant enzyme activity through the expression of Nrf2 and NF-κB transcription factors by insulin-dependent effector proteins (Akt kinase, MARK) [99].

Currently, OS reactions associated with hyperglycemia in DM are considered in the context of the

"metabolic memory" phenomenon, when the modification of biomolecules by ROS can lead to cellular dysfunctions a long time later after of DM manifestation [20]. Thus, newly identified DM1 and DM2large epidemiological studies showed that early and intensive interventions aimed at stabilizing hyperglycemia and risk factors associated with cardiovascular diseases prevent the onset and slow the progression of late chronic complications [34]. However, despite the improvement of DM control in the later period, hyperglycemia in the early stages necessarily leads to these specific complications onset and progression, even after 30 years [98]. It was demonstrated that AGEs and their receptors are involved in the "metabolic memory" formation by NF-κB factor activation, which increases the expression of genes responsible for vascular damage [28]. OS also determines epigenetic changes, such as chromatin modification (including histone modification) and DNA methylation. These changes allow cells to quickly adapt to environment changes, are "remembered" even in conditions of normoglycemia, and are passed on to the next generation [61,97].

Experimental studies of OS reactions in DM. Non-genetic models of alloxan (AX) and streptozotocin (STZ) diabetes are considered to be the most common, accessible, and easily reproducible experimental models in the study of OS reactions [16]. AX and STZ are structural analogs of glucose that can bind to glucose transporter GLUT2 and selectively accumulate in β-cells of the pancreas, damaging them by generating ROS [5]. These diabetogens are used in various concentrations to model DM1 [3]. To create a model of DM1, a high-calorie diet, various combinations of STZ with a high-calorie diet, or pre-administration of nicotinamide (a model of neonatal DM1) are most often used [23]. There are various experimental data reflecting the state of the LPO—AOD system and changes in the biochemical parameters of the functional detoxification system in rats when modeling AX DM [2]. Thus, chemiluminescence analysis showed an increase in the intensity of LPO processes in animal blood, heart, liver, and kidneys. A decrease in the number of thiol groups was observed, which confirmed disturbances of regeneration of low-molecular-weight antioxidant factors under conditions of AX DM [14]. It was found that hyperglycemia, LPO activation, atherogenic nature of lipid as well as in protein metabolism disorders, were observed [18]. On day 10 of AX DM, pronounced hyperglycemia, shifts in the pro- and antioxidant balance, a decrease in catalase and SOD activities in blood serum developed [22]. It was shown that the cytotoxic effect of AX is realized due to the action of free radical and oxidation of protein SH-groups, which leads to necrosis, as well as due to disturbances in calcium homeostasis and destabilization of mitochondrial membranes, followed by caspase cascade activation without participation of p53 protein (which activates apoptosis) [30].

The STZ DM model is also widely used for DM modeling. There are evidence of better validity of STZ DM model, due to intensification of OS reactions and longer animal lifespan [23]. For instance, in STZ DM model, there was a pronounced activation of LPO reactions, changes in energy metabolism (inhibition of aerobic ATP synthesis, accumulation of lactate, dissociation of oxidative phosphorylation and development of lactic acidosis), as well as alterations of the functional state of cell membranes (structural rearrangement of membrane lipids, microviscosity disorders, and a decrease in activity of insulin receptors and membrane-bound Na^+,K^+-ATPase and Ca^{2+}-ATPase) [12]. Recent studies have shown that even at the early stages of STZ DM in rats, along with hypertriglyceridemia and hypercholesterolemia, LPO intensity increases against the background of reduced activities of antioxidant enzymes and low level of ω3-fatty acids [13]. It was found that under experimental conditions OS develops and total NO metabolites concentration in the blood serum of animals decreased [7]. In DM alone and its combination with arterial hypertension in rats, the content of a molecular chaperone HSP60 that plays an important protective role against OS significantly decreased in the left-ventricular cardiomyocytes [4]. Streptozotocin-induced hyperglycemia is effectively reduced by increased expression of genes encoding SOD2 and catalase, which implies the involvement of key ROS in β-cell dysfunction [64]. It is important to emphasize that the response of antioxidant enzymes (SOD, catalase, and glutathione system enzymes) during the development of OS in experimental DM1 is very ambiguous and does not significantly depend on animal species and sex, as well as the type of cells [21]. The main factor determining the function of these enzymes is the duration of DM1: a compensatory increase in enzyme activity at the early stages of DM1 is followed by their depletion at the late stages. Moreover, high activity of SOD in many tissues (heart, skeletal muscles, kidneys, and liver), with catalase and GPx deficiency can be considered as an additional damaging factor at the early stages of DM1 [21]. It was shown that the developing OS induced by hyperglycemia in the adipose tissue of Wistar rats with STZ- and AX-induced DM is caused by an increase in the expression of xanthine dehydrogenase gene mRNA and post-translational oxidative modification of xanthine dehydrogenase activity [16].

Heterogeneity of the obtained results on the intensity of the LPO—AOD processes are probably determined by diversity of DM2 models and polygenic nature of the disease. In particular, the antioxidant

status in experimental DM2 is determined by a specific model — animal species, sex, and tissue [24,101,104]. However, certain regularity was revealed: an increase in OS and suppression of AOD with increasing the severity of diabetic complications. The introduction of antidiabetic drugs and/or antioxidants at the time of DM2 induction or at its early stages normalized animal condition and restored activity of the enzymatic part (chain) of the AOD system [21].

It has recently been noted that rat models of diabetic atherosclerosis, cardiomyopathy, and any other diabetic macrovascular complication do not reproduce the main aspects of the phenotypes of diabetic complications in humans [43]. In some studies, large animals, such as pigs or non-human primates, were used as the models; in these animals, the diabetic cardiovascular diseases are more similar to human cardiovascular diseases. In fact, further testing of ROS involvement in these models is an important next step [62].

Clinical studies of the OS reactions in DM. Most case-control studies postulate an increase in biomarkers of oxidative damage to lipids, proteins, and nucleic acids in patients with prediabetes and with DM1 and DM2 in comparison with the controls [31,35,44]. Similar results were obtained in patients with DM and micro- and macrovascular complications in comparison with the groups data without micro- and macrovascular complications [71,83]. Thus, it was shown that in patients with uncomplicated DM1, there is an increased generation of TBA-reactive products accompanied by a decrease in antioxidant enzyme activity [25]. Malondialdehyde (MDA) content in children and adolescents with unsatisfactory glycemic control significantly surpasses the control values and does not reach the norm at the early stages of compensation [26]. A positive correlation was found between the level of MDA and duration of DM1 [21]. It was noted that enhancement of LPO reactions leads to changes in the interaction of insulin with its receptors, because MDA covalently binds both lipids and proteins in cell membranes with the formation of cross-links [31,45]. This leads to a violation of insulin receptors internalization and a decrease in the number of insulin-binding sites and can serve as a causes of insulin resistance [52]. It was noted that progression of vascular complications in DM1 is associated with increasing AOD insufficiency, which is manifested by a decrease in the concentration of the main antioxidants (α-tocopherol, ceruloplasmin, and glutathione) [34,42]. In patients with DM1 and diabetic nephropathy (decompensated form), activation of LPO and inhibition of the antioxidant system is noted against the background of metabolic disorders [6]. The data about the antioxidant enzyme activity in red blood cells of patients with DM1 are contradictory. SOD activity increased or did not change [21]. GPx activity increased or decreased, while a positive correlation was found with the total antioxidant activity of plasma and glutathione content [31,45]. Some researchers reported that activity of GR and GPx did not differ from the standard values [21].

Among different biomarkers of OS assessed in patients with DM2, the most consistent results were the levels of TBA-reactive products, plasma AGE, proteins carbonyl groups in plasma, as well as urinary 8-hydroxy-deoxyguanine (8-OHdG) level [74]. These indicators were elevated and closely correlated with unsatisfactory control of glycaemia and DM2 course severity. In most studies, 8-iso-prostaglandin F2α (8-iso-PGF2a) and 8-OHdG levels in plasma and urine were also elevated in the prediabetic stage [44,72]. These biomarkers measured in urine are considered significant in predicting micro- and macrovascular complications of DM2 [72]. There are ample data about antioxidant system in patients with DM2. There was a decrease of blood plasma total antioxidant capacity, low level of non-enzymatic antioxidants (ascorbate, α-tocopherol, retinol, β-carotene, uric acid, and glutathione), while the normalization of glycaemia did not eliminate the manifestations of OS in patients [27]. Insulin therapy normalized OS parameters in patients with DM1, but did not change them in DM2 [21]. Comparative studies showed an increase in SOD activity, catalase, and GPx in red blood cells of patients with poorly controlled DM2, as well as those burdened with coronary heart disease and stroke [19]. At the same time, in DM complicated by cardiovascular diseases patients, activities of SOD, GPx, and GR significantly decreased, and men had lower activity of SOD and GPx in comparison with women [31,45]. New data also indicate a relationship between paraoxanase 1 (PON1) and hemoxygenase 1 (HO1) in the serum of patients with DM2 and its complications, and a recent meta-analysis showed that PON1 is significantly associated with susceptibility to DM2and the development of macro- and microangiopathies [87].

There are data that OS plays a crucial role in systemic inflammation, which contributes to the pathophysiology of macro- and microvascular complications in DM [33]. DM significantly changes the lipid profile and makes cells more susceptible to LPO. According to recent studies, not only LDL lipids, but also apolipoprotein component that forms insoluble aggregates, is responsible for oxidative damage in diabetic complications [29]. It is believed that oxidized lipoproteins (Ox-LDL) contribute to cardiovascular complications in DM, and LDL oxidation in patients with DM is significantly increased compared to the corresponding control groups [10]. At the same time, the most atherogenic LDL are also the most exposed to free radical oxidation. It was proven that there is a gen-

eral molecular mechanism of primary pre-atherogenic damage to the vascular wall in atherosclerosis and DM, which consists in enhanced carbonyl-modified LDL formation and accumulation in foam cells [11]. It is suggested that increased LPO in LDL in hypercholesterolemia and DM is associated with the activation of cholesterol or glucose autoxidation under oxidative or carbonyl stress, respectively. The obtained results reveal a possible mechanism of atherosclerosis progression in the presence of DM [10].

Currently, it is proved that the nature of metabolic reactions in DM depends on many factors, including age, sex, and ethnic factors [8]. Significant ethnic variability in the course of DM may be due to both different living conditions (external environmental factors) and differences in the frequency of occurrence of predisposing and protective genetic markers in populations, as well as the presence of markers specific to different populations. Earlier studies showed low incidence of DM among the indigenous Northern peoples and people of Siberia in the Russian Federation, which is largely due to the presence of protective alleles for this nosology [56]. Thus, the data of the Research Center for Family Health and Human Reproduction Problems showed that Buryats are characterized by a low frequency of DM1 and not similar to Caucasians HLA-alleles and genotypes association [58]. Low genetic conditionality of DM1 in the Buryat group contributes to the development of certain features of metabolic reactions in representatives of this ethnic group, which allowed them to be attributed to the group of "relative ethnic norm" [60]. Thus, it was shown that the intensity of LPO processes in patients of Buryat ethnic group with DM1 was reduced compared to Russians (lower level of primary and intermediate products, increased values of total antioxidant activity), which is confirmed by low values of OS coefficient. DM1 course in Buryats is also characterized by reduced values of total lipids, triglycerides, total cholesterol, and LDL, which can probably contribute to a more favorable course of the disease confirmed by clinical data [57]. The sex factor can also determine the nature of the course of diabetes. So, we established peculiarities of carbonyl stress and OS in men with DM2 complicated with lower extremities macroangiopathy, consisting in AGEs increasing the concentration and the thiol-disulfide system function reducing, which allowed to calculate the risk prediction coefficient of vascular complications development [59]. It was found that in women of reproductive age with DM1, menstrual function disorders occur with a lack of α-tocopherol, GSH, low SOD activity, an increase in the oxidized glutathione concentration, normal retinol levels, and an increase in the range of changes in the primary and end products LPO content [37].

Despite of the fact that the significance of various OS biomarkers in the genesis of vascular complications of DM is established, new methods for its assessment, in particular the method of kinetic chemiluminescence (determining antioxidant and prooxidant plasma activity) are introduced in practice [15]. Its use in combination with clinical, laboratory, and instrumental studies makes it possible to better assess the patient's condition for the purpose of diagnosis and choice of therapy.

Possibilities of antioxidant therapy in DM. Considering that OS is significant for numerous DM complications, extensive studies on the antioxidant effect of various substances, including natural antioxidants of plant origin, were conducted [81]. Thus, the data indicating the role of various antioxidants (glutathione, coenzyme Q10, and α-lipoic acid) in restoring insulin sensitivity were obtained [91]. It was shown that α- and γ-tocopherol, retinol, β-cryptoxanthin [77], ascorbic acid [68], α- and β-carotene, lutein and zeaxanthin [86], and lycopene [51] significantly reduce DM complications. It was found that phytochemical components (>10,000 components are identified) of food and medicinal plants exhibit powerful anti-radical and anti-inflammatory activity, regulate activities of α-glucosidase and lipase, reduce the level of glycaemia, improve the function of the pancreas, have a synergistic effect with hypoglycemic drugs and, thus, are highly effective in the DM treatment [103]. Thus, phytochemicals, including anthocyanins and polyphenols act as antioxidants, blocking the synthesis of prostaglandins, proinflammatory cytokines and transcription factors, in particular, NF-κB-factor [50]. Curcumin is considered suitable for the prevention and reduction of the risk of DM complications, due to its anti-inflammatory and antioxidant activity [80]. Butein, an antioxidant polyphenol, inhibits the formation of NO *in vitro*, protects pancreatic β-cells under conditions of excessive inflammation, and can be used to prevent the progression of DM1 [65]. Resveratrol modulates the expression of genes associated with the DM2 development by inducing the expression of several β-cell genes and insulin expression in pancreatic α-cells [50]. The effect of various components with antioxidant action on the DM course was studied under experimental conditions. Thus, the introduction of coenzyme Q10 together with L-arginine contributed to OS suppression, a significant increase in the NO content, and its introduction against the background of the NO synthesis inhibitor, Nω-nitro-L-arginine methyl ether, partially abolished the effect of the inhibitor on the LPO—AOD indicators and the NO concentration. In all variants of the study, coenzyme Q10 stimulated the expression of eNOS and NO bioavailability due to proatherogenic cholesterol fractions concentration

decrease [7]. The effectiveness of coenzyme Q10 was shown in clinical settings [6] and the positive effect of the synthetic biguanide derivative N-[imino(1-piperidinyl)methyl]guanidine on free radical homeostasis, aconitate hydratase activity, and citrate content in the liver and blood serum of rats with DM2 [17].

Epigallocatechin gallate, a green tea compound, was shown to be highly effective with respect to OS parameters and plasma antioxidant capacity [32]. The data of our studies showed that the use of N-acetylcysteine is pathogenetically justified in patients with DM2 complicated by microangiopathy of the lower extremities [38]. The use of this drug leads to the carbonyl stress indicators decrease due to glyoxal and methylglyoxal levels decrease and stabilization of the cells redox potential, and also due to reduced cysteine and glutathione fractions increase and decrease in their oxidized fractions [38,59]. The use of catalytic antioxidants, such as SOD/catalase mimetics and functional GPx mimetics, was greatly developed in the experiment, but no significant changes were detected in clinical conditions [84]. Among domestic drugs, ethylmethylhydroxypyridine malate and ethylmethylhydroxypyridine succinate exhibiting antioxidant, antihypoxic, and membrane-protective properties against vascular DM complications should be mentioned [9].

Despite numerous studies of the effectiveness of antioxidants in DM1 and DM2, there is still no evidence that the use of a single antioxidant drug has a complete therapeutic effect, while it is clearly established that antioxidants should be a part of the therapeutic process [81]. At the same time, there is controversial information about the lack of a pronounced clinical effect of well-known anti-oxidant drugs, especially in patients with DM2. This may be due to the multifactorial nature of the disease, the use only one drug or several drugs with similar properties and targets, and the irreversibility of certain changes and numerous complications [40]. Special attention should also be paid to the properties of the antioxidants themselves: they can exert prooxidant effect in high doses, have poor solubility and low permeability of cell biomembranes, lack of stability and specificity of action, *etc*. [73]. In this regard, modern therapeutic strategies for the DM treatment should include antioxidants new delivery methods, including microparticles, nanoparticles and liposomes, as well as the synthesis of agents that affect the sources of ROS and the modulation of gene expression. Drug delivery in the form of a microparticle system can contribute to the supply of antioxidants with poor membrane permeability (for example, SOD). It was found that encapsulation of SOD caused a 60% reduction in superoxide production, while free SOD had a small effect [102]. Nanoparticles are another way to increase the antioxidants bioavailability. For example, biodegradable encapsulated curcumin nanoparticles delayed cataract progression in a model of rats with DM [46]. Another study showed that curcumin also has a higher antioxidant capacity when encapsulated in liposomes (artificial lipid bilayer vesicles) [102]. Taken together, the new antioxidant delivery methods have excellent therapeutic potential in the DM treatment. Another type of new therapeutic strategy that has made significant progress in the treatment of DM and its complications is direct exposure to ROS sources — development of targeted antioxidants. MitoQTPP and TEMPOL are two mitochondrial antioxidants that are used to reduce OS and improve vascular prognosis in patients with DM [100].

Besides, suppression of non-mitochondrial sources is of great importance, especially with the use of NOX inhibitors including GKT137831, GKT136901, APX-115, and VAS2870 [53]. Suppression or redox modification of some proteins (IKKβ, PKC, and Keap1) that potentiate the DM development, may also be a promising therapeutic approach. These studies show that a significant effect can be achieved by regulating the Nrf2/Keap1/ARE pathway [78]. Regulation of redox modification of PKC may also have great potential in the treatment of diabetic complications [102].

Despite many years of research on the intensity of oxidative stress reactions as a pathogenetic factor in the development of DM and its complications, these studies are still relevant today. New emphasis is placed on the identification of significant biochemical markers of free radical reactions, as well as the relationship of oxidative stress reactions with carbonyl stress and inflammation, including in the context of the "metabolic memory" phenomenon, which can be used as additional criteria for monitoring the disease progression. Modulating the redox imbalance by using a personalized approach that takes into account gender and ethnic factors, as well as targeting ROS sources, represents a potentially new therapeutic approach in the DM treatment.

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