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REVIEW ARTICLE
ОБЗОРНАЯ СТАТЬЯ

Oxidative stress and antioxidant defense system in atherosclerosis and diabetes mellitus type 2

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Abstract. *Relevance.* Cardiovascular diseases are the leading cause of death, and the current therapy is imperfect, as it has many side effects, and is ineffective for about a third of patients. In this review, we consider the role of oxidative stress in diseases of atherosclerotic genesis, such as type 2 diabetes mellitus and coronary heart disease. The key targets for molecular and cellular therapy of oxidative stress in diseases of atherosclerotic genesis can be, firstly, receptors localized on the cell membrane, the binding of which to the end products of glycolysis and proinflammatory interleukins leads to the activation of inflammatory cascades; secondly, antioxidant molecules, the content of which must be maintained at an optimal level both by alimentary and local infusion. Since the processes of β-cell damage and death are in most cases mediated by the activity of the NLRP-3 inflammasome, it is necessary to study possible ways of destabilizing this protein complex, which help prevent the maturation and secretion of interleukins-1β and –18. *Conclusion.* In addition to direct treatment, careful monitoring of biochemical markers signaling the onset of a pathological process is required, a tool for which can be tests for determining the antioxidant status. In addition, it is recommended to promote a healthy lifestyle among individuals prone to diabetes mellitus 2 and cardiovascular diseases, consisting of reducing the consumption of foods rich in fats and carbohydrates (in parallel with enriching the diet with fiber-rich, vitamins and preventing oxidative stress), increasing beneficial physical activity and quitting smoking.

Keywords: atherosclerosis, diabetes mellitus type 2, ischemic heart disease, oxidative stress, macrophages, reactive oxygen species, interleukins

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Introduction

Cardiovascular diseases of atherosclerotic genesis continue to occupy a leading place in the structure of mortality among non-infectious diseases of humans. In this regard, the study of new risk factors for the development of atherosclerosis and its complications does not lose its relevance. Mortality from atherosclerosis has long been the leading cause of death in the world and, despite all the achievements of modern medical practice, these statistics remain [1]. According to the definition of experts from the World Health Organization (WHO), «atherosclerosis is a variable combination of changes in the intima of the arteries, including the accumulation of lipids, lipoproteins, complex carbohydrates, fibrous tissue, blood components, calcification and associated changes in the middle layer (media) of the vascular wall». Epidemiological studies have shown that atherosclerosis is a complex multifactorial disease underlying most of the circulatory system ones, including coronary heart disease (CHD) and its forms: angina pectoris, myocardial infarction, sudden death; cerebrovascular diseases or vascular [2]. Mortality from them has long been the number one cause in the world and, despite all the advances in medicine, this deplorable statistic remains unchanged. In recent years, the incidence of atherosclerosis has reached alarming proportions, surpassing such causes as injuries, infectious diseases and oncological diseases in terms of the risk of developing loss of ability to work, disability and mortality [3]. The number of deaths due to cardiovascular diseases is approximately 17.9 million per year, according to WHO [4]. In 2010 alone, global costs for cardiovascular disease were $863 billion and are expected to increase by 22% by 2030 [5].

In the last few years, special interest of researchers has been focused on the free radicals' role in these pathologies [6]. Free radicals have a short lifetime: superoxide anion radical, 10^{-6} sec; hydroxyl radical, 10^{-9} sec; hydroperoxide radical, 10^{-12} sec. The superoxide anion radical is the initial product of the oxygen molecule activation, likewise the source of other reactive oxygen species (ROS) forming, notwithstanding its relative inactivity. The hydroperoxide radical (HO2) is more damaging than the superoxide anion radical [7]. In cells, the main damaging agent is $OH^{\cdot -}$. It can break covalent bonds such as C — H and C—C. Currently, the term «ROS» includes both oxygen radicals and non-radical molecules, which can be easily converted into free radicals. With regard to active nitrogen species, these include molecules formed from NO, such as peroxynitrite (ONOO-), nitrosyl radical ($ONOO^{-}$), and nitrogen dioxide (–ON·) and nitrogen dioxide (NO_2) [7, 8].

Oxidative stress is manifested by the accumulation of lesioned DNA nitrogenous bases, protein oxidation products and lipid peroxidation, as well as decreased antioxidant levels and the associated increased susceptibility of lipids alongside with membrane lipoproteins to the ROS effect [9]. Most often, oxidative stress occurs when antioxidant defense systems fail to fully cope with the influx of free radicals that are generated during cellular metabolism for some reasons [10].

Many cells of macrophage and monocyte origin come as ROS sources in the body [11]. A superoxide anion formed in phagocytes and smooth muscle cells of blood vessels causes very low density lipoproteins (VLDL) to oxidate [12]. Hence, oxidatively modified LDL may cause unregulated cholesterol accumulation in macrophages, which initiates the atherosclerotic lesions development. Albeit, the leading role in atherogenic oxidative modification of LDL is played not by the acylhydroperoxides accumulation in phospholipids located on the LDL particles' outer layer, but by chemical modification of the only LDL protein, i.e. apoprotein B-100, which free radical oxidation of lipids secondary products, such as 4-hydroxynonenal, malonic dialdehyde and other natural dicarbonyls, trigger. In numerous studies investigating LDL oxidation in vitro, LDL from patients with CHD, coronary heart disease, or type 2 diabetes mellitus (T2D) have been shown to be more susceptible to oxidation compared to LDL from healthy donors [13].

In this review, we consider the role of oxidative stress in diseases of atherosclerotic genesis, particularly, CHD and T2D.

Epidemiology of atherosclerosis and type 2 diabetes mellitus

DM is a group of pathologies of carbohydrate metabolism, the main feature of which is chronic hyperglycaemia resulting from insulin secretion and action defects or a combination of both. The metabolic abnormalities seen in diabetes may be caused by a low-levelled insulin production and/or insulin resistance of target tissues. The disease affects primarily skeletal muscle and adipose tissue, but also the liver at the insulin receptors level, signal transduction systems, effector enzymes or genes [14]. There are three main types of DM: T1D, T2D and gestational DM. T2D is the most common one, accounting for about 90–95% of all diagnosed DM cases [15].

T2D is a major global health problem in the 21st century. The International Diabetes Federation estimates that 9.0% of adults aged 20 to 79 years (415 million people) have diabetes, and this figure is projected to reach 642 million adults by 2030[16]. However, the statistics of many countries take into account only patients on dispensary observation, while according to epidemiological studies the number of people with this disease may be exceeded several times over[17]. DM is an independent risk factor for cardiovascular disease in both men and women. This information is consistent with well-known studies such as MRFIT (Multiple Risk Factor Intervention Trial) [18]. The large number of adverse cardiovascular outcomes in diabetes is explained by the accumulation of risk factors such as, for example, heart muscle damage, diabetic cardiomyopathy, macro- and microvascular complications of diabetes [19].

Reduced cell sensitivity to insulin leads to lipid profile abnormalities, namely a significant increase in blood lipid levels after meals [20]. There is a concept in the literature called 'lipid triad', which is characterized by elevated triglycerides, low cholesterol, high-density lipoprotein (HDL) and increased LDL levels [20].

Hyperlipoproteinaemia, especially hypertriglyceridaemia, tends to occur in diabetic patients. LDL particles undergoing non-enzymatic glycosylation due to high blood glucose levels in diabetes are rapidly and intensively phagocytized by macrophages, thereby stimulating atherogenesis. Hyperinsulinaemia causes vascular endothelial damage. Hyperglycaemia leads to multiple biochemical changes such as glycosylation of proteins in arterial walls, which contributes to the development of diabetic atherosclerosis. The non-enzymatic reaction between glucose and arterial wall proteins leads to the glycation end products formation [21]. In addition, hyperglycaemia increases the ROS formation, inhibiting the production of endothelial

nitric oxide, a potent vasodilator and platelet activation regulator [14].

The aforementioned factors lead to diffuse generalized vascular endothelial dysfunction, adhesion of circulating monocytes to the endothelium and increased propensity to thrombosis [22].

It follows that the accumulation of risk factors, such as cardiac muscle damage, macrovascular and microvascular diabetic complications, increases the adverse cardiovascular outcomes likelihood in people with DM.

Oxidative stress definition and mechanisms

Oxidative stress was first defined in 1985 by biochemist H. Sies, who formulated it as «a disturbance in the prooxidant-antioxidant balance in favor of the former, leading to potential damage» [23]. H. Sies provides a table (expanded in subsequent publications) of the main ROS, which includes oxygen ions, free radicals, peroxides of inorganic and organic origin:

1. Superoxide anion: an ion of an oxygen molecule that has one unpaired electron;
2. The perhydroxyl radical: the protonated form of superoxide, which has greater solubility in fats;
3. Hydrogen peroxide formed by dismutation from the perhydroxyl radical, or directly from molecular oxygen;
4. Hydroxyl radical most commonly produced by macrophages and microglia; exhibits significant reactivity;
5. Alkoxyradical: an oxygen-centred organic (e.g. lipid) radical;
6. Organic hydroperoxides including hydroperoxides formed from polyunsaturated fatty acids and sterols (e.g. cholesterol) enzymatically or non-enzymatically (e.g. via lipid oxidation);
7. Peroxyradical formed from organic hydroperoxides by hydrogen scavenging;
8. Singlet oxygen: the common name for two metastable states of molecular oxygen with higher energy than the ground, triplet state;
9. Excited carbonyl compounds formed from ethylene glycol as an intermediate product;
10. Ozone: a very reactive oxygen form, posing a health hazard in oxidative stress affecting lungs and other vulnerable tissues;
11. Chloronic acid and bromonic acid produced from hydrogen peroxide by myeloperoxidase within the phagocytic vacuoles of neutrophils [24].

It is important to note that ROS concentration may change under certain circumstances since they are constantly both produced and eliminated, therefore it should be remembered as a dynamic parameter, so steady-state ROS concentrations should be analyzed first and foremost. Thus, in 2011, V.I. Lushchak offered the following definition: "oxidative stress is a situation when steady-state ROS concentration is transiently or chronically elevated, disturbing cellular metabolism and its regulation and damaging cellular constituents" [25]. However, as indicated below, it did not fully reflect the pathology's essence, so it has been further supplemented. ROS act not only as harmful agents, as they are also involved in a few processes occurring within the framework of normal physiology. Hence, they play a role in the development, activation and apoptosis of T-lymphocytes [26]. In addition, it has been shown that ROS are capable of behaving as signaling molecules involved in mitohormesis, i.e. their moderating effects on mitochondria, which, by essentially putting them under stress, trigger a wide range of cytosolic and nucellar adaptive responses designed to develop resistance to higher levels of mitochondrial stress, with positive effects on health and longevity [27].

Based on recent data, in 2021 V.I. Lushchak together with K.B. Storey proposed the most modern version of the definition of oxidative stress, according to which «oxidative stress is a transient or long-term increase of steady-state ROS levels, disturbing cellular metabolic and signaling pathways, particularly ROS-based ones, and leading to oxidative modifications of an organism's macromolecules that, if not counterbalanced, may culminate in cell death via necrosis or apoptosis» [28].

The intracellular ROS sources are well known: one of them are peroxisomes containing a variety of enzymes associated with the hydrogen peroxide metabolism, which are necessary for xenobiotics detoxication and

utilization. In mammals, these organelles are involved in a lot of metabolic reactions, such as fatty acids α- and β-oxidation, amino acids catabolism, and the oxidative step of the pentose phosphate pathway, whereas ROS are by-products of these chemical processes. Thus, hydrogen peroxide is produced predominantly by flavoproteins, e.g. acyl-CoA oxidases, uratoxidases, D-aspartate oxidase, xanthine oxidase (potentially also a source of superoxide anion), etc. [30].

In addition to peroxisomes, similar processes are observed in the agranular endoplasmic reticulum. It contains cytochrome P_{450}, a broad group of haemoprotein monooxygenases that perform substrate oxidation necessary for the neutralization of poisons and drugs, as well as biosynthesising sterols, fatty acids, eicosanoids and vitamins. The catalytic cycle of cytochrome P450 proceeds as follows: the initial step of the reaction is the substrate (R-H) binding with the haemothiolate group iron (Fe^{3+}). The iron of this group is then reduced from Fe^{3+} to Fe^{2+} through one-electron reduction by P_{450} NADHD cytochrome reductase, facilitating oxygen-iron binding. Then, cytochrome-P_{450}-reductase reduces the Fe^{2+}-O_2 complex with the addition of a second electron, activating the oxygen in it (Fe^{2+}-O_2^{-}). Addition of two protons (H^+) cleaves the O-O and releases H_2O. Next, the FeO^{3+} complex cleaves a proton from the substrate (R), leaving the reactive intermediate $RFe^{\bullet 3+}OH^-$. Further, the hydroxyl group is transferred to the substrate radical with the oxidized substrate being released in progress [31].

Previously, it was assumed that these cytochromes are capable to produce ROS directly [32]. However, it is now believed that there are two shunts in their catalytic cycle, the so-called 'reaction decoupling', because of which free radicals are produced when substrate oxidation is not yet complete. The degree of dissociation efficiency depends on many factors: pH, oxygen content in the medium, substrate concentration, as well as on the structural differences in the binding sites of certain cytochrome isoforms [33].

In the cell, the key ROS source is the mitochondrial respiratory chain. The primary ROS produced in mitochondria through univalent autoxidation of electron carriers is superoxide anion. It undergoes conversion to hydrogen peroxide via superoxide dismutase (SOD) activity. The peroxide, in turn, is converted to a hydroxyl radical by the Fenton reaction [34].

The primary mitochondrial ROS formation cites are located in respiratory complexes I and III. Complex I transfers two electrons from NADH to ubiquinone, pumping four protons into the intermembrane space. Located at the hydrophilic site, flavin mononucleotide (FMN) forms FMNH2 by accepting two electrons derived from the oxidation of NADH, which is generated in the tricarboxylic acid cycle in the mitochondrial matrix. The electrons then pass through a series of iron-sulfur clusters arranged from low to high potential and reduce ubiquinone to ubiquinol (QH2) at the Q binding site, which is located at the junction of the membrane and matrix arms. During this process, mtROS can be produced in the matrix by complex I at both the IF (flavin mononucleotide site) and IQ (Q binding site) sites. In addition, complex I produces mtROS via reverse electron transfer from QH2 to NAD^+ [35].

Complex III is the general site of ROS generation in the electron-transport chain. Most of the superoxide in complex III is formed as a result of autoxidation of ubisemiquinone, an intermediate product produced in complex III during the Q-cycle. Ubisemiquinone has been shown to be the major direct electron donor capable of reducing O2 to superoxide [35].

Complex II produces ROS at the IIF site, associated with succinate dehydrogenase. Under normal conditions, the level of ROS produced by it is insignificant, but the increase in the number of free radicals observed in diseases associated with mutations of complex II is chiefly due to the IIF site. The study of isolated mitochondria from rat skeletal muscle also showed that the maximum degree of ROS production by the IIF site is very high, and is second only to the IIIQo site and, possibly, the IQ site [36].

It is also known that ROS are formed during the activity of immune cells. Neutrophils have been found to have NADPH-oxidase on their plasmalemma (as well as on the membrane of their own phagosomes). In resting cells, it stays in a dormant state, but is activated in response to pro-inflammatory mediators, the presence of microorganisms and/or pattern recognition receptors. NADPH oxidase consists of six subunits:

gp91phox, p22phox (at rest composing a heterodimeric flavocytochrome b558, the catalytic core), p40phox, p47phox, and p67phox coupled to a GTPase, usually Rac1 or Rac2. The functions of the subunits are as follows: gp91phox is an electron transferase: its cytosolic domain accepts electrons from NADPH and transfers them across the membrane to molecular oxygen, producing superoxide anion; p22phox functions as a binding site for a regulatory trimeric complex of the remaining subunits located in the cytosol of the resting cell, which interact with p47phox. Separation of the oxidase complex components into two groups and their distribution between different subcellular compartments prevents spontaneous activation and potential damage in the resting host cell.

Being activated, NADPH oxidase catalyzes the transfer of electrons from NADPH to molecular oxygen, producing superoxide anions as the main product. To minimize damage, cells are equipped with antioxidant enzymes such as SOD and catalase. SOD and glutathione peroxidase can further convert these forms to water, which limits the extent of damage to the cell. On the other hand, superoxide anion may be converted into other ROS, potentially damaging nucleic acids, proteins and cell membranes. Myeloperoxidase (MPO) localized in granules can convert hydrogen peroxide into hydrochloric acid, enhancing the body's clearance of invading pathogens. MPO can also directly convert superoxide anion to singlet oxygen. In addition, the conversion of superoxide anion and hydrogen peroxide to hydroxyl radical is also carried out by iron (Fig. 1) [37].

ROS actively react with the most important classes of biomolecules, lipids, proteins and nucleic acids. The target of free radicals are lipids with double carbon bonds, especially polyunsaturated fatty acids. These reactions pose a threat to the cell membrane: lipid peroxidation processes are accompanied by disruption of the interaction between MPO and polar heads of phosphoglycerides, in this connection the ability of phosphatidylcholine of liposomes to convert HOCl/ClO^- into less toxic and not initiating lipoperoxidation reactions HO_2Cl/ClO_2^- was found, at the same time, HOCl/ClO^-, with the participation of MPO, implements low-density lipoproteins and phosphatidylcholine interaction, activating the atherosclerotic effect [38].

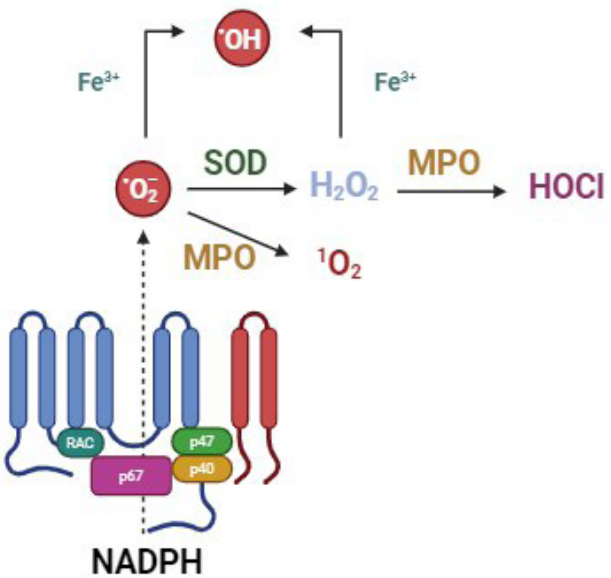

Fig. 1. Mechanisms of ROS formation during NADPH oxidase activity: a superoxide radical produced by NOX during NADPH oxidation is ultimately conversed into other ROS, such as hydroxyl radical, H_2O_2 and singlet oxygen by contact with iron ions, SOD and MPO (NOX — NADPH oxidase, SOD — Superoxide dismutase, MPO — Myeloperoxidase)

Free radicals are able to carbonylate proteins by the following mechanisms: direct oxidation of the primary structure of the polypeptide leading to its shortening; oxidation of side chains by lysine, arginine, proline and threonine; interaction of amino acid residues of histidine, cysteine and lysine with aldehydes formed during, e.g., lipid peroxidation; non-enzymatic glycosylation of lysine residues with Amadori and Heyns rearrangements leading to the formation of glycolysis end products. Carbonylated proteins are generally catalytically less active, less thermostable [39]. Carbonylation disrupts cytoarchitectonic and cell division: thus, direct oxidation by 4-hydroxynonenal affects the structural protein vimentin, actin and tubulin.

When DNA is damaged, free radicals attack either the furanose ring of deoxyribose or oxidize the bases themselves. In the former case, interaction with the C-4 position is most common [40]. When the hydrogen of a given atom is accepted by the free radical, the ring becomes capable of reacting with the oxygen in the medium, transforming first into a peroxyl radical and then a hydroperoxyl radical. The latter undergoes a Criegee rearrangement to become a carbocation, whereby the ring becomes six-atomic and is stabilised by delocalization of charge to two adjacent oxygen atoms, leading to the formation of an oxonium cation. It undergoes dehydration and the ring opens to form an enamine derivative, which becomes an unsaturated imine on loss of the phosphoric acid residue. With water being added to carbon, a hydroxyacetal derivative is formed, fragmenting next into an acrylaldehyde base. In a low oxygen environment, the original radical becomes an oxonium cation and nucleophilically attacked by a water molecule, and then decomposes into a free base and various fragments [41].

As for the interaction of free radicals with bases, 8-OH-deoxyguanosine (8-OH-dG) is considered as a biomarker for atherogenic diseases developed against the background of oxidative stress. When this base interacts with a hydroxyl radical, the latter attaches to the C8 position in the guanine molecule to form 8-OH-G-radical, $(G\text{-}OH)^{\bullet}$, which is converted into 8-OH-dG after the loss of another electron and proton [42]. Its high concentration in plasma has been shown to indicate high mortality in patients with cardiovascular disease, obesity, atherogenic dyslipidaemia, and insulin resistance [43].

The understanding of the basic processes of oxidative stress is constantly evolving since free radicals are an integral part of human physiology. Formed by a variety of metabolic reactions and interacting with a wide range of biologically important molecules in the body, they can pose a serious threat if their concentration remains high.

Oxidative stress, antioxidant system in CHD and T2D

The human antioxidant defense system is represented by the specialized enzymes discussed above. These include SOD, catalase, glutathione peroxidase, glutathione transferase, haem-containing peroxidases, ceruloplasmin, as well as non-enzymatic compounds of different chemical nature. To the latter compounds belong substances chelating metal ions of variable valence — transferrin, lactoferrin, albumin; free radical scavengers — ascorbate, vitamin E, reduced glutathione, coenzyme Q, uric acid, bilirubin. The enzymes catalase and glutathione peroxidase degrade hydrogen peroxide and lipid hydroperoxides (products of phospholipid peroxidation) to non-radical products [44]. SOD plays a major role in the detoxification of superoxide anion radicals. These enzymes catalyze the dismutation reaction of two superoxide anion radicals to H_2O_2 and O_2. Antioxidants have been shown to play an important role in protecting the human body from the development of oxidative stress and may have therapeutic value in the treatment of T2D [45].

In type 2 diabetes, ‘reference’ conditions for the formation of oxidative stress are formed: the content of oxidation substrates (glucose and lipids) increases, the formation and activity of natural participants of antioxidant systems such as glutathione, SOD, catalase and glutathione peroxidase decreases. Lipid changes and lipoprotein oxidability are also considered as contributors to oxidative stress in diabetes mellitus. Moreover, oxidative stress induced by hyperglycaemia triggers mechanisms of β-cell damage and thus accelerates the progression of type T2D [46].

The pathogenesis of atherosclerosis lies in the infiltration of lipids and immune system cells into the subendothelial space of the vessel walls. It is here that the deleterious effects of free radicals that oxidize fats are observed. This triggers an inflammatory response: endotheliocytes activate and begin to release cytokines alongside with adhesion molecules attracting monocytes circulating in the bloodstream to the site of inflammation. Migrating into the vessel walls, they become macrophages engulfing oxidized LDL, transforming, in turn, into fat-laden foam cells, accompanied by their release of chemokines that attract additional monocytes and T-lymphocytes. Their deposition creates a primary fatty streak, which may eventually develop into a more complex fatty plaque [47]. Oxidized cardiolipin (oxCL) has been found to have a pronounced proinflammatory effect, the amount of which increases after ischaemia, when the functional activity of mitochondria is restored, and the accumulated succinate is oxidized [48]. OxCL can trigger the production of leukotriene B4 in macrophages and neutrophils, which is involved in the pathogenesis of not only atherosclerosis but also myocardial infarction and stroke [49].

Vascular smooth muscle cells (VSMC) are usually localized in the medial layer of arteries, although humans have VSMC in the intima, too. However, the release of mitogens, inflammatory cytokines and chemoattractants, including PDGF (platelet-derived growth factor) and TNF-α (tumor necrosis factor-α), attract VSMC to the intima. These cells switch from a contractile to a synthetic phenotype, secreting extracellular matrix that forms a protective fibrous covering around the atheroma core. However, the integrity of the fibrous plaque may be compromised, leading to thinning and eventual rupture. When the plaque ruptures, a thrombogenic core is exposed, stimulating platelet aggregation. The resulting thrombus may occlude the artery, leading to ischaemia and infarction of the underlying vessel [50].

Endotheliocytes themselves are producers of both free radicals and their scavenger. The latter, paradoxically, is NO synthesized from L-arginine by calcium-calmodulin dependent endothelial NO synthase. NO is involved in attenuating platelet activity and aggregation, regulating migration coupled with leukocyte adhesion to endotheliocytes, and inhibiting VSMC proliferation. As a scavenger, NO limits NADPH oxidase activity, enhances the breakdown of peroxynitrite to nitrate and nitrite [51]. When endotheliocytes are saturated with oxidized LDL, the breakdown of tetrahydrobiopterin, a cofactor of eNOS, occurs: this is most likely the primary cause of eNOS dissociation along with depletion of the substrate L-arginine, accumulation of asymmetric dimethylarginine and S-glutathionylation.

In addition, there is a link between protein carbonylation and the development of insulin resistance: plasma detectable proteins such as VEGFR-2 (vascular endothelial growth factor receptor-2), MMP-1 (metalloproteinase-1), argin, MKK-4 (mitogen-activated protein kinase kinae-4) and complement component C5 serve as biomarkers of this disease. Thioredoxin-interacting protein, TxNIP (thioredoxin-interacting protein), a critical component in the signaling pathway based on high concentration of glucose and ROS, which induces mitochondrial and total cellular hydrogen peroxide production via NADPH oxidase isoform (NOX4) in mesangial cells, is also involved in its development [52].

Peroxynitrite also contributes to the development of endothelial dysfunction [53]. Together with prostaglandin H2, it affects TPr (thromboxane-prostanoid receptor), which activates NADPH-oxidase, increasing the concentration of free radicals, resulting in a vicious circle [54].

Interleukins associated with the formation of free radicals: IL-1-β, IL-4, IL-6, IL-18 play a significant role in the development of atherosclerosis. The formation of ROS and IL-6 through targeted proteolysis depends on the NLPR3 (NLR family pyrin domain containing 3) inflammasome, which consists of the NLRP3 protein proper, ASC (apoptosis-associated speck-like protein containing CARD) and caspase-1. The activation of this caspase involves mtROS, as well as cholesterol crystals, dead cell debris, impaired blood flow, hypoxia, and acidosis (Fig. 2) [55–56].

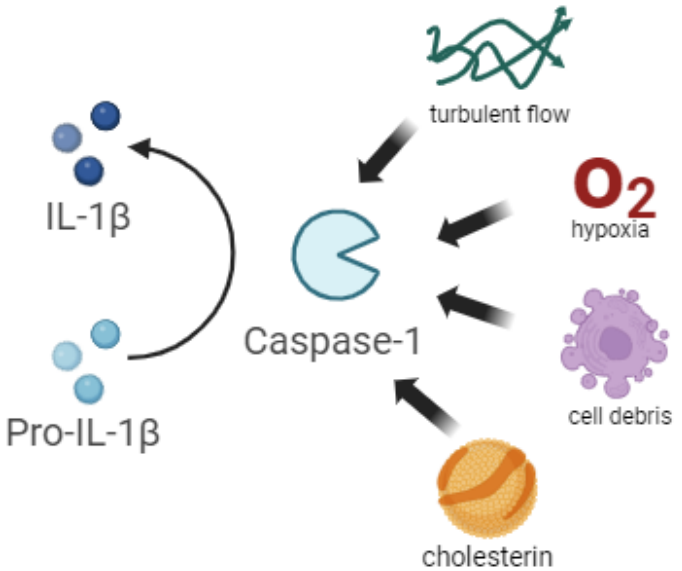

Fig. 2. Caspase-1 activation factors

Back in the 80s of the last century, it was hypothesized that IL-1 activates inflammatory functions of human endotheliocytes [57], participates in anticoagulation processes, and stimulates the expression of leukocyte-recruiting molecules, including ICAM-1 (intercellular adhesion molecule-1) and VCAM-1 (vascular cell adhesion molecule-1) [58]. In addition, IL-1 can autoinductively stimulate the expression of its own gene, in which it is encoded in endotheliocytes and VSMC [59].

The effects of IL-1 on blood vessels are diverse: 1) Autocrine induction of platelet-derived growth factor production, which induces VSMC to proliferate; 2) VSMC production of IL-6, a mediator of atherothrombosis: It stimulates hepatocytes, causing them to produce acute phase response reactants, especially fibrinogen, plasminogen inhibitor and C-reactive protein; 3) Aggravation of the ischaemia-reperfusion syndrome course together with cardiac remodeling, i.e. chronic and progressive ischaemia-reperfusion syndrome, a process leading through gene expression to molecular, cellular and interstitial transformations manifesting as changes in the size, shape and function of the heart. It has been shown that the use of antagonists of this interleukin limits the release of C-reactive protein and mitigates cardiac remodeling; 4) Involvement in arterial hyperplasia with intima thickening (according to experiments on pigs); 5) Direct involvement in inflammation processes and fatty streak formation (according to the results of experiments on lipoprotein E-knockout mice) [60–65].

Previously considered an anti-inflammatory interleukin [66], IL-4 is now, according to accumulating evidence, considered a proinflammatory agent as well. It synergistically increases the expression of IL-1β, TNF-α, and LPS-inducible molecule VCAM-1 in vascular endothelium and accelerates endothelial cell apoptosis, which contributes to atherogenesis [67–69].

It is worth noting that the relationship between IL-4 and oxidative stress lies in the induction of the latter: for example, it was shown that IL-4 induced ROS formation through microglial NADPH-oxidase in the hippocampus, which led to neurodegeneration [70]. In atherogenesis studies, it was shown that cells of HAEC (human airway epithelial cells) and HUVEC (human umbilical vein epithelial cells) lines produced more ROS than controls after IL-4 exposure [71–72]. On the other hand, therapy with antioxidants such as pyrrolidine dithiocarbamate, N-acetylcysteine and epigallocatechin gallate suppressed IL-4 induced overexpression of IL-6 and MCP-1 (monocyte chemoattractant protein-1) [73–75].

IL-6, in turn, also combines pro- and anti-inflammatory qualities. In low doses, it can inhibit TNF-α and IL-1 production, as well as induce TIMP-1 (tissue inhibitor of metalloproteinase-1), preventing proteolysis. Nevertheless, in general, it has a negative effect on the cardiovascular system, and its levels increase with age and with oxidative stress, concomitantly with a decrease in SOD and thiol groups, allowing it to be considered as a marker of inflammation associated with cardiovascular risk. Hypertension, vasoconstriction and atherogenesis together with chronic inflammation at high IL-6 levels often indicated unfavorable prognosis for patients and significantly increased the risk of death from cardiovascular diseases (in particular, ischaemia) [76].

IL-6 influences the development of atherogenesis through a variety of mechanisms: 1) Induces the formation of C-reactive protein in hepatocytes, which stimulates leukocyte recruitment and aggravates the inflammatory response in endotheliocytes, leading to their dysfunction; 2) Induces the production of fibrinogen in hepatocytes, which increases blood coagulation and increases the risk of thrombosis; 3) Activates the secretion of MCP by macrophages to recruit monocytes across the endothelium; 4) Induces expression of LDL-receptor on the surface of macrophages, enhancing their capture of LDL, accelerating their transfer to foam cells for lipid deposition; 5) Increases the expression in macrophages of the adhesion molecule CD44, which by positive feedback mechanism increases the secretion of IL-6 itself in these cells; 6) Increases the synthesis of matrix metalloproteinase, which, by degrading the extracellular matrix, increases the risk of plaque rupture; 7) It aggravates the expression of VCAM-1 and ICAM-1, which provide leukocyte aggregation on vascular cells, which increases inflammation; 8) It increases the expression of angiotensin II receptors on vascular smooth muscle cells, which worsens the course of oxidative stress and atherogenesis; 9) It promotes the differentiation of naive T-lymphocytes into T-helper cells, which support the spread of inflammatory response [77–85].

Thus, direct involvement of the immune system in atherogenesis associated with reduced activity of antioxidant proteins has been established. The ‘reference condition’ for the development of atherosclerosis is endotheliocyte dysfunction together with chronic inflammation.

The link between atherosclerosis, T2D and oxidative stress

Type 2 diabetes and atherosclerosis are closely related [86], as their pathology is based on endothelial and β-cell dysfunction triggered by hyperglycaemia. Chronic excessive glucose concentration is dangerous. Firstly, it leads to non-enzymatic glycation of proteins, lipids and DNA, resulting in the formation of advanced glycation end products (AGE). Secondly, it depletes the NADPH pool due to increased conversion of glucose to sorbitol, which reduces glutathione formation, leading to aggravation of oxidative stress [87].

AGE can be formed by three mechanisms: through the Maillard reaction, lipid peroxidation and oxidation of glucose itself, and depending on which substance has been converted into AGE, different pathogenic intra-organismal effects leading to the development of T2D will occur: 1) most plasmatic proteins are glycated, and the glycation of human serum albumin, fibrinogen, apolipoprotein and transferrin is particularly important: such structural conversion adversely affects the physiology of the organism: (a) due to the modification of serum albumin, new epitopes arise, involving the immune system in pathogenesis, (b) glycated fibrinogen forms a dense, rigid fibrin network, which increases the risk of cardiovascular disease in diabetic patients, (c) ApoA-IV glycation significantly reduces the body’s biochemical defense against the development of atherosclerosis, impairs glucose uptake by cells and suppresses insulin production, stimulates hypertension, atherogenesis, cardiovascular remodeling, aneurysm development, d) glycation of ferritin increases lipid peroxidation, resulting in the formation of free radicals, and reduces its ability to bind iron ions, 2) in the case of glycation of lipids, particularly LDL, endothelial dysfunction is observed because LDL-AGE, by activating TLR-4 (toll-like receptor-4) dependent signaling pathway and interactions with AGE receptors such as NOX4, induce the production of pro-inflammatory cytokines and ROS leading to

endothelial dysfunction, and the following markers are detected in terms of chemistry: 8-isoprostane, malonic dialdehyde, TBARS (thiobarbituric acid reactive substances), 3) DNA glycation produces a deleterious glycotoxin that poses a risk to antitumour agents; in addition, characteristic markers are produced: N(2)-carboxymethyl-2'-deoxyguanosine (CMdG), N(2)-1(carboxyethyl)-2'-deoxyguanosine (CEdG) and 8-OH-deoxyguanosine (mediated by free radical production during glucose oxidation)[88–94].

If the functional activity of antioxidants, especially SOD, catalase, glutathione reductase and glutathione peroxidase (GPx), is impaired in hyperglycaemia, the threat of β-cell damage develops, since the expression of these genes in islets of Langerhans is reduced and glutathione peroxidase is inactive [95–98]. Increasing concentration of free radicals suppresses the expression of PDX1 (pancreatic and duodenal homeobox 1) and MafA (v-Maf musculoaponeurotic fibrosarcoma oncogene family transcription factor A) factors necessary for β-cell proliferation and maturation by the following mechanisms: 1) reduction of PLUTO lncRNA expression, 2) stimulation of JNK-dependent FOXO1 activity, 3) inhibition of mTORC (mammalian target of rapamycin complex 1) signaling, 4) increase of SHP2 (small heterodimer partner 2) expression together with reduction of FAM3A (familial sequence similarity 3A) level [99]. The table below summarizes the main functions of these proteins (Table 1):

Table 1

List of the proteins essential for β-cells optimal functioning

Protein	Function	Reference
PDX1	Plays a significant role in β-cell maturation by controlling the activation of insulin and genes responsible for glucose sensitivity, such as GLUT2 (glucose transporter type 2) and glucokinase. It also binds and inhibits some of the α-cell genes like MAFB (glucagon activator).	[100]
MafA	Insulin transactivator protein in pancreatic β-cells. It ensures preservation of the mature phenotype of β-cells. When its production is reduced, their dedifferentiation is observed along with increased expression of MAFB gene.	[101]
SHP2	Suppresses PDX1 transcriptional activity and inhibits the expression of insulin transcription enhancers such as RIPE3b1/MafA.	[102]
FAM3A	Plays a critical role in the regulation of glucose and lipid metabolism in the liver, where it activates the PI3K-Akt signalling pathway through a Ca2+/CaM-dependent mechanism.	[103]

So far, deleterious effects from AGE have been considered. However, glucose can also lead to increased formation of hydrogen peroxide, superoxide anions and hydroxide radicals through: 1) auto-oxidation, 2) excessive loading on the hexosamine pathway, when insulin, GLUT2 (glucose transporter 2) and glucokinase gene expression is significantly reduced due to excess glucose, and 3) loading on the polyol pathway, when NADPH and GSH are depleted but protein kinase C is activated and AGE content increases.

A characteristic feature of T2D is insulin resistance. The exact mechanism explaining the relationship between insulin resistance and free radicals has not yet been elucidated, but studies point to three significant factors: 1) stress-dependent signaling pathways, 2) impaired translocation of GLUT4 from the cytoplasm to the plasma membrane where it becomes functionally active, and 3) secretion defects.

The first involves stress-dependent signaling pathways, JNK (C-Jun N-terminal kinase), ERK (extracellular signal-regulated kinase) and NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) during which IRS (insulin receptor substrate) degradation is observed; these pathways are summarized in the table below (Table 2).

Table 2

The list of stress-dependent signals

Pathway	Pathogenesis	Reference
JNK	T2D is associated with chronic low-level inflammation. One of the latter's factors is TNF-α: it mediates the phosphorylation and activation of the intracellular signaling molecule JNK, whose effect is also to phosphorylate. IRS-1 serine sites, thus inhibiting insulin signal transduction.	[104]
ERK	Activated by IL-1β. Influences pathogenesis directly and indirectly. Firstly, it phosphorylates IRS-1 by serine 636. Second, increased ERK activity causes hypertrophy of adipocytes, which in turn synthesize and secrete diabetogenic factors: free fatty acids, MCP-1, PAI-1 (plasminogen activator inhibitor-1), IL-6, TNF-α.IL-6, TNF-α a) enhance the expression of SOCS-proteins (suppressors of cytokine signaling) that bind to IRS-proteins and promote their degradation, b) independently inhibit IRS-1 expression at the transcriptional level.	[105], [106], [107]
NF-κB	Initiation point for other cascade reactions under conditions of glycaemia-dependent free radicals overproduction. RAGE/NF-κB signaling also activates NLRP3 inflammasome formation. AGE receptor overexpression also promotes de novo synthesis of NF-κB p65. NF-κB p65, on the other hand, directly induces insulin resistance by repressing transcription of the glucose transporter protein GLUT4 by binding to its gene promoter.	[104]

NLRP3 inflammasome in response to cellular stress signals mediates the cleavage of caspase-1 and promotes the maturation and secretion of key inflammatory cytokines IL-1β/IL-18. Various studies in patients have established a correlation between increased NLRP3 expression and insulin resistance [108—110].

In the second case, ROS production is shown to be associated with impaired glucose transporter GLUT4 translocation from the cytoplasm to the plasma membrane. Hyperinsulinaemia has been found to lead to rapid and sustained production of hydrogen peroxide: excessive insulin stimulates peroxide production by affecting NADPH-oxidase. Peroxide promotes the activation of casein kinase-2, which disrupts the sorting of GLUT4 into vesicles for translocation to the membrane [111, 112]. In the third case, there is an increased production of free radicals by mitochondria caused by an increase in the level of inorganic phosphate in serum, since its uptake by mitochondria causes hyperpolarisation [113]. In normality, δΨm levels are maintained between 0.8–1.5 mM, but in pathological processes, such as chronic renal failure, can exceed 2 mM [114–115]. As it was previously indicated, pancreatic β-cells have reduced expression of genes encoding antioxidant proteins, so increased concentrations of Pi may be detrimental for them. In addition, β-cells carry out more intensive protein folding and are predisposed to ER-stress, which is caused by oxidative stress due to the close interaction between mitochondria and EPR [116]. Due to impaired folding, there is an accumulation of defectively folded proteins that do not have the desired functions [117].

So, oxidative stress has been established to affects both pathologies (T2D and CHD) under conditions of hyperglycaemia, in which undesirable modifications of antioxidants occur, several stress-dependent signaling pathways are activated, exacerbating chronic inflammation, insulin hormone function is impaired when pancreatic β-cells are damaged, and vascular endothelial cells are damaged.

Antioxidant system
Total blood antioxidant status in T2D and CHD

The first works on the study of antioxidant status as a phenomenon date back to the nineties of the last century [118]. Total Antioxidant Status (TAS) is a generally accepted concept reflecting the dynamic balance between the activity of the body's antioxidant system and the level of pro-oxidants, and according to the literature it is synonymous with the concept of TAS — Total Antioxidant Capacity. TAS has been proposed as a useful tool for assessing the risk of oxidative stress. TAS assessment is based on the analysis of the ability of the test sample to resist artificially recreated oxidative stress, i.e. to quantify the possible oxidative buffer capacity of the sample. In blood testing, plasma or serum is most used as the most easily obtained liquid sample, but blood cells themselves can also be tested. In most cases, testing is performed

using a commercial kit from various manufacturers. The speed and relatively low cost of the blood antioxidant status assay has made it a routine clinical diagnostic test that can be performed at the nearest clinical diagnostic center. Despite the too general conclusion that can be drawn from the results of this test, the determination of blood TAS may be informative, and changes in its level beyond the reference values may be associated with a number of pathologies [119, 120].

The blood cells' antioxidant potential represents the ability of these cells to neutralize free radicals that can damage cellular structures and cause oxidative stress. Blood cells such as white blood cells as well as postcellular structures (red blood cells and platelets) contain various antioxidants such as glutathione, vitamin C and vitamin E that help protect them from damage caused by oxidative stress. Several major types of antioxidant molecules and enzymes already listed above (ascorbic acid), vitamin E (tocopherols), glutathione and glutathione peroxidase, SOD, catalase) are present in plasma and blood formations.

Patients with T2D and other comorbidities have impaired antioxidant status, including: 1) decreased levels of antioxidant enzymes such as SOD, catalase and glutathione peroxidase, 2) decreased concentrations of antioxidant vitamins such as vitamins A, C and E, 3) increased levels of lipid peroxidation products such as malonic dialdehyde: overall, these indexes indicate oxidative stress aggravation[121, 122]. Disturbance of antioxidant status in T2D may be associated with hyperglycaemia and depletion of antioxidant reserves, leading to enhanced production of free radicals and chronic inflammation. Enhanced mitochondrial ROS production in T2D also occurs as a result of impaired glucose metabolism [123, 124]. The impaired antioxidant status in T2D may contribute to the development of complications, including: damage to proteins, lipids and DNA, which leads to endothelial dysfunction and atherosclerosis [125].

Epidemiological studies show lower morbidity and mortality from CHD in people consuming higher amounts of antioxidants in foods or supplements.

Disruption of antioxidant status in CHD may be related to several factors. Atherosclerosis, a chief cause of the former, is associated with oxidative damage to LDL and accumulation of oxidized LDL in arterial walls. Smoking, one of the major modifiable risk factors for CHD, leads to free radical formation and depletion of antioxidant reserves. Hypercholesterolaemia and hypertriglyceridaemia, also risk factors for CHD, are associated with increased production of free radicals [126].

Disruption of antioxidant status in CHD may contribute to the development of complications including: 1) oxidative damage to endothelial cells lining blood vessels, leading to endothelial dysfunction and atherosclerosis, 2) increased platelet aggregation, which increases the risk of thrombus formation in narrowed arteries, and 3) myocardial (heart muscle) damage due to ischaemia and reperfusion injury.

Disturbance of antioxidant status is an important factor in the development and progression of CHD. Improving antioxidant defense through diet, supplements and medications may help prevent or delay complications associated with CHD [127].

Thus, TAS is an important indicator of general health and the risk of developing various chronic diseases associated with oxidative stress: lower TAS is associated with a high risk of developing T2D and CHD.

Methods for antioxidant activity determination

TAS of blood cells, plasma or serum can be assessed by various biochemical methods. Because of the difficulty in detecting free radicals, researchers have resorted to analyzing the activity or content of antioxidant defense enzymes when studying oxidative stress. One of the most common is the FRAP (ferric-reducing ability of plasma) reaction, which assesses the ferric-reducing ability of a sample. FRAP is a colorimetric assay based on the ability of plasma antioxidants to reduce the iron tripyridyltriazine complex ($Fe3^{+}$-TPTZ) to the divalent form at low pH. The final product (Fe2+-TPTZ) has an intense blue color with absorbance at 593 nm measured using a spectrophotometer. The application of the FRAP method has some limitations due to the labor intensive preparation of the reagent for analysis and its instability. A modification of the FRAP assay that uses copper

ions rather than iron ions is called CUPRAC: the resulting reaction of the Cu+ chromophore absorbs at 450 nm [128]. Another common colorimetric test for TAS analysis is the measurement of Trolox equivalent antioxidant capacity (TEAC — Trolox equivalent antioxidant capacity) [129]. The TEAC assay is based on the inhibition by antioxidants of sample absorption of the cation radical $ABTS^+$ (2,2'-azinobis(3-ethylben zothiazoline 6-sulfonate)), which has a characteristic absorption spectrum. with maxima at 415, 660, 734 and 820 nm. When antioxidants are added or already present in the sample, $ABTS^+$ is reduced to ABTS and loses its color. Thus, this method also spectrophotometrically tracks the colorimetric changes of the stable radical to measure the relative antioxidant capacity of the samples. This assay is referred to as the TEAC method because the reaction rate is usually calibrated using Trolox, a vitamin E analogue, as an antioxidant standard.

The next group of tests is based on the measurement of sample fluorescence: ORAC test (oxygen radical absorbance capacity) and DCFH-DA (2,7′-dichloro dihydrofluorescein diacetate) assay, which allows to investigate the level of intracellular free radicals. The ORAC test evaluates the activity of antioxidants in a sample by measuring the quenching of fluorescence of radical-sensitive probes. In fact, this assay measures the ability of an antioxidant to inhibit oxidation caused by peroxyl radicals, which 2,2'-azobis(2-amidinopropane) dihydrochloride or 2,2'-azobis(2,4-dimethylvaleronitr ile) are used to induce the formation of.

DCFH-DA is a compound that is hydrolyzed by cellular esterases to 2',7'-dichlorodihydrofluorescein and then oxidized to 2',7'-dichlorofluorescein predominantly by hydrogen peroxide. Its level is subsequently detected using a fluorimeter, flow cytometer or fluorescence microscope.

Currently, researchers and developers continue to improve tests to detect free radicals or the level of antioxidant molecules in a sample. We summarize the main ones that have gained the most widespread use.

Effect of antioxidant supplementation on the outcomes of atherosclerosis and T2D

Numerous studies have shown that antioxidant supplementation can help prevent oxidative stress that contributes to atherosclerosis, T2D and other comorbidities. Some interventions are theoretically able to improve antioxidant status in patients with CHD and DM2. To improve antioxidant status, interventions may help: (a) an antioxidant-rich diet that includes fruits, vegetables, and vitamin-rich foods, (b) cholesterol-lowering medications such as statins, which also have antioxidant properties, (c) antioxidant supplements, such as vitamin C, vitamin E, (d) controlling blood sugar levels with medications and lifestyle changes, (e) exercise and weight loss, (f) smoking cessation, exercise and weight loss and other lifestyle measures [125, 130, 131].

The most effective way to prevent oxidative stress is through a combination of healthy lifestyle and medication, if necessary, after consultation with a physician.

Conclusion

Targeted therapy for oxidative stress in CHD and T2D seeks to affect key factors underlying these pathologies to reduce damage and improve health. The fundamental targets for this therapy to reduce oxidative stress are:

1. Enhancement of antioxidant defense can be accomplished by increasing glutathione levels through dietary supplements or enhancing its synthesis can improve antioxidant defense. Likewise, stimulation of SOD and catalase activity can also reduce oxidative stress.

2. Free radical formation: a) inhibition of NADPH oxidase may be a promising therapy b) improvement of mitochondrial function and reduction of ROS production can be achieved by various antioxidants such as coenzyme Q10, α-lipoic acid, and other mitochondrial stimulants.

3. Inflammation may be reduced by inhibiting the production or activity of TNF-α, NF-κB and IL-6.

4. Improvement of endothelial function may be achieved by stimulation of NO synthase activity.

5. Blocking AGE receptors may prevent their interaction with modified proteins leading to increased oxidative stress (Fig. 3).

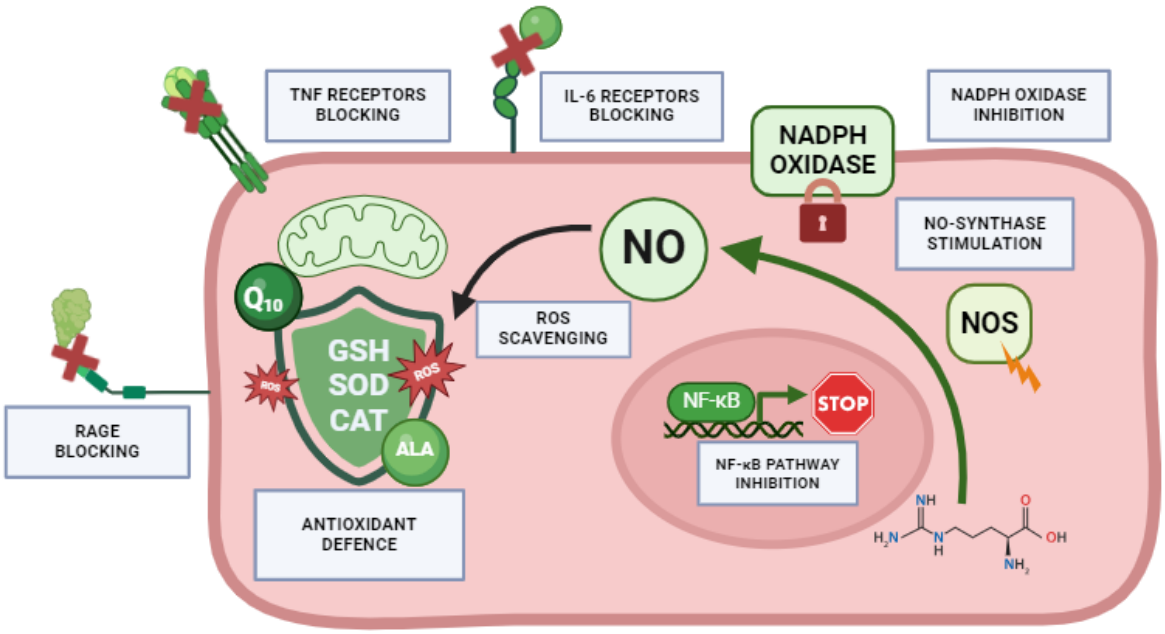

Fig. 3. Anti-oxidative stress therapy targets. Such a strategy must be developed to get the receptors contacting with pro-oxidative stress molecules blocked as well as to increase the concentration of ROS-neutralizing chemicals and to inhibit internuclear pro-inflammatory pathways

Targeted therapy for oxidative stress is currently under active development. More research is needed to determine the efficacy and safety of these approaches.

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Окислительный стресс и система антиоксидантной защиты при атеросклерозе и сахарном диабете 2 типа

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Аннотация. *Актуальность*. Сердечно-сосудистые заболевания находятся на первом месте среди основных причин смертности, а существующая на данный момент терапия несовершенна, так как имеет много побочных эффектов, и в отношении около трети пациентов оказывается неэффективной. В данном обзоре мы рассматриваем роль окислительного стресса при заболеваниях атеросклеротического генеза, таких как сахарный диабет 2 типа и ишемическая болезнь сердца. Ключевыми мишенями для молекулярно-клеточной терапии окислительного стресса при заболеваниях атеросклеротического генеза могут выступать, во-первых, локализованные на клеточной мембране рецепторы, связывание которых с конечными продуктами гликолиза и провоспалительными интерлейкинами (IL) приводит к активации воспалительных каскадов; во-вторых — молекулы-антиоксиданты, чье содержание необходимо поддерживать на оптимальном уровне как алиментарным, так и локально-инфузионным путем. Поскольку процессы повреждения и гибели β-клеток в большинстве случаев опосредованы активностью инфламмасомы NLRP-3, следует изучить возможные способы дестабилизации

данного белкового комплекса, способствующие предотвращению созревания и секреции интерлейкинов-1β и –18. *Выводы.* Помимо непосредственно лечения требуется тщательный мониторинг биохимических маркеров, сигнализирующих о наступлении патологического процесса, инструментом которого могут служить тесты для определения антиоксидантного статуса. Кроме того, рекомендовано пропагандирование здорового образа жизни среди склонных к сахарному диабету 2 и кардиоваскулярным заболеваниям индивидов, заключающееся в снижении потребления богатой жирами и углеводами пищи (параллельно с обогащением рациона богатыми клетчаткой и предупреждающими окислительный стресс витаминами), повышении полезной физической активности и отказе от курения.

Ключевые слова: атеросклероз, сахарный диабет 2 типа, ишемическая болезнь сердца, окислительный стресс, макрофаги, активные формы кислорода, интерлейкины

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