Oxidatively modified protein products and lipid peroxidation products in hypertensive patients

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Abstract

Oxidative stress is considered to be one of the key factors responsible for the development of this disease. It has been proven that the increased production of free radicals and reactive oxygen species, and thus the decreased antioxidant activity of the organism, can lead to the oxidative modification of biomolecules important for the organism, including proteins and lipids. The imbalance between pro and antioxidant factors may have a direct impact on the development and course of cardiovascular diseases, including arterial hypertension. This thesis presents the most important information about the oxidative stress and the etiology of arterial hypertension, characterizes various types of products of oxidative modification of proteins and lipid peroxidation, and presents the results of research confirming the significant role of oxidative stress in the development of this disease.

Key words: hypertension; biomarkers of oxidative stress; oxidatively modified proteins; lipid peroxidation products; antioxidants

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Free radicals, reactive oxygen species and their physiological role in the human body

Free radicals, atoms or molecules with one or more unpaired electrons are highly reactive to biologically relevant molecules [1, 2]. Reactive oxygen species (ROS) are a group of oxidants that include not only free radicals, but also molecules capable of generating them. They include, among others: hydrogen peroxide H_2O_2, superoxide anion radical $O_2^{\bullet-}$, hydroxyl radical $HO^{\bullet}$, hypochlorous acid (I) HOCl, nitric oxide NO, singlet oxygen $^1O_2$ and organic radicals [1, 2]. Exogenous factors generating ROS include, mainly ionizing and non-ionizing radiation, and chemical oxidizing agents [1]. Biological sources of ROS include an invasion of pathogenic microorganisms (bacteria and viruses) and various biochemical processes occurring naturally in cells [1, 3]. Another source of free radicals, in particular, $O_2^{\bullet-}$, for cells is the oxidation of xenobiotics (e.g., food ingredients, medicaments and pesticides) in the microsomal electron transport chain in the human body [1]. ROS are also formed in some enzymatic reactions, particularly those catalyzed by the enzymes belonging to the class of oxidoreductases [1–3]. When describing the effects of ROS on the human body, their participation in the defense against infections must be mentioned [2, 3]. Moreover, ROS are essential mediators of cellular sig-

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naling; they induce gene expression and apoptosis, enhance glucose transport to tissues and participate in the release or inactivation of NO [3, 4].

The concept of oxidative stress and its impact on the human body

The formation of ROS in the human body is inevitable. A prooxidant-antioxidant balance is maintained if their production remains under strict control of the antioxidant defense system, which includes antioxidant enzymes and low-molecular-weight antioxidants [3]. The disturbance of homeostasis resulting from excessive production of ROS by pro-oxidants or inhibition of the antioxidant system leads to oxidative stress [3]. This condition, especially when it is chronic, intensifies adverse cell reactions induced by ROS. They have been shown to negatively affect all biologically essential compounds (lipids, proteins, lipoproteins and DNA) in cells [3, 4]. It has been demonstrated that high concentrations of ROS cause peroxidation of unsaturated fatty acids that are part of phospholipids, resulting in dysfunctions of cell membranes. Their interaction with nucleic acids leads to breaking phosphodiester bonds and cell mutagenesis. Reactions of ROS with proteins primarily cause modification of amino acid groups and breaking of peptide bonds in polypeptide chains, which result in the fragmentation of protein molecules [3, 4]. The consequence of oxidative modification of proteins under the influence of ROS is also the loss or impairment of their enzymatic activity [3, 4]. Selected effects of ROS on cell components are shown in Figure 1. Long-term exposure to high concentrations of ROS can cause significant changes in the functioning of cell organelles and cells themselves. This condition leads to the destruction of biomolecules, which causes mutations, changes in gene expression, impairment of cell division, tissue damage, organ dysfunction and weakening of the body's resistance to stress [3]. Severe and chronic oxidative stress can contribute to the development and progression of diabetes, cancer, metabolic disorders, neurodegenerative diseases (Parkinson's disease, Alzheimer's disease), as well as diseases of the cardiovascular system, including atherosclerosis and hypertension [3, 4].

Biomarkers of oxidative stress

The World Health Organization has defined a biomarker as any substance, structure or process that can be measured in the body or its products and influence or predict the occurrence of an outcome or disease [5]. The accurate assessment of the concentration of ROS in biological material is difficult because they are unstable molecules and have a very short half-life. The concentrations of the following oxidative stress biomarkers are often analyzed in clinical studies: lipid peroxidation products, oxidized purine bases in DNA and oxidatively modified proteins, i.e., more stable and more persistent compounds [5]. In contrast, the most clinically relevant markers of ROS-mediated protein modification are nitrotyrosine, carbonyl groups, Maillard reaction products in proteins and advanced protein oxidation products [5–7]. One of the products of DNA damage resulting from free-radical reactions is 8-hydroxy-2'-deoxyguanosine, high concentrations of which initiate point mutations in DNA and is currently the most studied marker of DNA oxidation [3]. Assessing the concentrations of oxidative stress biomarkers makes it possible to estimate what type of modification took place in the body, which chemical structures were affected and what factor triggered it [6]. In addition, such analysis makes it possible to estimate the severity of oxidative stress in the body, which helps to diagnose and assess the severity of many diseases [6]. Moreover, searching for new biomarkers of oxidative stress and assessing their potential diagnostic utility is one of the leading directions in this field.

Oxidatively modified proteins

Carbonyl groups

The formation of reactive carbonyl groups (C=O) in the side chains of amino acids is one of the most important mechanisms of the oxidative modification of proteins. Carbonylated proteins have the advantage of high stability and relatively early formation during oxidative stress [7]. The direct oxidation of lysine, arginine, proline, and threonine side chains forms carbonyl derivatives. Research indicates that carbonyl derivatives of amino acids can form cross-links during reactions with free amino groups of lysine residues in the same or different protein molecules [8]. Carbonyl derivatives are also synthesized through α-amidation, oxidation of glutamyl side chains or oxidative cleavage of the protein skeleton [7, 8]. Protein carbonylation can also occur through reactions with aldehydes, such as 4-hydroxy-2-nonenal (HNE) and malondialdehyde (MDA) produced during lipid peroxidation or with reactive carbonyl derivatives [8]. The designation

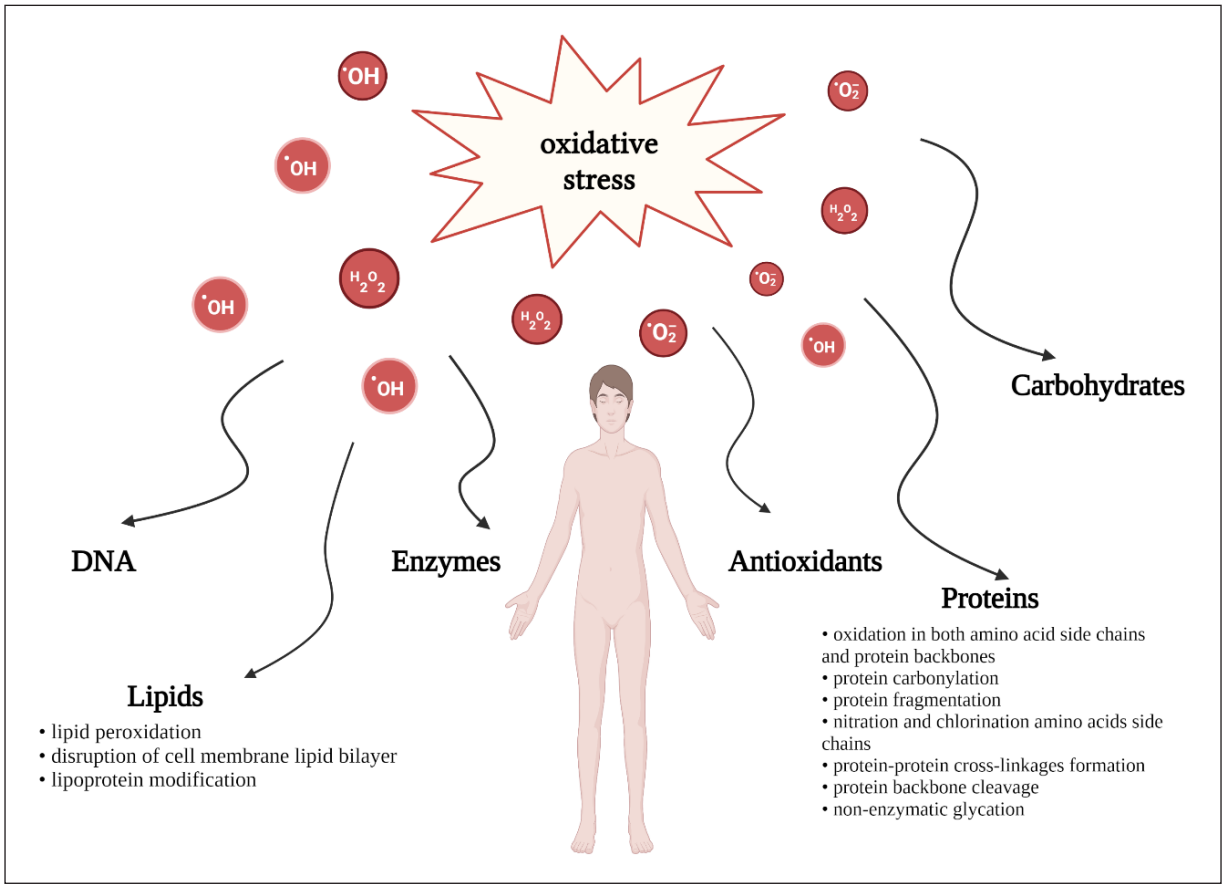

Figure 1. The effect of prooxidative-antioxidative imbalance on biologically essential molecules, and in particular proteins and lipids. Created with BioRender.com

of carbonyl derivatives involves the derivatization of carbonyl groups using 2,4-dinitrophenylhydrazine under strongly acidic conditions, which leads to the formation of a stable product, 2,4-dinitrophenylhydrazone, which concentration is determined spectrophotometrically [9].

Advanced glycation end products

Advanced glycation end products (AGEs) are a diverse group of macromolecules produced in a complex process involving numerous steps known as glycation. This non-enzymatic modification involving the covalent bonding of proteins, peptides, amino acids, phospholipids, or nucleic acids with reducing sugar molecules, such as glucose or fructose, is a physiological process [10]. The sources of AGEs can be exogenous, derived from tobacco or food products, or endogenous. Protein glycation is a naturally occurring process in all living organisms associated with ageing. However, in some disease states, this process intensifies, leading to an increase in AGEs concentrations. Such disorders include hyperglycemia, renal failure, and rheumatoid arthritis. Ageing, oxidative stress, and inflammation also contribute to the acceleration and exacerbation of the protein glycation process [10, 11]. The glycation process occurs in multiple stages. Initially, the carbonyl group of sugar reversibly binds to the free amino group of the protein or other compound mentioned above, forming the Schiff base. In the second stage, the compound undergoes a transformation, forming 1-amino-1-deoxyketose, also known as the Amadori product. These changes lead to the formation of early glycation products [12]. Subsequently, AGEs are produced from these substances in the process proposed by Maillard. Under aerobic conditions, due to autoxidation, highly reactive dicarbonyl compounds, such as glyoxal, methylglyoxal, or 3-deoxyglucosone are formed indirectly, accompanied by the release of ROS [12, 13]. It has been shown that AGEs inhibit the activity of antioxidant enzymes [14, 15]. Consequently, ROS and AGEs disrupt the functioning of cellular proteins, calcium channels, and enzymes such as endothelial nitric oxide synthase, resulting in decreased NO concentration and endothelial

dysfunction, affecting cytokine levels, intensifying inflammation, and smooth muscle cell proliferation [14]. Their participation in the oxidative modification of low-density lipoprotein (LDL) cholesterol and the impact on increased macrophage uptake cannot be ignored, as it contributes to atherosclerotic plaque development [14]. The adverse effects of oxidative stress and AGEs on the blood vessels and the activity of antioxidant enzymes are presented in Figure 2 below.

The non-enzymatic protein glycation process significantly modifies protein structure, thereby causing changes in their functioning [14, 16]. Many AGEs, including Nε-(carboxymethyl)lysine, Nε-(carboxyethyl)lysine, and argpyrimidine, have been identified as participating in the pathogenesis of arterial hypertension and atherosclerosis [14].

Advanced oxidation protein products

Advanced oxidation protein products (AOPPs) have been found to be used as biomarkers to estimate the degree of oxidative damage to proteins under oxidative stress. In addition, they have also found use as indicators of monocyte/macrophage and neutrophil activation and as exponents of the severity of the inflammatory process [17]. AOPPs are derivatives of oxidatively modified albumin, fibrinogen and lipoproteins and mainly formed in the myeloperoxidase/H2O2 system during the reaction between chlorinated oxidants (e.g., cholic acid (I))

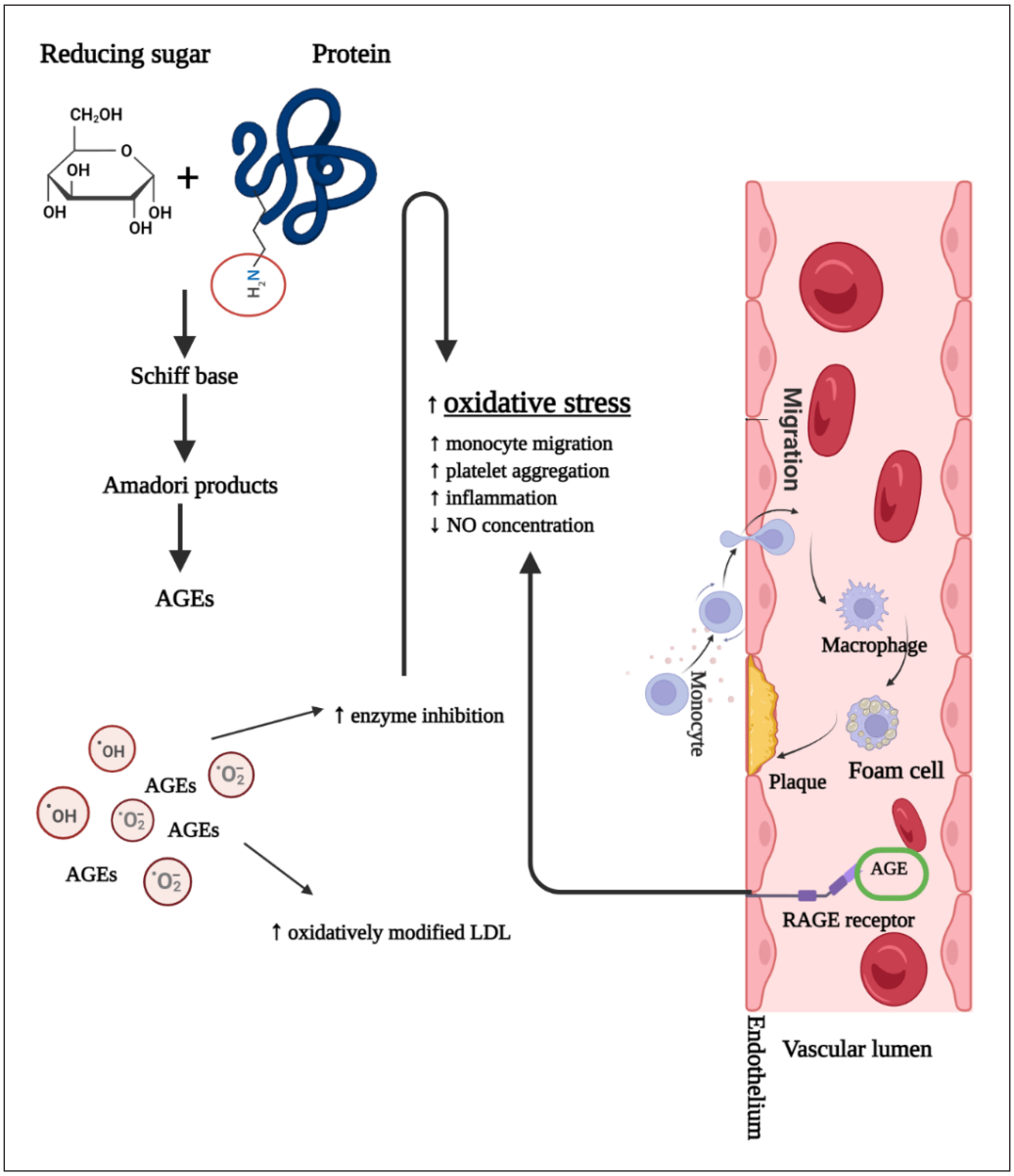

Figure 2. Adverse effects of advanced glycation end products (AGEs) and oxidative stress on blood vessels. Created with BioRender.com

and plasma proteins [1]. The structure of AOPPs has yet to be fully understood, although it has been confirmed that these compounds contain dityrosine, carbonyl groups, modified tyrosine, tryptophan, lysine, and arginine residues [6]. The concentration of AOPPs closely correlates with the concentration of carbonylated proteins and dityrosine in the plasma of dialysis patients [18]. Elevated levels of AOPPs are found in hypertension, atherosclerosis, type 2 diabetes and cardiovascular diseases [19]. The most commonly used analytical methods to determine the concentration of AOPPs in biological material are spectrophotometric and chromatographic methods such as HPLC-MS [6].

Selected lipid peroxidation products

Malondialdehyde

The most well-known chain free-radical process in the human body is the peroxidation of lipids, particularly polyunsaturated fatty acids. This process is specifically dangerous for cells because the unsaturated fatty acids make up the phospholipids in cell membranes. It has been shown that early lipid peroxidation products are broken down into short-chain and more stable compounds, including MDA, which is considered the end product of the peroxidation of unsaturated fatty acids [20]. Moreover, MDA can react with primary amines on proteins or DNA to form cross-links [21]. These covalent modifications lead to changes in the structure and functioning of DNA and proteins, which consequently accounts for their cytotoxicity [21]. The high reactivity of MDA towards proteins leads to accumulation of the pigment lipofuscin in cells, which contributes to increased stiffness of cell membranes and disruption of cell function and consequently accelerates their ageing [22]. Furthermore, it has been confirmed that MDA has mutagenic and carcinogenic effects [23]. Moreover, NO and ROS may initiate the oxidative modification of lipids and thus contribute to the development of cardiovascular diseases, including hypertension [24]. Elevated levels of MDA among patients with arterial hypertension and other lipid oxidation products, namely lipid peroxides, increase the risk of atherosclerotic complications [24, 25].

4-hydroksy-2-nonenal

HNE is a chemical compound recognized as a biomarker of oxidative stress in arterial hypertension and is considered one of the most cytotoxic products of lipid peroxidation [26]. HNE is formed in the human body due to the peroxidation of arachidonic acid and linoleic acid (fatty acids belonging to the $\omega 6$ family) and in enzymatic reactions catalyzed by lipoxygenase and cyclooxygenase-2 [27]. Food can also provide HNE, which is formed in it resulting from changes occurring during storage and processing [27]. The action of HNE in the body involves inhibiting the activity of α-ketoglutarate dehydrogenase, causing inhibition of respiration in mitochondria [26]. Additionally, it suppresses the synthesis of DNA and proteins, stimulates phospholipase A, causes oxidative damage to proteins and lipids, induces inflammation, and exhibits genotoxic activity, contributing to cell apoptosis [28].

Hypertension

Cardiovascular diseases such as ischemic heart disease, stroke or left ventricular hypertrophy with myocardial failure are the most common causes of death globally [29]. One of the leading causes of the diseases mentioned above is hypertension [29]. It is a complex, multifactorial disorder in which pathophysiological mechanisms cause functional and structural changes in the circulatory system while interacting [29]. By most influential guidelines, hypertension can be detected if blood pressure is greater than or equal to 140 mmHg systolic and/or 90 mmHg diastolic in at least two different measurements performed during two separate visits [30]. There are two types of hypertension: primary and secondary, differentiated depending on whether the mechanism that controls the systolic and diastolic pressure is acquired or congenital. These tasks include processes that control the functioning of the heart muscle and kidney function and the tension of the walls of blood vessels [31]. The renin-angiotensin-aldosterone system, the sympathetic system and substances produced by the vascular endothelium aid in performing these functions [32]. Primary hypertension, caused by genetic and environmental conditions and idiopathic causes, occurs in more than 90% of cases [29]. Secondary hypertension is much less frequent due to different kidney diseases, primary sodium retention syndromes, severe stress (burns), hyperglycemia, and serious surgeries, caused by the high volume of intravascular fluid or toxic compounds such as alcohol or drugs [31]. Many previous studies pointed towards oxidative stress having a significant impact on the development of hypertension while also possessing a complicated pathomechanism [29]. It is still unclear whether increased levels of oxidative stress products are the cause or

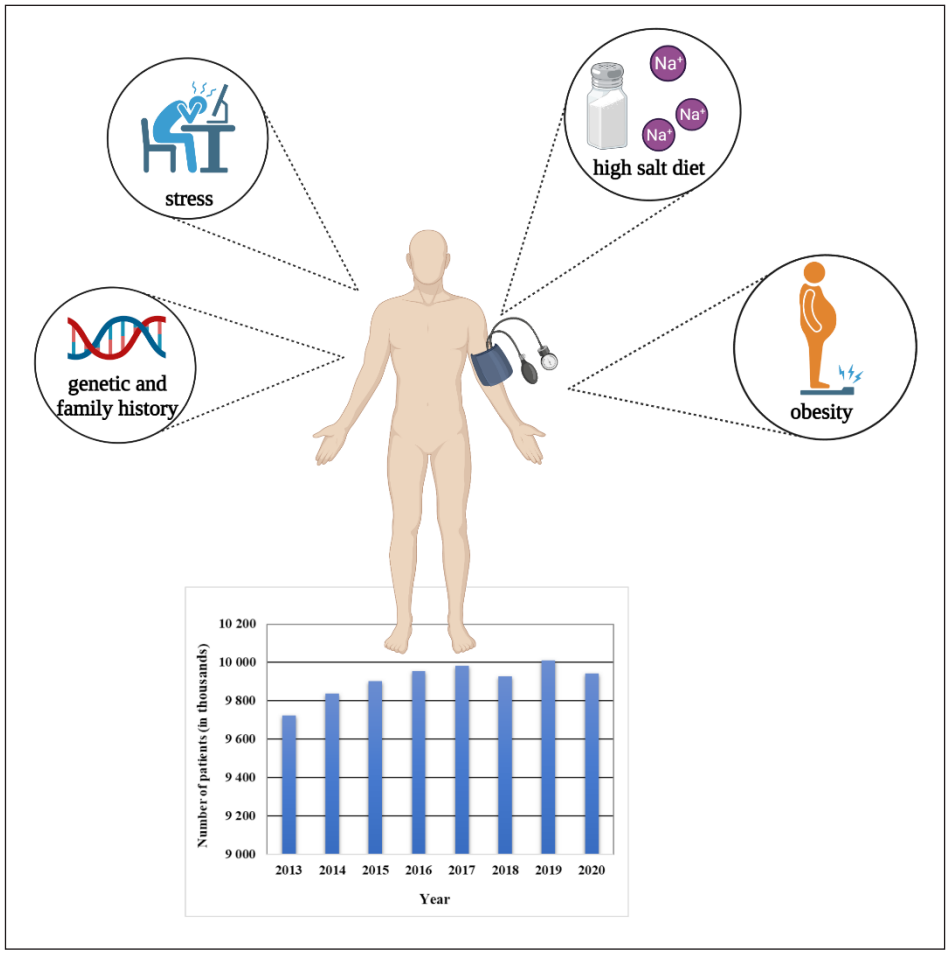

Figure 3. Prevalence of arterial hypertension among adults in Poland and the main risk factors for high blood pressure following National Health Found report form 2019. Created with BioRender.com

the effect of high blood pressure, which most likely occurs due to feedback [33]. Excessive production of ROS might be caused by mechanical stimuli acting on the vascular wall, which increases with hypertension [33]. The prevalence of arterial hypertension among adults in Poland and the main risk factors of hypertension based on National Health Found are presented in Figure 3.

Products of free radical reactions, the concentration of which rises substantially during the intensity of oxidative stress, show various (although primarily adverse) effects on blood vessels, leading to the increase of peripheral vascular resistance, inflammation as well as prothrombotic activities, which are the most common cause of hypertension [33]. The vascular endothelium plays crucial role in its regulation because it produces and secretes many vasoconstrictor and vasodilator compounds [33]. Vasomotor tension depends on the balance between vasoconstrictive forces and vasodilators, which can be disturbed by oxidative stress. Compounds produced by the endothelium are as follows: NO, prostacyclin (PGI2), endothelial hyperpolarizing factor, C-type natriuretic peptide, endothelin (ET1), prostaglandin H2 (PGH2) and thromboxane A (TXA2) [32, 33]. However, nitric oxide is very impermanent and quickly deactivated by excessive ROS. It is one of the leading cause of vasoconstrictor substances (TXA2, ET1, $ONOO^-$) becoming the majority, leading to hypertension [29]. It was also mentioned that $O_2^{\bullet-}$ plays a crucial role in that process. It converts NO into $ONOO^-$, which lowers its bioavailability and results in vessel dilation. $ONOO^-$ is a vasopressor, leading to further dilation of the vessel [29]. There is quite a bit of evidence proving that increased production of ROS contribute to protein oxidation and activation of the cascade of cellular signals. They result in the endothelial dysfunction and the activation of matrix metalloproteinases (MMPs), which leads to vasoconstriction and endothelial dysfunction, enhancing cell migration and vessel remodeling. It is believed that in-

teraction between ROS and MMPs causes an increased vasoconstrictions and limits the endothelial relaxation, thus leads to hypertension [29]. Another vasoconstrictive factor is lipid peroxidation, taking place in the vessel wall. These compounds, while present in the blood vessels, make said vessels more vulnerable to damage, stiffer and lessen their efficiency, which manifests itself as hypertension [3]. Furthermore, ROS also intensify the influx of calcium ions into the cell and the release of calcium ions from the endoplasmic reticulum, which increases the contractility of the muscle's vessel, contributing to hypertension [32]. The hypotensive activity of antioxidants is a crucial prerequisite pointing towards ROS taking part in the pathogenesis of hypertension [32]. It is worth mentioning the groundbreaking study of Nakazano et al. from 1991. The study showcased that administering hypertensive rats with superoxide dismutase led to decreasing their blood pressure up to 50 mm Hg [32, 34]. Many research teams postulate that increased ROS and oxidative stress are primary phenomena preceding increased blood pressure [32, 35].

The role of oxidatively modified proteins in the pathogenesis of hypertension

Hypertension is one of the main factors impairing kidney function and increasing the risk of chronic kidney disease [19]. Moreover, it is well-known that hypertension intensifies oxidative stress in blood vessels and vascularized organs, especially in the kidneys [36]. Chronic accumulation of AOPPs in plasma may intensify inflammation in the kidney, which has been confirmed in patients with diabetes [37]. Conti and co-authors showed a significantly higher serum AOPPs concentration of patients with type 2 diabetes (with diabetic nephropathy) and patients with type 2 diabetes (with chronic kidney disease) compared to the control group and type 2 diabetes (without neunephropathy), respectively [19]. A significantly higher AOPPs level in the group of patients with hypertension (with kidney impairment) than in the control group was also found. The study's results suggested that the elevated concentration of AOPP in serum may be considered an independent risk factor for endothelial dysfunction among patients with type 2 diabetes and hypertension. In addition, the authors pointed to the potential clinical use of AOPPs as a predictive factor to estimate the progression of kidney damage in patients with the above-mentioned healthy issues [19].

Saliva is still not a popular body fluid used in laboratory research, its importance increases, if only because it is a non-invasive diagnostic tool, which is of key importance when collecting this material for testing from children and adolescents [38]. Maciejczyk et al. evaluated the AGEs and NO concentration, total antioxidant capacity and the activity of selected antioxidant enzymes in stimulated and unstimulated saliva and blood plasma in a group of 53 hypertensive children compared with the control group [38]. The study showed a statistically significantly higher AGEs level in the stimulated and unstimulated saliva and in the blood plasma of children with hypertension compared to the control group. Moreover, studies have shown a positive correlation between AGEs levels in unstimulated saliva and plasma from normotensive patients. Researchers have confirmed that hypertension in children is associated with disturbed antioxidant-prooxidant balance, which is reflected in, among others, significantly higher AGEs level and markers of lipid peroxidation in all examined diagnostic tools in hypertensive children [38].

Hypertension is one of Polish society's most critical epidemiological problem [39]. The epidemiological studies reveal the occurrence of this disease significantly correlates with patients' age [39]. For this reason, an essential aspect of clinical and epidemiological studies is the measurement of the concentration of products of oxidative modification of proteins generated due to increased oxidative stress accompanying the progression of hypertension associated with the ageing process. In studies performed by Yavuzer et al., significantly higher AOPPs and C=O levels were found in the group of hypertensive patients over 60 years of age compared to the group of patients aged 20 to 50 years and compared to the control group with normal blood pressure over the age of 60 [40]. Significantly higher AOPPs level was also noted in patients aged 20 to 50 compared to the control group with normal blood pressure. The levels of AOPPs and endocan, a potential marker of inflammation and endothelial dysfunction, were evaluated in a group of adults with hypertension by Klisic and co-authors [41]. Studies have shown significantly higher concentrations of both biomarkers in the hypertensive group compared to the control group. Moreover, the independent correlation between endocan and AOPPs with hypertension in the adult population makes these tested markers potential to differentiate patients with hypertension from normotensive ones [41].

Caner's team conducted interesting studies to assess the concentration of C=O, thiol groups in proteins and the activity of CuZn-SOD in a group of patients with hypertension and a group of patients with white coat hypertension [42]. Significantly lower C=O concentration was found in the control group compared to both study groups. The correlation between the patient's age and the severity of oxidative stress was demonstrated. In addition, the study's authors indicate a significant relationship between elevated C=O concentration and endothelial dysfunction, which has been confirmed in a group of patients with long-term hypertension. The importance of C=O as a biomarker of oxidative stress is also emphasized by Jawalekar's team, highlighting the high diagnostic usefulness of carbonyl groups resulting from the relatively rapid appearance of these groups and the high stability of carbonylated proteins [20]. The researchers estimated the concentration of C=O, MDA and lipid profile in hypertensive patients compared to the control group, patients with ischemic heart disease and those with stroke. The authors indicate the importance of determining the lipid profile parameters even among healthy people to assess the risk of coronary artery disease and markers of oxidative stress, such as C=O and MDA, because oxidative stress plays a crucial role in abnormalities of the cardiovascular system [20].

Arterial hypertension classification and cardiovascular risk assessment are crucial in diagnosis and treatment in everyday medical practice. It is worth mentioning resistant hypertension, which, unlike mild hypertension (MH), is characterized by a higher risk of heart failure, stroke, renal failure and increased oxidative stress. The intensity of oxidative stress in the group of subjects with mild (MH) and resistant hypertension (RH) compared to the normotensive study group (C) was assessed by Gryszczyńska's team, which showed a significantly higher concentration of AGEs in the RH group compared to C [43]. Elevated AGEs concentration indicates increased oxidative stress and oxidative modification of protein in the pathogenesis of hypertension. The present study showed no significant differences in AGEs levels between patients in the RH and MH groups. According to the researchers, the lack of gradation in AGEs concentration according to the disease severity may result from more intense oxidative stress accompanying mild hypertension, despite significantly lower systolic blood pressure and fewer complications than the RH group. The study's authors suggest that there may be adaptive mechanisms inhibiting further protein modifications in resistant hypertension. The results may indicate much lower protection against oxidative stress and its adverse effects in patients with mild hypertension than those with the resistant stage [43].

Numerous prospective studies have revealed a significant relationship between low vitamin D3 levels and the risk of hypertension, type 2 diabetes, multiple sclerosis and rheumatoid arthritis [44–46]. AGEs are compounds that accumulate in many tissues, including the kidneys, blood vessels and skin, during the ageing process [46]. Few literature reports explain whether accumulated AGEs in the skin can interfere with the synthesis of vitamin D3. In a cross-sectional study of hypertensive patients, skin autofluorescence, plasma vitamin D3 and AOPPs levels, and plasma fluorescence-associated AGEs were performed. A significantly higher skin autofluorescence was found in hypertensive patients than those with normal blood pressure [46]. The research results indicate that vitamin D3 deficiency does not affect the increased synthesis of AGEs in skin and plasma of people with normal blood pressure. Moreover, the authors showed that the skin accumulation of AGE does not interfere with the synthesis of vitamin D3 [46].

The role of lipid peroxidation products in the pathogenesis of hypertension

Jawalekar et al. analyzed the lipid profile (total cholesterol, high-density lipoprotein cholesterol, LDL, triglycerides) and MDA concentration to determine the relationship between the concentration of these parameters and the formation of atherosclerotic plaque in patients with cardiovascular diseases [20]. One subgroup included patients with hypertension, and the second one included patients with ischemic heart disease and the third included patients after a stroke. The control group consisted of 60 healthy persons who did not take medications or follow restrictive diets. The study revealed that the concentration of MDA was significantly higher in all three studied groups compared with the control group. The authors indicated that oxidative stress causes disturbance of the heart and blood vessel functions, so antioxidant therapy could be beneficial in preventing cardiovascular diseases [20].

Vaziri's team conducted the experiment using rats after nephrectomy treated with lazaroid (a potent antioxidant and lipid peroxidation inhibitor), rats after nephrectomy receiving a placebo and rats who did not undergo any surgery (control group) [47].

Blood pressure and MDA levels were measured in rats two and four weeks after the surgery. Four weeks after the surgery lazaroid was administered (for two weeks) in the target group, and blood pressure and plasma MDA were measured again in all rats. Blood pressure values obtained before, during, and two weeks after treatment with lazaroid correlated with corresponding MDA values. Researchers have shown that oxidative stress causes an increase in the process of lipid peroxidation, and thus in MDA, which contributes to the development of hypertension [47].

Literature data indicate that the number of people aged 30–79 years diagnosed with hypertension in recent years has doubled compared to data from 1990 [38]. As for children and adolescents, it is estimated that 3 to 5% of the world's population of people under 18 currently suffer from hypertension [38]. It has been proven that in most cases, the condition in younger children is secondary and is most often associated with heart defects, endocrinopathy, or renal parenchymal dysfunction. In contrast, in adolescents, half of the cases are primary hypertension, undoubtedly influenced by the increasing prevalence of obesity and insulin resistance in this population. The authors of many papers agree that oxidative stress is also involved in the pathogenesis of primary hypertension in children, leading to the destruction of biological structures, including lipid peroxidation and, among other things, vascular endothelial dysfunction [38, 48]. Wawro and co-authors included 24 subjects aged 5 to 18 diagnosed with uncomplicated primary hypertension. The study showed significantly higher concentrations of MDA in the erythrocytes of the study group compared to the control group and significantly lower activity of glutathione peroxidase, which belongs to the enzymatic antioxidant system, indicating increased lipid peroxidation and an imbalance between pro- and antioxidant factors [48].

Highly reactive molecules, the concentration of which significantly increases during oxidative stress, not only damage biologically essential molecules but also create inflammatory mediators. An interesting study aimed at assessing the concentrations of selected oxidative stress markers in patients with hypertension and hypertension with CKD was conducted by Jawad and associates [49]. The study included 84 men aged 25–65 years, divided into three groups: the hypertensive group, the second group of hypertensive patients with chronic kidney disease, and the third group of healthy individuals. The following markers and parameters were evaluated for each study participant: HNE, inducible nitric oxide synthase (iNOS), albumin, urea, creatinine, and total serum protein. Significantly higher HNE and iNOS levels in both groups: patients with arterial hypertension and men with hypertension and CKD, compared to healthy volunteers, were found. The authors postulate that increased concentrations of analyzed oxidative stress markers may result from tissue damage, accompanying arterial hypertension progression and CKD. HNE adducts were confirmed in patients with diagnosed hypertension, particularly in the inner layer of the aorta, especially in elderly patients with advanced arterial atherosclerosis [49]. Hammed's team analyzed the relationship between the concentrations of selected oxidative stress markers and the risk of cardiovascular diseases [26]. The researchers investigated, among others, iNOS, albumins, and HNE in the blood serum of 56 men, who were divided into two groups: hypertensive patients and a control group. It was shown that the concentration of HNE was significantly higher in the group of hypertensive patients compared to individuals with normal blood pressure [20]. The authors confirmed a positive correlation between the concentration of HNE and the occurrence of hypertension, which may be related to increased oxidative stress, favoring lipid peroxidation in the cell membrane of blood vessel cells, leading to the formation and accumulation of HNE. It was also pointed out that there is a significant relationship between obesity and increased oxidative stress, hence the need to maintain a normal body mass index to prevent hypertension [20].

Prospects for the use of antioxidants in the treatment of hypertension

The antioxidant system, consisting of ROS-scavenging enzymes and antioxidants. protects excessive ROS in the body. The results of many in vitro and in vivo studies indicated the significant anti-inflammatory, antioxidant and anti-apoptotic-modulatory potential of many compounds of natural origin, which on this basis, have been classified as exogenous antioxidants [50–52]. Flavonoids, a large heterogeneous group of benzopyran derivatives found in fruits, vegetables and herbs, are characterized by such properties. One of the most widespread flavonoids in the plant world, primarily in fruit and vegetables, is quercetin, which prevents oxidative damage and cell apoptosis by removing FR and ROS, chelating transition metal ions, and therefore limiting lipid peroxidation [50].

A significant water-soluble antioxidant that acts both extracellularly and intracellularly is vitamin C. It has been proven that ascorbic acid administered in high doses can reduce endothelial dysfunction in atherosclerosis and conditions predisposing to atherosclerosis, such as hypertension, diabetes, and hypercholesterolemia [53]. Vitamin C scavenges $O_2^{\bullet-}$, releases NO from S-nitrosothiols, and enhances the synthesis of citrulline, a by-product of NO synthesis, in endothelial cells [53]. The mechanisms demonstrate vitamin C's beneficial effects on the endothelium [53].

Tocopherol, a low-molecular-weight compound that acts in lipophilic spaces, is also an important antioxidant. It is an antioxidant with a high scavenging potential that primarily prevents the oxidation of LDL and membrane phospholipids. Based on observations in the Cambridge Heart Antioxidant Study, vitamin E intake significantly reduced cardiovascular events [54]. Not all studies have confirmed the beneficial effects of vitamin E. Some studies reported that using vitamin E, zinc, vitamin C, and β-carotene resulted in a slight reduction in high blood pressure during 8 weeks of treatment, while other studies showed a primarily complete lack of effect of vitamin E supplementation [54]. On the other hand, a diet with a limited supply of vitamin E may lead to increased serum levels of lipid peroxidation products and is responsible for attenuating endothelial agonist-mediated vasorelaxation

It is worth citing a study by Martin Rodriguez-Porcel, which confirmed the involvement of oxidative stress in myocardial vascular dysfunction in hypertension [55]. The experiment was conducted on two groups of pigs, which were examined after 12 weeks of treatment for hypertension. The test group was subjected to daily supplementation with antioxidants (100 IU/kg vitamin E and 1 g vitamin C), and then the results were compared with the control group. Based on the study, conclusions were drawn depicting vitamin C and E as endogenous scavengers, reducing $O_2^{\bullet-}$ concentrations [55]. Clinical studies have shown that other antioxidants, such as lazaroid, dimethylthiouracil and coenzyme Q, can lower blood pressure [53]. Numerous synthetic drugs that treat hypertension have antioxidant activity and improve endothelial function. Such drugs include lacidipine, which is a dihydropyridine calcium channel agonist. Administration of this drug to hypertensive patients for approximately 12 weeks has been shown to reduce levels of oxidative stress markers such as plasma and lipid hydroperoxides present in LDL [53]. Carnitine administration has been confirmed to benefit dialysis patients by reducing oxidative stress and chronic inflammation. In addition, carnitine increases glutathione peroxidase (GPx) activity and glutathione concentrations while it decreases MDA and carbonylated proteins [56]. Silymarin, a compound found in spotted thistles, accompanied by vitamin E, reduces MDA concentrations and increases GPx activity in patients suffering from end-stage renal failure [57].

Conclusions

ROS in physiological conditions play an important role in regulating cardiovascular functions. However, their over-production or impaired removal by the antioxidant system intensifies oxidative stress. ROS cause oxidative modification of each cell component, such as proteins and lipids, resulting in structural changes, functions, and cellular metabolism, leading to cell death. Study findings discussed in this paper provide evidence that ROS, products of oxidative modification of proteins, and lipid peroxidation occur in the pathomechanism of hypertension. Analysis of the biomarkers of oxidative stress allows us to assess the intensity of the process in the body and might aid in determining the severity of arterial hypertension. Nevertheless, conducting research on oxidative stress, the role of antioxidants, exercise and a balanced diet in preventing and treating hypertension is advisable.

Conflicts of interest

The authors declare no conflict of interest.

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Author contributions

A.K. — conceptualization; writing — original draft preparation; writing — review and editing; supervision; KS — database searching; writing — original draft preparation; writing — review and editing; MD — database searching; writing — original draft preparation; writing — review and editing; WJ — database searching; writing — original draft preparation; writing — review and editing; NS — database searching; writing — original draft preparation; writing — review and editing; BBK — content-related supervision; review and editing; BG — conceptual-

ization; database searching; writing — original draft preparation; writing — review and editing; visualization; content-related supervision.

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