

*The concept of oxidative stress is widely used to describe damage caused by reactive oxygen and nitrogen species. This concept is actively developing and is the basis for the rational use of antioxidants.*

*The purpose of the work is to analyze the literature data on the development of the doctrine of oxidative stress and its role in normal and pathological conditions.*

*Literary sources were searched in PubMed and Google Scholar databases and the sources analyzed in this work were selected.*

*The founders of the doctrine of oxidative stress have described that it can be a result of not only external factors, but also internal cellular mechanisms. This condition is characterized by the generation of reactive forms of oxygen and nitrogen in the cell, changes in antioxidant protection, oxidative modification of macromolecules and impaired redox balance. An important discovery was the fact that redox reactions are used in the cell signaling. Oxidative stress was detected in physiological conditions and involved in many diseases as their cause or consequence. The development of the oxidative stress doctrine relates to the improvement of strategies for its detection and quantitative evaluation, so the previously used indicators are supplemented with new ones, a comprehensive approach based on indices is introduced. It is believed that intense oxidative stress should be diagnosed to prevent the development of free-radical pathology and premature aging in a timely manner.*

*Understanding of oxidative stress developed to the idea of oxidant-antioxidant equilibrium and the need for its normal slight shift to the side of oxidative processes to maintain homeostasis. This approach warns against excessive administration of exogenous antioxidants, which can disrupt the balance.*

**Key words:** oxidative stress, reactive oxygen species, antioxidant, redox balance, redox cell signaling.

#### **The connection of the publication with planned research works.**

The article was prepared within the initiative research work of the Department of Pharmacology, Clinical Pharmacology and Pharmacy of Poltava State Medical University "Pharmacological research of biologically active substances and medicinal products for the development and optimization of indications for their use in medical practice" (state registration number 0120U103921).

#### **Introduction.**

It is well known that prolonged exposure to increased levels of oxidative factors of free radical origin can cause structural defects and functional changes in cells, and the modern lifestyle associated with processed foods, the impact of a wide range of chemicals and hypokinesia plays an important role in its induction [1]. In modern physiology and pathophysiology, there is a complex dialectical approach to this problem. It relates to the concept of oxidative stress (OS).

More than thirty-five years ago, when Sies H, Cadenas E (1985) first introduced the term "oxidative stress", few people were aware of the impact of this contribution [2]. The concept of OS was introduced for research in redox biology and medicine. At the same time, knowledge of pro-oxidants and antioxidants, their endogenous and exogenous sources was presented [3]. Over the last few decades, the chemistry of free radicals has gone far beyond chemistry and has become a widely known interdisciplinary field of chemistry, biology and medicine. More and more researchers are now being used OS to describe the state of disorders, damage and pathogenesis caused by reactive species of oxygen (ROS) and nitrogen. Despite the great progress, the concept of OS continues to evolve [4] and is the basis for pathogenetic

therapy of many diseases and rational preventive use of antioxidants [5, 6, 7].

#### **The aim of the study.**

To analyze the literature data on the development of the doctrine of oxidative stress and its role in normal and pathological conditions.

#### **The object and research methods.**

The search was conducted in Google Scholar and PubMed databases. Google Scholar includes most of the reviewed online journals in Europe and USA. This gives a huge number of results that have been specified by searching for the same keywords in the PubMed database, which presents publications of leading international medical journals. Based on the number of publications on certain aspects of the article, the most pressing issues of the modern OS doctrine were identified and the article was built accordingly to them.

#### **Main part.**

The founders of the OS doctrine described a wide range of evidence that free radicals can be detected by various biomarkers and lead to cell damage [2, 3]. They noted that oxidative damage can be a result of not only external factors, such as irradiation and chemical toxicants, but also internal cellular mechanisms, such as hydroperoxide production due to normal metabolism, activation of monooxygenase in response to xenobiotics, formation of the singlet oxygen. OS as a violation of pro-oxidant-antioxidant balance in favor of the first is characterized by four categories of biological changes [2, 3, 4]. The first category is an increase in the generation of ROS and reactive nitrogen in the cell, which can be either in radical forms (superoxide, hydroxyl radicals, peroxy radicals, and nitric oxide), or in non-radical forms (hydroperoxide, singlet oxygen, ozone, and peroxynitrite). The second category describes changes in antioxidant protection: a decrease in the content of low

molecular weight antioxidants, such as  $\alpha$ -tocopherol, ascorbic acid, glutathione and carotenoids; reduction of the activity of antioxidant enzymes, such as superoxide dismutase, catalase, glutathione peroxidase and their auxiliary enzymes, such as glutathione reductase, glucose-6-phosphate dehydrogenase and isocitrate dehydrogenase. The third category of OS biomarkers reflects the oxidative modification of macromolecules (peroxide oxidation of lipids, oxidation of proteins and DNA). Finally, a violation of the redox balance in the cell is also considered as evidence of OS (for example, a changed ratio of reduced and oxidized glutathione).

Given the variety and range of pro-oxidant and antioxidant enzymes and compounds, attempts were made to classify the forms of OS [8] and conceptually introduce a scale of intensity in the range from physiological OS to excessive oxidative load [9]. There are nutritional (dietary, postprandial), physiological, photo-oxidative (ultraviolet, infrared), radiation-induced OS, as well as nitrosative and reductive stress. The intensity of OS can be basal, low, medium and high.

The noticeable discovery was the fact that redox reactions in living cells are used in fundamental regulation processes [4]. Cell signaling (signal transduction) is one of the three means (besides hormones and synapsis) by which cells respond to an external stimulus through temporary allosteric or covalent modifications of proteins or changes in gene expression [4]. Redox signaling is the process in which cells use ROS as signaling molecules for transformation and differentiation [10]. The role of redox switches has attracted attention recently, primarily as a dynamic role of cysteine in proteins, which opens the field for the redox proteome [11]. The bridge between phosphorylation / dephosphorylation and reduction / oxidation of protein cysteine is provided by the redox sensitivity of critical cysteinyl residues in phosphatases, opening a molecular pathway for signaling cascades as fundamental processes in all biological systems.

It is now established that a wide range of cellular functions, including growth, adaptation and aging, is associated with the redox transmission of signals. At least five categories of cell answers can be stimulated by ROS, including modulation and secretion of cytokines, growth factors or hormones; ion transport, transcription, neural modulation, and apoptosis. Almost half of the above effects require the participation of nuclear factor (NF)  $\kappa$ B and mitogen-activated protein kinase (MAPK). Regulation of protein tyrosine phosphatase by ROS plays a major role in redox signaling. Its constant activation due to reducing medium can make enzymes unable to respond to redox changes and realize functional adjustments. Although MAPK and NF $\kappa$ B are the most studied, other signaling pathways are increasingly being identified as sensitive to redox disturbances, such as PGC-1 $\alpha$ 28, AMPK29, FoxO family transcription factors, and sirtuins [12, 13].

The discovery that some antioxidant enzymes may adapt to the increased formation of ROS under various pathological and physiological conditions indicate that organisms can change their internal resistance to oxidative influence to achieve a new balance, that is pro-oxidant-antioxidant homeostasis [4]. The OS may mean that the system has not been able to adapt or resist oxidizers or has reacted excessively to the initial OS, so

this condition is sometimes defined as a violation of the redox signals transmission and control [14].

Paradoxically, the effectiveness of protection against oxidative damage and reparation can also be increased after exposure to ROS, as the expression of many DNA repair enzymes is intensified during OS. It is argued that the best strategy of increasing the level of endogenous antioxidants is OS itself [15].

Organized response to dangers relating to molecular structures associated with damage (MSAD) include interaction with OS [16]. Under its conditions, the TRC40 protein targeting factor functions as an ATP-independent chaperone [17].

Modern data on the connection of OS with inflammatory reactions open new perspectives for understanding redox regulation. For example, inflammatory macrophages release glutathionylated peroxiredoxin-2, which then acts as a danger signal to induce the production of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) [18].

The scenario in which the conjugation of OS and inflammation takes place is as follows [19]. Inflammation occurs in response to invading pathogens or internal damage as an adaptive defense. The initial infiltration by polymorphonuclear neutrophils of the affected tissue promotes the formation of superoxide by NADPH oxidase located on the membrane of neutrophils, with subsequent production of superoxide, hydroperoxide and hydrochloric acid to "disinfect" the site of damage. However, excessive inflammation can be accompanied by excessive production of pro-inflammatory cytokines such as TNF- $\alpha$  and interleukins-1 and -6, as well as activation of NF $\kappa$ B. Escalation of local inflammation due to NF $\kappa$ B activation leads to an increase in the level of C-reactive protein in the blood plasma, which is considered a biomarker of systemic inflammation. Chronic inflammation after the initial response can attract neutrophils and macrophages to the site of injury and further increase ROS generation, forming a vicious cycle.

The OS is determined by the imbalance between high levels of ROS and the low activity of antioxidant mechanisms. Intense OS can cause damage to cellular structures and potentially destroy the tissues [20]. The OS was detected in physiological conditions, such as adaptation, regeneration, aging, physical activity [21-25]. New studies indicate that antioxidants can control OS in the aging body, interrupting the formation and spread of ROS, improving immune function and increasing healthy longevity [26].

OS is shown to be involved in more than one hundred diseases as their cause or consequence. These include cancer [27], neurodegenerative diseases [28], cardiovascular diseases [29, 30], and diabetes [31]. Numerous clinical studies have confirmed the connection of the OS markers and periodontitis [32]. OS is associated with the development of skin diseases, including photo-aging, cancer, psoriasis, atopic dermatitis, etc [33].

There are two main mechanisms through which OS contributes to disease. The first involves excess production of ROS, which directly oxidize macromolecules, including membrane lipids, structural proteins, enzymes, and nucleic acids, leading to cell dysfunction. The second mechanism of the pathogenetic effect of OS is a failure of redox signaling, and both of these mechanisms can operate in the same disease [34], for example, in diabetes, when glycation products accumulate and, at



Figure – Homeostatic and pathogenetic role of the oxidative stress (a scheme).

the same time, abnormal activation of signaling pathways occurs, leading to complications of diabetes [35]. The involvement of OS in the pathogenesis of diseases is characterized by the non-specific nature of its targets, which differs from the specific effect of basal OS on the cellular signaling while maintaining homeostasis (fig.).

Strict scientific assessment under clearly defined conditions is mandatory for control of oxidative processes in medicine, because, along with intense OS, there is redox stress. Inadequate consumption of antioxidants can cause a state of “antioxidant stress”. If the administration of antioxidant supplements reduces the basal OS level, it may interfere with the immune system to fight the pathogens and remove damaged cells, including cancer cells [36].

The development of the OS doctrine is not possible without improving strategies for its detection and quantification. It is very important to develop new methods and find appropriate biomarkers that can be used to assess OS *in vivo*. Previously used indicators, such as substances that react with 2-thiobarbituric acid, are gradually supplemented by new ones, such as isoprostanes or allantoin [37].

To determine the presence of OS, both ROS formation and antioxidant defense potential should be measured. Free radicals have a very short half-life, so they are difficult to determine in the laboratory. Nevertheless, there are currently enough methods available to measure OS and each of them has its own advantages and disadvantages [38]. At the same time, different approaches are used for identification of free radicals either directly using paramagnetic electron resonance or indirectly by detecting some more stable intermediate products (estimation of the consequences of radical attack of biological molecules using high-performance liquid chromatography, gas-liquid chromatography, or colorimetric studies). Antioxidant status can be assessed by colorimetric, immunological, and enzymatic methods [36].

Direct methods of ROS detection relate to superoxide, hydrogen peroxide, hydroxyl-anion radical, but they are very reactively capable ROS and it is difficult to determine them in the body. Indirect methods are used to overcome these problems. They usually measure changes in endogenous antioxidant protection systems or determine the damage of cellular components caused by ROS [38]. Methods have been developed to

identify and quantify the oxidative damage of proteins, lipids and DNA. Of course, the final products should be specific to oxidative damage, to respond clearly to the OS, but to remain unchanged in the absence of oxidative events [39].

There is growing interest in measuring antioxidant status for clinical evaluation [40]. Protection of cells from unwanted oxidation is achieved mainly by enzymes, while non-enzymatic antioxidants play a major role in plasma. Radical-scavenging antioxidants are consumed during reactions, and antioxidant status can be used indirectly to assess free radical generation.

One of the approaches is the measurement of the content of individual antioxidants (in particular, ascorbate,  $\alpha$ -tocopherol, and urate) in the blood, plasma or tissue homogenates. For the fullness of the evaluation it is necessary to simultaneously measure the activity of all antioxidants, but this approach is time-consuming, expensive and technically demanding, may not detect the synergistic effect between antioxidants and does not take into account the effect of unknown antioxidant substances at the moment [41]. Another approach is to determine the overall antioxidant capacity by exposing samples of controlled OS and measuring the oxidation rate or time required to oxidize the substrate.

There is a lack of consensus regarding the validation, standardization, and reproducibility of methods for measuring ROS in blood cells using flow cytometry, markers based on ROS-induced modifications of lipids, DNA and proteins, the activity of antioxidant enzymes and the total antioxidant capacity of human body fluids [42]. It has been hypothesized that the limitations of each method can be overcome with OS indices that include more than one marker, and the choice of markers to be considered in a global index should be dictated by the purpose of the study and its design. Several indices have been proposed to measure OS in humans in relation to health and disease, among which the following can be distinguished: OS index, thiol ratio, reduced and oxidized glutathione ratio, which have proven to be reliable, practical, and clinically useful [43].

The problem with such studies is that determining antioxidant potential alone is not enough, as it is difficult to establish how individual antioxidants work: by preventing the formation of ROS, scavenging free radicals, inducing signaling pathways, or repairing oxidative damage. In addition, antioxidant status varies significantly between individuals and between laboratory methods used in humans [38]. Reference values of OS markers have not yet been established. In addition, there is no direct correlation between OS markers in blood and their levels in cells, and analysis of patient blood samples can be misleading.

Long-term OS effects will occur if antioxidant status is low and free radical levels are high. No specific clinical symptoms are associated with this condition in the early stages of the imbalance. Therefore, OS is not diagnosed until damage is inevitable, and the consequences are not a sign of the disease. It is believed that efforts should be made to recognize intensive OS in a timely manner and eliminate oxidative imbalance in order to prevent or delay the development of free radical-related diseases and premature aging [44]. Since no single biomarker can predict the development of disease as a consequence of long-term excess peroxidation, it is im-



portant to use multiple methods to detect and quantify OS to increase their validity.

### Conclusions.

According to the literature data, scientific circles are still interested in OS and its management with the help of supplements and drugs of the antioxidant action. The understanding of OS from the initial thought on the negative effect of an excess of ROS has developed to ideas about the redox balance and the need for its normal small shift to the side of OS to maintain homeostasis.

The most important thing is to maintain the redox balance, and not to completely stop the production of ROS and reactive nitrogen, because certain types of free radicals are involved in cell signaling pathways, immune processes and the induction of the antioxidant protection systems themselves. This approach warns medical professionals against excessive administration of exogenous antioxidants, which can disrupt these processes.

### Prospects for further research.

Our further work will be devoted to the analysis of modern skills and principles of antioxidant therapy.

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### ОКСИДАТИВНИЙ СТРЕС: КЛАСИЧНА ДОКТРИНА ТА ЇЇ ОНОВЛЕННЯ

Важнича О. М., Балюк О. Є., Боброва Н. О.

**Резюме.** *Вступ.* Коли вперше був запропонований термін «оксидативний стрес», мало хто усвідомлював вплив цього внеску. Нині все більше дослідників застосовують це поняття для опису пошкодження, спричиненого активними формами кисню та азоту. Концепція оксидативного стресу продовжує еволюціонувати і є базисом для раціонального застосування антиоксидантів.

*Мета роботи* – проаналізувати дані літератури щодо розвитку вчення про оксидативний стрес і його роль в нормі та в патології.

*Об'єкт та методи дослідження.* Було здійснено пошук літературних джерел у базах даних PubMed та Google scholar і відібрано окремі з них, проаналізовані надалі в даній роботі.

*Основна частина.* Засновники вчення про оксидативний стрес описали, що він може бути результатом не тільки зовнішніх факторів, а й внутрішніх клітинних механізмів, Цей стан визначається генерацією активних форм кисню і азоту в клітині, змінами антиоксидантного захисту, окисною модифікацією макромолекул і порушенням окисно-відновного балансу. Примітним відкриттям стало уявлення про те, що окисно-відновні реакції використовуються в клітинній сигналізації. Водночас, відкриття того, що деякі антиоксидантні ферменти можуть адаптуватися до підвищеного утворення активних форм кисню показало, що організми здатні змінювати свою внутрішню резистентність для досягнення нового рівня оксидантно-антиоксидантного гомеостазу. Оксидативний стрес був виявлений при фізіологічних станах і причетний до понад ста захворювань як їх причина або наслідок. Розвиток уявлень про оксидативний стрес не можливий без удосконалення стратегій його визначення та кількісної оцінки, тому раніше використовувані показники доповнюються новими, впроваджується комплексний підхід на основі індексів. Вважають, що слід прагнути своєчасно розпізнати інтенсивний оксидативний стрес, щоб запобігти або відстрочити розвиток захворювань, пов'язаних із вільними радикалами, та передчасне старіння.

*Висновки.* Розуміння оксидативного стресу від початкового погляду на негативний вплив надлишку активних форм кисню розвинулось до уявлень про оксидантно-антиоксидантну рівновагу і необхідність її нормального невеликого зрушення вбік оксидативних процесів для підтримання гомеостазу. Такий підхід застерігає медичних професіоналів від надмірного введення екзогенних антиоксидантів, яке здатне порушити цю рівновагу.

**Ключові слова:** оксидативний стрес, активні форми кисню, антиоксидант, окисно-відновна рівновага, окисно-відновна клітинна сигналізація.

### OXIDATIVE STRESS: CLASSICAL DOCTRINE AND ITS UPDATE

Vazhnichaya E. M., Baliuk O. Ye., Bobrova N. O.

**Abstract.** *Introduction.* When the term oxidative stress has been first proposed, few realized the impact of this contribution. Nowadays, more and more researchers are using this concept to describe the damage caused by reactive forms of oxygen and nitrogen. The concept of oxidative stress continues to evolve and is a basis for the rational use of antioxidants.

*The purpose of the work* is to analyze data from the literature on the development of the oxidative stress doctrine and its role in normal and pathological conditions.

*Object and research methods.* Literature sources were searched in PubMed and Google scholar databases and some of them were selected and analyzed in this paper.

*Main part.* The founders of the doctrine of oxidative stress described that it can be a result not only of external factors, but also of internal cellular mechanisms. This condition is determined by the generation of active forms of oxygen and nitrogen in the cell, changes in antioxidant protection, oxidative modification of macromolecules, and disruption of the redox balance. A remarkable discovery was the fact that redox reactions are used in cell signaling. At the same time, the discovery that some antioxidant enzymes can adapt to increased formation of reactive oxygen species has shown that organisms are able to change their internal resistance to achieve a new level of oxidant-antioxidant homeostasis. Oxidative stress has been identified in physiological conditions and is implicated in more than a hundred diseases as their cause or consequence. The development of ideas about oxidative stress is not possible without improving the strategies for its determining and quantitative assessment, therefore previously

used indicators are supplemented with new ones, and a comprehensive approach based on indices is introduced. It is believed that efforts should be made to recognize intense oxidative stress in a timely manner in order to prevent or delay the development of free radical-related diseases and premature aging.

**Conclusions.** The understanding of oxidative stress, from the initial view of the negative impact of an excess of reactive oxygen species, has developed into ideas about the oxidant-antioxidant balance and the need for its normal small shift to the side of oxidative processes to maintain homeostasis. This approach cautions medical professionals against excessive administration of exogenous antioxidants, which can disrupt this balance.

**Key words:** oxidative stress, reactive oxygen species, antioxidant, redox balance, redox cell signaling.

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There is no conflict of interest.

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## THE USE OF SURGICAL THREADS IN KIDNEY SURGERY

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*The work highlights the topographic and anatomical location of the kidney and its importance in the life process; the history of development and research of the kidney, as well as diseases and surgical treatment are essential topics in the field of kidney surgery, understanding the anatomy and physiology of the kidney is necessary for the correct diagnosis and treatment of kidney diseases, taking into account the factors affecting the effectiveness and duration of suture resorption, the immune response to suture material and drug treatment are among the factors that affect the success of surgical procedures, drug treatment is given as an example of dialysis, disease and surgical treatment that play an essential role in the treatment of various kidney diseases, including kidney tumours, kidney cysts, kidney stones, in which such surgical methods as partial nephrectomy, radical nephrectomy, lithotripsy, surgical materials are widely used. Examples of suture materials such as Polydioxanone (PSD), Polyglecapron (Monocryl), Polyglactin 910, Desmosin, and Silk are given. Each of these threads has its composition, structure, features, advantages and tissue reaction to suture material. Further research on suture materials in kidney surgery is necessary to increase the effectiveness and safety of surgical interventions and their relevance in further research on suture materials in kidney surgery.*

**Key words:** kidney, suture material, kidney surgery.

### Connection of the publication with planned research works.

The publication is a fragment of the research work "Experimental-morphological substantiation of the effect of new suture materials, implants and covering surfaces on various organs when used in experiments and clinical practice" (state registration number 0118U004459).

### Introduction.

The kidney, one of the vital organs of the human body, plays a crucial role in maintaining general health. Its primary function is to filter waste products and ex-

cess fluid from the blood, regulate electrolyte balance and produce hormones that control blood pressure and produce hormones that stimulate the production of red blood cells, such as erythropoietin. However, like any other organ, the kidneys are prone to diseases that can disrupt their normal functioning.

### The aim of the study.

Conduct an analytical review of the literature on using suture material in kidney operations.

### Main part.

**Anatomy and topography of the kidney.**