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EFFECTS OF OXIDATIVE STRESS ON HEMATOLOGICAL PHYSIOLOGICAL PARAMETERS

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Abstract: *Oxidative stress is a complex biological process resulting from an imbalance between the production of reactive oxygen species (ROS) and the capacity of the antioxidant defense system. The blood system is highly susceptible to oxidative stress, which induces significant functional alterations in erythrocytes, leukocytes, platelets, plasma proteins, and hemostatic mechanisms. Due to their continuous exposure to oxygen and the propensity of hemoglobin to undergo auto-oxidation, erythrocytes are particularly vulnerable to ROS-mediated damage, including membrane lipid peroxidation, reduced deformability, hemolysis, and eryptosis. In leukocytes, oxidative stress enhances the production of inflammatory mediators, modulates immune responses, and contributes to the development of chronic inflammation. In platelets, ROS promote activation, aggregation, adhesion, and thrombus formation, thereby increasing the risk of thrombosis. Consequently, oxidative stress is closely associated with a wide range of hematological parameters, including erythrocyte count, hemoglobin concentration, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), leukocyte differential count, platelet count, and coagulation-related indices.*

Keywords: *Oxidative stress; blood physiology; erythrocytes; hemoglobin; leukocytes; platelets; hemostasis; antioxidant defense system; reactive oxygen species; blood rheology.*

Blood is the principal fluid connective tissue of the body and plays a crucial role in numerous vital physiological processes, including the transport of oxygen and carbon dioxide, delivery of nutrients, removal of metabolic waste products, immune defense, thermoregulation, and hemostasis. The maintenance of stable hematological parameters is essential for preserving systemic homeostasis and ensuring the proper functioning of biological systems.

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However, a variety of endogenous and exogenous factors, including infection, inflammation, hypoxia, toxins, psychological and physiological stress, poor nutritional status, metabolic disorders, and aging, can disrupt redox homeostasis and promote oxidative stress within the circulatory system. Oxidative stress is defined as a condition in which the production of reactive oxygen species (ROS), such as superoxide anion, hydrogen peroxide, hydroxyl radicals, and other reactive oxidizing molecules, exceeds the neutralizing capacity of the antioxidant defense system. This imbalance results in oxidative damage to lipids, proteins, nucleic acids, and cellular membranes, ultimately impairing cellular structure and function.

The blood system is particularly vulnerable to oxidative stress because its cellular components are continuously exposed to oxidizing conditions. Erythrocytes are constantly in contact with oxygen and are therefore highly susceptible to oxidative damage. Platelets exhibit considerable sensitivity to redox-dependent signaling pathways, whereas leukocytes actively generate reactive oxygen species as part of the innate immune response against invading pathogens. Consequently, oxidative stress plays a pivotal role in regulating blood cell function and contributes significantly to the pathophysiology of numerous hematological, cardiovascular, metabolic, and inflammatory disorders.

Recent scientific evidence has increasingly highlighted the importance of erythrocyte redox biology, reactive oxygen species (ROS)-mediated signaling in platelets, and the relationship between oxidative stress and thrombosis. Recent reviews published in 2024 have demonstrated that disturbances in redox homeostasis within erythrocytes can significantly affect membrane integrity, cellular deformability, and lifespan. In platelets, ROS are no longer considered merely harmful by-products of cellular metabolism; rather, they are recognized as important signaling molecules involved in platelet activation, aggregation, and thrombus formation.

Oxidative Stress and the Antioxidant Defense System

Under normal physiological conditions, low levels of reactive oxygen species (ROS) are continuously generated within the body. These molecules play essential roles in cellular signaling, immune defense, and metabolic adaptation. However, when ROS production exceeds physiological levels or the antioxidant defense system becomes impaired, oxidative stress develops. In the circulatory system, antioxidant protection is maintained through two major defense mechanisms.

The enzymatic antioxidant defense system consists of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR), and peroxiredoxins. The non-enzymatic antioxidant system includes glutathione, ascorbic acid (vitamin C), tocopherol (vitamin E), uric acid,

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bilirubin, albumin, transferrin, and ceruloplasmin.

Despite lacking a nucleus and intracellular organelles, erythrocytes possess a highly efficient antioxidant defense system. This is primarily due to their continuous role in oxygen transport and their constant exposure to oxidative conditions. Furthermore, the auto-oxidation of hemoglobin contributes to the generation of reactive oxygen species (ROS), increasing the susceptibility of erythrocytes to oxidative damage.

When oxidative stress is enhanced in erythrocytes, hemoglobin undergoes oxidation, leading to the formation of methemoglobin, while membrane proteins and lipids become damaged, resulting in a reduction of cellular elasticity.

Erythrocytes are among the blood cells most susceptible to oxidative stress. This heightened vulnerability is primarily attributable to their continuous exposure to high oxygen concentrations, the propensity of hemoglobin to undergo auto-oxidation, the abundance of polyunsaturated fatty acids within their membrane structure, the absence of mitochondria despite active redox metabolism, and their requirement for exceptional deformability to traverse narrow capillaries. Consequently, oxidative stress induces a variety of significant physiological and structural alterations in erythrocytes.

Membrane Lipid Peroxidation: Reactive oxygen species (ROS) oxidize lipids within the erythrocyte membrane, resulting in decreased membrane fluidity, disruption of the phospholipid bilayer structure, and alterations in cell morphology. These changes impair the ability of erythrocytes to pass through narrow capillaries efficiently. Reduced erythrocyte deformability increases blood viscosity and compromises microcirculatory function. A study published in Frontiers in Physiology demonstrated that oxidative damage can significantly impair the rheological properties of erythrocytes, thereby adversely affecting blood flow and tissue perfusion.

Hemoglobin Oxidation: During oxygen transport, hemoglobin may undergo oxidation from the ferrous (Fe^{2+}) state to the ferric (Fe^{3+}) state, resulting in the formation of methemoglobin. Unlike functional hemoglobin, methemoglobin is unable to bind and transport oxygen efficiently, leading to a reduction in oxygen delivery to peripheral tissues and the development of tissue hypoxia.

Consequences of Prolonged Oxidative Stress: When oxidative stress persists, hemoglobin function becomes progressively impaired, and Heinz bodies may accumulate within erythrocytes as a result of oxidative damage to hemoglobin. In addition, the susceptibility of erythrocytes to hemolysis increases, ultimately leading to reduced oxygen-carrying capacity and the potential development of tissue hypoxia.

Reduced Erythrocyte Deformability: Healthy erythrocytes possess a biconcave disc shape that enables them to traverse

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extremely narrow capillaries. Oxidative stress damages key membrane cytoskeletal proteins, including spectrin, ankyrin, and band 3 protein, thereby compromising membrane integrity and reducing erythrocyte elasticity. As a consequence, the rheological properties of blood become impaired. Erythrocyte deformability is a critical determinant of efficient blood circulation, and it has been reported that even a small proportion of rigid erythrocytes can significantly increase whole-blood viscosity and adversely affect microcirculatory blood flow.

Effects on Hematological Parameters: Oxidative stress can influence a wide range of parameters routinely evaluated in complete blood count (CBC) analyses.

Erythrocyte Count (RBC): Chronic oxidative stress shortens the lifespan of erythrocytes. Under normal physiological conditions, erythrocytes survive for approximately 120 days. However, excessive oxidative damage accelerates their removal by macrophages in the spleen and liver, leading to a reduction in circulating erythrocyte numbers.

Hemoglobin Concentration (Hb): Oxidative stress may decrease hemoglobin levels through two major mechanisms: enhanced erythrocyte destruction and oxidative modification of hemoglobin, resulting in the loss of its functional activity. These alterations may manifest clinically as anemia, tissue hypoxia, fatigue, dizziness, and reduced physical performance.

Hematocrit (Hct): Hematocrit represents the proportion of blood volume occupied by erythrocytes. A decline in erythrocyte count or an increase in hemolysis generally leads to a reduction in hematocrit values. However, dehydration, inflammatory conditions, or alterations in plasma volume may result in a relative increase in hematocrit despite underlying oxidative stress.

Red Cell Distribution Width (RDW): RDW reflects the degree of variation in erythrocyte size within the circulating blood population. Oxidative stress may cause heterogeneous damage to erythrocytes, thereby increasing RDW values. Elevated RDW has been recognized as an important prognostic marker in cardiovascular diseases, chronic inflammatory conditions, and metabolic disorders.

Oxidative stress can also affect erythrocyte membrane integrity and hemoglobin synthesis, leading to alterations in erythrocyte indices such as mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC). For instance, hemolysis and regenerative erythropoiesis may increase the proportion of young erythrocytes in circulation, resulting in elevated MCV values. Conversely, disturbances in iron metabolism may contribute to reductions in both MCH and MCHC levels.

Effects of Oxidative Stress on Leukocytes

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Leukocytes are the principal cellular components of the immune system and exhibit a bidirectional relationship with oxidative stress. On the one hand, neutrophils and macrophages generate reactive oxygen species (ROS) as part of the host defense mechanism to eliminate invading microorganisms. On the other hand, excessive ROS production can damage leukocytes themselves, leading to cellular dysfunction and the uncontrolled amplification of inflammatory responses.

Neutrophils and Reactive Oxygen Species (ROS): During phagocytosis, neutrophils generate large amounts of reactive oxygen species through a process known as the respiratory burst. This mechanism is essential for the effective destruction of invading microorganisms and constitutes a critical component of innate immune defense. However, under conditions of chronic inflammation, excessive and prolonged ROS production can result in collateral damage to surrounding tissues and circulating blood cells, thereby contributing to the progression of inflammatory pathology.

Lymphocyte Function: Oxidative stress can significantly influence lymphocyte proliferation, cytokine production, and the development of immunological memory. Excessively high levels of reactive oxygen species (ROS) may enhance apoptotic processes in lymphocytes, leading to a reduction in their viability and functional capacity. Consequently, prolonged oxidative stress may contribute to immune dysfunction and impaired immune responses.

Leukocyte Differential Count: Inflammatory conditions associated with oxidative stress are often characterized by several alterations in leukocyte profiles, including neutrophilia, lymphopenia, an increased neutrophil-to-lymphocyte ratio (NLR), monocyte activation, and secondary changes in eosinophil and basophil counts. Among these parameters, the neutrophil-to-lymphocyte ratio (NLR) has emerged as a simple yet valuable biomarker for assessing the interplay between oxidative stress and inflammation. Elevated NLR values are frequently associated with enhanced inflammatory activity, increased oxidative burden, and adverse clinical outcomes in various pathological conditions.

Effects on Platelets and Risk of Thrombosis

Platelets are the primary cellular components of the hemostatic system and play a crucial role in preventing blood loss following vascular injury. However, oxidative stress can induce excessive platelet activation, thereby increasing the risk of thrombotic events. Recent reviews published in 2024 have highlighted that reactive oxygen species (ROS) enhance platelet activation, aggregation, and thrombus formation through glycoprotein VI (GPVI)- and protease-activated receptor (PAR)-mediated signaling pathways. Furthermore, other studies have demonstrated that oxidative stress contributes to an increased risk of cardiovascular diseases and thrombosis,

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particularly in elderly and frail individuals.

The major consequences of oxidative stress in platelets include enhanced platelet aggregation, activation of adhesion molecules, increased thromboxane A_2 production, reduced bioavailability of nitric oxide (NO), exacerbation of endothelial dysfunction, and activation of the coagulation cascade. Collectively, these alterations promote a prothrombotic state and contribute to the pathogenesis of thrombotic and cardiovascular disorders.

Collectively, these mechanisms contribute substantially to the development and progression of myocardial infarction, ischemic stroke, venous thromboembolism, diabetic angiopathy, and chronic inflammatory disorders, highlighting the critical role of oxidative stress in cardiovascular and systemic disease pathophysiology.

Effects on Plasma Proteins and Hemostasis

Oxidative stress affects not only blood cells but also plasma proteins and the coagulation system. Major plasma proteins, including albumin, fibrinogen, immunoglobulins, and various coagulation factors, are susceptible to oxidative modification. Oxidation of fibrinogen can alter the structural organization of fibrin fibers, resulting in the formation of denser and more degradation-resistant thrombi. Consequently, fibrinolytic activity is impaired, leading to delayed thrombus breakdown and an increased risk of thrombosis.

Endothelial Dysfunction: Oxidative stress reduces the bioavailability of nitric oxide (NO), a key signaling molecule responsible for vasodilation and the inhibition of platelet aggregation. A decrease in NO levels promotes vasoconstriction, enhances platelet activation, elevates blood pressure, impairs microcirculatory function, and shifts hemostatic balance toward a procoagulant state. These alterations contribute significantly to vascular dysfunction and increase the risk of thrombotic and cardiovascular complications.

The Relationship Between Erythrocytes and Thrombosis

Traditionally, erythrocytes were regarded primarily as oxygen-transporting cells. However, emerging evidence indicates that erythrocytes also play an active role in thrombus formation and the regulation of hemostatic processes. Under conditions of oxidative stress, phosphatidylserine becomes externalized on the erythrocyte membrane surface, providing a catalytic platform for the assembly of coagulation complexes. This procoagulant surface facilitates thrombin generation and promotes thrombus formation. The association between erythrocyte oxidative stress and thrombosis has been extensively discussed in recent review articles, highlighting the important contribution of red blood cells to thrombotic

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pathophysiology beyond their traditional role in oxygen transport.

Blood Rheology and Microcirculation

Blood rheology refers to the study of the flow properties of blood and the factors that influence its circulation within the vascular system. Key determinants of blood rheology include blood viscosity, erythrocyte deformability, erythrocyte aggregation, plasma protein composition, and hematocrit levels. Oxidative stress impairs blood rheology through several mechanisms, including reduced erythrocyte elasticity, enhanced erythrocyte aggregation, elevated plasma fibrinogen concentrations, increased platelet activation, and endothelial dysfunction. These alterations collectively compromise microcirculatory function and tissue perfusion.

As a consequence, microcirculatory disturbances may develop, particularly in highly perfused and metabolically active organs such as the brain, heart, kidneys, and peripheral tissues, which are especially vulnerable to oxidative damage. Impaired microcirculation has been associated with chronic tissue hypoxia, fatigue, cognitive decline, cardiovascular diseases, and metabolic syndrome, underscoring the significant role of oxidative stress in the pathophysiology of systemic disorders.

Biomarkers of Oxidative Stress

A variety of laboratory biomarkers are used to assess oxidative stress and its impact on biological systems.

Markers of Oxidative Damage include malondialdehyde (MDA), 4-hydroxynonenal (4-HNE), protein carbonyls, oxidized low-density lipoprotein (ox-LDL), 8-hydroxy-2′-deoxyguanosine (8-OHdG), methemoglobin, and nitrotyrosine. These biomarkers reflect oxidative modifications of lipids, proteins, nucleic acids, and other cellular components.

Markers of Antioxidant Defense include superoxide dismutase (SOD) activity, catalase activity, glutathione peroxidase (GPx) activity, total antioxidant capacity (TAC), reduced glutathione (GSH), oxidized glutathione (GSSG), and the GSH/GSSG ratio. These parameters provide valuable information regarding the efficiency of the antioxidant defense system and the maintenance of cellular redox homeostasis.

Hematological and Hemostatic Markers Associated with Oxidative Stress include hemoglobin (Hb), red blood cell count (RBC), hematocrit (Hct), red cell distribution width (RDW), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), white blood cell count (WBC), neutrophil-to-lymphocyte ratio (NLR), platelet count (PLT), mean platelet volume (MPV), fibrinogen, and D-dimer.

When evaluated collectively, these biomarkers provide a comprehensive assessment of the impact of oxidative stress on blood physiology, redox balance, inflammatory responses, and hemostatic function.

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Clinical Significance

Oxidative stress is associated with alterations in hematological parameters in a wide range of pathological conditions. These include cardiovascular diseases, diabetes mellitus, chronic kidney disease, obesity, hypertension, atherosclerosis, chronic inflammatory disorders, autoimmune diseases, aging, infectious diseases, anemia, and thrombosis.

The relationship between oxidative stress, antioxidant enzyme activity, and inflammatory markers in diabetes mellitus was further demonstrated in a 2025 study published in Scientific Reports. The study evaluated several biomarkers, including superoxide dismutase (SOD), glutathione peroxidase 1 (GPX1), catalase, interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor-alpha (TNF-α), highlighting the complex interactions between oxidative stress, inflammation, and metabolic dysfunction.

Oxidative stress also increases with advancing age. Age-related alterations in redox homeostasis can affect erythrocyte membrane integrity, platelet activity, and immune cell function, thereby contributing to an elevated risk of cardiovascular complications. Furthermore, studies have reported that oxidative stress and enhanced platelet activation are closely associated with an increased risk of thrombosis in frail individuals, emphasizing their clinical relevance in age-related vascular disorders.

Scientific Conclusion

Oxidative stress exerts multifaceted effects on the blood system. Its role extends beyond the induction of cellular damage, encompassing the regulation of physiological signaling pathways, immune responses, hemostatic mechanisms, microcirculatory function, and metabolic adaptation. Therefore, oxidative stress should not be regarded solely as a detrimental phenomenon but rather as a biological regulator whose effects depend on its intensity and duration.

At physiological levels, reactive oxygen species (ROS) serve essential signaling functions. For example, immune cells generate ROS as part of the host defense response against invading microorganisms. Similarly, ROS-mediated signaling in platelets may be necessary for maintaining normal hemostatic function. However, excessive ROS production disrupts redox homeostasis, leading to erythrocyte damage, platelet hyperactivation, amplification of inflammatory responses by leukocytes, and a shift of the coagulation system toward a procoagulant state. These alterations collectively contribute to the development and progression of numerous hematological, cardiovascular, and metabolic disorders.

Conclusion

Oxidative stress exerts profound and multifaceted effects on hematological physiology. In erythrocytes, it induces membrane lipid peroxidation, hemoglobin oxidation, reduced deformability, eryptosis, and hemolysis. In leukocytes,

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oxidative stress enhances inflammatory responses and disrupts immune homeostasis. In platelets, it promotes activation, aggregation, and thrombus formation, thereby increasing the risk of thrombosis. Furthermore, oxidative modification of plasma proteins and coagulation factors shifts the hemostatic balance toward a procoagulant state.

Therefore, the assessment of oxidative stress should not rely on a single biomarker but rather on a comprehensive evaluation of hematological, biochemical, inflammatory, and hemostatic parameters. Future studies integrating erythrocyte deformability, red cell distribution width (RDW), neutrophil-to-lymphocyte ratio (NLR), mean platelet volume (MPV), fibrinogen, D-dimer, superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx), and lipid peroxidation biomarkers may provide deeper insights into the role of oxidative stress in blood physiology and its contribution to disease pathogenesis.

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