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Chronic Kidney Disease and Oxidative Stress

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SUMMARY

Disturbance of the balance between production of oxygen free radicals (or some other radical species) and activity of antioxidative system of protection causes the so called oxidative stress Protection of an organism from oxygen free radicals implies activity of enzymatic (catalase, SOD, glutathione peroxidase, glutathione reductase etc.) and nonenzymatic (vitamin E. vitamin C. glutathione, uric acid etc.) systems of protection. An organism can tolerate a mild oxidative stress but a higher disturbance between the production of free radicals and the activity of the antioxidative protection results in lipid protein and DNA as well as numerous diseases. In this article we analyze oxidative stress role as an important cofactor contributing to endothelial dysfunction, inflammation, atherosclerosis,glomerulosclerosis, anemia, tubulointerstitial nephritis and ischemia-reperfusion injury to chronic kidney disease patients.

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Introduction

Oxidative stress defines an imbalance between formation of reactive oxygen species (ROS) and antioxidative defence mechanisms. Oxygen-free radicals and reactive-oxygen species are involved in the pathogenesis of many clinical disorders by damaging lipids, proteins,and DNA or by altering cellular signal transduction.

Mitochondria are the main cellular source of reactive oxygen species (ROS) [1,2]. Electrons can be released from the respiratory chain and can combine with oxygen to form superoxide, an ROS. The respiratory chain is composed of 4 multi-subunit complexes (I, II, III, and IV) linked by the mobile electron carriers coenzyme Q10 and cytochrome c. (Figure 1) The reduced forms of nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH2) are formed from the citric acid cycle and the beta-oxidation of fatty acids in the mitochondrial matrix. The respiratory chain transfers electrons from NADH (via complex I) and from reduced flavoproteins (via complex II and electron transfer flavoprotein-coenzyme Q oxidoreductase [ETF-Qo]) to coenzyme Q10, then complex III, cytochrome c and finally complex IV. At the same time, complexes I, III, and IV pump electrons across the inner mitochondrial membrane from the matrix to the intermembrane space. The influx of these electrons (protons) back into the mitochondrial matrix releases energy that is used in the phosphorylation of ADP (adenosine diphosphate) to ATP (adenosine triphosphate) by complex V (ATP synthetase), which is also embedded in the inner mitochondrial membrane Complex I and III and to a lesser extent Complex II are thought to be the major sites contributing to mitochondrial ROS generation. ROS have multiple effects. They can directly damage (through oxidation) proteins, lipids and nucleic acids. But perhaps more importantly, they act as second messengers in signaling pathways. For example, high levels of ROS production can lead to oxidation of cardiolipin and release of cytochrome c, which triggers the caspase cascade in apoptosis [1].

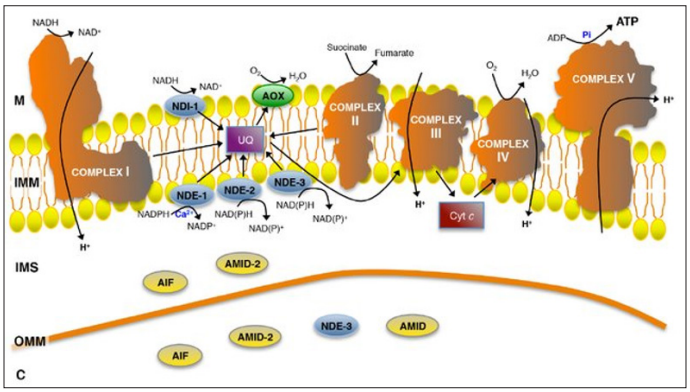

Figure 1: Representation of the mitochondrial respiratory chain, alternative NAD(P)H dehydrogenases and alternative oxidase systems. M: mitochondrial matrix; IMM: mitochondrial inner membrane; IMS: intermembrane space; OMM: mitochondrial outer membrane; C: cytosol; UQ: ubiquinone; Cyt c : cytochrome c.

It is generally accepted that ROS such as hydrogen peroxide (H_2O_2) or hypoclorus acid (HOCl), and free radicals such as superoxide (O^-_2), hydroxyl radical (OH), and nitric oxide (NO), are continuosly formed in vivo [3].Thus, detection of ROS per

se does not yet define oxidative stress;however, in a situation where antioxydative defence mechanisms are attenuated, it is the imbalance between formation of ROS and defence mechanisms that creates oxidative stress.

Renal sources for ROS are activated macrophages, vascular cells and various glomerular cells [4]. The balance between formation of ROS and antioxidative defence mechanisms depends on the activity of enzymes such as superoxide dismutases (SOD), catalase, NO-synthase, and glutathione peroxidase [5]. This balance, however, is rather fragile, difficult to predict, and strongly dependent on environmental conditions, ROS can be formed from vascular and glomerular cells including fibroblasts, from leucocytes, and from renal interstitial cells [3,6]. Different cellular enzymes, including mitochondrial oxidases, lipoxygenase, cyclooxygenase, myeloperoxidase, NADPH oxidase, xanthine oxidase, and, in the case of L-arginine or tetrahydrobiopterin depletion, NO-synthase have been identified as cellular sources of ROS formation [7-11].

The role of oxidative stress as an important cofactor contributing to endothelial dysfunction, inflammation, atherosclerosis and glomerulosclerosis has substantially increased over the last years. ROS may affect cells of the host organism, in particular at sites of inflammation. The latter plays a role in a variety of renal diseases, such as glomerulonephritis, acute or progressive renal failure, or tubulointerstitial nephritis, contributing for example to proteinuria. ROS are also considered to contribute to the pathogenesis of ischaemia□reperfusion injury [4,12]. Furthermore, due to their impact on cell cycle regulation, oxygen radicals may contribute to hypertrophy of tubular cells [13,14].

Oxidative stress is diagnosed by measuring several markers in blood, mainly malondialdehyde (MDA) for lipid peroxidation, advanced oxidation protein product (AOPP) for protein oxidation, oxidized low-density lipoprotein (oxLDL) for lipoproteins oxidation, and various markers for nucleic acid oxidation – mainly 8-hydroyguanine [15-17].
Also, it is of major interest to monitor the effectiveness of antioxidant mechanism by measuring enzymatic, such superoxide dismutase (SOD) and glutathione peroxidase (GPX) and non-enzymatic antioxidant markers such as vitamins C and E and coenzyme Q10 (CoQ10) [18,19].

Role of Oxidative Stress in Vascular Calcification and Atherosclerosis of Ckd Patients

Inflammation plays a crucial role in calcification [20,21]. Infiltrating macrophages release proinflammatory cytokines that drive the influx of lymphocytes and smooth muscle cells [22]. Cellular microvesicles released from macrophages or apoptotic macrophages form a nidus for calcification, and macrophage-derived inflammatory regulators, such as matrix metalloproteinases and cathepsin S, contribute to the disintegration of elastic fibers and matrix components in the vessel wall, all which may promote calcification. Inflammation also drives oxidative stress, which contributes to vascular calcification [23]. In turn, many antioxidant treatments have been proposed to ameliorate calcification, mediated by the Kelch-like ECH-associated protein 1/NF-E2-related factor 2 (KEAP/NRF2) system, a highly evolutionary conserved defense system against oxidative stress [24].

Patients with CKD are at high risk of developing cardiovascular disease. The acceleration of the atherosclerosis process is very common in patients with severe CKD and haemodialysis patients, and oxidative stress markers increase significantly with the progression of CKD, with the highest values, except for glutathione, seen in haemodialysis patients. This latter group is affected by many external factors such as the contact of blood with biocompatible membranes, which increase the effect of oxidative stress [25].

Atherosclerosis is considered as an inflammatory disease with chronic fibroproliferation of the vascular wall [26]. The fixation of monocytes and T lymphocytes on the injured endothelium followed by their migration into the intima is one of the most crucial steps in the development of atherosclerotic lesions [27]. When monocytes and endothelial cells are activated, they express several active molecules such as adhesion molecules, cytokines, coagulation and fibrinolytic factors, metalloproteinases, and vasoactive substances [28]. All of these molecules could contribute to atherogenesis and thrombosis. A significant correlation between advanced oxidation protein product (AOPP) and monocyte activation markers was reported [29]. Thus, AOPP may represent a new class of proinflammatory and proatherogenic mediators [25].The levels of oxidized low-density lipoprotein (oxLDL) increased with the deterioration of renal function. Furthermore, oxLDL is highly implicated in the development and progression of atherosclerosis, and its measurement could help in the early diagnosis of different cardiovascular diseases. For the management of atherosclerosis and other cardiovascular diseases in CKD patients we think that reducing the level of oxLDL would be an open treatment strategy to be investigated in further studies.

For ideal functioning of different organs, cells structure and functions must be well kept and controlled for toxin accumulation and membrane integrity. Likewise, vascular endothelium plays a key role in the vascular tone regulation in response to different stimuli such as prostacyclin, endothelin, and nitric oxide (NO) [30]. The various cell types constituting the vascular wall produce in abundance radical and non-radical ROS and reactive nitrogen species (RNS), responsible for oxidative stress development [31]. ROS and RNS are important modulators of signal transduction pathways and gene expression, which are implicated in the normal vascular homeostasis [32]. Any disruption of this balance will induce endothelial problems [33]. Oxidative stress and inflammation are two major proatherogenic factors, responsible for modification of vascular wall integrity [34].

The vascular wall integrity and cellular function can be compromised by several factors such as hypertension, hypercholesterolaemia, and diabetes, which induce harmful oxidative stress through the activation of nicotinamide adenine dinucleotide phosphate NAD(P)H oxidases and the mitochondrial respiratory chain, and by decreasing NO bioavailability [35].

Atherosclerotic lesions begin following a pro-oxidant imbalance, leading to oxLDL formation and multiple cellular dysfunctions such as synthesis of pro-inflammatory mediators and promotion of cell proliferation factors, in addition to the adhesion of monocytes to the endothelial cells, platelet aggregation, cellular apoptosis or necrosis, and finally the rupture of atherosclerotic plaques [36]. In the atheroma plaque, several macrophage populations were identified with different phenotypes linked to inflammation (pro-inflammatory: M1, anti-inflammatory: M2) or with redox changes in the environment (Mox), increased oxidative stress markers such as AOPP, myeloperoxidases (MPO), and decreased antioxidant markers such as gluthations [37]. It seems that oxidative stress and inflammation are crosslinked and play an important role in (i) endothelial dysfunction, by decreasing endothelial NO

(eNO) bioavailability and increasing inducible NO (iNO), (ii) LDL oxidation, (iii) lesion remodelling by proteases and antiproteases regulation, and (iv) smooth muscle cell (CML) proliferation, because CML are the second most abundant cell type in atherosclerotic damage after macrophages. CML hyperproliferation results from cells dedifferentiation from a contractile secretory phenotype, increasing their proliferative and migratory capacity [38]. Intracellular lipids oxidation such as malondialdehyde (MDA) is a common pathophysiological response to oxidative stress and hyperlipidaemia. oxLDL contains hundreds of different oxidised lipid molecules [39]. oxLDL can be found in various abnormal cells such as apoptotic cells and in pathological tissues and in the blood stream in the case of different diseases [40,41]. Therefore, oxLDL is a valuable biomarker for hyperlipidaemia and atherosclerosis. oxLDL molecules penetrate the subendothelial space where they undergo many oxidative modifications induced by ROS produced by the wide cell population of blood vessels, mainly monocytes, endothelial cells, and vascular smooth muscle cells (VSMCs), leading to the development of atherosclerosis
[41].

Oxidative Stress and Acute Kidney Injury

Iron-mediated oxidative stress is thought to contribute to **ischemia-reperfusion injury**. Mislocalized iron in the kidney occurs in experimental ischemia-reperfusion injury. Neutrophil gelatinase-associated lipocalin (NGAL) is a kidney protein that induces kidney cell differentiation and binds a siderophore that traps iron with high affinity. NGAL is induced in the kidney after ischemic injury, and the release of unbound iron that occurs as a consequence of ischemic injury can promote the formation of reactive oxygen species. The delivery of a lipocalin-siderophore-iron complex preserves kidney histology in mice following ischemic injury [42]. In one study, ferroportin, an iron export protein, contributed to ischemia-reperfusion injury [43]. Hepcidin is an endogenous acute-phase hepatic hormone that binds and degrades ferroportin and attenuates acute kidney injury. Furthermore, hepcidin-deficient mice are more susceptible to ischemia-reperfusion injury [44].

Oxidative Stress and Anemia of Ckd Patients

The uraemic state and the bio-incompatibility of haemodialysis (HD) are associated with an increased oxidative stress in HD patients presumably caused by both an increased generation of oxygen-free radicals reactive-oxygen species and decreased levels of different antioxidants [45]. Oxidative stress is thought to be the most likely explanation for the shortened life span of red blood cells (RBCs) in HD patients [46].

The antioxidant defenses of blood are composed of: (1) plasma antioxidants and (2) the antioxidant capacity of the RBCs. According to Beutler's hypothesis, RBCs can be looked upon as small detoxyfying packets removing harmful substances from the plasma [47,48]. Disturbances in the antioxidant metabolism of RBCs in uraemic patients have been reported by various authors. There are, however, conflicting data on some points. The levels of reduced glutathione (GSH), or the activities of antioxidant enzymes such as glutathione peroxidase (GSH-PX) or superoxide dismutase have been found to be decreased normal or even increased in the RBCs of uraemic patients. An impaired flux through the hexose monophosphate shunt (HMPS) has been the subject of controversy [46,48-53].

The antioxidant capacity of erythrocytes usually is determined by measuring various antioxidants, metabolites, or antioxidant enzymes in haemolysates. It is uncertain, however, whether these indirect methods may reflect the true antioxidant capacity of intact erythrocytes. Other ways of determining the antioxidant capacity in RBCs include the measurement of MDA production or the estimation of radical generation with chemiluminescence after treatment with tert-butylhydroperoxide (t-BOOH) treatment [54,55].

Electron paramagnetic resonance (EPR) with spin trapping is the only direct method of detection and identification of free radicals. Free-radical processes in RBCs have been successfully investigated by EPR [56,57]. Using ERP, showed a decrease in membrane protein mobility of RBCs after t-BOOH treatment, and with this method were able to observe the generation of hydroxyl radicals during HD. Using EPR show that the antioxidant potential of erythrocytes is extremely high for the hydroperoxide t-BOOH, without any difference between HD patients and controls [5]. The slower elimination of peroxyl and alcoxyl radicals, generated by t-BOOH after inhibition of the GSH system in HD patients compared with controls indicates a defect in the antioxidants outside the GSH system and could be one reason for the reduced life span of erythrocytes in the uraemic state. There are benefits of correcting anaemia for lowering oxidative stress; erythrocytes are powerful antioxidant scavengers, and an increase in erythrocyte number increases the antioxidant potential of blood [5].

Conclusion

Oxidative stress is defined as all the molecular alterations within the organism cells induced by an increased production of reactive oxygen species (ROS), which escape to mechanisms of antioxidant stress regulation. Our knowledge about stimuli and sources of oxidative stress, and about its role as an important cofactor contributing to endothelial dysfunction, inflammation, atherosclerosis and glomerulosclerosis has substantially increased over the last years. However, even though partial prevention of CVD by antioxidant treatment in haemodialysis patients could be achieved, no clinical end-point study using various antioxidant treatments was able to clearly show a beneficial effect on total mortality in non-renal or renal patients. Thus, a major task for the coming years will be to design effective antioxidant protocols and to analyse them in clinical intervention studies with hard end-points, including mortality, to prove whether the concept holds true.

Conflicts of Interest and Sources of Funding

The authors declare no conflict of interest.

Authors' contribution

All the authors contributed to the following aspects of this study: Conceptualization: M.S.,A.T; resources: C.C..;writing- original draft preparation:M.S.,A.T., and G.B.; writing – review and editing:M.S., and A.T writing- finalization:M.S.,A.T., and G.B.

The authors have given their approval for this article to be published. All of the authors have participated sufficiently in the work and take public responsibility for appropriate portions of the content. All of the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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