CHRONIC KIDNEY DISEASE AND OXIDATIVE STRESS

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Abstract: Chronic kidney disease (CKD) is a persistent kidney injury and glomerular filtration rate is used to identify and classify patients. People with CKD have a high risk of death from stroke or heart attack and CKD may also progress to total and permanent renal failure (end-stage renal disease), in which case dialysis or transplantation is then necessary. CKD is associated with cardiovascular risk factors and non-traditional risk factors, such as inflammation and oxidative stress. Excessive reactive oxygen species production and/or inadequate antioxidant systems lead to oxidative stress. Oxidative stress seems to increase as CKD progresses and correlates significantly and inversely with the level of glomerular filtration rate.

Chronic kidney disease is considered as the persistent kidney injury characterized by a glomerular filtration rate <60 ml/min per 1.73 m² for more than 3 months (which is the period considered by the nephrologists for the kidney to recover from an episode of acute kidney failure). CKD is associated with high traditional cardiovascular risk factors such as diabetes, hypertension, and hyperlipidemia and with other, non-traditional risk factors, such as renal-specific risk factors: uraemia or dialysis. These extra renal risk factors also include proteinuria, chronic volume overload, increased renin-angiotensin system activity, inflammation, infection, oxidative stress, altered calcium and phosphorus metabolism, anemia, malnutrition, elevated levels of homocysteine, uraemic toxins, depressed nitric oxide availability, and thrombogenic factors. Some of these latter extra-risk factors may act by producing accelerated atherogenesis.(1) Epidemiological studies reveal other strong risk factors for CKD, such as previous episodes of acute kidney damage, exposure to nephrotoxins, obesity, smoking, and increasing age.(2)

CKD is accompanied by oxidative stress which consists in the damage of biological structures by reactive oxygen or nitrogen species due to excessive generation and impaired efficiency of antioxidant defence mechanisms. Generation of oxidative compounds is physiologically important as part of a defence mechanism against invading microorganisms or malignant cells, as well as of tissue repair, healing and remodelling. Reactive oxygen species (ROS) play a vital role in many physiologic functions. They are known regulators of nitric oxide synthesis, intracellular signalling cascades, and are also involved in the modulation of immune responses, apoptosis and mutagenesis.(3)

ROS production mainly occurs in the mitochondria (mitochondrial electron transport system), and mitochondrial cytochrome oxidase enzymes, such as cytochrome P450, account for ~90% of the oxygen metabolizes in mammalian cells. ROS are also produced by peroxisomal β-oxidation of fatty acids, stimulation of phagocytosis by pathogens or lipopolysaccharides, arginine metabolism and tissue specific enzymes: the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, xanthine oxidase, cyclooxygenase, lipooxygenase, glucose oxidase, and uncoupled nitric oxide synthases.(4,5)

The first ROS obtained by one electron reduction of molecular oxygen is the superoxide anion (O₂⁻). It can be metabolized by superoxide dismutase (SOD) to hydrogen peroxide (H₂O₂), and then converted to the highly reactive hydroxyl radical (OH) by ferrous iron (Fe²⁺). Normally the H₂O₂ is reduced by catalase or by glutathione peroxidase to H₂O. H₂O₂ and chloride (Cl⁻) are metabolized by myeloperoxidase to hypochlorous acid (HOCI) in activated phagocytes. O₂ also reacts with nitric oxide (NO) to yield peroxynitrite (ONOO⁻), which is not only cytotoxic, but it is also responsible for both increased platelet aggregation and vasoconstriction.(6,1)

In physiological conditions, ROS are completely inactivated by cellular and extracellular defence mechanisms, counteracting the damaging effects. There are two lines of enzymatic and non-enzymatic antioxidant defence within the cell. The most important non-enzymatic antioxidants are: vitamin C, glutathione, vitamin E, β-carotene, coenzyme Q, along with the enzymes: SOD, catalase, glutathione peroxidase.(1)

Figure no. 1. Production and metabolism of ROS

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NOS indicates nitric oxide synthase; Glutathione disulfide (GSSG), glutathione disulfide; catalase (CAT); SOD; GPX, glutathione peroxidase; and myeloperoxidase (MPO), (reproduced from Vaziri).(5)

Direct measurement of ROS in vivo is very difficult because of their low concentration, highly reactive nature and short half-life. That is why we often measure the oxidative by-products of different ROS pathways or the antioxidants levels. The most known biomarkers of oxidative stress in CKD patients are summarized in table no. 1.(6)

Table no. 1. Circulating biomarkers of oxidative stress in CKD patients

<table>
<thead>
<tr>
<th>Lipids</th>
<th>Arachidonic acid derivatives</th>
<th>Carbohydrates</th>
<th>Amino acids</th>
<th>Proteins</th>
<th>Nucleic acids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malondialdehyde (MDA)</td>
<td>F2-isoprostanes</td>
<td>Reactive aldehydes</td>
<td>Cysteine</td>
<td>Thiol oxidation</td>
<td>8-Hydroxy 2′-deoxyguanosine (8-OHdG)</td>
</tr>
<tr>
<td>Lipid hydroperoxides</td>
<td>Isoprostanes</td>
<td>Advanced glycosylation end products (AGEs)</td>
<td>Homocysteine</td>
<td>Carbonyl formation</td>
<td></td>
</tr>
<tr>
<td>Oxidized low-density lipoprotein (ox-LDL)</td>
<td>Advanced lipoxidation end products (ALEs)</td>
<td></td>
<td>Isoaspartate</td>
<td>Advanced oxidation protein products (AOPPs)</td>
<td></td>
</tr>
<tr>
<td>Exhaled alkanes</td>
<td></td>
<td></td>
<td></td>
<td>Amine oxidation</td>
<td></td>
</tr>
<tr>
<td>Advanced lipoxidation</td>
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</table>

In hemodialysis patients, the additional stimulus for increased ROS production can be the hemodialysis procedure itself.(7,8) It is mainly due to inflammatory cell activation caused by insufficiently biocompatible membranes, which is amplified by various bacterial products passing across from the dialysate to the blood compartment and directly or indirectly stimulate release of ROS by neutrophils.(9,10) During the hemodialysis procedure the dialysis membrane is subjected to immunologic response by low molecular weight plasma constituents such as IgG, platelet activating factor (PAF) and complement components (C3 and C5a) which may then stimulate neutrophils.

Oxidative stress can cause damage to all molecular targets: DNA, proteins and lipids, often, it is not clear which is the first point of attack, since injury mechanism overlap widely. Lipid peroxidation of polyunsaturated fatty acids and cholesterol will alter cell membrane fluidity and permeability characteristics and may induce widespread membrane damage. ROS can stimulate oxidation of LDL and oxidized low-density lipoprotein (ox-LDL), which is not recognized by the LDL receptor, can be taken by scavenger receptors in macrophages leading to foam cell formation and atherosclerotic plaques.(11) Foam cells are the main component of fatty streaks, which is the first step in atheromatous plaque formation, and they trigger antigenic reaction in T-lymphocytes that will either initiate or increase the immunological response.(12)

ROS can oxidize non-enzymatically arachidonic acid in lipoproteins and cell membrane phospholipids, which leads to generation of vasoconstrictive proinflammatory products such as isoprostanes. These by-products can contribute to the rise of blood pressure and renal and cardiovascular complications.(13)

Many studies have reported that there is an inverse correlation between different markers of oxidative stress and glomerular filtration rate because ROS increase in a graded manner as renal function deteriorates.(14)

The presence of p22phox subunit gene polymorphism of NADPH oxidase is associated with oxidative stress in patients with CKD and individuals with CC genotype present higher oxidative stress status.(15)

The management of oxidative stress in CKD includes:

- Reduction of inflammatory cell activation
  - By using biocompatible dialysis membranes (e.g. polycrylonitrile or polysulfone);(8)
  - By using ultrapure dialysate;(16)
  - By removal of focal infections (i.e. dental, tonsillar, and other)
- Removal of inflammatory mediators
  - By haemolipodialysis (addition of α-tocopherol incorporated liposomes to dialysate);(9,10)
  - By using electrolysed reduced water (which releases hydrogen on the cathode during electrolysis);(17)
- Administration of antioxidants
  - By administration of antioxidants
    - α-tocopherol (administered orally or intramuscularly, or even bonded to the hemodialysis membrane) with benefits on cardiovascular complications;(18,19,20,21)
    - Ascorbic acid;(22,23)
    - N-acetylcysteine;(24)
    - Reduced glutathione;(25)
- Administration of angiotensin converting enzymes inhibitors and angiotensin II receptor blockers;(26,27)
- Administration of statins;(28)
- Administration of allopurinol;(29)

The role of oxidative stress in renal dysfunction is not yet fully understood. Oxidative stress is the cause for endothelial dysfunction and left ventricular hypertrophy (1,30), for hypertension.(5) Along with inflammation, dyslipidemia and malnutrition, oxidative stress represents a key element for the development of atherosclerosis process and cardiovascular disease, leading to a higher mortality of the patients with CKD than the general population.

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