Oxidative Stress in Uremia: The Role of Anemia Correction

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Patients with chronic kidney disease (CKD) are prone to develop cardiovascular disorders. Numerous reports have shown the association between uremia and oxidative stress, which increases patients’ risk for cumulative injury to multiple organs. Anemia is a common and disabling feature of CKD and seems to be a main cause of oxidative stress; correction of anemia represents an effective approach to reduce oxidative stress and, consequently, cardiovascular risk. There is increasing evidence that correction of anemia with erythropoiesis-stimulating agents could protect from oxidative stress in patients with CKD and ESRD. However, iron deficiency frequently complicates anemia in patients with CKD, and ferrous iron cation is a co-factor that is needed for hydroxyl radical production, which can promote cytotoxicity and tissue injury. This has raised a justifiable concern that prescription of intravenous iron may exacerbate oxidative stress and, hence, endothelial dysfunction, inflammation, and progression of cardiovascular disease, which are widely known consequences of CKD. Correction of anemia represents an effective approach to reduce oxidative stress and, consequently, cardiovascular risk. Iron deficiency is a common cause of resistance to erythropoiesis-stimulating agents, and the overall risk-benefit ratio favors use of intravenous iron to treat iron deficiency in patients with CKD. Consecutive or combined treatment with intravenous iron and erythropoiesis-stimulating agents clearly is beneficial for patients with CKD and iron deficiency, and anemia and could contribute to prevent the risk for cardiovascular events in these patients.

Oxidative Stress: Definition and Components

Oxidative stress can be considered an imbalance between reactive oxygen species (ROS) production and antioxidant defense. This imbalance can lead to the oxidation of molecules, resulting in tissue damage. The “oxidant condition” mainly depends on the oxidative processes inside the organism (1). Alterations in mitochondrial enzyme complex cytochrome oxidase accounts for an important part of oxidative processes, because the mitochondria handles 90% of total oxygen in a human. A fraction of oxygen that is metabolized in the mitochondria can leak through the electron transport chain, forming reactive oxygen intermediates and oxygen free radicals such as superoxide anions and hydrogen peroxide. These ROS can diffuse out of the mitochondria, being an important source of oxidative stress (1,2). Another source of ROS is the NAD(P)H oxidase, which is important in endothelial and phagocytic cells. In addition, xanthine oxidase is a main source of oxygen species in occlusion-reperfusion situations. On the other side, a number of enzyme activities such as superoxide dismutase, catalase, glutathione (GSH) reductase (GRed), and GSH peroxidase (GPx) are determinants of antioxidant defense, leading to ROS clearance and buffering (1,3,4). Reduced GSH is a primary antioxidant that has been proposed as a major scavenger of ROS. Levels of GSH are maintained in the cells by the GPx/GRed system. GPx catalyzes the reduction of H₂O₂ to H₂O, which is coupled to the oxidation of GSH to its disulfide form, GSSG. The reduction of GSSG to GSH is coupled to the oxidation of NADPH to NADP⁺ through GRed. Erythrocytes play a key role in the maintenance of both systemic and local redox balance, as a result of their ability to recycle GSH formation through the GPx/GRed system. Therefore, evaluation of GSH system parameters in erythrocyte is considered a reliable method to study redox status (4).

Oxidative Stress and Cardiovascular Disease

ROS are part of the unspecific defense system of an organism. However, ROS also may affect cells of the host organism, in particular at sites of inflammation, which plays a role in a variety of renal diseases, such as glomerulonephritis, acute or progressive renal failure, or tubulointerstitial nephritis (1,3), contributing to proteinuria. ROS also are considered to contribute to the pathogenesis of ischemia-reperfusion injury (5).

From a vascular point of view, many studies have shown that atherosclerosis and risk factors for the development of the disease are associated with an exaggerated production of ROS. Atherosclerosis involves the participation of several cell types and processes, such as endothelial dysfunction, oxidation, inflammation, and fibrinolytic imbalance (6). ROS are determinants for the oxidation of LDL, which are taken up by macrophages, leading to the formation of foam cells. In addition, ROS and, specifically, superoxide anions parti-
Anemia was associated independently with an increased risk for cardiovascular disease (11). Several studies showed that in patients with ESRD, low hematocrit levels were associated with a marked increased in cardiovascular morbidity and mortality (12). There are several reasons to explain the relationship between anemia and adverse cardiac outcomes. First, anemia is a marker of poor cardiac function. Second, it is a causative risk factor for cardiac ischemia, because coronary artery disease limits the ability to extract oxygen from hemoglobin. Third, the physiologic adaptive response to anemia is an increase in cardiac output. This initial compensatory benefit is limited, because a chronic adaptation to low hemoglobin levels may increase left ventricle growth in response to increased myocardial workload. In fact, several studies demonstrated the association between anemia and left ventricular hypertrophy in nonrenal patients and in patients who had CKD, were on dialysis, or received a renal transplant (13).

Oxidative Stress in Uremia

Recent studies have shown that oxidative stress is highly present in patients with renal disease (1,3). It is known that LDL from uremic patients present an elevated susceptibility to oxidation, being an indication of accelerated atherosclerosis in these patients. Uremic oxidative stress is characterized from a biochemical point of view as a state of reactive aldehyde and oxidized thiol group accumulation, together with depletion of reduced thiols groups, which are particularly important as part of antioxidant defense. As a consequence of diminished renal catabolism and function, uremic oxidant mediators accumulate, favoring vascular cell dysfunction and progression of atherosclerosis. In addition to the mentioned oxidized thiols groups, homocysteine accumulates in uremic patients and may contribute to atherosclerotic disease (8). Epidemiologic studies have correlated hyperhomocysteinemia with atherosclerotic disease not only in the general population but also in hemodialysis patients. It should be mentioned that elevated inflammatory markers such as C-reactive protein and cytokines are highly prevalent in patients with ESRD (8). In fact, a linkage among increased oxidative stress, inflammation, and endothelial dysfunction in hemodialysis patients was described recently. Furthermore this synergistic linkage could contribute to increased cardiovascular risk in uremic patients (9).

Oxidative stress occurs when ROS exceed antioxidant defense, which is replenished continually by ingestion of nutrients. Malnutrition is relatively common in uremic patients and may contribute to increased oxidative stress (10). In fact, malnourished uremic patients present increased markers of oxidative stress than well-nourished uremic patients (9,10).

Anemia and Cardiovascular Disease

Anemia is a common and disabling feature of CKD. There is increasing evidence from epidemiologic studies of an association between anemia and cardiovascular mortality. The Atherosclerosis Risk In Communities (ARIC) study revealed that individuals with anemia had a worse prognosis than those with normal hemoglobin levels and demonstrated that anemia was associated independently with an increased risk...
Iron treatment was associated with the elevation of malondialdehyde levels, an index of lipid peroxidation. Erythrocyte GSH/GSSG ratio decreased after iron treatment. This was due to a net decrease of GSH without changes in GSSG. Administration of α-darbepoetin returned malondialdehyde levels to values comparable to those observed before iron treatment and markedly increased GSH/GSSG ratio. This was due to an important elevation of GSH by treatment and markedly increased GSH/GSSG ratio. This was observed since values were not followed a normal distribution.

| Table 1. Effect of iv iron saccharate and α-darbepoetin treatments on erythrocyte redox status |
|---------------------------------|-----------|----------------|----------------|
|                                 | Baseline  | Intravenous Iron | α-Darbepoetin   |
| Erthrocyte Concentration        |           |                 |                |
| (μmol/g Hb)                     |           |                 |                |
| MDA                             | 1.8 ± 0.1 | 3.2 ± 0.6      | 2.2 ± 0.1      |
| GSSG                            | 0.9 ± 0.1 | 1.5 ± 0.2      | 1.1 ± 0.2      |
| GSH                             | 4.8 ± 0.8 | 3.3 ± 0.73     | 8.8 ± 1.8      |
| GSH/GSSG (25.5)                 | 4.9       | 2.07 (2.18)    | 9.96 (41.1)    |
| GPx                             | 28.8 ± 2.3| 41.6 ± 9.5     | 17.5 ± 4.5     |
| GRed                            | 2.6 ± 0.3 | 5.2 ± 1.1      | 3.6 ± 0.4      |

*Data are means ± SD or median (interquartile range) as appropriate. GSH, reduced glutathione; GPx, glutathione peroxidase; GRed, glutathione reductase; GSSG, oxidized glutathione; Hb, hemoglobin; MDA, malondialdehyde.*

*P < 0.05 baseline versus intravenous iron.

*P < 0.05 intravenous iron versus α-darbepoetin.

*Kruskal-Wallis test was performed because values were not followed a normal distribution.


17. Locatelli F, Canaud B, Eckardt KU, Stenvinkel P, Wanner C, Zoccali C: Oxidative stress in end-stage renal disease:

