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Review Article

Brief Description of Oxidative Stress in the Pathogenesis of Cardiovascular Diseases and their Prevention

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Abstract

This short review concerns the role of reactive oxygen species in cardiovascular diseases and the strategical ways of prevention. ROS have been implicated in the development of atherosclerosis and other CVDs due to their critical contribution to the oxidative stress, inflammation process, and impairment of blood vessels. Much attention is given to the enzyme NAD(P)H oxidase as an important source of ROS, especially in vascular cells. This enzyme also contributes to the formation of oxidative stress, especially in states such as hyperglycemia, a common condition in diabetes leading to vascular complications and heart disease. Oxidative stress may also be caused by hyperhomocysteinemia, which elevates stroke risk factors. The vitamins C, E, and β-carotene are suggested to be used as antioxidants against oxidative stress. These antioxidants strengthen the body's defense systems and reduce the risk of atherosclerosis. Another mineral playing an important role in heart health is magnesium; its poor levels may lead to many cardiovascular diseases. Magnesium regulates blood pressure and heart function. Magnesium status is highly related to heart health, which needs a diet of high consumption from leafy greens, nuts, and seeds. The review also includes, among others, the biomarkers of oxidative stress in CVD: isoprostanes, malondialdehyde, and oxidized low-density lipoprotein. These markers are employed in assessing oxidative damage and predicting the development of a disease. Their correct quantification is important to understand the influence of oxidative stress on cardiovascular health.

Keywords: *Oxidative Stress; Atherosclerosis; Magnesium; Antioxidants; Biomarkers*

Pathogenesis of cardiovascular diseases

Cardiovascular disease is a major public health problem. As the cause of high premature mortality, before age 65 [1], there are numerous arguments for the direct or indirect involvement of oxygen-reactive species in the cellular mechanisms of atherosclerosis [2].

Reactive oxygen species have been shown to be important molecules in cardiovascular function. Oxidative stress can cause cardiomyopathy, coronary artery disease [3,4] and cardiovascular disease by causing inflammation of heart muscle and blood vessels [3-6].

Vascular complications are often due to oxidative stress induced by the hyperglycemia characteristic of diabetic syndromes. These vascular injuries account for most of the morbidity and mortality observed in patients with diabetes [7]. Recent work has shown that NAD-(P)-H oxidases are major sources of superoxide in vascular cells and myocytes. The biochemical characterization, activation paradigms, structure and function of this enzyme are now partially understood [8]. It should be recalled that NADPH oxidase is a membrane enzyme complex belonging to the class of oxidoreductases. This enzyme catalyzes the oxidation reaction of NADPH with dioxygen (O_2), producing $NADP^+$, H^+ and O_2^-. The latter two will react to form hydrogen peroxide H_2O_2. H_2O_2 will react with H^+ (proton) and Cl^- (chloride) to give hypochlorous acid (HOCl) and one molecule of water (H_2O). This enzymatic complex therefore allows the synthesis of ROS [9].

In response to growth factors and cytokines, NAD-(P)-H oxidases produce superoxide, which is metabolized to hydrogen peroxide, and these two reactive oxygen species serve as second messengers to activate multiple intracellular signaling pathways. Vascular NAD-(P)-H oxidases have been shown to be essential in the physiological response of vascular cells, including growth, migration and modification of the extracellular matrix. They have also been linked to hypertension and to pathological conditions associated with uncontrolled growth and inflammation, such as atherosclerosis. NAD-(P)-H-oxidase has been associated with the formation of ROS in the vascular system when glucose levels are high. This leads to the depletion of intracellular NADPH which is a cofactor for nitric oxide synthase (NOS), an enzyme protein that synthesizes nitric oxide, a free radical found in the blood stream. NO-synthase refers to the enzymatic system which catalyzes the synthesis of NO from arginine and NADPH [8].

Oxidative stress may occur as a side effect, for example as a result of mild hyperhomocysteinemia. Hyperhomocysteinemia is the increase in homocysteine in plasma (the liquid part of blood), which causes an increase in risk factors for stroke affecting arteries and veins, thus causing dysfunction of cardiovascular system autonomy after oxidative stress of the liver [8].

Antioxidant treatments of decreased levels of NADPH and NOS, and ROS have been largely ineffective [8].

Prevention

The harmful effect of free radicals can be stopped by antioxidants

Among the powerful antioxidants, mention is made of the vitamins C, E and β-carotene. Once recovered in a rich and healthy diet, these drugs improve the anti-oxidative defense systems and the immune system, thus reducing the impact of ROS and their role in the generation of atherosclerosis. Fat-soluble vitamin E (alpha-tocopherol) is an antioxidant known to protect against lipoperoxidation (oxidation of unsaturated lipids). The antioxidant micronutrients (β-carotene, vitamin E, vitamin C, selenium, zinc, copper...) thus prevent cardiovascular diseases initiated by ROS. Adequate dietary intake of these nutrients would be essential for protection against cardiovascular disease [10-16].

Special case of magnesium - A mineral essential for heart health

Preventing heart disease begins with adequate intake of magnesium. Lack of magnesium can lead to deterioration of cellular metabolism and mitochondrial function which can lead to several health problems. Several studies have highlighted the importance of magnesium for heart health. It is also very important to have an adequate balance between magnesium and calcium. Lack of magnesium can cause muscle spasms and affect the heart. Magnesium is an electrolyte that is essential for the electrical signals essential for the heart to pump blood and for the functioning of the brain [17].

Magnesium deficiencies or an imbalance in the magnesium/calcium ratio have been observed in hypertension (high blood pressure), cardiac arrhythmia, cardiovascular disease (CVD) and cardiac death [18].

Magnesium is essential for the control of blood pressure, which is a risk factor for heart disease and stroke. Increased magnesium intake has been associated with decreased blood pressure in people with magnesium deficiency [18].

Magnesium has been shown to relax and dilate blood vessels, which helps to reduce blood pressure [18].

Magnesium nutrition and heart health

Magnesium levels can be optimized by eating a diet high in magnesium, eating whole and organic foods, and consuming large amounts of leafy greens. As regards green leafy vegetables, the following are among the most magnesium-rich: spinach, beet, turnips, beet, cabbage, broccoli, romaine lettuce. The nutritional quality of vegetables also depends on the richness of the soil in magnesium [19].

The following foods are also particularly rich in magnesium: Fruits, including red fruits, herbs and spices, include coriander, chives, cumin seeds, parsley, mustard seeds, fennel, basil and cloves, cocoa beans, avocados, seeds and nuts, squash and finally fatty fish [19].

Magnesium/calcium ratio and vascular problems

Magnesium levels are inversely associated with calcification of the arteries. Coronary artery calcification (CAD) has often been linked to low blood levels of magnesium. An increase of 0.17 milligrams per deciliter (mg/dl) of serum magnesium was associated with a 16% reduction in CAC [18].

Symptoms of magnesium deficiency

A diet high in processed foods and low in leafy greens is a major risk factor for magnesium deficiency [20].

Also, lack of sleep, use of alcohol and certain drugs such as diuretics and certain antibiotics that contain fluorine, intensive sport sessions, and high levels of insulin decrease magnesium in the blood. Chronic magnesium deficiency can cause much more severe symptoms, such as abnormal heart rhythms and coronary spasms, seizures, numbness and tingling, and changes in personality and behavior [20-24].

The optimal recommended daily intake of magnesium should vary from 600 to 900 mg per day depending on age and gender [25].

Bio-markers of oxidative stress and cardiovascular diseases

Identifying markers of oxidative stress in cardiovascular disease has been the focus of much research. Their study is of prime importance given their action, which leads to a multitude of processes that promote cardiovascular pathobiology. One of the main challenges is the precise quantification of reactive oxygen species with a very short half-life. Oxidative stress-sensitive proteins with important cellular functions are limited to signaling microdomains in cardiovascular cells and are not readily available for quantification. A common approach to measuring oxidative stress is to measure stable by-products modified by this oxidative stress entering the bloodstream. However, these cannot accurately reflect redox stress at the cell/tissue level. Several of these modifications are “functionally silent”.

Below we list some biomarkers of oxidative stress in cardiovascular diseases:

- Isoprostanes: Can be detected in various samples (serum, urine) and have been shown to be elevated in the presence of a range of cardiovascular disease risk factors [26-29].
- Malondialdehyde: Technically easy to quantify by spectrophotometry. Studies show that MDA can predict progression of coronary artery disease, carotid artery disease, and atherosclerosis by age 3 years [30-33].
- Nitrotyrosine produces nitration of tyrosine, is identified as an indicator or marker of cellular damage, inflammation and NO (nitric oxide) production. Nitrotyrosine is formed in the presence of nitric oxide which is a free radical [34,35].

- S-glutathionylation: Sarco/endoplasmic Ca^{2+}-ATPase reticulum (SERCA), endothelial nitric oxide synthase (eNOS) and Na^{+}-K^{+} pump, demonstrated as biomarkers with a role in cardiovascular pathogenesis [36,37].
- Myeloperoxidase is an oxidoreductase that has been correlated with cardiovascular disease [38].
- Oxidized low density lipoprotein (LDL); (OxLDL) is elevated in patients with cardiovascular disease, and its increase correlates with an increase in clinical severity. OxLDL is also predictive of cardiovascular disease in a healthy population [39,40].
- ROS-induced gene expression [41,42].
- The antioxidant capacity of the serum via the assay of glutathione peroxidase I (GPX-I), an antioxidant enzyme, was found to be inversely proportional to coronary artery disease [43].

Conclusion

Excessive oxidative stress, caused by reactive oxygen species (ROS) such as superoxide and hydrogen peroxide, has an influence on cardiovascular diseases (CVD). Atherosclerosis, coronary artery disease, and cardiomyopathy are all caused by these ROS. NADPH oxidase is the key enzyme in ROS production and is considered a significant contributor to diabetes.

In diabetes, a high glucose level adds to oxidative stress and further damages the ability to produce nitric oxide needed for the vasculature. Vascular health depends on adequate production of nitric oxide which is affected in Diabetes. Individually, vitamins, such as C and E, and even selenium, magnesium, and other antioxidants actively participate in alleviating oxidative damage. Magnesium is crucial in the regulation of blood pressure and the health of the heart. Heart diseases are often associated with magnesium deficiency. Lack of magnesium in the body can cause hypertension and even result in arrhythmias.

The progression of CVD can be monitored with the use of certain biomarkers, which also help identify oxidative stress, including isoprostanes, malondialdehyde, and oxidized LDL. In CVD, diet, along with magnesium supplements, plays an important role in preventing oxidative stress – vital for reducing the risk and impact of cardiovascular diseases.

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Conflict of Interest

The author(s) declare that there are no conflicts of interest regarding the publication of this paper.

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