

## THE ROLE OF TRACE ELEMENT SELENIUM IN CARDIOVASCULAR DISEASE DEVELOPMENT (REVIEW)

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<https://doi.org/10.35339/ic.6.2.77-81>

### **Abstract**

Balanced levels of trace element selenium are of high importance for many of the body's regulatory and metabolic functions. Reduction in selenium supply in humans can lead to an increased risk of various pathologies, including cardiovascular diseases. This article considers the contemporary opinions on the role of selenium in physiology and pathophysiology of the cardiovascular system. A particular attention is paid to the effects of selenium deficiency on the development of acute coronary syndrome, including myocardial damage after ischemia/reperfusion and postinfarction remodeling of the left ventricle. Also, the intrinsic properties of selenium for inhibition of apoptosis are highlighted.

**Keywords:** *selenium, selenoproteins, cardiovascular disease.*

The data of the latest research suggest that disturbance in the metabolic balance of several trace elements can contribute to development and prognosis of cardiovascular disease (CVD) [23]. These minerals include selenium, a microelement, which possesses significant biological activity and a narrow profile of safety, and is important for human health. Selenium was first discovered by a Swedish scientist Berzelius in 1818. The biological function of selenium is determined by its position in the periodic system and is closely related to the chemical properties of this element and its compounds [1].

In humans, as well as in animal experiments, spontaneous or experimental reduction in selenium supply can lead to an increased risk of various pathologies, including CVD. Selenium deficiency, which is usually a result of alimentary shortage, demonstrates a particularly negative influence in geochemical provinces with low selenium content in the soil. The most reliable

sources of selenium in the human diet are the following: seafood, animal liver, meat, cereals, and vegetables – garlic, onion, cabbage (especially broccoli) [2]. According to the recommendations of the Food and Drug Administration (FDA) of the United States, the daily need for selenium is 50–200 mg. At the same time, a prolonged excessive (over 400 mg/day) consumption of selenium performs a toxic effect on human body.

Selenium mediates its effects mainly due to inclusion to various selenoproteins. More than 25 selenium proteins are known at present. These include the group of glutathione peroxidase enzymes (GPO), iodothyronine deiodinase (ITD), thioredoxine reductase (TRR), selenoproteins (SP), K, R, S, O, W and others. A wide range of biological functions is characteristic for the majority of selenium-dependent enzymes, such as the regulation of the inflammatory response, the proliferation and differentiation of some immune cells, maintenance of thyroid hormones balance, spermatogenesis, etc. [17]. Selenium is an important factor for biological protection of vascular endothelial cells, DNA, and chromosomes. It is an extremely important nutrient for the prevention of coronary heart disease (CHD). Selenium inhibits atherosclerosis development and suppresses malignant tumors

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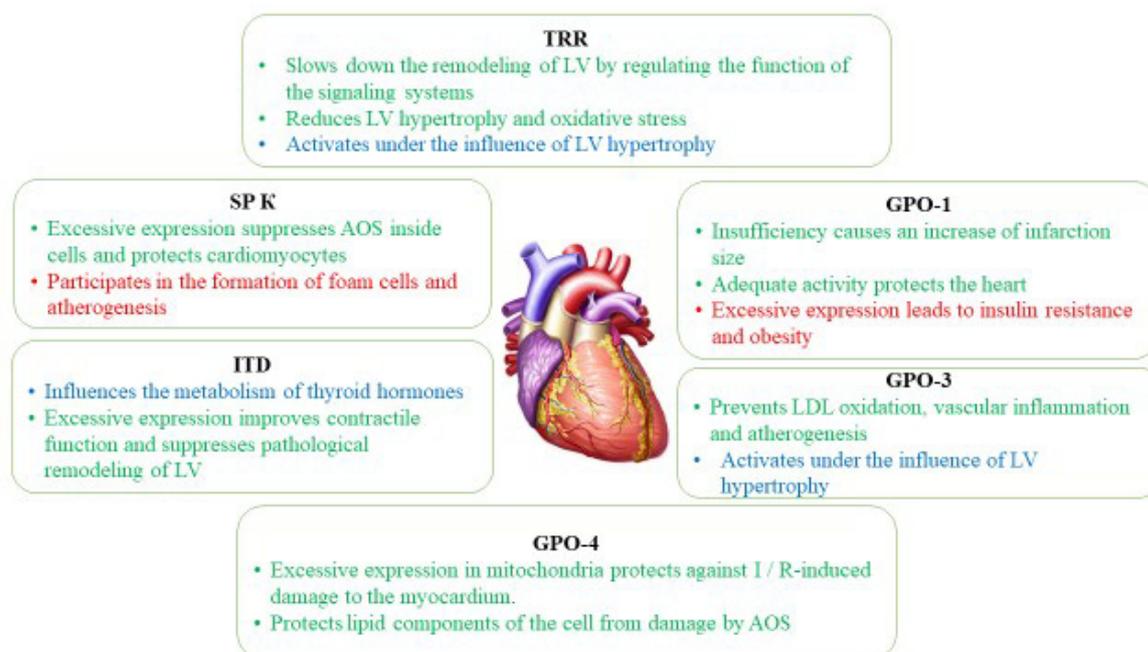
formation [5]. Selenium is considered to be the cornerstone of the body's antioxidant defense. Selenium acts only as an antioxidant and almost never behaves as a prooxidant, unlike other metals with variable valence [2]. In addition, previous studies have shown that selenium compounds can affect, and thus control the function of leukocytes: migration, adhesion and phagocytosis [4]. The main aspects of selenoproteins influence on the function of the cardiovascular system (CVS) are shown in *figure*.

The influence of selenium on development and prognosis of cardiovascular diseases is performed in several ways, the main path is the activation of the antioxidant system. The current research data suggest that excessive formation of reactive oxygen species (ROS) plays an important role in the pathogenesis of CVD, such as coronary heart disease and heart failure. When excessive ROS formation exceeds the potential of endogenous antioxidant defense system, an oxidative stress develops, causing adverse effects on the myocardium, including the decrease of contractility and ultrastructural changes [18]. Trace elements such as selenium mainly prevent ROS-induced damage to cells by increasing the activity of antioxidant enzymes.

The most studied group among selenoproteins is GPO, which provides neutralization of active forms of oxygen and nitrogen, thereby limiting myocardial damage after ischemia/reperfusion (I/

R). Lubos E. et al. have proved that the low level of GPO1 in erythrocytes significantly increases the risk of cardiovascular events, such as myocardial infarction and stroke [12]. TRR also plays an important role. It exerts the regulatory influence on the cardiovascular system, due to the oxidation of intracellular and extracellular signaling molecules [14] and the impact on adaptive mechanisms, such as left ventricular remodeling [3]. According to G. Flores-Mateo, selenium levels in the blood reversely correlate with the risk of CHD development [7]. At the same time, the AtheroGene study revealed no effect of low selenium concentrations on the development and progression of stable angina, but it has shown that selenium deficiency is associated with an increased risk of cardiovascular death in patients with acute coronary syndrome [13].

The exact role of other selenoproteins in support of the cardiovascular system function as well as in the possible development of CVD is only partially understood. It is believed that most selenoproteins act as antioxidants that regulate various signaling processes by influencing the oxidation-reduction homeostasis and intake of calcium ions  $Ca^{2+}$  into the cell [17]. In particular, it has been proved that selenoprotein K is involved in the mechanisms of antioxidant defense of cardiomyocytes [11]. In this regard, K. Venardos et al. demonstrated in experiments in rats that the



The role of selenoproteins the CVS functioning: GPO – glutathione peroxidase, TRR – thioredoxine reductase, ITD – iodothyronine deiodinase, SP – selenoproteins, LV – left ventricle, LDL – low density lipoprotein, AOS – active oxygen species, I / R – ischemia / reperfusion.

deficiency of selenium leads to an increase of myocardial damage by increasing the peroxidation of proteins and lipids after I/R [21]. These data have been further confirmed by Tanguy and co-authors, who have shown that selenium deficiency in rats leads to more significant myocardial damage and delayed heart function recovery after I/R [20]. The same research groups demonstrated a significant positive effects from supplemental selenium provision (using selenium-containing drugs or high-selenium diet), which were the following: decrease of myocardial damage as a result of I/R, better restoration of the contractile function, reduction of the infarction size and the decrease of frequency of post-ischemic ventricular arrhythmias. The main causes for these results remain only partly understandable and cannot be explained solely by the antioxidant properties of selenium and its compounds. Therefore, there is a need for additional research to further study the effects of selenium on the functioning of the cardiovascular system.

In addition to antioxidant action, selenium has intrinsic properties for apoptosis inhibition. Experimental studies conducted on different types of cells report very heterogeneous results. However, the data of S. Mukherjee and co-authors is worth paying attention. They have shown that a high-selenium diet has a cardioprotective effect and reduces the damaging effect of ischemia and reperfusion by generating an anti-apoptotic signal through the activation of several survival proteins, such as Akt and Bcl-2 [16]. Another argument in favor of the anti-apoptotic effect of selenium was provided by studies in animals that were accompanied by artificial suppression of selenoproteins synthesis. Research by P. Crack et al. [6] on GPO-1-knockout mice showed that GPO-1 plays an important regulatory role in protecting nerve cells from apoptosis induced by I/R. In addition, it has been shown that ischemic stress in astrocytes activates the gene expression of selenoprotein S, and inhibition of the expression of this gene by small interfering RNAs significantly increases astrocytes apoptosis in ischemia [8]. These results indicate that the optimal expression of selenoproteins is a key factor for survival signaling under oxidative stress conditions.

Cardioprotective properties of selenium are also associated with its ability to suppress the cascade of nuclear factor-kappa B transformations (NF- $\kappa$ B). Increased activation of transcription factor NF- $\kappa$ B is usually associated with survival signals in cardiomyocytes, as well as in other cell

types. However, a prolonged and excessive formation of ROS can lead to activation of proinflammatory and proapoptotic pathways through disbalance between tyrosine kinase and tyrosine phosphatase, which regulate the translocation of NF- $\kappa$ B [10]. Therefore, overstimulation of NF- $\kappa$ B in myocardium during ischemic episodes leads to the increased production of cytokines and tumor necrosis factor – alpha (TNF- $\alpha$ ). Selenium reduces nuclear translocation of NF- $\kappa$ B during myocardial infarction in rats, it also decreases the size of myocardial injury and inhibits post-ischemic TNF- $\alpha$  production. Selenoprotein S can directly interact with the inflammatory process, and thus limit the formation of cytokines [15].

An important function of selenium is the ability to reduce dephosphorylation of connexin-43 (Cx-43). Excessive ROS formation and following tyrosine kinase activation can lead to dephosphorylation of Cx-43 (this protein is responsible for intercellular communication and an electrical bond between cardiomyocytes), which is a determining factor in progression of cell death and thus affects the size of myocardial infarction and left ventricle post-infarction remodeling. Adequate supply of selenium to the body suppresses Cx-43 dephosphorylation, reduces the incidence of post-reperfusion arrhythmias, limits the size of infarction and inhibits cardiac remodeling [19].

Apart from the numerous positive effects of sufficient selenium supply, it makes sense to consider the aspects of its toxic effects, which occur at long-term excessive intake of this trace element. Chronic selenium overdose can lead to negative consequences for the body as a whole and for CVS in particular. The long-term overdose of selenium increases the risk of type 2 diabetes and dyslipidemia [9]. Excessive expression of GPO-1, as well as other selenoproteins, which possess antioxidant action, causes development of insulin resistance and obesity due to distortion of the course of oxidation-reduction reactions and changes in the functioning of the intracellular and extracellular signaling systems [22]. The excessive concentrations of selenium have the ability to accumulate in the form of selenomethionine in various tissues and organs, including the heart. Replacement of methionine with selenomethionine changes stability of proteins, in particular, it affects calmodulin, which may alter calcium metabolism in cardiomyocytes and cause negative consequences for the processes of contraction and relaxation of the myocardium [24].

## Conclusions

Thus, recent studies have created a significant evidence base on the important role of selenium and its compounds in the cardiovascular system functioning. Although the data on the role of selenium in CVD prevention remain controversial, it is important to establish the impact of selenium deficiency on the course and prediction of an acute coronary syndrome, in which the patient is exposed to ischemia/reperfusion and the rapid activation of oxidative stress. Therefore, the

relationship between selenium ingestion, selenium content in the body and the state of the cardiovascular system requires additional experimental evidence in order to provide a new understanding of the role of selenium in the biology of human heart. Further studies should be performed to find out the main mechanisms that associate selenium provision to the body with the end points of the CVD, and also to determine the influence of selenium on cardiovascular risk factors.

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*Received: 02-Apr-2019*  
*Accepted: 10-June-2019*