IMPORTANCE OF SELENOPROTEINS FOR THE FUNCTIONAL STATE OF MUSCULOSKELETAL SYSTEM

Ruseva Boryana, Ivelina Himcheva
Medical University-Pleven, Faculty of Medicine, Department of Physiology
5800 Pleven, 1 "Kliment Ohridski" str., Bulgaria
e-mail: ruseva.bk@mail.bg

ABSTRACT

The trace element selenium (Se) influences development of musculoskeletal system modifying expression of selenoproteins: glutathione peroxidases (GPx), thioredoxin reductases (TrxR) and iodothyronine deiodinases (D). These enzymes participate in cellular processes acting as antioxidants, and modulating redox status and metabolism of thyroid hormones. In human osteoblasts are expressed GPx, TrxR, D and selenoprotein P. Fibroblasts and skeletal muscle cells have expression of selenoprotein N except these three families' selenoenzymes. The influence of selenoproteins expression on the antioxidative status, effect of thyroid hormones, parathyroid hormone, vitamin D and growth factors plays important role for development and functioning of bones and muscles.

This study presents participation of selenoproteins in normal and pathological remodeling of musculoskeletal system.

Keywords: *selenoproteins, remodeling, bones, muscles*

Introduction

Selenium (Se) is essential trace element for all known forms of life. It is component of unique amino acid selenocystein. The first understanding for physiological importance of Se for nutrition was discovered in 1973, when it was described that Se has been essential component of some mammalian enzymes, such as glutathione peroxidases. The importance of selenium for human health was discovered in 1979, when Chinese scientists proved a statement true that the children lived at areas of selenium deficiency suffered from cardiomyopathy, known as Keshan disease, and symptoms of this disease were reversible after Se supplementation. Extension of research work on the role of selenium for human organism leads to origination of advisable daily requirements of Se intake by Word Health Organization in 1989 (21, 29).

More than 25 selenoproteins (Sel) are described in humans, the most of them have enzyme activity. They are divided into three families: glutathione peroxidases (GPx), thioredoxin reductases (TrxR), and iodothyronin deiodinases (D). All selenoproteins contain one or more selenocystein residues in primary structure. All selenoproteins, except one have enzyme activity, because selenocystein residues are situated at catalytic site, where they participate in redox reactions. Sequence of amino-acids, different expression in the tissues, and the other molecular properties of different family members vary in high degree. Under physiological conditions these enzymes perform metabolic and physiologic functions as: antioxidant defense, fertility, development and functioning of muscles, metabolism of thyroid hormones, and immunity. Selenium is important and for processes of cellular growth and modulation of action of transcriptional factors and cell-signaling systems. Several selenoproteins more of them with not well cleared up function and distribution were identified: SelP, SelS, Sel15, SelN, SelX, SelW, SelT, SelH, SelI, SelK, SelM, SelO and SelV (21).

The main biological form of selenium is selenocystein (Sec), analog of cystein that is synthesized from a serine, bound to tRNA. selenocystein is identical with cystein, except the fact that instead of sulfur, it contains selenium atom that is ionized under physiological pH. Replacements of selenocystein by cystein into selenoproteins results of dramatically decrease of enzyme activity. This shows that Se atom is crucial for proper protein function (11, 21).

Se-containing enzymes

Glutathione peroxidases (GPx) in humans are the family of close related antioxidant enzymes, coded by genes from GPX1 to GPX6. Cytosolic GPx1 is the most powerful antioxidant enzyme of this family. It is expressed by all cells of the organism and catalyzes reduction of hydrogen peroxide (H_2O_2) and the other organic peroxides.

Three thyoredoxin reductases (TrxR) are established. They catalyze NADPH-dependent reduction of oxidized thyoredoxin that participates in different redox systems (ribonucleotide reductase - essential for DNA synthesis, control of transcriptional factors, and processes of cell growth).

There are tree isoforms of iodothironin deiodinases:

Type 1 deiodinase (D1) is cytosolic and membrane enzyme that is expressed in thyroid gland, lien, kidney and hypophisis. It transforms thyroid pro-hormone thyroxin (T_4) into active hormone tri-iodothyronin (T_3), catalyzing elimination of iodine from T_4.

Type 2 deiodinase (D2) is an enzyme situated in endoplasmic reticulum and cellular membrane that is expressed in thyroid gland, brain, heart, gats and skeletal muscles. Its function is the same as the function of D1.

Type 3 deiodinase (D3) is present in cytosol and cellular membranes of the cells of the brain, placenta and skeletal muscles. It transforms T_3 into inactive rT_3, catalyzing elimination of iodine from T_3.

Selenium enters organism mainly by food. It was established that a diet containing 0.1 μg Se/g of food was enough for normal growth and reproduction for all mammalian organisms. Recommended daily allowance Se intake for adult men and women equals 55 μg/day (29).

Regulation of selenoprotein synthesis depends on daily selenium intake that influences stability of mRNA. Under low Se content diet, GPx1 levels dramatically decrease. It is explained as the result of concomitant loss of proteins that correlates with loss of mRNA. Selenium supplementation increases selenoprotein synthesis because of increased levels of Sec-tRNA, leading to more efficient selenocystein incorporation (11).

Normal bone development and linear growth depends on the coordinated contributions of various genetic, environmental, endocrine and nutritional factors and continues until closure of the epiphyseal growth plate following puberty.

Selenoproteins in remodeling of musculoskeletal system

The aim of this study is to present participation of selenoproteins in process of remodeling of musculoskeletal system influenced by the different selenium intake.

Bones are built up and remodeled by the action of osteoblasts (OB) and osteoclasts (OC). Bone formation begins from mesenhymal cells when they form cluster of cells. These cells either differentiate into bone forming OB in flat bones or into chondrocytes that lay down a cartilage mould in long bones. The OB are derived from bone-marrow stromal cells that enter the primary spongiosum via capillaries. OC develop from myeloid precursors and are terminally differentiated cells of the monocyte/phagocyte lineage.

Selenoproteins are involved in mechanisms of cell differentiation and defense. They protect cells from reactive oxygen and nitrogen species (ROS; RNS) and oxidative damage. It is established that in human osteoblasts GPx, TRxR, D and SelP are expressed (5, 10, 15, 23, 28, 30). An increase in oxidative stress achieved experimentally either by elevating intracellular ROS or adding H_2O_2 at micromolar concentrations, has been shown to inhibit growth in wide variety of mammalian cells.

ROS are produced under the action of NADPH oxidases when cell surface receptors are bound with growth factors and various cytokines, because of increased metabolism. These species (especially hydrogen peroxide and superoxide) have been shown to be important signaling molecule at submicromolar levels and they induce growth, but higher concentrations induce apoptosis or necrosis. The maintenance of intracellular homeostasis is dependent on a complex of antioxidant enzymes like selenoproteins GPx and TRxR. The results from *in vitro* studies shown that the activity of GPx and TRxR -1 and TRxR -2 is dependent on Se supply. Selenium supplementation

increased activity of these enzymes and Se deprivation decreased it. TRxR-1 was identified as a 1,25-$(OH)_2$ vitamin D- responsive early gene in fetal human OB, and its activity could only be stimulated by vitamin D, the hormone that stimulates bone cell growth and differentiation, after Se supplementation. TRxR in OB participated also and in regulation of transcription factor for nuclear signaling of steroid hormone receptors (9, 15). Selenoprotein P is positively associated with bone turnover in humans, because it is a main Se transporter for bones (23).

Normal bone remodeling is dependent on the controlled function of ROS. The process of bone resorption produces large amounts of ROS, which may damage cells and extracellular matrix constituents. The cells of the monocyte/macrophage/osteoclast pathway of differentiation express high level of antioxidant enzymes. Using the animal models it has been established that Se deficient male rats developed osteopenia, impaired bone metabolism and growth retardation (22, 27). When selenoprotein expression was decreased due to low Se intake, ROS levels and phosphorylation status remained elevated and contributed to pathological exacerbated signaling and enhanced OC activity. Adequate Se intake is necessary to support the antioxidative system of OB for relevant defense of ROS produced by OC during bone remodeling. OC are known to be activated by inflammatory cytokines released at low levels by OB (12).

There are evidences that Se deficiency causes osteopenia and it is a risk factor for development of osteoporosis (1, 12, 25). Kashin Beck disease is a form of osteoarthritis occurring in regions of Central Africa and China that are known for their low Se supply. The clinical course of this form can be ameliorated by Se supplementation (21).

Thyroid hormone is essential for normal development of endochondral and intramembranous bone and plays an important role in linear growth and maintenance of bone mass.

Selenium is regulator of T_3 production trough modulation of deiodinases expression that controls individual exposition of the different tissues to T_3 changing the rate of their expression. Most circulating T_3 is derived from outer ring deiodination of T_4 mediated by the D1 enzyme. D2 isoenzyme regulates intra-cellular T_3 supply and determines saturation of the nuclear T_3-receptor (TR), whereas D3 inactivates T_3 and T_4 to prevent hormone availability and reduce TR-saturation. D1 activity was indetectable in chondrocytes, OB and OC. D2 activity was present in mature OB and it is essential for normal osteoblast function. Using animal models it was established that normal mineralization and bone strength requires normal D2 expression in OB. D3 activity was evident throughout chondrocyte, OB and OC differentiation in primary cell cultures (5, 28). The investigation of influence of thyroid hormones on bone turnover in humans with hyper- and hypothyroidism showed that the bone loss was caused by impaired osteoblast function and increased bone resorption rate (6, 16).

Trace elements can act on the ageing process modulating oxidative damage and DNA repair capacity and increasing the risk for age related diseases, because of long term inadequate intake. Selenium may be a key element for bone ageing processes, because of many selenoproteins expressed in bones (14, 17, 20).

Skeletal muscle cells have expression of several selenoproteins: GPx1, D1, D2 and SelW and SelN. They have performed development of skeletal muscles and their protection against oxidative stress (2, 3, 18,). It has been established that for normal function of skeletal muscles two main selenoproteins Sel W and Sel N are very important. The molecular action of SelW is not poorly understood, but the researchers suggest that SelN participates in regulation of oxidative stress and calcium homeostasis (3, 8, 19, 21). Satellite loss and impaired muscle regeneration was described in SelN deficiency (7). Experimental study showed that Se and viamin E deficiency caused fatal myopathy in guinea pig (13). Selenoprotein N deficiency causes several inherited neuromuscular disorders named SEPN1-related myopathies, characterized by early onset, generalized muscle atrophy and muscle weakness of axial muscles, leading to spine rigidity, severe scoliosis and respiratory insufficiency (2,3,8).

It is known that biological role of selenium includes prevention from cancer, cardiovascular diseases, and viral mutations. Se is responsible for optimal endocrine function and modulation of inflammatory response. It has participated in antioxidative defense, normal growth and fertilization. Under insufficient selenium intake redistributing changes occur, because of mobilization of se from GPx stores of the liver, muscles, skin, and the other tissues and guidance of selenium to the brain, endocrine glands and reproductive organs. It is important to optimize and monitor daily Se intake to prevent pathological changes caused by decreased selenoprotein expression (4, 26).

The link between low antioxidative capacity and enhanced ageing of bone with consecutive fragility remains to be shown by animal models and clinical cohort studies. The fact that big population on over Europe has a low Se intake should be a signal for professionals to promote Se supplementation preventing development of atherosclerosis, cancer incidence and probably osteoporosis.

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