

Therapeutic Potential of Selenium Nanoparticles

Warda Majeed, Maryam Zafar, Attya Bhatti* and Peter John

National University of Sciences and Technology (NUST), Sector H-12, Islamabad, Pakistan

Abstract

Selenium plays essential role in regulating function of many selenoproteins in body. It is an important micronutrient and its supplementation provides tremendous health benefits. It has been found that humans have 25 selenoproteins that play important roles in the body. Therefore, deficiency of selenium can lead to many chronic diseases such as rheumatoid arthritis. Selenium is also important in reducing inflammation, decreasing oxidative stress and in improving bone health. Selenium improves functioning of immune system, maintains oxidative balance in body and decreases bone resorption. Toxicity issues related to selenium have moved the direction of research towards nano particles (NPs) of selenium as in nano form selenium is less toxic and safer for living systems. In nano form the entire properties of selenium are changed as compared to its bulk form. In this review, we have described the various health-care applications of SeNPs (selenium nanoparticles). It is also discussed that how nanoselenium can act as a promising agent in treating chronic health disorders.

Keywords: Nanotechnology; Selenoproteins; Antioxidant activity; Bone health; Toxicity

Introduction

Selenium is an important trace element, it was previously considered toxic but a decade ago researchers proved its importance to the human health [1]. The function of selenium in body is achieved by its incorporation into selenoproteins as selenocysteine, 21th amino acid at active site of selenoproteins [2]. The UGA codon in mRNA allows the incorporation of selenocysteine into selenoproteins under specific conditions along with other factors. Importance of selenoproteins to human health has been identified by single nucleotide polymorphisms (SNPs) in genes encoding these proteins [3]. In mammals, at least 30 selenoproteins have been identified and it has been found that humans have 25 selenoproteins that play important roles in the body [2]. Therefore, deficiency of Se leads to severe health disorders like Rheumatoid Arthritis (RA). A number of studies have been conducted to determine the status of selenium in patients of rheumatoid arthritis and it was found that concentration of Se (selenium) was low in serum and synovial fluid of RA patients [4,5]. Rheumatoid arthritis is a chronic, progressive, inflammatory autoimmune disease that is described by synovial joint pain, swelling and tenderness which ultimately leads to disability and short life span [6]. RA affects 0.5 to 1% of the population globally. Genetic and environmental factors both contribute to progression of RA [7]. The well-known genetic risk factor for RA is HLA locus that accounts for 30-50 percent of the overall genetic susceptibility to RA [8]. Some clinical trials showed anti-arthritis potential of selenium while others do not. An open trial with 160 ug of selenite as supplement in ten RA patients had positive effect but a double blind study on active RA patients with 256 ug of yeast selenium produced no anti-inflammatory effects [9]. The common forms of selenium in foods are selenomethionine, selenocysteine, selenoneine (2-selenyl-Na,Na,Na-trimethyl-L-histidine), Se-methylselenocysteine and γ -glutamyl-Se methylselenocysteine, Sodium selenite and selenite [10]. In USA the dietary selenium intake ranges from 7 μ g per day to 4990 μ g per day, with mean values of 40 μ g per day in Europe and 93 μ g per day (in women) to 134 μ g per day (in men) [11]. In plasma and serum the selenium level varies from country to country that is much lower in Europe than Canada, Venezuela, Japan, and USA. In New Zealand intake of Se has been improved after the use Australian wheat rich in selenium [12] because selenium has many health benefits due to its anti-oxidative and anti-inflammatory properties. It also prevents

bone resorption in disorders like osteoporosis. Recently, SeNPs are gaining more attention due to their low toxicity and excellent biological activities [13]. In this review we have discussed that how selenium therapy can prove to be effective for treatment of many diseases.

Significance of Selenium to Human Health

Selenium supplementation has positive impact on Human health. Many studies have shown importance of selenium in normal immune functions. Supplementation of selenium (400 g/day) to elderly volunteers in Arizona increased T cell count. Increase in CD4+ T cells subset was observed along with increased cytotoxicity of natural killer cells (NKCs) [14]. Supplementation of selenium in form of sodium selenite to head and neck cancer patients during radiation and surgery led to improved cell mediated immune responses [15]. Selenoproteins are important for normal function of activated T cells because T cells are sensitive to ROS and due to deficiency of selenoproteins involved in decreasing ROS they cannot proliferate in response to T cell receptor stimulation [16]. Selenium is also important for normal functioning of brain. Its depletion cause irreversible brain injury. Selenium is delivered to brain by selenoprotein P by binding to apoER2 a member of the lipoprotein-receptor family. Selenoprotein P improve neuronal survival and prevent cell death caused by beta-amyloid accumulation [17]. A study suggests that nanoparticles of selenium in size range of 5-15 nm depleted amyloid β (A β) plaque accumulation in brain by decreasing ROS production and appeared as a potential therapeutic agent for the treatment of Alzheimer's disease (AD) [18]. In addition, selenium is crucial in fertility, reproduction, normal thyroid hormone production and in prevention of cancer and type 2 diabetes [9]. SeNPs delivered in liposomes showed antidiabetic potential by preserving

*Corresponding author: Attya Bhatti, National University of Sciences and Technology (NUST), Sector H-12, Islamabad, Pakistan, Tel: 03352569369; E-mail: attyabhatti@asab.nust.edu.pk

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the integrity of pancreatic β cells with increase in insulin secretion, decrease of oxidative stress inhibition of inflammation in pancreas [19]. One human study also showed the significant antiviral effects of selenium supplementation (Figure 1) [20].

Role of Se in Reducing Oxidative Stress

The imbalance between the generation and detoxification or neutralization of the free radicals produced as a result of aerobic metabolism by the body is referred as oxidative stress [21]. In living systems the most important class of free radicals are ROS and RNS. The free radicals derived from oxygen are superoxide radical, peroxyl radical, perhydroxyl radical, hydroxyl radical and non-free radical species such as hydrogen peroxide and singlet oxygen, while the reactive nitrogen species include nitric oxide, nitrogen dioxide and peroxyxynitrite [22]. These reactive species are highly unstable because they contain one or more unpaired electrons in their outermost shell and remove electrons from other compounds to attain stability leading to chain reaction cascade generating more reactive species [23]. It has been found that in physiological system high level of ROS exert oxidative stress that leads to many diseases by damaging lipids, proteins and DNA [24]. To protect against the oxidative stress, living systems have a set of antioxidant enzymes such as glutathione peroxidase (GPx), thioredoxin reductase (TrxR) and iodothyronine deiodinases (IDD) and selenium is main component of these antioxidant enzymes [25]. Therefore its deficiency can lead to many chronic diseases.

Role of Se in Reducing Inflammation

Many studies have shown that selenium can reduce inflammatory response in body caused due to auto-immune disorders or inflammatory diseases. Inflammation is the normal response of the living body to any injury leading to the accumulation of body fluids and white blood cells along with release of prostaglandins and many inflammatory mediators [26]. NFkB pathway is involved in activation of inflammatory responses by enhancing the expression of many pro-inflammatory cytokines such as IL-6 and TNF alpha. A recent study revealed significant decrease in expression of these pro-inflammatory cytokines when selenium as supplement was given because Se incorporates into selenoproteins and significantly increase their

antioxidant function leading to decrease in inflammatory responses in autoimmune and inflammatory diseases [27]. The major problem regarding use of selenium is its bioavailability and toxicity. Therefore researchers have moved towards use of selenium as the nanoparticles. NPs have entirely different properties than bulk form of that same compound [28]. A recent study on inflammation induced irradiated rats showed that in addition to antioxidant activity nano selenium also decreases the expression of genes of pro inflammatory mediators like TNF- α , PGE2 and TBAR [29]. Thus SeNPs are also effective in reducing inflammation.

Effect of Se on Bone Health

Studies related to selenium status in humans showed that Se concentration in plasma has an inverse relation with bone turnover rate [30]. In a case control study it was revealed that consumption of selenium, β -carotene and vitamin E had an inverse association with risk of hip fracture in elder smokers [31]. In patients of osteoporosis the activity of the enzyme Glutathione peroxidase (GPx) was found lower [32] which is the most abundant selenoprotein in mammals and protects cells from damage caused by oxidative stress. It reduces H_2O_2 into H_2O using glutathione otherwise the increased level of H_2O_2 can damage cellular components [33]. Some previous studies showed that Na_2SeO_3 inhibited differentiation of osteoclasts by decreasing ROS production and also induced apoptosis in these cells by mitochondrial pathway [34] as high level of ROS stimulates osteoclast differentiation and maturation [35]. Increased activity of osteoclasts makes bone weaker by decreasing bone mass and lowering bone mineral density and can also lead to osteoporosis [32]. In another study it was revealed that in second generation selenium deficient male rats growth was retarded and also caused osteopenia and disturbed bone metabolism [36]. In a performed study pre-treatment with selenite prevented the adverse effect of H_2O_2 on induced inhibition of osteoblastic differentiation of MSCs. Moreover, it also suppressed the activation of ERK (extracellular signal-regulated kinase). Selenite pre-treatment also increased the gene expression and activity of GPx and reduced glutathione and lipid peroxidation in treated bone marrow stromal cells. This shows inverse relation of selenium status with risk of osteoporosis [37].

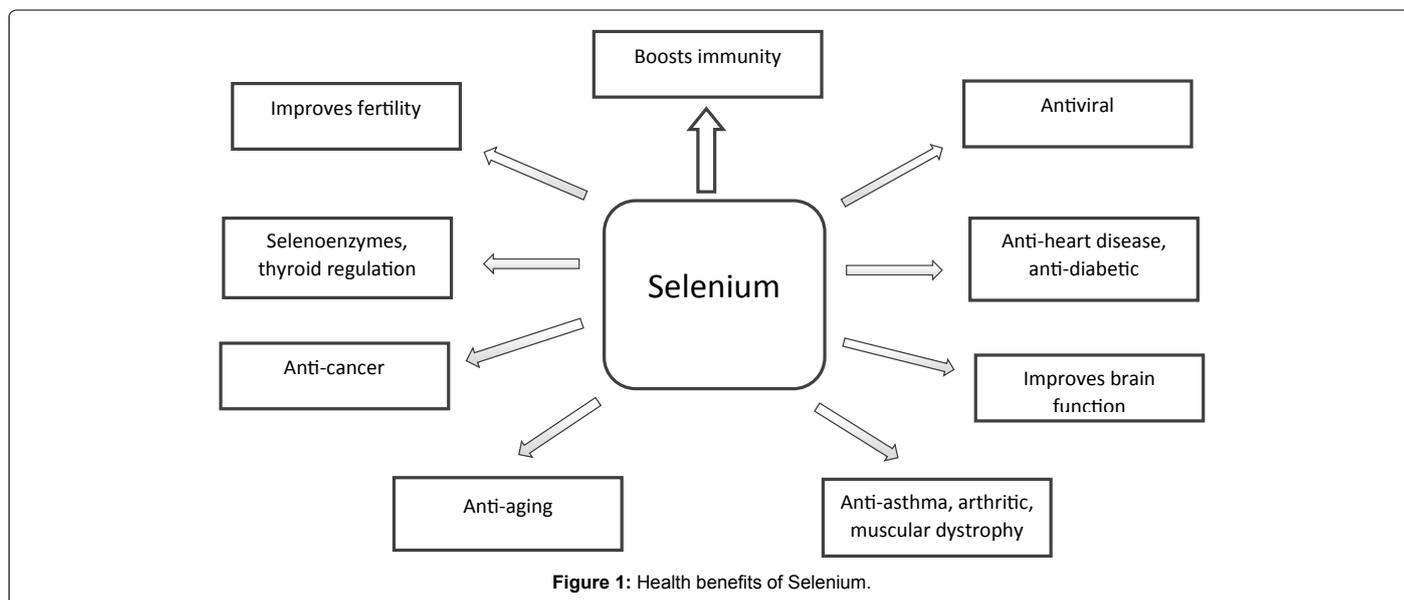


Figure 1: Health benefits of Selenium.

Therapeutic Efficacy of Se Based Nanoparticles

No doubt selenium is an important trace element but it causes toxicity at level not much greater than the level required for its beneficial effects [38]. Therefore, research is going on nanoparticles of selenium for lowering its toxicity. Nanotechnology is the branch of science that focuses on understanding and controlling the objects at Nano scale. The prefix 'Nano' refers to 10^{-9} or one billionth part of any matter. Its concept was proposed by well known Richard P Feynman in meeting of American Physical Society in 1959 during his lecture "there's plenty of room in bottom"[39]. A lot of research is carried on diagnostic and therapeutic agents based on nanoparticles to treat pain, asthma, allergy, infections and different diseases like cancer, Alzheimer, diabetes etc. On Nano scale many fundamental properties of materials such as solubility, drug diffusion and release, half-life in blood and immunogenicity can be modified [40]. The best example is of antibody-conjugated quantum dots that are useful for disease detection as they show promising effects in targeting of in-vivo systems. Both Quantum Dots and liposomes of nano size are more effective than conventional drugs that have less directed delivery protocols [41]. Selenium in nano form has also shown excellent biological activities [42,43]. In a research it was revealed that SeNPs down-regulate mRNA expression of pro-inflammatory cytokines including inducible NO synthase (iNOS), interleukin IL-1 and TNF- α thus reducing inflammation [44]. SeNPs-SPS complexes made by decorating SeNPs with water-soluble derivative of *Ganoderma lucidum* polysaccharides (SPS) also have the potential to decrease inflammation by inhibiting NF- κ B, JNK 1/2 and p38 MAPKs activation partially [44]. SeNPs can increase the activity of selenoenzymes with equal efficacy causing less toxicity to the cells as compared to selenite, Se-methylselenocysteine and selenomethionine [45]. Bioavailability, toxicity and antioxidant activity of selenium depends on its chemical form. Selenomethionine is the most widely used form of Se in food and supplements, though it has less toxicity and excellent bioavailability but some reports show that its excessive use can lead to toxic effects [46]. Therefore, instead of selenomethionine Nano-Se can be used as its effect on upregulating glutathione peroxidase and thioredoxin reductase is comparable with selenomethionine with much lower toxicity [38]. Additionally, Nano-Se is a better chemopreventive agent compared with Se-methylselenocysteine [43]. In a study performed in 2015 SeNP at concentration of 250 mg/kg b.w. was given and results showed that SeNPs acted as potent anti-inflammatory agent and significantly reduced arthritis induced parameters [47]. SeNPs are also used in cancer drug and gene delivery systems displaying combined effect of Se with the therapeutic drug cargo thus improving their anticancer activity [48].

Conclusion

Selenium is an essential micronutrient as it is required by many selenoproteins for their proper functioning. Due to importance of Se in reducing inflammation, decreasing oxidative stress and in improving bone health it is necessary to maintain its level in the body. Se supplementation trials in patients of RA showed beneficial effects but due to toxicity of Se in bulk form SeNPs are gaining more attention by the scientists. Nanoparticles of Se are less toxic and have some advanced properties in terms of diffusion, solubility and immunogenicity but chemicals used to reduce selenium salts can be harmful to patients, therefore, improvements are needed to make Se therapy more effective and safe.

More influence should be given on biological synthesis methods of selenium nanoparticles as an alternative to chemical and physical

methods because green synthesis of nanoparticles is more economical, safe and eco-friendly. Nanoparticles produced as a result of this method are less toxic and safe to use of living organisms. Se NPs can also be used as micronutrient and as an alternative to antioxidant and anti-inflammatory drugs. These nanoparticles may help in providing new diagnostic techniques and systems for early diagnosis of diseases. Tissue repairing systems and targeted drug delivery systems can also be improved using Se NPs. The future outcomes of Se NPs seem to be very promising in increasing the efficacy of existing treatments and development of new therapies.

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