# Selenium, an essential element in human and animal nutrition in health and disease

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## HOW DOES SELENIUM WORK?

Selenium (Se) is a member of the sulfur family of elements, and shares some chemical properties with sulfur. Selenium is present in soil at concentrations ranging from 0.1 μg to 1,000 μg/kg. In drinking water Se rarely exceeds 10 μg/liter with higher concentrations found in alkaline waters.

In the late 1950s the work of Schwartz and Foltz helped to elucidate the role of selenium as a necessary (essential) component of balanced nutrition and good health. Schwarz found that selenium could prevent liver condition in experimental animals due to a diet deficient in vitamin E, sulfur amino acids (cysteine, methionine) and selenium. In the 1970s Rotruck and colleagues discovered that the enzyme glutathione peroxidase operating body's own antioxidant, glutathione system (GSH), has selenium as an indispensable part of its structure. Glutathione peroxidase catalyzes oxidation of glutathione, which is a mechanism to neutralize free radicals, prevent lipid peroxidation and safeguard integrity of cell membranes. The reaction of GSH with hydrogen peroxide, an example of free-radical, may illustrate the anti-oxidant mechanism of glutathione and the selenium containing glutathione peroxidase [I].

$$\text{Reduced GSH} + H_2O_2 \xrightarrow{\text{glutathione peroxidase}} \text{Oxidized GSH} + H_2O \quad \text{[I]}$$

The oxidized glutathione formed in this reaction is regenerated to its reduced form by a subsequent reaction with nicotinamide-adenine-dinucleotide phosphate (NADPH). The discovery of role of selenium in glutathione system also provided a rationale for naming selenium as an antioxidant, because it was established that the glutathione peroxidase-dependent mechanism protects cellular components from oxidative stress and damage.

The selenium-dependent glutathione system is one of the key mechanisms in maintaining body's homeostasis and preventing disease. In one study, glutathione concentrations were measured in 33 people over 60 years of age, residents of Michigan, and the values were related to the self-reporting of health status. Glutathione concentrations correlated positively with age and good health. The association with health was independent of age.

Further understanding of the biological mechanism of selenium derives from the discoveries in the 1980s and 1990s of proteins other than glutathione peroxidase whose structures require the presence of selenium. Some of these selenoproteins have been identified in bacteria and several selenoproteins have been isolated from mammals.

Some of the most important selenoproteins discovered include a type I iodothyronine deiodinase (an enzyme necessary for the proper thyroid function and conversion of thyroxine (T4) into triiodotyronine (T3)); selenoprotein of mouse sperm mitochondria (assisting in sperm movements); selenoprotein W found in skeletal muscle of a rat (assisting functioning of the muscles); selenoprotein of rat prostate (the potential importance of this selenoprotein stems from epidemiological studies that show an inverse relationship between the status of selenium and the incidence of prostate cancer); selenoproteins which may encode the human genes responsible for expression and regulation of cellular immunity.

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## SELENIUM IN HEALTH AND DISEASE

The role of selenium supplementation as an essential microelement for human health is becoming increasingly important because selenium deficiency in the food chain is now well recognized. Selenium deficiency poses a serious problem in livestock worldwide which ultimately may affect the selenium status in men.

Selenium deficiency has been linked with a number of disease symptoms in different animals (Table I). Human selenium deficiency has been well documented in the pathogenesis and pathology of Keshan disease – a multifocal myocarditis occuring in a particular region of China, province of Keshan, where soil is lacking selenium. Besides cardiomyopathy the following clinical and/or laboratory manifestations of selenium deficiency in humans have been described: myositis, whitening of the fingernail beds, pseudoalbinism, elevated creatine kinase derived from muscles macrocytosis and osteoarthropathy known as Kashin-Beck disease.

**Table I** - Selenium deficiency associated diseases in livestock animals

| Disease | Species |
|---|---|
| Exudative diathesis<br>Nutritional pancreatic dystrophy<br>Encephalomalacia<br>Impaired immunodevelopment<br>Reduced egg production<br>Increased embryonic mortality<br>Impaired growth | Chicken |
| Reduced fertility<br>Retained placenta<br>Cystic ovarian disease<br>Unthriftiness<br>Anemia<br>Mastitis | Cow |
| Nutritional muscular dystrophy | Fish |
| Nutritional muscular dystrophy | Horse |
| Hepatosis dietetica<br>Mulbery heart disease<br>Nutritional muscular dystrophy<br>Edema<br>Impaired spermatogenesis<br>Nutritional muscular dystrophy | Pig |
| Unthriftiness<br>Infertility in ewes | Sheep |

## ROLE OF SELENIUM IN DEVELOPMENT AND PREVENTION OF CANCER

Correlation between selenium deficiency and higher death rate due to cancer has been found for both sexes worldwide. In a study conducted in China, a strong association was demonstrated between low selenium content of grain and incidence of the liver cancer. In South Africa significantly lower blood selenium levels were demonstrated in populations with high incidence of esophageal cancer, as compared to populations with the low incidence of the disease. An inverse association was found between selenium levels in the water and cancer mortality in Texas. Low colorectal cancer mortality in Seneca County, New York State, was observed in conjunction with high environmental selenium – conversely, high colorectal cancer mortality (colorectal cancer is second deadliest cancer in the US causing 50,000 deaths per year in this country alone) was found in surrounding counties with low environmental selenium.

Selenium, as a single ingredient or in combination with other anti-oxidants (e.g. alpha-tocopherol and beta-carotene) has been shown to reduce total cancer incidence and mortality in cancer prevention trials. In a pioneering trial conducted by Dr. Larry Clark in the USA from 1983 to 1993 there was a 37% reduction in total cancer incidence with a 200 μg supplement of selenium daily for 10 years, as compared to the non-supplemented group. The 50% reduction in total cancer mortality was also observed in the Se-supplemented population which developed cancer. In a preventive trial in China population received 200 μg of elemental selenium for 4 years which resulted in a significantly lower incidence of primary liver cancer as compared to the placebo group. The results of the exemplified trials strongly indicate that selenium supplementation may reduce the incidence of, and mortality from various forms of cancer.

The data on the role of selenium in cancer prevention is particularly important in view of epidemiologic data that implicate selenium deficiency in the development of cancer in various sites of the body including cancers of liver, mammary gland, esophagus, stomach, colon, rectum, lung, urinary tract, prostate, female reproductive organs, thyroid, hematologic system, oral cavity, pharynx and skin. However, the effect of selenium supplementation on cancer risk may still depend on primary risk factors, eg, smoking history, alcohol use, age, gender, and diet.

Interestingly, it has been reported that areas of low selenium ingestion also tend to be areas of greater affluence. The levels of environmental selenium may have an important impact on the magnitude of the protective effects of the nutritional supplementation of selenium. For example, nutritional intervention with selenium in areas with low environmental selenium, like Finland, may have a greater protective effect against cancer. Conversely, populations with levels of selenium exposure above or approaching the levels at which cancer risk plateaus, may not benefit from the dietary selenium supplementation. The anti-carcinogenic action of selenium may or may not be mediated by its anti-oxidant properties or alterations in the glutathione peroxidase function. Another probable anti-carcinogenic mechanism is restoring the programmed cell death by selenium in cancerous cells.

## SELENIUM IN PREVENTION AND MANAGEMENT OF VIRAL DISEASES

The potential protective effect of selenium in viral diseases including human immune-deficiency virus (HIV) infection has been considered because of selenium's recognized effect against a number of viral pathogens and because symptoms of impaired immune response, similar to that in AIDS, were associated *in vitro* and *in vivo* with selenium deficiency.

The relationship between selenium deficiency and coxackievirus-caused myocarditis (inflammation of the heart muscle) in mice has been studied. It was found that selenium deficient mice inoculated with the benign virus produced a mutant virus with a virulent phenotype, which resulted in severe myocarditis. Animals that had adequate levels of selenium did not develop the disease. The authors of this report hypothesize that the selenium adequate status prevented viral genome mutations directly and/or by strengthening the immune response to a viral challenge. According to theory by Taylor on mechanism of HIV infection a class of selenoproteins may have a propensity to bind with viral genetic material (DNA), acting as a suppressor of HIV virus proliferation. According to Taylor's theory, once the virus uses up the reserves of selenium in the infected cell, the virus's repressed ability to proliferate is de-repressed and it infects adjacent cells in a "search" for the unexploited sources of selenium, thereby spreading the infection throughout the body.

The epidemiological data indicate that low levels of serum selenium coincide with clinical progression of HIV

infection (Table II). So far studies on selenium's therapeutic role with AIDS patients show moderate improvement of the clinical status of the patients. In one intervention study, selenium supplementation was shown to improve AIDS-related cardiomyopathy. In another study 12 patients with AIDS were treated with oral selenium supplements. Serum selenium levels were raised to normal, with subjective clinical improvement, but no improvement or changes in hemoglobin, erythrocyte sedimentation rate, or CD4 cell counts were noted.

**Table II** - Selenium, zinc, immunological and hematolgical serum of patients with HIV infections vs. healthy (control)

| Group | Selenium µmol/L (Mean) | Zinc µmol/L (Mean) | Hemoglobin g/L (Mean) | ESR mm/h (Mean) | CD4 T-cells/mm³ (Mean) |
|---|---|---|---|---|---|
| Group 1 (SF) | 1.18 | 12.4 | 138 | 9 | 850 |
| Group 2 (PGL) | 0.87 * | 13.6 | 136 | 17 | 350 |
| Group 3 (ARC) | 0.86 * | 13.5 | 114 | 39 | 245 |
| Group 4 (AIDS) | 0.82 * | 12.8 | 101 * | 67 * | 110 |
| Group 5 (C) | 1.30 | 13.2 | 153 | 5 | 970 * |

SF: Symptom-free subjects; PGL: Persistent generalized lymphadenopathy; ARC: AIDS related complex - AIDS: Acquired immunodeficiency syndrome; C: Controls; * $p < 0.001$

NORMAL VALUES (males): Hemoglobin: 140-170 g/L; ESR: 1-12 mm/h; CD4 (T-cells/mm³): 38% of lymphocyte number found in the white cell count.

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There is general agreement that the nutritional requirement for selenium and other essential nutrients needs to be considered carefully in the complex therapy with which AIDS patients are treated. The effective dose of selenium required for intervention in the disease development is of particular importance. Some researchers predict that this dose needs to be higher than the nutritional dose range required for dietary selenium supplementation.

## POSSIBLE ROLE OF SELENIUM IN BLOOD COAGULATION AND AS AN ANTI-ARRHYTHMIC AGENT

Some findings concerning the role of selenium in modifying the body's homeostasis relate to its effect on blood coagulation and its potential as an anti-arrhythmic agent – both mechanisms playing role in prevention of the cardiovascular disease risk. Selenium deficiency in rats significantly decreased aortic prostacyclin synthesis (a anti blood clotting compound) but did not affect the platelet thromboxane synthesis (a compound increasing blood clotting). It has been postulated that the unusually high mortality rate from cardiovascular disease in southeastern Georgia may be due to selenium deficiency.

Selenium supplementation is increasingly considered to be an adjuvant or a sole treatment modality of cardiac arrhythmias. In one report ventricular tachycardia resistant to several standard therapeutic agents was normalized after selenium supplementation to the patient.

## SAFETY AND EFFICACY OF SELENIUM SUPPLEMENTATION

The bioavailability, efficacy and ultimately safety of selenium supplementation may depend on a number of factors, including the amount of selenium in the diet, its chemical form, its interaction with other nutrients and the physiological state of the host.

The role of a safer form of selenium supplementation should not be minimized, because selenium may have toxic effects at levels only four to five times the level normally ingested in the human diet (Agency for Toxic Substances and Disease Registry, 1989).

A discussion of the biological effectiveness of seleno-organic (eg L-selenomethionine, gamma-glutamyl-Se-methylselenocysteine) compounds vs. inorganic selenium (sodium selenite) is one of the important aspects of the selenium safety issue. L-selenomethionine is recognized as a safer form of selenium than sodium selenite. The role of methionine in aiding the safe metabolism of selenium is part of that safety mechanism. Methionine yields in the body S-adenosylmethionine which provides methyl groups for the sequential methylation of toxic products of selenium metabolism like hydrogen selenide.

Seleno-organic compounds, like seleno-methionine, are also generally recognized as biologically more effective that the inorganic forms of selenium such as selenite.

Dietary supplementation with L-seleno-methionine, sodium selenite and seleno-cysteine in experimental animals showed that the highest increase in tissue selenium levels was accomplished with L-selenomethionine.

Both organic and inorganic forms of selenium have a synergistic effect in lowering the risk of cancer when administered with vitamin A, vitamin E and beta carotene. On the other hand, any protective effect of sodium selenite against mammary carcinoma in rats was nullified by supplementation with ascorbic acid or vitamin C. It is significant to note that the protective effect of L-selenomethionine was not affected by vitamin C administration.

The above considerations were included in reasoning by the National Cancer Institute (NCI) in selecting L-seleno-methionine as a source of selenium for the NCI sponsored 12 year prospective study in prevention of prostate cancer in American male.

The NCI study that started during summer 2001 will evaluate a preventive effect of L-selenomethionine in a dose of 200 µg of elemental selenium daily. This and the previous preventive trials support the notion that the health benefits of selenium supplementation can be accomplished at much higher doses than the currently recommended 50-100 µg per day elemental selenium supplementation. As previously mentioned, the effective dose of selenium in potential management of some viral infections should be considered even higher than 200 µg per day.

One of the proposed solutions to the dilemma of higher doses of selenium required for its biological activity is optimizing its absorption and its bioavailability, or maximizing its presence in the target tissue. Sabinsa sponsored bioavailability of selenium evaluated in a double blind study with 10 volunteers, five of whom received 50 µg elemental selenium in the form of L-selenomethionine alone, whereas five received 50 µg elemental selenium in the form of L-selenomethionine, supplemented with 5 mg of piperine extracted from black pepper in the form of a preparation known as Bioperine®. Over the course of a 6-week supplementation regimen, serum selenium levels were evaluated before the study and at 2-, 3-, and 6-week intervals. The serum selenium levels were approximately 30% higher in the group receiving selenium with Bioperine®. This increase was detected after 2 weeks of supplementation, with a plateau in the subsequent time-points tested. None of the volunteers in the experimental groups reported any adverse effects from the supplementation. The serum selenium levels were within normal limits in both groups at all time-points tested.

Because the essentiality of selenium for human nutrition is well established, and because it has a considerable potential in the prevention and treatment of broad range of pathology its intelligent use is at stake now. The supplemental role of selenium should be stressed both in human and animal health because selenium deficiency maybe responsible for serious problem in livestock worldwide. This ultimately may affect the selenium status in men.

References available from the authors upon request