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Selenium Supplementation and Human Health a New Zealand Perspective

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Selenium is an essential micronutrient, for which frank deficiency has been linked with muscle wasting diseases. However, an increasing accumulation of evidence is also associating low selenium status with increased risk of various degenerative diseases including cardiovascular disease, cancer and diabetes, and increased susceptibility to and virulence from viral infections. Low selenium can synergise with low iodine status. New Zealand soils are notoriously deficient in selenium, leading to sub-optimal levels in humans eating food plants grown on such soils, and/or animals grazing on such plants. Selenium is known to play a role in protection against oxidative stress. Selenium dependent glutathione peroxidase removes the products of free radicals and other reactive oxygen species, while thioredoxin reductase is a selenocysteine-containing enzyme that regulates the reduction of exposed disulphide groups. Although these selenoproteins are known to be involved in the repair of oxidative damage, there have been no available data to show whether these enzymes are at high enough levels in New Zealand to cope adequately with DNA damage. The single cell gel electrophoresis or COMET assay measures DNA breakage in individual cells. We have used this assay to question whether initial blood selenium levels relate to susceptibility to leucocyte DNA damage, in a high cancer-risk group of men in Auckland whose serum selenium content averaged 97.8 ng/ml. In those individuals whose Se status was below the mean, there was a statistically significant inverse relationship between serum selenium and average level of DNA breakage in circulating blood leucocytes. The data lead us to question some of the assumptions in setting the current recommended daily allowance of selenium in New Zealand and other countries.

Key Words: Selenium, New Zealand, Human disease

INTRODUCTION

Selenium (Se) was originally only recognised as a toxicant,[1] and it was not until the 1950s that Schwartz and Foltz[2] drew attention to its nutritional requirements. Selenium is an essential microelement for both humans and animals, and its deficiency leads to various diseases usually associated with muscle wasting. Cardiovascular diseases including Keshan disease and Progressive Chagas' Cardiomyopathy may

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result from severe selenium deficiency; while the severity of the disease also shows a link.[3~5] Kashin-Beck disease is associated with joint swelling, pain, short stature and secondary osteoarthritis, while low selenium levels have also been associated with infertility, spontaneous abortions, hypothyroidism, and White muscle disease in animals.[3,6] Selenium deficiency also seems to interact with low iodine status.

The importance of selenium in human nutrition is generally associated with its functional role in more than 30 selenoproteins, not all of whose actions are known.[7] Deficient antioxidant functions have been associated with the development and progression of cancer, heart disease and diabetes. The best-recognized selenium-dependent antioxidant enzyme is glutathione peroxidase, but thioredoxin reductase, selenoprotein P and selenoprotein W also have antioxidant functions. Muscle metabolism also appears to involve selenoprotein W.[8] Sperm capsule selenoprotein is essential for male fertility, while the synthesis of thyroid hormones requires iodothyronine deiodinase.

The metabolic pathway of selenium is illustrated in Fig. 1, revealing a key human nutritional role of selenomethionine (SeMet). Traditional sources of selenium are organ meats, eggs and seafood,[9] as well as plants. Plants take up Se from the soil, and nutritionally important plants convert Se primarily into SeMet, the major food form of Se. Plants do not concentrate Se against a gradient, and the plant Se content generally reflects the soil Se content. However, it is possible to develop plants that have exceptionally high selenium levels, and there is considerable interest in selenium-rich broccoli and selenium-rich garlic for nutritional purposes.[10] Brewers yeast, grown on Se-rich media, also takes up Se and converts it to SeMet, and has been used as a Se supplement in human clinical trials.[11]

In general, selenium has a wide range of roles and is of critical importance to human health.[6] Some of its known functions are described below. We also describe a New Zealand-based study that may hint that currently-accepted levels of selenium are too low for adequate maintenance of all its key roles.

DISCUSSION

1) Importance of Se during early growth and development

It has generally been observed that selenium levels in kidney, liver and heart of newborns and infants are low, and increase during normal growth and development.[12] Low selenium levels have been reported in premature babies; whereas full-term infants had blood selenium levels between 0.6～1.8 mM, premature babies had values between 0.3～0.5 mM Se.[12] This

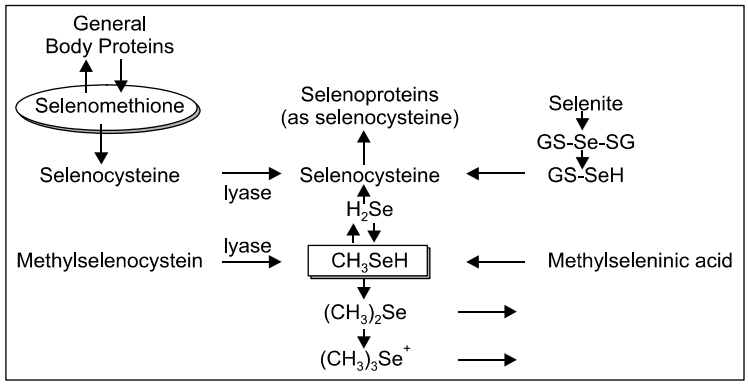

Fig. 1. General selenium metabolic pathway.

would be predicted to lead to potential problems with muscle development, and enhanced oxidative stress. Reid and Tervit also associated low selenium levels with the risk of sudden infant death syndrome and placental disorders.[13)]

Bottle-fed babies may also be at risk of Se deficiency, despite the presence of Se in baby formulas. The problem can be seen in reference to the metabolic pathway (Fig. 1). SeMet is the form in which Se would normally be present in mother's milk, being readily incorporated into body proteins, and available for other parts of the pathway. However, baby formulas are usually fortified with inorganic Se (Na selenite or Na selenate), which is not significantly incorporated into body proteins. Because of the high Se requirements of the developing child, extra is also required by the mother during pregnancy and lactation. Supplementation with a source of SeMet, such as Selenised yeast, can prevent the decline of Se levels in human milk.

2) Selenium and cardiovascular disease

A number of epidemiologic studies have related low serum selenium to high risks of cardiovascular mortality.[14)] The antioxidant effects of Se are thought to play a key role in the development of atherosclerosis. This is known to be initiated by oxidation of low density lipoprotein (LDL), leading to the activation of the expression of two key proteins: MCP-1 and M-CSF, and to the entry and activation of monocytes to macrophages. Further oxidation of LDL (ox-LDL) leads to a product that is recognised by macrophages, leading to the formation of foam cells and vessel blocking. The antioxidant effects of Se may be important in preventing the initial oxidation of LDL; immune regulatory effects may also play a role.

Se deficiency is associated with congestive heart failure and may enhance the clinical severity of the disease.[15,16)] Se also appears to play a structural role in arterial endothelial cells[17,18)]; there are serious ultrastructural changes in the heart in Se-deficient rodents.[17)]

3) Selenium and diabetes

The role of Se in protecting against diabetes has been less clearly delineated. It is certainly true that low selenium status is often true of blood cells of patients with diabetes mellitus.[19)] Se protection against oxidative stress may be important. In a rat model of diabetes induced by streptozotocin, it is possible to show a protective role of intraperitoneally administered vitamin E and selenium on antioxidative defense mechanisms. It is known that Se deficiency may simulate hyperglycemic conditions, and has been shown that Se supplementation protects against diabetes-associated renal injury in rat models.[20)]

4) Selenium and viruses

Several parts of China are exceptionally low in Se, and supplementation has been suggested as desirable. It appears that along with other desirable effects, supplemental Se reduces hepatitis and liver cancer incidence in these parts of China.[21)] Coxsackie B virus may remain dormant or harmless for years but may become lethally pathogenic under Se deficiency,[22)] while influenza and other viruses become more virulent.[23,24)] Se also inhibits virally- induced mammary tumorigenesis in mice.[22)]

Selenium may play a particular role against Human Immunodeficiency Virus (HIV).[25)] It appears that HIV contains UGA codons which may encode selenoproteins.[26)] HIV replication is accompanied by production of oxygen radicals, which damage host cells and towards which antioxidant effects of Se may be beneficial. The viral genome may also be damaged by low Se levels, increasing the pathogenicity of HIV and other viruses.[27)]

Adequate selenium and antioxidant vitamin intakes should have a protective effect in early phases of HIV infection. In a phase III clinical trial, Se in the form of Selenised-yeast proved beneficial in AIDS and ARC (AIDS-Related Complex) patients.[22)]

At least in a murine model, Se supplementation de-

creased the incidence of Coxsackievirus-induced heart disease during the course of AIDS development.[28)]

5) Selenium and cancer

In the 1960s and 1970s, a number of correlational studies revealed inverse associations between Se intakes and cancer mortalities in different countries. More than 100 experimental studies have been published to date, using a range of different animal models. Of these, 2/3 show a positive benefit of selenium supplementation, while approximately half show more than a 50% reduction in cancer incidence. Doses of Se vary from those that could be considered nutritional in human populations, to those that are super-nutritional. A range of forms of Se have been used.[29)]

The most compelling data on selenium and cancer comes from double-blind human intervention studies. Se-rich yeast was used by Larry Clarke and coworkers.[11)] This study considered subjects who had had a squamous cell carcinoma removed, and asked whether supplementation with 200 mg Se yeast (primarily as SeMet) would prevent the recurrence of cancer. While the Se did not appear to protect against squamous cell carcinoma, it significantly reduced the incidence of cancer generally, and especially prostate, colon and lung cancers. The protective effect of Se against prostate cancer was also implied by a trial of more than 20,000 individuals, where the level of Se as measured in toenail clippings correlated strongly with the risk of various cancers.

(1) Mechanisms: Microarray methodologies have been used in order to establish which genes are affected by Se deficiency in tissue culture cells.[30)]

The authors reported that a considerable range of genes were activated. These included known genes for enzymes controlling DNA repair and protecting against oxidative stress. Genes controlling cell cycle and growth were also affected. In contrast, the activity of other genes was significantly reduced. Genes affected included those for enzymes involved in selenoprotein synthesis, xenobiotic metabolising enzymes (cytochrome P450s and glutathione S-transferase), enzymes regulating lipid transport and others involved in angiogenesis, cell adhesion, cell cycle and cell growth. It will be noted that many of these will have major roles in the development and progression of cancer. These studies add to the accumulating database of mechanistic studies in animals, to lead to suggested mechanisms of cancer prevention as summarized in Table 1.[31)]

(2) New Zealand selenium levels and cancer: New Zealand (NZ) is recognised as having an exceptionally low Se Status. Data from 1988 suggested that blood Se levels (ng/ml) in NZ ranged from 20～60, while USA levels were typically between 200 and 400. The NZ levels had increased by the early 1990s, with the import of high-Se wheat from Australia, and Se supplements in animal feed. The North Island has higher levels than the South Island. Thus, it is of concern that our recent trial in Auckland (in the North Island) suggested that levels are still unacceptably low by international standards, with approximately half the tested population having serum levels below 97.4 ng/ml.

We used a biomarker approach to testing cancer risk in this group of middle aged men from Auckland. These are measurable indicators of exposure, or of disease risk. There is no need to wait for the disease to develop, so answers can be obtained very quickly. The assay we have chosen is the single cell gel electrophoresis (comet) assay, as developed by for biomonitoring studies.[32)] Blood samples have been taken from all NZ subjects and comet assays used to

Table 1. Some suggested mechanisms of Se action (Fleming *et al.*, 1996)

Reduced carcinogen bioactivation
redox (thioredoxin reductase)
changed metabolism
Inhibits
initiation
proliferation
angiogenesis
Reverses dysplasia
Enables apoptosis

test the relationship between DNA strand breaks (or oxidized bases or resistance to peroxide-induced breakage) in circulating blood leucocytes, and serum selenium. Full details are to be published elsewhere. However preliminary data show that for that half of the population whose blood selenium level is below the mean, there is a statistically significant inverse relationship between the level of DNA breakage and serum selenium concentration. Furthermore, in this group of men, selenium supplementation may be beneficial.

6) Implications for the recommended daily allowance of selenium

The recommended daily allowance (RDA) of selenium is usually based on the levels necessary for maximal activity of GPX. For example, the World Health Organization (WHO) recommended a minimum RDA of 40 mg/day based on 2/3 the level desirable for maximal GPX. New Zealand regulations suggest desirable quantities of 60 mg/day (males) or 44 mg/day females. However, our Auckland population were mostly reaching these levels. The preliminary data from the Auckland study suggested that Se has no apparent effect on the accumulation of oxidized bases. However it may affect the accumulation of other types of damage, and the ability to repair other types of damage. That is, the GPX levels may be adequate but there is a question whether this is true for other types of damage. This has serious implications for the RDA, and leads us to join other authors such as Combs[33] in questioning the current standards.

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