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THE ROLE OF SELENIUM IN CANCER AND VIRAL INFECTION PREVENTION

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Abstract
The role of selenium, the essential trace mineral in human health and disease, is currently a subject of intense interest. The recent 30 years have been an exciting time in selenium research. Selenium has important health effects related to the immune response and cancer prevention, which are possibly not exclusively linked to their enzymatic functions. Selenium appears to be a key nutrient in counteracting the development of virulence and inhibiting HIV progression to AIDS. An elevated selenium intake may be associated with reduced cancer risk. Large clinical trials are now conducted both in Europe and the USA to confirm or reject this hypothesis. In the context of health effects, low or diminishing selenium status in some parts of the world, notably in some European countries, is giving cause for concern.

Key words:
Selenium, Viral infections, Cancer

INTRODUCTION

The role of selenium (Se), the essential trace mineral in human health and disease, is currently a subject of intense interest. Although an excess of selenium in the diet has been first recognized to be deleterious to health, it was subsequently observed that its deficiency could also have devastating effects. Se toxicological properties were first recognized; its essential role for animals was discovered in the 1950s [1] and for humans in the 1970s [2,3]. The recent 30 years have been an exciting time in selenium research. The predominant biological action of Se in both animals and humans occurs via selenium-dependent proteins [4,5]. About 35 selenoproteins have been identified, though many of their roles have not yet been fully elucidated. The best known is the enzyme glutathione peroxidase (GPx). This selenoenzyme, along with other enzymes such as catalase and superoxide dismutase, prevent oxidative damage to cells by breaking down hydrogen peroxide and other reactive oxygen species. The fact that GPx is a selenoprotein and an antioxidant has led investigators to seeking a role for selenium in a wide variety of cellular functions and disorders, including immunity, mutagenesis, carcinogenesis, inhibition of viral expression, and heart diseases. Selenium has additional important health effects in relation to the immune response and cancer prevention, which are possibly not exclusively linked to these enzymatic functions [6,7].

The concentration of selenium in human organism varies between geographical areas, depending on its dietary intake, content in soil and plants, bioavailability and retention, mineral interactions and other factors [8]. Se enters the food chain through plants, which take it up from the soil. Se deficiency has therefore been identified in parts of the world notable for their low soil Se content. The lowest plasma Se levels, reported so far in the selenium deficient

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areas of China, are associated with Keshan disease, an endemic juvenile cardiomyopathy, and Kashin-Back disease, deformic arthritis. Both these conditions are believed to have other causative cofactors [9].

Acid soils frequently with iron or aluminum reduce Se uptake by plants in many parts of Europe. The lowest serum Se concentrations in Europe have been found in subpopulations of Eastern Europe [10–13]. Se intakes in most parts of Europe are considerably lower than in the USA [14,15]. When considering their adequacy we need to have appropriate standards against which to compare them. There is no consensus on this issue. The opinions about the recommended daily allowance differ widely and range from 30 μg/day according to the World Health Organisation (WHO) to 400 μg/day according to Yang and Zhou [16].

There is evidence that Se deficiency can have adverse consequences for disease susceptibility and the maintenance of optimal health. Low Se status may contribute to the etiology of the disease, but in some cases it may be an outcome of the condition itself and may exacerbate disease progression. Investigations based on animal and human models have delivered increasing evidence of Se involvement in the functioning of the immune system [7]. Selenium is normally found in significant amounts in immune tissues such as liver, spleen, and lymph nods. Spallholtz [17] has demonstrated that selenium and its associated enzyme, glutathione peroxidase, occur in most lymphoid cells, B and T cells and in macrophages. Numerous studies suggest that deficiency of selenium is accompanied by loss of immunocompetance. Both cell-mediated immunity and B-cell function can be impaired [17].

Even at so called replicated levels of plasma Se produced by normal dietary intake in the USA (plasma concentration levels 120–130 μg/l), supplementation with selenium has marked immunostimulant effects, especially by enhancement of proliferation of activated T cells (clonal expansion) [18]. Lymphocytes from volunteers supplemented with selenium as sodium selenite, at 200 μg per day, showed an enhanced response to antigen stimulation and an increased ability to develop into cytotoxic lymphocytes and to destroy tumor cells. Supplementation resulted in a 118% increase in cytotoxic-lymphocyte-mediated tumor cytotoxicity. Natural-killer-cell activity was also increased [18]. In chronic gut failure patients on total parenteral nutrition, lymphocyte responses to various antigens and mitogens were subnormal on a diet containing 20 μg/day of selenium, but improved after two month on a diet containing 200 μg/day of selenium [19]. The mechanism appears to be closely related to the Se ability to upregulate the expression of receptors for the growth-regulatory cytokine interleukin-2 on the surface of activated lymphocytes and natural-killer cells. This interaction is crucial for clonal expansion and differentiation into cytotoxic T cells [14,20]. Additionally, cells of the immune system may have an important functional need for selenium. Activated T cells show upregulated selenophosphate synthase activity [14], directed towards the synthesis of selenocysteine, the essential building block of selenoproteins, which show the importance of selenoproteins to activated T-cell-function and the control of the immune response. The mRNAs of several T-cell-associated genes have the theoretical capacity to encode functional selenoproteins [21]. All these facts suggest that the role of selenium in the immune system may be much more diverse than previously suspected.

SELENIUM AND CANCER

From the 1970s, epidemiological studies have provided evidence of an inverse relation between Se intake and cancer mortality. In the study of Schrauzer et al. [3], Se dietary intake in 27 countries was found to correlate inversely with total age-adjusted cancer mortality. In the investigation of the relation between forage-crop selenium and country levels of cancer mortality in the USA, cancer mortality rates for the major cancer sites were found to be significantly higher in low Se countries [22].

The epidemiological evidence from prospective human studies is inconsistent; some investigations show an increased risk of cancer in individuals with the lowest Se status, whereas other studies report null results [23–27]. There have been eight trials with human subjects conducted on the influence of selenium on cancer incidence or biomarkers. Se-enriched yeast is the major form of se-

lenium used in such trials [24]. In prospective studies published in the 1990s, involving a large number of individuals (from 8000 to 11 000), low Se status was associated with a significantly increased risk of cancer incidence and mortality. Risk has been from two-fold to six-fold higher in the lowest tertile or quintile (according to the study) of serum Se concentration [28,29].

Clark et al. [23] performed a multicenter, double-blind, randomized, placebo controlled cancer prevention trial in a western population, designed to test the hypothesis that Se supplementation could reduce the risk of cancer. In 1312 individuals with a history of non-melanoma skin cancer who were randomized to placebo or 200 μg selenium (as selenium yeast) per day, there was no effect on the primary endpoint of non-melanoma skin cancer. However, those receiving selenium showed secondary endpoint effects of 50% lower total cancer mortality and 37% lower total cancer incidence, with 63% fewer cancers of the prostate, 58% fewer cancers of the colon, and 46% fewer cancers of the lung. Van den Brandt et al. [26] have recently published data from the Netherlands Cohort Study and found a 31% reduced risk for *de novo* development of prostate cancer for patients with the highest quintile of Se levels compared with those with the lowest quintile. One possible reason for the decreased incidence may be the enhanced immune responsiveness or, more likely, the ability to produce anti-tumorigenic metabolites (e.g., methyl selenol or its precursors) that can perturb tumor-cell metabolism, inhibit angiogenesis, and induce apoptosis of cancer cells [14]. These results suggested the exciting possibility that significant reductions in cancer risk may be realized with low, non-toxic doses of selenium. Waters et al. [27] conclude that in general, cancer risk is more profoundly influenced by Se status in men than in women. The cancer protective effects of selenium may be mediated by selenoproteins operating within enzymatic systems, which are saturated at relatively low Se levels, or by Se metabolites that increase substantially under conditions of supranutritional selenium intake [30].

The cytosolic glutathione peroxidase (GPx-1) is the first and best characterized mammalian selenoprotein. Genetic variants of GPx-1 in the human population have been described, including a single nucleotide polymorphism that results in either proline (Pro) or leucine (Leu) at codon 198 [31]. It was determined that frequency of the Leu allele was greater in individuals with lung cancer than in controls ($p < 0.001$). Moreover, the calculated odds ratios were 1.8 for heterozygotes and 2.3 for homozygotes for the Leu-containing allele compared with Pro-containing individuals. Similarly, a significant difference in GPx-1 genotype at codon 198 was also associated with increased risk of bladder cancer as well as tumor stage [32]. In addition to the polymorphism at codon 198, there is an additional common polymorphism in which there are a variable number of tandem alanine codons, 4, 5, or 6 repeats, in GPx-1 exon 1 [31]. Two case-control studies have indicated an association of a particular variant with the risk of cancer, i.e. 4 repeats were associated with breast cancer risk [33], whereas 6 repeats were associated with young onset prostate cancer [34].

Selenoprotein 15 (Sep 15) was initially characterized in 1998 as a major Se-labeled protein detected in human T cells [35]. It is expressed at relatively high levels in the prostate, liver, brain, kidney and testis, whereas it is low in muscles, trachea and the mammary gland. Genetic data have supported a role for Sep 15 in cancer etiology. There is a significant difference in allele frequency in DNA obtained from either breast cancer or cancers of the head and neck compared with DNA obtained from cancer-free individuals. LOH at the Sep 15 locus is likely to account for much, if not all of the differences in the Sep 15 allele frequency [36]. In a detailed analysis of LOH of Sep15 in breast cancer, 28% of heterozygotes were observed at a genetic marker tightly linked to Sep 15 [37]. An analysis of other microsatellite markers along human chromosome 1p did not detect a significant difference in the heterozygosity indices for these markers between breast tumor and control DNA. These data indicate that the loss of either Sep 15, or perhaps another very tightly linked gene, is a common and important event in breast cancer development [38].

With regard to cancer, few extensive clinical trials are conducted. The PRECISE (Prevention of Cancer by Intervention with Selenium) trial, recruits about 33 000 European individuals. Furthermore, the US National Cancer

Institute founded a 12-year study, SELECT (Selenium and Vitamin E Cancer Prevention Trial), where 32 000 men will be recruited to ascertain the effect of supplementation with selenium (200 μg per day) and vitamin E on the risk of prostate cancer [14].

SELENIUM AND VIRAL INFECTIONS

Selenium deficiency is linked to the occurrence, virulence, or disease progression of some viral infections [39]. Beck [40] has shown that in selenium-deficient host, harmless viruses can become virulent. In a study conducted in China, the rates of hepatitis infections were lower in a township receiving selenium supplementation as compared to townships not receiving supplementation [41]. When selenium-deficient mice were inoculated with a benign strain of coxackie virus, mutations occurred in the genome to give a myocarditis with similarities to those seen in humans. In the case of coxackie virus, six separate point mutations were identified with the development of virulence, causing myocarditis in the host [40]. A similar study on mice that were unable to make glutathione peroxidase (GPx) showed this enzyme essential for the avoidance of oxidative damage to the RNA-viral genome that results in the myocarditic mutations [42]. Coxackie virus has been isolated from the blood and tissues of people with Keshan disease and is thought likely to be a cofactor in the development of cardiomyopathy [9]. The discovery that the endemic juvenile cardiomyopathy is likely to have a dual etiology that involves both nutritional deficiency as well as infection with an enterovirus provided the impetus for additional studies of relationship between nutrition and viral infection.

A myocarditic strain of coxackie virus B3, CVB3/0, converted to virulence when inoculated into Se-deficient mice. This conversion was accompanied by changes in the genetic structure of the virus so that its genome closely resembled that of other known virulent CVB3 strains. Similar alterations in virulence and genomic composition of CVB3/0 could be observed in mice fed normal diets but genetically deprived of the antioxidant selenoenzyme glutathione peroxidase (knockout mice) [43]. If these findings were to be applicable to other RNA viruses (such as poliovirus, hepatitis, influenza, HIV), they would have considerable public-health implications [14].

More recent research has shown that a mild strain of influenza virus, influenza A/Bangkok/1/79, also exhibits increased virulence when given to Se-deficient mice. Thus increased virulence is accompanied by multiple changes in the viral genome in a segment previously thought to be relatively stable [44].

Epidemic neuropathy in Cuba has features that suggest a combined nutritional/viral etiology. The illness could manifest as optic neuropathy, peripheral sensory neuropathy or a mixture of both. Four separate case-control studies demonstrated that the illness was associated with the decreased frequency, quality and quantity of food intake. Summarized data from several laboratories showed the existence of oxidative stress in the Cuban population during the epidemic. Viral isolation attempts from cerebrospinal fluid (CSF) of neuropathy patients unexpectedly yielded viruses resembling enteroviruses from 84% of CSF specimens cultured [45]. The epidemic of optic and peripheral neuropathy in Cuba suggests the possibility of a virus mutating in an oxidatively stressed host and thus presenting with new pathogenic characteristics.

RNA viruses make up the vast majority of all viruses. They are continually evolving due to their lack of proofreading enzymes. The emergence of new viral diseases or the increase in infection from known viruses is often attributed to such things as global warming, destruction of the rain forests, agricultural practices, etc. However, the influence of host nutrition of the evolutionary process of RNA viruses is rarely considered [44].

Selenium seems to be a crucial nutrient for HIV-infected individuals. Selenium has been shown to inhibit HIV activation *in vitro* [46]. Many authors report a progressive decline in plasma Se in parallel with the ongoing loss of CD4 T cells in HIV-1 infection. This decline in Se status occurs even in early stages of disease when malnutrition or malabsorption cannot be a factor [47]. Dietary Se levels may influence the diffusion of HIV-1 in Sub-Saharian Africa [48–50]. Such countries as Zaire, Uganda, Tanzania, Kenya and South Africa, where AIDS is now the major

cause of mortality, are all known to be selenium deficient. Keshan disease and myxoedematous cretinism caused by joint selenium and iodine deficiency also occurs in Sub-Saharian Africa [9]. Cowgill [48] has shown that variations in dietary selenium are influencing the diffusion of HIV-1 in the United States, especially in the black population. A kind of pattern exists between the geographical distribution of selenium and AIDS mortality that an inverse relationship persists between Se quantity and AIDS mortality in the same area. Baum et al. [51] showed that Se-deficient HIV patients are nearly 20 times more likely to die from HIV-related causes than those with adequate Se levels. In a prospective study among HIV-infected drug-using men and women in Miami, Florida, in which 21 HIV-related death were observed during the follow-up period, Se deficiency was strongly associated with AIDS-related mortality (relative risk, 19.9; 95%CI). Se deficiency is defined by Baum as plasma concentration at or below 85 μg/l, the concentration not attained in many European countries [11–14]. Low plasma selenium is a significantly greater risk factor for mortality than low helper-T-cell count and confers a more significant risk than deficiency of any other nutrient. HIV-positive women with low selenium concentration are more likely to infect their sexual partners than HIV-positive females with higher selenium levels [52]. Campa et al. [53] confirmed in a pediatric cohort that low plasma Se level is an independent predictor of mortality in HIV infection, and it appears to be associated with faster disease progression. Taylor et al. [39,54] have demonstrated that HIV-1 encodes for a homologue of one of the human glutathione peroxidases. To prove that this apparent section of the HIV-1 genetic code really permitted it to produce the mammalian selenoenzyme glutathione peroxidase, Zhao et al. [55] cloned the gene and transfected canine kidney cells and the MCF7 cells with it. In both cases, the cells receiving the HIV-1 gene greatly increased their production of glutathione peroxidase. This proves beyond any doubt that HIV-1 is capable of producing glutathione peroxidase at the expense of its host. As a consequence, replication of the virus must deprive seropositive individuals not only of this form of selenoenzyme, but also of its four basic components: selenium, cysteine, glutamine and tryptophan [50]. As long as there is enough selenium around, cellular immunity will be high and the host cell will be less likely to die (by apoptosis). The best viral strategy is therefore to replicate at very low levels and establish a persistent infection. Under low Se conditions, increased oxidative stress and apoptosis activate the virus, which must replicate at higher rates to escape from a dying cell [48].

Prospective clinical trials to determine whether selenium – as a chemoprotectve agent – can alter the course of HIV disease processes are now underway. Selenium, the latest nutrient admitted to the Recommended Dietary Allowances, with a possible role in etiology of other chronic and infectious diseases, may still provide us with many surprises [56]. The previously unsuspected role of host Se status in the emergence of cancer and viral disease promises some new strategies for prevention and treatment. We must be careful not to encourage the overconsumption of Se supplements, while awaiting the results of the PRECISE, SELECT and other clinical trials. It must be remembered that selenium is a toxic mineral with a fairly small therapeutic window.

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