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Selenium: Its role in health and disease
Christine D Thomson
Department of Human Nutrition, University of Otago, Dunedin, New Zealand

Introduction
New Zealand was once known as one of the lowest selenium (Se) environments in the world, but the implications in terms of human health were not clear. In 1988 Ray Burk described the situation as “selenium deficiency in search of a disease” (1), which reflected the uncertainties at that time. Clearly there were many ‘selenophiles’ who believed that Se was a cure for all ills, including cancer, cardiovascular disease (CVD), rheumatoid arthritis, male infertility and many others, while other researchers were more cautious because of the lack of clear evidence for these associations. We now know much more about Se deficiency and function, which helps to clarify the role of Se in health and disease, but there are many questions remaining. This paper will review briefly what we currently know about Se’s role in health and disease, with particular reference to those conditions of interest for the New Zealand population.

Se exerts its functions through the selenoproteins, which contain selenocysteine residues, usually at their active sites (2). There are 25 mammalian selenoproteins, not all of which we know the function. When Se intake is limited, there is a clear priority for Se supply, both to certain tissues and to certain selenoproteins, resulting in a “hierarchy” of importance of selenoproteins (3). Many of the effects of Se deficiency or health effects can be attributed to these proteins, but some actions of Se, such as proposed anti-cancer properties, may operate independently of the selenoproteins.

Selenium deficiency
Muscular syndrome in New Zealand
One of the first indications of a possible role for Se in human health in New Zealand was a mysterious fibromyalgia widespread amongst residents of Southland (4), which sparked our interest in Se in the late 1960s. The late Dr Peter Snow, a Tapanui GP, referred to Southland residents, who seemed to be prone to an epidemic form of muscular rheumatism (personal communication). These patients sought help from their veterinary surgeons who advised the use of Se in the form of ‘Selovet’ – a veterinary preparation for treatment and prevention of white muscle disease and other Se-responsive conditions in sheep and cattle. Se appeared to help the condition and Peter Snow believed that there was sufficient evidence to correlate the Se responsive conditions in livestock with the endemic rhematism in humans. A double blind trial was undertaken to determine the effectiveness of Se supplementation in preventing these muscular symptoms in humans. Symptoms improved in approximately half of the subjects in both placebo and supplemented groups, suggesting that beneficial effects ascribed to Se may have been due to a placebo effect (5). The usual dose taken by farmers at that time was 5 mg Se as sodium selenate, nearly 100 times the current recommended intake of 60-70 µg/day (6), and there was concern about the effects of such large intakes on the human population.

Selenium deficiency in total parenteral nutrition patients
This muscular syndrome was mirrored in a surgical patient in New Zealand, who had been on total parenteral nutrition (TPN) for some time, and presented with a severe muscular syndrome that prevented her from walking (7). At that time alimentation fluids did not contain trace elements and Se deficiency was suspected. Supplementation dramatically reversed the symptoms (8). Se deficiency in TPN was subsequently reported in other parts of the world with patients presenting with varying symptoms of cardiomyopathy and muscle syndromes including muscle pain, fatigue and proximal weakness (9). But this was not a natural deficiency, and inclusion of trace elements in fluids has now eliminated this problem. The mechanism behind this muscular involvement is unknown. It is tempting to speculate that selenoprotein W, which is abundant in skeletal and cardiac muscle, but is eliminated from tissues in Se deficiency, or selenoprotein N may be involved (10). The reason that only a small number of Se-deficient patients present with skeletal muscle disorders is unclear and possibly related to cofactors, such as viral infections and drugs (9).

Keshan Disease and Kaschin-Beck Disease
The only known natural deficiency diseases are Keshan Disease, an endemic cardiomyopathy that occurs during preadolescent and adolescent years and Kaschin Beck disease, an endemic osteoarthritis, both of which occur in low Se areas of China (11). Intakes in areas where Keshan Disease was endemic were around 7 µg/day. Because of the seasonal nature of the disease, other factors are thought to be involved. The most likely candidate is a virus. Co-existing iodine and Se deficiency may be involved in the aetiology of Kaschin-Beck disease (12). These intakes are much lower than in New Zealand and most other countries. Severe Se deficiency such as in these conditions is not a
problem of western countries such as New Zealand and Australia, with access to a variety of foods, even when the soils in a particular region may be lacking in Se. Furthermore, with the supplementation programmes in place in China, the incidence of Keshan Disease is decreasing.

**Human Immuno-Deficiency Virus (HIV) infection**

The host’s nutritional status is important in infectious diseases and poor Se status appears to be associated with disease progression and early mortality in HIV-positive patients (13). There is a progressive decline in Se status and this parallels loss of immune stability. Low Se status may be an outcome of the disease itself and then exacerbate disease progression. Plasma Se is a strong predictor of the outcome of HIV infection. Se-deficient HIV patients are 20 times more likely to die from HIV-related causes than those with adequate levels (14). Se appears to have a multifactorial role in HIV infection and affects HIV disease progression through various potential mechanisms. These include protection against oxidative stress through the GPxs, control of viral emergence and evolution and enhancement of resistance to infection through modulation of both cellular and humoral immunity. These findings suggest that administration of Se may be an effective way to slow disease progression and enhance survival (13). Such trials are currently underway.

Thus, conditions associated with Se deficiency fall into three categories: those resulting from insufficient Se intake in low-Se soil areas such as Keshan Disease, Kaschin-Beck Disease and possibly muscular fibromyalgia in New Zealand; cardiomyopathy and muscular syndromes associated with parenteral nutrition; and chronic conditions associated with oxidative stress such as HIV infection.

**Consequences of sub-optimal selenoprotein levels**

There is a gap between the intake of Se associated with overt Se deficiency of Keshan disease and the amount to maximize activities of the selenoenzyme glutathione peroxidase (GPx), on which requirements and recommendations are based (15). This gap may be referred to as marginal deficiency. The relevance of long lasting GPx depression due to marginal Se deficiency to the development of chronic disease is a matter of ongoing debate. Because of New Zealand’s low soil Se and low Se status, New Zealanders have so far existed in this gap. The question frequently asked was how could the New Zealand population be so healthy and active with such low Se status? In spite of extremely low Se status in the 1960s to 1980s, we could not find any adverse effects on generally healthy New Zealanders (16). This is perhaps partly due to lack of appropriate biomarkers for sub-clinical effects of Se deficiency. However, there has been some progress in recent years, and there is increasing evidence that Se intakes in the range between overt deficiency and requirements for selenoproteins are associated with increased risk from a number of medical conditions including cancer, CVD, altered immune function, male infertility, inflammatory disorders, auto-immune thyroid disease, viral infection and several others (13), some of which will be discussed below.

**Immune Function**

It has been recognized since the 1970s that adequate Se intake is necessary for optimal immune function (17). Se deficiency seriously impairs cell-mediated and humoral immunity and appears to play a part in the pathogenesis and exacerbation of some chronic inflammatory viral diseases. The selenoproteins are involved in most aspects of cell biochemistry and function, including antioxidant defence and thyroid hormone metabolism, so there is much potential for Se to influence immune function. Supplemental Se has been shown to improve immune function in British residents who consume diets that are marginal in Se content (18).

**Protection against viral infection and/or replication**

Se deficiency is linked to the occurrence and virulence of disease progression of some viral infections (19). In Se deficient hosts, harmless viruses can become virulent. This may be the additional factor involved in the development of Keshan disease. When Se deficient mice were inoculated with a benign myocarditic strain of Coxsackie’s virus, mutations occurred in the genome to give a cardio-virulent form of the virus that caused myocarditis. This conversion was accompanied by changes to the genetic structure of the virus so that its genome closely resembled other known virulent CVB3 strains. It was shown that GPx1 was essential for the avoidance of oxidative damage to the RNA-viral genome that results in the myocarditic mutations (19). More recent research has shown that a mild strain of influenza virus, A/Bangkok/1/79, also exhibits increased virulence when give to Se-deficient mice. These findings may also be applicable to other RNA viruses such as poliovirus, hepatitis or HIV.

The acquisition of viral virulence by mutation is being discussed as a phenomenon that might contribute to the emergence of new pathogens in general (20). The emergence of new strains of influenza virus in China or the first crossing over of the HIV virus to human beings in the selenium deficient population of Zaire might also be explained. Now, some manufacturers of dietary supplements are using the current fear associated with bird flu to market their supplements suggesting that they might offer protection against avian flu.
Inflammation
Se is involved in several biochemical pathways associated with rheumatic diseases. As an antioxidant, GPx can hinder propagation of free radicals, and as an anti-inflammatory agent it can diminish inflammatory prostaglandin production and modulate the respiratory burst (13). Researchers hypothesize that Se status may affect disease severity or progression. The benefit of Se supplementation in patients with rheumatoid arthritis remains to be demonstrated (21). Similarly, some have speculated that Se may reduce the severity of the inflammatory reaction in asthma (22).

Male infertility
Se has long been recognized as essential for successful reproduction in livestock in animal husbandry (13). In early development, the selenoenzyme GPx4 (phospholipid GPx) may regulate proliferation and/or differentiation, while in mature spermatozoa, GPx4 represents a structural component of the mitochondrial matrix (23). This dual role of GPx4 in both formation and normal development of spermatozoa is believed to explain Se dependency. A small number of human studies suggest that Se is essential for male fertility. Supplementation of a group of sub-fertile British males with Se for three months significantly increased sperm motility and improved fertility (24), but these observations were not repeated in sub-fertile Polish men (25). As this selenoprotein in high on the hierarchy of selenoproteins, the New Zealand population is unlikely to be deficient in this enzyme.

Thyroid disorders
Myxoedemetic cretinism, a disorder of skeletal growth, neurological development, hypothyroidism and thyroid atrophy occurs in areas of both severe Se and iodine deficiency. This contrasts with neurological cretinism, which occurs in areas of very severe iodine deficiency and deficient or adequate Se (26). These conditions have never occurred in New Zealand, in spite of a history of iodine deficiency goitre prior to salt iodization in the 1930s (27). There is some evidence of associations between low Se status and elevated thyroid volume, and alterations in thyroid hormone concentrations in individuals with and without low iodine status, but at present there is no direct evidence for Se-dependent alteration of deiodinase expression or activities in humans in vivo (28). Our research indicates that the mild Se deficiency in New Zealand does not affect expression of deiodinases, because of their high position in the hierarchy of selenoproteins, the New Zealand population is unlikely to be deficient in this enzyme.

Possible beneficial effects ‘supranutritional intakes: requirements for optimal health
Around the time of the review of the US/Canadian Dietary Reference Intakes, there was a move to consider another criterion when making nutrient recommendations, the intake that allows for optimal nutrition and optimal health. This has renewed interest in the possible health effects of nutrients, such as antioxidants, in larger than recommended intakes, often termed ‘supranutritional’ intakes. The beneficial effects might include maintenance of good health and the reduction of other disease not caused by nutritional deficiencies, such as cancer and CVD. Se is now regarded as one of these nutrients, as evidence grows for a protective effect against some forms of cancer, and enhancement of immune function (13). However, few clinical trials have been conducted to determine whether Se intakes above the level to maximize GPx activity affect disease outcome favourably.

Selenium and cancer
The evidence for beneficial effects of supranutritional intakes of nutrients is often conflicting and controversial, particularly for Se. The earliest writing on Se and cancer focussed on Se as a carcinogen, but there is increasing evidence for it’s cancer protective role (30). This comes from in vitro and animal studies, case-controlled prospective studies with human subjects and a limited number of randomized controlled trials (RCT) of Se supplementation in humans. The strongest support comes from the Nutritional Prevention of Cancer (NPC) trial, in which subjects with a risk of skin cancer were supplemented with 200µg Se/day or a placebo for several years, with the effect of Se on skin cancer as the primary outcome (31). There was no effect on skin cancer, but there was a dramatic reduction in risks of other cancers, notably prostate cancer. Some have viewed these results with caution, because they were not primary outcomes of the trial, and observations have yet to be confirmed. Furthermore, new evidence from the NPC trial showed that, although other cancer risk reductions were achieved, squamous cell carcinoma and total nonmelanoma skin cancers increased by 25% and 17% respectively in patients receiving Se (32). Further trials are necessary to confirm the findings.

New Zealand has a high incidence of certain cancers, especially prostate and colon cancers, but it is difficult to correlate this with Se status. Ferguson et al (33) have reported an inverse correlation between regional differences in soil Se levels and regional differences in incidence of colon cancer across the country. However, it is likely that any regional differences are related to importation of high Se Australian wheat, as bread and wheat products are the only major food sources of Se that show geographical variation (34, 35). Fruit and vegetables contribute little to total Se
intake, and animal foods, which provide most of our dietary Se do not show much variation in Se content because livestock in low Se areas are all supplemented.

Mechanisms of cancer prevention.
The mechanism often quoted as being the cancer-protective effect is Se’s role as an antioxidant. There is some evidence for a role for selenoproteins in cancer prevention through antioxidant roles of GPx enzymes, redox regulation roles of thioredoxin reductase and hormonal regulation of deiodinases (30, 36). However, the known metabolic functions of the selenoproteins do not fully explain the chemotherapeutic effects. In most studies preventive effects were observed at Se dosages that far exceeded those needed for maximal expression of GPx enzymes. Thus, should the cancer protective effect of Se be confirmed, evidence suggests that intakes required are higher than recommendations based on those necessary to prevent nutritional deficiency or for optimization of functional proteins (15). Low molecular Se compounds have also been implicated. There is evidence for anti-carcinogenic activities of several intermediary metabolites of Se including seleno-D-gluathione, hydrogen selenide, methyl selenol and methylated metabolites of selenide, which are directly anti-carcinogenic (30). In fact Drake (37) provides convincing arguments that pro-oxidative rather than antioxidant properties of Se compounds best account for their observed anti-cancer effects. This supports the hypothesis that supranutritional exposures of Se can reduce cancer risk. However, it is likely that Se can function as a cancer preventive agent through both nutritional and supranutritional mechanisms.

Nutrigenomics is the study of how individual genetic differences can affect the way we respond to nutrients in foods we eat, and therefore, how gene makeup affects our nutrient requirements and susceptibility to disease. This usually refers to the association of a gene variant (single nucleotide polymorphism, SNP) with differential responses to nutrients and then relating this to disease states. Several different SNPs in selenoproteins have been identified (36). Research suggests that for some individuals who are genetically predisposed to cancer, requirements for Se differ from those in the normal human population (36). For example, individuals carrying a nucleotide polymorphism at codon 593 of human GPx1, which changes cytosine (C) to thymine (T), appear to have an increased risk of lung, breast and prostate cancers (36). This risk may be associated with increased susceptibility to DNA damage and to differences in response to Se supplementation.

Cardiovascular disease
Although early epidemiological studies suggested that the risk of CVD is higher in people with low Se intake, evidence from more recent clinical studies is controversial and inconclusive (13, 38). The only large RCT investigating the efficacy of Se supplementation alone in the prevention of CVD, indicated no overall benefit of supplementation (39). Nevertheless, because of the antioxidant potential of several selenoproteins, a number of potential links between Se status and mechanisms leading to atherosclerosis have been studied, including LDL oxidation, platelet aggregation and endothelial dysfunction (13, 20). However, the hypotheses implicating the possible role of selenoproteins in these processes are also controversial (20).

Conclusions
In less than 40 years Se has gone from being a feared toxin to an essential nutrient and potential anti-carcinogenic agent. Recommendations for Se as outlined in the new New Zealand Nutrient Reference Values are based on physiological requirements for optimal levels of selenoproteins such as GPx (6), but there is a move towards recommending higher intakes of Se for prevention of cancer and other chronic diseases. It is clear that there may be different levels of requirements depending on criteria used (15). In New Zealand, we are still are left with the paradox of a community with low Se status living in a naturally Se-deficient environment for animals, yet with apparently healthy human residents, albeit with relatively high incidence of CVD and some cancers. There is an increasing tendency towards supplementation and fortification of foods with some nutrients, but for Se, it is not clear whether this is necessary, even less so now our Se status is increasing (40). We were often criticised for not recommending intervention on a national scale, but in fact the evidence available has not been strong enough to justify it, particularly in this era of evidence-based medicine and public health. The definitive studies on possible cancer or CVD protective effects have yet to be completed. Furthermore, we need to be aware of the risk from high intakes of a trace element such as Se, which has a long early history of toxicity effects.

References