Review

The importance of selenium to human health

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The essential trace mineral, selenium, is of fundamental importance to human health. As a constituent of selenoproteins, selenium has structural and enzymic roles, in the latter context being best-known as an antioxidant and catalyst for the production of active thyroid hormone. Selenium is needed for the proper functioning of the immune system, and appears to be a key nutrient in counteracting the development of virulence and inhibiting HIV progression to AIDS. It is required for sperm motility and may reduce the risk of miscarriage. Deficiency has been linked to adverse mood states. Findings have been equivocal in linking selenium to cardiovascular disease risk although other conditions involving oxidative stress and inflammation have shown benefits of a higher selenium status. An elevated selenium intake may be associated with reduced cancer risk. Large clinical trials are now planned to confirm or refute this hypothesis. In the context of these health effects, low or diminishing selenium status in some parts of the world, notably in some European countries, is giving cause for concern.

The trace mineral selenium is an essential nutrient of fundamental importance to human biology. This has become increasingly obvious as new research has shown a hitherto unsuspected role for this element in areas important to human health.

As selenocysteine, the 21st aminoacid, selenium is a component of selenoproteins, some of which have important enzymic functions.[1] It has now been recognised that all these enzymes are selenium-dependent, generally with selenocysteine at the active site.[1] Here selenium functions as a redox centre, for instance when the selenoenzyme, thioredoxin reductase, reduces nucleotides in DNA snyhthesis and helps control the intracellular redox state,[2] or when the selenium-dependent iodothyronine deiodinases produce active thyroid hormone from inactive precursor.[1] The best-known example of this redox function is the reduction of hydrogen peroxide and damaging lipid and phospholipid hydroperoxides to harmless products (water and alcohols) by the family of selenium-dependent glutathione peroxidases.[1–3] This function helps to maintain membrane integrity,[3,4] protects prostacyclin production,[4] and reduces the likelihood of propagation of further oxidative damage to biomolecules such as lipids, lipoproteins, and DNA with the associated increased risk of conditions such as atherosclerosis and cancer.[3,4] About 35 selenoproteins have been identified, though many have roles that have not yet been fully elucidated.[5] Table 1 details known selenoproteins that carry out nutritional functions of selenium.[1–3,5–9]

Selenium has additional important health effects particularly in relation to the immune response and cancer prevention, which are almost certainly not exclusively linked to these enzymic functions.

Health conditions associated with selenium deficiency

Recognition of the important role of selenoproteins in metabolism helps to explain the adverse consequences of selenium deficiency in human and animal health. Selenium enters the food chain through plants, which take it up from the soil. Selenium deficiency has therefore been identified in parts of the world notable for their low soil content of selenium, such as volcanic regions.[10] Acid soils and complexation, frequently with iron or aluminium, also reduce the uptake of selenium by plants, as in many parts of Europe.[10] Animal deficiency-diseases have been identified since the 1950s on a wide scale in livestock in countries, including the UK, that have such soil conditions, examples being reproductive impairment, growth depression (ill-thrift), and white-muscle disease, a myopathy of heart and skeletal muscle principally affecting lambs and calves.[10] These disorders have had such serious economic consequences that measures to increase selenium intake (such as top dressing of pasture land with selenised fertilisers, mineral mixes, boluses, drenches) are now applied to prevent their occurrence.[10]

Human dietary intakes also range from high to low according to geography. Human selenium-deficiency diseases have been recognised in some regions: Keshan disease, an endemic cardiomyopathy, and Kashin-Beck disease, a deforming arthritis, were first identified in an area of China where the soil is extremely low in selenium.[10] Both these conditions are believed to have other causative cofactors.

Health effects of less-overt selenium deficiency

There is evidence that less-overt selenium deficiency can have adverse consequences for disease susceptibility and the maintenance of optimal health. Low selenium status may contribute to the aetiology of the disease process but in some cases it may be an outcome of the condition itself and may exacerbate disease progression (eg, HIV infection). These difficulties are largely overcome in prospective epidemiological studies, particularly where the first few years of follow-up are excluded from the analysis, and in randomised controlled trials of selenium supplementation.

Immune function

Numerous studies suggest that deficiency of selenium is accompanied by loss of immunocompetence, probably not unconnected with the fact that selenium is normally found

Lancet 2000; **356:** 233–41

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Selenoprotein	Function
Glutathione peroxidases (GPx1, GPx2, GPx3, GPx4)	Antioxidant enzymes: remove hydrogen peroxide, and lipid and phospholipid hydroperoxides (thereby maintaining membrane integrity, modulating eicosanoid synthesis,modifying inflammation and likelihood of propagation of further oxidative damage to biomolecules such as lipids, lipoproteins, and DNA).[1,2,3,6]
(Sperm) mitochondrial capsule selenoprotein	Form of glutathione peroxidase (GPx4): shields developing sperm cells from oxidative damage and later polymerises into structural protein required for stability/motility of mature sperm.[7]
Iodothyronine deiodinases (three isoforms)	Production and regulation of level of active thyroid hormone, T3, from thyroxine, T4.[1]
Thioredoxin reductases (probably three isoforms)	Reduction of nucleotides in DNA synthesis; regeneration of antioxidant systems;[2] maintenance of intracellular redox state, critical for cell viability and proliferation;[2] regulation of gene expression by redox control of binding of transcription factors to DNA.[2]
Selenophosphate synthetase, SPS2	Required for biocynthesis of selenophosphate, the precursor of selenocysteine, and therefore for seleoprotein synthesis.[2]
Selenoprotein P	Found in plasma and associated with endothelial cells. Appears to protect endothelial cells against damage from peroxynitrite.[1,2,8]
Selenoprotein W	Needed for muscle function.[1,2]
Prostate epithelial selenoprotein (15kDa)	Found in epithelial cells of ventral prostate. Seems to have redox function (resembles GPx4), perhaps protecting secretory cells against development of carcinoma.[9]
DNA-bound spermatid selenoprotein (34 kDa)	Glutathione peroxidase-like activity. Found in stomach and in nuclei of spermatozoa. May protect developing sperm.[9]
18 kDa selenoprotein	Important selenoprotein, found in kidney and large number of other tissues. Preserved in selenium deficiency.[5]

Table 1: **Known selenoproteins that carry out nutritional functions of selenium**

in significant amounts in immune tissues such as liver, spleen, and lymph nodes. Both cell-mediated immunity and B-cell function can be impaired.[6]

By way of contrast, supplementation with selenium, even in "selenium-replete" individuals, has marked immunostimulant effects, including an enhancement of proliferation of activated T cells (clonal expansion).[11] 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 tumour cells. Natural-killer-cell activity was also increased. Supplementation resulted in a 118% increase in cytotoxic-lymphocyte-mediated tumour cytotoxicity and an 82% increase in natural-killer-cell activity compared with baseline.[11]

The mechanism appears to be closely related to the ability of selenium to upregulate the expression of receptors for the growth-regulatory cytokine interleukin-2 on the surface of activated lymphocytes and natural-killer cells, thereby facilitating their interaction with interleukin-2. This interaction is crucial for clonal expansion and differentiation into cytotoxic T cells. Even at so-called replete levels of plasma selenium produced by normal dietary intake in the USA (120–134 μg/L), supplementation with 200 μg selenium per day has considerable immunoenhancing effects.[11] Such effects have been demonstrated by the same research group in patients undergoing therapy for head and neck cancer.

Additionally, cells of the immune system may have an important functional need for selenium. Activated T cells show upregulated selenophosphate synthetase activity,[12] directed towards the synthesis of selenocysteine, the essential building block of selenoproteins, which shows the importance of selenoproteins to activated T-cell function and the control of the immune response. The mRNAs of several T-cell-associated genes (eg, interleukin-2-receptor α-subunit, CD4) have the theoretical capacity to encode functional selenoproteins, suggesting that the roles of selenium in the immune system may be more diverse than previously suspected.[13]

Viral infection

Selenium deficiency is linked to the occurrence, virulence, or disease progression of some viral infections.[14]

Beck and colleagues have shown that in a selenium-deficient host harmless viruses can become virulent,[15] a situation that is likely to be relevant to the development of Keshan disease. When selenium-deficient mice were inoculated with a benign strain of the coxsackie virus (CVB3/0), mutations occurred in the genome to give a cardiovirulent form of the virus that caused myocarditis with similarities to that seen in human beings. Furthermore, when the virus from these mice was inoculated into mice that had adequate selenium, it still induced heart damage, showing the irreversibility of the mutation. In the case of the coxsackie virus, six separate point mutations were identified with the development of virulence, causing myocarditis in the host. A similar study on mice that were unable to make glutathione peroxidase (GPx1-knock-out mice) showed that this enzyme is essential for the avoidance of oxidative damage to the RNA-viral genome that results in the myocarditic mutations.[16]

Coxsackie 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 the cardiomyopathy.[15,16] It seems probable, therefore, that human selenium deficiency similarly affects the viral genome resulting in the development of the heart pathology.

If these findings were to be applicable to other RNA viruses, such as poliovirus, hepatitis, influenza, or HIV, there would be considerable public-health implications. The steady emergence of new strains of influenza virus in China with its selenium-deficient belt, or the first crossing-over of HIV to human beings in the selenium-deficient population of Zaire, might also be explained.[15]

Selenium seems to be a crucial nutrient for HIV-infected individuals. It is a potent inhibitor of HIV replication in vitro.[17] The progress of HIV can be thought of as being synonymous with the progressive loss of CD4 helper T cells. More than 20 papers report a progressive decline in plasma selenium in parallel with the on-going loss of CD4 T cells in HIV-1 infection.[18] This decline in selenium occurs even in early stages of disease when malnutrition or malabsorption cannot be a factor.[18] In fact, plasma selenium is a strong predictor of the outcome in HIV infection. Baum and colleagues showed that selenium-deficient HIV patients are nearly 20 times more likely ($p<0{\cdot}0001$) to die from HIV-related causes than those with adequate levels.[19] Selenium deficiency is defined by these workers as a plasma concentration at or below 85 μg/L, a concentration not attained in many northern European countries—eg, a mean concentration of 60 μg/L was found in a Scottish study.[20] Baum and colleagues showed that low plasma selenium is a significantly greater risk factor for mortality than low

helper-T-cell count, by a factor of 16, and confers a more significant risk than deficiency of any other nutrient investigated. In HIV-infected children, low levels of plasma selenium were significantly and independently related to mortality (relative risk 5·96; p=0·02) and faster disease progression.[21]

Selenium also appears to be protective in individuals infected with hepatitis virus (B or C) against the progression of the condition to liver cancer.[22,23]

Viruses may be capable of hijacking the selenium supply of the host by incorporating selenium into viral selenoproteins, thereby reducing the ability of the host to mount an effective immune response. There is experimental evidence that this is possible from the work of Moss's group in the case of the pox virus, molluscum contagiosum, which makes a homologue of GPx,[24] and both theoretical and experimental evidence from Taylor's group that the capability of making viral selenoproteins (such as GPx) is common to many human viral pathogens such as HIV-1 and 2, coxsackie virus B3, hepatitis B and C viruses, and the measles virus.[25,26] Good selenium status may protect against HIV progression by maintaining host immune competence and appropriate redox control. Taylor suggests that 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 selenium conditions, however, increased oxidative stress and apoptosis activate the virus, which must replicate at higher rates to escape from a dying cell thus leading to increased pathogenic effects.

Reproduction

Selenium has long been recognised in animal husbandry as being essential for successful reproduction.[27] Idiopathic miscarriage has been shown to be associated with selenium deficiency in veterinary practice,[28] while in sheep,[28] selenium supplements have been shown to prevent early pregnancy loss.[29] Investigating whether this could also be relevant to human beings, Barrington and colleagues found significantly lower serum selenium in women who had had either first-trimester or recurrent miscarriages.[30,31] They suggest that early pregnancy loss may be linked to reduced antioxidant protection of biological membranes and DNA by low concentrations of the selenium-dependent GPx. A subsequent study found lower selenium levels in non-pregnant women who had experienced recurrent miscarriage, than in controls, but the difference did not reach significance.[32] However, the choice of control group can be criticised in this study because it did not exclude women who had had a miscarriage.

Selenium is essential for male fertility, being required for testosterone biosynthesis and the formation and normal development of spermatozoa.[33] Selenium concentration of seminal plasma correlated positively with concentration of spermatozoa in a group of subfertile Norwegian men.[34] Animals fed selenium-deficient diets show structural abnormalities in the sperm midpiece that are linked to poor motility and a tendency for the tail to break off[35] thus decreasing the chance of fertilisation. An explanation for these findings has been afforded by the work of Ursini and colleagues.[7] They found that a form of glutathione peroxidase (GPx4), believed to shield developing sperm cells from oxidative damage, polymerises in mature spermatozoa into a structural protein in the mitochondrial capsule of the midpiece region. As GPx4 accounts for about 50% of the capsule material, this polymerisation probably confers the structural integrity required for sperm stability and motility.

Work done at Glasgow Royal Infirmary supports this interpretation.[36] In studies by Scott and co-workers, supplementation of subfertile men with 100 μg selenium per day for 3 months significantly increased sperm motility. 11% of men receiving the active supplement fathered a child compared with none in the placebo group. However, administration of double the quantity of selenium to subfertile Polish men over a similar period showed no beneficial effect on sperm motility.[37]

Mood

There are a number of indications that selenium is important to the brain: during selenium depletion the brain receives a priority supply;[38] the turnover rate of some neurotransmitters is altered in selenium deficiency;[39] supplementation with selenium reduced intractable epileptic seizures in children;[40,41] low plasma selenium concentrations in the elderly were significantly associated with senility and accelerated cognitive decline;[38,42] and brain selenium concentration in Alzheimer's patients was only 60% of that in controls.[38] Furthermore, the brain is deficient in catalase,[41] thus peroxidation products such as hydrogen peroxide and primary peroxides must be removed by the antioxidant selenoenzymes.

A beneficial effect of selenium status on mood has been shown, at least when selenium status is "marginal". In three studies, low selenium status was associated with a significantly greater incidence of depression and other negative mood states such as anxiety, confusion, and hostility.[38,43,44]

In a study in the USA, selenium deprivation led to depressed mood and more hostile behaviour as measured by a questionnaire.[38] The lower the initial selenium status, the more the mood scores decreased indicating a worsening of mood, as a result of the low selenium diet. In a second US study, where individuals were fed either a low or a high selenium diet for 15 weeks, those on the low selenium diet had significantly decreased clearheaded/confused and elated/depressed subscores.[43] (The dietary selenium intake on this low-selenium diet was 32·6 μg per day, similar to current UK intakes of 29–39 μg per day).[45]

In contrast to these findings, high dietary selenium or supplementation with selenium appears to improve mood. In the US study referred to above,[43] those on the high selenium (226·5 μg per day) diet significantly improved in the clearheaded/confused, confident/unsure, and composed/anxious subscores, and total mood disturbance was significantly less. The results of this study are shown in figure 1 as the ratio of mean mood scores (six categories) in weeks 11–14 to those in weeks 2–5, for both the high and low selenium diets. A similar finding was obtained in a double-blind crossover study done in the UK, where a 100 μg selenium supplement significantly decreased anxiety, depression, and tiredness,[44] the effect being greatest in those whose diets were lowest in selenium.

Thyroid function

Although deiodinase activity is relatively protected in conditions of marginal selenium availability,[1] current

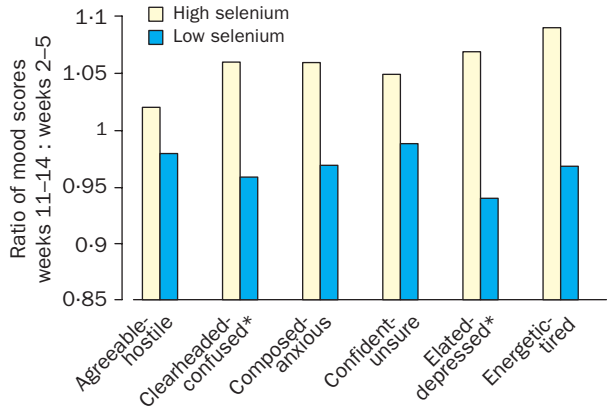

Figure 1: **Influence of selenium content of diet on mood states, measured by the "Profile of Mood States—Bipolar Form" questionnaire**

The higher the score, the better the mood. *Significant difference between groups (p<0·05). (Bar chart constructed from reference 43.)

European levels of selenium intake may nonetheless compromise thyroid-hormone metabolism. For example, plasma T3:T4 ratios in young Scottish people were as low as those normally found in elderly populations (J R Arthur, personal communication). Furthermore, selenium supplementation in a small group of elderly individuals decreased plasma thyroxine (T4) concentrations, consistent with increased deiodinase activity and improved conversion to the active hormone, T3.[46] A combination of selenium and iodine deficiency exacerbates hypothyroidism and may manifest itself as myxoedematous cretinism, such as is seen in the Democratic Republic of Congo (Zaire) where deficiencies of both these minerals exist.[47]

Cardiovascular disease

Selenium may be protective against cardiovascular disease.[4] On theoretical grounds, this hypothesis is supported by the ability of GPx to combat the oxidative modification of lipids and to reduce platelet aggregation.[4] GPx4 reduces hydroperoxides of phospholipids and cholesteryl esters associated with lipoproteins[48] and may therefore reduce the accumulation of oxidised low-density lipoproteins in the artery wall. GPx is required for the metabolism of hydroperoxides produced in eicosanoid synthesis by the lipoxygenase and cyclo-oxygenase pathways.[6] In selenium deficiency, a build-up of these hydroperoxides inhibits the enzyme prostacyclin synthetase that is responsible for the production of vasodilatory prostacyclin by the endothelium, but stimulates the production of thromboxane, which is associated with vasoconstriction and platelet aggregation.[4] The balance is therefore tipped towards the proaggregatory state. In men with coronary artery disease, platelet aggregability is inversely related to selenium status.[4,49]

Prospective epidemiological studies have had mixed findings. While Salonen and colleagues found a two-fold to three-fold increase in cardiovascular morbidity and mortality for individuals with serum selenium concentrations below 45 μg/L compared with individuals above that concentration at baseline,[50] Virtamo's group found no significant associations with selenium concentrations above and below that cut-off point except for stroke mortality.[51] A study by Suadicani and colleagues showed that middle-aged and elderly Danish men with serum selenium below 79 μg/L had a significantly increased risk of ischaemic heart disease.[52] However, about half a dozen other studies have not shown a clear association between cardiovascular risk and low selenium, although these differ from the above studies in having included few or no people with low selenium concentrations.[4,53] That a low selenium status may be relevant was suggested by the findings of Kardinaal and colleagues in the ten-centre EURAMIC study where a significant inverse association between toenail selenium levels and risk of myocardial infarction was shown only for the centre with the lowest selenium (Germany).[54] Thus the effect may only be apparent in populations of low selenium status, lower than the concentrations obtaining in the USA and a large part of Europe. The disparity between studies may also be explained to some extent by the status of other antioxidants such as vitamin E, which may compensate for a deficiency in selenium in protection against atherosclerosis.[54]

A further factor to be taken into consideration when assessing these studies is that atherosclerosis is an imflammatory state and will provoke the acute-phase response to a degree related to its severity. Being an acute-phase reactant,[55] some fall in plasma selenium concentration might be expected in people who have atherosclerosis, even before the occurrence of an event.

Other oxidative-stress or inflammatory conditions

Selenium behaves both as an antioxidant and anti-inflammatory agent. This is because selenium in its antioxidant role, notably as GPx, can: reduce hydrogen peroxide, lipid and phospholipid hydroperoxides, thereby dampening the propagation of free radicals and reactive oxygen species; reduce hydroperoxide intermediates in the cyclo-oxygenase and lipoxygenase pathways diminishing the production of inflammatory prostaglandins and leukotrienes; and modulate the respiratory burst, by removal of hydrogen peroxide and reduction of superoxide production.[6]

Any condition associated with increased oxidative stresss or inflammation might be expected to be influenced by selenium levels, which may be the case in rheumatoid arthritis, pancreatitis, and asthma.

In a case-control study nested within a Finnish cohort of 18 709 men and women who had no arthritis at baseline, the adjusted relative risk between the highest and lowest tertiles of serum selenium was 0·16 (p for trend=0·02) for rheumatoid-factor-negative arthritis.[56] There was no association for rheumatoid-factor-positive disease.[56] In a double-blind randomised trial in a small group of patients with rheumatoid arthritis,[56] supplementation with 200 μg selenium as selenium-yeast for 3 months, significantly reduced pain and joint involvement.[57]

There is evidence for a protective effect of selenium in pancreatitis, a disorder associated with a high level of oxidative stress. At Manchester Royal Infirmary, administration of selenium (600 μg per day) along with other antioxidants to patients with chronic and recurrent pancreatitis significantly reduced pain and frequency of attacks. Treatment has been revolutionised by obviating the need for surgery for pancreatic pain.[58] Selenium has also shown benefit in acute pancreatitis. In a small controlled trial in Rostock, Germany, intravenous administration of selenium to patients

with acute necrotising pancreatitis reduced mortality from 89% in controls to zero in the treatment group.[59]

A protective relationship was found between dietary selenium intake and asthma in adults in a large population-based case-control study in London (odds ratio per quintile increase=0·84; p=0·002).[60] In a small nested case-control study, current wheeze among New Zealand children was more common in those with low concentrations of selenium in serum samples collected 8 years previously (odds ratio=3·1).[61] Another small study in intrinsic asthmatics showed significant clinical improvement on supplementation with selenium at 100 μg per day as sodium selenite.[62]

Selenium supplementation may be of benefit in preventing ischaemia-reperfusion injury: a selenium-enriched diet had a significant effect ($p<0·05$) in preventing reperfusion-induced arrhythmias in an animal model.[63]

Cancer

Epidemiological studies since the 1970s have provided evidence of an inverse relation between selenium intake and cancer mortality. In a study by Schrauzer and colleagues,[64] dietary intake of selenium in 27 countries was found to correlate inversely with total age-adjusted cancer mortality, while in an investigation of the relation between forage-crop selenium and county levels of cancer mortality in the USA, cancer mortality rates for the major cancer sites were found to be significantly higher in low selenium counties.[65]

In prospective studies published in the 1980s and early 1990s involving from 8000 to 11 000 individuals, low selenium 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 selenium concentration,[66,67] although in one case[67] the effect was only apparent in men.

Some later studies have reinforced the beneficial effect of higher selenium status. A nested case-control study within a cohort of 9000 Finnish individuals showed the adjusted relative risk of lung cancer between the highest and lowest tertiles of serum selenium to be 0·41.[68] For hepatocellular carcinoma (HCC), a significant inverse association was shown between selenium concentrations in stored plasma and later development of the disease in a cohort of 7342 Taiwanese men with chronic hepatitis-virus (B or C) infection, a risk factor for the development of this disorder.[23]

A prospective study on the association between selenium intake and prostate cancer involved 34 000 men from the Harvard-based Health Professionals' Cohort Study.[69] Those in the lowest quintile of selenium status, as measured by toenail selenium, were found to have three times the likelihood of developing advanced prostate cancer as those in the highest quintile (p for trend=0·03). Only cases diagnosed more than 2 years after collection of the samples were counted.

There have been few intervention trials with selenium as a single agent. Some of these have been done in China where HCC is the third highest cause of cancer mortality. There are several hot-spots where the incidence of HCC is particularly high. One of these is the Qidong county, around 40 miles north of Shanghai. In this region about 15% of adults carry the hepatitis B surface antigen and these people are 200 times more likely to develop HCC. In a study where 226 hepatitis B antigen carriers were randomised to either 200 μg of selenium yeast or placebo, no case of HCC occurred in the supplemented group after 4 years, while seven individuals in the placebo group had developed HCC.[22]

In another study, 130 000 people from five townships were recruited. The people of one township had their salt fortified with selenium as sodium selenite (at 15 mg per kg). The other townships had unfortified salt. After 6 years the incidence of HCC had fallen by 35% in the supplemented township while remaining unchanged in the control townships.[22]

The Nutritional Prevention of Cancer (or NPC) Trial, carried out by Clark and co-workers in the USA, was the first double-blind, placebo-controlled intervention trial in a western population, designed to test the hypothesis that selenium supplementation could reduce the risk of cancer.[70] In 1312 individuals with a history of non-melanoma skin cancer who were randomised to placebo or 200 μg selenium per day (as selenium yeast), 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 (p=0·002) and 37% lower total cancer incidence (p=0·001) with 63% fewer cancers of the prostate, 58% fewer cancers of the colon, and 46% fewer cancers of the lung.

Analysis of treatment effect in the NPC trial by initial plasma selenium status showed that the strongest effect was seen in people in the lowest tertile of plasma selenium, ie, those whose plasma selenium level was below 106 μg/L at entry to the trial (table 2).[71] Selenium supplementation reduced the risk of cancer in this tertile by 48%.

Plasma or serum selenium concentrations (more or less equivalent) measured within the 1990s in a selected number of European locations are shown in figure 2. The upper level of the bottom tertile in the NPC trial is marked on the figure and these locations fall well within that tertile. Consequently, it might be predicted that a repeat of the NPC trial in these European locations would show a large treatment effect.

The NPC trial was carried out in a region where dietary selenium intake is 90 μg per day,[70] low in US terms, but already well above the level needed to optimise selenoenzyme activity.[72] While this observation does not preclude a role for the selenoenzymes in cancer prevention, it suggests the operation of additional important mechanisms. Thus the anticancer effect of selenium may relate more closely to its ability to enhance the immune response or, more likely, to its ability to produce anti-tumorigenic metabolites (eg, methyl selenol or its precursors) that can perturb tumour-cell metabolism, inhibit angiogenesis, and induce apoptosis of cancer cells.[66,73] In this context, there is considerable interest in defining the species of selenium present in selenium yeast (of which the major proportion is believed to be selenomethionine) with a view to identifying the most active anticarcinogenic component.

Baseline plasma selenium (μg/L)	Selenium cases	Placebo cases	Relative risk	95% CI	p
<106	28	56	0·52	0·33–0·82	0·005
106–121	34	49	0·64	0·40–0·97	0·40
>121	45	41	1·00	0·65–1·54	0·99

Table 2: **Total cancers 1983–96 by plasma selenium level at baseline**

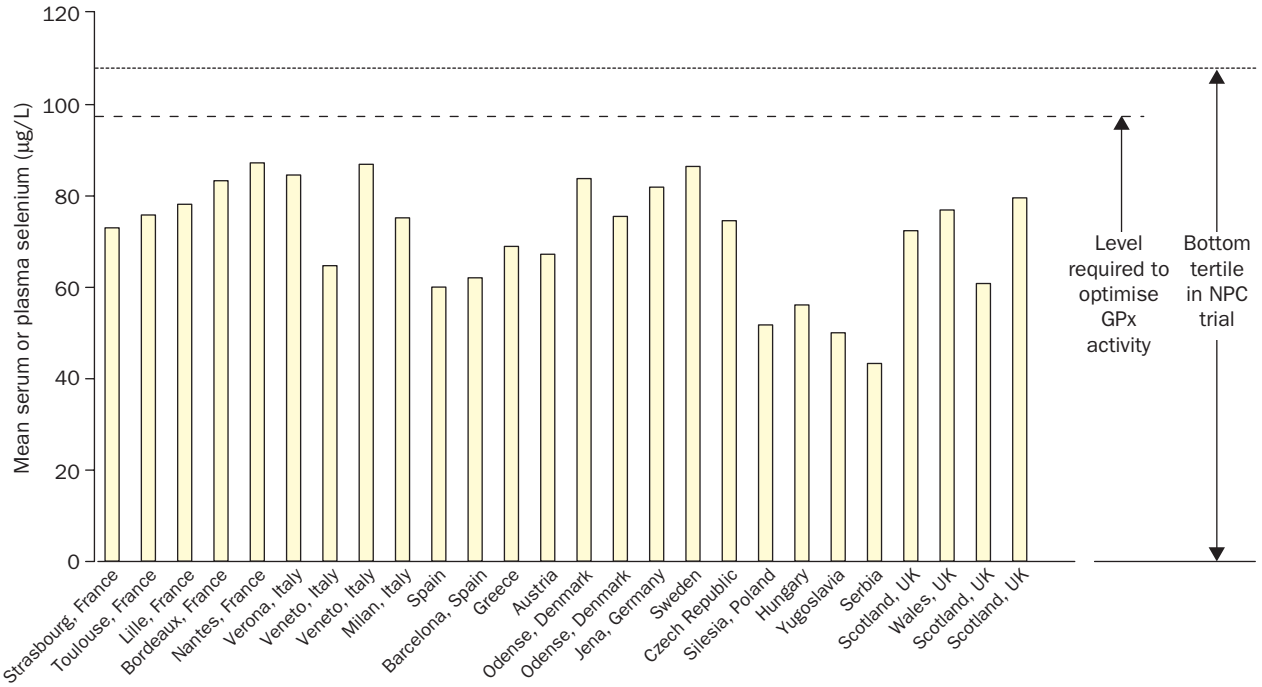

Figure 2: **Mean concentrations, measured since 1990, of serum or plasma selenium in Europe compared with NPC trial levels and concentration required for optimal plasma GPx activity[72,76]**
Sources of data available from the author.

Current selenium intake and status in Europe

Selenium intakes in most parts of Europe are considerably lower than in the USA, soils being a poorer source of selenium.[74] Selenium intake levels in some European countries are shown in table 3. When considering the adequacy or otherwise of these levels, we need to have appropriate standards against which to compare them. There is no consensus on this issue.

The UK Reference Nutrient Intake (NRI) of 75 μg per day for men and 60 μg per day for women has been determined as the intake believed to be necessary to maximise the activity of the antioxidant selenoenzyme GPx in plasma,[74] which occurs at a plasma selenium concentration around 95 (range 89–114) μg/L.[72,76] Current UK intakes are only about half the RNI, having declined considerably over the past 25 years.[77] The significant inverse correlations found between baseline selenoenzyme activities in UK individuals and percentage change in activity upon supplementation suggests suboptimal enzyme activity at the current intake.[78] This may have implications for normal cell metabolism and disease risk,[78] not only in the UK but in other European countries with intakes in the same range (table 3).

The American Recommended Dietary Allowance (RDA), revised in April, 2000, is derived from two studies that investigated the selenium intake required to achieve plateau concentrations of plasma GPx,[79] namely the Chinese study from which the previous RDA (70 and 55 μg per day for men and women, respectively) was derived, and a 1999 New Zealand study.[76] The Panel on Dietary Antioxidants and Related Compounds arrived at a new RDA of 55 μg per day for both men and women, choosing, by their own admission, to interpret the New Zealand data in a conservative manner. Using the interpretation of the New Zealand data published by the authors themselves in the *American Journal of Clinical Nutrition*,[76] and the method of computation applied by the Panel, I calculate the RDA to be the considerably-higher value of 73 μg per day. This apparent disparity would appear to justify a further carefully-designed study.

Country	Intake (μg per day)	Information source
UK	29–39	UK Ministry of Agriculture, Fisheries, Food, 1997
Belgium	28–61	Robberecht and Deelstra, 1994
France	29–43	Lamand and colleagues, 1994
Germany (Bavaria)	35	Kumpulainen and Salonen, 1996
Netherlands	67	Kumpulainen, 1993
Denmark	38–47	Danish Government Food Agency, 1995
Sweden	38	Kumpulainen, 1993
Switzerland	70	Kumpulainen, 1993
Poland	11–24 (estimate)	Kvícala and colleagues, 1995, 1997
Slovakia	38	Kadrabova, 1998

Table 3: **Daily selenium intakes in some European countries**

Arguments can be advanced that full expression of GPx activity is not necessary. A WHO/FAO/IAEA expert group, working from the Chinese data referred to above, recommended an intake level of only 40 μg per day for men and 30 for women, on the arbitrary basis that only two-thirds of the full expression of GPx activity was required.[80]

Both the Chinese and New Zealand studies, on which these recommendations are based, were small supplementation studies where selenium of good bioavailability (selenomethionine) was administered to individuals whose excretion patterns were likely to have been well adapted at the outset to selenium conservation.[72] Generalisability to other population groups or other forms of selenium intake is therefore not absolute.

If the requirement of saturation of GPx activity in the platelets, rather than the plasma, is used as the measure of selenium repletion, then a higher level of intake is needed, ie, around 80–100 μg per day.[81]

When considering requirements, the following factors should be borne in mind: the form of selenium ingested afffects the response of the selenoenzymes;[76,78] the concentration of some selenoenzymes is affected more than others by scarce selenium supply, owing to the hierarchy of selenoprotein expression;[5] there is significant

($p<0{\cdot}001$) variation between individuals in the extent of the response of the selenoenzymes to supplementation, therefore requirements will differ between individuals in the same population;[78] and adaption to low selenium intake can occur by sparing excretion.[72]

At low, or fairly low, selenium intake; serum or plasma selenium is well correlated with erythrocyte GPx activity.[10] At higher intakes, GPx activity reaches a plateau.[10] With the caveats mentioned above, serum or plasma selenium, being readily accessible, is therefore a useful marker of status in populations with a low or fairly low, level of intake. This situation applies in European locations (figure 2) where serum or plasma selenium concentrations are below the level required for saturation of GPx activity.[72,76] It seems, though, that levels of selenium intake that saturate the activity of plasma GPx, while satisfying the enzymic or antioxidant role of selenium, are insufficient to optimise the immune response, and reduce cancer risk. This insufficiency would be even more marked were we to accept levels of selenium intake that give only two-thirds of the full expression of GPx activity.

A new functional marker of selenium status is being sought, representative of biologically-effective concentrations. However, selenium has diverse biochemical roles. These different roles may require a range of markers of status according to the function, or disease, under investigation. A number of selenoenzymes are candidates for functional markers. It is unlikely, however, that these markers will be appropriate for roles of selenium that relate, for instance, to the production of anticarcinogenic selenium metabolites.

Sources and bioavailability of selenium

With the exception of Brazil nuts (which are said to accumulate radioactive barium: R J P Williams, personal communication) and kidney, there are few good food sources of selenium in many European countries. Crab, liver, other shellfish, and fish are moderately good sources, although studies show marked differences in the ability of selenium from fish to increase selenium status.[79,82,83] (The existence of different selenium compounds in fish, their dependence on fish species or source, or interaction wirh mercury or arsenic, known contaminants of fish, may explain this disparity.)[82,83] Many people rarely eat foods that are good sources of selenium. In North America, wheat is a good source but the same cannot be said for European wheat because of the low availability of selenium in most European soils.[74] Despite that, bread and cereals, being commonly consumed, make a substantial contribution to selenium intake in northern Europe (around 22% in the UK[45]). Meat, poultry, and fish make the biggest contribution (about 36% in the UK[45]). Selenium consumed in foods and supplements exists in a number of organic and inorganic forms including selenomethionine (plant and animal sources and supplements), selenocysteine (mainly animal sources), selenate and selenite (mainly supplements). Bioavailability and tissue distribution depend on the form ingested. For instance, selenomethionine is more effective in increasing apparent selenium status because it is non-specifically incorporated into proteins (eg, haemoglobin, albumin) in place of methionine.[72] However, it has no catalytic activity there and must be catabolised to an inorganic precursor before entering the available selenium pool. Selenomethionine is a less-available metabolic source of selenium than selenite or selenate, since these need only be reduced to selenide to provide selenophosphate, the precursor of selenocysteine, the active form of selenium in selenoproteins.[2] Despite this, organic forms (eg, high-selenium yeast), are often preferred in interventions, partly because they are less acutely toxic.[79] Such organic forms may, however, be more toxic during long-term consumption, owing to non-specific retention of selenium as selenomethionine in body proteins, rather than its excretion.

Interaction with toxic metals in the food supply

Selenium seems to reduce the toxicity of several metals by forming inert metal selenide complexes. Mercury or methyl mercury in marine foods is found combined with selenium, which may protect against mercury toxicity.[10] This binding may, incidentally, reduce the bioavailability of selenium from such foods.

Selenium research—the way ahead

The past 5 years have been an exciting time in selenium research. The previously-unsuspected role of host selenium status in the emergence of viral disease promises some new strategies for prevention and treatment.[15,19] Elucidation of the importance of novel viral selenoproteins may improve our understanding of HIV.[14,25] Baum's group is currently running two double-blind, placebo-controlled randomised trials on selenium supplementation of HIV-positive individuals: one in a cohort of 100 children from the Dominican Republic, which should provide results this year; the other in 350 drug users in Miami, scheduled to finish towards the end of 2002. Survival is the primary outcome measure.

With regard to cancer, an extended repeat of the NPC trial is now planned with cohorts in three European countries and the USA, to see if the reduction of cancer risk and mortality with selenium supplementation previously observed can be replicated in other population groups. Baseline plasma selenium concentrations in these European countries, the UK, Denmark, and Sweden would fall clearly into the bottom tertile of the NPC trial as outlined above. This new trial, the PRECISE trial (Prevention of Cancer by Intervention with Selenium), will recruit about 33 000 European individuals of whom 11 000 will be from the UK, where I am the cohort leader. Pilot studies have already begun in the UK and Denmark. As an adjunct to the 500-person UK pilot, the effect of selenium supplementation on mood and quality of life is being investigated.

Furthermore, the US National Cancer Institute has agreed to fund 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 as selenomethionine) and vitamin E on the risk of prostate cancer, in a 2×2 factorial design.

In this context, it will be interesting to see whether the 15 kDa selenoprotein found in the glandular epithelial cells of the prostate[9] is implicated in the apparently-protective effect of selenium against carcinoma in this organ.

Conclusions

Recent evidence has reinforced the importance to health of adequate selenium status. Selenium intakes may be

suboptimal with respect to disease risk, notably in populations of adults in the UK, parts of Europe and China, New Zealand, and even in the USA. Indications that this may be the case are strongest for cancer—where selenium intake at a much higher level than that required to saturate the selenoenzymes would appear to be beneficial—and HIV progression to AIDS. Further research is needed to clarify the optimal nutrition level with respect to selenium. In this context, the planned PRECISE and SELECT trials should give the definitive answer on the ability of selenium to reduce cancer risk.

If similar results were to be obtained to those of the NPC trial, addition of selenium to the food supply in countries such as the UK would be a possible outcome. This has been achieved in Finland, where selenium intakes were formerly very low, by addition of selenium to fertilisers since 1984.

A word of warning, however, is in order: while awaiting the results of PRECISE, SELECT and other clinical trials, we must be careful not to encourage the overconsumption of selenium supplements. While an intake of selenium of around 15 μg/kg bodyweight per day is thought to be without prolonged impact on human health, it must be remembered that selenium is a toxic mineral with a fairly small therapeutic window. In some sensitive individuals, the maximum safe dietary intake may be as low as 600 μg per day.[84] It would therefore seem prudent to restrict adult intake from all sources to an upper limit of 400–450 μg/day as recommended by several expert panels.[75,79,80]

I gratefully acknowledge the support of the Cancer Research Campaign for the UK pilot of the PRECISE trial. Thanks are also due to the many scientists who generously shared their results before publication.

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