Selenium – what are the issues? A review of requirements relating to different clinical settings

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Introduction

Selenium is an essential trace element. It is required for production of 25 selenoproteins. Their functions range from thyroid homeostasis, promoting fertility, optimising immune/antioxidant function[1] and cancer-risk reduction. Mild to moderate selenium deficiency occurs in several parts of the world including Europe and New Zealand[2], with implications for health status. Some areas of China are seriously deficient.

Dietary advice may vary according to which health issues are being addressed. In addition, individual circumstances and geographical location are important. The aim of this paper is to provide illustrative examples of the different clinical scenarios that might arise.

Background

Sources of dietary selenium

Selenium is incorporated into plants from soil, thence via herbivores to animals. Uptake depends on soil quality, with significant geographical variation. Heavy rainfall leaches soluble forms of selenium away. It is lower in volcanic regions. Microbial soil activity converts insoluble selenium to soluble forms, but acid pH[3], extensive organic matter or sulphur-containing fertilisers hamper this process.

Dietary selenium sources include Brazil nuts, offal and seafood, and garlic, onions, broccoli, mushrooms, cabbage, bread and cereals[1], when grown in selenium rich soils[4]. Bioavailability is improved with antioxidants (e.g. vitamin C) [5]. Cooking methods are important. Potato skins have higher levels than the flesh[4]. Food preparation affects bioavailability, lowered with boiling, with decreased pH or with added salt[4]. Since cereals are an important staple, changes to EU- sourced from USA-grain has significantly reduced UK selenium intake over the last 20 years.

Average daily selenium intakes have been geographically mapped, with Poland, UK and France recorded as significantly below levels estimated to maximise plasma GPx (antioxidant) activity. In contrast, much of North America is above this threshold.[4,6]

Selenium requirements

Among the different selenoproteins, glutathione peroxidases represent an important family (GPx1, GPx2, GPx3, GPx4, etc.) with a variety of antioxidant functions that reduce viral virulence and cancer risk while increasing thyroid protection and improving sperm motility and maturation. Other selenoproteins include iodothyronine deiodinase, required for thyroid hormone production (T3), and selenoprotein R (methionine sulphoxide reductase) which has anti-ageing properties, repairing oxidative damage to proteins.

UK RNI is 75mcg/day for men, 60mcg/day for women (calculated to maximise plasma GPx). Current estimated dietary intakes are shown in Table 1. Plasma selenium has been the most widely used clinical marker[7], however, plasma selenoprotein P concentration (with anti-cancer properties) has been judged as the best plasma biomarker for assessing optimal expression of all selenoproteins, requiring a larger Se intake than for GPx activity.[2]

In addition, individual selenium requirements increase with obesity, cigarette smoking, exposure to arsenic/mercury (e.g. as in fish)[4], CVD/infection/inflammatory conditions and with 'undernourished status' (e.g. low vitamin E levels).

Individual capacity to make selenoproteins varies. Selenoprotein P is produced in the liver, GPx in the kidneys. If these organs are compromised, a higher intake is required. SNPs in selenoprotein genes hamper efficient selenoprotein synthesis.[4]

Dietary assessment

Initial risk appraisal addresses geography, medical status, family history, nutritional status and which selenoprotein function is being considered, all within a Functional Medicine approach. Ideally selenium plasma concentrations are measured, plus C-reactive protein levels (CRP:to ensure that acute phase response is not depressing values)[1]. Increasing dietary selenium uptake is challenging, given variability in arable soils (e.g. even for Brazil nuts[4]), unless sources are known. Adequate dietary intake from European foods is hard to achieve[6], unless fortified. Supplementation provides another option, with organic sources preferred[8]. Selenomethionine is more effective than selenite in supporting plasma GPx activity[5]. Selenium yeast contains selenomethionine (~60%) plus potentially important metabolites[5]. Yeast forms a biological barrier, protecting from accidental overdose[6]. Intervention studies show Se-yeast enhances immune responses, prevents cancer and HIV progression to AIDS.

The geographic scenarios described below include:

- UK, Scotland, Poland, France with low Se exposure; and
- Mid-West USA, with more substantial background Se exposure.

The conditions addressed include HIV-positive, fertility issues, planning a pregnancy, familial hypothyroid and a family history of prostate cancer. Table 1 summarises the average intake and recommended supplementation by condition and geography.

Table 1: Summary of selenium status, supplementation of first choice and additional concerns in relation to health problem and geography[3,4,6]

	Average Se intake (mcg/day)	Plasma Se (mcg/L)	First choice Supplement	Additional issues*
HIV, *UK*	29-39	60-80	200mcg/day Se as Se-yeast	Monitor plasma Se
Fertility, *Scotland*	29-39	60	100mcg/day Se as Se-yeast	Both partners need good nutritional support. Females also need iodine, folic acid, long chain Ω3 fatty acids and may need Fe.
Elderly, *Poland,*	11-24/30-40	50	100mcg/day Se as Se-yeast	General health check to assess inflammatory status; vitamin D, B12, etc.
Mid-West USA	106	>100	None	
Planned pregnancy, *UK*	29-39	60-80	100 mcg/day Se as Se-yeast	Both partners need good nutritional support. Females also need iodine, folic acid, long chain Ω3 fatty acids and may need Fe.
Hypothyroid			200 mcg/day Se	?SNPs**

family history, *France*	29-43	70-85	as Se-yeast	Avoid goitrogens
Prostate, *UK*	29-39	60-80	100mcg/day Se as Se-yeast	?SNPs**

- plus assessment of nutrition, medical history & current status, smoking, family history followed by advice to stop smoking, improve antioxidant status, avoid obesity, increase dietary selenium, etc. as necessary, using the Functional Medicine model.
- **SNPs=single nucleotide polymorphisms

An HIV-positive man in the UK

Advice:

High selenium levels increase cellular immunity, boost T-cell production, counteract increased virulence and stop HIV developing into AIDS[3]. In selenium deficiency, normally harmless viruses can become dangerous. Selenium protects against other viruses which accompany AIDS.
Selenium yeast is a safe addition to anti-retroviral drugs.
If plasma selenium levels fail to rise >100mcg/L after three months, recommend a higher dosage (300mcg/day), since HIV can 'steal' selenium for its own metabolic needs, compromising the host immune response.

Justification:

Se-deficient HIV patients are 19.9 times more likely to die from AIDS than those with adequate levels[9]. Plasma selenium <85mcg/L carries a higher mortality risk[9] and can decline during the early stage. Significantly higher Se levels are required than to just saturate selenoenzymes. 200mcg/day taken by HIV+ individuals decreased hospital admission rates (38%) over a 2-year trial[10] and suppressed viral burden after 9 months.[11]

A Scottish couple with unexplained fertility

Advice:

Males and females: 100mcg/day selenium yeast, minimum ~6 months.

Justification:

Males: Selenium is required for testosterone synthesis and sperm formation, development, maturation and motility[6], and as an antioxidant at early spermatogenesis. Later structural integrity is conferred to the mid-piece spermatozoa region[3,6,12].
Sub-fertile Glaswegian men taking 100microg/day for 3 months demonstrated increased sperm motility and 11% achieved paternity[13], but higher doses (300mcg/d) may reduce sperm motility.
Females: low serum selenium is a risk factor for miscarriage during the first trimester.[4]

An elderly woman living in Poland. Would your advice change if she lived in the American mid-West?

Advice:

Check overall health status/risk assessment (e.g. kidney function, inflammatory state, etc.).
Reconsider supplementation levels if evidence of additional need.

Justification:

Low Se plasma status has been associated with increased mortality[14,15]. Se yeast (100mcg/day), acting as an immunostimulant, prevented age-related cognitive decline[6,16].
If this elderly woman was living in the USA? A previous study showed that 200mcg/day improved immunity in healthy volunteers[4], but I would not recommend this. I would recommend dietary sources only, in the absence of specific clinical indications supported by low plasma Se levels.

A young UK woman planning pregnancy

Advice:

Consider whether to offer iodide supplementation plus folic acid.
If +ve for thyroid peroxidase antibodies, increase supplementation to 200mcg/day during pregnancy/post-partum.

Justification:
Low Se serum has been associated with 1st trimester miscarriages/recurrent miscarriages[17] and increased risk of pre-eclampsia[18].
Pregnancy stresses the thyroid. T3 is essential for brain development and function, especially during 2nd & 3rd trimesters. Marginal iodine deficiency is relatively common in the UK. Selenium and iodine are both important for thyroid T3 function.
If autoimmune thyroiditis is suspected, confirm and supplement with 200mcg Se Methionine (+post-partum) to lower risk of post-partum thyroid disease and permanent hypothyroidism.[19]

A French woman with a family history of hypothyroidism (autoimmune thyroid disease)

Advice:
Ensure adequate iodide levels: e.g. fish, seaweed, iodised salt, supplement.
Check for anaemia and correct if necessary.
Cook cassava, millet, sweet potato, beans, cruciferous vegetables (goitrogens) thoroughly.
Justification:
Low Se levels in Europe are associated with reduced thyroid volume, increased tissue damage, goitre, and thyroid cancer. 200 microg/day of Na selenite or selenomethionine lowered inflammation and thyroid antibody levels in autoimmune thyroiditis, but 100mcg was ineffective[4].
T4 production creates H_2O_2 (ROS) during iodination of tyrosine to T4. Selenoenzymes, GPx and thioredoxin can protect the thyroid but Se deficiency means that excess ROS will not be disarmed, resulting in thyroid damage by failing to provide sufficient GPx. Selenoenzymes convert T4→T3, essential for growth, development and metabolism. Goitrogens prevent production of T3.

A middle aged man living in the UK with a family history of prostate cancer. Would our advice be different if he had been diagnosed with localised prostate cancer?

Advice:
Reassure: Prostate cancers grow slowly and have a long latency[20]. Selenium can reduce prostate cancer risk[8].
Enquire into possibility of genetic polymorphisms.
If localised prostate cancer is diagnosed later, establish plasma Se levels and adjust supplementation accordingly.
Justification:
Optimum plasma Se is 120mcg/l for the anti-cancer effect and 100mcg/l for GPx activity[8]. Selenium yeast offers diverse interventions at different phases of cancer development (risk, progression, metastases) via selenium metabolites and selenoproteins[8,20] - reducing oxidative stress/DNA damage, lowering vascular EGF, directly killing cancer cells[5]. Cancer risk reduces from between 84mcg/l and 150mcg/l. If localised cancer is diagnosed, the higher levels are necessary, correlating with cancer protective intakes of between 75-125mcg/d. Prospective studies show localised prostate cancer is more strongly linked to protective effects of Se when PSA >4ng/ml[8].
Prostate cancer treatment may employ brachytherapy radioactive seeds. Consider supplementation with 200mcg/day (as sodium selenite), since this significantly enhanced cell-mediated immunity in head and neck radiotherapy.[21]

Regarding prostate cancer, the SELECT (The Selenium and vitamin E Prevention Trial) 'interim' results have added to the debate about the efficacy of selenium supplementation, with and without vitamin E, since no change in prostate cancer incidence was observed and there was a very marginal increase in Type 2 diabetes incidence[22]. However, the National Prevention of Cancer (NPC) trial, on which SELECT was based, was undertaken in an area where Se intake was low[23,24], whereas the SELECT subjects were Se-replete[25,26,27]. Cancer risk reduction was achieved in the NPC trial among subjects with lower baseline selenium[28,29]. It has been suggested that Europe, where serum Se levels

are generally lower, would have been a more suitable place to conduct a cancer prevention trial[30]. The two trials were dissimilar in other ways too. For instance, NPC supplemented daily with 200mcg Se-yeast, whereas SELECT used 200mcg l-selenomethionine.

Therefore, in terms of prostate cancer risk in a UK subject, the most important concern is the subject's selenium status. Genomic considerations are also an important part of the picture.

Conclusion

Chronic marginal selenium intake predisposes to many chronic diseases[6]. In Europe, the challenge is to increase intake while recognising significant individual variability. Dietary sources are unpredictable. Brazil nuts may also contain harmful radium and barium[3,4]. Functional foods may help. Regarding supplementation, selenium yeast offers useful properties.

Recommendations for supplementary intake will require adjustment for geography and individual circumstances. The strengths and limitations of markers of Se status need to consider further the effects of a range of factors including different populations, varying intakes, baseline Se levels and the influence of genotype[7], both in selenoproteins and related pathways[31]. Following a study of Se-deficient Chinese subjects in Sichuan Province, China, 75mcg per day as selenomethionine was postulated as allowing full expression of selenoproteins among US residents[2], although the EC tolerable upper limit has been set at 300mcg/day.[5]

Much remains unknown about some selenoproteins and their functions[5]. Adaptation to low Se status may involve reduced excretion. Risk assessment requires a balanced judgement, since high intake may predispose to Type 2 diabetes[4,23,32], and has been found to be associated with adverse blood lipid profile[33]. Some USA manufacturers are already downgrading their supplement formulations because of this (personal communication).

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