Selenium

Selenium		Women	Men	Children		
	µg/d			2-5 y	6-9 y	10-13 y
Recommended intake	RI	50	60	25	30	40
Average requirement	AR	30	35			
Lower intake level	LI	20	20			
Upper intake level	UL	300	300			

Introduction

Selenium is found in all tissues, mainly as selenomethionine, an analogue to the sulphur-containing methionine, and as selenocysteine in various selenoproteins. The main biological functions of selenium are thought to be mediated by the glutathione peroxidase enzymes and other selenoproteins. Severe selenium deficiency may cause cardiomyopathy but, on the other hand, toxic symptoms are caused by excessive selenium intake. Organic and inorganic selenium compounds have different kinetics and different bioavailability for man.

Dietary sources and intake

Foods contain a number of selenium compounds. In animal foods there are specific selenoproteins containing selenocysteine. Foods of both animal and plant origin contain selenomethionine and possibly also some selenocysteine incorporated into proteins. Inorganic forms of selenite and selenate are used in dietary supplements but they are not normally found in food.

Selenium intake is difficult to assess on the basis of food composition databases because the composition varies annually depending on the quality of crops and the contribution of imported foods. Fish and other seafood, eggs and offal are relatively rich in selenium globally. Cereal products and vegetables grown in the Nordic countries, with the exception of Finland after 1984, have low selenium content, whereas wheat imported from North America has high selenium content. The selenium concentration of meat and milk depends on the amount of organic selenium in animal feeds. Fodder is generally enriched with selenite, which has a limited effect on the selenium concentration of meat and milk. In Finland, agricultural fertilizers

have been supplemented with selenium since 1984 (35). Plants convert inorganic selenate to selenomethionine. It has been assumed that selenium is not essential for plants, but evidence from Finland suggests that selenium at low levels has beneficial effects on plant growth via several mechanisms (36). Supplementation of fertilizers has increased the intake of organic selenium of both people and animals in Finland. Meat (40 %), dairy products and eggs (25 %) and cereal products (20 %) are the most important sources of selenium in the diet of Finns nowadays (35). In Norway and Iceland, the intake of selenium has been influenced by high-selenium wheat imported from North America. In Norway, an increased use of domestic-grown wheat the last 20 years has reduced the average selenium intake of the population, reflected in a reduction in blood selenium concentrations (37).

Different chemical forms of selenium have different bioavailability and metabolism. Organic selenium and most inorganic selenium salts are easily absorbed from the gut. Selenium in serum is most effectively increased by selenium-rich wheat or yeast, which is non-specifically incorporated into proteins. Inorganic selenite and selenate are less effective in increasing serum selenium concentration, but they effectively increase the activity of GSHPx by incorporation via selenide and selenocysteine.

Selenium intake (per 10 MJ) in the Nordic countries according to recent dietary surveys is 55-60 µg in Sweden, 40-45 µg in Denmark, 60-80 µg in Norway, 80-90 µg in Finland and around 90 µg in Iceland (35, 38, 39, Riksmaten 2010-11, 41). The average serum selenium concentration in Sweden and Denmark is 70-80 µg/L, and in Finland 110 µg/L (35, 38). The average serum concentration found in 2003 in adult Norwegian men and women was 80 µg/L. (37).

Physiology and metabolism

Water-soluble selenium compounds and dietary selenium (mainly organic selenium in forms such as selenomethionine and selenocysteine) are effectively absorbed; selenates and organic selenium somewhat better than selenites. Selenium compounds are converted to selenides before they are incorporated into specific selenoproteins. Selenomethionine is incorporated as such in a number of unspecific proteins, and inorganic selenium salts are retained less effectively since a major proportion is excreted in the urine. At high intakes, detoxified excretory products such as dimethyl selenide and trimethyl selenonium ions are formed. The former is exhaled via the lungs and the latter excreted in the urine. Dietary selenium affects the selenium concentrations in serum and red blood cells, which are useful biomarkers for organic selenium intake. Selenium concentration in toenails has been recommended as the best indicator of the long-term intake of organic selenium.

The bioavailability of selenium from fish has been poor in some studies in experimental animals, but there have been differences between various fish species. In humans, selenium has been shown to be readily available from Baltic herring and rainbow trout (1, 2). In a study with stable isotopes, selenium from trout showed apparent absorption equal to, and retention higher than, that of selenate (1). Even some human studies have suggested reduced bioavailability from fish compared with other selenium-containing foods (3, 4). The reasons for the observed differences in bioavailability are not clear. Selenium reduces the availability of mercury in fish (5).

Men and women have similar selenium concentrations in serum despite different intakes. Part of selenium in tissues is composed of functional selenoproteins. The human selenoproteome has been reported to consist of 25 selenoproteins. These include the glutathione peroxidases: cellular (cGSHPx), extracellular (eGSHPx), phospholipid hydroperoxide (phGSHPx) and gastrointestinal (giGSHPx) which, together with certain other metalloenzymes, protect tissues against oxidative damage. It is anticipated that the essentiality of selenium is based on the effect of GSHPx and other selenoproteins. The types I, II and III iodothyronine deiodinases that produce tri-iodothyronine and related metabolites from thyroxine are selenoproteins. Selenium also affects the activity of the selenoproteins thioredoxin reductases, which have a number of physiological functions (6). Selenoprotein P (SePP) is synthesised mainly in the liver and is present in plasma. It has a double function, both as Se transport protein and as an antioxidative protective enzyme, and may protect endothelial cells and low density lipoproteins against lipid peroxidation (7, 8, 9). Other selenoproteins with unknown functions are selenoprotein W and prostatic epithelial selenoprotein (10).

Requirement and recommended intake

Three main deficiency syndromes appear to exist: Firstly, a type of cardiomyopathy, affecting particularly children and young women, which is associated with low intake of selenium (<20 µg/day). It has been found in certain parts of China and is referred to as Keshan disease (11), and a similar cardiomyopathy has been observed in some isolated cases during parenteral nutrition without selenium supplementation. Secondly, an osteoarthropathy affecting children in the low-selenium areas of China, is characterized by metaphyseal involvement with swollen joints and shortened fingers and toes, and is presumably caused by selenium deficiency in combination with other pathogenetic factors. And thirdly, the combination of low intakes of iodine and of selenium can lead to myxoedema with development of cretinism, which has been described in the endemic goitre area of central Africa (12).

In two Finnish studies from the 1970s, low serum selenium levels (<45 µg/L) were associated with increased risk of cardiovascular death (13), and in Denmark men with serum selenium concentrations within the lowest third of the population, below about 75 ug/L, were reported to have increased risk of myocardial infarction (14). These observations are essentially consistent with a more recent meta-analysis of Se and coronary heart disease, which included 25 observational (14 cohort and 11 case control studies) and 6 randomized trials (15). In the meta-analysis, four of which were published after 2000, the pooled relative risk between highest and lowest blood or toenail selenium categories was 0.85 (95 % confidence interval 0.74 - 0.99). However, in the 6 randomised controlled trials the difference between the selenium supplemented groups and the placebo groups was marginal (relative risk was only reduced to 0.89 by selenium) and it was not statistically significant. But the basic selenium levels in the latter supplemented groups were higher than threshold value (45 µg/L) reported in the early Finnish studies.

Available evidence does not indicate a cause and effect relationship between selenium and traditional risk factors of cardiovascular disease. However, selenoprotein P may protect low density lipoprotein against oxidation.

The daily losses of selenium are determined by previous dietary intake and tissue stores and give only limited information about requirements. The requirement is assumed to depend on body size. Selenium intakes of 30-40 µg/day are needed in order to achieve maximal GSHPx activity in serum. In red blood cells and platelets, intakes of 80 µg/day and 120 µg/day, respectively, are needed for maximal GSHPx activity. It is not apparent, however, that maximal GSHPx activity in all tissues is necessary for optimal health. In a 40-week supplementation study in Chinese subjects with a mean body weight of 48 kg, the plasma GSHPx activity was optimised by 35 µg/day and the SePP concentration by 49 µg/d of selenium (17).

In a study of subjects with an estimated baseline Se intake of 55 µg/d in the UK, it was found that the SePP concentration was optimised by a supplement of 50 µg yeast selenium (16). Smaller doses were not studied and the effects were not analysed separately for men and women. The effect of varying selenium intakes on the activity of newly discovered selenoproteins has not been studied in humans.

Information on selenium requirements for children and pregnant and lactating women is incomplete. During continued lactation, the selenium concentration of mother's milk is reduced over time when selenium intake is less than 45-60 µg/day, but remains unchanged at intakes of 80-100 µg/day.

The recommendations of different countries have been based on a Chinese study showing maximal stimulation of plasma GSHPx activity in serum by selenium supplementation (30 µg/day) in people whose basal intake was 11 µg/day (18). In NNR 2004 the recommendation was based on the mean + 2SD of this study and adjusted for difference in mean body weight. The recommended intake was set to 50 µg/day for men and 40 µg/day for women.

Now, it appears more reasonable to base the recommendation on the optimisation of the plasma selenoprotein P concentration (16, 17). This implies that the reference intake in the Nordic countries should be 60 µg/d for men and 50 µg/d for women. The recommendation of the EU SCF and the US Institute of Medicine is 55 µg/day for both men and women (19, 20).

For pregnant and lactating women, the EU SCF recommendation is 55 and 70 µg/day, respectively, and the recent US recommendation 60 and 70 µg/day. The NNR 2004 recommendation was 55 µg/day for both pregnant and lactating women. Based on the considerations above, the NNR 2012 recommendation for pregnant and lactating women is increased to 60 µg/day. The lower intake level for adults is kept unchanged from NNR 1996, i.e. 20 µg/d. The RI values for children and adolescents are derived from the values for adults.

According to experimental animal studies and some observational epidemiological studies, higher selenium intakes than the recommended levels, might reduce the risk of certain types of cancer (21). In the Chinese Linxian supplementation study with 50 µg/d yeast selenium combined with beta-carotene and vitamin E the incidence of stomach cancer was reduced (22).

In the NPC study (Nutritional Prevention of Cancer) in USA, patients with non-melanoma skin cancer (n = 1312), were randomized to placebo or 200 µg Se/day as selenised yeast (23, 24). After 4.5 years of treatment and 6.5 years of follow-up, no effect was found on the primary end-point of non-melanoma skin cancer. However, in those subjects receiving Se, significant secondary end-point effects of 50% lower total cancer mortality were found, with fewer prostate and lung cancers. The protective effect appeared to be stronger in former smokers. Analysis of treatment effect by initial plasma Se status in this NPC trial has shown that the strongest evidence was in subjects in the lowest tertile of plasma Se at baseline, i.e. those whose plasma Se was <106 ug/L at entry, i.e. intake < 60 – 80 ug Se/day. The Se yeast supplementation was found to reduce total cancer incidence in this tertile by 49% and prostate cancer incidence by 86%. In contrast, a later Selenium and Vitamin E Cancer Prevention Trial (SELECT) (25) reported that supplementation with (organic) L-selenomethionine, when given to a population in selenium-adequate regions of USA and Canada, did not reduce the risk of prostate cancer. The possible anti-carcinogenic effects of some inorganic Se species, including metabolites from selenite or selenised yeast, have been discussed by Lee and co-workers (26) and Rayman and co-workers (27). Olm and co-workers (28) have found that selenite can act cytotoxic on some malignant cells, and may thus retard the promotion and progression of some cancer cell-lines.

There is no information from clinical trials on the effects of selenium supplementation in healthy Western populations (29). Therefore it is at present impossible to take explicitly into account in the recommendations the possible benefits of increased selenium intakes on cancer risk in Nordic populations. Some findings suggest that selenium deficiency might be associated with the development of new, more virulent virus strains (30) and that the selenium-dependent cardiomyopathy might be one example of the interaction between selenium deficiency and viral infection.

Reasoning behind the recommendation

Saturation of plasma selenoprotein P activity is today considered a better measure of adequate selenium status than the earlier used plasma GSHPx. Optimisation of selenoprotein P requires higher intake of selenium than optimisation of GSHPx. 50 µg Se/day optimised Selenoprotein P in a recent, study with Chinese participants (Xia et al 2010). Correcting for body size, this indicates a recommended dietary intake of 50 µg/d for women and 60 µg/day for men in Western populations. The recommendation for pregnant and lactating women is increased to 60 µg /day which includes an allowance for increased needs for tissue growth and lactation. For children the recommended intake levels are based on extrapolation from the adult values.

Upper intake levels and toxicity

Selenium intoxication is rare in man but well known in animals. Acute toxicity has been observed after consumption of a large (250 mg) single dose or after multiple doses of ~30 mg. The symptoms include nausea, vomiting and garlic-like breath odour. Other toxic symptoms are nail and hair deformities and, in severe cases, peripheral nerve damage and liver damage. Because of the risk of toxicity, high doses of selenium are not recommended. A no observed adverse effect level (NOAEL) for clinical signs of selenium toxicity and a threshold of 850 µg/day for inhibited prothrombin synthesis were found in Chinese studies. An upper level of 300 µg/day

was derived by the SCF using a factor of 3 to allow for uncertainties in different studies (21).

In some cross-sectional studies, high serum selenium levels have been associated with high serum cholesterol levels (31), but randomised trials of selenium supplementation have not shown significant effects on serum lipid levels. Conflicting results have been reported on associations between selenium and type 2 diabetes. In the US population with high average selenium intake, high selenium status has been associated with increased risk of type 2 diabetes. The supplementation with 200 µg/d of selenium in patients with skin cancer in the NPC study in USA increased the incidence of self-reported diabetes, particularly in subjects with high baseline serum selenium levels (32). However, in patients with prostate cancer, selenium supplements of 200 and 800 µg/d did not affect serum glucose levels (33). In the European SU.VI.MAX study supplementation for 7.5 years with selenium 100 µg/d together with vitamins C and E, beta-carotene and zinc did not influence fasting blood glucose levels (34). There are no apparent biological mechanisms of selenium that are known to disturb glucose or lipid metabolism or insulin sensitivity.

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