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Are there functional consequences of a reduction in selenium intake in UK subjects?

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Dietary Se levels in the UK have fallen over the last 20 years and recent surveys indicate that average Se intakes are 30–40 μg/d, which is well below the current UK reference nutrient intake for adult men (75 μg/d) or women (60 μg/d). Functional consequences of this decline have not been recognised, although epidemiological data suggest it may contribute to increased risk of infections and incidence of some cancers. Previous data have indicated that biochemical changes in Se-dependent proteins occur in otherwise healthy UK subjects given small Se supplements. The current studies have focused on the effect of small Se supplements on the immune response since there is evidence of specific interactions between Se intake and viral replication, and since the potential anti-cancer effects of Se may be mediated by non-antioxidant effects of Se such as changes in immune function. Data indicate that subjects given small Se supplements (50 or 100 μg Se/d) have changes in the activity of Se-dependent enzymes and evidence of improved immune function and clearance of an administered live attenuated virus in the form of poliovirus vaccine. Responses of individual subjects to Se supplements are variable, and current work is evaluating potential explanations for this variability, including genetic variability and pre-existing Se status.

Selenium intake: Selenium supplements: Immune response: Se-dependent proteins

There is clear evidence that the dietary intake of Se has fallen in the UK and other western European countries over the last 20 years. Dietary survey data published by the UK Government indicate that the average intake may be as low as 30–40 μg/d (Ministry of Agriculture, Fisheries and Food, 1997) compared with values of approximately 60 μg/d reported in 1974. The UK reference nutrient intake (RNI) for Se is 75 μg/d for adult men and 60 μg/d for adult women (Department of Health, 1991). Rayman (1997) has compiled retrospective data indicating that this fall in dietary intake has been accompanied by a dramatic fall in circulating Se concentrations, and this finding has been supported by recent intervention studies and survey data examining UK subjects in specific geographical areas (Brown *et al*. 2000; Bates *et al*. 2002; Broome *et al*. 2004).

Data on the distribution of Se in foodstuffs indicate that meat and meat products contribute >30 % of the Se intake in the UK (Ministry of Agriculture, Fisheries and Food, 1997), and therefore it might be predicted that vegetarians or vegans are at specific risk. A small amount of data is supportive of this risk (Ministry of Agriculture, Fisheries and Food, 2000), but this finding is not universal. In the elderly there is evidence from international studies that Se levels are reduced (Berr *et al*. 1993; Olivieri *et al*. 1994, 1995), but again the small amount of data available from the UK is contradictory (Campbell *et al*. 1989; Bates *et al*. 2002).

Whether the relatively low levels in the UK diet have any functional importance is the subject of considerable debate. Rayman (1997, 2000) has argued persuasively that UK intakes are sufficiently low to warrant government intervention to help reduce the incidence of a number of chronic disorders, including various cancers and CVD, although the relevant UK Government expert committee (Department of Health, 1998) have concluded that intervention is not warranted.

Effects of selenium deficiency

Overt Se deficiency has been associated with dilated cardiomyopathy, skeletal muscle myopathy, osteoarthropathy and cretinism (in I-deficient populations), while more marginal deficiencies have been linked to increased

Abbreviations: GPx, glutathione peroxidase; RNI, reference nutrient intake.
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occurrence of some cancers, increased viral disease and a reduced immune function (Rayman, 1997, 2000). Keshan disease is a severe endemic cardiomyopathy that occurred in the Keshan region of China. It was localised primarily in areas with low soil Se content and has been effectively eliminated by Se supplementation, although an infectious agent is also thought to play a role (Ge & Yang, 1993). A Se-responsive joint disorder, Kashin-Beck disease, has also been reported in low Se areas of China. In animals Se deficiency is associated with a wider range of features, and when in combination with vitamin E deficiency in farm animals can cause commercially-important myopathies of cardiac and skeletal muscle (white muscle disease).

The level of dietary Se at which overt deficiency disorders become apparent in man is not clear. Countries such as New Zealand have long been recognised to have extensive regions with Se-deficient soils, although no overt human Se-deficiency disorders have been recognised. Epidemiological studies have linked low Se levels to an increased risk of specific cancers, including cancers of the lung, prostate, oesophagus and colon (Combs, 2001), and cancer mortality rates have been found to be markedly lower in areas of the USA with higher Se intakes compared with those where levels are lower (Clark *et al*. 1991). An apparent link between low Se levels and increased risk of cardiovascular disorders has also been identified by epidemiological studies (Salonen *et al*. 1982; Virtamo *et al*. 1985; Beaglehole *et al*. 1990).

Both animal and human studies have highlighted a link between Se status and immune function. In experimental models marginal Se deficiency can affect all components of the immune system, including the development and expression of humoral and cell-mediated responses to non-specific stimuli, leading to a general immunosuppression (Bonomini *et al*. 1995; Taylor, 1995; Finch & Turner, 1996; McKenzie *et al*. 1998; Combs, 2001). Se supplementation in experimental animals has been associated with increases in natural killer cell activity, T-cell proliferation, lymphokine-activated killer cell activity, delayed-type hypersensitivity skin responses and vaccine-induced immunity (McKenzie *et al*. 1998; Combs, 2001). Less clear evidence links dietary Se with human immune function, although supplementation with Se has been reported to increase proliferation of peripheral blood lymphocytes in response to mitogen (Peretz *et al*. 1991; Roy *et al*. 1994), increase the expression of high-affinity IL-2 receptor (Roy *et al*. 1994) and improve cytotoxic lymphocyte-mediated tumour cytotoxicity and natural killer cell activity (Kiremidjian-Schumacher *et al*. 1994).

Se deficiency has also been linked to the occurrence, virulence or disease progression of some viral infections, including HIV (Beck *et al*. 1995, 1998; Taylor, 1997). Beck *et al*. (1995, 1998) have reported findings that directly link Se deficiency with the virulence of RNA viruses. In Se-deficient mice the harmless Pircorna virus coxsackie B3 becomes cardiotoxic. When Se-deficient or glutathione peroxidase (GPx)-knock-out mice are inoculated with the benign strain of the coxsackie virus, mutation occurs in the genome to give a cardio-virulent form of the virus that causes myocarditis. This deficiency-driven evolution of pathogenicity is stable and daughter coxsackie virus isolates from the Se-deficient mice retain their newly-acquired cardio-virulence. The mechanisms are unclear, but may be a result of either an increased replication rate of virus in hosts with impaired immunity or to increased free radical damage to the viral genome (Beck *et al*. 1998).

Approaches to understanding the functional effects of a relative selenium lack

Evaluation of whether the relative deficit in UK subjects has functional consequences has been complex. The major approach followed has been to examine the responses of volunteer subjects to levels of Se supplementation that will result in a total intake exceeding the RNI. Arthur and colleagues (Brown *et al*. 2000), in Aberdeen, have examined the effect of small Se supplements on the activity of Se-dependent enzymes in leucocytes of otherwise healthy Scottish individuals. They have found that 50 μg Se/d causes variable increases in the activity of GPx, the magnitude of the changes being inversely related to the baseline activity. Thus, the inference is that subjects with the lowest initial Se status show the largest rise in Se-dependent enzyme activities following Se supplementation.

An alternative approach to the evaluation of whether the relative deficit in UK subjects has functional effects would be potentially to study the effect of Se supplements on the incidence of specific cancers or cardiovascular disorders. This type of approach is complicated by the large number of subjects that must participate in order to provide

Table 1. Summary of effects of selenium supplementation on lymphocyte function (data from Broome *et al.* 2004)*

	Group supplemented with:	
	50 μg Se	100 μg Se
T lymphocyte proliferation	Increase compared with placebo	Increase compared with placebo
Interferon-γ release	Increase compared with placebo	Increase compared with placebo and 50 μg groups
IL-10 release	Increase compared with placebo	Increase compared with placebo
IL-2 release	No significant effect	No significant effect
IL-4 release	No significant effect	No significant effect

*Groups of adult UK subjects with relatively low plasma Se concentrations (<1·2 μmol/l, approximately 60% of the total screened) were allocated to one of three groups that received daily supplements of 50 or 100 μg Se (as sodium selenite) or placebo for 15 weeks.

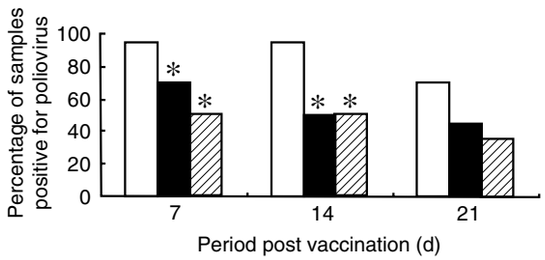

Fig. 1. Percentage of subjects in which poliovirus was detected in faeces at 7, 14 and 21 d post polio vaccination. Groups of UK adult subjects with relatively low plasma Se concentrations (<1·2 μmol/l; approximately 60% of the total screened) were either given 50 (■) or 100 (▨) μg selenium (as sodium selenite)/d or placebo (□) for 6 weeks before vaccination. Mean values were significantly different from those for the placebo group at the same time point: *$P<0{\cdot}001$. (Data derived from Broome *et al.* 2004.)

sufficient discrimination (i.e. 'power') for the study in which disease incidence is used as an end point, and by data demonstrating that Se supplements may affect disease incidence even where baseline diets exceed the RNI for Se. Clark *et al.* (1996), in a long-term double-blind placebo-controlled study in 1312 individuals in the USA, have found that supplementation with 200 μg Se/d reduces the incidence of prostate, colo-rectal and lung cancer by 63, 58 and 45% respectively. Total cancer mortality and incidence are also reduced. The baseline dietary Se intake for these subjects, approximately 90 μg/d, is in excess of the UK values and the RNI for this nutrient.

In the third type of approach the effects of Se supplementation on immune function and the rates of clearance and mutation of a Picorna virus in otherwise healthy UK subjects have been examined (Broome *et al.* 2004). Groups of adult UK subjects with relatively low plasma Se concentrations (<1·2 μmol/l; approximately 60% of the total screened) were allocated to one of three groups that received daily supplements of 50 or 100 μg Se (as sodium selenite) or a placebo for 15 weeks. All subjects received an oral live attenuated poliomyelitis vaccine 6 weeks after commencing the Se supplement or placebo and an intravenous injection of enriched stable ^{74}Se 3 weeks later. All analyses were undertaken in a double-blind manner. The Se-supplemented groups were reported to have increased plasma Se concentrations, an increase in their body exchangeable Se pool (measured from dilution of the intravenous ^{74}Se) and an increase in lymphocyte phospholipid GPx and cytosolic GPx activities. Se supplements were found to augment cellular immune response by increased production of interferon-γ and other cytokines, an earlier peak T-cell proliferation and an increase in the T-helper cell population (Table 1), although the humoral immune response was unaffected. The functional effect of this enhanced immune response

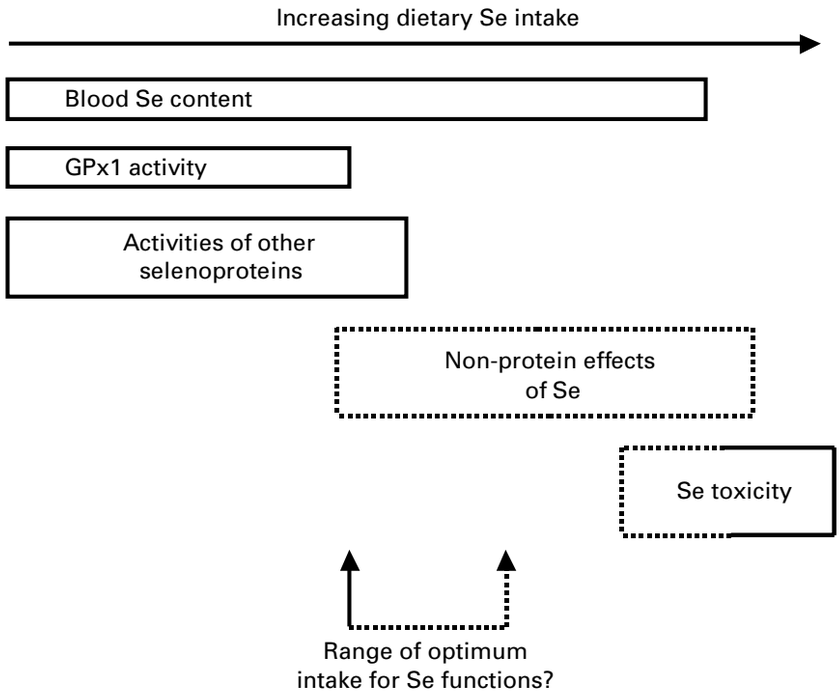

Fig. 2. Hypothetical representation of the effect of changing dietary selenium intake on circulating selenium content, selenium-dependent enzyme activities and functional effects of selenium that are not related to selenoproteins. The range of optimum intake for selenium functions is assumed to require both maximum selenoprotein activity and stimulation of non-protein effects without inducing toxicity. GPx1, glutathione peroxidase 1. (——), Variables for which reasonable experimental data are available and to which values can be ascribed; (····), hypothetical relationships for which no experimental data are currently available.

was demonstrated by a more rapid clearance of the poliovirus in the supplemented subjects (Fig. 1). Analysis of the RT–PCR products from faecal samples indicated that the recovered poliovirus product from Se-supplemented subjects contains a lower number of mutations (Broome *et al*. 2004).

The conclusion from these data is that these UK subjects have a functional Se deficit leading to a suboptimal immune status and deficit in viral handling. Careful examination of these data also illustrates that there is substantial inter-subject variability in responses. It also seems clear that there is no direct correlation between the change in activity of Se-dependent enzymes and functional changes in immune status. Most notably, supplementation with 50 μg Se causes no marked increase in lymphocyte or granulocyte GPx activities (GPx1 or GPx4), but does cause marked changes in cytokine responses of lymphocytes (Table 1) and influences viral handling by the gut (Fig. 1; Broome *et al*. 2004).

Such data suggest that alternative modes of action of Se may play a role in the functional responses seen. GPx1 (cytosolic GPx) has previously been claimed to be a storage protein for Se (Burk, 1989) and, once saturated, any further absorbed Se may not be specifically incorporated into selenoproteins but may increase the level of the seleno-metabolite pool. These small seleno-metabolites are of growing interest, as it has recently been demonstrated in cell culture that they can directly modulate a number of cellular processes, including NF-κB and other transcription factors, apoptosis and cell cycle arrest (Gasparian *et al*. 2002). These metabolites have also been shown to affect viral replication within infected cells (Cermelli *et al*. 2002). Thus, it may be that saturation of protein pools of Se is required in order to achieve maximum functional benefit. However, Se toxicity is reported to occur at relatively low levels of supplementation, with the maximum safe recommended intakes being as low as 400 μg/d in the USA (Food and Nutrition Board, 2000) and 450 μg/d (Department of Health, 1991) in the UK. A schematic illustration of these concepts is shown in Fig. 2.

In conclusion, recent data indicate clearly that UK subjects given small Se supplements show responses that indicate they initially had a functional Se deficit leading to a suboptimal immune status and deficit in viral handling. However, further research is clearly required to resolve the precise level of additional supplements that will provide optimum benefit and the mechanism of action of the additional Se.

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