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Workshop Report

Functional markers of selenium status: UK Food Standards Agency workshop report

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The workshop was organised to discuss the validity and limitations of existing functional markers of Se status in human subjects and to identify future research priorities in this area. Studies presented as part of this workshop investigated: the bioavailability of Se from different dietary sources; potential functional markers of Se status; individual variation in response to Se; the effect of marginal Se status on immune function. The workshop highlighted the need to define the relationship between functional markers of Se status and health outcomes.

Selenium status: Bioavailability: Immune function: Food Standards Agency workshops

The UK Food Standards Agency (FSA) convened a workshop on 11 June 2003 to review and evaluate current knowledge regarding the assessment of Se status. The results from recently completed studies were presented, both FSA- and non-FSA-funded, and the workshop was chaired by Professor Roger Sunde.

Background

The mineral Se is essential for a wide range of biochemical functions, which are mediated by at least twenty-five Se-containing proteins (selenoproteins); these include glutathione peroxidases (GPx), iodothyronine 5′-deiodinases, sperm capsule selenoprotein and thioredoxin reductase (Behne & Kyriakopoulos, 2001; Kryukov *et al.* 2003). Se functions in the body as an antioxidant, in thyroid hormone metabolism, redox reactions, reproduction and immune function.

Se is present in foods mainly as the amino acids selenocysteine (animal products) and selenomethionine (cereal products). Se supplements contain either Se-enriched yeast, predominantly as selenomethionine, or the inorganic forms, selenite or selenate; some Se-enriched yeast supplements may also contain significant amounts of selenite (Rayman, 2004). The inorganic forms of Se appear less effective than selenomethionine in raising plasma Se concentrations and GPx activity (Levander *et al.* 1983; Xia *et al.* 2005). The absorption, distribution and excretion of Se from food is similar to selenomethionine, but different from sodium selenite (Hawkes *et al.* 2003), making it difficult to extrapolate results from studies using inorganic forms to foods.

Dietary intakes of Se are largely determined by geochemical environment, i.e. the Se content of the soil from which foods are derived. The dietary Se intake of European populations has fallen by approximately 50 % over the last 30 years and this is probably related to the decreased use of North American wheat for bread flour and its replacement by European Union varieties, which produce flour and bread of a much lower Se content (Rayman, 1997). Current average

Abbreviations: FSA, Food Standards Agency; GPx, glutathione peroxidase; 3′UTR, 3′ untranslated region.

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Se intakes are above the threshold for deficiency diseases, but are below dietary reference values.

Dietary reference values for Se intake have been based on the assessment of the amount required to maximise blood or plasma GPx activity. Blood and plasma GPx activities plateau once intakes of selenomethionine reach 40–50 μg/d (Yang *et al.* 1987; Duffield *et al.* 1999; Xia *et al.* 2005). It is unclear what changes in GPx activity truly represent. A prospective study of patients with suspected coronary artery disease observed an inverse association between erythrocyte GPx activity and risk of CVD; sex and smoking status were associated with erythrocyte GPx activity, but there was only a weak association with plasma Se concentrations (Blankenberg *et al.* 2003). It is important, therefore, to reliably and accurately define Se status and Se requirements for optimal health.

Assessment of selenium status

There are a number of biochemical indices used to assess Se status, including short-term measures, such as plasma or serum and urinary Se concentrations, and longer-term status measures, such as erythrocyte, toenail and hair Se concentrations. There are, however, no accepted 'normal' reference ranges due to the variation in Se status between countries (Thomson, 2004).

There are limitations with the use of plasma Se concentrations as a measure of Se status. The organic forms of dietary Se, but not the inorganic forms, have been shown to be incorporated non-specifically, in the place of methionine, into erythrocyte Hb and plasma albumin (Burk *et al.* 2001). Plasma Se concentrations have also been shown to be negatively associated with C-reactive protein concentrations (Sattar *et al.* 1997; Ghayour-Mobarhan *et al.* 2005).

Measurement of individual selenoproteins, therefore, may provide more accurate and useful information than total Se alone (Patching & Gardiner, 1999). Measurement of the concentration or activity of only one selenoprotein, however, may be insufficient, because of differences in the responses of selenoproteins to various levels of Se. Animal and *in vitro* cell-culture work suggests that turnover rates differ among selenoproteins in response to Se depletion and there is preferential incorporation of Se into some selenoproteins (Patching & Gardiner, 1999; Behne & Kyriakopoulos, 2001; Pagmantidis *et al.* 2005). There is unlikely to be any single indicator of functional Se status, but rather a series of markers that apply to specific aspects of Se status (Thomson, 2004).

Four Se-containing GPx are found in different cell fractions and tissues of the body (classical, GPx1; gastrointestinal, GPx2; plasma, GPx3; phospholipid hydroperoxide, GPx4) (Arthur, 2000). There is a close relationship between plasma GPx activity, and erythrocyte GPx activity, and blood Se concentrations up to 1·27 μmol/l (100 μg/l), above which enzyme activity plateaus (Thomson *et al.* 1977; Rea *et al.* 1979). Platelet GPx may be a more sensitive indicator of increasing Se intake than erythrocyte GPx, showing increases in activity within 1–2 weeks of commencing supplementation (Levander *et al.* 1983; Thomson, 2004), which might be related to the shorter lifespan of 8–14 d of platelets, compared with 120 d for erythrocytes.

There are two selenoproteins in human plasma, GPx3 and selenoprotein P. Selenoprotein P is the major form and is involved in Se transport (Åkesson *et al.* 1994; Persson-Moschos, 2000; Burk *et al.* 2003); two isoforms of selenoprotein P may exist in human plasma (Gao *et al.* 2004).

Professor BjörnÅkesson presented results from studies investigating the plasma concentrations and activity of the selenoproteins selenoprotein P and GPx3. Selenoprotein P was shown to account for at least 40 % of total plasma Se and GPx3 for between 10 and 16 %, with the remainder probably being protein-bound selenomethionine, mainly to albumin (Huang & Åkesson, 1993).

A study of healthy adults from seventeen European regions demonstrated considerable variation in selenoprotein P concentrations (Marchaluk *et al.* 1995). Serum Se and selenoprotein P concentrations were strongly correlated, with some indication of a plateau in selenoprotein P concentration. Dietary Se intakes, for example, from fish, have been associated with increased plasma selenoprotein P and GPx3 concentrations (Åkesson *et al.* 1997; Hagmar *et al.* 1998).

Selenoprotein P concentrations were shown to increase in response to Se supplementation in subjects with a low Se status (baseline intake 40 μg/d), but not in subjects with a higher status (baseline intake 100 μg/d) (Persson-Moschos, 2000). In response to selenomethionine supplementation, selenoprotein P concentrations may plateau at a higher intake level than plasma GPx activity (Xia *et al.* 2005). The different plateaux attained by different selenoproteins could represent useful functional markers of Se status in different ranges of Se status.

Professor John Arthur presented the results from an FSA-funded trial in healthy subjects (*n* 69) with low plasma Se concentrations (< 1·0 μmol/l) who were randomised into one of three groups supplemented for 6 weeks with either 50 μg sodium selenite daily (*n* 23), 100 μg sodium selenite daily (*n* 23), or placebo (*n* 23).

Se supplementation increased plasma Se concentrations and resulted in a dose-dependent increase in plasma selenoprotein P concentrations; GPx3 activity was increased by the higher dose only. In granulocyte and lymphocyte analyses, Se supplementation had no effect on GPx4 activity and lymphocyte GPx4 mRNA abundance; however, the higher selenite dose did increase lymphocyte, but not granulocyte, GPx1 activity and 5-lipoxygenase activity.

Overall, the results support the determination of several selenoproteins as the best method to assess population Se status. Plasma selenoprotein P concentrations did not plateau at the highest supplemental dose of selenite in the population studied.

The absorption and metabolism of selenium from different dietary sources

Professor Sue Fairweather-Tait presented results from a study investigating how the dietary source of Se affects its absorption and metabolism in human subjects (Fox *et al.* 2005). Wheat, garlic, and cod fish were intrinsically labelled with ^{77}Se or ^{82}Se stable isotopes. Labelled meals were fed in random order to fourteen adults, with a minimum washout period of 6 weeks between each test meal. Apparent absorption was measured as luminal loss using a faecal monitoring technique over an 8 d period. Plasma appearance of the isotope was measured at 7, 24 and 48 h post-ingestion. Se absorption was higher from wheat (81·0 (SD 3·0) %) and garlic (78·4

(SD 13·7) %) than from fish (56·1 (SD 4·3) %). The lowest plasma concentration was observed after the fish meal at all three time points, with a peak at 24 h, whereas wheat produced the highest plasma concentration at all three time points and peaked at 7 h. Se absorption from wheat and garlic was higher than from fish, and inter-individual variation was low. The forms of Se and food constituents appear to be key determinants of post-absorptive metabolism.

The results of this project demonstrate that Se from fish, wheat, garlic, yeast and selenite is metabolised differently, demonstrating that supply to body tissues depends on chemical form.

Influence of selenium on viral pathogenesis and host immune function

The discovery that the juvenile cardiomyopathy, Keshan disease, is likely to have a dual aetiology involving both a deficiency of Se and an infection with an enterovirus has led to the study of the relationships between nutrition and viral infection (Beck *et al.* 2000, 2003). Of particular interest is the potential effect of Se deficiency in the host on the virus and the overall host–virus interaction.

Dr Jean Handy described how an amyocarditic strain of coxsackievirus B3 (a member of the enterovirus family of picornaviruses) converted to virulence when inoculated into Se-deficient mice, not only producing myocarditis in the deficient mice, but also acquiring virulence in adequately nourished animals. This conversion was accompanied by point mutations at six of seven RNA bases where the amyocarditic coxsackievirus B3 differs from a known virulent strain; each of these six positions mutated to the base found in the virulent virus (Beck *et al.* 2003).

In *GPX* knockout mice fed an Se-adequate diet, the virus developed the same virulence-enhancing mutations as in the Se-deficient mice (Beck *et al.* 1998), supporting the hypothesis that the effect of dietary Se was related to its antioxidant activity. This hypothesis is further supported by experiments in which mice fed on a diet adequate in Se, but deficient in vitamin E, were infected with the amyocarditic coxsackievirus B3, and the virus again developed similar alterations in virulence and identical base changes in the genome to those observed in Se-deficient mice (Beck, 1997). The reasons why a deficiency of antioxidants might promote accelerated viral mutation are a subject for further investigation, and could include direct oxidative damage to the viral RNA as well as oxidative stress-mediated alterations of cellular components involved in viral replication.

A mild strain of influenza, influenza A/Bangkok/1/79, also exhibits increased virulence when given to Se-deficient mice (Beck *et al.* 2001). This increased virulence is accompanied by multiple changes in the viral genome, in a segment previously thought to be relatively stable. These findings highlight the importance of adequate host nutrition to help protect against viral challenge.

Professor Malcolm Jackson presented findings from an FSA-funded study that investigated the effect of Se status and subsequent supplementation on immune function and poliovirus handling in adults with marginal Se status (Broome *et al.* 2004). Adult subjects (*n* 60) with relatively low plasma Se concentrations ($<1{\cdot}2$ μmol/l; approximately 60 % of those screened) received 50 or 100 μg Se (as sodium selenite) or placebo daily for 15 weeks in a double-blind trial. All subjects received an oral live attenuated poliomyelitis vaccine after 6 weeks and enriched stable ^{74}Se intravenously 3 weeks later.

Se supplementation resulted in a dose-dependent increase in plasma Se concentrations and the body exchangeable Se pool (measured by using ^{74}Se); the higher dose increased lymphocyte GPx4 and GPx1 activities.

The production of interferon-γ and IL-10, measured after *in vitro* stimulation of whole blood with the poliovirus antigen 0, 7, 14 and 21 d after poliovirus vaccination, was increased in the supplemented groups on day 7. Peak interferon-γ and IL-10 production in the placebo group occurred on day 14, suggesting that an earlier response had occurred in the supplemented groups. T cell proliferation also peaked earlier in the supplemented groups. The humoral immune response was unaffected.

Se-supplemented subjects also showed more rapid clearance of the poliovirus, and the poliovirus RT–PCR products recovered from the faeces of the supplemented subjects contained a lower number of mutations. The segment of the viral genome that was amplified is a region that is known to be naturally variable between poliovirus isolates and these data indicate that Se supplementation reduces this natural variability possibly through reducing replication of the virus.

Se supplementation enhanced immune function and viral handling in subjects with a low baseline plasma Se concentration. If these findings are applicable to other RNA viruses, then other important pathogens may be affected by host Se status; this is potentially relevant to emerging viral diseases, where the Se nutrition of the host may play a role in viral evolution.

As observed elsewhere (Brown *et al.* 2000), there was considerable individual variation in response to Se supplementation, which may have implications for attempts to improve Se status across populations.

Individual variation

The incorporation of Se into selenoproteins involves synthesis of selenocysteine tRNA and incorporation of the amino acid selenocysteine into the selenoproteins during translation of the mRNA (Hesketh & Villette, 2002). This process requires a specific structure, the selenocysteine insertion sequence, within the 3′ untranslated region (3′UTR) of the selenoprotein mRNA. Animal and cell-culture studies indicate that 3′UTR sequences are important in determining the prioritisation of Se for synthesis in one selenoprotein rather than another when Se supply is limiting (Bermano *et al.* 1996). Selenoprotein mRNA are degraded and selenocysteine incorporation efficiency is affected under Se-limiting conditions according to their ranking in the hierarchy of selenoproteins (Muller *et al.* 2003).

Professor John Hesketh presented results from an FSA-funded study which identified a common single nucleotide polymorphism (T/C at position 718) in the 3′UTR of the *GPX4* gene that was close to, but not within, the predicted selenocysteine insertion sequence element. In sixty-six subjects, the observed frequencies of the allelic variants at this position were 25 % *TT*, 34 % *CC* and 41 % *TC* (Villette *et al.* 2002). No correlation between genotype and lymphocyte

GPx4 activity was observed; however, individuals with the *CC* genotype had higher lymphocyte 5-lipoxygenase total product concentrations than the *TT* and *TC* genotypes. This suggests that GPx4 may play a regulatory role in leucotriene synthesis.

Analysis of samples from selenite supplementation trials showed no effect of supplementation on lymphocyte GPx1, GPx4, thioredoxin reductase 1 and 2, and selenoprotein X mRNA abundances. Se supplementation may affect concentrations of these selenoproteins during translation of mRNA into protein. Individual variation in response to different dietary Se intakes may also occur during translation.

Genetic variation in a variety of selenoprotein genes could influence selenoprotein activity and response to dietary Se (Méplan *et al.* 2006), including one that has been reported to affect GPx1 activity (Hu & Diamond, 2003).

Discussion

There is a growing body of evidence suggesting that intakes of Se above the normal nutritional range may confer health benefits, and that it may no longer be appropriate to rely on blood or plasma GPx activity to indicate optimal Se intake (Rayman, 2002). A detrimental effect of higher Se intakes on sperm motility has also been demonstrated, however (Hawkes & Turek, 2001), which requires further investigation with regard to its consequences for male fertility. What the consequences of less than maximal selenoprotein activity and expression are, and whether optimal health depends upon their maximisation, has yet to be determined.

The metabolism of the different dietary forms of Se needs further investigation, using food-based and supplemental approaches, to determine the pools into which Se is channelled.

Food sources of Se may contain other components that affect Se-dependent processes and such potential confounding factors should be considered when Se-responsive genes and proteins are measured as indicators of human Se status. For example, fish also contain *n*-3 PUFA which have been shown to increase both GPx1 and GPx4 expression *in vitro* (Sneddon *et al.* 2003); equally, I deficiency may induce both iodothyronine deiodinase activity and GPx1 activity (Arthur, 1999). Se has strong interactions with heavy metals such as Cd, Ag and Hg in marine foods and may protect against the toxic effects of these metals (Furst, 2002). Binding of Se to these metals may, in turn, reduce the bioavailability of Se from foods (Rayman, 2000).

It will be important to determine the response of different selenoproteins to dietary forms of Se in dose–response trials; equally, it will be important to associate functional consequences, for example, immune function, with different dietary intakes. Establishing the various plateaux reached by different selenoproteins in response to dietary forms of Se and, in particular, their relation to health outcomes will be paramount in determining optimal Se status and intakes.

Screening for relevant polymorphisms with functional consequences may also lead to a greater understanding of individual variation in Se requirements. There is considerable information on the roles of selenoproteins in rodents (Behne & Kyriakopoulos, 2001), but the distribution and roles of selenoproteins in different human tissues are not well known. Further research is required to elucidate the role and metabolic functions of selenoproteins in human subjects.

The possible effects of confounders, such as smoking and kidney and liver damage, on the concentrations of individual selenoproteins may limit their utility as markers of Se status and need to be adjusted for when using these measures.

Conclusions

The associations between Se status, immune function and viral response represent key areas for future research. It was noted, however, that no health problems have been attributed to the low Se status in the New Zealand population (Robinson, 1988). Adaptive responses to decreased intakes of Se, for example, reduced excretion (Hawkes *et al.* 2003), may be important. In Europe, there is as yet no evidence to suggest that there have been adverse effects associated with the decrease in Se intake.

Recommendations

The following research recommendations were identified:

(1) Further investigation of the role of Se in immune function;
(2) Further development of functional measures of Se status;
(3) Further investigation of the metabolism of the different dietary forms of Se;
(4) Further research into individual variation in response to Se.

Participants

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