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Reflecting on 'Selenium in Global Food Systems'

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This paper looks back on the setting and messages of the review 'Selenium in Global Food Systems'[1] (see Abstract, Fig. 1) and highlights related findings over the 20 years since its publication. Key papers are cited.

The setting

The review was the first comprehensive discussion of the metabolic functions and health roles of the nutritionally essential trace element Se in the context of food systems, that is, those factors affecting its occurrence in foods and ultimately determining its utilisation by humans. Its publication came after several decades of study that had revealed that combined deficiencies of Se and vitamin E cause a variety of pathological lesions in experimental animals and livestock[2]; that deprivation of Se can increase carcinogenesis in animal models; that endemic se deficiency was associated with Keshan disease, a myocarditis presenting in children and young women[3]; that selenosis in humans (e.g. from regular intakes > 3 mg Se/person/d) causes dermatological lesions (mostly involving hair and nails)[4]; and that Se functions as an essential component of a handful of redox-active enzymes in the form of a previously unrecognised amino acid, selenocysteine, which is biosynthesised by a novel co-translational mechanism[5]. At the time of its publication, interest in the anticarcinogenic potential of Se was particularly high, as that effect had recently been demonstrated in persons of moderate Se status[6]. It was also a point of inflexion to a period of more vigorous Se research.

Although the nutritional essentiality of Se had been recognised since the 1960s, dietary standards for Se were not established until 1989; those had recently been revised as Dietary Reference Intakes (DRI)[7]. These standards were based on Se intakes associated with maximal expression of a single selenoenzyme, extracellular glutathione peroxidase, based on only two small human studies[8,9]. Those somewhat discrepant results were averaged to set the Dietary Reference Intake for adults (55 mcg Se/d), from which DRI for children were extrapolated based on body weight. These estimates failed to consider the chemical form of ingested Se, which animal studies had shown to affect the bioavailability of the element. Understandably, within a few years, various national advisory panels had produced a range of recommended intakes (25–125 mcg/d)[10].

Food systems need to produce enough of the essential trace element Se to provide regular adult intakes of at least 40 μg/d to support the maximal expression of the Se enzymes, and perhaps as much as 300 μg/d to reduce risks of cancer. Deprivation of Se is associated with impairments in antioxidant protection, redox regulation and energy production as consequences of suboptimal expression of one or more of the Se-containing enzymes. These impairments may not cause deficiency signs in the classical sense, but instead contribute to health problems caused by physiological and environmental oxidative stresses and infections. At the same time, supranutritional intakes of Se, that is, intakes greater than those required for selenocysteine enzyme expression, appear to reduce cancer risk. The lower, nutritional, level is greater than the typical intakes of many people in several parts of the world, and few populations have intakes approaching the latter, supranutritional, level. Accordingly, low Se status is likely to contribute to morbidity and mortality due to infectious as well as chronic diseases, and increasing Se intakes in all parts of the world can be expected to reduce cancer rates.

Fig. 1. 'Selenium in Global Food Systems'[1].

The messages

Despite their limitations, these estimates of Se needs naturally led to questions about sources of Se and the prevalence and geographic distribution of Se deficiency. Therefore, 'Selenium in Global Food Systems'[1] undertook to consolidate findings concerning the roles of Se in nutrition and health with relevant findings concerning Se in food systems. This scope was novel. The paper was also the first (and, probably, only) to collate the published data on the Se status, as assessed by blood Se levels, of healthy individuals around the world. Collecting those data was undertaken with the goal of generating a world map of human Se status; however, the spotty nature of sampling, both among and within countries, meant that such a map would be a combination of gaps and often misleading national averages. Therefore, blood Se data were presented instead in tabular form. This collection indicated that Se deficiency (i.e. adult intakes < 50 mcg/d) occurred in 10–50 % of residents in most countries for which data were available.

The discussion of relevant findings from several fields afforded a global view of Se in food systems, which also was novel. This included the geographic, agronomic and physiological bases for variations in Se contents of foods, as well as the implications to the Se status to the health of people living in different parts of the world. It showed that the Se contents of foods ultimately depend on the capacities of plants to obtain the element from soils, including the regional variation in soil Se content, as well as the abilities of animals to obtain the nutrient from plants. It showed that the dominant food form of Se is the amino

Abbreviations: SeMet, selenomethionine.

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acid, selenomethionine (SeMet), which is non-specifically incorporated in plant and animal proteins *in lieu* of methionine; that the bioavailability of food Se is largely dependent on the digestibility of those SeMet-containing proteins; and that the major sources of Se in most human diets are meats and grains. It is likely that the multidisciplinary relevance of this extensive information has made this paper widely cited.

Subsequent research

At the time that 'Selenium in Global Food Systems'[1] appeared, Se research was about to double in the rate of published papers – a rate that would be sustained for more than a decade.[1] Whether this review may have contributed to that increase is doubtful, but it is clear that the paper revealed research needs in at least three areas:

Assessment of Se status

The surge in research included the identification of additional selenocysteine enzymes, including two intracellular glutathione peroxidases, three thioredoxin reductases, three iodothyronine 5'-deiodinases and a Se transporter, selenoprotein P[11]. Genomic analyses revealed twenty-five human selenoprotein genes, implying additional selenocysteine enzymes[12]. Plasma Se was found to be comprised of selenocysteine in selenoprotein P and extracellular glutathione peroxidase, and SeMet incorporated non-specifically (and non-functionally) in other proteins (principally, albumin)[13,14]. These findings offered additional biomarkers of Se status, as well as the insight that these factors responded differently to the amount and form of Se consumed[15].

Health implications of Se status

Low blood Se levels were associated with increased risks of infection, inflammation and thyroid disease. Many of these effects involve compromised immune function, and Se supplementation was found to be immunostimulatory[16]. RNA viruses, some of which were isolated from hearts of Keshan disease fatalities, were implicated in the aetiology of that disease, a hypothesis supported by findings that at least some (e.g. Coxsackie B4 and an influenza strain) can mutate to more pathogenic forms when passed through Se-deficient murine hosts[17,18].

The anticarcinogenic significance of Se intakes greater than required for maximal selenoenzyme expression remains a subject of debate. Supranutritional intakes of inorganic and organic forms of Se were demonstrated to be antitumorigenic in animal models[19] apparently *via* mechanisms not involving selenoenzymes but, instead, may be mediated by methylated Se metabolites[20]. Yet, systematic reviews of the clinical data have differed in their assessments[21–27], noting the apparently conflicting results of the two major intervention trials. The Nutritional Prevention of Cancer Trial (NPC) found supplemental Se to reduce risks to total carcinomas, cancer mortality, and cancers of the prostate and colon-rectum[6], whereas the much larger Selenium and Vitamin E Cancer Trial (SELECT) found no protective effects of supplemental Se against prostate cancer[28]. However, consideration of the blood Se levels of each cohort shows that, in fact, their results were consistent: SELECT subjects had relatively high baseline plasma Se levels (averaging 136 ng/ml), that is, comparable to those of NPC subjects that did *not* show prostate cancer risk reduction by Se – risk reduction was noted *only* among NPC subjects in the lowest tertile of baseline plasma Se status (< 106 ng/ml). Many have missed this point.

Questions were also raised about whether supranutritional Se intakes may increase risks to type 2 diabetes[29,30]. This hypothesis has had mixed support from animal studies[31], but none from clinical trials[32–35]. Nevertheless, questions about the effects of supplemental Se on anticancer efficacy and T2D risk have lingered, with apparently stifling effects on Se research activity in the mid-2010s.

Se fortification

Despite (and, likely, because of) decades of productive research, a salient question remains: *Who can benefit from increased Se intake?* The answer has two aspects. First, it is clear that adults with Se intakes < ~50 mcg/d respond to additional Se with increased circulating levels of extracellular glutathione peroxidase and selenoprotein P, and that the magnitudes of those responses depend on the extent to which baseline plasma Se levels were < ~70 ng/ml. Such individuals, particularly females, will also show increases in the total Se content of plasma if they consume Se as the dominant food form, SeMet[32]. Second, it is possible that supplemental Se may reduce cancer risk for adults of apparently adequate Se status, that is, plasma Se of ~70–~106 ng/ml. When supplemented with SeMet, these individuals will show increases in plasma Se largely due to increases in non-specifically bound Se; they will *not* show increases in extracellular glutathione peroxidase or selenoprotein P[32].

Therefore, in many countries, there may be public health benefits to developing sustainable ways of increasing Se intakes by 50–100 mcg/d. This can be done using Se-containing agricultural fertilisers to increase the Se contents of plant feeds and foods. This strategy has been used in Se-deficient areas to prevent veterinary morbidities[36], and, in 1984, Finland implemented a national Se fertilisation programme to improve human Se status. The programme increased the Se contents of feeds and foods[37]; within a few years, it raised *per capita* Se intake from deficient (~25 mcg/d) to adequate levels (110–120 mcg/d) and increased adult average serum Se levels from ~70 ng/ml to ~119 ng/ml[38].

Final note

Research on Se, the last nutrient recognised as a dietary essential, has yielded useful, if not complete, understandings of its metabolism, biochemical functions, health roles and distributions in foods. These understandings should be employed to correct prevalent low Se status where it remains.

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