Selenium

Selenium is an essential trace element that is incorporated into proteins in the form of the 21st amino acid, selenocysteine (Sec), via the specific transfer RNA[Sec]. Bioinformatic studies led to the identification of a total of 25 selenoprotein genes. Selenoproteins such as glutathione peroxidases (GPXs) 1–4 efficiently metabolize cellular peroxides and function as an antioxidant defense mechanism that protects against reactive oxygen/nitrogen species. Thioredoxin reductases (TRs) 1–3 are oxidoreductases that regulate the redox status of proteins such as thioredoxin as well as small molecules such as lipoic acid, tetrathionate, and others. Deiodinases 1–3 cleave iodine-carbon bonds in the metabolism of thyroid hormones, leading to the mono-deiodination of prohormone thyroxine (T4) to the active form triiodothyronine (T3). A progressive decrease of the T3/T4 ratio (because of increased T4 concentrations) and of erythrocyte GPX activity has been observed with advancing age that negatively correlates with increases in reactive oxygen species. Human selenoprotein P (SEPP1) contains 10 Sec residues and functions mainly to deliver selenium to other body organs after its synthesis in the liver. SEPP1 and GPX3, which are present in the plasma, are often used as biomarkers for assessing body selenium status.

Deficiencies

Selenium deficiency can result from poor dietary intake of selenium and can be induced or aggravated by certain types of stresses—nutritional, chemical, and infectious. Many classical selenium-deficiency diseases in animals are inextricably linked with a concurrent vitamin E deficiency.

Keshan disease and Kashin-Beck disease

Keshan disease is prevalent in children aged >15 y and women of childbearing age and is characterized by congestive cardiomyopathy caused by dietary selenium deficiency combined with additional stressors such as chemical exposure or the presence of a mutated strain of coxsackievirus. Fortifying common salt with exact doses of sodium selenite dramatically decreased the incidence of the disease. Kashin-Beck disease is a disabling disorder of the cartilage, bone, and joints that results in stunted growth and deformity that leads to restricted movement and joint enlargement. Seen primarily in Tibet, other parts of China, Siberia, and North Korea, the etiology of Kashin-Beck disease has remained controversial. Its pathogenesis is likely multifactorial, with selenium deficiency being one of the underlying factors that alone cannot explain its occurrence.

Cancer

Based on animal models, increasing selenium intake above the requirement to saturate selenoprotein expression has been shown to lessen the incidence of cancer. Clark et al. (2) suggested individuals with high plasma and nail selenium as a result of self-selected diets tend to have a lower incidence of cancer. A report that looked into the etiological relation between selenium exposure and cancer risk and the efficacy of selenium supplementation for cancer prevention in humans concluded that although an inverse association between selenium exposure and the risk of some cancers were found in some cohort studies, including subcohort-controlled studies and nested case-controlled studies, this could not be taken as evidence of a causal relation (3). Studies in poorly nourished rural China, US nonmelanoma skin cancer patients (4), and the Health Professional Follow-Up Study in prostate cancer subjects are in agreement with the possibility that intake of high concentrations of selenium, above those needed to maximize selenoprotein expression, may have an anticancer effect (5). However, large-scale randomized studies to understand the efficacy of anticancer function of various chemical forms of selenium with the type and stage of cancer, the sex and age of the patients, and the body selenium status are needed.

Dietary Recommendations

Estimated average requirement and RDA

Selenium is required for all age groups and is the 30th nutrient required by US law to be supplemented in infant formula. The estimated average requirements (EARs) of selenium for children and adolescents have been extrapolated from adult values that are needed to maximize plasma GPX3 activity. Based on the data from selenium-deficient Chinese children, a calculated EAR has been suggested to prevent Keshan disease. Table 1 summarizes the EAR and RDA recommendations by age and sex group. A recent report that used saturation of selenoprotein P as a criterion suggested increased reference intakes in Germany, Austria, and Switzerland, particularly in lactating women, to 75 μg/d (6).

Bioavailability

Most of the selenium in plant foods is present in the organic form as selenomethionine that is absorbed much like methionine followed by its release via the transulfuration pathway for incorporation into selenoproteins. Selenomethionine has over 90% bioavailability, whereas inorganic forms such as selenate (SeO₄²⁻) and selenite (SeO₃⁻) that are commonly used to fortify food as supplements are also highly bioavailable (5). Once absorbed, a considerable fraction of selenite is lost in the urine before being incorporated into amino acids or proteins. On the other hand, selenite is relatively better absorbed and retained. An additional factor that also regulates the
bioavailability of selenite is its interaction with the constituents in the lumen of the gut, including the microbiota.

**Food Sources**

Selenium is present in a wide variety of foods. The selenium concentrations in soil where plants are grown or animals are raised dictate the selenium content in foods, leading to tremendous variation in selenium. Whereas the food distribution systems in the United States and Canada may buffer variations in selenium content, this is not likely to be the case in developing and underdeveloped countries. In plants, which do not appear to require selenium and do not express selenoproteins, selenium is metabolized through pathways of sulfur metabolism, leading to the formation of selenomethionine, selenocysteine, and other metabolites. Nuts (Brazil nuts), seeds, green vegetables, and shiitake/white button mushrooms are good sources of selenium when there are adequate concentrations in the growing medium. Unlike plants, animals consume selenomethionine and other inorganic forms of selenium to form selenoproteins. Fish, sea foods, bread, beef, and poultry are all good sources of selenium—again when produced in areas where it is adequately available. The Tolerable Upper Intake Level for selenium through diet or supplements for ages $\geq 19 \text{ y}$ is set at $400 \mu g (5.1 \mu mol)/d$.

**Toxicity**

Despite the limited data on and rare occurrence of selenium toxicity in humans, chronic selenium poisoning has been well studied in animals. Clinical features of selenosis (chronic toxicity) are hair and nail brittleness and loss, gastrointestinal disturbances, skin rash, garlic breath, fatigue, irritability, and nervous system abnormalities. Biochemical assessment of toxicity involves measuring tissue selenium concentrations. It is essential to know the form of selenium ingested because inorganic selenium causes toxicity at concentrations much lower than organic selenomethionine.

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### TABLE 1 DRIs for selenium$^1$

<table>
<thead>
<tr>
<th>Age</th>
<th>Males $\mu g/d$</th>
<th>Females $\mu g/d$</th>
<th>Males $\mu g/d$</th>
<th>Females $\mu g/d$</th>
<th>AI, $\mu g/d$</th>
<th>UL, $\mu g/d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–6 mo</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>45</td>
<td>60</td>
</tr>
<tr>
<td>7–12 mo</td>
<td>17</td>
<td>17</td>
<td>20</td>
<td>20</td>
<td>60</td>
<td>70</td>
</tr>
<tr>
<td>1–3 y</td>
<td>17</td>
<td>17</td>
<td>23</td>
<td>23</td>
<td>60</td>
<td>100</td>
</tr>
<tr>
<td>4–8 y</td>
<td>23</td>
<td>23</td>
<td>30</td>
<td>30</td>
<td>150</td>
<td>280</td>
</tr>
<tr>
<td>9–13 y</td>
<td>35</td>
<td>35</td>
<td>40</td>
<td>40</td>
<td>280</td>
<td>400</td>
</tr>
<tr>
<td>14–18 y</td>
<td>45</td>
<td>45</td>
<td>55</td>
<td>55</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td>$\geq 19$ y</td>
<td>45</td>
<td>45</td>
<td>55</td>
<td>55</td>
<td>400</td>
<td>400</td>
</tr>
</tbody>
</table>

Pregnant

|            | $\leq 18$ y     | $19–50$ y       |                  |                  |               |               |
|            | $–$             | $–$             | $–$             | $–$             | $–$           | $–$           |

Lactating

|            | $\leq 18$ y     | $19–50$ y       |                  |                  |               |               |
|            | $–$             | $–$             | $–$             | $–$             | $–$           | $–$           |

$^1$Values are from (9). AI, adequate intake; EAR, estimated average requirement; UL, Tolerable Upper Intake Level.

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### Research

Selenium plays an important role in many aspects of human and animal health. This section draws attention to research on the diverse role of selenium in inflammation, cancer, immune function, and diabetes.

#### Selenium and inflammation

Epidemiological data suggest a positive association between selenium deficiency and the prevalence of atherosclerosis, rheumatoid arthritis, and viral infections, including HIV-AIDS, where chronic inflammation forms the underlying basis of the disease. Selenium supplementation of patients with these chronic disorders has improved their health status and quality of life. In septic shock patients characterized by acute inflammation accompanied by severe pathology, selenium supplementation at high concentrations lessened mortality and improved health status. Adequate concentrations of selenium are essential for initiating immunity in addition to regulating excessive immune responses and chronic inflammation. In animal models of inflammation, selenium supplementation at concentrations higher than those required to saturate selenoprotein expression lowered the expression of proinflammatory mediators, including cytokines and chemical mediators in the form of eicosanoids. Selenium-dependent effects were mediated via the downregulation of the redox-sensitive transcription factor NF-$\kappa$B in addition to the epigenetic control of gene expression regulation. Although high selenium intake resolved inflammation during ulcerative colitis and 2-stage colon carcinogenesis models in rodents, data in human inflammatory bowel disease subjects are inconclusive with regard to the requirement of selenium.

#### Selenium and cancer

Despite the fact that prospective observational studies and randomized clinical trials (RCTs) have shown a tendency to lower the incidence of cancer with high selenium diets, this cannot be taken as evidence of a causal relation. Therefore, these results should be interpreted with caution. However, many animal studies have suggested that supplementation with various forms of selenium at concentrations higher than those required to maximize selenoprotein expression are effective in mitigating cancer. Whereas cancer stem cells (particularly in myeloid leukemias) are particularly sensitive to excess selenium, many other cancer cells have shown increased sensitivity to inorganic and organic forms of selenium. These encouraging studies need to be complemented with large-scale trials but cannot be used as a basis to determine the everyday requirements for dietary selenium.

#### Selenium and immune function

Selenium deficiency adversely affects the activation, differentiation, and proliferative capacity of immune cells. Through its incorporation into selenoproteins, selenium plays an important role in initiating “normal” immunity as well as regulating excessive immune responses. Using mouse models that lack specific selenoproteins, there is evidence that points to their role in signaling, calcium flux, oxidative burst, and effector functions, including migration, adherence, cytokine/chemokine production, and
phagocytosis. Higher than adequate concentrations of selenium skewed the differentiation of T lymphocytes toward a Th1 type and increased the concentration of CD25<sup>+</sup> Foxp3<sup>+</sup> Treg cells. Selenoprotein K in T cells regulated Ca<sup>2+</sup> flux, proliferation, and migration along with protection against apoptosis induced by endoplasmic reticulum stress. In mouse models, selenoprotein K was essential for palmitoylation and cell surface expression of CD36 in macrophages for low-density lipoprotein uptake. Selenium supplementation also affected macrophage polarization more toward an alternatively activated phenotype that is important in wound healing and/or the resolution of inflammation. Supplementing volunteers with 50–100 μg sodium selenite/d for 15 wk increased antipoliovirus and antitoxin immunity, whereas supplementing HIV patients with 200 μg sodium/d decreased the viral load and improved the immune system. TR1 expression in macrophages and T lymphocytes negatively affected HIV transcription by the redox modulation of Tat, a key proviral transcriptional activator.

**Selenium and diabetes**

Selenium is likely to exert a dual role in glucose (energy) metabolism, insulin physiology, and susceptibility of developing diabetes. Selenium compounds were shown to improve insulin synthesis and secretion and to act as an insulin mimic in enhancing glucose uptake in cultured and/or primary cells (islets). Relatively high doses of inorganic and organic selenium (~10–15 μmol/(kg body weight · d)) were administrated to alleviate symptoms in both type 1 and type 2 diabetic animals. In addition, inverse associations between blood/toenail selenium concentrations and blood glucose concentrations or diabetes incidence were found in several epidemiological studies. Furthermore, improved metabolic status in type 2 diabetes (T2D) patients occurred consequent to dietary selenium supplementation. Nonetheless, several animal studies have revealed an intriguing role of supranutritional selenium acting as a diabetogenic factor. Prolonged feeding of high doses of selenium (0.4–3 mg Se/kg of diet) led to hyperinsulinemia and insulin resistance in mice, rats, and pigs. The high dietary selenium intake affected glycolysis, gluconeogenesis, and protein synthesis. Overexpression of GPX1 induces T2D-like phenotypes, and knockout of Sepp1 improves insulin signaling in mice. Other selenoproteins, including S, R, and T and deiodinase 2, have also been linked to glucose metabolism and diabetes risk.

Rayman and Stranges (7) reviewed human studies and highlighted positive associations between serum/plasma selenium and T2D or fasting plasma glucose in 5 of 8 cross-sectional studies in adults, such as the French SU.VI.MAX and the American NHANES III and NHANES 2003–2004. Of the 5 RCTs, an increased risk of T2D occurred only in the Nutritional Prevention of Cancer Trial, with statistical significance reached in subjects in the highest selenium tertile at baseline. Similarly, a meta-analysis of 4 RCTs has derived no evidence to support selenium supplementation for T2D prevention in Caucasians. However, a RCT in 60 T2D patients showed adverse effects of supplementation with 200 μg Se/d (as sodium selenite) compared with placebo for 3 mo on blood glucose and lipid profiles (8). In summary, as in a U-shaped relation, both selenium deficiency and oversupply seem to dysregulate glucose and lipid metabolism and potentiate the risk of T2D in several animal studies, with less clear associations discovered in human studies.

**Acknowledgments**

We thank John Arthur for his comments. Both authors have read and approved the final manuscript.

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1Supported by the NIH grants DK077152/CA162665 (KSP) and DK053018 (XL) and USDA-National Institute of Food and Agriculture Hatch project number 4475 (KSP).

2Author disclosures: KS Prabhu is a scientific cofounder of Nemean Pharma Corporation and XG Lei is a consultant for the Institute of Nutrition and Health, China National Cereals, Oils and Foodstuffs Corporation, Beijing, China.

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