Epidemiology of selenium deficiency

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Disclosures

I have nothing to disclose
Outline

- Epidemiology of Selenium – Consequences of Selenium deficiency and excess.
- Metabolic pathway
- Selenium compounds.
- Se and Public Health: Cancer and Diabetes
Selene... A Goddess on Earth

Selenium was initially thought to be toxic, and it is only in the last few decades that it has shown its many beneficial effects.

Selenium, the element of the moon
Selenium and Metabolism

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4. The relationship of selenium tolerance and speciation in Lecythidaceae species.
# Selenium Levels for Reference

<table>
<thead>
<tr>
<th>Serum</th>
<th>µg/l</th>
<th>µmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced</td>
<td>&lt; 65</td>
<td>&lt; 0.81</td>
</tr>
<tr>
<td>Suboptimal</td>
<td>65-100</td>
<td>0.81-1.25</td>
</tr>
<tr>
<td>Optimal</td>
<td>101-135</td>
<td>1.26-1.71</td>
</tr>
</tbody>
</table>

The recommended intake for the population ranges from 20 to 55 $\mu$g/day in the age group 1-17 years, and 55 $\mu$g/day in the age group between 18 and $\geq$ 75 years (including pregnant women), while increases to 70 $\mu$g/day in infants.

The maximum tolerable level (tolerable upper intake level, UIL) ranges from 60 to 250 $\mu$g/day in the range 1-17 years and is always 300 $\mu$g/day in adults (including pregnant women and infants).
Selenium Epidemiology

Selenium < 50µg/l

Selenium < 40µg/l
Selenium Epidemiology

Selenium > 140μg/l
Selenium Epidemiology

Keshan Disease

Selenium <20μg/l
Kashin-Beck Disease

Selenium Chemistry

Selenomethionine

Se-Methylselenocysteine

Sodium Selenite
Selenium metabolic pathway. Selenomethionine can be incorporated into proteins in place of methionine because it readily acylates Met-tRNA

General body proteins

Selenomethionine

Selenocysteine

Selenoproteins (as selenocysteine)

Selenophosphate

H$_2$Se

CH$_3$SeH

$(\text{CH}_3)_2\text{Se}$

$(\text{CH}_3)_3\text{Se}^+$

β-lyase

Methylation

GS-Se-SG

GS-SeH

Selenite

Selenite

## Selenoproteins, which are expressed in the thyroid

<table>
<thead>
<tr>
<th>Selenoproteins</th>
<th>Abbreviation</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glutathione peroxidases</td>
<td>GPx</td>
<td>Catalyze the reduction of $\text{H}_2\text{O}_2$, protection from oxidative stress</td>
</tr>
<tr>
<td>Cytosolic GPx1</td>
<td>cGPx-1</td>
<td>Antioxidative defense</td>
</tr>
<tr>
<td>Extracellular GPx</td>
<td>pGPx-3</td>
<td>Antiinflammatory action</td>
</tr>
<tr>
<td>Phospholipid GPx</td>
<td>GPx-4</td>
<td>Decreases phospholipid hydroperoxides, moderates apoptosis</td>
</tr>
<tr>
<td>Iodothyronine deiodinases</td>
<td>DI-I</td>
<td>Catalyze the conversion of $\text{T}_4$ to $\text{T}_3$ and $\text{rT}_3$</td>
</tr>
<tr>
<td>Type I DI</td>
<td>DI-I</td>
<td>Systemic $\text{T}_3$ production</td>
</tr>
<tr>
<td>Type II DI</td>
<td>DI-II</td>
<td>Local (intracellular) $\text{T}_3$ production</td>
</tr>
<tr>
<td>Type III DI</td>
<td>DI-III</td>
<td>Production of $\text{rT}_3$ from $\text{T}_4$</td>
</tr>
<tr>
<td>Thioredoxin reductases</td>
<td>TRx</td>
<td>Oxidoreductase system with NADPH as a cofactor, modulates transcription factors and signal transduction</td>
</tr>
<tr>
<td>Cytosolic TRx</td>
<td>TRx-1</td>
<td>Regulates cellular redox level, cell development, and proliferation</td>
</tr>
<tr>
<td>Mitochondrial TRx</td>
<td>TRx-2</td>
<td>Regulates cell proliferation, tissue development</td>
</tr>
<tr>
<td>Various</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selenoprotein P</td>
<td>SePP</td>
<td>Selenium transport, antioxidant defense</td>
</tr>
<tr>
<td>Selenoprotein N</td>
<td>SeP15</td>
<td>Degradation $\text{H}_2\text{O}_2$</td>
</tr>
</tbody>
</table>

NADPH, Reduced nicotinamide adenine dinucleotide phosphate.

*Duntas LH, J Clin Endocrinol Metab, 2010.*
About Se mechanisms of action

- In Se - deficient humans, Se supplementation in form of selenomethionine or as yeast, increases enzymatic antioxidant activity and decreases lipid peroxidation (Burk RF, Biofactors, 2001).

- It may also reduce the production of inflammatory prostangladins and leukotrienes by neutralizing peroxide intermediates (Rayman MP, Lancet, 2000).
Plasma selenium following 28 months SeMet administration: W=orange and M=blue

Combs GF Am J Clin Nutr 2009
Relationships of responses of plasma Se levels to selenomethionine supplementation for men (M) and women (W): dose-responses over time

Combs GF et al., British Journal of Nutrition, 2011.
Response of plasma Selenium and GPx activity to SeMet administration

Plasma selenoproteins following Selenomethionine administration

**Effects of Selenium Supplementation for Cancer Prevention in Patients With Carcinoma of the Skin. A Randomized Controlled Trial**

*Clark LC et al., JAMA, 1996.*

- **Interventions:** Oral administration of 200 μg of selenium per day or placebo.

- **Main Outcome Measures:** Patients (1312) were treated for 4.5 (2.8) years and had a total follow-up of 6.4 (2.0) years. The primary end points for the trial were the incidences of basal and squamous cell carcinomas of the skin. The secondary end points, established in 1990, were all-cause mortality and total cancer mortality, total cancer incidence, and the incidences of lung, prostate, and colorectal cancers.

- **Results:** Selenium treatment did not protect against development of basal or squamous cell carcinomas of the skin. However, results from secondary end-point analyses support the hypothesis that supplemental selenium may reduce the incidence of, and mortality from, carcinomas of several sites.
Number of publications per year yielded a Medline search using the terms “selenium” and “cancer” (solid line) and “selenium,” “cancer,” and “humans” (dotted line).

A pilot study of serum selenium, vitamin D, and thyrotropin concentrations in patients with thyroid cancer

Jonklaas J, Danielsen M, Wang H, Thyroid, 2013

- **Patients**: 65 patients at an academic medical center who were scheduled for thyroidectomy for thyroid cancer, suspicion of thyroid cancer, or nodular disease.

- **Methods**: Blood samples were obtained 2-4 weeks prior to thyroidectomy. Samples were analyzed for thyrotropin, free thyroxine, total triiodothyronine, selenium, and 25 hydroxyvitamin D.

- **Results**: Although selenium concentrations were not significantly lower in patients with thyroid cancer, serum selenium concentrations were inversely correlated with disease stage (p value< 0.011).
Association of selenium tertiles with prognostic factors and thyroid cancer stage

<table>
<thead>
<tr>
<th></th>
<th>Tertile 1</th>
<th>Tertile 2</th>
<th>Tertile 3</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selenium (both labs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N in tertile (min-max values)</td>
<td>10 (92-107)</td>
<td>25 (110-120)</td>
<td>13 (124-140)</td>
<td>---</td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td>2.1 ± 1.9</td>
<td>2.7 ± 1.8</td>
<td>1.8 ± 0.8</td>
<td>0.62</td>
</tr>
<tr>
<td>Extrathyroidal extension</td>
<td>6 (60%)</td>
<td>12 (48%)</td>
<td>6 (46%)</td>
<td>0.53</td>
</tr>
<tr>
<td>Multifocality</td>
<td>5 (50%)</td>
<td>11 (44%)</td>
<td>8 (62%)</td>
<td>0.53</td>
</tr>
<tr>
<td>Number of foci</td>
<td>2.6 ± 2.3</td>
<td>1.9 ± 1.2</td>
<td>2.4 ± 1.6</td>
<td>0.75</td>
</tr>
<tr>
<td>Number of positive LN</td>
<td>3.8 ± 7.5</td>
<td>1.4 ± 2.6</td>
<td>4.6 ± 6.6</td>
<td>0.71</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>1 (10%)</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
<td>---*</td>
</tr>
<tr>
<td>TCR Stage 1</td>
<td>3 (30%)</td>
<td>10 (40%)</td>
<td>9 (69%)</td>
<td>0.061†</td>
</tr>
<tr>
<td>TCR Stage 2</td>
<td>3 (30%)</td>
<td>6 (24%)</td>
<td>2 (15%)</td>
<td></td>
</tr>
<tr>
<td>TCR Stage 3</td>
<td>3 (30%)</td>
<td>8 (32%)</td>
<td>2 (15%)</td>
<td></td>
</tr>
<tr>
<td>TCR Stage 4</td>
<td>1 (10%)</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>TNM stage 1</td>
<td>4 (40%)</td>
<td>14 (56%)</td>
<td>11 (85%)</td>
<td>0.055†</td>
</tr>
<tr>
<td>TNM stage 2</td>
<td>2 (20%)</td>
<td>3 (12%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>TNM stage 3</td>
<td>3 (30%)</td>
<td>7 (28%)</td>
<td>2 (15%)</td>
<td></td>
</tr>
<tr>
<td>TNM stage 4</td>
<td>1 (10%)</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
</tbody>
</table>

### Serum selenium levels and the risk of lung cancer

<table>
<thead>
<tr>
<th>Selenium level</th>
<th>Cases (%) n=86</th>
<th>Controls (%) n=86</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤60</td>
<td>37 (40.0)</td>
<td>12 (14.0)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>61–70</td>
<td>23 (26.7)</td>
<td>18 (20.9)</td>
<td>0.40 (0.15–1.09)</td>
<td>0.07</td>
</tr>
<tr>
<td>71–80</td>
<td>12 (14.0)</td>
<td>29 (33.7)</td>
<td>0.11 (0.03–0.33)</td>
<td>0.0001</td>
</tr>
<tr>
<td>&gt;80</td>
<td>14 (16.3)</td>
<td>27 (31.4)</td>
<td>0.10 (0.03–0.34)</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

### Serum selenium levels and the risk of laryngeal cancer

<table>
<thead>
<tr>
<th>Selenium level</th>
<th>Cases (%) n=87</th>
<th>Controls (%) n=87</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤60</td>
<td>33 (37.9)</td>
<td>13 (14.9)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>61–70</td>
<td>23 (26.4)</td>
<td>16 (18.4)</td>
<td>0.59 (0.21–1.65)</td>
<td>0.32</td>
</tr>
<tr>
<td>71–80</td>
<td>15 (17.2)</td>
<td>23 (26.4)</td>
<td>0.35 (0.14–0.87)</td>
<td>0.02</td>
</tr>
<tr>
<td>&gt;80</td>
<td>16 (18.4)</td>
<td>35 (40.3)</td>
<td>0.23 (0.09–0.56)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Jaworska K et al., PLOS One, 2013.
# Genotypes for selected selenoproteins and the risk of lung cancer

<table>
<thead>
<tr>
<th></th>
<th>Cases (%) n = 95</th>
<th>Controls (%) n = 176</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GPX1 (rs1050450)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>53 (55.8)</td>
<td>79 (44.9)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>33 (34.7)</td>
<td>83 (47.2)</td>
<td>0.54 (0.31–0.95)</td>
<td>0.03</td>
</tr>
<tr>
<td>TT</td>
<td>9 (9.5)</td>
<td>14 (7.9)</td>
<td>0.85 (0.33–2.19)</td>
<td>0.73</td>
</tr>
<tr>
<td><strong>GPX4 (rs713041)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>39 (41.1)</td>
<td>54 (30.7)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>47 (49.5)</td>
<td>97 (55.2)</td>
<td>0.71 (0.41–1.22)</td>
<td>0.21</td>
</tr>
<tr>
<td>TT</td>
<td>9 (9.5)</td>
<td>25 (14.2)</td>
<td>0.47 (0.19–1.17)</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>SEP15 (rs5845)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG</td>
<td>54 (56.8)</td>
<td>100 (56.8)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>AG</td>
<td>35 (36.8)</td>
<td>68 (38.6)</td>
<td>1.03 (0.62–1.72)</td>
<td>0.91</td>
</tr>
<tr>
<td>AA</td>
<td>6 (6.3)</td>
<td>8 (4.5)</td>
<td>1.52 (0.51–4.5)</td>
<td>0.45</td>
</tr>
<tr>
<td><strong>TXNRD2 (rs1139793)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG</td>
<td>55 (57.9)</td>
<td>109 (61.9)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>AG</td>
<td>33 (34.7)</td>
<td>56 (31.8)</td>
<td>1.16 (0.69–1.95)</td>
<td>0.58</td>
</tr>
<tr>
<td>AA</td>
<td>7 (7.4)</td>
<td>11 (6.3)</td>
<td>1.27 (0.49–3.32)</td>
<td>0.63</td>
</tr>
</tbody>
</table>

*Jaworska K et al., PLoS ONE, 2013.*
It appears that among smoking individuals, those with the *Sep15 1125 AA genotype* may benefit most from a higher Se intake, whereas in those with the GG or GA genotype, a higher Se status may increase the risk for lung cancer.
Survival distributions for each plasma selenium concentration quartile group

Akbaraly NT et al., Clinical Chemistry, 2005.
The results this study reinforce the importance of adequate selenium status for health maintenance in an aging population.

Even if it is premature to portray selenium as a longevity indicator, the data support those of large interventional randomized trials, which suggest that this essential trace element may play a role in health maintenance during the aging process.

Akbaraly NT et al., Clinical Chemistry, 2005.
Possible Explanations for discrepancies and controversies among the various studies

- Se optimal dose range has not been established.

- Baseline Se status of participants has not always been defined.

- Genotype of various selenoproteins of the cohort should be taken into consideration.
Bi-Modal action of Se

- It is suggested, to rationalize some apparently discrepant results, that health risk may be associated with Se status according to a ‘U’- shaped dose-response curve. It has been shown that at high dietary exposures Se can cause DNA damage in cells and induce apoptosis. This may be a mechanism of anti-cancer Se effect; when manifest in non-tumorigenic cells, it may also indicate Se-toxicity.

- Such a bi-modal dose-response relationship would suggest that Se may be beneficial for those individuals of relatively low Se status?

Combs GF et al., British J Nutr 2011
The U-shaped dose response curve defines a risk-benefit profile for predicting the consequences of dietary selenium supplementation.

Chiang EC et al., Dose Response, 2009.
Μη δεν ἀγαπᾷ

Nothing in excess
Apollo, Delphi
Cumulative incidence of type 2 diabetes

Adjusted ORs (curves) and 95% CIs (gray shading) for diabetes (A) and adjusted differences (and 95% CI) in fasting glucose (B) and glycosylated hemoglobin (C) by serum selenium concentration. Serum selenium was modeled as restricted quadratic splines with nodes at the 5th, 50th, and 95th percentiles.

1st Tertile: ±0.9µg/l

2nd Tertile: ±1.1µg/l

2nd Tertile: ±1.3µg/l

Laclaustra et al., Environ Health Perspect, 2009.
Serum selenoprotein P (SeP) concentrations in control subjects and those with (A) nonalcoholic fatty liver disease (NAFLD) and (B) visceral obesity.

*Choi HY et al., Diabetes Metab J, 2013.*
The U-shaped dose response curve defines a risk-benefit profile for predicting the consequences of dietary selenium supplementation.
Proposed algorithm for Se supplementation

**Deficient (Less than RDA)**
- Keshan Disease
- Hypothyroidism
- Suppressed immunity
- Susceptibility
- No infections
- Supplementation

**Adequate (75-200% RDA)**
- Optimal (90-120ng/ml)
- Protection of cancer and DMT2
- Regulation of thyroid function
- Functioning immune response
- No supplementation

**Excess (> 200%)**
- Selenosis
- Increased risk for DMT2, Cancer
- Pro-oxidative function
- Insulin resistance
- No supplementation

Deficiency of selenium can lead to diseases such as Keshan Disease and Hypothyroidism. Adequate levels (75-200% RDA) are optimal for health, including protection against cancer and diabetes type 2, regulation of thyroid function, and functioning immune response. Excess selenium (> 200%) is not recommended as it can lead to selenosis, increased risk for diseases like DMT2 and cancer, and pro-oxidative effects, leading to insulin resistance. Supplementation is recommended for deficient levels, while adequate and excess levels do not require supplementation.
Conclusions

✓ Low Se levels have a severe impact on health.
✓ A selenium level below 60 mg/l is associated with a high risk of both lung and laryngeal cancer.
✓ High serum selenium concentrations are associated with higher prevalence of diabetes and higher fasting plasma glucose and glycosylated hemoglobin levels. Given the high selenium intake in the U.S. population, further research is needed to determine the role of excess selenium levels in the development or the progression of diabetes and or insulin resistance and obesity.
✓ Supplementation with Se should carefully consider the indications and the optimal level.
Factors other than Se intake, such as genotype can contribute to variance in Se biomarkers used to assess Se status and it is possible that these factors may contribute to heterogeneity in biomarker responses to Se-supplementation.
Selenoprotein synthesis, feedback regulation of thyroid hormone synthesis and secretion, and metabolism

Dumitrescu AM et al., Nature Genetics, 2005.
Histopathology, thyroid weight and TgAb levels

A

Relative weight of thyroid (mg/100g)

* 25
   20
   15
   10
   5
   0

8 wk 16 wk

Control AIT AIT+Se

B

Control AIT AIT+Se

C

Serum TgAb levels (OD value)

* 1
   0.8
   0.6
   0.4
   0.2
   0

8 wk 16 wk

Control AIT AIT+Se

Xue H et al., Endocrine Journal 2010.
Grazie mille per l’ invitozione e l’ attenzione