Selenium – rol in organism
Selenium in intensive care?

Probably not a magic bullet but an important adjuvant therapy.
Human

Incorporated in selenocompounds - small molecular weight that influence human health.
Micronutrients

Called *micronutrients* because they are needed only in **minuscule amounts**, these substances are the “**magic wands**” that enable the body to produce enzymes, hormones and other substances essential for proper growth and development.

- **Microminerals (trace elements)**
- **Vitamins**
## Essential micronutrients

<table>
<thead>
<tr>
<th>Trace elements</th>
<th>Vitamins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cu</td>
<td>A Retinol</td>
</tr>
<tr>
<td>Se</td>
<td>D Cholecalciferol</td>
</tr>
<tr>
<td>Zn</td>
<td>E Alpha-tocopherol K</td>
</tr>
<tr>
<td>Fe</td>
<td>Phyloquinone B1 Thiamin</td>
</tr>
<tr>
<td>Mn</td>
<td>B2 Riboflavin</td>
</tr>
<tr>
<td>Mo</td>
<td>B3 Niacin(PP)</td>
</tr>
<tr>
<td>Cr</td>
<td>B5 Pantothenic acid B6</td>
</tr>
<tr>
<td>F</td>
<td>Pyridoxine</td>
</tr>
<tr>
<td>I</td>
<td>B8 Biotine(H)</td>
</tr>
<tr>
<td>Co</td>
<td>B9 Folic acid</td>
</tr>
<tr>
<td></td>
<td>B12 Cobalamin</td>
</tr>
<tr>
<td></td>
<td>C Ascorbic acid</td>
</tr>
</tbody>
</table>

Fores Nilsen, *New essential trace elements for the life science*, Biological Trace Element Research, 1989, 599-611
Forms

Inorganic forms

- metallic forms
- oxyanions - selenite $\text{SeO(OH)}_2$
  - selenate $\text{SeO}_2(\text{OH})_2$

Organic forms

- selenocisteina $\text{SeCys}$
- seleomethionine $\text{SeMet}$

Kazuo T. Suzuki Metabolomics of Selenium: Se Metabolites Based on Speciation Studies

Journal of Health Science, 51(2) 107–114 (2005)
Sourses of Selenium

- **SeCys** is present in plants and animals (vegetables and meats in foods)
- **SeMet** in general proteins in foods (vegetables and meats)
- selenite and selenate in drinking water and foods

Sourses of Selenium

Selenium accumulators

- selenite-accumulators (broccoli and cucumber),
- SeMet-accumulators (grains such as wheat, and mushroom)
- MeSeCys-accumulators (garlic and onion)

Can you see me I’m in here!
Human active forms

- Glutation peroxidazaza (GPx)
- Thioredoxin reductazaza
- Thyroid hormone deiodinase
- Selenoproteins
# Antioxidant/Redox Reactions Involving Selenoproteins

1. **Detoxification of peroxides:**
   \[
   \text{GPx}\quad R-O-O-H + 2\text{GSH} \quad \rightarrow \quad R-O-H + \text{GSSG} + H_2O
   \]

2. **Regeneration of reduced thioredoxin:**
   \[
   \text{Trxrd}\quad \text{Trx-S}_2 + \text{NADPH} + H^+ \quad \rightarrow \quad \text{Trx-(SH)}_2 + \text{NADP}^+
   \]

3. **Reduction of oxidized methionine residues:**
   \[
   \text{Sel R}\quad \text{peptide-Met-R-O} + \text{Trx-(SH)}_2 \quad \rightarrow \quad \text{peptide-Met} + \text{Trx-S}_2 + H_2O
   \]
Potential Role of Selenoenzymes and Antioxidant Metabolism in relation to Autism Etiology and Pathology.

Raymond LJ, Deth RC, Ralston NV
Potential Role of Selenoenzymes and Antioxidant Metabolism in relation to Autism Etiology and Pathology.

Raymond LJ, Deth RC, Ralston NV
Role ....... in the body

- Sepsis, septic shock
- Antioxidant
- Decreased the risk of lung, colorectal, and prostate cancers
- Antitoxic (Pb. Hg, Ar)
- Immunomodulator

1. Matthias W. A. Angstwurm, Selenium in ICU SIRS – sepsis patients, Crit Care Med 2007 Vol. 35, No. 1
Role …… in the body

- Alfa 1 antitripsina deficiency
- Autism
- Masculin infertility
- Regulate thyroid hormone synthesis
- Cardioprotection in cardiomyopathy
disease

1. Catherine M. Greene et al., “There a Therapeutic Role for Selenium in Alpha-1 Antitrypsin Deficiency?” Nutrients 2013, 5, 758-770
2. Laura J. Raymond et al., “Potential Role of Selenoenzymes and Antioxidant Metabolism in relation to Autism Etiology and Pathology” Autism Research and Treatment, volume 2014, Article ID 164938, 15 pages
Main actors

- Glutathione Peroxidases (GPx1-6)
- Thioredoxin Reductases
- Deiodinases
- Selenoprotein (H-W)
- Selenophosphate-synthetase 2
Glutathione Peroxidases (GPx1)

- the **most abundant** and ubiquitously expressed selenoproteins
- highly sensitive to changes in **Se status**
- oxidative stress has been shown to reduce levels of **GPx1**
- **GPx1** recovers most rapidly
- role for **GPx1** in **cancer prevention**
- plays an important role in protecting against **neurodegenerative diseases**
Glutathione Peroxidases (GPx1)

- slightly higher risk of type-2 diabetes in Se supplemented humans as described above as well as the strong correlation found between increased erythrocyte GPx1 activity and insulin resistance in gestational diabetic women

Glutathione Peroxidases (GPx2)

- expressed in the gastrointestinal tract, in liver
- protect intestinal epithelium from oxidative stress
- GPx2 is upregulated in cancers of gastrointestinal tract (1)
- A recent study show that lower expression of GPx2 increased migration and invasion of cancer cell clones, but decreased their growth (2)

Glutathione Peroxidases (GPx3)

- Source of GPx3 in plasma is the kidney

- Decreased GPx3 activity led to platelet hyper-reactivity and an increased risk of thrombosis [2]

- GPx3 and Sel P role for this selenoprotein in modulating NO concentration or other aspects of the vascular environment.

- Affects susceptibility to stroke or other cardiovascular disorders [3]

Glutathione Peroxidases (GPx4)

- subcellular localization between cytosol, nuclear, and mitochondria [1]
- protective role (reversing oxidation of lipid peroxides)
- involved in metabolism of lipids (arachidonic acid and linoleic acid) [2]
- contribute to the pathogenesis of Parkinson Disease or Alzheimer’s Disease [3]
- protective role in cardiovascular disease (decreasing lipid peroxidation and inhibiting the sensitivity of vascular cells to oxidized lipids) [4]
- associated with infertility [5]

Thioredoxin Reductases (Trx)

- catalyze the reduction of oxidized thioredoxin (1)
- exists in all living cells
- defense against oxidative damage due to oxygen metabolism, and redox signaling using molecules like hydrogen peroxide and nitric oxide (2)
- In cancer treatment: is essential for cell growth and survival, it is a good target for anti-tumor therapy (4)
- In cardiomyopathy: two mutations in the TrxR2 gene are found in patients diagnosed with DCM and not in a control population (control oxidative damage in cardiac myocytes) (3)

Iodothyronin Deiodinases

- **three enzymes**: types 1, 2, and 3 (1)

- **thyroid hormone metabolism** (3)

- **regulated (D2)** stability in response to changes in iodine supply, to cold exposure, and changes in thyroid gland function (2)


## Selenoproteins

<table>
<thead>
<tr>
<th>Letter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>relatively high in early stages of embryonic development</td>
</tr>
</tbody>
</table>
| P | Se transporter  
- glutathione peroxidase activity, heparin binding, and heavy metal ion complexation  
- important defense against heavy metals  
- lower circulating Sel P during inflammatory conditions like sepsis and Crohn’s disease |
| I | involved in a phospholipid biosynthesis pathway |
| R | protection from neurodegeneration, lens cell viability, and oxidative damage during aging |
| K | localized to the endoplasmic reticulum membrane, human heart  
- function of Sel K remains unclear |
| S | participate in the removal of misfolded proteins from the ER lumen for degradation and to protect cells from oxidative damage and ER stress-induced apoptosis  
- associated with genetic variations in Sel S: cardiovascular disease and stroke, preeclampsia, rheumatoid arthritis, and gastric cancer |
| M | role for this selenoprotein in limiting the development of cancer |
| T | biological role for Sel T in calcium mobilization? |
| N | a transmembrane protein localized to the ER membrane  
- high expression of Sel N in fetal tissue and proliferating cells are suggestive role in early muscle formation |
| V | potential roles of Sel V in male reproductive biology |
| O | no information regarding its tissue distribution, subcellular location, or physiological role |
| W | functions in muscle growth and differentiation by protecting the developing myoblasts from oxidative stress |

Selenium status varies by country and corresponds to dietary selenium intake and dietary supplements.

- in the USA, 50% of the population takes dietary supplements
Impact on micronutrient status

Selenium in ICU

- Oxidative stress
- Inflammation
- Organ failure
Berger, Negative balances – the causes in critically ill, NCP 21: 438, 2006
Micronutrients losses during CVVH

Berger MM et al., Amer. J Clin Nutr, 410, 2004
Se balance after major trauma

Berger MM et al., J Trauma 40:103, 1996
249 patients in severe sepsis or septic shock: 1000 mcg Se or placebo daily for 2 weeks after a loading dose.

- The estimated mean survival time was 19.7 days in Se1 patients compared with 16.4 days in the Se0 group ($p < .0476$).

- The absolute mortality reduction with adjuvant selenium treatment was 17.6% ($p < .024$; OR, 0.48; 95% CI, 0.25–0.91).

- The 28-day mortality rate was with 14.3%, significantly lower, in Se1 patients.
Secondary End Points

- APACHE II score decreased from day 1 to day 28 in the Se1 group (27.6%, \(p < .0002\)), comparable to the Se0 group (24.1%, \(p < .0002\)).

- The incidence of ARDS also was not significantly different in Se1 (5.4%) and Se0 (4.1%) patients.

- The maximum serum Selenium concentrations were found on day 14.
Discussion

- selenoprotein P is rapidly generated (1), preventing endothelial cells from oxidative damage followed by a diminished activation

- decreased tumor necrosis factor-α-induced intercellular adhesion molecule and selectin expression (2)

- GPx and thioredoxin reductase diminish the production of inflammatory prostaglandins and leukotrienes

Is there any evidence that selenium supplementation in ICU patients is beneficial?

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Critical illness</th>
<th>No. of patients</th>
<th>Daily Se/ebelsen</th>
<th>Mortality Se+</th>
<th>Mortality Se-</th>
<th>Included in meta-analysis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuklinski 1991[1]</td>
<td>Pancreatitis</td>
<td>17</td>
<td>Se 500 g 8 days</td>
<td>0/8</td>
<td>8/9</td>
<td>Avenell Heyland (+/-)</td>
</tr>
<tr>
<td>Zimmerman 1997[2]</td>
<td>SIRS</td>
<td>40</td>
<td>Se 1000 g bolus + 1000 g 28 days</td>
<td>3/20</td>
<td>8/20</td>
<td>Avenell Heyland</td>
</tr>
<tr>
<td>Berger 1998[3]</td>
<td>Burns</td>
<td>20</td>
<td>Se 159 g 8 days</td>
<td>1/10</td>
<td>0/10</td>
<td>Heyland</td>
</tr>
<tr>
<td>Angstwurm 1999[2]</td>
<td>Sepsis/SIRS</td>
<td>42</td>
<td>Se 535 g for 3 days then reducing</td>
<td>7/21</td>
<td>11/21</td>
<td>Avenell Heyland</td>
</tr>
<tr>
<td>Porter 1999[4]</td>
<td>Trauma</td>
<td>18</td>
<td>Se 200 g 7 days</td>
<td>0/9</td>
<td>0/9</td>
<td>Heyland</td>
</tr>
<tr>
<td>Berger 2001[5,6]</td>
<td>Trauma</td>
<td>32</td>
<td>Se 500 g 5 days</td>
<td>2/20</td>
<td>1/12</td>
<td>Heyland</td>
</tr>
<tr>
<td>Berger 2002[7]</td>
<td>Trauma</td>
<td>21</td>
<td>Se 500 g 5 days</td>
<td>2/9</td>
<td>1/11</td>
<td>Avenell</td>
</tr>
<tr>
<td>Berger 2004[8,9]</td>
<td>Burns</td>
<td>21</td>
<td>Se 380 g 14-21 days</td>
<td>1/11</td>
<td>1/10</td>
<td>Heyland</td>
</tr>
<tr>
<td>Lindner 2004[10]</td>
<td>Pancreatitis</td>
<td>70</td>
<td>Se 2000 g bolus + 1000 g 7 days</td>
<td>5/35</td>
<td>3/35</td>
<td>Avenell</td>
</tr>
<tr>
<td>Mishra 2007[11]</td>
<td>Sepsis/SIRS</td>
<td>40</td>
<td>Se 474 g for 3 days then reducing</td>
<td>11/18</td>
<td>15/22</td>
<td>Avenell</td>
</tr>
<tr>
<td>Forceville 2007[12]</td>
<td>Septic shock</td>
<td>60</td>
<td>Se 4000 g on first day, then 1000 g/day 9 days</td>
<td>14/31</td>
<td>13/29</td>
<td>No</td>
</tr>
<tr>
<td>Angstwurm 2007[13]</td>
<td>Sepsis/SIRS</td>
<td>249</td>
<td>Se 1000 g bolus then 1000 g/day 14 days</td>
<td>46/116</td>
<td>61/122</td>
<td>Avenell Heyland</td>
</tr>
</tbody>
</table>
Forest plot comparing mortality among selenium-treated patients to controls by treatment dosages.

http://www.plosone.org/article/info:doi/10.1371/journal.pone.0054431
Randomised trial of glutamine, selenium, or both, to supplement parenteral nutrition for critically ill patients

Peter J D Andrews, professor of critical care, consultant,1,2 Alison Avenell, clinical senior lecturer,3 David W Noble, consultant,4 Marion K Campbell, director,5 Bernard L Croal, consultant,5 William G Simpson, consultant,5 Luke D Vale, professor of health technology assessment,5,6 Claire G Battison, trial manager,1 David J Jenkinson, research fellow in medical statistics,7 Jonathan A Cook, methodologist3 and the SIGNET (Scottish Intensive care Glutamine or seleNium Evaluative Trial) Trials Group

Formulation:
- Glutamine
- Selenium
- Glutamine + selenium
- Neither

Cumulative survival

Time after randomisation (days)

parenteral nutrition supplemented with selenium for ≥5 days - reduction in new infections
Erythrocyte selenium concentration predicts intensive care unit and hospital mortality in patients with septic shock: a prospective observational study

Nara Aline Costa¹, Ana Lúcia Gut¹, José Alexandre Coelho Pimentel², Silvia Maria Franciscato Cozzolino², Paula Schmidt Azevedo¹, Ana Angélica Henrique Fernandes³, Bertha Furlan Polegato¹, Suzana Erico Tanni¹, Rafael Dezen Gaiolla¹, Leonardo Antonio Mamede Zornoff¹, Sergio Alberto Rupp de Paiva¹ and Marcos Ferreira Minicucci¹

Key messages

Erythrocyte selenium concentration is a predictor of

- ICU and hospital mortality in patients with septic

- not due to influence on GPx1 activity
Products

sodium selenite pentahidrat

Decan (Baxter, Aquettant) 153μg/40ml

Microsol Selenium (Boiron) 40μg/vial

Nonan (Baxter, Aquettant) 40μg/40ml

Tracitran (Fresenius) 105,2μg/40ml

Tracutil (B.Braun) 78,9μg/10ml

Addamel (Fresenius) 32μg/10ml
DOSES

- Recommended Daily Allowance (RDA) of selenium is 60 μg for women and 75 μg for men/day.

- The World Health Organisation suggests 40 μg/day of selenium is necessary to prevent disease.

- In the UK, current intake is estimated at 34 μg/day.

What is the optimal dose of selenium for supplementation on the ICU?

There may be a benefit from supplementing parenteral nutrition administered during critical illness with 500 μg of selenium daily for at least five days.

- the safe upper limit for short term supplementation is 1,000 μg/day
- for long-term supplementation is 400-550 μg/day

1. Peter J D Andrews et al., Randomised trial of glutamine, selenium, or both, to supplement parenteral nutrition for critically ill patients, BMJ 2011;342:d1542
Products
sodium selenite pentahidrat

Decan (Baxter, Aquettant) 153μg/40ml

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Tracutil (B.Braun) 78,9μg/10ml

Addamel (Fresenius) 32μg/10ml
Selenium Trace Element, 40 mcg/mL, 10mL Vial
<table>
<thead>
<tr>
<th>Author</th>
<th>Supplementation</th>
<th>Patients</th>
<th>No. of patients</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zimmerman et al. [117], 1997</td>
<td>1000 µg/day Na-selenite IV vs no selenium. + 500 mg Vit C orally</td>
<td>SIRS+organ failure</td>
<td>40</td>
<td>Se supplementation reduced mortality.</td>
</tr>
<tr>
<td>Forceville et al. [97], 1998</td>
<td>40 µg/day Na-selenite +11.2IU Vit E + 500 mg Vit C IV</td>
<td>Adult ICU patients</td>
<td>134</td>
<td>3-fold increase in morbidity and mortality in patients with low selenium concentrations. Efficacy of Se supplementation needs further investigation. Significant decrease in bronchopneumonia infection and shorter hospital stay with trace element supplementation.</td>
</tr>
<tr>
<td>Berger et al. [116], 1998</td>
<td>159 µg selenium +40.4 µmol copper +406 µmol zinc + 32 µg selenium + 20 µmol copper +100 µmol zinc</td>
<td>Major burn</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Satio et al. [128], 1998</td>
<td>150 mg ebselen twice daily orally</td>
<td>Subarachnoid hemorrhage</td>
<td>286</td>
<td>Ebselen reduced brain damage and may be a promising neuroprotective agent.</td>
</tr>
<tr>
<td>Angstwurm et al. [118], 1999</td>
<td>535 µg/day Na-selenite (3 days), then 285 µg (3 days), then 155 µg (3 days) vs 35 mg Vit E IV</td>
<td>SIRS+APACHE&gt;15</td>
<td>42</td>
<td>Se replacement seems to improve clinical outcome and reduce incidence of acute renal failure requiring hemodialysis.</td>
</tr>
<tr>
<td>Porter et al. [114], 1999</td>
<td>50 µg/6h sodium selenite IV+400IU Vit E, 100 mg VitC, 8 gm N-acetylcysteine 6/8h orally</td>
<td>Surgical ICU trauma patients</td>
<td>18</td>
<td>Antioxidant supplementation was associated with fewer infectious complications and fewer organ dysfunctions.</td>
</tr>
<tr>
<td>Berger et al. [113], 2001</td>
<td>500 µg Na-selenite only IV</td>
<td>Critically ill trauma patients</td>
<td>31</td>
<td>Earlier normalization of T4 and reverse T3 plasma levels with Se supplementation.</td>
</tr>
<tr>
<td>Berger et al. [128], 2002</td>
<td>380 µg selenium + 59 µmol copper +574 µmol zinc vs placebo</td>
<td>Burn</td>
<td>17</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Andrews et al. [129], 2004</td>
<td>Glutamine containing and non-glutamine containing parenteral nutrition with or without Na-selenite</td>
<td>ICU patients requiring parenteral nutrition</td>
<td>500</td>
<td>Not available-personal communication</td>
</tr>
<tr>
<td>Angstwurm et al. [129], 2004</td>
<td>500 µg/day IV</td>
<td>ICU patients with nonthyroidal illness</td>
<td>41</td>
<td>Se supplementation in patients with nonthyroidal illness improved morbidity.</td>
</tr>
<tr>
<td>Mishra et al. [127], 2006</td>
<td>474 µg/day Na-selenite (3 days), 316 µg (3 days), 158 µg (3 days), then 31.6 µg/day IV vs 31.6 µg/day from the beginning</td>
<td>Severe sepsis</td>
<td>40</td>
<td>Se supplementation did not reduce oxidative damage or requirement for renal replacement therapy.</td>
</tr>
<tr>
<td>Angstwurm et al. [128], 2007</td>
<td>1000 µg/day Na-selenite IV vs placebo</td>
<td>Severe SIRS, sepsis and septic shock</td>
<td>249</td>
<td>Se supplementation reduced mortality in patients with severe sepsis and septic shock.</td>
</tr>
</tbody>
</table>

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Normal value

0-3 mo: 18-64 μg/L
4-11 mo: 32-101 μg/L
1-5 y: 58-116 μg/L
6-16 y: 69-121 μg/L
> 16 y: 74-139 μg/L

For optimal selenoprotein activity = 100 μg/L

EU average is 79 μg/L (1)

< 40 μg/L - Selenium deficit
  - loss of glutathione peroxidases activity

Selenium monitoring – plasma

When?

Sepsis, septic shock
Burns
Trauma
Pancreatitis
TPN
CVVH
Warning !!!!!!!

> 2.400μg/day  TOXIC for human (1)

dose above 500–800 μg/day selenium should not be administered in routine practice in ICU patients (2)


2. Xavier Forceville et al. Effects of high doses of selenium, as sodium selenite, in septic shock, Critical Care 2007: Vol 11 No 4
Conclusions - Se

- essential for its **antioxidant function** in critically ill patients
- dose of **500 µg/day** seems to be safe and effective
- supplementation is **inexpensive**
- for ICU patients, in whom the literature suggests it should be **supplemented parenterally**
- reduce mortality rate in ICU