From A to Zinc: the evolving concept of micronutrient supplementation

Micronutrients and cancer prevention

T. Grune (DE)
Micronutrients and Cancer Prevention

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Institute of Nutrition
Friedrich Schiller University Jena
Micronutrients and Metabolism

- Hormonal Regulation
- Enzym Cofactors
- Micro-nutrients
- Cell physiologie
- Redox-regulation
- Intermediate Metabolism
- Sensoric Functions
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Micronutrients and their roles in various metabolic processes.
Oxidative Stress

Disturbance of the antioxidant and prooxidant system in favor of the prooxidants (Sies, 1985)

At least two major problems are associated with manipulating the redox status.
Antioxidative Defenses

Non-enzymatic:

a) Low molecular
   - hydrophilic
     • Vitamin C
     • Urate
     • Glutathion
   - lipophilic
     • Carotinoids
     • Vitamin E

b) Proteins
   - Metall-binding

Enzymatic:

• SODs (CuZn, Mn)
• Peroxidases
  – Catalase
  – GSH-Peroxidases
  – Peroxiredoxins
• Reductases
  – GSSG-Reductase
  – Glutaredoxin
  – Thioredoxin/-reductase
• Phase I- and Phase II-enzymes
  – NQOR1
  – GSH-transferases
  – ...
• Repair enzymes
Low molecular weight antioxidants

Endogenic:
- Uric acid
- Bilirubin
- Glucose
- Proteins
- Fe- and Cu-binding

Exogenic:
- Vitamins (β-Carotin, E, C)
- Carotinoids
- Ubichinon
- Lipoic acid
- Flavonoids, Polyphenols
# Low molecular weight antioxidants

## Concentrations

<table>
<thead>
<tr>
<th>Antioxidants</th>
<th>Plasmagehalt (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hydrophil</strong></td>
<td></td>
</tr>
<tr>
<td>Ascorbat</td>
<td>30-150</td>
</tr>
<tr>
<td>Glutathion</td>
<td>1-2</td>
</tr>
<tr>
<td>Urat</td>
<td>160-450</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>5-20</td>
</tr>
<tr>
<td><strong>Lipophil (mit Lipoproteinen assoziiert)</strong></td>
<td></td>
</tr>
<tr>
<td>α-Tocopherol</td>
<td>15-40</td>
</tr>
<tr>
<td>γ-Tocopherol</td>
<td>3-5</td>
</tr>
<tr>
<td>α-Carotin</td>
<td>0.05-0.1</td>
</tr>
<tr>
<td>β-Carotin</td>
<td>0.3-0.6</td>
</tr>
<tr>
<td>Lycopin</td>
<td>0.5-1.0</td>
</tr>
<tr>
<td>Lutein</td>
<td>0.1-0.3</td>
</tr>
<tr>
<td>Zeaxanthin</td>
<td>0.1-0.2</td>
</tr>
<tr>
<td>Ubichinol-10</td>
<td>0.4-1.0</td>
</tr>
</tbody>
</table>

from: Sies et al., Ann N Y Acad Sci 669: 7-20, 1992
Low molecular weight antioxidants Interactions

Antioxidant Interaction

- LOO·
- Uric acid
- Vitamin E
- α-Lipoic acid
- Vitamin C

Low molecular weight antioxidants

Interactions

Problem 1
Micronutrients and Redox Regulation

Oxidants and Radicals

Food

Oxidants
Xenobiatica
(Irradiation)

ER / CyP

Metabolism

Lipids

Proteins

Chromatin
Micronutrients and Redox Regulation

Food

Oxidants

Xenobiotica (Irradiation)

Antioxidants

Antioxidants

Proteins

Chromatin

Metabolism

Lipids

ER / CyP

Problem 2
Micronutrients and Redox Regulation

Problem 2

Blocking of regulatory effects !!!!
Why micronutrient supplementation?
Why micronutrient supplementation?

Disbalance / no evolutionary adaptation to food processing

→ Requirement of supplements / measurements by biomarkers
Antioxidant supplementation

Vitamin supplementation helps if nutrition is not adequate. Is there an additional benefit of higher doses?
Antioxidant supplementation

Vitamin supplementation helps if nutrition is not adequate. Is there an additional benefit of higher doses?

High vitamin doses might be not healthy or have side effects. High antioxidant supplementation might suppress redox regulation.

Research: moderate multivitamins might be more effective. Studies: testing often single (high dosis) vitamins
Micronutrients and Cancer

Gaziano et al. JAMA 2012

Multivitamins in the Prevention of Cancer in Men
The Physicians’ Health Study II Randomized Controlled Trial

**Conclusion** In this large prevention trial of male physicians, daily multivitamin supplementation modestly but significantly reduced the risk of total cancer.
Micronutrients and Cancer

Gaziano et al. JAMA 2012
Micronutrients and Cancer

Gaziano et al. JAMA 2012

Design:

- Male physicians (N=14642)
- 11.2 years treatment
- age: 64 ± 9 years (baseline)
- 2669 cancer cases (1373 prostate cancer)

- Mutivitamins:
  • Vit E 400 IU (until 2007)
  • Vit C 500 mg (until 2007)
  • beta carotin (until 2003)(Lurotin/BASF 50mg)
Micronutrients and Cancer

Gaziano et al. JAMA 2012

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Total Men in Analysis</th>
<th>No. of Men</th>
<th>No. of Events</th>
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<th>Adjusted HR (95% CI)</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>Total cancer</td>
<td>14,641</td>
<td>7317</td>
<td>1290</td>
<td>7324</td>
<td>1379</td>
<td>0.92 (0.86-0.998)</td>
<td>.04</td>
</tr>
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<td>Total epithelial cell cancer d</td>
<td>14,641</td>
<td>7317</td>
<td>1158</td>
<td>7324</td>
<td>1244</td>
<td>0.92 (0.85-0.997)</td>
<td>.04</td>
</tr>
<tr>
<td>Total cancer minus prostate cancer e</td>
<td>14,641</td>
<td>7317</td>
<td>641</td>
<td>7324</td>
<td>715</td>
<td>0.88 (0.79-0.98)</td>
<td>.02</td>
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<tr>
<td>Total mortality f</td>
<td>14,641</td>
<td>7317</td>
<td>1345</td>
<td>7324</td>
<td>1412</td>
<td>0.94 (0.88-1.02)</td>
<td>.13</td>
</tr>
<tr>
<td>Cancer mortality</td>
<td>14,641</td>
<td>7317</td>
<td>403</td>
<td>7324</td>
<td>456</td>
<td>0.88 (0.77-1.01)</td>
<td>.07</td>
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Importance:
- large scale
- randomized
- long-term
- multivitamins
## Micronutrients and Cancer Metaanalyses

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<th>Studies</th>
<th>N</th>
<th>Mortality</th>
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<tr>
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<td>1.414</td>
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<td>Macpherson et al. (2013) Multivitamin-multimineral supplementation and mortality</td>
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Bjelakovic et al. JAMA 2007

Mortality in Randomized Trials of Antioxidant Supplements for Primary and Secondary Prevention
Systematic Review and Meta-analysis

Design:
- 68 studies
- 232,606 participants
- mortality
Micronutrients and Cancer Metaanalyses

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Systematic Review and Meta-analysis

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Data Synthesis  When all low- and high-bias risk trials of antioxidant supplements were pooled together there was no significant effect on mortality (RR, 1.02; 95% CI, 0.98-1.06). Multivariate meta-regression analyses showed that low-bias risk trials (RR, significantly associated with mortality. In 47 low-bias trials with 180 938 participants, the antioxidant supplements significantly increased mortality (RR, 1.05; 95% CI, 1.02-

Conclusions  Treatment with beta carotene, vitamin A, and vitamin E may increase mortality. The potential roles of vitamin C and selenium on mortality need further study.
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Micronutrients and Cancer Metaanalyses

Biesalski et al. Nutrients, 2010

Article

Reexamination of a Meta-Analysis of the Effect of Antioxidant Supplementation on Mortality and Health in Randomized Trials

Hans K. Biesalski 1,*, Tilman Grune 2, Jana Tinz 1, Iris Zöllner 3 and Jeffrey B. Blumberg 4

Design:
- same 68/66 studies / 232 606 participants
- primary end-point (+1/0/-1)
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<tr>
<td>All studies (66 RCTs)</td>
<td>+1</td>
<td>24</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>39</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>-1</td>
<td>3</td>
<td>4</td>
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Biesalski et al. Nutrients, 2010

Table 1. Study outcome (intervention effects of antioxidant trials) with respect to primary goal and study type.

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<td>39</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>−1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Primary prevention studies (20 RCTs)</td>
<td>+1</td>
<td>8</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>12</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>−1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Secondary prevention studies (34 RCTs)</td>
<td>+1</td>
<td>10</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>17</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>−1</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Therapeutic intervention studies (16 RCTs)</td>
<td>+1</td>
<td>6</td>
<td>37.5</td>
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<tr>
<td></td>
<td>0</td>
<td>10</td>
<td>62.5</td>
</tr>
<tr>
<td></td>
<td>−1</td>
<td>0</td>
<td>0</td>
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→ More such studies are needed.
Thank you!