Balancing vitamin A intake to mitigate the risk of excessive stores

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What is vitamin A?

An essential micronutrient needed in small amounts for life
Functions of vitamin A

Ross et al. (2000) Physiol. Rev. 80:1021-54

vitamin A
β-cryptoxanthin
β-carotene
fruit and vegetable intake
Vitamin A

- Retinol
- Retinal
- Retinoic acid
- Retinyl palmitate
Provitamin A carotenoids

\[ \alpha\text{-carotene} \]

\[ \beta\text{-carotene} \]

\[ \beta\text{-cryptoxanthin} \]
Important Abbreviations

- EAR – Estimated Average Requirement
- RDA – Recommended Dietary Allowance
- AI – Adequate Intake
- UL – Tolerable Upper Intake Level
Important Definitions

• EAR – A nutrient intake value estimated to meet the requirements of 50% of healthy individuals in a group.

• RDA – The average daily intake level sufficient to meet the nutrient requirement of nearly all (97-98%) healthy individuals in a group.

  - RDA = EAR + 2 standard deviations
Important Definitions

• AI – A value based on observed or experimentally determined estimates of nutrient intake by a group of healthy people – when an RDA cannot be determined.

• UL – The highest level of a daily nutrient intake that is likely to pose no risks of adverse health effects to almost all individuals in the general population.
Establishing Dietary Recommended Intakes

- EAR
- RDA
- UL

Risk of Inadequacy

Risk of Adverse Effects

AI
RDA for Vitamin A

- 700 µg retinol activity equivalents (RAE) for adult women
- 900 µg RAE for adult men
- 1500 µg for Daily Value up until 2018-9
- How can that be?
Current rule!

- Up until 2016, a huge discrepancy existed between the Daily Value and the RDA for vitamin A. The Daily Value, which is used on Supplement and Nutrition Facts panels, was based on the 1960’s RDA value of 1500 µg retinol equivalents. However, on 26 July 2016, the final rule was changed and by July 2018 and 2019 for larger and smaller food manufacturers, respectively, the labels must be updated to the current RDA for adult males as 100% as the Daily Value, i.e., 900 µg RAE.
Vitamin A homeostasis?

Body content

- Optimal level
- Increased efficiency of absorption
- Decreased efficiency of absorption

Intake
Does the body regulate absorption of vitamin A?

- Most likely we regulate the conversion of β-carotene to retinol.
- Most of the vitamin A that enters the body, however, gets absorbed. At least this is what is commonly accepted.
Well then how much vitamin A do I need for optimal health?

Likely the EAR!
<table>
<thead>
<tr>
<th>Adults</th>
<th>EAR</th>
<th>RDA</th>
<th>Tolerable upper intake level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females 14-18 y</td>
<td>485</td>
<td>700</td>
<td>2800</td>
</tr>
<tr>
<td>Females &gt; 19 y</td>
<td><strong>500</strong></td>
<td>700</td>
<td>3000</td>
</tr>
<tr>
<td>Males 14-18 y</td>
<td>630</td>
<td>900</td>
<td>2800</td>
</tr>
<tr>
<td>Males &gt; 19 y</td>
<td><strong>625</strong></td>
<td>900</td>
<td>3000</td>
</tr>
<tr>
<td>Pregnancy 14-18 y</td>
<td>530</td>
<td>750</td>
<td>2800</td>
</tr>
<tr>
<td>Pregnancy 19-50 y</td>
<td>550</td>
<td>770</td>
<td>3000</td>
</tr>
<tr>
<td>Lactation 14-18 y</td>
<td>885</td>
<td>1200</td>
<td>2800</td>
</tr>
<tr>
<td>Lactation 19-50 y</td>
<td>900</td>
<td>1300</td>
<td>3000</td>
</tr>
</tbody>
</table>
Bioconversion factors

• It is best to get your vitamin A from the β-carotene and other provitamin A carotenoids in fruits and vegetables.
• However, then you need to convert the carotenoids into vitamin A equivalents known as retinol activity equivalents (RAE).
Bioaccessibility = \frac{\beta CE_{\text{released}}}{\beta CE_{\text{total}}}

Bioavailability = \frac{\beta CE_{\text{absorbed}}}{\beta CE_{\text{total}}}

Bioconversion = \frac{\text{Retinol}}{\beta CE_{\text{absorbed}}}

Bioefficacy = \frac{\text{Retinol}}{\beta CE_{\text{total}}}

Tanumihardjo et al., IJVNR 2010
Bioconversion factors
Retinol activity equivalents

<table>
<thead>
<tr>
<th>Compound</th>
<th>Retinol</th>
<th>Amount needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinyl palmitate</td>
<td>1 µg</td>
<td>1.8 µg</td>
</tr>
<tr>
<td>Retinyl acetate</td>
<td>1 µg</td>
<td>1.15 µg</td>
</tr>
<tr>
<td>Supplemental β-carotene</td>
<td>1 µg</td>
<td>2 µg</td>
</tr>
<tr>
<td>β-carotene</td>
<td>1 µg</td>
<td>12 µg</td>
</tr>
<tr>
<td>β-cryptoxanthin</td>
<td>1 µg</td>
<td>24 µg</td>
</tr>
<tr>
<td>α-carotene</td>
<td>1 µg</td>
<td>24 µg</td>
</tr>
</tbody>
</table>
But wait, my vitamin pill container is in IUs.

What does that mean?
International Units (IUs)

- 1 IU of vitamin A is equivalent to 0.3 μg of retinol or 0.6 μg of β-carotene
What is in your supplement?

Usually retinyl acetate or retinyl palmitate
Throw those away!

Search for one formulated with β-carotene or take them every other day
### Centrum silver

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Amount Per Serving</th>
<th>% Daily Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A 2,500 IU (40% as Beta-Carotene)</td>
<td></td>
<td>50%</td>
</tr>
<tr>
<td>Vitamin C 60 mg</td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>Vitamin D 1,000 IU</td>
<td></td>
<td>250%</td>
</tr>
<tr>
<td>Vitamin E 50 IU</td>
<td></td>
<td>167%</td>
</tr>
<tr>
<td>Vitamin K 30 mcg</td>
<td></td>
<td>38%</td>
</tr>
<tr>
<td>Thiamin 1.5 mg</td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>Riboflavin 1.7 mg</td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>Niacin 20 mg</td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>Vitamin B6 3 mg</td>
<td></td>
<td>150%</td>
</tr>
<tr>
<td>Folic Acid 400 mcg</td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>Vitamin B12 25 mcg</td>
<td></td>
<td>417%</td>
</tr>
<tr>
<td>Biotin 30 mcg</td>
<td></td>
<td>10%</td>
</tr>
<tr>
<td>Pantothenic Acid 10 mg</td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>Calcium 220 mg</td>
<td></td>
<td>22%</td>
</tr>
<tr>
<td>Phosphorus 20 mg</td>
<td></td>
<td>2%</td>
</tr>
<tr>
<td>Iodine 150 mcg</td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>Magnesium 50 mg</td>
<td></td>
<td>13%</td>
</tr>
<tr>
<td>Zinc 11 mg</td>
<td></td>
<td>73%</td>
</tr>
<tr>
<td>Selenium 19 mcg</td>
<td></td>
<td>27%</td>
</tr>
<tr>
<td>Copper 0.5 mg</td>
<td></td>
<td>25%</td>
</tr>
<tr>
<td>Manganese 2.3 mg</td>
<td></td>
<td>115%</td>
</tr>
<tr>
<td>Chromium 50 mcg</td>
<td></td>
<td>42%</td>
</tr>
<tr>
<td>Molybdenum 45 mcg</td>
<td></td>
<td>60%</td>
</tr>
<tr>
<td>Chloride 72 mg</td>
<td></td>
<td>2%</td>
</tr>
<tr>
<td>Potassium 80 mg</td>
<td></td>
<td>2%</td>
</tr>
<tr>
<td>Nickel 5 mcg</td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>Silicon 2 mg</td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>Vanadium 10 mcg</td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>Lutein 250 mcg</td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>Lycopene 300 mcg</td>
<td></td>
<td>*</td>
</tr>
</tbody>
</table>

*Daily Value (DV) not established.*
What’s in this supplement?

- 2500 IU vitamin A
- 50% of the Daily Value
- 40% as β-carotene
What’s in this supplement?

• 2500 IU vitamin A is 50% DV so the DV is 5000 IU on this supplement.
• But most supplements are 100%!
• Therefore let’s do those calculations:
  – 40% as β-carotene or 2000 IU
  – 60% as vitamin A or 3000 IU
What’s in this supplement?

- 3000 IU vitamin A X 0.3 µg = 900 µg
- 2000 IU β-carotene X 0.6 µg = 1200 µg

- How much over: 900 µg – EAR
- Women 900 µg – 500 µg = 400 µg excess
- Men 900 µg – 625 µg = 275 µg excess

- And there is still β-carotene!!!
What happens when you take the supplement
What is the current focus of the World Health Organization?
Current dimensions of major forms of malnutrition

Intra-uterine growth retardation
- 30 million/year (23.8% of all births)

Protein-energy malnutrition
- 159 million under-5 children

Iodine deficiency disorders
- 740 million

Vitamin A deficiency
- 190 million under-5 children

Anaemia including iron deficiency
- 2 billion

Obesity
- >300 million people

→ Low birth weight
→ Brain damage
→ Increased morbidity & mortality
→ Brain damage
→ Blindness
→ Increased morbidity & mortality
→ Impaired motor development
→ Reduced physical activity
→ CVD & Diabetes
Methods to alleviate vitamin A deficiency

• Targeted supplementation with preformed retinyl palmitate
• Fortification of staple crops and processed foods with preformed retinyl palmitate
• Promotion of dietary diversity through inclusion of more provitamin A carotenoid sources
• Biofortification of staple crops with β-carotene and/or β-cryptoxanthin
The Interim –
High Dose Supplements
Supplements alone are not enough!
Fortification

Addition of minerals or preformed vitamin A to commonly consumed foods, such as sugar, oil, maize flour, rice and wheat.
Examples

• Vitamin A added to milk in the 1940’s in the US. Mandatory in 1978 because of the popularity of skim and lower fat milks.
• Sugar in Guatemala
• Maize meal and wheat flour in South Africa
• Oil in many African and Asian countries
People in the US have access to fortified foods and supplement usage, especially multivitamins, is high (>70%).
Milk consumption has decreased
US Cadaver Study

- Matched serum and liver samples were procured from cadavers \((n = 27; 70.7 \pm 14.9 \text{ y}, 49-101 \text{ y})\)
- Circle is serious vitamin A deficiency!

\[ r = 0.50, P = 0.008 \]

\[ r = 0.0, P = 0.95 \]
Serious vitamin A toxicity!

\[ r = 0.43, \quad P < 0.001 \]
Distribution of liver values

- Hyper-vitaminotic (>1.0 μmol/g) 33%
- Deficient (<0.1 μmol/g) 22%
- Optimal (0.1 - 0.7 μmol/g) 41%
- High (0.7 - 1.0 μmol/g) 4%
Recent case study

- Ultimate Antiox Full Spectrum (Serv. Size 3 capsules; dosage 8,300 IU) Mixed carotenoids from palm tree fruit
- Acnutrol (Serv. Size 6 capsules; dosage 5,000 IU) Vitamin A as retinyl palmitate
- Bio-Ae-Mulsion Forte (Serv. Size 1 drop; dosage 12,500 IU; 6 drops 3 times/day) Vitamin A as palmitate
Moving to the continent of Africa

Zambia
Advantages of biofortification to enhance provitamin A carotenoids

- Targets the poor: eat high levels of food staples
- Rural-based: complements fortification and supplementation
- Cost-effective: research at a central location can be multiplied across countries and time
- Sustainable: investments are front-loaded, low recurrent costs
“Pumpkin nshima”
Good choice for Zambians
Partnerships, sensitization and engaging the community

- ZamSeed, National Food and Nutrition Commission, Tropical Research and Development Center, and University of Wisconsin – Madison
- Met with Provincial Health offices and did a baseline survey
- Hired locals as much as possible
Hiring nutritionists
Grinding the maize
Setting up kitchens
Cooking the maize
Stirring and stirring....
If you don’t have help!
Cleaning up the mess
Estimation of total body reserves of vitamin A using isotopic methods
The “blue” group was administered the recommended daily allowance for vitamin A, which is 400 µg retinol activity equivalents/day, six days/week. The other groups received placebo oil (214 µL/d) with or without orange maize.
Daily dosing with the RDA or placebo oil
Children adapted to the orange maize!

A total of 133 children were successfully enrolled and analyzed.
Orange maize was as good as the supplement!

\[ P = 0.0034 \]

When values are ranked

Gannon et al., Am J Clin Nutr 2014
Degree of concern for baseline status

- Scientific published finding
- Assumes 80% is stored in the liver
- 59% of the children have hypervitaminotic liver stores corrected for inflammation
- Defined as $\geq 1 \, \mu\text{mol/g liver}$

Gannon et al., Am J Clin Nutr 2014
Should this really surprise us?
Evaluation of baseline liver retinol reserves were 0.57 μmol/g liver, well above deficient (0.1 μmol/g liver).

One year after sugar fortification was implemented, liver reserves increased to 1.2 μmol/g liver. In 9 of 21 children, liver vitamin A concentrations were hypervitaminotic.

More than enough for the day in the children’s porridge in Zambia!
Mangoes

Green leaves - all kinds of them
Fish are eaten whole
Opportunity to follow-up on other biomarkers of status

- Dietary intake surveys that capture exposure and seasonality
- Serum carotenoid profiles
- Markers of bone turnover
Supporting evidence of high stores

- Serum carotenoids: Reference is three staff in the Tanumihardjo lab
- N is 126 Zambian children at baseline

<table>
<thead>
<tr>
<th>Lutein</th>
<th>Zeaxanthin</th>
<th>β-Cryptoxanthin</th>
<th>Lycopene</th>
<th>α-Carotene</th>
<th>β-Carotene</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.103</td>
<td>0.036</td>
<td>0.070</td>
<td>0.309</td>
<td>0.128</td>
<td>0.155</td>
<td>0.803</td>
</tr>
<tr>
<td>0.86 ± 0.52</td>
<td>0.035 ± 0.032</td>
<td>0.10 ± 0.092</td>
<td>0.20 ± 0.29</td>
<td>0.62 ± 0.47</td>
<td>0.73 ± 0.51</td>
<td>2.55 ± 1.23</td>
</tr>
</tbody>
</table>

+735% same similar -35% +384% +371 218%

βC 0.19 (ND-1.43) αC 0.05 (ND-0.71) Lycopene 0.15 (ND-0.74)

Spannaus-Martin et al., EJCN, 1998
Rivals all published values
(μmol/L)

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>β-carotene</td>
<td>0.65 (0.50, 1.00)</td>
<td>0.74 (0.51, 1.14)</td>
<td>0.61 (0.40, 0.91)</td>
<td>0.57 (0.29, 1.00)</td>
<td>0.42</td>
</tr>
<tr>
<td>α-carotene</td>
<td>0.49 (0.35, 0.62)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.81 (0.47, 1.06)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.46 (0.29, 0.73)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.45 (0.26, 0.67)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.0016</td>
</tr>
<tr>
<td>β-cryptoxanthin</td>
<td>0.07 (0.05, 0.10)</td>
<td>0.07 (0.03, 0.19)</td>
<td>0.07 (0.05, 0.12)</td>
<td>0.10 (0.07, 0.13)</td>
<td>0.60</td>
</tr>
<tr>
<td>Lutein</td>
<td>0.95 (0.67, 1.23)&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>0.50 (0.39, 0.67)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.77 (0.41, 1.15)&lt;sup&gt;bc&lt;/sup&gt;</td>
<td>0.98 (0.81, 1.23)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.0003</td>
</tr>
<tr>
<td>Zeaxanthin</td>
<td>0.04 (0.03, 0.06)</td>
<td>0.02 (0.02, 0.03)</td>
<td>0.04 (0.02, 0.06)</td>
<td>0.04 (0.03, 0.06)</td>
<td>0.07</td>
</tr>
<tr>
<td>Lycopene</td>
<td>0.13 (0.09, 0.16)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.34 (0.26, 0.57)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.11 (0.10, 0.37)&lt;sup&gt;bc&lt;/sup&gt;</td>
<td>0.20 (0.12, 0.54)&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Really?? Orange hands??

The balancing act
Tanumihardjo, J Clin Densitom 2013

- Under normal conditions, bone formation and breakdown are tightly linked through a variety of regulatory signals.
- The influence of vitamin A and provitamin A carotenoids is not entirely known.
Bone remodeling cycle

Procollagen type 1 N-terminal (P1NP) formation

Carboxy-terminal collagen crosslink (CTX) breakdown

Why did we choose these?

- **P1NP**: Low inter-individual variability, relatively stable, and recommended by the Bone Marker Standards working group. Specific product of proliferating osteoblasts and fibroblasts.

- **CTX**: Bone breakdown product derived from collagen. Low variability and stable in blood samples.
Bone turnover markers

**CTX**

- VA-
- Orange
- VA+

**P1NP**

- VA-
- Orange
- VA+

- \( P = 0.31 \)
- \( P < 0.0001 \)
Repeated measures

Type 3 Tests of Fixed Effects

Effect    Pr > F
trt       0.060
time      < 0.0001
trt*time  < 0.0001
Overall there is a positive correlation and each line has a different intercept….so we need more research.
Methods to assess vitamin A status

<table>
<thead>
<tr>
<th>VITAMIN A STATUS CONTINUUM</th>
<th>Deficient</th>
<th>Adequate</th>
<th>High</th>
<th>Hypervitaminotic</th>
<th>Toxic</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIVER VA (µmol/g)</td>
<td>&lt; 0.1</td>
<td>0.1 – 0.7</td>
<td>0.7 – 1</td>
<td>&gt;1</td>
<td></td>
</tr>
</tbody>
</table>

- Clinical signs and tests
- Serum retinol
- Breast milk retinol
- Dose response tests
- Isotope dilution
- Liver sample

Is this 3 µmol/g?
### Maintaining balance or else...

<table>
<thead>
<tr>
<th>Vitamin A deficiency</th>
<th>Adequacy</th>
<th>High stores</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate intake</td>
<td>Adequate intake</td>
<td>Excessive intake</td>
<td></td>
</tr>
<tr>
<td>Xerophthalmia</td>
<td>Lecithin:retinol acyltransferase</td>
<td>Catabolism</td>
<td></td>
</tr>
<tr>
<td>Serum retinol</td>
<td>β-carotene dioxygenase activity</td>
<td>Serum retinyl esters</td>
<td></td>
</tr>
<tr>
<td>apo-RBP</td>
<td>Mortality</td>
<td>Osteoporosis risk</td>
<td></td>
</tr>
<tr>
<td>Resistance to infection</td>
<td></td>
<td>Liver fibrosis</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td>Liver cirrhosis</td>
<td></td>
</tr>
</tbody>
</table>

Altered immune function (?)

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Increasing habitual daily vitamin A intake

Tanumihardjo et al., 2016
The bottom line...
All things in moderation except vegetables!
Dietary diversification

Teach them how to garden!
Thank you for your attention!

Any questions or discussion points?