Vitamin A and Zinc

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Vitamin A – History

• Sir Frederick Gowland Hopkins discovered that milk prevented death among rats fed purified diets (fat, starch, salts, and purified milk proteins)
  • Fat-soluble A
  • What other nutrient was in Fat-soluble A?
  • World War I: Butter, an important source of fat-soluble A, scarce
  • Nobel Prize 1929 (with Christiaan Eijkman)
  • McCollum and Davis extracted “Vitamin A” from butter, egg yolk and cod liver oil

Vitamin A – Forms & Measurement

• Forms
  • Animal sources - Preformed vitamin A
    • Retinol, retinal
  • Plant sources - Carotenoids
    • accessory pigments - ~600 - only 50 are pro-vitamin A
• Measurement
  • Retinol Activity Equivalent (RAE)
    • 1 RAE = 1 µg Retinol
    • 1 µg beta-carotene = 1/2 RE if dissolved in oil; 1/12 RE if in the diet

Vitamin A – Common Sources

• Sources
  • Liver, fish oils (cod liver oil), organ meats
  • ~6500 µg in liver
  • Cream, butter, fortified milks
  • ~684 µg in butter; 265 µg in cheddar cheese
  • Tropical fruits, carrots, sweet potatoes
  • ~835 µg in carrots; 709 µg in sweet potato; 38 µg in mango
  • Breast milk
  • Supplements

Dietary Reference Intake

• Adults
  • Males: 900 µg/day
  • Females: 700 µg/day
    • Pregnancy: +70 µg/day
    • Lactation: +600 µg/day
Vitamin A - Absorption

- Retinol & Carotenoids easily absorbed in the presence of fat
- Carried in chylomicrons
- Stored in liver as retinyl esters
- Retinol transported in plasma bound to RBP
- Absorption enhanced with increased dietary fat
- Excess intake stored in the liver
  - Developed countries - 200-300 µg/g
  - Less-developed countries - <40 µg/g

Vitamin A - Functions

- Vision - retinal comprises Rhodopsin
- Changes in gene expression and transcription
- Epithelial differentiation
- Structural proteins - skin keratins
- Enzymes - Alcohol Dehydrogenase
- Growth (Bone remodeling)
- Reproduction
- Apoptosis

Vitamin A: Rhodopsin

Vitamin A and Embryonic Development

- Development of structures posterior to the hindbrain
  - Vertebrae and spinal cord
- Development of the limbs, heart, eyes, and ears
- Excess is teratogenic
Vitamin A and Immunity

- Innate Immunity
  - Maintenance of Epithelial Integrity
  - Acute phase response - increase in serum amyloid A and C-reactive protein
  - Enhanced monocyte differentiation and function
  - Increased cytotoxicity of natural killer cells
  - Improved neutrophil function
- Adaptive Immunity
  - Increase in T-cell counts, particularly CD4 cells
  - Increase in the antibody response to vaccines - tetanus toxoid and measles

Assessment of Vitamin A Status

- Clinical Signs
  - Xerophthalmia
  - Functional
    - Night blindness
    - Serum Retinol

Serum Retinol & Vitamin A Deficiency

- Prevalence among children > 1 year of levels ≤ 0.7 µmol/L
- Limitations: Acute Phase Reaction

Acute Phase Reaction

- Response to injury or inflammation
- Acute Phase Proteins
  - Positive - Plasma concentrations increase
  - C-Reactive Protein (CRP)
  - Negative - Plasma concentrations decrease
  - Albumin, Retinol-binding Protein (RBP)

Assessment of Vitamin A Status

- Clinical Signs
  - Xerophthalmia
- Functional
  - Night blindness
- Serum Retinol
  - Not ideal in infection/inflammation
- Dose Response

Relative Dose Response

- After fasting blood (A0), 600 µg retinol
- Breakfast
- 5 hours later second blood sample (A5)
- RDR= (A5-A0/A5)x100
- Vitamin A deficiency: RDR > 20%
- Public health problem if abnormal RDR:
  - mild < 20%; moderate 20-30%; severe >30%
- Limitation: Invasive
**Modified Relative Dose Response**

- Fasting dose of 1.5 mg of 3,4-didehydroretinol analog
- Single blood sample 4-6 hours later
- MRDR = 3,4-didehydroretinol/retinol
- Vitamin A deficiency MRDR ≥ 0.06
- Public health problem abnormal MRDR
  - mild <20%; moderate 20-30%; severe >30%

**Assessment of Vitamin A Status**

- Clinical Signs
  - Xerophthalmia
- Functional
  - Night blindness
  - Serum Retinol
  - Not ideal in infection/inflammation
- Dose Response
- Retinol Isotope Dilution
  - Most sensitive biomarker of liver reserves

**Biomarkers of vitamin A status relative to qualitative liver reserves of vitamin A.**

**Deficiency**

- Vision
  - Night blindness (rods)
  - Keratomalacia (epithelium)
  - Xerophthalmia

**Vitamin A Deficiency: Eye Signs**

![Vitamin A Deficiency: Eye Signs](http://chemistry.gravitywaves.com/CHE452/images/ChemVitaminA.gif)
Deficiency

- Vision
- Night blindness (rods)
- Keratomalacia (epithelium)
- Xerophthalmia
- Growth retardation
- Infections
  - Increased number and severity
- Child mortality


Public Health Problem

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Prevalence in population at risk (6 months to 6 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nightblindness</td>
<td>&gt;1%</td>
</tr>
<tr>
<td>Bitot's spots</td>
<td>&gt;0.5%</td>
</tr>
<tr>
<td>Corneal Xerosis/Corneal Ulceration/Keratomalacia</td>
<td>&gt;0.01%</td>
</tr>
<tr>
<td>Corneal Scarring</td>
<td>&gt;0.05%</td>
</tr>
<tr>
<td>Serum Retinol (≤0.70 µmol/L)</td>
<td>&gt;20%; 10-19%; 2-9%</td>
</tr>
</tbody>
</table>

http://www.who.int/vmnis/indicators/retinol.pdf

Global Perspective

Vitamin A Deficiency - Magnitude

- Vulnerable groups
  - Pregnant women
  - Children
    - During periods of rapid growth
  - More than half the countries in the world affected
  - Areas with high infectious disease burden
  - 250 million preschool children
  - 250,000-500,000 vitamin A-deficient children become blind every year
  - 50% of these children die within 12 months of losing their sight

World Health Organization
Vitamin A Deficiency

Based on serum retinol

World Health Organization

Vitamin A Deficiency

Night Blindness

World Health Organization

Global Vitamin A Deficiency

World Health Organization

Vitamin A and Childhood Mortality

• Early 1980s: observational studies in Indonesia (Sommer) - children with xerophthalmia were more likely to die, compared to children without xerophthalmia

• Large community trial in Aceh, Indonesia (Sommer) - children (16 mo.) who received vitamin A supplementation every 6 months were significantly less likely to die, compared to those who did not receive vitamin A

Sommer, 1983; Sommer, 1986

Vitamin A and Childhood Mortality - Preschool

FIGURE 1 Impact of vitamin A on mortality. Relative mortality among children 6 mo-59 mo of age randomized to receive periodic large-dose vitamin A supplementation. Eight major randomized clinical trials, 6 in Asia and 2 in Africa, randomized rural children to receive periodic vitamin A supplements at regular intervals. All of the trials observed clinically and statistically significant reductions in mortality, 19-54%, compared with controls. Reproduced with permission (3).

Sommer A. Nutr 2008;138:1835-1839
Vitamin A and Childhood Mortality

- Led to substantial investments in research, and implementation of periodic vitamin A supplementation to children in 170 countries ($0.02 US $/dose)

- Issues
  - Timing
  - Dosage

**Vitamin A and Neonatal Mortality**

**Table 1. Neonatal Mortality by gender and birth weight**

<table>
<thead>
<tr>
<th>Gender</th>
<th>Death rate (per 1,000)</th>
<th>Birth weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>6.51</td>
<td>2.58</td>
</tr>
<tr>
<td>Female</td>
<td>7.50</td>
<td>2.57</td>
</tr>
<tr>
<td>Neonatal</td>
<td>11.05</td>
<td>2.57</td>
</tr>
</tbody>
</table>

**Vitamin A and Neonatal Mortality**

*Imdad A, et al. Cochrane Database of Systematic Reviews 2010;12*

*Vitamin A and Childhood Mortality - 2 wks to 6 mo*


*WHO/CHD. Lancet 1998;352:1257-1263*

*Vitamin A and Neonatal Mortality*

Vitamin A and Maternal Mortality

Bangladesh

Vitamin A and Maternal Mortality

Bangladesh

Ghana

Vitamin A and Maternal Mortality

Vitamin A and Infections

Vitamin A Interventions

Crop Modification

- Biocassava Plus
  - 2nd most important source of calories in sub-Saharan Africa
  - #1 food crop - 117 million tonnes in 2008

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Energy (kJ)</th>
<th>Protein (g)</th>
<th>Iron (mg)</th>
<th>Zinc (mg)</th>
<th>Vitamin A (µg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rice</td>
<td>1721</td>
<td>7.5</td>
<td>0.8</td>
<td>0.0</td>
<td>10</td>
</tr>
<tr>
<td>Golden</td>
<td>1630</td>
<td>6.0</td>
<td>2.7</td>
<td>1.0</td>
<td>3</td>
</tr>
</tbody>
</table>

After references 1501 Food and Agricultural Organisation, PHE estimated daily requirement is 700 µg.

Biocassava Plus

Golden Rice

- New improved variety
  - A cup of golden rice can supply 50% of daily vitamin A requirement in rice-based societies

www.goldenrice.org

Vitamin A Supplementation

- Most common method
- Periodic supplementation after 6 months of age
  - 6-11 months: 100,000 IU
  - 12-60 months: 200,000 IU every 3-6 months

Vitamin A Summary

- Vitamin A deficiency is a major public health problem
- Supplementation in children after 6 months of age reduces morbidity and mortality; at birth, may reduce mortality
- No evidence of benefits of supplementation in mothers, who are not vitamin A deficient
- Role in infections - more in later classes

Zinc - History

- Syndrome of Dwarfism, Hypogonadism, and Anemia in Iran and Egypt
- First cases of human zinc deficiency

Zinc - Dietary Reference Intake

- Men: 11 mg
- Women: 8 mg
  - Pregnancy: 11 mg
  - Lactation: 12 mg

Zinc – Common Sources

- Dietary sources
  - Animal products: meat, seafood, milk
  - Oysters: 76.7 mg per serving (6 medium)
  - Cashews, Almonds
  - Baked beans, chickpeas, peas, kidney beans

Zinc Metabolism

- 10-40% absorbed in small intestine
- ~25% absorbed from mixed diets
- Absorption decreased by:
  - Iron
  - Phytate
  - Malabsorptive states
  - Excreted in the stool
- No specific Zinc store
- needs to be consumed regularly
Zinc - Functions

• Functions
  - Activating cofactor for 70 important enzyme systems
  - Carbonic anhydrase, dehydrogenases, carboxypeptidases
  - DNA and RNA Polymerase
  - Growth
  - Protects against lipid peroxidation; tissue repair/wound healing
  - Immune function
  - Reduced B- and T-cell function
  - Decreased phagocytosis and cytokine production

Shankar and Prasad. AJCN 1998; 68:447S.

Assessment of Zinc Status

• Plasma Zn
  - Responsive to supplementation
• Hair Zn levels
• Functional assays
  - Alkaline phosphatase
  - High risk of deficiency at the population level
  - Prevalence of low plasma zinc concentration ≥ 20%
  - Prevalence of inadequate dietary intake of zinc ≥ 25%
  - Prevalence of stunting in under-five year olds ≥ 20%

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Zinc Deficiency

• Syndrome of Dwarfism, Hypogonadism, and Anemia in Iran and Egypt
• Congenital Zinc deficiency/Acrodermatitis enteropathica
  - Treatment: Lifelong Zinc supplements
• Malabsorptive states
  - Crohn’s disease
  - Celiac disease
  - Cystic fibrosis

Zinc Deficiency - Symptoms

• Deficiency symptoms
  - Growth failure
  - Primary hypogonadism
  - Skin disease - skin ulcerations, alopecia
  - Impaired taste/smell
  - Cognitive impairment
  - Impaired immunity - recurrent infections

Zinc and Growth

Zinc Deficiency - Symptoms

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Trial in Paris

• 57 breastfeed infants aged 4-9 months, many of African origin
• Randomization: 5 mg Zinc daily or Placebo
• Followed for 3 months

Walravens et al., Lancet 1992; 340:683
Zinc and Growth

| TABLE II—CHANGES IN WEIGHT, LENGTH, AND Z-SCORES FOR ZINC AND PLACERED GROUPS |
|---------------------------------|--------|--------|--------|
|                                | Mean (SE) | p     |
| ---                            | ---     | ---    | ---    |
| Weight (kg)                    | 0.54 (0.07) | 0.34 (0.06) | 0.303 |
| 0-3 g                        | 1.15 (0.09) | 1.04 (0.08) | 0.007 |
| 0.5-7.5 g                     | 1.04 (0.10) | 1.04 (0.09) | 0.017 |
| Length (cm)                   | 5.5 (0.5) | 5.4 (0.5) | 0.990 |
| 0-2 mm                        | 5.5 (0.7) | 5.4 (0.6) | 0.556 |
| 0-2 mm                        | 4.1 (0.7) | 4.0 (0.7) | 0.053 |
| Weight for age Z-score        | 0.19 (0.04) | 0.19 (0.06) | 0.180 |
| 0-2 mm                        | 0.19 (0.07) | 0.17 (0.06) | 0.005 |
| 0-2 mm                        | 0.19 (0.11) | 0.11 (0.06) | 0.003 |
| Length for age Z-score        | 0.11 (0.10) | 0.00 (0.12) | 0.078 |
| 0-2 mm                        | 0.15 (0.10) | 0.08 (0.08) | 0.014 |
| 0-7 mm                        | 0.31 (0.13) | 0.19 (0.09) | 0.007 |

Zinc and Mortality

- RCT of 1154 full-term small-for-gestational age Indian infants randomized to:
  - Riboflavin
  - Riboflavin, Iron, folate, Ca, and P
  - Riboflavin and Zinc (5 mg)
  - Riboflavin, Zinc, Ca, P, folate, and Iron
- Daily dose between 30 and 284 days of age
- Household visits 6 times a week


Survival curves for zinc-supplemented and non-zinc-supplemented groups.

Mortality RR = 0.32 (0.12, 0.89)

Zinc and Mortality in Pemba


©2001 by American Academy of Pediatrics

Zinc and Mortality in Pemba

Sazawal S et al. Lancet 2007;369:927-934

Global Perspective

Stunting as a Proxy for Zinc Deficiency

Populations at Risk

- Infants, Children, and Pregnant/Lactating Women
- Elderly
- Malabsorptive states

http://www.zincg.org/news/stunting
Zinc Interventions

Options
- Food Fortification
  - Prevention
  - Staple and constant food vehicle - e.g. Wheat or corn flour for zinc
  - Stable fortificant
  - Dose delivered should be adequate for beneficial effect but not toxic to those who already are zinc-replete - Targeted?
- Dietary diversification or Modification
  - Household interventions for improving zinc bioavailability include fermentation, germination, and soaking to remove phytates
  - Supplementation

Zinc Summary
- Critical nutrient for child health and growth
  - More in the talk on Diarrhea and Respiratory Infections
  - Extent of dietary insufficiency is not known globally
  - Nor is the optimal method of improving zinc status....

Acknowledgments
- Christopher P. Duggan