Dietary-induced zinc deficiency in low income countries: challenges & solutions

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Outline

• Importance of Zn in human nutrition
• Etiology & prevalence of Zn deficiency world-wide
• Factors associated with inadequate Zn intakes
  – Low Zn intakes; poor bioavailability of Zn
• Food-based strategies to enhance Zn content & bioavailability
  – Household dietary strategies
  – Fortification
  – Biofortification
• How can Zn interventions help achieve Millennium Development Goals
• Conclusions
First cases of human Zn deficiency in 1960’s in Middle East

- Male adolescent dwarf

Clinical features
- Stunting
- Little or no secondary sexual development

Diet
- Unleavened wheat bread
- Low intake of flesh foods
- Practiced geophagia

WHO Global burden of disease – disability adjusted life years (2000)

From Ezzati et al. (2002)
Why is zinc essential in human nutrition?

• > 300 enzymes require Zn for function or regulation
• Biosynthesis of nucleic acids, amino acids, proteins, including specific hormones
  – insulin; adrenal corticosteroids; testosterone
• Growth
• Immune function
• Vitamin A metabolism: night vision
• Reproduction
• Neuro-behavioural function

What are the adverse health consequences of Zn deficiency?

• Impaired growth
  – Poor linear growth; poor weight gain
  – Disturbances in body composition
• Impaired immune competence
  – Increased morbidity: diarrhoea; ALRI
  – Increased mortality
• Adverse pregnancy outcomes
  – Increase in preterm births: meta-analysis of RCT Zn supplementation (n=13): 14% reduction
  – Maternal labor & delivery complications: variable?
• Abnormal neuro-behavioural function?
Assessment of Zn deficiency is difficult

Zn is a Type 2 nutrient — has no body store
Deficiency results in:
• No unique clinical symptoms of deficiency
  – Poor appetite; poor growth or stunting; wasting
  – Loss of function in tissue with rapid turnovers (i.e., immune function, skin)
• Ways to conserve body Zn
  – linear growth is reduced
  – excretion falls to very low levels
• Death may occur even though Zn concentrations in most tissues are normal

Recommended indicators to identify risk of zinc deficiency in populations

1. Dietary indicator
   Percent with Zn intakes below Estimated Average Requirement (EAR)
   High risk: public health concern > 25%

2. Biochemical indicator
   Percent with low serum Zn concentrations
   High risk: public health concern > 20%

3. Functional indicator
   Percent of children < 5 y with HAZ score < - 2.0 SD
   High risk: public health concern > 20%

Factors associated with the etiology of Zn deficiency

- Inadequate zinc intakes
- High physiological requirements
  - Infancy; adolescence; pregnancy; lactation
- Disease states associated with:
  - Excessive losses: diarrhea
  - Impaired absorption/utilization
- Combination of factors

Risk of zinc deficiency based on food balance sheet (FBS) data on Zn available for consumption

Only a few LICs have national data

2004: Brown et al.
Predicted national risks of inadequate Zn intakes from FBS 1992-2002

2012: Wessells & Brown
Updated estimates
17.3% of world’s population at risk of inadequate Zn intakes

Percentage at risk
Estimated country-specific prevalence of inadequate zinc intake based on food balance sheet data

Overall 17.3% of the world's population said to be at risk of inadequate zinc intakes

Identify populations at high risk of Zn deficiency
— due to inadequate intakes of dietary Zn

Evaluate food-based interventions
Dietary diversification & modification (DDM)
Fortification
Biofortification
Development of a dietary manual to assess Zn intakes in low income countries

1999: Gibson RS, Ferguson EL:

An interactive 24-hour recall for assessing the adequacy of iron and zinc intakes in developing countries.

ILSI Press, Washington DC


Factors associated with inadequate zinc intakes

• Low Zn intakes
  – and/or

• Poor bioavailability
Factors associated with low Zn intakes

• Low energy intake
  – food insecurity; poor child feeding practices
  – poor appetite
  – low dry matter content of complementary foods (~7%)

• Poor food selection patterns
  – starchy roots/tubers: lower [Zn] vs. cereals or legumes
  – low in cellular animal protein
    » economic; religious; health; animal welfare concerns

• Environmental factors
  – soils low in Zn: Iran, Egypt, Turkey, Pakistan, NE Thailand
  – crops affected: maize; sorghum; rice

Zn & phytate (mg/100g) & phytate: Zn molar ratios of plant staples

<table>
<thead>
<tr>
<th>Cereals</th>
<th>Zn</th>
<th>Phytate</th>
<th>Phy:Zn*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unrefined maize</td>
<td>2.2</td>
<td>792</td>
<td>36</td>
</tr>
<tr>
<td>Refined maize</td>
<td>0.9</td>
<td>211</td>
<td>23</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Legumes/ Oilseeds</th>
<th>Zn</th>
<th>Phytate</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Kidney beans, dried</td>
<td>1.5</td>
<td>460</td>
<td>72</td>
</tr>
<tr>
<td>Sesame seeds</td>
<td>2.5</td>
<td>1525</td>
<td>61</td>
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<tr>
<th>Starchy Roots &amp; Tubers</th>
<th>Zn</th>
<th>Phytate</th>
<th>Phy:Zn*</th>
</tr>
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<tbody>
<tr>
<td>Sago</td>
<td>0.1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Enset</td>
<td>0.1</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Cassava</td>
<td>0.6</td>
<td>59</td>
<td>10</td>
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Comparison of Zn levels in soils and rice in three regions of Thailand

<table>
<thead>
<tr>
<th>Region</th>
<th>Soil Zn (μg/g)</th>
<th>Rice Zn (μg/g)</th>
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</thead>
<tbody>
<tr>
<td>Central</td>
<td>1.35</td>
<td>77.0</td>
</tr>
<tr>
<td>South</td>
<td>1.7</td>
<td>31.9</td>
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<tr>
<td>N East</td>
<td>0.8</td>
<td>20.1</td>
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From Katyal and Vlek (1985)

Diets of NE Thai school children

- 51% energy from rice grown on low Zn soils
- Zn intakes below requirements

Biochemical Zn status

- 54% had low serum Zn values indicative of Zn deficiency

Factors associated with poor bioavailability of Zn

- Diets with high levels of phytate
  - potent inhibitor of Zn absorption
- Diets low in cellular animal source foods
  - enhancer of Zn absorption
Adjusting Zn requirement by dietary phytate content in adult men

<table>
<thead>
<tr>
<th>Phytate (mg/d)</th>
<th>EAR (mg)</th>
<th>RDA (mg)</th>
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<tbody>
<tr>
<td>0</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>1000</td>
<td>18</td>
<td>22</td>
</tr>
<tr>
<td>2000</td>
<td>27</td>
<td>32</td>
</tr>
<tr>
<td>3000</td>
<td>37</td>
<td>44</td>
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From Sandström (1987)

Zn & phytate (mg/100g) & phytate: Zn molar ratios of plant staples

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Daily intakes of zinc & phytate by diet type for Ethiopian women

<table>
<thead>
<tr>
<th>Variable</th>
<th>Maize</th>
<th>Enset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flesh foods (g)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Zn mg (mg)</td>
<td>6.3</td>
<td>3.7*</td>
</tr>
<tr>
<td>Phytate (mg)</td>
<td>1356</td>
<td>446*</td>
</tr>
<tr>
<td>Phy:Zn molar ratio</td>
<td>21</td>
<td>11*</td>
</tr>
</tbody>
</table>

Enset (*Enset ventriosum*)

*p<0.05

Major food sources of Zn (as %)

Non breast-fed children

- Mongolia
- Cambodia
- Malawi
- Ghana
- US

Women

- Ethiopia
- Malawi
- UK
- Australia
- NZ

Data compiled by RSG
Factors associated with the prevalence of inadequate zinc intakes in selected countries

- Low in bioavailable Zn
- Low soil Zn
- Low Zn content: Enset
- Leavened wheat bread
- Omnivorous diets

Food-based strategies to enhance content and bioavailability of zinc in plant-based diets in LICs

1. Promote exclusive breast feeding up to 6 mos age
2. Enhance energy, Zn (& other micronutrients) density of complementary foods + continued breast feeding to 2 yr
3. Enrich diets with cellular animal protein
4. Reduce phytate content of cereal-based diets
5. Fortify foods with zinc (+ other micronutrients)
6. Introduce biofortification to HHs eating foods from local or self production

NB: All strategies should be integrated with public health programs to enhance effectiveness
1. Promote exclusive breast feeding up to 6 mos: adequacy of Zn intakes from breast milk (BM) by age

Zn intake from BM is ~ 4 mg/d, then ~1.75 mg/d by 1 mo, & ~ 0.7 mg/d by 6 mo

BM Zn probably adequate for exclusively BF term infants until ~ 6 mos

BM Zn no longer adequate from about 6 mos when additional Zn must be provided from complementary foods (CF)

High phytate CFs may adversely affect Zn absorption from breast milk

Brown et al. (2009)

2. Enhance energy & Zn intakes by increasing dry matter (DM) content of CFs using amylase

• Hydrolysis of amylose & amylopectin to dextrins (& maltose)

• Viscosity of 16% DM porridge reduced without dilution with water

• 16% DM porridge has higher energy density & Zn content

From Hotz & Gibson (2005)
3. Enrich plant-based diets with animal-source foods: rich source of absorbable Zn

• Use formative research to develop & trial recipes:
  – household availability; nutrient value; acceptability; cost
  – Consult “Trials of Improved Practices” (TIPS): see PROПAN Manual

• Possible enrichers
  – Meat; poultry; liver
    » Beef, pork, lamb 6.8–3.0 mg Zn/100g; Poultry 1.1–2.7 mg Zn/100g
  – Indigenous foods: caterpillars; grubs; locusts; snails; frogs
  – Fish: small dried, powdered w.bones: Usipa: 25.4 mg Zn/100g
  – Egg yolk: 1.1 mg Zn/100g

4. Reduce dietary phytate content of cereal flours and legumes

• Use milled cereal flours
  – concurrent reduction in [Zn]

• Soak unrefined maize flour
  – 50% loss of water soluble phytate

• Ferment cereal porridges
  – phytate hydrolyzed via microbial phytase

• Germinate legumes
  – phytate hydrolyzed via endogenous phytase

Pound maize
Mix 1 part maize to 4 parts water
Soak 1 hour; decant excess water
Dry maize & mill
Can household phytate-reducing strategies increase Zn absorption?

No isotope studies w. household methods

- *BUT* other isotope studies: increase in Zn absorption with decrease in phytate
- ~50% phytate loss in maize via household methods only slightly less than level in low phytate (LP) maize (60% loss) shown here
- LP maize produces increase in fractional (FAZ) & total Zn absorption (TAZ)

Hence 50% phytate reduction via household methods likely to enhance Zn absorption

<table>
<thead>
<tr>
<th></th>
<th>Low phytate maize (60% loss)</th>
<th>Wild type maize</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zn, mg/d</td>
<td>8.3</td>
<td>10.0*</td>
</tr>
<tr>
<td>Phy, mg/d</td>
<td>1365</td>
<td>3457*</td>
</tr>
<tr>
<td>FAZ</td>
<td>0.285</td>
<td>0.151*</td>
</tr>
<tr>
<td>TAZ (mg/d)</td>
<td>2.4</td>
<td>1.5</td>
</tr>
</tbody>
</table>

*P<0.05

Hambidge et al. (2004)

Integrated approach for dietary diversification and modification (DDM) used in rural Malawi on infants and children aged 3-7 yr

- Increase consumption of animal source foods by infants and young children
- Alter content of absorption modifiers in diets to increase absorption of Zn (& Fe, Ca, vit A)
- Use thicker porridges to increase intake of energy, Zn & other micronutrients

All strategies implemented using a participatory approach
Social marketing strategies to promote adoption of DDM strategies

Drama: plays about project messages were conducted

Songs about messages were composed by village bands

Impact on other outcomes

Intervention vs. controls had:
- More diverse diets which were of higher quality*
- Lower prevalence of anemia (62 vs. 80%)*
- Lower morbidity*
- Greater muscle mass*
- But: No effect on growth

Efficacy of strategies to enhance content & bioavailability of Zn in Malawian children

Impact on other outcomes

Intervention vs. controls had:
- More diverse diets which were of higher quality*
- Lower prevalence of anemia (62 vs. 80%)*
- Lower morbidity*
- Greater muscle mass*
- But: No effect on growth

From Yeudall et al. (2002, 2007)
5. Fortification with Zn (+/- MNs): examples

- Fortified cereals
- Fortified spreads: plumpy-nut *
- Micronutrient powders: Sprinkles in serving size sachets *

*Mixed with prepared foods in the home

Why are fortified complementary foods required?
Micronutrient intakes as % of WHO estimated needs

<table>
<thead>
<tr>
<th>Intakes based on unfortified CFs</th>
<th>Intakes based on 40 g of fortified CFs</th>
</tr>
</thead>
<tbody>
<tr>
<td>NZ*</td>
<td>Rice</td>
</tr>
<tr>
<td>Indonesia*</td>
<td>Flour</td>
</tr>
<tr>
<td>Philippines *</td>
<td>Brown</td>
</tr>
<tr>
<td>Mongolia*</td>
<td>Rice</td>
</tr>
<tr>
<td>Cambodia*</td>
<td>Cereal &amp; legumes</td>
</tr>
</tbody>
</table>

*Infants 9-11 mos
**Young children 12-23 mos
Is zinc added as a fortificant bioavailable?

Effect of Zn fortificant level on fractional Zn absorption (FAZ) per meal in adults (as %)

Effect of Zn fortificant level on total Zn absorption (TAZ) (mg/meal) in adults

From Sandström et al. (1980)

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Does Zn fortification reduce the prevalence of low serum Zn in young children post-intervention?

Zambia: MN-fortified maize porridge
Cambodia: Sprinkles

Kirkseylecture04
How can we enhance efficacy of Zn fortification? Addition of phytase + MN fortificants in maize porridge on Zn status of school children after 23 wks

From Troesch et al. (2011) 2.5 mg Zn as ZnO; 2.5 mg Fe as NaFeEDTA

Biofortification of plant-based staples

Overall goal to increase Zn content of edible portion of staple crops

Methods
- Plant-breeding to increase
  - Zn in wheat, rice, maize, beans
- Agronomic practices
  - Zn fertilizers on low Zn soils
- Genetic modification ??
  - increase Zn & reduce phytate in cereals

Advantages
- Culturally acceptable & safe
- Sustainable over the long-term
- Relatively low cost
- Enhance MN status of entire HHs
- Fills gap left by fortification products more accessible to HHs eating staple foods from local or self production
Intake & absorption of zinc from biofortified or control pearl millet in Indian children

<table>
<thead>
<tr>
<th></th>
<th>B Fortified</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grain Zn, µg/g</td>
<td>84.1 ± 4.9</td>
<td>43.7*</td>
</tr>
<tr>
<td>Dietary Zn, mg/d</td>
<td>5.8 ± 2.1</td>
<td>3.3 ± 1.1*</td>
</tr>
<tr>
<td>FAZ</td>
<td>0.17 ± 0.08</td>
<td>0.20±0.04*</td>
</tr>
<tr>
<td>Total absorbed Zn, mg/d</td>
<td>1.0 ± 0.5</td>
<td>0.7 ± 0.2*</td>
</tr>
<tr>
<td>Grain phytate, mg/g</td>
<td>7.5+0.3</td>
<td>10.3+0.8</td>
</tr>
</tbody>
</table>

- Zn intake higher from 3 meals of BF millet than controls
- Zn absorption higher from BF millet vs. controls
- (Phy:Zn ratio 9 vs. 24)
- Increase in Zn absorption from BF millet sufficient to ensure that children aged 2 y could meet their physiological Zn requirement

From Kodkany et al. (2013)

Effect of Zn fertilizer on Zn content of rice grains grown in Pakistan

<table>
<thead>
<tr>
<th>Fertilizer Zn g/ha</th>
<th>Rice grain Zn µg/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>20.20</td>
</tr>
<tr>
<td>5</td>
<td>32.26</td>
</tr>
<tr>
<td>10</td>
<td>38.04</td>
</tr>
<tr>
<td>15</td>
<td>46.64</td>
</tr>
</tbody>
</table>

P<0.05; Khan et al.(2002)
How can Zn interventions help achieve MDGs?

• **MDG # 1: Reduce poverty & hunger**: restricts growth
  – Reduce stunting & underweight

• **MDG # 4: Reduce child mortality**
  – Reduce diarrhea ~ 27% in those >12 mos; Reduce ALRI ~15%
  – Reduce child mortality for those >12 mos ~ 18%

• **MDG # 5: Reduce maternal mortality**
  – May reduce protracted labor

• **MDG # 6: Combat malaria, HIV/AIDS**
  – May reduce severity of malaria
  – May reduce risk of diarrhea & pneumonia in HIV +ve children

More research needed

Conclusions

• Zn deficiency has far reaching consequences on maternal, infant, and child health

• In LICs inadequate Zn intakes are a major determinant of Zn deficiency

• WHO recommends when prevalence of inadequate Zn intakes > 25%, population is at elevated risk

• Food-based strategies can be used to increase intakes & bioavailability of Zn

• Zn interventions could help achieve MDGs #1, 4, 5 & 6

• There is a need to determine how best to deliver Zn interventions within existing public health programs
Acknowledgements: Collaborators

Papua New Guinea Institute of Medical Research: P Heywood
Cessiam: N Solomons
Univ. Malawi: B Mitimuni, T Cullinan ; Univ.Ghana: C Opare-Obisaw
Institute of Nutrition Mahidol Univ, Thailand: P Winichagoon, V Chavisth, E Wasantwisut
Cambodian NNP, A2Z, USAID, Gain, WHO: S Jack, P Harvey
Univ Zambia & London School of Hygiene & Tropical Medicine: Dr L Lasonga and Dr S Filteau
Harvest Plus: Dr C Hotz & Dr H Bouis;
Public Health institute, Mongolia: T Enkhjargal, J Barjargal
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- US Agency for International Development
- UNICEF Malawi
- World Vision Malawi
- Gates Foundation; DSM South Africa
- University of Otago Research Fund
- NERC & DIFID in the UK

Thank you
Galvanizing action: next steps for mainstreaming Zn in public health programs

- Collect information on population Zn status in LICs
- Mobilize interest in Zn nutrition
- Scale up therapeutic Zn supplements for diarrhea
- Conduct RCTs with Zn-biofortified crops to assess impact on Zn status & health in high risk groups
- Determine how best to deliver Zn interventions within existing Public Health programs:
  - Zn supplements in growth monitoring
  - Add Zn to Fe supplements for high risk pregnant women
  - Use appropriate Zn levels in fortification & biofortification
  - For all interventions: use effective behavior change & communication

FOOD — CARE — HEALTH
Evaluated prevalence of inadequate Zn intakes in the presence & absence of fortification of wheat and maize flours in children & women in Uganda

**Potential impact of Zn fortification in Ugandan national food consumption survey**

From Harvey et al. (2010)

Simulated impact of Zn biofortified maize on inadequate Zn intakes (as %) in Mexican rural preschoolers

Simulated impact of Zn biofortified rice on inadequate Zn intakes (as %) in Bangladeshi preschoolers

From Denova-Gutiérrez et al. (2008) From Arsenault et al. (2010)