Overview of micronutrient status biomarkers

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Overview

• **What** do we mean by the term biomarker?

• **Why** do we need biomarkers?
  – Population
  – individual

• **How?** Methodological challenges and future developments
What do we mean by biomarker?

“The term “biomarker”, a portmanteau of “biological marker”, refers to a broad subcategory of medical signs – that is, objective indications of medical state observed from outside the patient – which can be measured accurately and reproducibly.”

Strimbu and Travel, 2010, Curr Opin HIV AIDS
A nutritional biomarker can be any biological specimen that is an indicator of nutritional status with respect to intake or metabolism of dietary constituents. It can be a biochemical, functional or clinical index of status of an essential nutrient or other dietary constituent.

Potischman and Freudenheim, Journal of Nutrition 2003
Categories of Nutritional biomarkers

**Intake/Exposure**
- Diet diary
- 24 hour recall
- FFQ

**Body Status**
- Blood plasma, cells, urine,
- Accessible tissue e.g. hair, nails

**Functional/clinical outcome measure**
- Response to change in intake e.g. growth or immune function
Why do we need biomarkers?

**Individual level:**
- Clinical diagnosis and treatment
- Monitoring response to treatment
- Research e.g. understanding homeostatic mechanisms

**Population level:**
- Nutrition survey
  - Identify at populations risk of deficiency
  - Design effective and efficient intervention
  - Monitor and evaluate impact of intervention
Why do we need biomarkers?

- Setting micronutrient intake recommendations

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Recommended Daily allowance
Or
Reference Nutrient intake (RNI)

Intake level (percentage of population with adequate intake)
EURRECA
European micronutrient recommendations aligned

A European Commission Network of Excellence 2007-2012
EURRECA: A Network of Excellence

- **EURRECA:** EUropean micronutrient RECommendations Aligned

- 35 partners in 17 countries: scientists, SMEs, consumer organisations, nutritionists & nutrition societies and wider stakeholders

- Funded by the European Commission, 2007-2012

- Coordinated by ILSI, Europe

- [www.eurreca.org](http://www.eurreca.org)
EURRECA: key objectives

To produce a framework for micronutrient recommendations

- Aligned set of standards for establishing micronutrient requirements and devising micronutrient recommendations
- Needs of specific vulnerable groups
- Impact of socio-economic status, ethnic origin, inter-individual variability and vulnerability related to genotype and environmental factors
Selecting priority micronutrients

28 micronutrients were examined and 3 'a priori' criteria were used to rank them in order of importance:

A – amount of new evidence, especially from RCTs
B – public health relevance
C – variations in current DRVs

10 highest:
- vitamin D, iron, folate, vitamin B12, zinc, calcium, vitamin C, selenium, iodine, copper

Shortlist of 6 agreed, taking into account expertise/interest within EURRECA and avoidance of duplication of work done outside EURRECA

Se recommendations from different bodies

Abbreviations: JPN, Japan; PRT, Portugal; WHO, World Health Organisation; DNK, Denmark; FIN, Finland; ISL, Iceland; NOR, Norway; SWE, Sweden; EST, Estonia; MEX, Mexico; AUT, Austria; CHE, Switzerland; CHN, China; DEU, Germany; KOR, South Korea; SVN, Slovenia; FRA, France; POL, Poland; SVK, Slovakia; ALB, Albania; BGR, Bulgaria; IRL, Ireland; ITA, Italy; MNE, Montenegro; USA/CAN, United States of America/Canada; SEA, South East Asia region; ESP, Spain; AUS/NZL, Australia and New Zealand; HUN, Hungary; GBR, United Kingdom; BEL, Belgium; NLD, Netherlands; MKD, Macedonia.
Dietary Reference Values/Intakes (DRVs/DRIs)

• The Estimated Average Requirement (EAR/AR) is derived from a dose-response relationship for one or more ‘health’ endpoints.

• Recommended Dietary Allowance (RDA) or Population Reference Intake (PRI) = EAR + 2SD (if SD not known, the coefficient of variation is assumed).
  • e.g. 10% CV = EAR x 1.2; 15% CV = EAR x 1.3; 20% CV = EAR x 1.4.
Information required for setting DRVs

Intake -> Status -> Early biomarker of health -> Clinical outcome

Key relationships
Activities undertaken by EURRECA

RA1: Methodology
- Best practice
- Intake
- Status
- Concepts, definitions
- Current recommendations

RA2: Data extraction
- Systematic reviews
- Intake-status-health
- Factorial approach (requirements, losses, bioavailability)
- Vulnerable groups (risk of low intake)

RA3: Data analysis
- Deriving dietary requirements
- Meta-analysis of data from systematic reviews
- Narrative reviews
- Factorial approach
- Dose-response models (trivariate I-S-H model)

RA4: Integration
- Towards derivation of dietary recommendations
- Development of generic framework for deriving micronutrient reference values

IA1: Consumer science
IA2: Food industry
IA3: Individual phenotype
IA4: Integration, liaison & sustainability
Generic protocol for SRs on biomarkers of status

- **Primary question** to be answered: which biomarkers of status reflect change in intake over a minimum time scale?

- **Methodology** used: adaptation of the methods used by the Cochrane Collaboration

- **Inclusion criteria**: study design, supplement forms (bioavailability), minimum intervention period etc.

- **Type of studies** included: supplementation or depletion studies, RCTs > CCTs > before/after studies

- **Search strategy**: search terms and syntax; exclusion details and justification (language and/or date limits)

*Hooper et al. AJCN 2009; 89(6S): 1953S-1959S*
Biomarkers of Zn status: meta-analysis of Zn supplementation studies

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>No of studies (no of subjects)</th>
<th>Pooled effect size (95% CI)</th>
<th>Measure of heterogeneity $I^2$ (%)</th>
<th>Effective biomarker?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma/serum Zn concentration</td>
<td>50 (1454)</td>
<td>2.88 (2.24, 3.51)</td>
<td>93.6</td>
<td>Yes (in individuals with low/moderate status)</td>
</tr>
<tr>
<td>Urinary Zn (mmol/mol creatinine)</td>
<td>5 (373) with moderate status</td>
<td>0.31 (0.20, 0.43)</td>
<td>0</td>
<td>Yes</td>
</tr>
<tr>
<td>Hair Zn (ppm)</td>
<td>3 (93) with low/moderate status</td>
<td>13.24 (11.91, 14.56)</td>
<td>0</td>
<td>Yes</td>
</tr>
<tr>
<td>26 other biomarkers</td>
<td></td>
<td></td>
<td></td>
<td>Unclear</td>
</tr>
<tr>
<td>RBC Zn</td>
<td>7 (537) 5 (95) 6 (101) 5 (105)</td>
<td>2.2 (-4.58, 8.98) -0.05 (-0.21, 0.11) 0.05 (-0.13, 0.22) 0.09 (-1.12, 1.30) 4.14 (-2.38, 10.65)</td>
<td>0 37.7 83.3 76.0 56.6</td>
<td>No</td>
</tr>
<tr>
<td>Mononuclear cell Zn</td>
<td></td>
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<td></td>
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<tr>
<td>Polymorphonuclear cell Zn</td>
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<tr>
<td>Platelet Zn</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma alkaline phosphatase</td>
<td></td>
<td></td>
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</tbody>
</table>

Lowe et al. AJCN 2009
Systematic Reviews on Biomarkers of Status

**Aim:** To assess the usefulness of biomarkers of status for a range of micronutrients.
How? Methodological challenges and future developments

• Confounders
  – Acute Phase Response
  – Bioavailability
  – Multiple micronutrient deficiencies
Acute Phase Response

- Stress
- Tissue damage
- Infection
- Inflammation

Signalling molecules
- Hormones
- Neurotransmitters
- Cytokines
- Eicosanoides

Decreased serum
- Zinc
- Vitamin A
- Iron

Biomarkers Reflecting Inflammation and Nutrition Determinants of Anemia (BRINDA): Collaborative working group led by CDC/GAIN/NICHD

Micronutrient Forum June 3rd, 2014
Bioavailability

• Dietary components that modify absorption and utilisation of micronutrients

• Impact on biomarker of intake/exposure
# Results of Systematic review in Adult and Elderly populations

<table>
<thead>
<tr>
<th>Dietary component</th>
<th>Number of studies</th>
<th>Summary of effect on Zn absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phytate</td>
<td>30</td>
<td>Inhibitor</td>
</tr>
<tr>
<td>Micronutrient supplements</td>
<td>16</td>
<td>Ca- ?inhibitor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Folic acid- no effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Iron- no effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tin- inhibitor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ascorbic acid -?enhance</td>
</tr>
<tr>
<td>Zn (food and supplements)</td>
<td>10</td>
<td>Subject to homeostatic control</td>
</tr>
<tr>
<td>Proteins</td>
<td>13</td>
<td>Zn absorption enhanced from animal protein</td>
</tr>
<tr>
<td>Human Milk vs cows Milk vs whey based Formula</td>
<td>2</td>
<td>Zn absorption enhanced from human milk</td>
</tr>
<tr>
<td>Oxalate</td>
<td>1</td>
<td>No affect</td>
</tr>
<tr>
<td>Fat/Cholesterol</td>
<td>1</td>
<td>?enhancer</td>
</tr>
<tr>
<td>Tea</td>
<td>1</td>
<td>No affect</td>
</tr>
<tr>
<td>Maillard Browning</td>
<td>1</td>
<td>Inhibitor</td>
</tr>
<tr>
<td>Dairy</td>
<td>1</td>
<td>Enhancer</td>
</tr>
</tbody>
</table>
• Meta analysis reveal an overall effect of 14% reduction in fractional zinc intake from a high phytate diet (P:Zn molar ratio >15)

Prediction equations and models
• Hotz and Brown IZiNCG, Food and Nutrition Bulletin 2004
• Miller et al J Nutr 2007
Trivariate saturation response model model ;
– TDZ
– TDP
to predict TAZ

European Food Safety Authority  2014

Nutrition Reviews 2014. vol 72(5) 334-352

Critical Reviews in Food Science and Nutrition Volume 53, Issue 10, 2013 Special Issue: EURRECA Se, Iron Zn, Vit D
How? Methodological challenges and future developments

• Confounders
  – Acute Phase Response
  – Bioavailability
  – Multiple micronutrient deficiencies

• Future developments
Future developments

• “Low tech” field methods
  – Spectrophotometric assay for plasma [Zn]

• Point of Care technology
  – Fast (< 10 minute)
  – Low cost
  – Portable, easy to use devices

• Minimal sample
  – Dried blood spot
  – Protein microarrays (“lab on a chip")
Summary

• What? Nutritional biomarkers
  – Exposure (intake)
  – Status
  – Functional (clinical outcome)

• Why?
  – MMD’s still prevalent worldwide on-going worldwide public health challenge
  – Revision of DRVs is ongoing

• How? New technologies on horizon
Thank you