Critical Micronutrients for Clinical Consideration

NHAFP
April 5th, 2014
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Objectives

• To identify the most common micronutrients that patients have suboptimal intake levels of.
• To recognize the physiological roles of key micronutrients and the potential for environmental, genetic, and lifestyle influences on physiological needs.
• To identify the richest food sources of each micronutrient and to consider how food preparation influences the bioavailability of each.
World map of human migrations, with the North Pole at center. Africa, harboring the start of the migration, is at the top left and South America at the far right.

Region that was covered by ice or tundra in the last ice age

Motherly Lineages: Common divisions for mtDNA haplogroups:
- General European: H, V
- Southern European: J, K
- Northern European: T, U, X
- Near Eastern: J, N
- African: L, L1, L2, L3, L3*
- Asian: A, B, C, D, E, F, G (note: M is composed of C, D, E, and G)
- Native American: A, B, C, D, and sometimes X

Numbers represent thousand of years before present:
- Red: 170 - 130
- Orange: 70 - 60
- Light orange: 50 - 40
- Yellow: 35 - 25
- Light yellow: 15 - 12
- Light blue: 9 - 7
Cro-magnon humans, tall with powerful chests and large brains, emerged about 35,000 years ago.

In past 10,000 years humans have become roughly 10% smaller in both physique and brain size.

Early humans, right, evolved as hunter-gatherers.
Core Imbalances Responsible for Metabolic Syndrome

- Inflammation (driven by specific microbes, foreign proteins, oxysterols)
- Oxidative Stress (iron, excessive free radicals)
- Loss of Organ Reserve (DHA, EPA, B12, D, magnesium, K2)
- Hypomethylation (MTHFR)
- Dysglycemia (CHO density)
Micronutrient Characteristics

- Needed in small amounts (milligrams or micrograms as opposed to grams per day)
- Do not contain energy/calories
- Drive reactions as cofactors or catalysts
- Vital for life
Most Common Deficiencies

- Magnesium
- Zinc
- Vitamin D
- Vitamin B12
- Selenium
- Vitamin K
- Chromium
- Potassium
• Muscle relaxation (all muscle types)
• Detoxification enzyme production and function
• Bone structure and formation
• Glucose metabolism enzyme function (PFK, hexokinase and additional ATP related)
RDA for Magnesium

- Children 150mg
- Women 320mg
- Men 420mg
- One cup of buckwheat flour 325mg
- ¼ cup of pumpkin seeds 250mg
- 5 black mission figs 125mg
- Regularly outcompeted by calcium in the developed world
Fig. 1. Ischemic heart disease rates correlated with dietary calcium-to-magnesium ratios (adapted from Reference 50, Seelig M, Rosanoff A. The Magnesium Factor.)
U.S. Intake of Magnesium

Percent of U.S. population meeting Recommended Daily Allowance (RDA):

- Below RDA: 55%
- At or above RDA: 25%
- Significantly below RDA: 20%
Clinical Considerations

• Restless leg syndrome
• Frequent muscle cramps
• Hypertension
• Athletes with prolonged recovery times
• Constipation
• Headaches
• Insomnia
• Alcohol abuse
“Although intense research activities have been dedicated to Mg, there is still no simple, rapid, and accurate laboratory test to indicate total body Mg status in humans. However, taking into account all the more recent investigations, although serum Mg, 0·75 mmol/l still remains a useful measurement for severe deficiency, for values between 0·75 and 0·85 mmol/l, a loading test must be performed to identify the deficient subjects. Loading tests appear to be the gold standard for Mg status”
Fischer PW and Giroux A. An evaluation of plasma and erythrocyte magnesium concentration and the activities of alkaline phosphatase and creatine kinase as indicators of magnesium status

Clinical Biochemistry
Volume 24, Issue 2 April 1991, Pages 215-218

“Although significant, the correlations between intake and the enzyme activities were not strong. It is concluded that plasma magnesium concentration is the most useful indicator of magnesium status and that the activities of the two magnesium-requiring enzymes can only be used for the purpose of diagnosing severely deficient magnesium status.”
Sources

BEST (more than 33% of RDA)
- Swiss chard
- Spinach
- Buckwheat
- Pumpkin seeds
- Black mission figs
- Mustard greens
- Halibut

EXCELLENT
- Squash (all types)
- Blackstrap molasses
- Kale
- Quinoa
- Sunflower seeds
- Millet
- Sesame seeds
- Broccoli
- Tempeh
- Beans
Zinc

- Necessary for production of superoxide dismutase and many other critical enzymes (carbonic anhydrase, carboxypeptidase A, alcohol dehydrogenase, alkaline phosphatase, aminopeptidase, phospholipase C and many more)
- Required for testosterone and estrogen production
- Important roles in both macular lens protection and glucose metabolism
RDA

- Children 5mg
- Women 9mg
- Men 12mg
- 6 medium oysters provide 75-90mg
- ¼ cup of pumpkin seeds 5-7mg
- Absorption significantly inhibited by both phytates and calcium
- Large doses (>55mg) have been shown to lower HDLs
Clinical Considerations

- Strict vegetarians, but even lacto-ovo vegetarians more so.
- Individuals with light colored eyes
- Anyone supplementing with large doses of calcium
- Muscle weakness, no strength gains with training, loss of libido, chronic URTIs
Assessment Research

Nicola M Lowe, Katalin Fekete and Tamás Decsi

Methods of assessment of zinc status in humans: a systematic review


“This systematic review confirms that in healthy individuals, plasma, urinary, and hair zinc are reliable biomarkers of zinc status. Further high-quality studies using these biomarkers are required, particularly in infants, adolescents, and immigrant population groups for whom there are limited data. Studies are also required to fully assess a range of additional potential zinc biomarkers.”
Sources

- Oysters
- Shellfish
- Crab
- Ocean going fish
- Sea vegetables
- Pumpkin seeds
- Spinach
- Green peas
- Sesame seeds
- Navy beans

“the US economic burden due to vitamin D insufficiency from inadequate exposure to solar UVB irradiance was estimated at $40 billion to $56 billion in 2004, whereas the economic burden for excess UV irradiance was estimated at $6 billion to $7 billion.”
Figure 2
Annual erythemally-weighted ultraviolet-B exposure, kJ/m².
| Serum 25(OH)D, ng/ml | 6  | 8  | 10 | 12 | 14 | 16 | 18 | 20 | 22 | 24 | 26 | 28 | 30 | 32 | 34 | 36 | 38 | 40 | 42 | 44 | 46 | 48 | 50 | 52 | 54 | 56 | 58 | 60 | 62 | 64 | 66 | 68 |
|---------------------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Studies of Individuals |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Cancers, all combined |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Breast Cancer |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Ovarian Cancer |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Colon Cancer |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Non-Hodgkin's Lymphoma |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Type 1 Diabetes |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Fractures, all combined |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Falls, women |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Multiple Sclerosis |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Heart Attack (Men) |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Natural Experiments |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Kidney Cancer |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Endometrial Cancer |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Rickets |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |

Legend:
- All percentages reference a common baseline of 25 ng/ml as shown on the chart.
- %'s reflect the disease prevention % at the beginning and ending of available data. Example: Breast cancer incidence is reduced by 30% when the serum level is 4 ng/ml vs the baseline of 25 ng/ml. There is an 83% reduction in incidence when the serum level is 50 ng/ml vs the baseline of 25 ng/ml.
- The x's in the bars indicate 'reasonable extrapolations' from the data but are beyond existing data.

References:
- Reference serum 25(OH)D was 5 ng/ml.
- Rickets: Arnaud S.

Chart prepared by: Garland CF, Baggerly CA
no toxicity below 30,000 IU/d

no toxicity below 500 nmol/L (200 ng/mL)

15 studies of adults receiving vitamin D supplementation (means)

8 studies reporting toxicity (individual values)

Clinical Considerations and Assessment

- 25(OH)D3 less than 30ng/mL considered deficiency
- Recent research indicates 50ng/mL better for optimal health
- Muscle weakness
- Depression
- Inflammation
- Osteopenia/Osteoporosis
Vitamin D Considerations

- Large dosages may be contraindicated in cases of autoimmunity
- Fat soluble = loading phase with larger BMIs
- 15 minutes of sunlight on face and arms at Latitude 40° North = 5000 IUs, but only in May, June, and July
- 15 minutes of same exposure in Winter = 0
Vitamin B12

- Drives large number of methylation reactions
- Important for neurological tissue repair and maintenance, detoxification, cell differentiation, collagen formation, and muscle contraction
- Limited to bacteria and animal protein sources
RDA for B12

- Children 1.2mcg
- Women 2.4mcg
- Men 2.4mcg
- Pregnant women 2.6mcg
- Lactating women 2.8mcg
- 4oz of salmon 3.3mcg
- 4oz of sardines 34.0mcg
Clinical Considerations and Assessment

- Strict vegetarians
- Individuals over the age of 60
- Patients with stomach surgery
- PPI and metformin (Glucophage, Fortamet, Riomet, Glucophage XR) use
- Individuals with elevated MCV values
- High homocysteine levels
- Low 1/3 of serum B12 “normal range”
Clinical

- Depression
- Poor memory
- Numbness or tingling in hands or feet
<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of study</th>
<th>Duration</th>
<th>n (M)</th>
<th>Effect of metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>DeFronzo 1995</td>
<td>P-controlled, DB</td>
<td>29 weeks</td>
<td></td>
<td>B12 ↓ 22% (placebo: no effect)</td>
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<tr>
<td></td>
<td>M vs. placebo</td>
<td></td>
<td>143</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M vs. glibenclamide</td>
<td></td>
<td>210</td>
<td>B12 ↓ 29%</td>
</tr>
<tr>
<td></td>
<td>M + glibenclamide</td>
<td></td>
<td>213</td>
<td>B12 ↓ 29%</td>
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<tr>
<td>Wulffelé 2003</td>
<td>P-controlled, DB</td>
<td>16 weeks</td>
<td></td>
<td>B12 ↓ 14% (4.2–24%)</td>
</tr>
<tr>
<td></td>
<td>M + insulin</td>
<td></td>
<td>171</td>
<td>HCy ↑ 4% (0.2–8%)</td>
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<tr>
<td>Hermann 2001</td>
<td>P-controlled, DB</td>
<td>1 year</td>
<td>16</td>
<td>B12 unchanged</td>
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<tr>
<td></td>
<td>M + insulin</td>
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<tr>
<td>Bauman 2000</td>
<td>Sequential</td>
<td>3 months</td>
<td>14</td>
<td>B12 ↓ 29.5%</td>
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<tr>
<td></td>
<td>SU → M</td>
<td></td>
<td></td>
<td>Holotranscobalamin ↓ 36.6%</td>
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<tr>
<td>Wolever 2000</td>
<td>P-controlled</td>
<td>9 months</td>
<td></td>
<td>B12 ↓ 14% after M, B12 ↑ 12% after miglitol, placebo no effect</td>
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<td>M vs. miglitol</td>
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</tr>
<tr>
<td></td>
<td>M + miglitol</td>
<td></td>
<td>47</td>
<td>B12 unchanged after combination</td>
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<tr>
<td>Bagree 1999</td>
<td>Retrospective</td>
<td>9.8±1.9 years</td>
<td>517</td>
<td>B12 &lt; lower ref. level: 13.6% of M-treated, 10.6% of non-exposed</td>
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<tr>
<td></td>
<td>(abstract, no statistics)</td>
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<tr>
<td>Hoogeveen 1997</td>
<td>Cross-sectional</td>
<td>&gt; 6 months</td>
<td>40</td>
<td>HCy slightly elevated in M-treated (11.5 vs. 10.6 μmol/L in non-exposed)</td>
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<td>Smulders 1999</td>
<td>Epidemiological</td>
<td>not stated</td>
<td>31</td>
<td>B12 and HCy similar in M-treated and non-exposed</td>
</tr>
</tbody>
</table>

Key: P = placebo, DB = double blind, M = metformin, SU = sulphonylurea
B12 Sources

- Shellfish (exceptional)
- Sardines
- Snapper
- Halibut
- Salmon
- Yogurt
- Cheese
- Organ meats
- Poultry
Selenium

- Significant antioxidant role
- Critical for defense of thyroid gland
- Cytochrome p450 system induction
- Immune function
- Pancreatic enzyme production
RDA for Selenium

- Children 30mcg
- Women 55mcg
- Men 55mcg
- Pregnancy 60mcg
Clinical Considerations

• Individuals with microcytic anemia or iron deficiency
• Patients with hyperlipidemia
• Populations living East of the Mississippi that do not eat seafood and rely heavily on conventional, local produce
• Patients with hypothyroidism
• Children with poor growth and adequate macronutrient intake
• Individuals following raw food or vegan diet
“there was insufficient evidence to assess the usefulness of potential biomarkers of selenium status, including urinary selenium, plasma triiodothyronine:thyroxine ratio, plasma thyroxine, plasma total homocysteine, hair and toenail selenium, erythrocyte, and muscle glutathione peroxidase activity.”
Brewers Yeast
A rich source of thiamin, and a source of niacin. Sprinkle on food or in drinks.
A Stylized Map** of Selenium Distribution in the U.S.

adapted from [www.anisci.cornell.edu/plants/toxicagents/selenium/map1.html]
Selenium Sources

- Brazil nuts
- Red snapper
- Oysters
- Cod
- Halibut
- Sardines
- Shrimp (ocean only)

*These can be good sources depending on soil or agricultural system

- Mushrooms
- Sunflower seeds
- Barley
- Eggs
- Turkey
• K1 types made by plants (phyloquinones)
• Integral role in clotting cascade
• Also shown to help improve bone density by suppressing osteoclast activity
• K2 varieties made by bacteria (menaquinones)
• Help maintain artery wall elasticity
• Both types have demonstrated anti-inflammatory properties (lower IL-6 levels)
Estimated Adequate Intake for Vitamin K

- Children 60mcg
- Women 90mcg
- Men 120mcg
- 3.5 oz of most dark green leafy vegetables provide more than 200mcg
Clinical Considerations

- Cardiovascular disease (exacerbated by avoidance of K due to coumadin use)
- Osteopenia/Osteoporosis
- Individuals with long term antibiotic use
- Children and adults who avoid the color green or anything that contains live cultures.

The triage theory posits that some functions of micronutrients (the approximately 40 essential vitamins, minerals, fatty acids, and amino acids) are restricted during shortage and that functions required for short-term survival take precedence over those that are less essential. Insidious changes accumulate as a consequence of restriction, which increases the risk of diseases of aging.
Vitamin K Assessment

Serum vitamin K 0.2-3.2ng/Ml
highly influenced by past 24 hours of vitamin K intake

Prothrombin/Clotting Time
Undercarboxylated prothrombin
(PIVKAll>1.58 mcg

Undercarboxylated osteocalcin >3.3mcg
Sources

• K1
• Kale
• Spinach
• Collard greens
• Swiss chard
• Brussel sprouts
• Cilantro
• Dandelion greens
• Parsley
• Pumpkin seeds

• K2
• Natto cheese
• Yogurt
• Grass-fed goat and sheep cheeses
• Miso
• Sauerkraut
Chromium

- Pivotal role in glucose metabolism
- Insulin receptor production
- Insulin secretion
- Lipoprotein lipase activity
- Very susceptible to phytate activity
Estimated Adequate Intake for Chromium

- Children 15mcg
- Women 25mcg
- Men 35mcg
- Pregnancy 30mcg
- Lactating 45mcg
Clinical Considerations

- Type II Diabetes/Insulin resistance
- Patients with hyperlipidemia
- Individuals with high stress levels and/or elevated cortisol production
"To date, data from randomized clinical trials are sparse and inconclusive. Placebo-controlled randomized clinical trials in well-characterized, at-risk populations are necessary to determine the effects of chromium on concentrations of glucose, insulin, and Hb A$_{1c}$"
Glucose and insulin responses to dietary chromium supplements: a meta-analysis
Sources

Oysters
Onions
Most ocean going fish and shellfish
Brewer’s yeast
Romaine lettuce
Beer
Barley
Tomatoes
Potassium

- Developed world has intake dramatically lower than ancestral dietary values (20% or less)
- 98% of body’s stores are intracellular
- Critical for maintaining pH without reliance on renal system and bones
- PRAL = 0.49Pro(g) + 0.037Phosphorous(mg) – 0.021Potassium(mg) - 0.026Mg - .013Ca
- Outweighed by modern diet’s high sodium level
Estimated Adequate Intake for Potassium

- Children 3800mg
- Women 4700mg
- Men 4700mg
- Lactating 5100mg
Clinical Considerations

- Hypertension
- Osteopenia/osteoporosis
- Muscle cramps
- Muscle weakness / Poor response to strength training
- Fatigue and low energy
Recent Attention to Nutrient Density of Foods

- ORAC (antioxidant score)
- MDI (based solely on calcium, iron, vitamins A and C)
- ANDI (greater list of micronutrients included, but still disregards countless beneficial molecules)
<table>
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<th>Item</th>
<th>ANDI Score</th>
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</tr>
<tr>
<td>Cola</td>
<td>0.6</td>
</tr>
</tbody>
</table>

* Patent Pending
Recommended Resources

- Advanced Nutrition and Human Metabolism, 4th Ed. Gropper, Groff, and Smith
- www.WHfoods.com
- Whole Foods Companion, Diane Onstad
- www.nutritiondata.com
Thank You. Eat and Be Well.

For future clinical questions:
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