The B-Vitamins: Folate and B12

Saurabh Mehta, M.B.B.S., Sc.D.
Assistant Professor of Global Health and Nutrition
Division of Nutritional Sciences
Cornell University
September 22, 2011

History

- Discovered by Dr. Lucy Wills in India (1931)
  - Indian Research Fund Association and the Lady Tata Foundation
  - Wills factor in yeast extract for the treatment of pernicious anemia of pregnancy
- Wills factor shown to be Folic Acid - Dr. Edmond Snell in 1930s
- Extracted from spinach
Folate Biosynthesis

- *Folium* - Latin for leaf
- *De novo* only in bacteria and plants
- Ring structure cannot be made by eukaryotic cells

Requirements

- Recommended
  - Men: 400 µg/day
  - Women: 400 µg/day
  - Pregnancy: +200 µg/day
  - Lactation: +100 µg/day

Dietary Sources

- Green leafy vegetables - spinach (131 µg per 1/2 cup)
- Liver (Chicken liver has 770 µg per 3.5 ounces)
- Lentils (180 µg per 1/2 cup)
- Orange Juice (47 µg/serving)
- Fortified sources - breakfast cereals (100-400 µg)

Bioavailability and Absorption

- Dietary form: polyglutamyl folates
- Food preparation: 50-95% loss during cooking
- Drugs, Alcohol
- Polyglutamates cleaved by pteroylpolyglutamate hydrolases to monoglutamyl form before absorption (jejunum)
- Supplemental/fortified form: monoglutamate folic acid
- Folic acid is about twice as bioavailable as other folates

Vitamin B₁₂

Requirements

- Recommended intake
  - Men: 2.4 µg/day
  - Women: 2.4 µg/day
  - Pregnancy: 2.6 µg/day
  - Lactation: 2.8 µg/day
Dietary Sources

- Animal food sources:
  - Organ meat (60 µg per 3 ounces); Red meat (2 µg per 3 ounces)
  - Fish - Salmon (5 µg per 3 ounces)
  - Eggs (0.5 µg)
  - Milk (0.9 µg per cup)
  - Fortified Cereal

Absorption

Folate and B12 Functions

- Nucleotide Synthesis - ACTG (RNA and DNA Synthesis)
- Amino Acid Synthesis
- RBC and WBC formation

Metabolic Functions

Assessment of Folate Status

- Plasma or RBC concentrations of folate
- Folate deficiency
  - Serum: <5 µg/L or <7 nmol/L
  - Red Blood Cell: <140 µg/L or <315 nmol/L

Folate Deficiency

- Causes:
  - Poor dietary intake
  - Pregnancy/Lactation
  - Liver disease/Medications (MTX, SP)
  - Alcohol
  - Genetic Polymorphisms: MTHFR
**Homocysteine Metabolism**

- **Methionine**: Transformed to Homocysteine by Methionine Synthase
- **S-Adenosylhomocysteine (SAH)**: Produced from Methionine
- **Methionine Synthase**: Requires Vitamin B12 (Methylcobalamin)

**Metabolic Functions**

- **DNA Synthesis**
- **Cell Division**
- **Methylation**
- **Hyperhomocysteinemia**
- **CVD**
- **Alzheimer's**
- **Cancer**
- **Osteoporosis**

**Assessment of Vitamin B12 Status**

- Serum B12 concentrations (can be maintained with low tissue levels)
- Schilling test – oral administration of radiolabeled B12 - measure urine concentration

**Vitamin B12 Deficiency**

- Causes: Impaired absorption
  - Poor dietary intake common in strict vegans (20-30 years)
  - Gastric or Pancreatic Disease
  - Atrophic Gastritis (elderly)
  - Pernicious anemia
    - Lack of IF (gastric atrophy)
    - Deep subcutaneous shots
- "Methyl-folate trap"
- Anemia
  - Megaloblastic, macrocytic
  - Overcome by excess folate
- Neuropathy
  - Demyelination
  - Not overcome by folate therapy
- Hyperhomocysteinemia

**Folate Deficiency**

- DNA synthesis
- Cell division
  - Megaloblastic anemia
- Neural tube defects
- Cancer
- Methylation
  - Hyperhomocysteinemia
  - CVD
  - Alzheimer’s
  - Cancer
  - Osteoporosis

**Vitamin B12 Deficiency**

- "Methyl-folate trap"
- Anemia
  - Megaloblastic, macrocytic
  - Overcome by excess folate
- Neuropathy
  - Demyelination
  - Not overcome by folate therapy
- Hyperhomocysteinemia
Megaloblastic Anemia

- Involves all dividing cells
- Clinical effects predominate in the blood
- Abnormal nuclear maturation despite normal cytoplasmic maturation

Neural Tube Defects (NTDs)

- One of the most common congenital abnormalities
- Failure of the neural tube to close completely
- 23rd to 28th day of pregnancy
- Spina bifida
- Anencephaly

| Study | Dose Supplemented | Unsupplemented | RR  
|-------|-------------------|----------------|-----
| Laurence | 463 | 0.63 |  
| Smithells | 24/500 | 0.15 |  
| Holmess | 4/141 | 0.00 |  
| Sieckel | 2/41 | 0.00 |  
| Cawell | 4/1529 | 0.00 |  

Summary RR = 0.52 (95% CI: 0.36–0.75)
Public Health Measures

- January 1, 1998: The United States Food and Drug Administration (FDA) began requiring the addition of folic acid to enriched breads, cereals, flour, corn meals, pastas, rice, and other grain products
- 140 μg folic acid/100 g of the cereal grain product
- Expected to increase intake ~100 μg/day - Periconceptional
- Other countries (n=51) fortifying food products with folic acid
  + Canada
  + Australia (since 2009)
  + Middle East
  + Indonesia

Advantages: Fortification

- Reaches populations not usually targeted by supplementation programs
  + Education campaigns can increase use of supplements; however, maximum level of use achieved is less than 50%
  + More than 50% pregnancies in the U.S. unplanned
- No competition with other food items if mandatory for all producers to fortify
  + Iodized Salt in India, Fortified Flour/Milk

Folate and Cancer

- Epidemiologic evidence suggests that high folate intake lowers risk of cancer, particularly colon cancer
- High doses of folic acid may increase carcinogenesis at late stages

Folate and B12 Interaction

<table>
<thead>
<tr>
<th>Vitamin status</th>
<th>B12 Low</th>
<th>Folate Low</th>
<th>No. of Subjects</th>
<th>Percentage with outcome</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>913</td>
<td>2.5</td>
<td>0.5 (0.2, 1.2)</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>Normal</td>
<td>297</td>
<td>3.0</td>
<td>1.4 (0.62, 2.9)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>Normal</td>
<td>828</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>High</td>
<td>800</td>
<td>11</td>
<td>0.4 (0.2, 0.7)</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>Normal</td>
<td>20.3</td>
<td>20</td>
<td>1.4 (0.99, 2.3)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>High</td>
<td>42</td>
<td>40</td>
<td>4.5 (2.5, 8.6)</td>
<td></td>
</tr>
</tbody>
</table>

Morris AJCN 2007, Jolut AJCN 2009

Adenoma Recurrence Trial

<table>
<thead>
<tr>
<th>No. (%) of Participants</th>
<th>First Follow-up</th>
<th>Second Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Subjects</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>Hyperplasia</td>
<td>203 (60.6)</td>
<td>181 (59.4)</td>
</tr>
<tr>
<td>Adenoma</td>
<td>101 (61.2)</td>
<td>93 (60.9)</td>
</tr>
<tr>
<td>No. of Adenomas</td>
<td>16 (4.8)</td>
<td>12 (4.8)</td>
</tr>
</tbody>
</table>

Kim OH, et al., Cancer Causes Control 2010

Cole et al. JAMA 2007
Folate and Other Cancers

- Inconsistent evidence for decreased risk of GI, Breast, and Lung CA
- Alcohol may modify the risk associated with folate
- Short-term RCTs of high-dose folic acid - no benefit or increased risk
- MTHFR 677TT variant associated with increased risk of many cancers

Hyperhomocysteinemia

- Risk factor for:
  - Heart Disease
  - Vascular Disease
  - Alzheimer’s
  - Osteoporosis

Metabolic Functions

Folic Acid and Homocysteine

Homocysteine Lowering Trialists’ Collaboration AJCN, 2005
RR of CHD for a 25% Lower Homocysteine Level (3 μmol/L decrease)

- After adjustment for confounding:
  - RR of IHD = 0.89

Folate/B12 and Homocysteine

- Randomized trials - No evidence of a benefit on stroke or vascular disease prevention

Global Perspective
Folate and Vitamin B12 Deficiency

Birth Defects

Countries with Available Data

TABLE 1: Number of cases/conception by folic acid/nitric oxide, autoimmunological markers according to WHO Region

<table>
<thead>
<tr>
<th>Region</th>
<th>No. of Cases</th>
<th>National %</th>
<th>Subnational %</th>
<th>Total %</th>
<th>Subnational %</th>
<th>Rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>35</td>
<td>3.4%</td>
<td>0.7%</td>
<td>5.1%</td>
<td>0.7%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Asia</td>
<td>11</td>
<td>1.1%</td>
<td>0.4%</td>
<td>1.4%</td>
<td>0.4%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Europe</td>
<td>21</td>
<td>1.5%</td>
<td>0.3%</td>
<td>1.8%</td>
<td>0.3%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Americas</td>
<td>35</td>
<td>3.4%</td>
<td>0.7%</td>
<td>4.1%</td>
<td>0.7%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Total</td>
<td>112</td>
<td>2.8%</td>
<td>0.5%</td>
<td>3.3%</td>
<td>0.5%</td>
<td>1.5%</td>
</tr>
</tbody>
</table>
Folate Deficiency


Pune Maternal Nutrition Study


High-Risk HPV Infection in India


Vitamin B12 Deficiency
Does Folate Fortification Work?

Folate Fortification: Concerns

- Do men need the same amount of folate?
- Masking of vitamin B12 deficiency
- Cancer - Increased incidence

Vitamin B12 Fortification?

- Who will benefit?
  - Gender
  - Age group
  - Where?
  - Adverse effects?
    - Cost-benefit ratio or Risks vs. Benefits
  - How?

Acknowledgments

- Edward L. Giovannucci
- Julia L. Finkelstein
- Stephanie Chiuve