Lessons from Observational Studies
Evaluating Magnesium Intakes: Can They Predict Outcomes for Clinical Intervention

W. H. Linda Kao, PhD
The Johns Hopkins University
School of Hygiene and Public Health
Magnesium

- Second most abundant intracellular cation
- Adult human body contains ~24g of Mg
  - ~50% in bones
  - 49% in soft tissue
  - 1% in extracellular fluid
- Absorption inversely related to dietary intake
- Primarily regulated by the kidney and the gastrointestinal tract
- Physiologic functions
  - Reactions involving ATP and nucleotide triphosphates
  - Insulin receptor/tyrosine kinase signal transduction pathway
Assessment of Magnesium

- Serum magnesium concentration
- Erythrocyte magnesium concentrations
- Leukocyte magnesium concentration
- 24-hour magnesium excretion
- Intracellular magnesium concentration using nuclear magnetic resonance (NMR) spectroscopy
- Dietary magnesium intake using dietary questionnaires
Hypomagnesemia and Type 2 Diabetes

- Type 2 diabetes mellitus leads to
  - Excess risk of cardiovascular disease
  - Reduced life expectancy
  - Few well-established, modifiable risk factors
- In animal models, magnesium supplementation prevents diabetes
- In humans, magnesium
  - Enhances short-term glucose handling
  - Inversely associated with type 2 diabetes cross-sectionally
- Few large, population-based, prospective studies
Prevalence of Type 2 Diabetes by Serum Magnesium Status in 15,539 Middle-Aged Adults from the ARIC Study
Research Questions

- Can incident type 2 diabetes be predicted by
  - Low serum magnesium concentration
  - Low dietary magnesium intake
# Atherosclerosis Risk in Communities (ARIC) Study

<table>
<thead>
<tr>
<th>Design:</th>
<th>Prospective cohort study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants:</td>
<td>12,128 non-diabetic middle-aged adults from 4 US communities</td>
</tr>
<tr>
<td>Exposure:</td>
<td>Serum and dietary magnesium levels measured before onset of diabetes</td>
</tr>
<tr>
<td>Outcome:</td>
<td>Incident type 2 diabetes over 6 years of follow-up</td>
</tr>
<tr>
<td>Analysis:</td>
<td>Logistic regression model</td>
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</tbody>
</table>

Kao WHL Arch. Int. Med. 1999;159:2151-5159
Assessment of Magnesium and Type 2 Diabetes

- Serum magnesium at baseline (mEq/L) Calmagite method
- Dietary magnesium intake at baseline (gm/kcal) Modified Willett’s Food Frequency Questionnaire
- Type 2 diabetes was defined as the presence of any of the following:
  - Report of physician-diagnosed diabetes
  - Use of insulin or oral hypoglycemic agents
  - Fasting blood glucose $\geq 126$ mg/dL
  - Non-fasting blood glucose $\geq 200$ mg/dL
In incidence rate per 1000 person-years of diabetes over six years of follow-up:

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Serum Magnesium, mEq/L</th>
<th>0.5-1.4</th>
<th>1.5</th>
<th>1.6</th>
<th>1.7</th>
<th>1.8</th>
<th>1.9-2.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black</td>
<td></td>
<td>20.9</td>
<td>18.3</td>
<td>16.6</td>
<td>15.7</td>
<td>17.5</td>
<td>18.4</td>
</tr>
<tr>
<td>White</td>
<td></td>
<td>16.5</td>
<td>13.6</td>
<td>9.2</td>
<td>8.4</td>
<td>6.9</td>
<td>7.3</td>
</tr>
</tbody>
</table>
## Adjusted Relative Odds (95% CI) of Diabetes Associated with Serum Magnesium

<table>
<thead>
<tr>
<th>Mg, mEq/L</th>
<th>Black</th>
<th>White</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5-1.4</td>
<td>0.93 (0.48-1.79)</td>
<td>1.94 (1.22-3.07)</td>
</tr>
<tr>
<td>1.5</td>
<td>0.83 (0.43-1.58)</td>
<td>1.68 (1.11-2.55)</td>
</tr>
<tr>
<td>1.6</td>
<td>0.84 (0.46-1.59)</td>
<td>1.25 (0.84-1.87)</td>
</tr>
<tr>
<td>1.7</td>
<td>0.77 (0.40-1.48)</td>
<td>1.15 (0.77-1.72)</td>
</tr>
<tr>
<td>1.8</td>
<td>0.91 (0.45-1.82)</td>
<td>0.98 (0.63-1.52)</td>
</tr>
<tr>
<td>1.9-2.6</td>
<td>1.00 (ref.)</td>
<td>1.00 (ref.)</td>
</tr>
</tbody>
</table>

P for Trend: 0.636 < 0.001

Adjusted for age, sex, education, family history of diabetes, BMI, waist to hip ratio, physical activities, alcohol consumption, diuretic use, serum calcium and potassium
### Adjusted Relative Odds (95% CI) of Diabetes Associated with Dietary Magnesium

<table>
<thead>
<tr>
<th>Mg (mg/1000 kcal)</th>
<th>Black (95% CI)</th>
<th>White (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤130</td>
<td>1.09 (0.57-2.06)</td>
<td>1.11 (0.76-1.62)</td>
</tr>
<tr>
<td>130-160</td>
<td>1.28 (0.75-2.18)</td>
<td>1.01 (0.71-1.43)</td>
</tr>
<tr>
<td>161-190</td>
<td>1.44 (0.93-2.22)</td>
<td>1.13 (0.84-1.51)</td>
</tr>
<tr>
<td>&gt;190</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
</tbody>
</table>

**P for Trend** 0.722 0.374

*Adjusted for age, sex, education, family history of diabetes, BMI, waist to hip ratio, physical activities, alcohol consumption, diuretic use, dietary calcium and potassium.*
Conclusions

- Significant graded relationship between low serum Mg and incident type 2 diabetes in whites
- Lower serum Mg in blacks, but no association with incident type 2 diabetes
- No association between dietary Mg as measure by food frequency questionnaire and incident type 2 diabetes
Iowa Women’s Health Study

Design: Prospective cohort study
Participants: 35,988 non-diabetic women aged 55 – 69 yr. at baseline
Exposure: Dietary magnesium intake based on a 127-item food frequency questionnaire
Outcome: Self-reported incident type 2 diabetes over 6 years of follow-up
Analysis: Cox proportional model

### Adjusted Relative Risk (95% CI) of Diabetes Associated with Dietary Magnesium

**Iowa Women’s Health Study**

<table>
<thead>
<tr>
<th>Magnesium Intake (mg/day)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 242</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>242 – 270</td>
<td>0.82 (0.69 – 0.99)</td>
</tr>
<tr>
<td>271 – 297</td>
<td>0.86 (0.71 – 1.03)</td>
</tr>
<tr>
<td>298 – 332</td>
<td>0.88 (0.73 – 1.06)</td>
</tr>
<tr>
<td>&gt; 332</td>
<td>0.76 (0.62 – 0.95)</td>
</tr>
</tbody>
</table>

Adjusted for age, total energy intake, BMI, waist-to-hip ratio, education, smoking, alcohol intake, physical activity, and dietary intake of whole grains and cereal fiber.
Nurses’ Health Study

Design: Prospective cohort study
Participants: 84,360 non-diabetic women aged 34 - 59 yr. at baseline (1980)
Exposure: Dietary magnesium intake based on a 61-item food frequency questionnaire
Outcome: Self-reported incident type 2 diabetes over 6 years of follow-up
Analysis: Cox proportional model

### Adjusted Relative Risk (95% CI) of Diabetes Associated with Dietary Magnesium

**Nurses’ Health Study**

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>2</td>
<td>1.01</td>
<td>0.91 (0.74 – 1.10)</td>
</tr>
<tr>
<td>3</td>
<td>1.04</td>
<td>0.84 (0.69 – 1.03)</td>
</tr>
<tr>
<td>4</td>
<td>0.92</td>
<td>0.82 (0.67 – 1.01)</td>
</tr>
<tr>
<td>5</td>
<td>0.95 (0.56 – 1.61)</td>
<td>0.62 (0.50 – 0.78)</td>
</tr>
</tbody>
</table>

**P for trend** \(< 0.01\)

Adjusted for age, BMI, alcohol intake, family history of diabetes, prior weight change, energy intake, and potassium and calcium intake
Limitations of Existing Observational Studies

- Dietary assessment assessed at one point in time and may lead to misclassification
- Correlation between dietary assessment of magnesium intake and biomarkers of magnesium remains uncertain
- Difficulty in teasing apart effects of other minerals
- Other unknown potential confounders may exist
- Follow-up time may be inadequate
- Type 2 diabetes definition not by oral glucose tolerance test (the gold standard)
Can increasing magnesium intake prevent type 2 diabetes?
Guidelines for Establishing Causality

- Temporal relationship – exposure occurs before development of disease
- Strength of association – the stronger the more likely
- Dose-response relationship
- Replication of the findings
- Biologic plausibility
- Consideration of alternate explanations - confounding
- Cessation of exposure leads to reduced risk of disease
Implications

- Decreased serum magnesium may alter natural history of type 2 diabetes
- Decreased magnesium intake may increase risk of type 2 diabetes
- Better understanding of correlations between magnesium intake and biomarkers of magnesium warranted
- Pharmacologic doses of magnesium as a preventive measure for development of type 2 diabetes remains to be investigated