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

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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

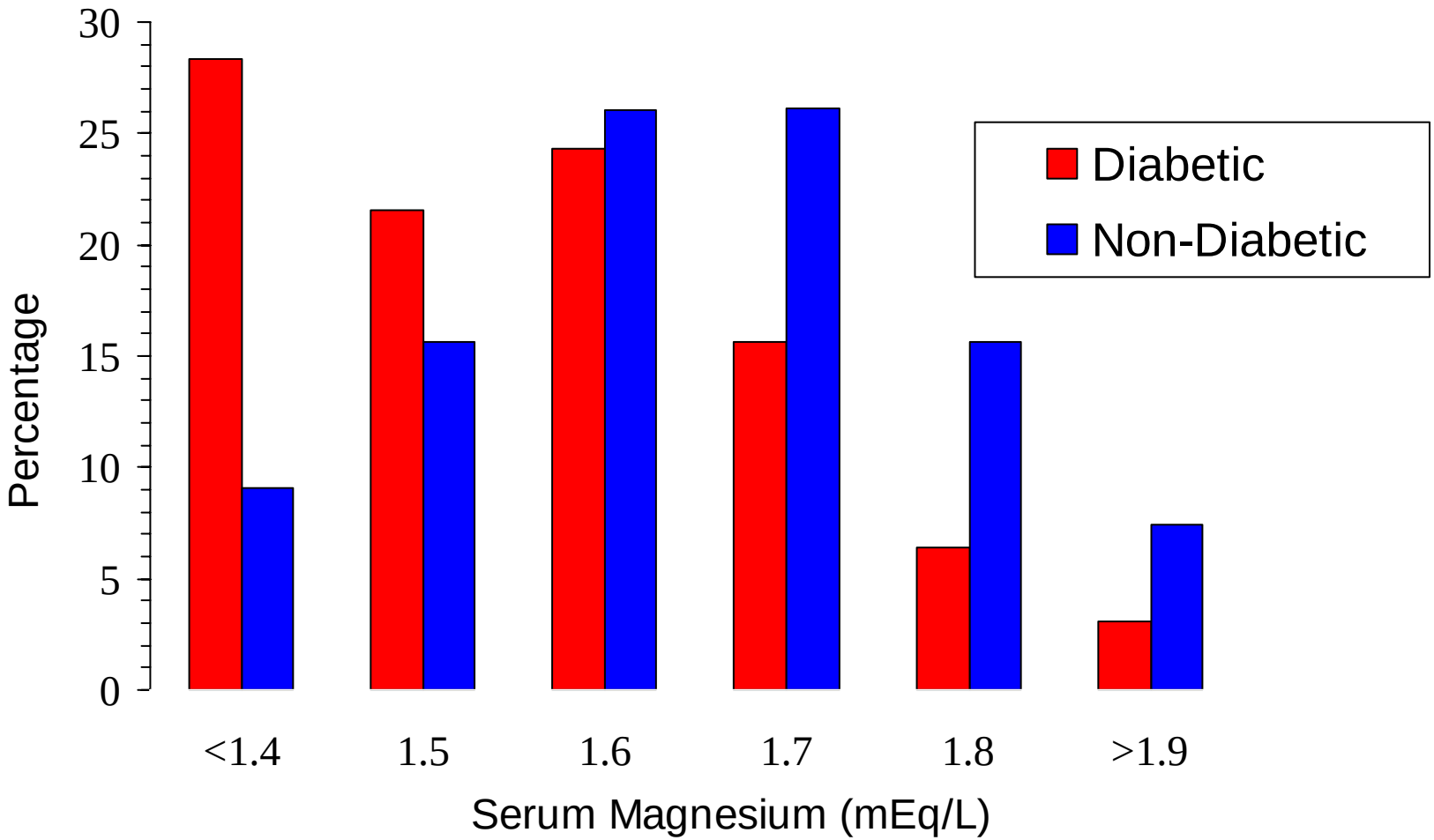
Assessment of Magnesium

- 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

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

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

Incidence Rate per 1000 Person-Years of Diabetes Over Six Years of Follow-Up

Ethnicity	Serum Magnesium, mEq/L					
	0.5-1.4	1.5	1.6	1.7	1.8	1.9-2.5
Black	20.9	18.3	16.6	15.7	17.5	18.4
White	16.5	13.6	9.2	8.4	6.9	7.3

Adjusted Relative Odds (95% CI) of Diabetes Associated with Serum Magnesium

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

Mg (mg/1000 kcal)	Black	White
≤130	1.09 (0.57-2.06)	1.11 (0.76-1.62)
130-160	1.28 (0.75-2.18)	1.01 (0.71-1.43)
161-190	1.44 (0.93-2.22)	1.13 (0.84-1.51)
>190	1.00 (reference)	1.00 (reference)
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

Meyer KA, Am J Clin Nutr 2000;71:921-30

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

Iowa Women's Health Study

Magnesium Intake (mg/day)	
< 242	1.00 (reference)
242 – 270	0.82 (0.69 – 0.99)
271 – 297	0.86 (0.71 – 1.03)
298 – 332	0.88 (0.73 – 1.06)
> 332	0.76 (0.62 – 0.95)

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

Colditz GA, Am J Clin Nutr 1992;55:1018-23

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

Nurses' Health Study

Magnesium Quintile	1980 – 1986 (N = 84,360)	1986 – 1992 (N = 65,173)
1	1.00 (reference)	1.00 (reference)
2	1.01	0.91 (0.74 – 1.10)
3	1.04	0.84 (0.69 – 1.03)
4	0.92	0.82 (0.67 – 1.01)
5	0.95 (0.56 – 1.61)	0.62 (0.50 – 0.78)
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