Magnesium Deficiency Is Associated With Insulin Resistance in Obese Children

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OBJECTIVE — Magnesium deficiency has been associated with insulin resistance (IR) and increased risk for type 2 diabetes in adults. This study was designed to determine whether obese children exhibit serum or dietary magnesium deficiency and its potential association with IR.

RESEARCH DESIGN AND METHODS — We studied 24 obese nondiabetic children (BMI ≥85th percentile) and 24 sex- and puberty-matched lean control subjects (BMI <85th percentile). We measured serum magnesium, indexes of insulin sensitivity, dietary magnesium intake (using a food frequency questionnaire), and body composition (by air displacement plethysmography).

RESULTS — Serum magnesium was significantly lower in obese children (0.748 ± 0.015 mmol/l, means ± SE) compared with lean children (0.801 ± 0.012 mmol/l) ($P = 0.009$). Serum magnesium was inversely correlated with fasting insulin ($r_s = -0.36$ [95% CI −0.59 to −0.08]; $P = 0.011$) and positively correlated with quantitative insulin sensitivity check index (QUICKI) (0.35 [0.06–0.58]; $P = 0.015$). Dietary magnesium intake was significantly lower in obese children (obese: 0.12 ± 0.004 vs. lean: 0.14 ± 0.004 mg/kcal; $P = 0.003$). Dietary magnesium intake was inversely associated with fasting insulin (−0.43 [−0.64 to −0.16]; $P = 0.002$) and directly correlated with QUICKI (0.43 [0.16–0.64]; $P = 0.002$).

CONCLUSIONS — The association between magnesium deficiency and IR is present during childhood. Serum magnesium deficiency in obese children may be secondary to decreased dietary magnesium intake. Magnesium supplementation or increased intake of magnesium-rich foods may be an important tool in the prevention of type 2 diabetes in obese children.

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The current epidemic of childhood obesity has been associated with an alarming rise in the prevalence of pediatric type 2 diabetes (1). Hyperinsulinemia and insulin resistance (IR) are the precursors of type 2 diabetes. Obesity and dietary macronutrients clearly play a role in the risk for type 2 diabetes, but the role of micronutrients in this process is not clear.

Magnesium is an important cofactor for enzymes involved in carbohydrate metabolism. A strong relationship between magnesium and insulin action has been reported (2,3). In adults, low serum and intracellular magnesium concentrations are associated with IR, impaired glucose tolerance, and decreased insulin secretion (4–6). Furthermore, large epidemiologic studies in adults indicate that lower dietary magnesium and lower serum magnesium are associated with increased risk for type 2 diabetes (7,8). However, the role of magnesium deficiency in the development of IR during childhood has not been clearly defined. The present study was designed to determine whether a relationship exists between magnesium homeostasis and IR in obese children and to evaluate potential mechanisms leading to magnesium deficiency in these children.

RESEARCH DESIGN AND METHODS

We studied 24 obese children (BMI ≥85th percentile for age and sex) aged 8–17 years with at least one risk factor for type 2 diabetes and 24 lean children (BMI <85th percentile) matched for sex and stage of pubertal development. Risk factors for type 2 diabetes included family history of type 2 diabetes in a first- or second-degree relative, ethnicity (African American, Hispanic, or Asian American), or clinical signs of IR (9). Children were recruited by public advertisement and by referrals from primary care physicians. Characteristics of the study subjects are summarized in Table 1. Children were excluded if they were anemic or pregnant. The study was approved by the University of Virginia Institutional Review Board. Written informed consent was obtained from both parents and children aged ≥15 years; informed assent was obtained from all children <15 years old.

Subjects were evaluated at the General Clinical Research Center early in the morning after a 10-h overnight fast. Upon arrival, both parent and child were questioned to confirm that the subject was fasting. A complete history and physical exam were performed. Weight was measured using a calibrated digital scale. Height was measured in triplicate to the nearest millimeter using a calibrated stadiometer. Tanner staging of breast devel-

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Abbreviations: HOMA, homeostasis model assessment; IR, insulin resistance; QUICKI, quantitative insulin sensitivity check index.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Characteristics and metabolic parameters of the study subjects*

	Obese subjects	Lean subjects	*P* value*
n	24	24	—
Sex (male/female)†	9/15	9/15	—
Age (years)	12.52 ± 0.49; 12.00 (9.94–16.23)	13.35 ± 0.43; 13.25 (10.04–15.96)	0.215
Race			
Caucasian	11	21	0.005
African American	11	1	
Other	2	2	
Pubertal stage†‡			—
Early puberty (Tanner 1 and 2)	6	6	—
Midpuberty (Tanner 3 and 4)	7	7	—
Late puberty (Tanner 5)	11	11	—
BMI (kg/m^2)	36.2 ± 2.1; 34.85 (24.84–47.07)	18.7 ± 0.6; 18.07 (14.79–22.88)	<0.001
BMI z score	2.36 ± 0.09; 2.46 (1.55–2.82)	−0.28 ± 0.19; −0.31 (−1.36 to 0.79)	<0.001
Percentage body fat	44.1 ± 1.5; 44.67 (36.39–52.68)	22.9 ± 1.1; 23.56 (15.01–29.00)	<0.001
Fasting glucose (mmol/l)	5.16 ± 0.05; 5.13 (4.55–5.60)	5.16 ± 0.10; 5.16 (4.87–5.45)	0.984
HbA_{1c} (%)	5.24 ± 0.11; 5.20 (4.69–5.62)	5.13 ± 0.07; 5.10 (4.69–5.61)	0.412
Fasting insulin (pmol/l)	178.8 ± 19.8; 186.92 (50.18–268.66)	63.2 ± 6.6; 57.47 (25.84–110.2)	<0.001
HOMA§	6.01 ± 0.76; 5.70 (1.62–9.94)	2.10 ± 0.22; 1.86 (0.77–3.54)	<0.001
QUICKI§	0.31 ± 0.01; 0.30 (0.28–0.36)	0.35 ± 0.01; 0.35 (0.32–0.40)	<0.001
Cholesterol (mmol/l)	4.34 ± 0.16; 4.22 (3.27–5.60)	3.76 ± 0.14; 3.63 (2.96–4.88)	0.009
Triglycerides (mmol/l)	1.12 ± 0.10; 1.07 (0.60–1.83)	0.84 ± 0.09; 0.77 (0.48–1.48)	0.039
LDL (mmol/l)	2.81 ± 0.14; 2.70 (2.03–3.79)	2.10 ± 0.12; 2.05 (1.42–3.10)	<0.001
HDL (mmol/l)	1.10 ± 0.04; 1.06 (0.82–1.35)	1.35 ± 0.07; 1.35 (0.96–1.73)	0.002
Serum magnesium (mmol/l)	0.748 ± 0.015; 0.740 (0.653–0.863)	0.801 ± 0.012; 0.822 (0.699–0.863)	0.009
Urinary magnesium-to-creatinine ratio (mg/mg)	0.077 ± 0.007; 0.067 (0.042–0.112)	0.081 ± 0.010; 0.070 (0.040–0.110)	0.762

Data are means ± SE; median (10th to 90th percentile). *By ANOVA for continuous variables and by exact test for categorical variables. †Subject matching criterion by design. ‡Tanner stage of breast development for girls and genital development for boys. §Formulas used for calculation of HOMA and QUICKI are shown in RESEARCH DESIGN AND METHODS.

opment in girls and genital development in boys was performed by a single pediatric endocrinologist. Children were classified as being in early puberty (Tanner 1 or 2), midpuberty (Tanner 3 or 4), or late puberty (Tanner 5). This classification was intended to account for the transient reduction in insulin sensitivity during puberty, which reaches a nadir at Tanner stage 3 or 4 and recovers to near prepubertal levels by Tanner stage 5 (10,11). BMI z scores were calculated using equations provided by the Centers for Disease Control and Prevention. Body density was measured by air displacement plethysmography (BodPod; Life Measurement Instruments, Concord, CA) and converted to a body composition estimate using the Siri equation (12).

Laboratory tests

A fasting blood sample was obtained for insulin, glucose, HbA_{1c}, serum magnesium, lipid profile, and chemistry panel. Serum magnesium was measured using a colorimetric assay in an Olympus AU 640 analyzer. Insulin was measured in duplicate by an enzyme-linked immunosorbent assay (Diagnostic Systems Laboratories), and the means were used for the analysis. Glucose was measured at the bedside using the glucose oxidase method in a Beckman Glucose Analyzer (Beckman Instruments, Fullerton, CA). Indexes of insulin sensitivity, homeostasis model assessment (HOMA) of IR index, and quantitative insulin sensitivity check index (QUICKI) have been validated and exhibit a good correlation with insulin sensitivity measured by a hyperinsulinemic-euglycemic clamp in children (13). HOMA was calculated using the formula (fasting insulin [μIU/ml] × fasting glucose [mmol/l])/22.5; QUICKI was calculated as 1/(log fasting insulin [μIU/ml] + log fasting glucose [mg/dl]). Renal handling of magnesium was evaluated by calculating the magnesium-to-creatinine ratio from a spot urine sample.

Dietary assessment

Nutritional evaluation was performed using the Youth and Adolescent Questionnaire. This 151-item questionnaire was developed based on the Nurses' Health Study semiquantitative food frequency questionnaire and has been previously validated for use in children aged 9–18 years (14,15). The Youth and Adolescent Questionnaire mean energy and nutrient intakes, including intake of magnesium, calcium, and potassium, are comparable to those obtained from 24-h diet recalls (15). Questionnaires were administered by a registered dietitian and analyzed at the Channing Laboratories (Harvard Medical School). Macronutrient and micronutrient intake was compared between the groups. Micronutrient intake was evaluated using unadjusted total daily intake and energy-adjusted intake. The latter was calculated to help reduce between-person variability due to under- or overreporting of intake, which may occur when collecting dietary information.

Statistical analysis

Differences between obese and lean children were examined for serum magnesium, indexes of insulin sensitivity, lipids, adiposity, and diet composition. *P* values for these comparisons were calculated via ANOVA. Weight status (lean, obese) served as the independent factor of the ANOVA models, and the 24 matched pairs were treated as independent blocks so that a within-matched-pair comparison could be formulated. Spearman correlations were used to examine the bivariate (unadjusted) linear associations between serum magnesium and indexes of insulin sensitivity, adiposity, dietary magnesium intake, and urinary magnesium excretion. Spearman correlations were also used to examine linear associations between dietary micronutrients and indexes of insulin sensitivity. CIs were calculated for the correlation constants via Fisher's *Z* transformation. If we a priori determined that confounding was possible, a Spearman partial correlation was used to account for the effects of potential confounders when calculating correlation coefficients. Statistical significance was set at $\alpha < 0.05$. All analyses were conducted using SAS version 8.2 (SAS Institute, Cary, NC) and S-Plus version 2000 for Windows (Insightful, Seattle, WA). Descriptive statistics include means ± SE and the 10th, 50th, and 90th percentile for each variable's distribution. Spearman correlation coefficients are presented with 95% CI.

RESULTS — Table 1 shows indexes of insulin sensitivity, glucose homeostasis, and lipid profile. Obese children exhibited IR as determined by a higher fasting insulin and HOMA ($P < 0.001$) and lower QUICKI ($P < 0.001$) than lean children. There were no significant group differences in fasting glucose or HbA_{1c}. Obese children had higher triglycerides ($P < 0.05$) and total and LDL cholesterol ($P < 0.01$) and lower HDL cholesterol ($P < 0.01$) than lean children.

Serum magnesium

Serum magnesium concentration was significantly lower in obese children compared with lean children (obese: 0.748 ± 0.015 vs. lean: 0.801 ± 0.012 mmol/l; $P = 0.009$). Serum calcium and potassium were measured in 12 obese children and all lean children. There were no significant differences in calcium (obese: 2.36 ± 0.02 vs. lean: 2.35 ± 0.01 mmol/l; $P = 0.984$) or potassium (obese: 4.03 ± 0.04 vs. lean: 3.95 ± 0.06 mmol/l; $P = 0.334$) between groups.

Serum magnesium and adiposity. Serum magnesium was inversely associated with adiposity as measured by BMI ($r_s = -0.44$ [95% CI −0.65 to −0.17]; $P = 0.002$), BMI z score (−0.42 [−0.63 to −0.14]; $P = 0.003$), and percentage body fat (−0.37 [−0.60 to −0.09]; $P = 0.009$).

Serum magnesium and insulin sensitivity. Serum magnesium was inversely correlated with fasting insulin ($r_s = -0.36$ [95% CI −0.59 to −0.08]; $P = 0.011$) and HOMA (−0.35 [−0.58 to −0.06]; $P = 0.015$) and positively correlated with QUICKI (0.35 [0.06–0.58]; $P = 0.015$). After adjusting for the effect of adiposity (using percentage body fat), the relationship between serum magnesium and insulin sensitivity was no longer statistically significant for HOMA ($r_s = -0.24$; $P = 0.104$), fasting insulin ($r_s = -0.22$; $P = 0.124$), and QUICKI ($r_s = 0.17$; $P = 0.252$).

Dietary magnesium

Nutritional data are summarized in Table 2. Dietary magnesium intake in mg/kcal was significantly lower in obese children compared with lean children (obese: 0.12 ± 0.004 vs. lean: 0.14 ± 0.004 mg/kcal; $P = 0.001$) Although unadjusted magnesium intake was 14.4% lower in obese compared with lean children (obese: 286.4 ± 18.3 vs. lean: 327.7 ± 16.6 mg/day; $P = 0.102$), this difference did not reach statistical significance. Serum magnesium concentration was correlated with total daily magnesium intake ($r_s = 0.40$ [95% CI 0.12–0.62]; $P = 0.005$) and energy-adjusted magnesium intake ($r_s = 0.41$ [0.14–0.63]; $P = 0.004$).

There were no significant differences between groups in total energy, fat, carbohydrate, or protein intake. Obese children had a greater percentage of calories derived from fat ($P = 0.022$) and a lower percentage of calories derived from carbohydrates ($P = 0.009$). Energy-adjusted fiber intake was significantly lower in obese children ($P = 0.004$). There were no other significant differences in unadjusted or energy-adjusted micronutrient intake.

Magnesium intake and insulin sensitivity. Magnesium intake in mg/kcal was inversely correlated with HOMA ($r_s = -0.43$ [95% CI −0.64 to −0.16]; $P = 0.002$) and fasting insulin (−0.43 [−0.64 to −0.16]; $P = 0.002$) and positively correlated with QUICKI (0.43 [0.16–0.64]; $P = 0.002$) (Fig. 1). There was no association between total daily magnesium intake and markers of insulin sensitivity.

Fiber intake and insulin sensitivity. There was a significant association between fiber intake in g/kcal and QUICKI ($r_s = 0.30$ [95% CI 0.01–0.55]; $P = 0.036$). However, after adjusting for magnesium intake in mg/kcal, this relationship was no longer statistically significant ($r_s = 0.00$; $P = 0.969$). The association between magnesium intake (mg/kcal) and QUICKI remained significant after adjusting for fiber intake (g/kcal) ($r_s = 0.33$; $P = 0.023$).

Urinary excretion of magnesium

Urinary magnesium-to-creatinine ratio was calculated in all subjects except one obese female on whom the measurement was missed. There was no group difference in urinary magnesium-to-creatinine ratio between groups (obese: 0.077 ± 0.007 vs. lean: 0.081 ± 0.010 mg/mg; $P = 0.762$). Urinary magnesium-to-creatinine ratio was not correlated with serum magnesium ($r_s = 0.15$ [95% CI −0.15 to 0.43]; $P = 0.308$).

Subanalysis in race-matched pairs

Due to the difference in racial distribution between groups, we performed a subanalysis comparing 13 obese children and 13 lean children matched for race, sex, and stage of pubertal development. Racial distribution for this subgroup was 84.6% ($n = 22$) Caucasian, 7.6% ($n = 2$) African American, and 7.6% ($n = 2$) Hispanic. Serum magnesium was significantly lower in obese children (obese: 0.765 ± 0.02 vs. lean: 0.822 ± 0.01 mmol/l; $P = 0.014$) compared with lean children. Serum magnesium was directly correlated with dietary magnesium intake in mg/day ($r_s = 0.50$ [95% CI 0.13–0.75]; $P = 0.009$). Dietary magnesium intake (mg/kcal) was inversely correlated with insulin sensitivity measured by HOMA (−0.41 [−0.69 to −0.01]; $P = 0.039$) and fasting insulin (−0.39 [−0.68 to −0.01]; $P = 0.039$) and directly correlated with QUICKI (0.41 [0.01–0.69]; $P = 0.049$) (Fig. 1).

Table 2 —*Summary of daily nutrient intake*

	Obese subjects	Lean subjects	*P* value*
Energy intake (kcal)	2,430.3 ± 141.5; 2,345.0 (1,633.2–3,449.5)	2,369.7 ± 527.5; 2,350.0 (1,662.8–3,058.4)	0.734
Protein (g)	92.0 ± 5.3; 96.0 (59.6–118.4)	90.7 ± 4.4; 91.5 (63.8–118.5)	0.852
Carbohydrates (g)	323.9 ± 21.5; 302.5 (203.0–465.2)	329.6 ± 15.6; 322.0 (242.4–430.6)	0.831
Fat (g)	88.2 ± 5.2; 85.0 (62.8–112.7)	80.5 ± 4.6; 79.0 (52.5–114.4)	0.276
Percent of calories from protein (%)	15.3 ± 0.5; 15.3 (12.4–18.9)	15.4 ± 0.4; 15.5 (12.6–18.0)	0.881
Percent of calories from carbohydrate (%)	52.8 ± 0.9; 51.8 (48.6–58.2)	55.7 ± 0.8; 55.2 (50.9–61.8)	0.009
Percent of calories from fat (%)	32.9 ± 0.8; 33.7 (27.8–37.4)	30.4 ± 0.7; 30.4 (25.0–34.8)	0.022
Unadjusted for energy intake			
Magnesium (mg)	286.4 ± 18.3; 280.0 (168.8–389.9)	327.7 ± 16.6; 307.5 (242.7–441.2)	0.102
Potassium (mg)	2,938.3 ± 206.3; 2,810.2 (1,742.6–4,028.2)	3,153.0 ± 186.9; 3,242.2 (2,179.1–4,324.8)	0.424
Calcium (mg)	1,151.8 ± 104.0; 1,001.7 (636.4–1,761.2)	1,149.4 ± 71.8; 1,250.7 (694.8–1,531.1)	0.985
Phosphorus (mg)	1,592.5 ± 106.3; 1,587.7 (965.8–2,192.3)	1,542.6 ± 76.1; 1,587.8 (1,107.5–1,935.3)	0.704
Sodium (mg)	2,908.7 ± 155.5; 2,842.0 (2,078.4–4,033.2)	2,840.6 ± 133.6; 2,842.0 (2,078.4–4,033.2)	0.741
Fiber (g)	17.4 ± 1.1; 17.3 (11.2–24.9)	20.5 ± 1.3; 19.9 (13.9–28.8)	0.095
Adjusted for energy intake			
Magnesium (mg/kcal)	0.12 ± 0.004; 0.12 (0.09–0.14)	0.14 ± 0.004; 0.14 (0.12–0.16)	0.001
Potassium (mg/kcal)	1.21 ± 0.05; 1.18 (0.89–1.53)	1.32 ± 0.05; 1.28 (1.02–1.64)	0.143
Calcium (mg/kcal)	0.47 ± 0.03; 0.42 (0.31–0.64)	0.48 ± 0.02; 0.46 (0.38–0.61)	0.738
Phosphorus (mg/kcal)	0.66 ± 0.02; 0.65 (0.51–0.82)	0.65 ± 0.02; 0.65 (0.53–0.76)	0.823
Sodium (mg/kcal)	1.21 ± 0.03; 1.20 (1.07–1.38)	1.20 ± 0.03; 1.22 (1.00–1.42)	0.887
Fiber (g/kcal)	0.007 ± 0.0004; 0.007 (0.006–0.009)	0.009 ± 0.0003; 0.008 (0.007–0.011)	0.004

Data are means ± SE; median (10th to 90th percentile). *By ANOVA.

CONCLUSIONS — The results of our cross-sectional study demonstrate that obese children have lower serum magnesium concentrations than lean children and that this may be secondary to decreased dietary intake of magnesium. Although lower serum (16) and intracellular (17) magnesium have been previously reported in obese children, our study is the first to report lower dietary magnesium intake in obese children compared with lean children. Serum magnesium and dietary magnesium were inversely associated with IR, providing the first evidence that the association between magnesium deficiency and IR is present during childhood. These associations were not evaluated in previous studies that measured serum or intracellular magnesium in obese children (16,17) but agree with studies in adults that found that low serum magnesium concentrations are associated with hyperinsulinemia, decreased insulin-mediated glucose disposal, and the metabolic syndrome (4,5,18). In the Atherosclerosis Risk in Communities study, Caucasian men with serum magnesium <0.58 mmol/l had a twofold increase in incidence of type 2 diabetes compared with those with a magnesium concentration >0.78 mmol/l (8).

The mechanism by which magnesium deficiency may lead to IR has not yet

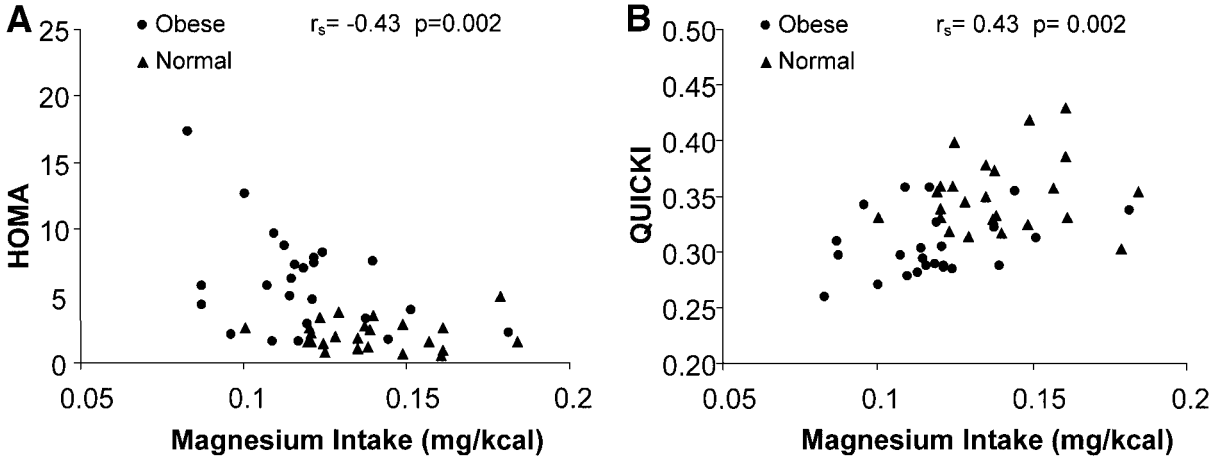

Figure 1—*Correlation of dietary intake of magnesium with insulin sensitivity. Dietary intake of magnesium in mg/kcal was inversely associated with HOMA* (A) *and directly correlated with QUICKI* (B) (n = *48*).

been fully elucidated. Magnesium is a cofactor for multiple enzymes involved in carbohydrate metabolism (2). Adipocytes placed in low-magnesium media show reduction in insulin-stimulated glucose uptake (19). Magnesium deficiency is associated with increased intracellular calcium levels, which may lead to IR (20). Low erythrocyte magnesium content increases membrane microviscosity, which may impair insulin interaction with its receptor (21). Tyrosine kinase activity is decreased in muscle insulin receptors of rats fed a low-magnesium diet (22). These findings indicate that magnesium deficiency may directly affect insulin signaling.

One potential cause for lower serum magnesium in obese youth is low dietary magnesium intake and a unique finding of this study was a lower calorie-adjusted magnesium intake in obese children compared with lean children. This lower calorie-adjusted magnesium intake was the result of the median reported energy intakes of the lean and obese groups being within 5 kcal (2,350 vs. 2,345 kcal, respectively) but the obese youth having a 14.4% lower reported magnesium intake. Moreover, both unadjusted and adjusted dietary magnesium intake correlated with serum magnesium, suggesting that the low serum magnesium observed in obese children may be secondary to decreased magnesium intake. Calorie-adjusted data rather than total daily intake values from food frequency questionnaires are considered more reliable because the instrument is best at measuring diet composition (23) and may be affected by underreporting of intake, particularly in obese adolescents (24). The lower magnesium intake of obese youth, despite very similar reported energy intakes, suggests that consumption of specific foods high in magnesium content may have accounted for the group differences. Analysis of specific foods from the food frequency questionnaires demonstrates that there were multiple sources of magnesium. Lean children consumed more magnesium from green leaf vegetables, fish, beans, yogurt, nuts, and peanut butter than obese children. Milk is a very important source of magnesium, but there were no differences in magnesium intake from milk or total dairy sources between groups.

Previously, the Continuing Survey of Food Intake by Individuals showed that one-third of school-aged children do not meet their estimated average requirements for magnesium (25); however, serum magnesium was not measured in that study. Our data show that hypomagnesemia (serum magnesium <0.78 mmol/l) was present in 27% of healthy lean children and 55% of obese children, indicating that serum magnesium deficiency may be more prevalent in children than previously suspected.

Obese children consumed a higher percentage of total calories from fat and a lower percentage of calories from carbohydrates. Fiber intake was lower in the obese group, while potassium, calcium, phosphorus, and sodium intakes were not different between groups. Other potential causes of lower serum magnesium in obese youth include reduced magnesium absorption secondary to higher fat intake and lower fiber intake. Dietary fat, calcium, and phosphate have clear effects on magnesium absorption in animal models; however, their effect on magnesium absorption in humans remains unsettled (26). The effect of dietary fiber on magnesium absorption depends largely on the type of fiber, but several human studies have shown that fermentable oligo- or polysaccharides enhance magnesium absorption (27). Decreased renal tubular reabsorption of magnesium could also lead to magnesium deficiency. We did not find any differences in the magnesium-to-creatinine ratio in spot urine between the groups; however, more extensive evaluation of renal handling of magnesium, including measurement of tubular reabsorption of magnesium, will be necessary in future studies.

The data reveal an inverse relationship between dietary magnesium and IR. To the best of our knowledge, this is the first study to report a physiologically relevant effect of deficient dietary magnesium intake in children. Studies in adults have shown that lower dietary magnesium intake is associated with IR and increased risk for type 2 diabetes (3,4,28–30). The Women's Health Study and the Atherosclerosis Risk in Communities study showed that dietary magnesium intake was inversely associated with fasting insulin (4,29). In the Health Professionals Follow-Up Study and the Nurse's Health Study, subjects in the highest quintile of magnesium intake had a 33% lower risk of developing type 2 diabetes than those in the lowest quintile of magnesium intake (7). Magnesium supplementation in subjects with IR and type 2 diabetes resulted in improvement of insulin sensitivity (31,32) and β-cell response to glucose (33). In an animal model of the metabolic syndrome, increased magnesium intake reduced the rate of development of type 2 diabetes (34). These results suggest a potential role of dietary magnesium in the prevention of type 2 diabetes. It will be important to test in future interventional studies whether increasing magnesium intake will improve insulin sensitivity and reduce the risk for type 2 diabetes in obese children.

Fiber intake was also correlated with insulin sensitivity. Previous studies (35) have shown an association between low fiber intake and IR. In our study, the relationship between fiber intake and insulin sensitivity was no longer significant after adjusting for magnesium intake. On the other hand, the relationship between magnesium intake and insulin sensitivity remained significant after adjusting for fiber intake, suggesting that the role of magnesium is independent of fiber.

One of the limitations of our study is the difference in race between the obese and lean groups. This may be important because increased prevalence of magnesium deficiency has been reported in African-American adults (4,36). However, epidemiologic studies in mostly white populations demonstrated the association between low serum and/or dietary magnesium and increased prevalence of type 2 diabetes (7,8). Comparison of race-matched children in our study confirms that serum magnesium is lower in obese children and correlated with dietary magnesium and that dietary magnesium intake is inversely associated with IR. Additional studies in larger populations of children will be required to determine whether the relationship between magnesium deficiency and IR is truly influenced by race.

Another limitation of this study is that intracellular magnesium, a more sensitive indicator of magnesium balance, was not measured (37). Magnesium is primarily an intracellular cation; roughly 1% of whole-body magnesium is found extracellularly, and the free intracellular fraction is the portion regulating enzyme pathways (3). However, serum magnesium exhibits a good correlation with intracellular free magnesium measured by nuclear magnetic resonance spectroscopy (38). It is very possible that an even greater proportion of children may have

intracellular magnesium deficiency than was detected in this study. This could also explain why the associations between dietary intake of magnesium and insulin sensitivity were stronger than those observed with serum magnesium.

The present study provides the first evidence showing that magnesium deficiency is associated with IR in children. The results suggest that serum magnesium deficiency may be related to decreased dietary intake of magnesium in obese children. These data have potential health policy implications, as they indicate that the association between magnesium deficiency and risk for type 2 diabetes begins in childhood. Further evaluation is required to determine whether increasing dietary consumption of foods with high magnesium content will be a useful approach in improving insulin sensitivity and preventing type 2 diabetes in children.

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References

1. Nesmith JD: Type 2 diabetes mellitus in children and adolescents. *Pediatr Rev* 22: 147–152, 2001
2. Paolisso G, Scheen A, D'Onofrio F, Lefebvre P: Magnesium and glucose homeostasis. *Diabetologia* 33:511–514, 1990
3. Nadler JL, Buchanan T, Natarajan R, Antonipillai I, Bergman R, Rude R: Magnesium deficiency produces insulin resistance and increased thromboxane synthesis. *Hypertension* 21:1024–1029, 1993
4. Ma J, Folsom AR, Melnick SL, Eckfeldt JH, Sharrett AR, Nabulsi AA, Hutchinson RG, Metcalf PA: Associations of serum and dietary magnesium with cardiovascular disease, hypertension, diabetes, insulin, and carotid wall thickness: the ARIC study. *J Clin Epidemiol* 48:927–940, 1985
5. Rosolova H, Mayer O Jr, Reaven GM: Insulin-mediated glucose disposal is decreased in normal subjects with relatively low plasma magnesium concentrations. *Metabolism* 49:418–420, 2000
6. Resnick LM, Gupta RK, Gruenspan H, Alderman MH, Laragh JH: Hypertension and peripheral insulin resistance: possible mediating role of intracellular free magnesium. *Am J Hypertens* 3:373–379, 1990
7. Lopez-Ridaura R, Willett WC, Rimm EB, Liu S, Stampfer MJ, Manson JE, Hu FB: Magnesium intake and risk of type 2 diabetes in men and women. *Diabetes Care* 27:134–140, 2004
8. Kao WH, Folsom AR, Nieto FJ, Mo JP, Watson RL, Brancati FL: Serum and dietary magnesium and the risk for type 2 diabetes mellitus: the Atherosclerosis Risk in Communities Study. *Arch Intern Med* 159:2151, 1999
9. American Diabetes Association: Type 2 diabetes in children and adolescents. *Pediatrics* 105:671–680, 2000
10. Goran MI, Gower BA: Longitudinal study on pubertal insulin resistance. *Diabetes* 50:2444–2450, 2001
11. Moran A, Jacobs DR Jr, Steinberger J, Hong C-P, Prineas R, Luepker RV, Sinaiko AR: Insulin resistance during puberty: results from clamp studies in 357 children. *Diabetes* 48:2039–2044, 1999
12. Siri WE: Body composition from fluid spaces and density: analysis of methods: In *Techniques for Measuring Body Composition.* Brozek J, Henschel A, Eds. Washington, D.C., National Academy of Sciences, National Research Council, 1961, p. 223–243
13. Gungor N, Saad R, Janosky J, Arslanian S: Validation of surrogate estimates of insulin sensitivity and insulin secretion in children and adolescents. *J Pediatr* 144: 47–55, 2004
14. Rockett HR, Wolf AM, Colditz GA: Development and reproducibility of a food frequency questionnaire to assess diets of older children and adolescents. *J Am Diet Assoc* 95:336–340, 1995
15. Rockett HR, Breitenbach M, Frazier AL, Witschi J, Wolf AM, Field AE, Colditz GA: Validation of a youth/adolescent food frequency questionnaire. *Prev Med* 26:808–816, 1997
16. Yakinci C, Pac A, Kucukbay FZ, Tayfun M, Gul A: Serum zinc, copper, and magnesium levels in obese children. *Acta Paediatr Japonica* 39:339–341, 1997
17. Takaya J, Higashino H, Kotera F, Kobayashi Y: Intracellular magnesium of platelets in children with diabetes and obesity. *Metabolism* 52:468–471, 2003
18. Guerrero-Romero F, Rodríguez-Morán M: Low serum magnesium levels and metabolic syndrome. *Acta Diabetol* 39:209–213, 2002
19. Kandeel FR, Balon E, Scott S, Nadler JL: Magnesium deficiency and glucose metabolism in rat adipocytes. *Metabolism* 45: 838–843, 1996
20. Draznin B, Sussman KE, Eckel RH, Kao M, Yost T, Sherman NA: Possible role of cytosolic free Ca concentrations in mediating insulin resistance of obesity and hyperinsulinemia. *J Clin Invest* 82:1848–1852, 1988
21. Tongyai S, Rayssiguier Y, Motta C, Gueux E, Maurois P, Heaton FW: Mechanism of increased erythrocyte membrane fluidity during magnesium deficiency in weanling rats. *Am J Physiol* 257:C270–C276, 1989
22. Suarez A, Pulido N, Casla A, Casanova B, Arrieta FJ, Rovira A: Impaired tyrosine-kinase activity of muscle insulin receptors from hypomagnesaemic rats. *Diabetologia* 38:1262–1270, 1995
23. Goran MI: Measurement issues related to studies of childhood obesity: assessment of body composition, body fat distribution, physical activity, and food intake. *Pediatrics* 101:505–518, 1998
24. Livingstone MB, Prentice AM, Coward WA, Strain JJ, Black AE, Davies PS, Stewart CM, McKenna PG, Whitehead RG: Validation of estimates of energy intake by weighed dietary record and diet history in children and adolescents. *Am J Clin Nutr* 56:29–35, 1992
25. Suitor CW, Gleason PM: Using dietary reference intake-based methods to estimate the prevalence of inadequate nutrient intake among school-aged children. *J Am Diet Assoc* 102:530–536, 2002
26. Brink EJ, Beynen AC: Nutrition and magnesium absorption: a review. *Prog Food Nutr Sci* 16:125–162, 1992
27. Coudray C, Demigne C, Rayssiguier Y: Effects of dietary fibers on magnesium absorption in animals and humans. *J Nutr* 133:1–4, 2003
28. Humphries S, Kushner H, Falkner B: Low dietary magnesium is associated with insulin resistance in a sample of young, non-diabetic black Americans. *Am J Hypertens* 12:747–756, 1999
29. Song Y, Manson JE, Buring JE, Liu S: Dietary magnesium intake in relation to plasma insulin levels and risk of type 2 diabetes in women. *Diabetes Care* 27:59–65, 2004
30. Meyer KA, Kushi LH, Jacobs DR Jr, Slavin J, Sellers TA, Folsom AR: Carbohydrates, dietary fiber, and incident type 2 diabetes in older women. *Am J Clin Nutr* 71:921–930, 2000
31. Paolisso G, Sgambato S, Pizza G, Passariello N, Varricchio M, D'Onofrio F: Improved insulin response and action by chronic magnesium administration in aged NIDDM subjects. *Diabetes Care* 12: 265–269, 1989
32. Guerrero-Romero F, Tamez-Perez HE, Gonzalez-Gonzalez G, Salinas-Martinez AM, Montes-Villarreal J, Trevino-Ortiz

JH, Rodriguez-Moran M: Oral magnesium improves insulin sensitivity in non-diabetic subjects with insulin resistance. *Diabetes Metab* 30:253–258, 2004
33. Paolisso G, Passariello N, Pizza G, Marrazzo G, Giunta R, Sgambato S, Varricchio M, D'Onofrio F: Dietary magnesium supplements improve B-cell response to glucose and arginine in elderly non-insulin dependent diabetic subjects. *Acta Endocrinol Copenhagen* 121:16–20, 1989
34. Balon TW, Gu JL, Tokuyama Y, Jasman AP, Nadler JL: Magnesium supplementation reduces development of diabetes in a rat model of spontaneous NIDDM. *Am J Physiol* 269:E745–E752, 1995
35. Ylönen K, Saloranta C, Kronberg-Kippila C, Groop L, Aro A, Virtanen SM, the Botnia Research Group: Associations of dietary fiber with glucose metabolism in nondiabetic relatives of subjects with type 2 diabetes: the Botnia Dietary Study. *Diabetes Care* 26:1979–1985, 2003
36. Lovejoy JC, Champagne CM, Smith SR, de Jonge L, Xie H: Ethnic differences in dietary intakes, physical activity, and energy expenditure in middle-aged, premenopausal women: the Healthy Transitions Study. *Am J Clin Nutr* 74:90–95, 2001
37. Nadler JL, Rude RK: Disorders of magnesium metabolism. *Endocrinol Metab Clin North Am* 24:623–641, 1995
38. Ryzen E, Servis KL, DeRusso P, Kershaw A, Stephen T, Rude K: Determination of intracellular free magnesium by nuclear magnetic resonance in human magnesium deficiency. *J Am Coll Nutr* 8:580–587, 1989