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DIET

ABSTRACT & COMMENTARY

Eat Nuts, Gain Less Weight

By Ellen Feldman, MD

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Dr. Feldman reports no financial relationships relevant to this field of study.

SYNOPSIS: A long-term, large-scale prospective study reveals an association between increased consumption of nuts, decreased weight gain, and decreased risk of obesity.

SOURCE: Liu X, Li Y, Guasch-Ferré M, et al. Changes in nut consumption influence long-term weight change in US men and women. *BMJ Nutr Prev Health* 2019;bmjnph-2019-000034. doi:10.1136/bmjnph-2019-000034. [Epub ahead of print].

Almost 40% of U.S. adults are classified as obese, with a body mass index (BMI) ≥ 30 kg/m^2. Because obesity is directly related to a range of disorders, such as type 2 diabetes mellitus, obesity-related cancers, and cardiovascular disorders, identification of measures to control or prevent obesity is a growing public health priority.[1] Yet, obesity remains a complex condition to tackle. The etiology is multipronged and includes a range of sociologic, genetic, and even psychological factors. Adulthood only seems to complicate matters further: U.S. adults gain an average of one pound yearly.[1,2]

Primary prevention programs addressing obesity and weight gain in adults have focused on activity and dietary changes, including an emphasis on decreasing soda consumption. These interventions may be effective; there has been a slight drop in sugary drink consumption and concurrent measurable increase in nut consumption among the public. Nut consumption has risen from 0.5 servings daily in 1999 to 0.75 servings daily in 2012. However, there are concerns that despite the known health benefits of nuts, their high fat content is a factor in weight gain.[3,4]

In this study, Liu et al carefully investigated the relationship of changes in nut consumption and concurrent weight change by analyzing responses from ongoing, long-term studies involving nutrition every four years over a 20- to 24-year period.

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Summary Points

- This analysis incorporated data from three prospective, longitudinal studies: 27,521 men from the Health Professionals Follow-Up Study; 61,680 women from the Nurses' Health Study; and 55,684 women from the Nurses' Health Study II.
- Weight change, changes in total nut consumption, and consumption of individual types of nuts were among the data collected.
- The association between these two parameters was investigated over consecutive four-year periods for 20-24 years.
- An increase in total nut consumption by 0.5 servings daily was associated with significantly less weight gain ($P < 0.01$) and lower risk of obesity ($P = 0.0036$).

Liu et al used three well-known, longitudinal, prospective studies conducted via responses to self-reported questionnaires. The Health Professionals Follow-Up Study (HPFS) began in 1986 and enrolled more than 50,000 male health professional adults age 40-75 years.[5] The Nurses' Health Study (NHS) began in 1976 with more than 100,000 nurses age 35-55 years, and the Nurses' Health Study II (NHS II) began in 1989 with a similar number, but a younger set of nurses (age 24-44 years).[6] Notably, the participants in all of the studies are primarily Caucasian, well-educated, and involved in healthcare.

These ongoing studies all collect information about nutrition, health habits, and disease via questionnaires mailed biannually, including a food frequency questionnaire (FFQ) every four years. The FFQ contains questions about nut consumption frequency, with a serving defined as 28 g, or 1 oz., of nuts. Although peanuts technically are legumes, they were included as part of overall nut consumption and measured individually as well. Peanut butter also was included, with a serving defined as one tablespoon (15 g).[5,6]

For the purposes of this analysis, Liu et al converted the questionnaire frequency measures to servings/day and looked not only at total nut consumption, but also at consumption of tree nuts (including walnuts, but not peanuts), walnuts, other tree nuts, peanuts, and peanut butter. The researchers then looked at the difference in weight over each four-year interval when the FFQ was administered.

Exclusions for this study included participants who did not complete the FFQ, those who were missing a BMI at baseline, or those who had specific medical diagnoses at baseline, such as cancer or diabetes mellitus. The final numbers of participants eligible for analysis for this study included 27,521 men from the HPFS and 117,364 women from the NHS and NHS II combined.

The multivariable analysis was comprehensive; data were adjusted for factors including age, BMI, physical activity, and relevant health habits, including quality of overall diet and caloric intake.

The results from the HPFS and NHS were analyzed from 1986 until 2010, while the NHS II results included data from 1991 until 2011. During this time span, the average weight gain among participants across all studies was 0.71 pounds yearly. Total nut consumption increased in each of the groups.

Increasing total consumption of nuts by more than 0.5 serving a day, or about 12 almonds daily, was associated with 0.419 pound less weight gain over a four-year period. Table 1 shows more specific data for each type of nut. All values in this category have a $P < 0.01$ (except for changes in peanut consumption in the NHS only).

Table 1 also depicts the risk estimates for both weight gain and becoming obese associated with increasing total and specific nut consumption by more than 0.5 servings daily.

■ COMMENTARY

The authors of this impressive study looking at long-term data regarding nut consumption and weight change showed findings consistent with several other shorter-term studies from the same respondent pools (HPFS, NHS, and NHS II) and from a five-year European study.[7,8] One strength of the Liu et

Table 1. Increased Nut Consumption > 0.5 Servings Daily Over a Four-Year Period

	Average Less Weight Gain per Four-Year Interval	Multivariable Adjusted Relative Risk for Weight Gain > 2 kg Within Four Years (*P* < 0.01)	Multivariable Adjusted Relative Risk for Obesity per Four-Year Interval
All Nuts	-0.419 lb (95% CI, -0.46 to -0.37)	4% (95% CI, 0.95-0.96)	0.97 (95% CI, 0.96-0.99) ***P* = 0.0036**
Walnuts	-0.81 lb (95% CI, -0.99 to -0.66)	10% (95% CI, 0.88-0.92)	0.85 (95% CI, 0.81-0.89) ***P* = 0.0002**
Other Tree Nuts	-0.79 lb (95% CI, -0.88 to -0.68)	7% (95% CI, 0.92-0.94)	0.89 (95% CI, 0.87- 0.91) ***P* < 0.001**
Peanuts	-0.33 lb (95% CI, -0.41 to -0.24)	3% (95% CI, 0.96-0.97)	0.98 (95% CI, 0.96-1.0) *P* is not significant
Peanut Butter	-0.33 lb (95% CI, -0.37 to -0.28)	2% (95% CI, 0.97-0.99)	0.99 (95% CI, 0.97-0.99) *P* is not significant

CI: confidence interval. P values in bold are significant.

al study includes combining the cohorts to look at data from both men and women. The study design, looking at weight changes associated with nut consumption every four years over a 24-year period, allowed time for a dietary change to affect weight and to observe such changes over a significant period of time. The data collected in the questionnaires permit adjustment for many other lifestyle changes and health factors.

Still, this remains an observational study. Causation is not assured and confounding by unknown or unanticipated factors is a real possibility. Additionally, generalization is limited by the homogeneity of the study population.

Another strength of the study is that the specificity of the questionnaires allowed analysis based on nut type. Future studies need to identify and analyze association of weight changes with specific preparation and presentation of nuts (e.g., raw, salted, packaged, incorporated in foods, etc.). The data on peanut and peanut butter consumption suggest that even these calorie-dense food items were not associated with obesity or significant weight gain.

It is important to note that this study did not measure absolute weight loss, as the focus of this work is on measuring changes in weight gain over time. Teasing out more specifics in the trajectory of weight will be a helpful component for future studies.

Liu et al speculated that the connection between nut consumption and lower risk of weight gain may be multifactorial, including the mechanical effort in chewing, high fiber content, and increase in resting energy expenditure due to the high content of unsaturated fatty acids in nuts. Certainly, future investigations will work toward defining a clear etiological pathway.

Future studies also are needed to determine if there is an upper boundary for quantity of nut consumption (i.e., when consumption of nuts is no longer associated with reduced risk of weight gain). Researchers for this study looked at an increase of > 0.5 servings of nuts consumed daily, but did not identify if there is such a point at which increased consumption of nuts becomes associated with weight gain.

For now, we can advise patients that an increase of nut consumption of at least 0.5 serving (0.5 oz.) daily is associated with reduced weight gain over time. In concrete terms, this may translate to one of the following: 12 almonds, nine medium-sized cashews, four brazil nuts, or 17 peanuts.[9] It is reasonable to inform patients that although the jury is still out on specifics, tree nuts appear to have a stronger association with this pattern than peanuts or peanut butter. Incorporating this information into a general visit can serve as a bridge to a more general discussion regarding diet and the essential role of nutrition in health. ■

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ABSTRACT & COMMENTARY

Childhood Gluten Intake and Risk of Celiac Disease

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SYNOPSIS: Data analysis from The Environmental Determinants of Diabetes in the Young (TEDDY) study, to evaluate risk of celiac autoimmunity and celiac disease in children who screened positive for at-risk human leukocyte antigen genotypes, demonstrated increased risk for both outcomes in genetically predisposed children correlating with increasing quantities of daily gluten intake during the first five years of life.

SOURCE: Aronsson CA, Lee H-S, Segerstad EMHA, et al. Association of gluten intake during the first 5 years of life with incidence of celiac disease autoimmunity and celiac disease among children at increased risk. *JAMA* 2019;322:514-523.

Celiac disease is a gastrointestinal autoimmune disease that affects 1% of the world population. Often, it manifests in early childhood. The pathophysiology of celiac disease autoimmunity involves both genetic and environmental factors. Individuals who are positive for certain inherited cell surface human leukocyte antigen (HLA) types (primarily HLA class II genes: DR3 in haplotypic association with DQ2 and DR4 in haplotypic association with DQ8) are at an increased risk of developing immunoglobulin A (IgA) autoantibodies to gliadin and tissue transglutaminase (tTG) upon exposure to dietary gluten, which in turn may attack intestinal and dermal epithelium.[1]

Symptoms associated with celiac disease are characteristic of malabsorption syndrome due to destruction of intestinal villi: diarrhea, bloating, iron-deficiency anemia, weight loss, malnutrition, and failure to thrive in young children. Celiac disease also is associated with a long-term risk of T-cell and non-Hodgkin lymphomas and small intestinal adenocarcinoma. Once celiac disease is diagnosed, current management guidelines include a strictly gluten-free diet, which is helpful for symptom management for many patients. However, when the typical Western diet contains 5 g to 15 g of gluten per day and gluten is present in rye, wheat, and barley flours, this is a difficult recommendation to implement and maintain, especially for children.[2]

Further, can celiac disease risk be mitigated by delaying or limiting gluten exposure in a child's diet? The European Society for Pediatric Gastroenterology recently updated guidelines for infant and childhood feeding practices to reduce the risk of gluten sensitivity.[3] One of the aims of this study was to bring us closer to an understanding of the association between celiac autoimmunity/celiac disease related to the timing of introduction and quantity of gluten intake in genetically at-risk children toward refining dietary recommendations.

Summary Points

- Increased intake of gluten during the first five years of life was associated with significantly increased risk of celiac disease autoimmunity and celiac disease in genetically predisposed children.
- Incidence was most notable between 2 and 3 years of age.
- Risk increased for every 1 g/day incremental increase in gluten intake over an average gluten reference intake determined at 2 years of age.
- Post-hoc analysis of data suggested a cut-off intake of 2 g/day or less at age 2 years to reduce the risk of celiac autoimmunity and celiac disease.

Aronsson et al analyzed data from The Environmental Determinants of Diabetes in the Young (TEDDY) study to identify whether increased gluten intake in the first five years of life was associated with an increased risk of celiac disease or celiac disease autoimmunity in at-risk children. TEDDY is a multinational, prospective cohort study following children from birth to age 15 years at six clinical research centers in Germany, Finland, Sweden,

and the United States. Their primary goal is to identify genetic and environmental risk factors associated with type 1 diabetes, celiac disease, or both. The TEDDY researchers enrolled participants from September 2004 to February 2010 with gluten intake data available in September 2017. Study participants were enrolled before the age of 4 months and consisted of 8,676 (40%) out of 21,589 eligible children who tested positive as neonates for HLA DR and DQ antigens known to be associated with type 1 diabetes and celiac disease.

Prevailing reasons for not enrolling eligible HLA-positive children included parental concerns about the demanding protocol, repeated blood draws, or other family circumstances. Out of the original 8,676 enrollees, 6,605 participants were determined to have adequate screening for tissue transglutaminase antibodies and sufficient dietary records of gluten intake to be included in analysis. Gluten intake was estimated using three-day food records collected by participants' parents at ages 6, 9, and 12 months and biannually at 18, 24, 30, and 36 months thereafter, until age 5 years. During the three-day food intake recordings, parents were encouraged to maintain their child's normal food habits. Dietary intake was analyzed using food composition databases from each country and mean gluten intake in grams/day was calculated from the estimated total intake of gluten-containing flours in foods reported in the three-day food diary. Subsequently, the gluten intake was calculated and categorized as absolute daily intake, residual intake, and gluten intake per 10 kg of body weight at a given age. Residual intake calculations use regression analyses and are commonly applied in epidemiologic nutritional studies to determine nutrient intake — gluten in this instance — adjusted for total energy intake, so that any association with a measured disease outcome can be attributed more robustly to the nutrient alone.

Testing for tTG autoantibodies started at 24 months and continued yearly thereafter. The primary outcome was celiac disease autoimmunity, defined as positive tTG autoantibodies found in two consecutive serum samples. The secondary outcome was celiac disease confirmed by intestinal biopsy or persistently high tTG autoantibody levels > 100 U in an average of two consecutive samples. Joint modeling was used to assess the time-to-event relationship between gluten intake and the primary and secondary outcomes, a widely accepted statistical modeling tool that considers multiple covariates, random effects, and imputations for missing data to improve individual-specific predictions. This longitudinal modeling included adjustments for energy intake (kilocalories/day), HLA genotype, sex, country of residence, and immediate family history of celiac disease.

In addition, two Cox regression analyses, based on observed data only, were performed to assess risk of celiac autoimmunity and celiac disease that included the most recent gluten intake and energy intake prior to the outcome event as time-dependent covariates. One analysis included all children, and the other analysis included children with gluten intake data available within one year prior to the outcome event to control for various lag times between gluten exposure and the event. Risk assessment results were similar for both the joint modeling and Cox regression analyses.

Average gluten intake at age 2 years, when tTG assessment commenced, was considered the reference level for comparisons. Results indicated that the incidence of both outcomes peaked between 2-3 years of age. Daily gluten intake was associated with higher risk of celiac disease autoimmunity and increased for every 1 g/day increase in gluten consumption over the reference level (hazard ratio [HR], 1.30; 95% confidence interval [CI], 1.22-1.38). Findings based on mean absolute daily gluten intake at 3 years of age indicated an absolute risk of 28.1% that rose to 34.2% if gluten intake was 1 g/day higher than the reference amount, an absolute risk difference of 6.1%. Daily gluten intake also was associated with higher risk of celiac disease for every 1 g/day increase in gluten consumption (HR, 1.50; 95% CI, 1.35-1.66). Absolute risk by age 3 years was calculated at 20.7% if the mean absolute daily reference amount of gluten was consumed, and rose to 27.9% if gluten intake was 1 g/day higher than this reference amount, an absolute risk difference of 7.2%. Results for the various daily gluten intake calculation methods (absolute, residual, and intake per 10 kg body weight), including absolute risk differences and 95% confidence intervals, are summarized in Table 1. In a post-hoc analysis, the authors noted a gluten intake cutoff point of 2 g/day in children at 2 years of age, over which a higher risk of celiac disease autoimmunity and celiac disease was statistically apparent.

■ COMMENTARY

This study adds to a body of population data from recent published research concerning early childhood gluten intake for children at risk for celiac disease, focusing on the timing of introduction and quantity.[3,4,5] For children with known at-risk HLA genotypes, 2 g of gluten intake per day appears to be a cut-off point, over which the risk of celiac autoimmunity and celiac disease is increased significantly.

Strengths include the prospective cohort design, a large multinational study population, and dietary monitoring and data recording that accounted for the variations in dietary content and composition characteristics of growing children. The study included a population of children from four different countries, offering a large genetic pool of at-risk children. It also employed a standardized process of accounting for variations in diet and the amount of gluten intake in these culturally diverse

Table 1: Absolute Risk for Developing Celiac Disease Autoimmunity and Celiac Disease in Children With At-Risk HLA Genotypes				
	Absolute Risk for Developing Celiac Disease Autoimmunity by Age 3 Years		Absolute Risk for Developing Celiac Disease by Age 3 Years	
Measurements of Gluten Intake	**If Reference Amount of Gluten Was Consumed, %[a]**	**If Amount of Gluten Consumed Was 1 g/day Higher Than Reference Amount, %**	**If Reference Amount of Gluten Was Consumed, %[a]**	**If Amount of Gluten Consumed Was 1 g/d Higher Than Reference Amount, %**
Absolute intake, g/day	28.1	34.2	20.7	27.9
Residual intake, g/day[b]	18.7	24.6	7.8	10.7
Intake/10 kg of body weight	51.9	70.2	35	55

[a]Assessed in relation to average daily gluten intake at 2 years of age.
[b]Adjusted for age and energy intake using the residual method.
CI: confidence interval

populations. Parents were not aware of their child's antibody status and, thus, parental changes in their children's dietary intake were minimized. The results not only were statistically significant, but also were clinically relevant as well. One gram of gluten, the increment associated with increased risk over the reference intake at age 2 years, is equivalent to about half a slice of white bread.

Nonetheless, the study had some limitations. Although the study design was created to minimize inaccuracies in dietary self-reporting, missing and inaccurate data on daily gluten intake is still possible with a self-report protocol. Despite the fact that this study gathered participants from four different countries, including four different U.S. locations, the study population might not be optimally representative of all at-risk groups. Including infants from other high prevalence countries — such as Ireland, Australia, northern Africa, and northern India — might be valuable, especially given the potential for varying infant feeding practices and exposure to processed cereal grains. Although an association between time and quantity of gluten intake and onset of celiac autoimmunity/disease was noted, other environmental factors may influence risk, including GI infections and rotavirus vaccination status. This is suggested by the finding that a subset of Swedish children appeared more prone to develop celiac disease in this study; although rotavirus vaccine was introduced in Sweden in 2014, it was not included in the Swedish national immunization program until 2019.

How best, then, to use these study results to counsel parents concerning infant and pediatric diet? Although early gluten intake is known to increase celiac autoimmunity/disease risk only in children with at-risk HLA genotypes, neonatal screening for at-risk HLA genotypes is not performed routinely, and physicians likely will not know their pediatric patient's genetic risk status. This study supports some specific recommendations for optimum pediatric gluten intake to be added to the current guidelines,[3] although the authors suggest that a randomized, placebo-controlled trial assessing varying amounts of gluten intake would be needed to confirm their findings and to establish gluten intake guidelines for patient counseling. Physicians can inform parents who express concern about their children's risk of celiac disease that preliminary results from this study indicate gluten intake of 2 g/day or less (the equivalent of one full slice of white bread or one 150 g serving of pasta) seems to be associated with lower risk of developing celiac autoimmunity and celiac disease. This dietary limit can be applied reasonably when a child has one of the at-risk genotypes or has a family history of celiac disease or type 1 diabetes. There may be no increased risk for children with negative family histories and without at-risk HLA genotypes and, therefore, gluten restriction for this group cannot be recommended. In the meantime, we await further studies to support our clinical practices in this domain. ■

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REVIEW

The Health Effects of Magnesium: Part 2

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Dr. Pantuso reports no financial relationships relevant to this field of study.

SYNOPSIS: Prospective outcomes studies are demonstrating that individuals are not meeting their daily magnesium intake needs and this may be contributing to a number of chronic health conditions including diabetes, hypertension, short sleep, and some pain conditions.

Editor's Note: This is the second of two parts exploring the clinical connections of this important mineral. Part 1 (see Integrative Medicine Alert, *October 2019) detailed the physiology of magnesium, the epidemiology of hypomagnesemia, recommended intake levels, food sources, medication interaction, supplementation forms, and testing. In this review, the clinical applications are described, including connections between hypomagnesemia and various disease states, and the possible use of supplemental magnesium in disease treatment.*

— David Kiefer, MD, Editor

Magnesium, a divalent cation, was first reported by Dr. Nehemiah Grew, who identified magnesium sulfate as the major ingredient of Epsom salt.[1,2] Epsom salt was extracted from a well in Epsom, England, and used to treat constipation, muscle strains, and abdominal pain. Magnesium was first isolated by Sir Humphrey Davy in 1808.[1,2] It has been theorized to be involved in the pathogenesis of numerous diseases and is used as a treatment for migraine, cardiovascular disease, and diabetes, among other conditions.[2-4] In this clinical review, we will cover clinical evidence for magnesium in preeclampsia, eclampsia, hypertension, insulin resistance, diabetes, pain, and sleep.

Summary Points

- The effects of chronic decreased magnesium dietary intake in humans is understudied and may be a contributor to chronic diseases.
- The absorption of magnesium in the human body has been found to have a genetic contribution of approximately 30%.
- The role of supplemental magnesium in the diet and its effects on the body are unknown.

PREECLAMPSIA/ECLAMPSIA

Ten percent of pregnant women will have elevated blood measurements at some time before delivery.[5,6] Preeclampsia is defined as the new onset of hypertension with significant end-organ dysfunction with or without proteinuria in pregnancy and is estimated to occur in approximately 5% of pregnancies worldwide.[5,6] Eclampsia is defined as the presence of grand mal seizure in addition to preeclampsia. Pregnant women who have mild to moderate hypertension without proteinuria have similar pregnancy outcomes to women with normal blood pressure.[5,6] However, women with severe hypertension or hypertension proteinuria have worse outcomes than women without hypertension or proteinuria. Although there are some management approaches for preeclampsia, the only cure for the condition is delivery.[5,6]

Major medical organizations worldwide consider magnesium sulfate as the drug of choice to prevent seizures in women with preeclampsia. The exact mechanism of action of magnesium is not well understood in either the development of preeclampsia or the treatment of eclampsia and preeclampsia. It is hypothesized that magnesium increases vasodilation through the relaxation of vascular smooth muscle. One line of inquiry into the pathophysiology of preeclampsia found a significant relationship between serum magnesium levels in the first trimester of pregnancy and the risk of developing preeclampsia.[7] Serum magnesium levels of ≤ 1.97 mg/dL measured in the first trimester had a sensitivity of 77% and specificity of 71.6% for the detection of subsequent preeclampsia.[7] In a Cochrane Review, authors found that magnesium sulfate treatment in women with preeclampsia showed a trend toward lower mortality (relative risk [RR] 0.54; 95% confidence interval [CI], 0.26-1.10).[8] One review showed that magnesium sulfate treatment in preeclamptic women reduced the risk of eclampsia by more than 50% (RR 0.41; 95% CI, 0.29-0.58).[8]

The use of magnesium in eclampsia and pre-eclampsia is a high-acuity situation that should take place in a hospital environment with definitive care and monitoring

available. There are strict protocols for the use of magnesium, administered intravenously, in this situation.[5-8]

HYPERTENSION

The largest contributor to cardiovascular disease worldwide is hypertension.[9] The World Health Organization estimates that 62% of all strokes and 49% of coronary heart disease events are due to hypertension.[9-12] Hypertension is a multifactorial disease with contributors including genetic factors, diet, physical inactivity, toxins, and psychosocial factors.[9-12] Diets that are high in fruits and vegetables and low in sodium (e.g., the Dietary Approaches to Stop Hypertension [DASH] diet) have been found to reduce blood pressure.[11-13] Such dietary approaches also are higher in magnesium, potassium, and calcium because of their emphasis on whole foods and decreased reliance on processed foods.[14] Interestingly, potassium intake has been associated with lower blood pressure by both clinical and epidemiologic evidence.[13,14]

There also may be a connection between magnesium and blood pressure; low serum magnesium has been linked to elevated blood pressure.[15] It is theorized that magnesium induces vasodilation by reducing intracellular calcium levels within vascular smooth muscle cells.[15] High concentrations of extracellular magnesium increase prostacyclin levels and decrease the production of nitric oxide, leading to increased vasodilation.[15] This association has borne out in clinical trials. One meta-analysis that pooled dietary magnesium estimates and hypertension risk from six prospective cohort studies with 180,566 participants (and included 20,119 cases) demonstrated a statistically significant inverse association relationship between dietary magnesium and hypertension risk (RR, 0.92; 95% CI, 0.86-0.98).[16,17] Notably, a 100 mg/day increment in magnesium intake was associated with a 5% reduction in the risk of hypertension (RR, 0.95; 95% CI, 0.90-1.00).[17]

The first report of using supplemental magnesium via intravenous infusion to lower blood pressure was in 1925.[2] A number of studies have demonstrated that oral magnesium intake reduces systolic and diastolic blood pressure; however, overall, the evidence is mixed. A Cochrane systematic review that included 12 randomized controlled trials with 545 participants investigated the effect of oral magnesium. Throughout eight to 26 weeks of blood pressure follow-up, researchers found a small decrease in diastolic blood pressure (DBP; -2.2 mmHg; 95% CI, -3.4 to -0.9), but not in systolic blood pressure (SBP; -1.3 mmHg; 95% CI, -4.0 to 1.5) when participants' average intake of oral magnesium was 413.6 mg per day.[10] Due to the low quality and heterogeneity of the studies, the authors suggest that larger, longer duration studies are required to assess the effects of magnesium supplementation on blood pressure.[10] Another meta-analysis found a dose-dependent effect of magnesium on blood pressure. For each 243.3 mg/day of magnesium, there was a corresponding drop of -4.3 mmHg SBP (95% CI, -6.3 to -2.2) and -2.3 mmHg DBP (95% CI, -4.9 to 0.0).[15] A meta-analysis of a subset of studies including patients being treated for hypertension with drugs found a more significant effect of oral magnesium on SBP (-18.7 mmHg; 95% CI, -14.95 to -22.45) and DBP (-10.9 mmHg; 95% CI -8.73 to -13.1).[15] In addition, Zhang and colleagues conducted a meta-analysis of randomized, double-blind, controlled trials and found that 300 mg of oral magnesium daily for one month may be sufficient to decrease SBP by 2.00 mmHg and DBP by 1.78 mmHg.[17]

DIABETES AND INSULIN RESISTANCE

There is an association between hypomagnesemia and the incidence of both insulin resistance and type 2 diabetes mellitus (T2DM), and with increased rates of diabetic complications and mortality from diabetes.[2,18] The pathophysiological connection may be through insulin receptors, which are a member of the kinase receptor family and require magnesium for signal function.[2] In addition, hypomagnesemia is associated with increased production of cytokines and other effectors, including IL-1, IL-6, IL-8, tumor necrosis factor (TNF) alpha, norepinephrine, epinephrine, and reactive oxygen species that are known to increase insulin resistance.[19] There appears to be a genetic component, because common single nucleotide polymorphisms in the TRPM6 gene responsible for magnesium transport are associated with increased insulin resistance and diabetes.[2]

DIABETES OBSERVATIONAL STUDIES

Serum Magnesium. At this time, a test to measure or to reflect total body magnesium is not available. Serum magnesium is used most frequently to measure magnesium levels, but it is not necessarily a reflection of total body magnesium. Therefore, measuring both dietary intake and serum levels is performed in observational studies.

The Canadian Health Measures Survey Cycle 3 found that people with type 1 or 2 diabetes were more likely to have lower serum magnesium levels.[20] Serum magnesium concentrations also have been found to be negatively associated with diabetes, body mass index, serum glucose and insulin, hemoglobin A1C, and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) values.[21] Data from the National Health and Nutrition Examination Survey (NHANES) 2001-2010, a secondary analysis of 14,338 adults, suggest that those who had sufficient magnesium intake were less likely to have metabolic syndrome. These respondents also were found to have higher high-density lipoprotein levels.[21]

In a recent study conducted in the Netherlands that measured serum magnesium levels in a cohort of patients with T2DM, the authors reported that 9.6% of the 929 patients had hypomagnesemia with a serum

magnesium level < 1.7 mg/dL.[22] Another study with 589 white participants assessed cardiometabolic risk in individuals carrying at least one risk factor (i.e., overweight/obesity, hypertension, dyslipidemia, dysglycemia, and family history for T2DM) and reassessed participants at follow-up, which was 5.6 ± 0.9 years.[23] The authors of this study found a significant negative correlation between magnesium levels, fasting glucose, and two-hour glucose tolerance test results.[23] These authors also found that magnesium levels were negatively correlated with fasting insulin levels and positively correlated with the lipid profile. They found a 20% decreased risk of T2DM for each 1 mg/dL increase of circulating magnesium.[23]

There appears to be a considerable genetic component in serum magnesium levels, with an estimated 30% heritable contribution.[3,24] In a recent study, 15,366 participants of European descent were evaluated for single nucleotide polymorphisms (SNPs) across the genome in association with micronutrients.[25] It was found that six different regions of the genome that contained the variants were involved.[6,25] These SNPs also were found to be associated with clinically defined hypomagnesemia and traits linked to serum magnesium levels, including kidney function, fasting glucose, and bone mineral density (BMD).[6,25]

Dietary Factors. Another meta-analysis of 25 prospective cohort studies with a total of 637,922 participants with 26,828 T2DM incident cases found an 8-13% reduction in the risk of T2DM for every 100 mg/day increment of dietary magnesium.[26]

Another interesting study has arisen from the fact that ketogenic diets sometimes are recommended for people with diabetes or insulin resistance; however, hypomagnesemia may occur from these types of diets.[27] Given the physiological role that magnesium plays in glucose control and insulin effects, there may be some concern about the long-term consequences of ketogenic or high-fat nutritional approaches in this demographic.

CLINICAL TRIALS: SUPPLEMENTAL MAGNESIUM

In a randomized, double-blind, controlled trial published in 2003, 65 participants with T2DM and a serum magnesium level ≤ 1.8 mg/dL were randomized to placebo (n = 31) or a magnesium chloride solution (total of 2.5 g magnesium chloride daily) (n = 32). The participants were given 5 mg of glibenclamide three times daily and were instructed to follow the same diet and exercise instructions for three months prior to the trial of magnesium chloride. The authors reported that the magnesium group had an increase in serum magnesium concentration (15.5%; $P < 0.001$) and reductions in fasting glucose (-37.5%; $P < 0.05$), hemoglobin A1C (-30.4%; $P < 0.05$), and HOMA-IR index (-9.5%; $P < 0.05$) more significant than those in the placebo group.[28]

In a 2017 systematic review investigating the effects of magnesium on insulin resistance in humans, the authors identified 1,720, but only 12 qualified.[29] The duration of the studies was between six and 24 weeks. Forms of supplemental magnesium included elemental magnesium, magnesium oxide, magnesium chloride, magnesium sulfate, magnesium picolinate, and magnesium L-aspartate hydrochloride.[29] All studies evaluated the HOMA-IR and fasting glucose, and five of them rated the oral glucose tolerance test. Eleven of the studies measured fasting glucose, four measured hemoglobin A1C, and only one evaluated the HOMA of B cell function and the quantitative insulin sensitivity check index (QUICKI) or the insulin sensitivity index (ISI) (either the ISI-Gutt or the ISI-Matsuda). The authors found that most of the studies demonstrated an improved fasting glucose and insulin resistance index. Few studies measured the effect of magnesium on fasting insulin or hemoglobin A1C.[29]

The observational evidence for hypomagnesemia being associated with metabolic syndrome, diabetes, and an increasing risk for diabetes complications is concerning. The research data in the form of randomized, controlled clinical trials are underwhelming, and much more work needs to be done. For now, we can advise that patients should be getting the recommended dietary intake of magnesium.

OSTEOPOROSIS

An estimated 50-60% of magnesium is stored in the bone, and serum magnesium levels are related closely to bone metabolism.[2] Magnesium is involved with the creation of new bone and has been shown to increase the solubility of phosphorus and calcium, affecting the crystal size and formation of the new bone.[2] Low levels of magnesium can result in elevated levels of cytokines such as TNF-alpha, interleukins, and substance P, which can lead to bone resorption.[2,19] In addition, low magnesium levels may lead to low levels of parathyroid hormone and vitamin D levels, again relevant to bone health.[2,19] In addition, low serum magnesium levels have been shown to be associated with osteoporosis.[2,30] The majority of the research investigating magnesium and osteoporosis has been performed in postmenopausal women.[3,30] In a 1991 study, researchers investigated the effects of 600 mg/day of magnesium and found an 11% increased BMD after 12 months.[30] However, this study also included a number of other supplemental compounds, including calcium, which prohibits limiting the study findings to just the effects of magnesium. Multiple small studies have shown that supplemental magnesium does increase BMD in limited amounts (1-3%).[2,31,32] Larger, high-quality studies need to be performed to further understand the effects of magnesium on bone, and specifically the role for magnesium supplementation in people with osteopenia and osteoporosis.

PAIN

Muscle Cramps. Muscle contractions are dependent on calcium being released from the sarcoplasmic reticulum and binding to troponin C and myosin, resulting in the conformation changes that result in contraction.[2,34] Magnesium is a calcium antagonist on calcium-permeable channels and binding proteins, which competes for the calcium-binding sites. When muscle cells are at rest, the intracellular concentration of magnesium is 10,000 times that of calcium. When the calcium is released from the sarcoplasmic reticulum, it competes with the magnesium for binding sites to result in a muscle contraction.[2,34] Lower magnesium levels lead to less calcium being required to displace magnesium, which leads to hypercontractility, clinically presenting as muscle cramps and spasms.

The evidence to support the treatment of muscle cramps and spasms with magnesium is mixed. A 2012 Cochrane Review included seven trials, with 406 individuals, 118 of which were involved in crossover studies.[35] The studies had lengths of 14 to 42 days, and the elemental magnesium dose per day ranged from 84 mg to 486 mg.[35] The authors did not show any significant reduction in the number of cramps after magnesium treatment (-3.93%; 95% CI, -21.12 to 13.26).[35]

Headaches and Migraines. The majority of the research investigating the effects of magnesium in the treatment of headache has been done in individuals with migraines. The first reports of using magnesium as a treatment for migraine were in the 1960s and 1970s.[2] Cortical spreading depression (CSD) is one theory for the etiology of migraine headache.[2] CSD is the term used to describe the neuronal membrane depolarization and repolarization phenomenon that occurs in neurons and glial cells. Low levels of magnesium in cerebrospinal fluid (CSF) can activate N-methyl-D-aspartate (NMDA) receptors, which may initiate CSD. Magnesium levels in the serum and CSF of migraine patients have been found to be lower. Lower levels may result in increased neuronal membrane excitability that results in CSD and leads to migraine.

Magnesium has demonstrated anti-inflammatory effects through the inhibition of IL-6 and TNF-alpha. Magnesium also has alpha-adrenergic antagonistic effects and inhibits calcium-mediated neuroendocrine secretion, which may affect nociceptive processing. Intravenous (IV) magnesium has demonstrated mixed results in delivering benefit for acute migraine and cluster headache.[2] The authors of a meta-analysis published in 2016 found that IV magnesium treatment for acute migraines demonstrated significant relief for 15-45 minutes (odds ratio [OR], 0.23), 120 minutes (OR, 0.20), and 24 hours (OR, 0.27).[36] Also, oral magnesium was shown to significantly reduce the frequency (OR, 0.20) and the intensity of attacks (OR, 0.27).[36]

SLEEP

Previous research has indicated an important role of magnesium in the sleep/wake cycle. Animal studies have demonstrated that low magnesium intake affects sleep organization and wakefulness, which was reversed when dietary magnesium was included in the diet. Magnesium fluxes occur daily and are theorized to regulate cellular time keeping. Magnesium also facilitates NMDA receptor function, which is important in sleep regulation. Magnesium also is a cofactor in the synthesis of melatonin. There is some clinical evidence supporting a connection between magnesium and sleep. The 2007-2008 NHANES analysis demonstrated lower magnesium intake was associated with very short (less than five hours) sleep.[37] The Jiangsu Nutrition Study conducted from 2002 to 2007 found that dietary magnesium consumption was inversely associated with falling asleep during the day in women, but not in men.[38] In addition, one placebo-controlled study conducted in the elderly demonstrated improvement in various sleep parameters, including sleep onset latency, sleep efficiency, and sleep time, with magnesium supplementation.[39]

OVERALL: MAGNESIUM AND INFLAMMATION

Magnesium's efficacy in improving clinical conditions may be restricted to magnesium-depleted individuals.[18,19] Individuals with low magnesium intake that may not be detectable with a serum magnesium level may have increased C-reactive protein (CRP) levels.[18,19] CRP is an acute phase protein that is produced in response to inflammation and is associated with an increased risk of chronic disease, including cardiovascular disease.[18,19] A number of studies have found that dietary magnesium intake is inversely associated with serum or plasma CRP levels.[18-19] Magnesium supplementation lowered elevated CRP levels in 17 patients with heart failure and in 62 men and nonpregnant women with prediabetes and hypomagnesemia.[16-19] The doses of magnesium used in these trials ranged from 300 mg to 382 mg/day.[16-19] Another study of 300 patients older than 25 years of age who had coronary heart disease found that elevated CRP was decreased in participants with a dietary magnesium intake of > 350 mg/day, measured by two-day dietary recall.[16-19]

Unfortunately, serum magnesium tests may not accurately measure total body magnesium. If patients have low serum magnesium and are asymptomatic with elevated CRP, repleting with oral supplementation is warranted while evaluating the elevated CRP (i.e., ruling out infection or other causes of inflammation). For patients who have hypertension, a trial of oral supplementation with magnesium also is warranted. However, choosing a high-quality magnesium supplement that has been tested by a third party is required to evaluate the amount contained within the supplement, as well as any heavy metals it may contain.

CLINICAL CONCLUSIONS: DOSING

Research on the use of supplemental magnesium in human studies is lacking, which makes it difficult to recommend supplemental magnesium use to patients across the board. Prospective outcomes studies demonstrate that a lack of dietary magnesium intake has numerous effects on the body, which is not surprising because magnesium is involved with more than 600 enzymatic reactions. Based on the existing evidence, counseling patients about the importance of a whole foods diet and foods rich in magnesium is fundamental. If patients have low serum magnesium without symptoms of hypomagnesemia, recommending a magnesium supplement is warranted. Also, clinicians should recommend supplemental magnesium to patients with insulin resistance, diabetes, or hypertension who have elevated CRP. There are a number of different forms of magnesium on the market, but research is lacking on whether one form is better than another. Another difficulty with recommending magnesium supplementation is that the body increases absorption of magnesium when it is depleted, so increased oral dosing may not be effective. Product quality should not be assumed, and recommending a product that has been third-party tested is ideal. Advising patients to get 350 mg/day of combined dietary and supplemental magnesium is good clinical practice at this time.

ADVERSE EFFECTS

Because there is a lack of research on the clinical use of magnesium and it is involved in a diverse profile of enzymatic reactions, one should exercise caution. Clinically, the most common adverse effect of the use of magnesium is its laxative effect, which usually is dose dependent. The magnesium oxide supplemental form has the more pronounced laxative effect. Magnesium should be used with caution in patients with renal disease. There also are specific medical conditions for which magnesium may be problematic. For example, magnesium sulfate, especially in the intravenous form used in preeclampsia and eclampsia, is contraindicated in people with myasthenia gravis since it can precipitate a severe myasthenic crisis.[5-8]

SUMMARY

There is evidence to support the use of supplemental magnesium for several clinical conditions, including eclampsia/preeclampsia, migraine and other headaches, diabetes, bone health, hypertension, and insomnia. Given the widespread suboptimal intake of magnesium in the United States, clinicians should be aware of clinical correlates of hypomagnesemia and situations when magnesium can be used therapeutically. Furthermore, a discussion of food sources of magnesium, supplemental forms, and adverse effects should be a part of any clinical encounter, but especially in those involving disease processes as reviewed in this magnesium overview. ■

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CME QUESTIONS

1. **Based upon a post-hoc analysis of pediatric gluten intake in at-risk children by Aronsson et al, which of the following represents a cutoff value for absolute gluten intake at age 2 years, over which higher intake is associated with increased celiac autoimmunity/disease?**
   a. 1 g/day
   b. 2 g/day
   c. 3 g/day
   d. 4 g/day

2. **Patients with diabetes and low serum magnesium often have:**
   a. a decreased risk of complications.
   b. the same risk of complications.
   c. an increased risk of complications.
   d. an unknown risk of complications.

3. **According to Liu et al, eating nuts:**
   a. of any type (including peanuts and peanut butter) is associated with less weight gain over time; this relationship becomes significant when portion sizes are increased by 14 g daily.
   b. is helpful for a variety of health conditions, including less weight gain over a period of four to five years, with the exception of peanuts and peanut butter, both of which are associated with weight gain if consumed more than twice weekly.
   c. is associated with less weight gain over time when serving sizes are controlled and under 24 g daily, with the exception of peanuts and peanut butter, both of which are associated with weight gain when consumed in this quantity.
   d. is associated with weight gain over time when portion sizes are greater than 24 g to 30 g daily, but there is an association with less weight gain over time when portion sizes remain under this level.

[IN FUTURE ISSUES]

Physical Activity Offsets Genetic Risk for Depression

Mindfulness and Attention-Deficit/Hyperactivity Disorder

Nutrition in Medical Education