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DIETARY AND SUPPLEMENTAL MAGNESIUM INTAKE DURING PREGNANCY AND ITS ASSOCIATION WITH GESTATIONAL DIABETES

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DIETARY AND SUPPLEMENTAL MAGNESIUM INTAKE DURING PREGNANCY AND ITS ASSOCIATION WITH GESTATIONAL DIABETES

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ABSTRACT

Background: Gestational diabetes mellitus (GDM) is a prevalent and growing epidemic that affected 8.2% of births in 2016 in the United States. Previous studies have shown that low magnesium (Mg) is associated with type II diabetes (T2DM), and the pathophysiology of GDM and T2DM is similar.

Objective: To determine if low total Mg intake is associated with the risk of having GDM.

Design: We did a cross-sectional secondary data analysis using data from the 2005-2007 Infant Feeding Practices Study II which used a validated diet history questionnaire to collect dietary data. We analyzed total Mg intake from 1217 pregnant women in their third trimester and ran unadjusted and adjusted logistic regression models. Adjusted models included age, pre-pregnancy BMI, family history of T2DM, energy intake from food, and smoking as covariates.

Results: Mean total Mg intake was 332±138mg/day and 8.8% of women consumed a dietary supplement containing Mg. In the unadjusted model, risk of GDM was not higher with low total Mg intake (OR [95% CI]: 0.96 [0.61, 1.51]). Adjusting for all covariates did not change the association (1.06 [0.64, 1.76]).

Conclusions: Total Mg intake was not significantly associated with a higher risk of developing GDM. While this study found no association, a study with a larger sample size and adequate power, using dietary intake to measure total Mg status may indicate more significant findings.

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PREFACE

This thesis was written to comply with the University of Rhode Island graduate school Manuscript Thesis Format. This manuscript has been written for publication to the *Maternal and Child Nutrition*.

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MANUSCRIPT

"Dietary and Supplemental Magnesium Intake During Pregnancy and its Association with Gestational Diabetes"

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Introduction

The prevalence of gestational diabetes mellitus (GDM) in the United States (US) reached 8.2% in 2016 (1) and globally impacts about 14% (18 million) of births each year (2–5). In the US in 2007, GDM-related health concerns cost an additional $3,305 per pregnancy, totaling $636 million in increased healthcare dollars (6). Gestational diabetes is traditionally identified between 24-28 weeks of gestation and is defined as a fasting blood glucose of ≥126 mg/dL or a 2 hour post prandial 75g oral glucose tolerance test (OGTT) value of over 200 mg/dL (2,7). Gestational diabetes can lead to adverse maternal and child health outcomes including increased risks at birth (e.g. high infant birthweight, macrosomia [a newborn with a birthweight ≥4000g larger than average], shoulder dystocia [when the neonate's shoulders are stuck in the mother's pelvis], cesarean section [c-section], and stillbirth) and increased risk for the child and mother to develop chronic diseases later in life (e.g. type II diabetes mellitus [T2DM], cardiovascular disease, and obesity) (3,4).

Gestational diabetes and T2DM are diagnosed via the same tests and criteria, as the pathophysiology of the two are similar (8–10). Gestational diabetes and T2DM occur when the pancreas still synthesizes insulin but the insulin is not effective, which is known as insulin resistance (8,9). Research shows low Mg intake is related to the prevalence of T2DM due to its role in the secretion of insulin and activation of the insulin receptor, which initiates a cascade for glucose uptake by cells (11–14). A randomized control trial by Asemi et al. (15) supplemented Mg for women with GDM which led to improved metabolic outcomes including decreased insulin and fasted plasma glucose (15). Like many other studies (14,16–19), Asemi et al. (15) used serum Mg to identify blood Mg

concentrations and assess Mg status. However, using serum Mg as a biomarker is a poor indicator for Mg total body status and dietary intake, as overall body Mg can be low without it being reflected in the serum (20). Therefore, it is important to target total Mg intake, as no current research to our knowledge uses low total Mg intake (which includes dietary Mg intake and Mg intake from dietary supplements) as their indicator for Mg status while assessing the risk of having GDM (2,10,17,18). While there is sufficient evidence to support the relationship between low Mg and T2DM, more research needs to be done to explore the effects of low total Mg intake and GDM.

This retrospective, cross-sectional, secondary data analysis uses the Infant Feeding Practices Study II (IFPS II) from 2005-2007 to identify whether a relationship between Mg intake and GDM exists. This research uses results from a dietary history questionnaire (DHQ) used in IFPS II study taken during the mothers' third trimester.

Methods

Study Design

We conducted a cross-sectional, secondary-data analysis using 2005-2007 IFPS II data collected by the Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC) which was Institutional Review Board approved by the FDA's Research Involving Human Subjects Committee and the US Office of Management and Budget (21,22). This study analyzed whether total Mg intake was significantly associated with self-reported GDM. We hypothesized low total Mg intake (< the recommended dietary allowance (RDA) during pregnancy, which is a 400mg/day for women 18 years old, 350mg/day for women 19-30 years old, and 360mg/day for women

over 30 years old (23)) would be significantly associated with a higher risk of self-reported GDM (11).

Study Population

The IFPS II was a longitudinal study for which pregnant women were recruited and postnatal follow-up on the mother and child continued until the child was 6 years old (22). Participants were recruited from a nationally distributed consumer opinion panel of 500,000 US households (22). In a survey that is annually collected from this consumer opinion panel, women who were pregnant with a singleton between the ages of 18-40 years old were identified and sent prenatal questionnaires, of which 4902 responded (must reside in zip codes unaffected by the Gulf Coast hurricanes of 2005) (22). From this cohort, 1749 were 28-32 weeks gestation and were sent a modified Dietary History Questionnaire (DHQ) during May-August 2005, of which 1444 women completed and returned before their infants were born (Figure 1) (22). The DHQ was modified from a validated quantitative food frequency questionnaire developed by the National Cancer Institute to better suit a pregnant population (modifications include recall period as 1 month instead of 1 year and questions were added about fish intake and dietary supplements) and included 149 questions (21,22). A more detailed explanation of the data collection methods can be found in a descriptive study by Fein et al. 2008 (22).

Statistical Analysis

Daily dietary Mg intake was calculated from the DHQ using Diet*Calc software, which estimates nutrient intake from the DHQ (24). Gestational diabetes was established in the prenatal survey in which participants answered “yes”, “no”, or “don’t know/not sure” to the question, “Have you had gestational diabetes with this pregnancy?” Those

who replied “don’t know/not sure” (n=141) to the question were excluded for analysis (Figure 1).

Statistical Analysis System (SAS) 9.4 software (SAS 9.4, Cary, NC) was used for all statistical analyses.

Logistic regression analysis was used to determine whether the risk of GDM prevalence differed between high (≥ RDA per age group) and low (< RDA per age group) total Mg intake. The statistically significant level was set at $p \leq 0.05$.

Potential confounding variables were identified in the literature, and included age, education, pre-pregnancy body mass index (BMI), and family history of diabetes (25–31). Age was included as older women are at a higher risk of developing GDM and decreased Mg intake (25,26). Education was considered as a confounding variable as less education is a risk factor for GDM and tend to have lower Mg intake (26,27). High pre-pregnancy BMI and family history of diabetes are risk factors for GDM (4,28). Additionally, a high pre-pregnancy BMI and low Mg intake are inversely associated with overweight and obese pre-pregnancy (28,31,32). If potential confounding variables were significantly associated with risk of having GDM ($p<0.05$), then they were included in the adjusted model. Of these potential confounding variables, age, pre-pregnancy BMI (4 categories), and family history of T2DM were included as covariates for adjusted model 1. Adjusted model 2 also controlled for age and family history of T2DM, but here we dichotomized pre-pregnancy BMI (underweight/normal BMI <25 kg/m2 and overweight/obese BMI ≥25 kg/m2), and included energy intake from food (residuals), and smoking.

Continuous variables (age and BMI) were examined for normality using a Kruskal Wallis test ($p<0.05$). Data distributions were examined for outliers outside of +/- 3 standard deviations from the mean (n=18) (Figure 1).

Effect size for high and low total Mg intake was calculated using this equation below (33).

$$\omega = \sqrt{\sum_{k=1}^{K} \frac{(P_{1k} - P_{0k})^2}{P_{0k}}}$$

With our sample of n=1217, we determined power at 0.107 and an effect size of 0.02 using G*power 3.0 and the results from this equation (34).

Results

Of the 1749 women who were in their third trimester, 305 women were removed if they had a previous diagnosis of diabetes resulting in 1376 participants. Women who responded "don't know/not sure" to the question "have you been diagnosed with GDM during this pregnancy?" (n=141), and if their total Mg intake was +/- 3 standard deviations from the media (n=18) were also excluded from this analysis, resulting in a total of 1217 women for this study (Figure 1). The average age of the women in this study cohort was 29.5±5.5 years old with the majority having some college education (36.9% some college, 37.2% college graduate). Of respondents, about 34.3% had a family history of T2DM and 45.2% reported normal pre-pregnancy BMI between 18.5-24.9kg/m^2, and 47.7% had a BMI over 25.0kg/m^2 (23.3% overweight, 24.1% obese). The mean total Mg intake was 332±138mg/day. There was no statistical significance for the risk of developing GDM between the 25th percentile of total Mg intake at 230mg/day, and

the 75th percentile at 406mg/day (p=0.18). Dietary supplements were used by 8.8% of participants and the mean total Mg intake for participants who reported dietary supplement intake was 344±143mg/day, while those who did not consume a dietary supplement had a mean Mg intake of 331±137mg/day. In total, 7.2% of participants responded "yes" when asked if they have been diagnosed with GDM during this pregnancy.

For the logistic regression, we identified total Mg intake as high (≥ RDA per age group) or low (< RDA per age group). Risk of having GDM was not significantly associated with low Mg intake in the unadjusted and adjusted models. In the unadjusted model, risk of having GDM was not higher with low total Mg intake (OR [95% CI]: 0.96 [0.61, 1.51]), dietary intake (1.00 [0.62, 1.62]), or for those who did use dietary supplements (0.75 [0.21, 2.64]). Adjusted model 1 for covariates did not change the association for total Mg intake (0.97 [0.59,1.58]), dietary Mg intake (0.95 [0.56, 1.59]), or use of dietary supplements (1.22 [0.27, 5.41]) and risk of having GDM (Table 2). Adjusted model 2 also had minimal effect for total Mg intake (1.06 [0.64, 1.76]), dietary Mg intake (1.03 [0.60, 1.75]), or use of dietary supplements (1.13 [0.23, 5.25]) and risk of having GDM (Table 2). Adjusted model 1 controlled for the covariates age, family history of T2DM, and pre-pregnancy BMI (4 categories), all of which were still significantly associated with risk of having GDM. Adjusted model 2 also controlled for age and family history of T2DM, but here we dichotomized pre-pregnancy BMI and included energy intake from food (residuals), and smoking. Energy intake from food was significantly associated with Mg intake (r^2=0.85), and smoking (0.45 [0.23, 0.84]) and

dichotomized BMI (0.40 [0.24, 0.67]) were significantly associated with risk of having GDM.

Discussion

In this secondary analysis of IFPS II study, total Mg intake was not significantly associated with the risk of having self-reported GDM for the adjusted and unadjusted models. The average total Mg intake was slightly below the recommended daily allowance (23) with a small percentage who consumed a dietary supplement. Differences in age, family history of T2DM, and pre-pregnancy BMI were considered significant, and used as covariates in the adjusted model.

Several studies have analyzed whether there is a relationship between Mg and GDM prevalence. When comparing other studies to our research sample characteristics were similar, however, these studies used different methods for diagnosing high and low Mg and GDM. One study by Tasdemir et al. (35) looked at ionized and total body Mg with a smaller dataset (n=85) in non-GDM compared to GDM participants. They found low ionized Mg in patients with GDM, which helped lead us to our hypothesis that low Mg intake would be associated with GDM. However, our results did not show a significant association like Tasdemir et al. (35) which could be because ionized levels of Mg may not directly reflect Mg intake, whereas measuring dietary Mg does. The mean age between non GDM (26.8±6.6) and GDM groups (30.8±6) were similar to ours (28.9±5.5 and 31±5.4, respectively) and like our sample, age was statistically significant for reported GDM (35). Those in the GDM group also had a similar percentage for family history of T2DM (47.5%) as our study (52.9%) and were significantly associated with GDM (35).

Another group of researchers (15) investigated Mg supplementation on metabolic status and its effect on pregnancy outcomes. This study also used a smaller sample size (n=70) compared to ours (n=1217) with a similar mean age of 29.3±3.9 (15). The results showed Mg supplementation was associated with decreased serum insulin and fasting plasma glucose, but like our results, did not find any direct association with GDM (15).

A randomized control trial conducted by Zarean and Tarjan 2017 (36) used a sample of 180 pregnant women and compared 3 groups of 60 participants with Mg supplementation (group 1: control group with serum Mg >1.9 mg/dL; group 2: serum Mg levels <1.9 mg/dL and given a multimineral tablet; group 3: serum Mg levels <1.9 mg/dL given a Mg supplement). This study also used serum Mg as its Mg status marker. The results showed those who received a Mg supplement were less likely to develop GDM, which is inconsistent with our results. These results could be different from ours as serum Mg is not a valid marker of total Mg intake (20).

The physiological mechanism of insulin resistance between T2DM and GDM is similar, and low Mg intake has shown to impact development of T2DM (4). The studies that investigated low serum Mg and GDM prevalence showed an inverse relationship between the two variables, while supplementing with Mg decreased GDM prevalence (15,35,36). However, our results did not show a significant association between low total Mg intake and risk of having GDM.

Our findings may have differed from previous research for a number of reasons. First being the risk of having GDM in the IFPS II dataset was self-reported, and therefore likely under-reported. A study done in New Zealand by Lawrence et al.(37) found one third of medically diagnosed GDM went unreported in a questionnaire. Additionally, our

study used Mg intake from a DHQ, while these studies used serum Mg or experimented with the effect of Mg supplements on GDM outcomes. Though there were other studies that also did not have significant findings (30,38), there were none that specifically analyzed total Mg intake compared to risk of having GDM in the US.

Our study has strengths and limitations that are worth reporting. The sample size is considered large (n=1217) when compared to other studies (15,35,36). However, we were unable to determine significant association between total Mg intake and risk of having GDM, which could be due to having low power. Our power was likely low because of the low amount of GDM diagnoses in this cohort (n=87, 7.2%). In order to increase power to 80%, we would need a sample size n=19,623 for an effect size of 0.08 which would allow for a larger cohort with reported GDM. The DHQ used by IFPS II was derived from the NCI by the FDA and CDC and was previously validated (22). A limitation of this study is the cross-sectional design, as it does not allow for the determination of a temporal relationship or causality between Mg intake and GDM onset. Additionally, the DHQ did not differentiate whether the multivitamins or prenatal vitamins the participants may be taking contained Mg, which could have affected total and dietary supplemental intake. However, prenatal vitamins typically do not contain Mg or if they do, they only contain about 150mg on average (about 40% of RDA during pregnancy) (39,40). There is also a possibility that participants had undiagnosed pre-existing type 1 or T2DM before this pregnancy, which could have interfered with the validity of GDM diagnosis. Additionally, in the past there was not a standardized diagnosis of GDM which could have an effect on true GDM diagnoses (4). It is also possible there were some confounding variables that we did not recognize and are not

adjusting for or were not included in the data. Though the study cohort collected in the IFPS II dataset was nationally distributed, it may not represent the whole US population (22). This is because the IFPS II data collection method used a self-selected consumer panel and not a random sample due to the cost of recruiting women in their third trimester, which may contribute to volunteer bias (22). Another limiting factor of this study is the use self-reported data from the prenatal questionnaire and DHQ, which may lead to response bias (22). However, DHQs are commonly used to asses total intake as they are easy to administer, noninvasive, inexpensive and currently the best method to measure Mg intake (41).

In conclusion, this secondary-data analysis revealed no significant association between total Mg intake and GDM. Contrary to other markers of Mg status or studies using interventions with Mg supplements, this research used dietary and dietary supplement intake to determine if there was an association which is currently the most accurate measure of Mg intake. Though it could not be proved with this study, it is still possible there is an association between low Mg intake and risk of having GDM. The low power for this sample may have contributed to the insignificant results, as only a small fraction of women reported having GDM. With a larger sample size, 80% power could be reached with an effect size of 0.08 so that significant differences could be detected if present. This research was an important foundational step to further this investigation of the relationship of total Mg intake and GDM, as it uses dietary intake to measure micronutrient status in relation to incidence of disease which may give reason for further exploration.

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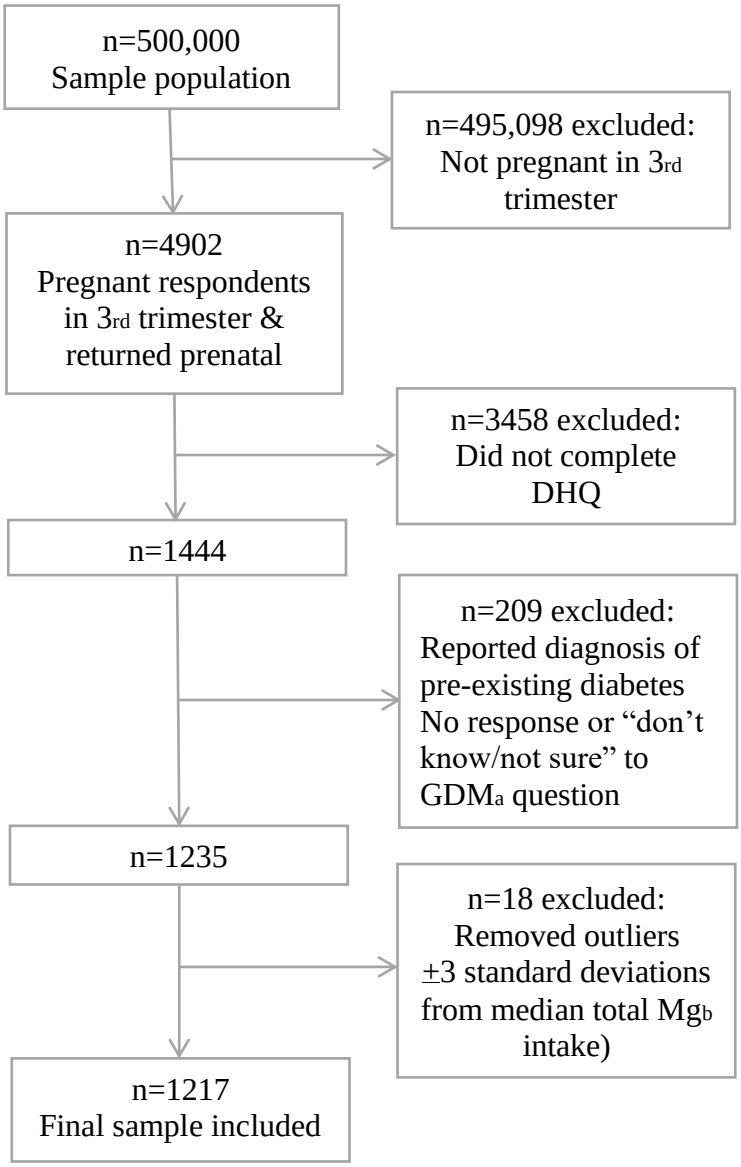
Figures and Tables

Figure 1: Flow chart of inclusion criteria for women in the Infant Feeding Practices Study II who provided diet history and GDM status used in this study.



aGestational diabetes mellitus
bMagnesium

Table 1: Maternal descriptive characteristics of the subsample population of 1217 women in the Infant Feeding Practices Study II who provided diet history and GDM status.

Maternal Characteristic	Total n=1217 (%)	Yes GDM[a] n=87 (7.1%)	No GDM n=1130 (92.9%)	P-value
Education*				
High school or less	229 (18.8%)	16 (18.4%)	213 (18.8%)	
Some college	449 (36.9%)	28 (32.2%)	421 (37.3%)	0.53
College graduate	453 (37.2%)	37 (42.5%)	416 (36.8%)	
No response	86 (7.1%)	6 (6.9%)	80 (7.1%)	
Age, years	28.9 ± 5.5	31 ± 5.4	28.8 ± 5.4	0.0003
Family history of diabetes[b]				
Type I*	55 (4.5%)	4 (4.6%)	51 (4.5%)	
Yes	992 (81.5%)	68 (78.2%)	924 (81.8%)	0.91
No	170 (14.0%)	15 (17.2%)	155 (13.7%)	
No response				
Type 2*	418 (34.3%)	46 (52.9%)	372 (32.9%)	0.0001
Yes	678 (55.7%)	33 (37.9%)	645 (57.1%)	
No	121 (10.0%)	8 (9.2%)	113 (10.0%)	
No response				
Pre-pregnancy BMI[c]*				
Underweight[d]	67 (5.6%)	1 (1.2%)	66 (5.8%)	
Normal weight	550 (45.2%)	25 (28.7%)	525 (46.5%)	0.0001
Overweight	288 (23.6%)	23 (26.4%)	265 (23.5%)	
Obese	294 (24.1%)	36 (41.4%)	258 (22.8%)	
No response	18 (1.5%)	2 (2.3%)	16 (1.4%)	
Mean total Mg[e] **intake** (mg/d)	332 ± 138	345 ± 134	331 ± 138	0.56
Mean dietary Mg intake (mg/d)	331 ± 137	335 ± 130	330 ± 138	0.58
Mean Mg intake with Mg supplement use (mg/d)	344 ± 143	346 ± 168	344 ± 141	0.45
Mg supplement				
Yes	107 (8.8%)	11 (12.6%)	96 (8.5%)	0.19
No	1170 (96.1%)	76 (87.4%)	1034 (91.5%)	

[a]Gestational diabetes mellitus

[b]Maternal siblings, aunts/uncles, or parents

[c]Body Mass Index

[d]Underweight <18.5 kg/m2, Normal weight = BMI 18.5-24.9 kg/m2, Overweight = BMI 25-29.9 kg/m2, Obese = BMI >30 kg/m2

[e]Total maternal magnesium intake calculated from DHQ responses using Diet*Calc software

*Missing data: education (n=131); type 1 diabetes (n=215); type 2 diabetes (n=166); BMI (n=63)

Table 2: Unadjusted and adjusted odds ratios (95% CI) from models examining Mg[a] intake status by GDM[b] prevalence from participants in the Infant Feeding Practices Study II who completed the prenatal diet history questionnaire.

Mg intake	Yes GDM n=87 (7.2%)	Unadjusted n=1217	Adjusted (1)[c] n=1172	Adjusted (2)[d] n=1072
Total Mg intake (n=1217)				
< RDA[e] (n=766)	54 (7.1%)	0.96 (0.61, 1.51)	0.97 (0.59, 1.58)	1.06 (0.64, 1.76)
≥ RDA (n=451)	33 (7.3%)	-	-	-
Dietary Mg intake[h] (n=1110)				
< RDA (n=701)	48 (6.9%)	1.00 (0.62, 1.62)	0.95 (0.56, 1.59)	1.03 (0.60, 1.75)
≥ RDA (n=409)	28 (6.9%)	-	-	-
Dietary supplement (n=107)				
< RDA (n=65)	6 (9.2%)	0.75 (0.21, 2.64)	1.22 (0.27, 5.41)	1.13 (0.23, 5.25)
≥ RDA (n=42)	5 (11.9%)	-	-	-

[a]Magnesium

[b]Gestational diabetes mellitus

[c]Adjusted for age, family history of type II diabetes, and pre-pregnancy BMI (<18.5 kg/m^2, normal weight = BMI 18.5-24.9 kg/m^2, overweight = BMI 25-29.9 kg/m^2, obese = BMI >30 kg/m^2)

[e]Total maternal magnesium intake calculated); missing n=138 due to no response from covariates

[d]Adjusted for age, family history of type II diabetes, pre-pregnancy BMI (2 categories: underweight/normal BMI <25 kg/m^2 and overweight/obese BMI ≥25 kg/m^2), energy intake from food (residuals), and smoking; missing n=145 due to no response from covariates

[e]Recommended daily allowance for Mg during pregnancy; 18 years old = 400 mg/day, 19-30 years old = 350 mg/day, and over 30 years old = 360 mg/day

[h]Missing data from those who consumed dietary supplement (n=107)

[i]Missing data from those who did not consume dietary supplement (n=1110)

APPENDIX A: EXTENDED LITERATURE REVIEW

Chapter 1: Magnesium

Background, Functions, and Distribution

Magnesium is the fourth most abundant cation in our body, and an essential mineral that has many physiological functions (18,42). It is a cofactor for over 600 enzymatic reactions, it activates over 200 enzymes, and is involved in processes like protein synthesis, energy production, muscle function, blood glucose regulation, nerve function, blood pressure, oxidative phosphorylation, and glycolysis (12,43). It was first identified as an essential mineral in 1926 by J. Leroy, and in the 1950s clinical effects from Mg deficiency were recognized, giving rise to the many roles requiring Mg (42). As an essential mineral is defined as a mineral or nutrient that is necessary for our bodies but cannot synthesize (44). When Mg is deficient, there can be detrimental effects including muscular and neurological symptoms (including tetany, spasms, and tremoring), poor appetite, nausea, and vomiting, so it is important we meet our required needs (11,45). Serum Mg deficiency, or hypomagnesemia, is typically defined as serum Mg levels less than 0.7-0.75 mmol/L, 1.4mEq/L, or 1.7 mg/dl and is prevalent among both developed and developing countries (12,43,46). It is associated with hypocalcemia as well, and side effects include weakness, fatigue, muscle cramping, tetany, feeling numb, and seizures (46).

Physiology

Our bodies cannot physically store Mg, therefore we retain Mg to maintain homeostasis based on physiological needs (47). Healthy adults typically have about 24g of Mg in their body, which amounts to about 0.4g/kg, where about 60-65% resides in our

bones, 27% in our muscles, 6-7% in other cells, and less than 1% extracellularly in the serum (39,42,46,48,49). Serum Mg is found either bound to a protein (25% albumin, 8% globulins), in a chelated fraction (meaning bound to a molecule, 12%), or in an ionized state where it is metabolically available for physiological functions (55%) (12,46).

Magnesium is an important cofactor for more than 600 enzymes, meaning Mg is required to be present and bound to the enzyme to catalyze the reaction (50,51). Additionally, Mg is an activator for over 200 enzymatic reactions which is a type of cofactor that enhances enzymatic activity (50,51). Without Mg, all of these enzymatic reactions like energy production, protein synthesis, and insulin activation would not be fulfilled (50).

The balance of Mg distribution and metabolism can be impacted by a variety of hormones including the parathyroid hormone (PTH), antidiuretic hormone (ADH), calcitonin, catecholamines, and insulin (12,20). Many impact Mg balance by controlling level of Mg resorption in different parts of the kidneys (20,52–54). Parathyroid hormone and Mg have a multifaceted relationship, as PTH will increase Mg resorption in the distal convoluted tubule of the kidneys, while Mg may reduce secretion of parathyroid hormone when calcium levels are low (20,52). When Mg levels are low, PTH will also stimulate release of Mg from the bones and increase absorption in the small intestine (53). Impaired PTH secretion and/or function can lead to hypomagnesemia which may induce hypocalcemia, while elevated calcium levels can lead to decreased Mg resorption (52,54). Antidiuretic hormone (or vasopressin) also has an effect on homeostasis of Mg (20). Similarly to PTH, ADH will stimulate Mg resorption in the distal convoluted tubule (53). Calcitonin regulates calcium in addition to Mg, by stimulating resorption in the thick

ascending limb of the nephron loop (loop of Henle) of the kidney (53). Catecholamines (like epinephrine, norepinephrine, and dopamine) can impact the intracellular balance of ions, including Mg distribution (55). As catecholamines are released, extracellular fluid increases resulting in a lower serum Mg (56). Insulin and Mg have a complex relationship as they both impact each other. Insulin contributes to maintaining total body Mg status, while Mg levels impact insulin activation and release from the beta cells of the pancreas (12,14). Insulin can regulate Mg uptake, as it can reduce serum Mg causing cytosolic levels of Mg to increase (57).

Dietary Sources, Requirements, and Intake

Magnesium is found in a variety of foods including green leafy vegetables, legumes, nuts and seeds, whole grains, water (variable) and typically most high fiber and high phytate foods (23,43,49). Even though Mg is present in a variety of foods available in a Western diet, most adult Americans do not meet their daily requirements (49). Since the early 1900s, Americans are now consuming half of the Mg of what they used to, dropping from about 500mg/day to 250mg/day (49). This may be due in part to the typical, overly processed American western diet which has decreased Mg content of food by about 85% (49,58). Americans have increased processed food consumption, which can therefore affect American's dietary Mg intake (49).

For women of reproductive ages specifically, the recommended dietary allowance (RDA) are 400mg/day, 350mg/day, and 360mg/day for ages 14-18, 18-30, and 31-50 years old, respectively (23). Magnesium needs increase during pregnancy by an additional 40mg/day due to the increased body mass (39). Magnesium toxicity is rare,

and has only occurred through consuming supplements with no reports of toxicity exclusively through dietary intake (11).

The use of Mg dietary supplements can increase Mg intake. Magnesium supplements are typically in the form of Mg oxide, citrate, stearate, acetyl taurate, or chloride (43,58). Magnesium citrate and Mg oxide are most frequently prescribed when dietary supplementation is necessary (58). A study performed on rats showed the highest levels of blood Mg when being supplemented using Mg malate, suggesting Mg malate is absorbed the most effectively, followed by Mg acetyl taurate suggesting these forms of Mg are the most bioavailable (58). Prenatal vitamins are typically not a good source of Mg intake, as only about 20% of prenatal supplements contain Mg (40). When Mg is in a prenatal vitamin, on average contributes to 7.6% of the daily value required for pregnancy (40). Therefore, if a woman is taking a prenatal vitamin, they would not be able to meet their Mg needs with the prenatal vitamin alone. She would need to consume food containing Mg or a Mg supplement to ensure adequate dietary intake. Previous studies show the benefits of supplementing Mg to reduce the risk of chronic diseases like T2DM, vitamin D deficiency, poor pregnancy outcomes (12,19,59).

Absorption

Only about 30-40% of dietary Mg intake is actually absorbed, but absorption can range from 25% when consuming high amounts of Mg to 75% when consuming inadequate amounts of Mg (20,46). Magnesium is absorbed as a free, unbound ion, Mg^{2+} and is absorbed best at a lower pH (47,60). It is absorbed passively primarily in the jejunum and ileum of the small intestine, and less absorption occurs in the colon (12,20). Absorption and retention of Mg is not affected by whether an individual has T2DM,

however, gastrointestinal diseases such as celiac disease, inflammatory bowel syndrome, and short bowel syndrome can have malabsorptive effects (12,47). Magnesium is excreted through bile and urine, and resorption occurs in the kidneys (12,20,47).

The highly processed foods within the American western diet typically contain phosphate additives (found in foods like processed meats and sugar sweetened beverages) and low calcium intake, which can increase the required amount of Mg in order to remain in a positive balance (49). On the other hand, excess amounts of calcium and vitamin D can also increase Mg needs (49). Fiber, free fatty acids, oxalate, phytate, and high levels of phosphorus, iron, copper, manganese, and zinc can inhibit Mg absorption as well (47,61). However, many studies that investigated these relationships were using physiologically improbable amounts of the minerals (47). Magnesium is found in many foods containing phytates, and many believe that phytates found in foods will lower Mg absorption and lead to Mg deficiency (49). However, resorption of Mg in the kidneys will decrease the amount lost in the urine to make up for the Mg bound to the phytates being excreted (49). Oxalic acid which is also found foods like spinach, cabbage, and brussels sprouts, can also inhibit absorption of Mg by binding to it thus decreasing its ability to absorb as a free ion (47). Aluminum consumption is another factor that can inhibit Mg absorption thus increasing dietary needs, as aluminum is used in a variety of cookware, packaging, and topical products (49).

Since Mg is typically consumed as a whole food complex and not as an isolated form, many studies have researched the impact macronutrients and other food components has on Mg absorption (47,62–66). A high protein has shown to improve Mg absorption when compared to lower protein intake due to its effect on preventing Mg and

calcium complexes from forming, which would decrease absorption (47,62–66). The type of lipids consumed can also have an effect on Mg absorption in the gastrointestinal tract, as medium chain triglycerides increase absorption compared to long chain triglycerides (47). Additionally, low soluble and insoluble fibers can impact Mg absorption in the large intestine (47,67). This is due to the fermentation that occurs in the colon which results in a decreased, more acidic pH, thus improving Mg absorption (47,67). Lastly, it is possible that lactose can enhance Mg absorption, as it has been shown in rats but there has been conflicting evidence for the effect on humans (47,68).

Magnesium Regulation

Serum Mg can vary throughout the day due to our body's regulatory mechanisms (60). Our bones and muscles have a mechanism that releases Mg into the serum to remain in homeostasis when Mg levels drop, therefore maintaining relatively constant serum Mg status (12,39). Continuous reduced Mg intake leads to Mg depletion, causing the bone to release Mg to maintaining Mg balance, which can negatively affect bone strength and contribute to bone-related deficiencies and diseases (46).

In addition to bones, the kidneys also help to regulate serum Mg homeostasis via renal resorption (20,46). About 96% of Mg is reabsorbed in the kidneys using active transport, thus requiring energy (46,47). This resorption occurs in the nephron of the kidney, and occurs to maintain balance of minerals (46). Ten to 30% of the Mg is reabsorbed in the proximal convoluted tubule using a sodium gradient, 40-70% reabsorbed in the thick ascending limb using cotransport and an electrochemical gradient, and 5-10% through the distal convoluted tubule using active transport (46).

Magnesium Status Measurements

The most common clinical diagnosis of hypomagnesemia uses serum Mg, but it is a poor indication of Mg intake or total body status (20). Total body depletion of Mg can be overlooked by a serum Mg reading, as serum Mg is a poor indicator of total body Mg and dietary intake due to the body's ability to regulate serum levels (20,46) Therefore, hypomagnesemia is commonly undiagnosed (20). One reason may be attributed to the homeostasis mechanisms of our bones and kidneys (12,20,39,46). Additionally, serum Mg measurements include protein-bound Mg, and therefore changes in serum protein concentrations may affect serum Mg measurements (20).

Magnesium status is also measured using ionized Mg, which may be a better indicator for total body Mg than serum Mg (69). Ionized Mg represents the most biologically available, unbound form of Mg and represents about 55% of Mg in the body (35,69). Therefore, changes in proteins that may be bound to Mg will not affect ionized Mg readings (20). However, the methodology of obtained ionized Mg still needs to be researched to ensure accuracy, as it requires an ultrafilterable Mg and is not routinely used (20,70). Obtaining ionized Mg is an invasive and complicated method to attain Mg status, as it requires blood draw and further testing afterwards (20,70). There is no documented method to accurately measure Mg status (70).

Measuring dietary intake using a food frequency questionnaire (FFQ) is the preferred method to obtain Mg status (43). Diet*Calc software can be used to import the nutrients into a Diet*Calc food database so they can then be analyzed (24). Diet*Calc can be edited if a FFQ is modified (24).

Magnesium and Diabetes

Due to its integral role in insulin activation and insulin release from the beta cells of the pancreas, many studies show low Mg is strongly linked to development of T2DM (13,14,71). A study by Mckeown et al.(13) reported high dietary and supplemental Mg intake can reduce the risk of impaired glucose tolerance and metabolism in adults by 37%. Another study found that hypomagnesemia (total serum Mg below 1.7mg/dL) was associated with T2DM due to its role with tyrosine kinase (TK) and activation of the insulin receptor (71,72). Based on previous research that shows low serum Mg is associated with T2DM onset, Pokharela et al. (71) evaluated the relationship between hypomagnesemia and T2DM in a Nepalese population sample using a case-control experimental design and found that hypomagnesemia was present in half of the participants with diabetes (71). Furthermore, low serum Mg was associated with insulin resistance and diabetes-related complications such as dyslipidemia, poor glycemic control, and renal insufficiency (71). The research by Pokharela et al.(71) indicates that low serum Mg is associated with insulin resistance, which creates the need to discuss the physiologic relationship between Mg and insulin.

Magnesium affects insulin activity in two major ways: 1) insulin secretion from the beta cells of the pancreas, and 2) activation of the insulin receptor (14,15). When Mg levels are inadequate, it can inhibit the beta cells of the pancreas to release insulin causing pancreatic beta cell dysfunction (14). Magnesium levels affect insulin secretion in two ways, as there are two major steps involved in insulin secretion (14). First, Mg can impact the phosphorylation by glucokinase after glucose entering the cell, as glucokinase activity directly depends on a Mg-adenosine triphosphate (ATP) complex (14). Therefore

when Mg levels are low, the cell cannot successfully entrap glucose by phosphorylation (14). In a normal healthy adult, the beta cells use changes in membrane potential to react to glucose in the blood and secrete insulin (14). This membrane potential can become disrupted when a potassium channel becomes blocked causing membrane depolarization (14). Magnesium's role in this second step is to activate and open the potassium channel which will stimulate the release of insulin (14).

The second major way Mg can impact insulin is through insulin receptor activation (48). Insulin activation begins with binding of insulin to the alpha subunit of its TK insulin receptor resulting in phosphorylation of the TK subunit (14). Magnesium is the main cofactor for the phosphorylating TK (69). More specifically, free intracellular Mg will bind to the phosphate groups on ATP to form a Mg-ATP complex (12,51). When Mg is attached to ATP, it improves the binding ability of ATP to active sites of protein kinases including TK (51,69,73). Once TK is phosphorylated and activated, it can subsequently initiate the effects of insulin activity, creating a cascade of reactions to bring glucose into cells for use or storage (13,72,74). Gestational diabetes is typically attributed to a combination of pancreatic beta-cell dysfunction and insulin resistance which can be caused by reduced TK phosphorylation (4). Therefore, when there is low intracellular Mg, TK cannot auto-phosphorylate as efficiently which results in disordered TK activity, thus insulin resistance (69).

A study done by Tasdemir, et al.(35) compared the ionized unbound Mg and total body Mg levels in women with and without GDM using in 85 pregnant women, of which 40 of were diagnosed with GDM. Tasdemir, et al.(35) hypothesized low Mg would be associated with insulin resistance during pregnancy based on previous research showing

an association between hypomagnesemia and impaired glucose. The results showed a relationship between low total Mg and low ionized Mg and development of GDM, thus suggesting Mg is a crucial ion in the development of GDM (35). Given that the pathophysiologic mechanism for both T2DM and GDM are the same in that both observe insulin resistance, it is critical to investigate how supplemental and dietary intake of Mg may be associated with GDM (10).

Chapter 2: Gestational Diabetes

Background, Prevalence, and Cost of GDM

Gestational diabetes is defined as glucose intolerance that is first recognized while pregnant, and is typically diagnosed between 24-28 weeks gestation without any prior diagnosis of type 1 or T2DM (4,7,75). Glucose intolerance is defined as a fasting blood glucose of ≥126 mg/dL or a 2 hour post prandial 75g oral glucose tolerance test (OGTT) value of over 200 mg/dL (2,7). Historically, GDM diagnosis was not always standardized, and therefore many cases may have gone undiagnosed (4). Undiagnosed and therefore untreated GDM can have continuous risks of morbidity and mortality for the mother and the baby (76). Screening, diagnosing, and treating cases of GDM is important for maternal and fetal health outcomes during and after pregnancy, as well as healthcare spending (6,77).

Gestational diabetes is also quite costly. In the US in 2007, GDM-related diagnoses cost an additional $3,305 per pregnancy, totaling $636 million in increased healthcare dollars (6). About 50% of GDM typically subsides postpartum, which means 50% continues on to T2DM contributing to the $327 billion spent on T2DM in 2017 (2,4,5,78). Gestational diabetes was estimated affect 1-14% (1 in 7) of pregnancies globally in 2017 (10,79) and represented 83-87.5% of all diabetic pregnancies globally (75). This prevalence marks GDM the most common condition women develop during pregnancy and diagnoses continue to increase worldwide (2,3). The suspected increase in GDM development may be due to the rise in obesity, reduction in physical activity, and increase in maternal age (10). It is recommended to complete screenings earlier in pregnancy (meaning at the beginning of the first trimester and/or when antenatal care

begins) for women who may have these risk factors so that non-GDM diabetes can be diagnosed if present, and therefore GDM is not being mistaken for pre-existing diabetes (10). To date, there is still no standard method of diagnosing GDM during an early pregnancy screening and it is still controversial, as physicians may use fasting plasma glucose, random plasma glucose, HbA1C, or 75g 2 hour OGTT (10). Gestational diabetes is typically diagnosed in a screening later in pregnancy during the third trimester (10).

Risk Factors & Adverse Outcomes of GDM

There are many factors that may increase the risk of developing GDM. Common risks include pre-pregnancy overweight or obesity, gestational weight gain, central adiposity, hypertension or preeclampsia during pregnancy, western diet patterns, micronutrient deficiencies (e.g. vitamins B_2, B_6, B_{12}, and folic acid which are vital in homocysteine homeostasis), maternal age ≥35 years old, and family history of diabetes (4,25,80). The risk of developing GDM increases as BMI increases, where a study showed it was 2.14 times higher in pregnant women who are overweight (BMI 25.0-29.9kg/m_2), 3.56 times higher in pregnant women who are obese (BMI 30.0-34.9kg/m_2), and 8.56 times higher in very obese pregnant women (BMI >35.0kg/m_2) when compared to pregnant women with a normal BMI (BMI 18.5-24.9kg/m_2) (81).

Gestational diabetes can lead to adverse maternal and fetal outcomes and has been studied extensively. The Hyperglycemic and Adverse Pregnancy (HAPO) Study looked at adverse pregnancy outcomes in pregnant women with obesity and GDM (82). This research showed that GDM and obesity are both independently associated with adverse pregnancy and birth outcomes, but together have an even stronger association with each outcome analyzed (82). Catalano et al.(82) used an OGTT to diagnose GDM which

showed women with GDM had a higher prevalence of higher birthweight, newborn body fat percent, c-section, and preeclampsia than women without GDM (82). An increase in fetal adiposity can develop with maternal hyperglycemia which can be a contributing risk factor for chronic diseases like cardiovascular disease and T2DM for the offspring later in life (82,83). Other common fetal consequences from maternal GDM that are increased when GDM is not recognized are macrosomia, large for gestational age, shoulder dystocia, and other kinds of birth trauma (76,84). A prospective 4-year cohort study by Yang et al.(3) found GDM prevalence was associated with high birth weight, as well as an increased risk for large for gestational age and macrosomia. Fetal macrosomia occurs in about 15-45% of babies born to mothers with diabetes which is 3 times more than mothers with normal blood glucose levels (85,86). This is due to a modification in lipid metabolism from maternal hyperinsulinemia which can occur as a response to hyperglycemia, resulting in increased protein and fat storage of the fetus (3,85,86). Hyperinsulinemia occurs when the beta cells of the pancreas overproduce insulin in response to continued elevated blood glucose levels from resistant insulin (87). A study by Ogonowski et al.(85) showed the rate of macrosomia and large for gestational age is decreased when maternal hyperglycemia is treated and controlled. This supports the need to screen for GDM so it can be properly treated to avoid adverse fetal outcomes (85).

Development of GDM can also lead to unfavorable maternal short and long term outcomes (75,88). The most common potential risks of developing GDM for mothers include c-section delivery, pre-eclampsia or pregnancy-induced hypertension, weight gain, increased triacylglycerol blood concentrations, decreased high-density lipoproteins, decreased insulin sensitivity post-partum and/or development of T2DM (60% of women

with GDM develop T2DM later in life), antenatal depression, and increased maternal adipose tissue (75,88–90). These studies, among many others (3,4,10,79), indicate that GDM can lead to unfavorable birth outcomes and development of chronic diseases for the mother and child, thus providing a strong foundation as to why it is important to examine strategies to decrease GDM prevalence.

Mechanism of Insulin in GDM

Insulin is made in the beta cells of the pancreas. When blood glucose levels are elevated, insulin is released in response to a change in membrane potential (10,14,87). Insulin acts by signaling the insulin-dependent GLUT transporter proteins by binding to their membrane receptors on the apical membrane of cells when glucose is elevated to transport glucose out of the blood and into the cell (45).The mechanism of GDM is similar to T2DM, where the beta cells do not release insulin in response to the elevated glucose levels, or the insulin that is released is is impaired and does not stimulate the GLUT transporter proteins in reaction to the stimulation of elevated blood glucose levels, and therefore does not facilitate glucose uptake into cells (87,88). Specifically, the translocation of GLUT4 that is normally stimulated by insulin to increase glucose uptake is impaired (7). This can lead to hyperglycemia, potentially hyperinsulinemia, as insulin initiates uptake of glucose by cells in the fed state (45). Gestational diabetes can occur when a mother is hyperglycemic due to these pathophysiological mechanisms of insulin (88).

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