Magnesium Supplementation: Is It Time for Diabetes Guidelines to Consider Its Inclusion?

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Abstract *This article aims to raise awareness about magnesium supplementation's potential role in diabetes care. It is intended to be an educational piece for clinicians, guideline writers and patients and highlights the importance of optimal magnesium status in disease management, particularly type 2 diabetes mellitus. The majority of the data was taken from published peer reviewed journals regarding magnesium's role in human health, and its relationship to various disease states, particularly diabetes. There is sufficient evidence to begin routinely recommending magnesium supplementation to diabetic patients once contraindications are ruled out. With magnesium's robust safety profile and growing evidence of its therapeutic effect, the potential benefits outweigh the potential risks. These evidence-based insights will provide clinicians with an additional tool for optimal management of diabetic patients, and possibly other chronic conditions.*

Introduction

The Canadian health care system continues to be burdened by the impact of diabetes, where 2.4 million (6.4%) Canadians live with this disease.[1] From 1998-2008, the prevalence of diabetes increased by 70%, along with a steady rise in the incidence. Furthermore, people with diabetes do not appear to be improving their health status. They were three times more likely to be hospitalized with cardiovascular disease (CVD), and 36.5% reported having two or more other serious chronic conditions.[1] Other significant findings suggest that 40% of people with diabetes rate their health as "fair" or "poor" compared to 10.3% for the population without diabetes. Nearly a third (29.9%) of individuals who died in 2008/09 had diabetes.[1] It appears that from a primary, secondary, and tertiary prevention standpoint, our current approach is not achieving its desired effect. Considering this growing burden, could there be other avenues that have not received adequate consideration?

Magnesium (Mg) research has grown substantially in the last decade, providing interesting insights into this element's role in human health. Growing evidence suggests the possibility of Mg deficiency playing a key role in the etiology of numerous disorders, particularly diabetes. This article will review the role of Mg in relation to human health, review the evidence suggesting the existence of a widespread Mg deficiency, and discuss the relationship of Mg with type 2 diabetes mellitus (T2DM). With a low risk profile, and growing evidence supporting beneficial outcomes, is it time for clinicians and guidelines to routinely consider Mg supplementation for all people who suffer from diabetes?

What is Magnesium?

Mg is a critical element for biological functioning. It is the fourth most abundant cation in the human body (following calcium, sodium & potassium), and the second most abundant in the intracellular environment.[2] Ninety-nine percent of Mg within the body exists in the intracellular space, where approximately 65% are in bone cells, 27% in muscle cells, 7% in other cells, and the remainder exists in extracellular fluid.[3] Furthermore, Mg plays a key role in the catalytic activity of over 300 enzymes, particularly those used for energy producing reactions.

The Biochemistry of Magnesium

Mg's role in the etiology of disease, particularly CVD and T2DM, becomes more easily understood when certain biochemical functions are clarified.

Magnesium and ATP. Mg is absolutely necessary for the production of energy. The molecule adenosine triphosphate (ATP) is well known for its role in the production of cellular energy. What is less known is that in order for ATP to become activated, it must bind with Mg, to form the MgATP complex, which itself is the very currency of metabolic energy in the cell.[4]

Magnesium and Insulin Sensitivity. Mg plays an important role as a secondary messenger in the action of insulin. Reduced intracellular magnesium results in a defective tyrosine kinase activity, which is critical to insulin signalling, thereby reducing insulin sensitivity.[5] Low intracellular Mg levels result in altered cellular glucose transport, impairment of post-receptor insulin action, and reduced pancreatic insulin secretion.[2] Observational studies also confirm Mg's role in insulin action. A 20 year prospective cohort study of approximately 4,500 Americans found a significant inverse relationship between magnesium intake and insulin resistance.[5] Another cohort study from Newfoundland consisting of 2,300 subjects also concluded there was an inverse relationship between Mg intake and insulin resistance.[6]

Magnesium and Atherosclerosis. Both animal and human studies have demonstrated an inverse relationship between Mg intake and the development of atherosclerosis.[7] Magnesium has an important role to play in atherosclerosis, blocking the uptake of calcium into smooth muscle cells and reducing soft tissue calcification. In vitro studies of cultured human endothelial cells showed increased inflammation in cells exposed to low Mg levels and increased endothelial permeability allowing low density lipoprotein's (LDL) to migrate into the media, become oxidized and more susceptible to combine with macrophages to form foam cells known to be linked to atherogenesis.[8] Furthermore, a recent cross-sectional study of 2,695 subjects found that Mg intake was inversely associated with arterial (coronary and abdominal aorta) calcification.[9]

Diabetes and Magnesium Wasting. Insulin is required for renal magnesium reabsorption.[2] Therefore, it has been suggested that insulin deficiency or resistance could promote urinary magnesium excretion. In addition, other investigations have found that although insulin may be a factor in increased Mg excretion, hyperglycemia is an independent factor that increases renal Mg excretion, regardless of insulin activity.[10] Interestingly it was found that hyperglycemia specifically affected Mg, whereas renal excretion of sodium and potassium remained constant. With Mg deficiency playing a role in poor glycemic control, this in turn leads to increased renal Mg excretion, establishing a vicious cycle which may lead to increasingly poor metabolic control and more risk of complications.

Magnesium and Inflammation. Mg has been shown to have anti-inflammatory properties, where a deficiency increases immune and oxidative stress, which in turn leads to systemic inflammation.[11] One hundred and eighty three peer reviewed studies that were published between 1990 and 2008 found that Mg deficiency was associated with the prevalence and increased risk of over 10 conditions, most of which are inflammation related.[12] Whereas in the early 20th century, health concerns were focused on infectious

diseases, presently, much of the burden of our health care system can be attributed to inflammatory diseases. With such evidence, it is important to assess the possibility of a widespread deficiency of Mg.

Magnesium Intake and Deficiency

In addition to T2DM, low magnesium intake and blood levels have been associated with metabolic syndrome, elevated C-reactive protein, hypertension, atherosclerotic vascular disease, sudden cardiac death, osteoporosis, migraine headache, asthma, and colon cancer.[13] Given these extensive associations, are North Americans consuming enough Mg?

Magnesium Intake

The recommended daily allowance (RDA, level at which 95% of the population's needs are met) of Mg varies by age and sex, but for women and men over 30, approximately 320mg and 420mg per day is recommended, respectively.[11] It has been suggested that the RDA is under-estimated however, and should range between 500-750mg per day. Another unit of measurement is the estimated average requirement (EAR, the level at which 50% of the population's needs are met), which also ranges by age and sex, but approximates 260 mg for women and 350 mg for men per day. An extensive US nutritional survey is conducted by the National Health and Nutritional Examination Survey (NHANES) every few years. In 2006, NHANES reported on Mg intake specifically, and assessed what percentage of the population consumed adequate amounts of Mg to meet the EAR. It was reported that 53% of men 19+ and 56% of women 19+ consumed less Mg than the EAR.[13] In some age groups 89% consumed less than the EAR. Considering that some suggest the Mg RDA is too low, and that the EAR is lower than the RDA, it can be assumed that these elevated percentages of people consuming inadequate amounts of Mg is an underestimate. Indeed, in 2000, NHANES reported that 79% of Americans consumed less Mg than the RDA.[11]

Magnesium in Food

Mg is rich in food sources that are typically considered healthy and unprocessed. Vegetables such as leafy greens (spinach, kale), legumes such as black beans, nuts and seeds including almonds and pumpkin seeds, fish products like mackerel and halibut, and pure dark chocolate are foods rich in magnesium.[14] On the other hand, meats & poultry, refined grains, white flour and most processed foods contain very little magnesium. Generally, individuals who consume adequate amounts of magnesium through food alone, eat highly nutritious, well-balanced diets. Others have theorized that with soil depletion due to modern farming techniques, adequate magnesium intake through diet alone is becoming increasingly challenging.[15] Although there is an intuitive understanding by the general population of the benefits of healthy eating, in 2009-2010 more than half of Canadians aged 12 years and older (55.9%) reported eating less than the recommended five servings of vegetables and fruits a day.[1]

Other Causes of Mg Deficiency

In addition to low dietary intake as a source of Mg deficiency, other possible explanations have emerged. Mg deficiency can be further exacerbated by excessive caffeine and alcohol intake, the use of diuretics, all of which increase Mg excretion.[16] Medications like proton pump inhibitors reduce intestinal absorption of Mg, and others like fluoroquinolone antibiotics bind to magnesium rendering it inactive.[16] Furthermore, it has been suggested that approximately 10-20% of the general population is affected by a congenital magnesium-losing disorder, whose etiology is genetically related.[17] Individuals affected by this require much larger amounts of Mg intake (600-1800mg/day) than the RDA, in order to prevent Mg deficiency and subsequent poor health outcomes.[17] Despite the impact of Mg deficiency, screening for deficiency remains a challenge.

Screening for Magnesium Deficiency

Screening for Mg deficiency via laboratory means is notoriously difficult.[11] The mainstream approach to determine Mg

status is by measuring serum levels, where approximately 0.65 to 0.95 mmol/L is considered normal range. Typically, if serum Mg levels are within this range, clinicians will rule out an Mg deficiency. As mentioned, Mg is primarily an intracellular cation, where only 1% of total Mg is in the serum. As well, Mg homeostasis mechanisms tightly control the Mg serum level. Therefore, serum Mg levels correlate poorly with total body stores. For example, in observational studies of neonates, Mg shifted from intracellular space to extracellular space in patients with acidosis, and vice-versa, Mg shifted from extracellular space to intracellular space in patients with alkalosis. Therefore, alkalotic patients may have low serum Mg levels with normal total stores, and acidotic patients may have normal serum Mg levels with deficient total body stores.[18] Others have estimated that serum levels could detect Mg deficiency 50% of the time, and thus have recommended elevated reference levels of 0.8 – 1.2mmol/L for determining total body status.[19] Although serum Mg remains a useful tool, it must be used with caution.

The current gold standard for measuring total body Mg stores is the 24 hour urine Mg loading test. This involves infusing a patient with a loading dose of Mg intravenously (IV), followed by a 24 hour urine collection. If less than 90% of the Mg load given IV is found in the urine, then the patient is considered deficient, since the body is retaining the loading dose due to low stores.[12] Although this test is relatively accurate and informative, it is inconvenient and time consuming, and rarely used in clinical practice. Accurate laboratory testing of an Mg deficiency remains a challenge. Likely, a more comprehensive approach to assessing Mg status is to utilize both laboratory testing and clinical findings such as: lifestyle, medical history, presentation of symptoms, improvement with supplementation, etc.[16] Patients who present with a history of T2DM for example, should be considered potentially deficient.

Magnesium and T2DM

As it was alluded to earlier, T2DM, a metabolic disorder, is increasing in prevalence and diabetes patients are usually living with multiple co-morbidities. Hypomagnesemia as defined by low serum levels is a common occurrence in patients with T2DM. Various reports have indicated that between 13.5% and 47.7% of non-hospitalized T2DM patients have hypomagnesemia compared to 2.5% and 15% for their non-diabetic counterparts.[20] Mg is well known to be essential for metabolic processes, and is quite possibly a missing link in medicine's approach to the management of T2DM.

Magnesium Intake and T2DM

A number of epidemiological studies have been carried out on the link between Mg intake and T2DM. A meta-analysis of prospective cohort studies with 286,668 participants showed a significant inverse association between Mg intake and the risk of T2DM in a dose response manner.[21] A similar and more recent meta-analysis involving 536,318 participants published nearly identical results.[22] While evidence suggests increasing Mg intake reduces risk of acquiring T2DM, increased Mg intake can also benefit those at risk, and those already diagnosed with T2DM. One study of 2,582 community dwelling participants evaluated Mg intake among persons with baseline metabolic impairment (pre-diabetes). At a seven year follow up, compared to those with the lowest Mg intake, those with the highest intake had a 32% decreased risk of developing T2DM.23 Another smaller study involving older adults (65+) diagnosed with T2DM, found that increased Mg intake improved metabolic parameters, and those with low intake had increased metabolic abnormalities.[24] Indeed, many studies have evaluated serum Mg levels and found increased hypomagnesemia in T2DM is predictive of poor diabetic control.[25]

Animal studies also support these associations. Different studies have evaluated rats who were induced into a diabetic state, whether through excessive diet or chemicals. Those with Mg supplementation had a delayed onset of diabetes compared to the control group, and Mg was shown to be an effective anti-diabetic agent.[26,27] Another

study using T2DM rat models, found that Mg supplementation improved insulin receptor sensitivity, decreasing insulin resistance compared to the control group.[28] Whether it is a preventative measure or method of improving metabolic functioning, it is important to consider magnesium status when dealing with T2DM. Further support of this are the human studies on Mg supplementation.

Magnesium Supplementation and T2DM

It is important to note that many of the epidemiological studies noted above measured Mg intake from all sources, including those taking supplements. However, in terms of controlled trials testing the effectiveness of Mg supplementation on diabetic subjects the numbers of studies are limited. Some early small studies showed contradicting evidence. The most thorough review of these studies is from Song et al. (2006), who performed a meta-analysis on all available randomized double blind controlled trials (RCT) existing up to 2005.[29] A total of nine trials fulfilled their criteria. Average daily supplementation was 360 mg. They concluded that 4-16 weeks of magnesium supplementation showed significant reduction in fasting plasma glucose levels and increased HDL levels compared to controls, but had no impact on glycated hemoglobin (A1C) and other lipid profiles. A more recent RCT evaluated magnesium supplementation over six months on obese insulin-resistant non-diabetic subjects (n= 52). The intervention group showed significant improvement in fasting blood sugar as well as insulin sensitivity indices.[30] These authors conclude that in addition to their research, results from previous trials and epidemiological studies provide convincing evidence for a positive effect of Mg supplementation on insulin resistance. Also noteworthy is a very recent RCT from 2014 which evaluated the effects of Mg supplementation on serum high-sensitivity C-reactive protein (hsCRP) on subjects with prediabetes and hypomagnesemia. After three months of supplementation, the experimental group had significantly lower serum hsCRP levels compared to the control group.[31] Although there is a limited amount of RCTs for Mg supplementation, the evidence remains positive. Importantly, none of the trials reported any serious adverse effects from the Mg supplementation.

Magnesium, Diabetes, and Cardiovascular Disease

The risk of cardiovascular disease is increased in diabetes patients. The Framingham Risk Score doubles if the patient has a history of T2DM. Minimizing CVD risk is an important aspect of providing care to diabetes patients. There is substantial evidence that Mg plays a cardio-protective role. A large meta-analysis of 16 prospective studies including 313,041 subjects was conducted to analyze the association of dietary Mg intake and circulating Mg, with CVD, ischemic heart disease (IHD), and fatal IHD. The authors concluded that circulating Mg was inversely associated with risk of CVD, IHD, and fatal IHD and dietary Mg intake was inversely associated with risk of IHD and fatal IHD.[32]

Another recent prospective study with a mean follow up of 10 years analyzed the association between dietary intake as measured by urinary excretion of Mg, and the risk of IHD in 7,664 subjects. Their investigation found that increased dietary intake of Mg was well correlated with increased urinary Mg excretion and therefore served as an accurate means of measurement. The results demonstrated that increased levels of urine Mg was inversely associated with risk of IHD. In this article, the authors also interestingly note four autopsy studies from decades ago on myocardial tissue post myocardial infarction, and all found low intracellular Mg levels.[33]

Other reviews have found that low Mg intake was linked with numerous CVD's such as stroke, atrial fibrillation and atherosclerosis, thus demonstrating a relationship between increased dietary Mg intake and a reduction in the risk of CVD.[8] Importantly, these reviews have found Mg supplementation to be safe, and no serious adverse effects were observed.[34] Regardless of all these observations, Mg supplementation is rarely used in the care of diabetes patients.

Current Guideline Recommendation on Magnesium

The Canadian Diabetes Association's (CDA) 2013 guidelines currently does not recommend magnesium supplementation, explaining that studies have shown conflicting results on its effect on A1C, referencing five studies for their position. Three of those studies were small RCT (n<60) from the mid-90's, that indeed showed no significant effect of Mg supplementation on metabolic parameters. The fourth study is an RTC from 2003 (n=63), where Mg supplementation over 16 weeks showed improvement in most metabolic parameters (fasting glucose, A1C, lipids, etc.).[35] And the fifth study is one which was mentioned earlier by Song et al., a meta-analysis of all RTC's up to 2005, which includes the four other studies referenced by the CDA. As mentioned previously, their conclusion was that Mg supplementation improved fasting glucose and HDL levels, but no significant effect was found on A1C.

Interpretation of These Studies

It is important to put these results into context. In Song et al.'s meta-analysis, the average duration of Mg supplementation on the experimental groups was approximately 9.7 weeks. As explained by the CDA, A1C is a reliable estimate of mean plasma glucose over the previous three to four months. The 30 days preceding blood sampling contributes to 50% of the results, and the prior 90 to 120 days contributes 10%. It is reasonable to consider that the length of intervention (9.7 weeks) may be a contributing factor to insignificant A1C results. Furthermore, restoring depleted total body Mg stores with oral supplementation takes time. Mg is mostly active in the intracellular space, and there is a lapse of time between beginning oral supplementation, and restoring total body magnesium stores to adequate levels,[36] thereby allowing optimal biochemical functioning. Lastly, different oral supplements have different bio-availability and absorption profiles, which can further influence varying results since the studies in Song et al.'s analysis used both different forms and different quantities of oral supplements.

There is a lack of clear published evidence between Mg oral supplementation's causal relationship with A1C levels, and inevitably more research is needed. However, all of the evidence from epidemiological, animal, numerous RCTs, and in vitro studies of Mg's role in various health issues that affect diabetes patients must also be taken into consideration. Is the lack of causal relationship between Mg supplements and A1C levels sufficient reasoning to exclude this therapeutic approach in diabetes care?

The Case For Magnesium Supplements in Diabetes Care

Ultimately, good medicine is about continually weighing the risk versus benefits of any therapeutic approach. Herein lies the importance of considering magnesium supplementation where the risks are minimal and the benefits are probable.

Safety Profile

Magnesium therapy has a robust safety profile. There has been no reports of severe adverse effects in Mg supplementation studies, with mild gastro-intestinal side-effects (abdominal discomfort, diarrhoea, nausea) reported less than 10% of the time by some studies.[34,29] To put in context, Mg in large doses is used in various medical situations. A typical daily supplementation of Mg may include 900 mg of Magnesium Citrate, which provides approximately 145 mg of elemental Mg.[37] In pre-eclampsia emergencies, standard treatment includes a loading dose of 6g's of Magnesium Sulphate (600 mg of elemental Mg) IV, followed by an IV maintenance dose of 1-3g's (100 to 300 mg elemental Mg) per hour.[38] Toxicity is uncommon in women with good renal function, and antenatal fetal assessment test results are not significantly altered. Other applications include bowel cleansing prior to colonoscopies, where 20 g (20,000 mg) of Mg Citrate is given orally, and is generally well tolerated.[39]

In the presence of good renal function, excess magnesium is readily excreted by the bowels and kidneys, thus toxicity is extremely rare [excess magnesium causes diarrhoea].

Contraindications to Mg therapy include: renal failure, myasthenia gravis, severe bradycardia, & bowel obstruction. In the absence of these conditions, Mg therapy demonstrates an excellent safety profile.

Level of Evidence and Other Guidelines

According to the centre for evidence based medicine (CEBM), a grade B recommendation requires consistent level 2+3 studies, which include cohort studies, case controlled studies, and small RCTs.40 With current evidence, it could be argued that Mg's health protective role for T2DM ranges in the B to strong C level. It is true that more evidence is necessary before Mg in diabetes can be graded in a strong B to A level. However, other guidelines make recommendations based on lower-grade evidence ratings. For example, the Canadian 2010 Osteoporosis Guidelines recommended calcium and vitamin D supplementation for healthy adults, and vitamin D for those at risk of deficiency, based on evidence grade B, D, C, respectively.[41]

Furthering this rationale is the examination of the mortality rate in diabetes patients. The CDA guidelines discuss numerous oral anti-hyperglycemic agents in the management of diabetes patients. A few of those include: sulfonylureas (Glyburide, Gliclazide), DPP-4 inhibitors (Sitagliptin, Saxagliptin), GLP-1 receptor agonists (Exenatide, Liraglutide), biguanide (Metformin), alpha-glucosidase inhibitor (Acarbose), and a number of others as well.[42] Of all the oral agents recommended by the CDA guidelines, only Metformin, and perhaps arguably Acarbose have been shown to reduce all-cause mortality in diabetes patients.[43] The other agents have demonstrated no such evidence. Similarly, no studies have demonstrated evidence that Mg supplementation reduces all-cause mortality in diabetes patients. That being said, Mg supplementation's exclusion should not be predicated on this, since many oral diabetic agents are included in the guidelines despite having no evidence in reducing mortality.

Types of Mg Supplements and Dosages

Recommending a specific supplement can be challenging for clinicians. As mentioned earlier, different supplements have different absorption profiles. The most well studied magnesium salts and perhaps the most commercially available include magnesium oxide (inorganic salt) and magnesium citrate (organic salt). Reports have demonstrated that magnesium citrate is more water soluble, and dissolves more easily in a pH environment similar to our GI tract than does Mg Oxide.[44] In addition, when giving equivalent elemental dosages of Mg citrate and Mg oxide, Mg citrate had a significantly greater impact on raising serum levels, urinary excretion and erythrocyte concentration levels.[44,45] Other organic Mg salts include Mg Malate, Mg glycinate, and Mg taurate, and it has been suggested, that most organic Mg salts show similar absorption profiles.[46] Clinical experience suggests that Mg Citrate is an excellent option when a deficiency is suspected and constipation issues are present, whereas Mg Malate is the preferred option for deficient patients with baseline regular bowel movements.

In terms of dosages, the more established daily supplement intake is recommended at approximately 350 mg of elemental Mg per day in adults, or 5 mg/kg/day.[37,11] Others have suggested to taper up the elemental Mg dosage by 50 mg/day every few days according to bowel tolerance, targeting 1-2 soft bowel movements per day.[11] Based on this author's clinical experience, 250 mg of elemental Mg given twice daily in the form of Mg Malate is a well-tolerated, safe, and effective approach to treating an Mg deficiency.

An Adjunctive Approach

Mg therapy is not meant to replace current recommended guidelines for diabetes care, but rather used as an additional tool aimed at improving outcomes. Furthermore, Mg appears to be most effective when consumed through a healthy diet, likely due to its synergistic effect with other trace minerals found in food. However, despite established benefits of a healthy lifestyle such as exercise and good nutrition,

many patients with T2DM find it difficult to achieve and maintain healthy behaviours.[47] Therefore, considering which foods have high Mg content, recommending increased Mg intake through diet alone may not be an effective approach.

In addition to proper pharmaceutical treatment, as well as ongoing reinforcement of health behaviours, magnesium supplementation should be considered for all patients with T2DM, to ensure total body stores are adequate, thereby increasing likelihood of better health outcomes.

Conclusion

Mg is a very important mineral, critical for hundreds of biochemical reactions, most of which are involved in energy production. There is growing evidence that low Mg intake and deficiencies are linked and could possibly be a factor in the development of T2DM. T2DM is an increasingly heavy burden on the health care system, where prevalence is increasing, and patients continue to be plagued with multiple co-morbidities, necessitating new and innovative approaches. In light of this, magnesium supplementation, as a means of primary, secondary, and tertiary prevention, should be considered by all clinicians and guidelines in diabetes care. Though further research is needed to establish Mg's causal relationships with various metabolic parameters, current evidence is sufficient to begin its inclusion in diabetic guidelines, under lower grade ratings. With the low cost of supplements, robust safety profile, and evidence of probable benefit, Mg therapy is an under-utilized tool with untapped potential.

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Competing Interests

The author declares that he has no competing interests.

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