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Metabolic and Renal Protective Benefits of Magnesium Supplementation in the Long-Term Management of Patients with Type 2 Diabetes Mellitus

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Abstract

Magnesium deficiency is common in patients with type 2 diabetes mellitus (type 2 DM). When adequate magnesium supplementation is chronically given, patients with type 2 DM appear to have improved glucose control and may have delayed chronic complications. In addition, magnesium supplementation may slow the progression of chronic kidney disease (CKD) and decrease the risk of contrast-induced nephropathy in patients with type 2 DM. Keeping serum magnesium at 2.0 mEq/L or greater appears to accomplish these benefits for patients with type 2 DM. Periodically measuring serum magnesium and estimated glomerular filtration rate (eGFR) allows a physician to adjust the supplemental magnesium dose to accomplish these therapeutic goals while avoiding hypermagnesemia.

Keywords

Hypomagnesemia, Contrast-Induced Nephropathy, Renal Function, SGLT2 Inhibitors, Type 2 Diabetes Mellitus

1. Foreword

A challenge when reviewing the literature on magnesium in the treatment of patients with type 2 diabetes mellitus (type 2 DM) is that serum magnesium can be reported as millimoles per liter (mmol/L), milliequivalents per liter (mEq/L) or

milligrams per deciliter (mg/dL). When comparing articles and determining clinically significant levels, we chose to standardize by converting to mEq/L. For readers who are used to other reported measurements, mg/dL multiplied by 0.411 converts serum magnesium to mmol/L; mmol/L divided by 0.5 converts serum magnesium to mEq/L; mmol/L multiplied by 2.43 converts serum magnesium to mg/dL. Another challenge when reviewing the literature on magnesium and the treatment of patients with type 2 DM is some studies are in humans and others are in experimental animals. The source of the data will be stated. Further, some studies compared normal versus magnesium rich diets with no serum magnesium levels measured; these issues will be mentioned.

2. Introduction

Magnesium is the most common mineral deficiency affecting about one-half of the United States population [1]. Perhaps more importantly, magnesium deficiency has been associated with the development of type 2 DM and cardiovascular disease [2]. Magnesium is mainly an intracellular cation; extracellular magnesium represents only 1% of total body magnesium and is primarily found in serum and red blood cells. A serum magnesium level reflects extracellular magnesium and does not always correlate well with total body magnesium [1]. Eighty percent of patients with type 2 DM have low intracellular magnesium [3].

Normal serum magnesium is 1.5 - 2.2 mEq/L. The normal adult body contains about 25 grams (2058 mEq) of elemental magnesium divided almost equally between the soft tissues and skeletal cells [4]. About one-third of intracellular skeletal magnesium is on the surface of the bone and is exchangeable and thought to serve as a reservoir to maintain the extracellular magnesium in the blood.

There are many consequences when the blood glucose is chronically elevated in patients with type 2 DM. When the hemoglobin A1C (HbA1C) is greater than 7%, platelets are less responsive to the antiplatelet activity of aspirin, polymorphonuclear leukocytes are less effective against bacterial infection, red blood cells are more rigid resulting in microvascular damage, and renal tubular reabsorption of filtered magnesium is less effective resulting in renal loss of the cation [1]. Eighty percent of serum magnesium is filtered at the glomerulus, 15% - 20% is reabsorbed in the proximal tubule, 65% - 70% is reabsorbed in the thick ascending limb of the loop of Henle, and 5% - 10% is reabsorbed in the distal tubule [4]. When serum blood sugar is greater than 250 mg/dL, glycosuria occurs, and glycosuria inhibits the normal reabsorption of magnesium from the tubule resulting in renal loss of magnesium. Further, a well-known side effect of metformin is chronic diarrhea leading to magnesium loss [4]. Accordingly, magnesium deficiency is common in patients with type 2 DM [3]. The objective of this article is to review the metabolic and renal protective benefits of magnesium supplementation in the long-term management of patients with type 2 DM.

3. Metabolic Benefits of Magnesium Supplementation in the Long-Term Management of Patients with Type 2 Diabetes Mellitus

Magnesium deficiency has been found to be common in patients with type 2 DM [3]. Magnesium's physiological role is primarily related to enzyme activity with over 300 enzyme systems dependent on its presence as a coenzyme [1] [4]. A common symptom in patients with chronic magnesium deficiency is fatigue. Magnesium modulates glucose transport through the membranes and is a co-factor in several enzyme systems involving glucose oxidation. Magnesium deficiency may increase insulin resistance [2]. Magnesium is an ATPase allosteric coenzyme involved in inositol transport, which contributes to the prevention or delay of the development of diabetic chronic complications, such as peripheral neuropathy or coronary artery disease [5]. Inositol or myo-inositol is a carbocyclic sugar and is made naturally in the human body from glucose. It modulates cell signal transduction in response to hormones, neurotransmitters and growth factors and participates in osmoregulation.

Data linking magnesium deficiency to type 2 DM are conflicting. The current recommendations of the American Diabetes Association is that only type 2 diabetics at high risk of hypomagnesemia, such as patients with chronic diarrhea, alcoholism or older ages with poor diet, should have serum magnesium assessed, and such levels should be replaced only if hypomagnesemia is found.

Two well-designed studies that support a role for magnesium in the management of patients with type 2 DM are described. People with metabolic syndrome have been found to be at increased risk of coronary heart disease and type 2 DM. Magnesium appears to play an important role in glucose metabolism and insulin homeostasis [2]. Epidemiological studies suggest that deficient magnesium intake may be an independent risk factor for the development of type 2 DM. However, the longitudinal association of magnesium intake and insulin in metabolic syndrome had not been investigated until recently. In the Coronary Artery Risk Development In Young Adults (CARDIA) study, 4637 Americans, age 18 - 30 years, who were free from metabolic syndrome or type 2 DM at baseline were prospectively examined for the association of magnesium intake and incidence of metabolic syndrome during 15 years of followup [6]. Diet was assessed by an interviewer-administered quantitative food frequency questionnaire, and magnesium intake was derived from the nutrient database developed by the Minnesota Nutritional Coordinating Center. During the 15 years of followup, 608 cases of the metabolic syndrome were identified. Investigators found that magnesium intake from diet and supplements was inversely associated with incidence of metabolic syndrome after adjustment for major lifestyle and dietary variables as well as baseline status of each component of the metabolic syndrome. The inverse associations were not modified appreciably by gender or race. Magnesium intake was also inversely related to individual components of the metabolic syndrome and fasting insulin levels. This study suggests that young adults

with higher magnesium intake have lower risk of development of metabolic syndrome.

Results from meta-analysis indicate that magnesium supplementation shows no significant effects on the lipid profile of either patients with metabolic syndrome, type 2 DM or nondiabetic individuals.

Some observational studies suggest that chronic magnesium supplementation may be beneficial in the treatment of patients with type 2 DM, improving glycemic control and preventing the development of chronic complications [7]. In these studies, the amount of daily magnesium supplements and period of replacement varied. Subsequently, the beneficial effects of magnesium supplementation in increasing doses on the control of type 2 DM have been studied in 128 patients in a clinical randomized, double-blind, placebo-controlled trial. Baseline HbA1C was in the 9.0% - 10.7% range [8]. Patients received either placebo, 41.4 mEq or 82.8 mEq per day of magnesium oxide in 3 doses for 30 days. A control group of 57 blood donors was used in the study as reference values for serum and intramononuclear magnesium concentrations. Of the study patients at baseline, 48% had low serum magnesium and 31% had low intramononuclear magnesium levels. Intracellular magnesium with diabetes was significantly lower than in the control population. Intracellular magnesium levels were lower in patients with peripheral neuropathy and in patients with coronary artery disease. In the placebo and in the 41.4 mEq magnesium oxide daily groups, neither a change in serum or intracellular levels nor an improvement in glycemic control were observed over the 30 days. However, replacement with 82.8 mEq of magnesium oxide daily tended to increase serum, intracellular and urinary magnesium and caused a significant fall in fructosamine suggesting improving glucose control in the last 2 weeks of study. Fructosamine has evolved as a reasonable alternative to HbA1C measurement in situations where HbA1C measurement is not reliable because of the short duration of the study. The measurement of fructosamine provides information on glucose control within the previous 2 to 3 weeks. Large scale prospective, double-blind placebo-controlled trials with more prolonged supplemental magnesium in doses higher than usual are needed to confirm benefits in patients with type 2 DM, by improving glucose control and/or delaying chronic complications.

4. Importance of Magnesium in Protecting the Kidney in Patients with Type 2 Diabetes Mellitus

Disorders of magnesium, once considered rare, are now diagnosed with greater frequency as laboratory methods for measuring magnesium have been perfected. In clinical practice, magnesium deficiency is far more common than magnesium excess. Day-to-day maintenance of magnesium balance in the body is via the kidneys [4]. Under normal circumstances, little endogenous magnesium (1% - 2%) is eliminated by the fecal route. Since the kidney is primarily responsible for magnesium excretion, patients with chronic kidney disease (CKD) are at risk of

hypermagnesemia [9]. Because the failing kidney cannot excrete large loads of magnesium, magnesium-containing antacids and laxatives should be avoided. Magnesium deprivation may also cause renal potassium and chloride wasting that resists therapy until body magnesium stores are replenished. Since magnesium depletion impairs parathyroid hormone secretion and action, hypocalcemia becomes another chemical complication [4]. Because reductions of all three cations commonly complicate the same clinical setting, coexisting hypokalemia and hypocalcemia should prompt a search for hypomagnesemia.

Renal magnesium excretion is normally in balance with dietary magnesium intake [4]. Accordingly, tubular magnesium reabsorption is increased in response to dietary magnesium deprivation. Under conditions of magnesium deprivation, the normal kidney is able to conserve magnesium, restricting excretion to as low as 1 mEq per day, indicating that this organ has an important regulatory role. A number of clinical studies have reported diminished urinary magnesium excretion with a normal serum magnesium concentration in the face of dietary restriction suggesting that renal cells increase transport rate to appropriately conserve magnesium [10] [11]. These previously reported studies were in humans. The effect of short-term dietary magnesium restriction on tubular magnesium reabsorption has also been studied in rats [12]. These studies found that the kidney is very sensitive to decreases in magnesium intake and that this renal cellular adaptation was rapid (within 5 hours), specific (without effect on sodium or calcium) and sensitive (without change in serum magnesium concentration). Micropuncture studies indicate that this adaptive response is primarily located within the loop of Henle. The mechanism of this adaptation remains to be determined.

Hypomagnesemia (serum magnesium less than 2.0 mEq/L) is a common problem among patients with type 2 DM. Patients with type 2 DM frequently become hypomagnesemic due to poor control with glycosuria, due to development of an acquired renal tubular defect and from chronic diuretic therapy. The FDA has warned that hypomagnesemia can also occur with prolonged use of a proton pump inhibitor (PPI) and is usually accompanied by hypokalemia and hypocalcemia [13]. Patients also taking other medicines that cause hypomagnesemia, such as loop diuretics, may be at increased risk. The exact mechanism causing hypomagnesemia from prolonged use of a PPI is unknown, but they may interfere with magnesium absorption. When the PPI is stopped, serum magnesium returns to normal in less than two weeks.

A study was designed to determine whether an association exists between serum magnesium levels per se, not necessarily total body magnesium deficiency, and deterioration rate of renal function in patients with type 2 DM [14]. Two hundred and fifty-two males and 298 females with a mean followup of 62.5 ± 22.5 months were included. Patients belonging to lower serum magnesium groups for both genders had significantly worse slopes of 1/SCr-vs-t plot, independent of the presence of hypertension (HTN) or use of ACEI/ARB, diuretics, HMG-CoA reductase enzyme inhibitors or aspirin. With a multivariant regres-

sion analysis controlling for age, HbA1C and various components of the lipid profile, serum magnesium less than 1.5 mEq/L remained an independent predictor for the slope of 1/SCr-vs-t. A trend for worse proteinuria based on routine urinalysis was observed among patients belonging to the lowest serum magnesium group (less than 1.5 mEq/L). This is the first clinical study to suggest that lower serum magnesium levels per se may be predictive of a more rapid deterioration of renal function and possibly the presence of proteinuria. This study was limited by its retrospective nature and predominantly Hispanic population. Nevertheless, it raises two important clinical questions: 1) does hypomagnesemia have a direct impact on the progression of renal disease; and 2) does magnesium supplementation have any renal protective benefit in patients with type 2 DM? Prospective studies to examine the benefit of magnesium supplementation to keep serum magnesium greater than 2.0 mEq/L on the development of diabetic nephropathy and progression of renal disease in patients with type 2 diabetes are warranted.

Contrast-induced nephropathy (CIN) is an injury to the kidney as a result of exposure to intravascular iodinated contrast medium [15]. It represents an increasing healthcare burden and challenge as the frequency of diagnostic imaging and interventional studies increase, particularly among populations at risk of developing CIN [16]. As the population ages, decreased renal function and increased atherosclerotic cardiovascular disease become more prevalent. An increasing incidence of obesity with resultant metabolic syndrome and/or type 2 DM also increases the population at risk for CIN. Coronary artery disease is a major complication of type 2 DM. Thus, patients with type 2 DM often require coronary angiography and coronary intervention and are at risk of CIN [17].

Hypomagnesemia (serum magnesium less than 2.0 mEq/L) may also be a correctable risk factor for CIN in patients with renal dysfunction (creatinine clearance less than 60 mL/min). This risk factor warrants further study because many patients become hypomagnesemic from chronic diuretic therapy in combination with low dietary magnesium intake. In addition, patients after renal transplantation who were given cyclosporine usually develop a cyclosporine-mediated renal tubular defect, which causes them to excrete excess magnesium and become hypomagnesemic [18]. Cancer patients undergoing chemotherapy with regimens containing cisplatin are at significant risk for hypomagnesemia [19]. Cisplatin impairs renal reabsorption of magnesium because it is directly toxic to the ascending limb of the loop of Henle and distal tubule [20]. Approximately 90% of patients who receive this nephrotoxic antineoplastic drug will become hypomagnesemic unless corrective supplementation is initiated. Further, magnesium supplementation when beginning cisplatin chemotherapy has been shown to attenuate the nephrotoxic effects of the antineoplastic drug [21]. Patients with longstanding type 2 DM also may acquire a renal tubular defect for magnesium and become hypomagnesemic. Comparing patients with a creatinine clearance of 60 mL/min with a serum magnesium of 1.9 ± 0.04 mEq/L versus patients with serum magnesium of 1.3 ± 0.03 mEq/L ($p < 0.05$), magnesium has been shown

to protect the kidney from contrast media-produced free radicals [22]. The renal protective effect of magnesium is likely multifactorial. Besides its role as an antioxidant and a coenzyme for compensatory sodium-potassium adenosine triphosphatase, magnesium has calcium channel blocking properties [15]. Based on these results, magnesium replacement in hypomagnesemic patients may be indicated before diagnostic studies using contrast medium.

5. Perspective: Other Metabolic Challenges in the Long-Term Management of Patients with Type 2 Diabetes Mellitus

Because patients have metabolic syndrome for many years before being diagnosed as type 2 DM, many often have evidence of early coronary artery disease with elevated coronary calcium scores and are at increased risk for the development of cardiovascular disease with adverse clinical outcomes, including disabilities and mortality. Accordingly, statin therapy is recommended. The use of statins is associated with reduced cardiovascular risk with studies of primary and secondary prevention, and the reduction is directly proportional to the reduction in LDL-C. However, in both observational studies and randomized trials, statin use has been associated with elevated blood sugar and increased risk of diabetes, particularly in a population at high risk of type 2 DM [23] [24]. The mechanism by which statins increase blood sugar remains unclear. Of note, magnesium is a natural regulator of HMG-CoA reductase. A new expanded meta-analysis of 23 trials with a total of more than 150,000 participants confirms the long-known effect that statin treatment has on raising blood glucose levels and causing type 2 DM, but it also documented that these effects are small and any risk they pose to statin users is dwarfed by the cholesterol-lowering effect of statins and their ability to reduce risk for atherosclerotic cardiovascular disease (ASCVD) [24]. The data show that high-intensity statin treatment (atorvastatin at a daily dose of at least 40 mg or rosuvastatin at a daily dose of at least 20 mg) led to an average increase in HbA1C levels of 0.08 percentage points among patients without diabetes and 0.24 percentage points among patients already diagnosed with type 2 DM. Blood glucose levels rose by an average of less than 1 mg/dL in those without diabetes and by an average of about 4 mg/dL in those with diabetes. Patients who received low- or moderate-intensity statin regimen had significant but smaller increases. Thus, a small number of people cross the diabetic threshold of a HbA1C of 6.5%, which is set somewhat arbitrarily based on an increased risk for developing retinopathy. Two examples from the meta-analysis to illustrate the relatively small risk posed by statin therapy compared to its potential benefits are: 1) treating 10,000 people for 5 years with a high-intensity statin regimen with established ASCVD (secondary prevention) would result in an increment of 150 extra people developing diabetes because of the hyperglycemic effect of statins compared with an expected prevention of 1000 ASCVD events; 2) among 10,000 people at high ASCVD risk and taking a high-intensity statin regimen for primary prevention for 5 years of treatment would result in

approximately 130 extra cases of incident of type 2 DM while preventing about 500 ASCVD events. Thus, patients at high risk for type 2 DM should be monitored during statin therapy. Since the benefit of cardiovascular risk reduction prevails, even in statin-associated diabetic patients, there is no evidence to date that this risk should change the recommendations for starting statin therapy in individuals based on guidelines [25] [26].

Patients with type 2 DM often also have HTN. The body of evidence implicating magnesium as a major determinant of blood pressure is inconsistent. In a meta-analysis of 20 clinical trials, there were nonsignificant reductions in systolic and diastolic blood pressure of 0.6 and 0.8 mmHg, respectively. In a more recent trial, elemental magnesium 360 mg (29.6 mEq) daily for three months caused minor 2 mmHg/1.78mmHg lowering of blood pressure. Overall, it appears that magnesium supplementation in the general population has little impact on blood pressure. However, the combination of elevated magnesium and elevated potassium intake along with reduced sodium intake and fruits and vegetables is more effective, lowering blood pressure significantly approximately 5.6 mmHg/2.8mmHg [27] [28] [29].

Choice of antihypertensive agents in type 2 DM patients is important with potential long-term benefits. ACE inhibitors and ARBs tend to decrease the risk of type 2 DM in patients with HTN. Dihydropyridine calcium channel blockers and mineralocorticoid receptor blockers have a neutral effect on risk of type 2 DM in patients with HTN. If thiazide-type diuretics are used in lower doses (*i.e.*, 12.5 mg) and serum potassium is kept in the 4.0 - 5.0 mEq/L range and serum magnesium is kept above 2.0 mEq/L, the risk of developing hyperglycemia from thiazide-type diuretics is low [30]. Both weight loss and regular low resistance exercise, such as walking 30 minutes a day, decrease the risk of patients with HTN of developing type 2 DM. The protective effect of increasing physical activity is even observed in subjects with an excessive BMI and elevated glucose levels [31]. Physical activity and weight control are critical factors in type 2 DM prevention in patients with either normal or impaired glucose regulation. In a recent report, less than 2% of outpatients with obesity and type 2 DM and potentially eligible for bariatric surgery underwent the procedure [32]. Results showed that patients who had bariatric surgery had an average weight loss of 11.8 ± 18.5 kg, and their use of medications was reduced: 10.2% were on lower glucose-lowering medications and 8.4% were on fewer antihypertensive medications. The median post-surgical followup was 722 days. Bariatric surgery has become safer and more accessible. Given the large portion of patients potentially eligible for metabolic surgery, this report demonstrates a substantial missed opportunity to impact weight loss, diabetes management and cardiovascular risk factor control.

Since the release of carvedilol in 1997, there has been much research interest in the use of this beta-blocker. Carvedilol is a third generation, fat-soluble molecule that combines properties of a nonspecific beta-blocker and a specific alpha-1 blocker in a ratio of 2:3. Carvedilol also possesses antioxidant properties

and has no intrinsic sympathomimetic activity. Carvedilol is approved for the treatment of HTN. Type 2 DM is an important and independent predictor of cardiovascular morbidity and mortality in patients with HTN. Increased sympathetic nervous system activity has been implicated in the pathogenesis of HTN and type 2 DM [33]. Traditional beta-blockers have been shown to worsen insulin resistance, facilitate weight gain and increase triglycerides. Carvedilol in hypertensive patients with type 2 DM already receiving renin-angiotensin system blockade has been found during a six-month trial to have a neutral effect on insulin resistance, weight and triglycerides [34]. In these hypertensive, diabetic patients, progression to microalbuminuria was less frequent with carvedilol than metoprolol tartrate. These favorable metabolic and renal protective effects suggest carvedilol is a better choice compared to traditional beta-blockers in the long-term treatment of high-risk patients. In addition, in patients with renal impairment, dose adjustment of carvedilol is not necessary. Thus, clinical trials have demonstrated the metabolic and renal protective effects of carvedilol.

In summary, decreasing the risk of type 2 DM in hypertensive patients should be of concern to physicians, particularly when high-risk patients face many years to decades with the disease. Further, preventing, or at least slowing, the transition from impaired glucose intolerance to type 2 DM using weight loss, regular aerobic exercise, ACE inhibitors, ARBs, carvedilol and possibly magnesium supplementation are important recommendations with long-term benefits for patients. While not the focus of this review, supplemental magnesium to keep serum magnesium at 2.0 mEq/L or greater also decreases the risk of patients developing atrial fibrillation, helps in rate control in patients with persistent atrial fibrillation, suppresses ventricular ectopy, and decreases the risk of sudden cardiac death [35] [36].

6. Perspective: Other Pharmacological Agents in the Long-Term Management of Type 2 Diabetic Chronic Kidney Disease

A new joint statement by the American Diabetes Association and major international nephrology organizations encourage clinicians caring for patients with type 2 DM to have a more aggressive approach to using combined medical treatments proven to slow the relentless progression of CKD [37]. It reemphasizes the key role of current first-line treatment with a renin-angiotensin system inhibitor (an ACE inhibitor or ARB), metformin and a statin. The statement elevates treatment with an agent from the sodium-glucose cotransporter-2 (SGLT2) inhibitor class to first-line for patients with diabetes and laboratory-based evidence of advancing CKD. There are increasing reports demonstrating the cardiorenal protective effects of SGLT2 inhibitors, even in patients without diabetes [38] [39] [40]. The new statement also urges clinicians to consider adding treatment with the new nonsteroidal mineralocorticoid receptor antagonist finerenone for further renal protection in patients suitable for treatment with this agent (*i.e.*, normal level of serum potassium) [41]. The statement also recom-

mends the second-line addition of a glucagon-like peptide-1 (GLP-1) receptor agonist as the best add-on for any patient who needs additional glycemic control on top of metformin and an SGLT2 inhibitor. Adoption of this evidence-based approach by U.S. clinicians will both increase the number of agents that many patients receive and increase the cost and complexity of patient care.

Lifestyle optimization is a core first-line element of managing patients with type 2 DM and CKD, including a healthy diet, regular aerobic exercise, smoking cessation and weight control. Other important steps for management include optimization of blood pressure, glucose and lipids.

Guidelines recommend annual screening of patients with type 2 DM for the onset of advanced CKD. Patients whose estimated glomerular filtration rate (eGFR) drops below 60 mL/min/1.73m^2 as well as those who develop microalbuminuria with a urinary albumin/creatinine ratio of at least 30 mg/g or both for more than three months have a stage of CKD that warrants the drug interventions recommended in the guidelines [37]. For more than three decades, medications that block the renin-angiotensin system (RAS) have been the most widely used strategy to slow CKD progression. The medications lower both systemic blood pressure and intraglomerular pressure, and they may prevent glomerulosclerosis. The degree of albuminuria reductions by RAS blockers appear to correlate with the ability of these agents to preserve renal function. When patients with a reduced eGFR, but normal albuminuria (most patients with CKD) receive RAS blockers, they do not have the same level of renal protection as those with clinically significant albuminuria. The reduced benefit from RAS blockers in patients with CKD who have normal albuminuria emphasize the need for additional approaches to renal protection, such as magnesium and SGLT2 inhibitors. The SGLT2 protein in the proximal tubule of the kidney mediates both glucose and sodium reabsorption. Inhibition of SGLT2 results in glucosuria, osmotic diuresis and modest natriuresis. A plausible mechanism for renal protection is that increased sodium delivery to the macula densa cells of the juxtaglomerular apparatus, through glomerulotubular feedback, causes afferent arteriolar vasoconstriction, decreases hyperfiltration and intraglomerular pressure and, thus, preserves glomeruli [42]. While originally developed to treat hyperglycemia in patients with type 2 DM, SGLT2 inhibitors have been shown to lower risk of progression of kidney disease or death from cardiovascular causes compared to placebo [38] [39] [40]. In most trials, SGLT2 inhibitors were added to RAS inhibitors since RAS inhibitors should be standard of care. Further, a retrospective post-hoc analysis of 20 SGLT2 inhibitor trials in patients with type 2 DM found an almost 40% decrease in incidence of kidney stones in treated patients versus placebo during a median 1.5 years of treatment [42]. If this association is proven, SGLT2 inhibitors in the future may be used to decrease the risk of kidney stones, at least in patients with type 2 DM and maybe also in patients without diabetes.

A final question to be addressed in this review is whether SGLT2 inhibitors can be used in the treatment of hypomagnesemia. There are close links between hypomagnesemia and metabolic syndrome and between hypomagnesemia and

type 2 DM. Administration of SGLT2 inhibitors has been found to decrease insulin resistance, increase serum magnesium levels and reduce urinary magnesium excretion [43]. A meta-analysis of 18 randomized controlled trials, including 15,309 patients with type 2 DM, showed that SGLT2 inhibitors increased serum magnesium levels by 0.08 - 0.2 mEq/L in individuals without CKD. This increase in serum magnesium was noted after at least 5 weeks of SGLT2 inhibitor therapy and thought to be due to improved renal magnesium reabsorption. There are a number of case reports of patients with intractable hypomagnesemia despite significant magnesium supplementation which improved when SGLT2 inhibitors were added, again due to improved magnesium reabsorption [44].

7. Magnesium Requirements and Supplementation

In the long-term management of patients with type 2 DM, keeping the serum magnesium level at 2.0 mEq/L or greater appears to accomplish metabolic and renal protective benefits. Changes in the American diet over the last half of the 20th century have resulted in increasing prevalence of magnesium deficiency [45]. According to data from the National Health and Nutritional Examination Survey (NHANES) 1999-2000, the median magnesium intake among men and women (ages 31 to 65 in the United States) is below the recommended daily allowance of 420 mg (34.6 mEq) for men and 320 mg (26.3 mEq) for women, indicating that more than half of American adults do not receive enough magnesium in their diet. This is, in part, a result of the evolution of the American diet from natural food products to processed foods. Magnesium is found naturally in many foods and added to some fortified foods. Magnesium-rich foods include nuts, legumes, seeds and whole grains, brown and wild rice, vegetables including yellow corn and dark leafy vegetables (the greener the leaf, the higher the magnesium content), milk, yogurt, some other milk products, eggs, fruits, including bananas, dates and avocados, dark chocolate, fatty fish and other seafood, meat and poultry. Hard water contains more magnesium than soft water. A diet high in fat may cause less magnesium to be absorbed.

Magnesium supplementation is safe, if serum levels are monitored periodically to be certain that the recommended therapeutic goal of at least 2.0 mEq/L is achieved and for early detection of hypermagnesemia to avoid serious outcomes [9]. Magnesium oxide 400 mg (240 mg or 19.8 mEq elemental magnesium) daily is commonly added after magnesium-rich foods and may be increased as needed with diarrhea occurring at higher doses in some patients. The magnesium in magnesium oxide 400 mg tablets is converted to free magnesium and magnesium chloride at the low pH of the stomach for absorption in the small intestine. When magnesium supplementation is started, patients usually notice less fatigue within 2 to 3 weeks, likely due to resolution of intracellular magnesium deficiency. Similarly, blood sugar has been noted to improve within 2 to 3 weeks of supplementation [8]. Once intracellular magnesium has been replaced, serum (extracellular) magnesium levels can be measured periodically as a guide for long-term supplementation.

Magnesium supplements are available in the forms of tablets, extended-release tablets, capsules, liquid-filled capsules, powder, powder for solution, chewable tablets and oil. Thus, magnesium can be administered orally, intravenously or topically. Forms of magnesium supplements available besides magnesium oxide include magnesium citrate, magnesium lactate, magnesium chloride, magnesium malate, magnesium tartrate and magnesium sulfate. Companies may advertise specific properties of the different magnesium preparations they offer, but their claims may be anecdotal or based on limited studies and more research is needed in humans to confirm results found in animal studies. Moreover, comparing results on bioavailability of inorganic or organic forms of magnesium is complicated given the disparity in the establishment and control of the dependent and independent variables [46]. Thus, the choice of the form of magnesium supplementation may be based on mode of delivery, affordability, side effects or efficacy.

Besides supplementation to replace magnesium loss from drugs, such as metformin, diuretics and proton-pump inhibitors, attention must be paid to magnesium supplementation and its effects or interactions with other drugs, such as certain antibiotics and bisphosphonates [47].

8. Summary and Conclusions

Magnesium deficiency is common in patients with type 2 DM. Magnesium's physiological role is primarily related to enzymatic activity with over 300 enzyme systems dependent on its presence as a coenzyme. A common symptom in patients with chronic magnesium deficiency is fatigue. When adequate magnesium supplementation is chronically given, patients with type 2 DM appear to have improved glucose control and delayed chronic complications. In addition, magnesium supplementation may slow the progression of CKD and decrease the risk of contrast-induced nephropathy in patients with type 2 DM. Keeping serum magnesium at 2.0 mEq/L or greater appears to accomplish these benefits for patients with type 2 DM. Periodically measuring serum magnesium and eGFR allows the physician to adjust the supplemental magnesium dose to accomplish this therapeutic goal while avoiding hypermagnesemia. The apparent metabolic and renal protective benefits of magnesium supplementation in patients with type 2 DM warrant further study in large-scale prospective, double-blind placebo-controlled trials. If these benefits are confirmed, magnesium supplementation should be added to type 2 DM therapy guidelines.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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