Hypomagnesemia in Patients with Type 2 Diabetes

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Hypomagnesemia has been reported to occur at an increased frequency among patients with type 2 diabetes compared with their counterparts without diabetes. Despite numerous reports linking hypomagnesemia to chronic diabetic complications, attention to this issue is poor among clinicians. This article reviews the literature on the metabolism of magnesium, incidence of hypomagnesemia in patients with type 2 diabetes, implicated contributing factors, and associated complications. Hypomagnesemia occurs at an incidence of 13.5 to 47.7% among patients with type 2 diabetes. Poor dietary intake, autonomic dysfunction, altered insulin metabolism, glomerular hyperfiltration, osmotic diuresis, recurrent metabolic acidosis, hypophosphatemia, and hypokalemia may be contributory. Hypomagnesemia has been linked to poor glycemic control, coronary artery diseases, hypertension, diabetic retinopathy, nephropathy, neuropathy, and foot ulcerations. The increased incidence of hypomagnesemia among patients with type 2 diabetes presumably is multifactorial. Because current data suggest adverse outcomes in association with hypomagnesemia, it is prudent to monitor magnesium routinely in this patient population and treat the condition whenever possible.

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Type 2 diabetes accounts for approximately 90 to 95% of all diagnosed cases of diabetes (1). In addition to hyperosmolar coma and ketoacidosis, patients with type 2 diabetes may have cardiovascular disease, nephropathy, retinopathy, and polyneuropathy. With its associated complications, diabetes was reported to be the sixth leading cause of death listed on US death certificates in 2000 (1). The treatment of the patients with diabetes requires a multidisciplinary approach whereby every potential complicating factor must be monitored closely and treated. In particular, although hypomagnesemia has been reported to occur with increased frequency among patients with type 2 diabetes, it is frequently overlooked and undertreated.

Magnesium and Cell Physiology

Magnesium is the fourth most abundant cation in the human body and the second most abundant intracellular cation. It may exist as a protein-bound, complexed, or free cation. It serves as a co-factor for all enzymatic reactions that require ATP and as a key component in various reactions that require kinases. It is also an essential enzyme activator for neuromuscular excitability and cell permeability, a regulator of ion channels and mitochondrial function, a critical element in cellular proliferation and apoptosis, and an important factor in both cellular and humoral immune reactions (reviewed in references [2–6]).

Diagnosis of Hypomagnesemia

Traditionally, hypomagnesemia refers to a low serum magnesium (Mg) concentration because this measurement has long been readily available. Clinically, hypomagnesemia may be defined as a serum Mg concentration ≤1.6 mg/dl or >2 SD below the mean of the general population (7,8). However, because Mg is mostly an intracellular cation, it has been questioned whether one can use measurements of serum Mg concentrations to study the impact of Mg on various physiologic conditions. Some investigators, instead, have used measurements of intracellular Mg concentrations. Clinically, it has been suggested that in a patient with suspected Mg deficiency, a low serum Mg concentration is sufficient to confirm the diagnosis. If the serum Mg level is normal in the same patient, then other more sensitive tests should be performed (reviewed in references [5,9]). Although controversies still exist as to how hypomagnesemia is best gauged, our current understanding on the clinical impact of hypomagnesemia in human is influenced by studies that have relied predominantly on the measurements of serum Mg concentrations.

Incidence of Hypomagnesemia among Patients with Type 2 Diabetes

Hypomagnesemia, defined by low serum Mg concentrations, has been reported to occur in 13.5 to 47.7% of nonhospitalized patients with type 2 diabetes compared with 2.5 to 15% among

their counterparts without diabetes (7,8,10–13). The wide range in the reported incidence of hypomagnesemia most likely reflects the difference in the definition of hypomagnesemia, techniques in Mg measurements, and the heterogeneity of the selected patient cohort. In terms of gender difference, it is interesting to note that independent studies have reported a higher incidence of hypomagnesemia in women compared with men, at a 2-to-1 ratio (7,14). In addition, men with diabetes may have higher ionized levels of Mg (15).

Hypomagnesemia and Diabetes: Cause and Effect

Not only has hypomagnesemia been associated with type 2 diabetes, but also numerous studies have reported an inverse relationship between glycemic control and serum Mg levels (7,10,16–19). Although many authors have suggested that diabetes *per se* may induce hypomagnesemia, others have reported that higher Mg intake may confer a lower risk for type 2 diabetes (20–23). It is interesting that the induction of Mg deficiency has been shown to reduce insulin sensitivity in individuals without diabetes, whereas Mg supplementation during a 4-wk period has been shown to improve glucose handling in elderly individuals without diabetes (18,24). In patients with type 2 diabetes, oral Mg supplementation during a 16-wk period was suggested to improve insulin sensitivity and metabolic control (25). The mechanisms whereby hypomagnesemia may induce or worsen existing diabetes are not well understood. Nonetheless, it has been suggested that hypomagnesemia may induce altered cellular glucose transport, reduced pancreatic insulin secretion, defective postreceptor insulin signaling, and/or altered insulin–insulin receptor interactions (26–29). Not all studies, however, observed a correlation between glycemic control and serum Mg levels or improvement of diabetic control with Mg replacement (11,30–32). The conflicting data may reflect different study designs and populations studied.

Hypomagnesemia and Adverse Clinical Associations in Type 2 Diabetes

Hypomagnesemia at the Cellular Level

There is considerable evidence to suggest that hypomagnesemia may adversely affect various aspects of cellular physiology. Available data suggest that low Mg levels may promote endothelial cell dysfunction and thrombogenesis *via* increased platelet aggregation and vascular calcifications (33). Low Mg levels also may lead to the induction of proinflammatory and profibrogenic response (34–36), reduction of protective enzymes against oxidative stress (37), induction or augmentation of vasoconstriction and hypertension (38–40), and stimulation of aldosterone (41,42), among others. Moreover, because Mg is crucial in DNA synthesis and repair (43), it is possible that Mg deficiency may interfere with normal cell growth and regulation of apoptosis.

Hypomagnesemia in the Clinical Setting

Clinically, there are significant data linking hypomagnesemia to various diabetic micro- and macrovascular complications.

Cardiovascular. In a study that involved 19 normotensive individuals without diabetes, 17 hypertensive individuals without diabetes, and 6 hypertensive individuals with diabetes, Resnick *et al.* (44) documented the lowest mean intracellular Mg concentration among the last group. Similarly, based on data from the Atherosclerosis Risk in Communities (ARIC) Study, a multicenter, prospective cohort study that lasted 4 to 7 yr and involved 13,922 middle-aged adults who were free of coronary heart disease at baseline, an inverse association between serum Mg and the risk for coronary heart disease was observed among men with diabetes (45).

Diabetic Retinopathy. The link between hypomagnesemia and diabetic retinopathy was reported in two cross-sectional studies that involved both "insulin-dependent" patients and patients with type 2 diabetes. Not only did patients with diabetes have lower serum Mg levels compared with their counterparts without diabetes, but also the serum Mg levels among the cohort with diabetes had an inverse correlation with the degree of retinopathy (46,47). A similar link, however, was not observed when Mg was measured within mononuclear cells. In a study that involved 128 patients with type 2 diabetes and poor glycemic control (glycosylated hemoglobin >8.0%), intramononuclear Mg concentrations were not observed to be lower among those with diabetic retinopathy but rather among those with neuropathy and coronary disease (11).

Foot Ulcerations. Given the link between hypomagnesemia and risk factors for the development of diabetic foot ulcers (*e.g.*, polyneuropathy, platelet dysfunction), Rodriguez-Moran and Guerrero-Romero (48) suggested that hypomagnesemia may be associated with an increased risk of diabetic foot ulcers. Indeed, they observed a higher incidence of hypomagnesemia among their patients with diabetic foot ulcers compared with those without the condition (93.9% of the 33 patients with diabetic foot ulcers compared with 73.1% of the 66 patients without diabetic foot ulcers; $P = 0.02$).

Nephropathy. In a comparative study that involved 30 patients who had type 2 diabetes without microalbuminuria, 30 with microalbuminuria, and 30 with overt proteinuria, Corsonello *et al.* (49) observed a significant decrease in serum ionized Mg in both the microalbuminuria and overt proteinuria groups compared with the nonmicroalbuminuric group. Accordingly, in a recent retrospective study, an association between low serum Mg levels and a significantly faster rate of renal function deterioration in patients with type 2 diabetes was reported (7).

Others. Finally, there also are data to suggest the association between hypomagnesemia and other diabetic complications, including dyslipidemia and neurologic abnormalities (6). Because hypomagnesemia has been linked to various micro- and macrovascular complications, a better understanding of Mg metabolism and efforts to minimize hypomagnesemia in the routine management of diabetes are warranted.

Normal Mg Metabolism

Gastrointestinal Metabolism

On an average American diet, 250 to 350 mg of Mg is consumed daily. Twenty-five to 60% of dietary Mg is absorbed in the gastrointestinal tract. Gastrointestinal absorption occurs predominantly in the small intestines *via* paracellular simple diffusion at high intraluminal concentrations and active transcellular uptake *via* Mg-specific transporters at low concentrations (reviewed in reference [50]). Active intestinal Mg absorption is presumed to involve transient receptor potential channel melastatin 6 (TRPM6), which is expressed along the brush border membrane of the small intestine (51). Mutations of TRPM6 have been reported to be associated with hypomagnesemia with secondary hypocalcemia (52,53).

Renal Metabolism

Glomerular Filtration. Approximately 70 to 80% of plasma Mg is ultrafilterable in the ionic form (70 to 80%) and complexed with anions such as phosphate, citrate, and oxalate (20 to 30%) (54,55). The ultrafilterability of Mg depends on glomerular filtration, volume status, various metabolic states that would enhance the selection for ionized Mg (*e.g.*, acidemia, reduced serum content of negatively charged species), and the integrity of the glomerular basement membrane.

Proximal Tubules. Once Mg is filtered through the glomerulus, 15 to 25% is reabsorbed in the proximal tubules (Figure 1). Reabsorption at the proximal tubule is mainly passive and proportional to sodium and water reabsorption, although at a lower rate (55).

Loop of Henle. Approximately 65 to 75% of the Mg filtered load is reabsorbed *via* the paracellular pathway in the thick ascending limb of the loop of Henle (TAL) (55) (Figure 1). Paracellular Mg reabsorption at this nephron segment has been suggested to be facilitated by claudin 6, also known as paracel-

lin 1. Paracellin 1 is a tight junction protein whose mutation is associated with severe hypomagnesemia with hypercalciuria and nephrolithiasis (56,57). Parathyroid hormone, calcitonin, glucagon, and antidiuretic hormone have been suggested to enhance Mg transport in the TAL *via* the second messenger cAMP (55). Insulin also has been implicated to play a role at this nephron segment by increasing the favorable transepithelial potential difference for Mg reabsorption (58).

Distal Convoluted Tubules. The distal convoluted tubule (DCT) reabsorbs approximately 5 to 10% of the filtered Mg *via* an active and regulated transcellular pathway (Figure 1). Although this is a low percentage of the filtered Mg load, it represents 70 to 80% of Mg that is delivered from the TAL. In addition, because a negligible amount of Mg is reabsorbed distal to this segment, Mg reabsorption at the DCT is of great importance because it determines the final urinary Mg concentration (50).

Recently, Mg reabsorption at the DCT was shown to occur *via* the transient receptor potential channel melastatin TRPM6 (Figure 2) (52,53,59,60). It has been postulated that upon entry into the cells, Mg binds to divalent-binding proteins such as parvalbumin or calbindin-D28K for transport across the cell to the basolateral membrane, where Mg is taken into the interstitium by a basolateral Na^{2+}/Mg^{2+} exchanger and/or ATP-dependent Mg pump (51,61–63).

It is interesting that the regulation of magnesium reabsorption at the DCT was studied extensively before the actual identification of TRPM6 (Figure 2) (62). Peptide hormones such as parathyroid hormone (PTH), calcitonin, glucagon, and vasopressin all have been implicated. The mediating mechanisms are unknown but seem to involve, in part, stimulation of cAMP release and activation of protein kinase A, phospholipase C, and protein kinase C. Insulin also has been suggested to enhance intracellular Mg uptake, presumably *via* tyrosine kinase. Moreover, insulin may stimulate the production of cAMP and
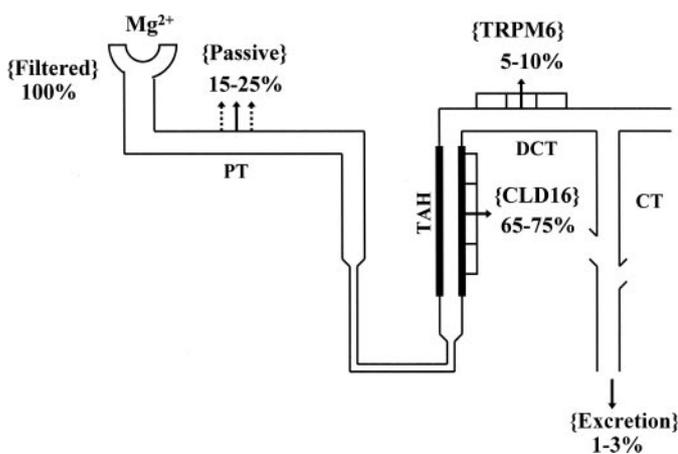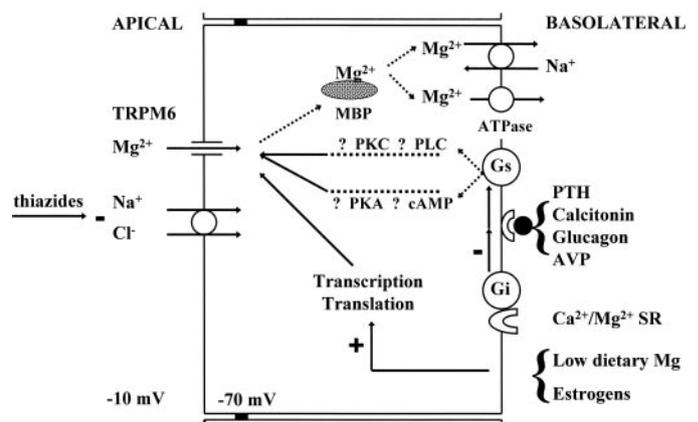

Figure 1. Renal magnesium (Mg) handling. After glomerular filtration, ionized magnesium is reabsorbed passively in parallel to sodium reabsorption at the proximal tubules (PT); paracellularly *via* claudin 6 (CLD16; paracellin 1) at the thick ascending limb of the loop of Henle (TAH); and transcellularly *via* transient receptor potential channel melastatin (TRPM6) at the distal convoluted tubule (DCT). CT, collecting tubules.

Figure 2. Regulation of Mg handling at the DCT. AVP, arginine vasopressin; Ca^{2+}/Mg^{2+} SR, Ca^{2+}/Mg^{2+} sensing receptor; G_i, inhibitory G protein; G_s, stimulatory G protein; MPB, Mg^{2+}-binding protein; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; PTH, parathyroid hormone. Adapted from reference (62), with permission.

potentiate Mg uptake *via* other cAMP-dependent hormones, including PTH (62). In addition, the Ca^{2+}/Mg^{2+} sensing receptor on the basolateral side may modulate hormone-stimulated Mg transport through G-protein coupling (62). Finally, low dietary Mg intake and estrogens have been shown to upregulate renal TRPM6 expression and reduce urinary Mg excretion (64).

Possible Causes of Hypomagnesemia in Type 2 Diabetes

Hypomagnesemia in the patient with diabetes may result from poor oral intake, poor gastrointestinal absorption, and enhanced renal Mg excretion (Table 1).

Gastrointestinal Causes

Diabetic autonomic neuropathies that may reduce oral intake and gastrointestinal absorption include esophageal dysfunction, gastroparesis, and diarrhea (65). Whether gastrointestinal Mg absorption *via* TRPM6 is reduced in the patient with diabetes is not known.

Renal Causes

Enhanced Filtered Load. In the patient with diabetes, the ultrafilterable Mg load may be enhanced by glomerular hyperfiltration, recurrent excessive volume repletion after hyperglycemia-induced osmotic diuresis, recurrent metabolic acidosis associated with diabetic ketoacidosis, and hypoalbuminemia (50). The last two conditions may increase the serum ionized Mg fraction and, hence, ultrafilterable Mg load and subsequent

Table 1. Possible causes of hypomagnesemia in patients with type 2 diabetes

Decreased intake
  poor oral intake
  esophageal dysfunction
  diabetic gastroparesis
Enhanced gastrointestinal loss
  diarrhea as a result of autonomic dysfunction
Enhanced renal magnesium loss
  enhanced filtered load
    glomerular hyperfiltration
    osmotic diuresis (glucosuria)
    volume expansion as a result of excessive volume
      replacement
    metabolic acidosis (diabetic ketoacidosis)
    hypoalbuminemia
    microalbuminuria and overt proteinuria
  reduced renal reabsorption
    endocrinologic dysfunction: insulin deficiency or
      resistance
    metabolic acidosis (diabetic ketoacidosis)
    electrolyte abnormalities: phosphate and potassium
      depletion
    diuretics
    others

urinary loss. In addition, it is conceivable that significant microalbuminuria and overt proteinuria among patients with diabetic nephropathy may contribute to renal Mg wasting as a result of protein-bound magnesium loss.

Enhanced Tubular Flow. Overly aggressive volume reexpansion and glomerular hyperfiltration also may induce renal Mg wasting at the proximal tubule and TAL, independent of the filtered load. Because Mg reabsorption parallels sodium reabsorption in the proximal tubules, volume expansion can decrease both sodium and Mg reabsorption at this level. Similarly, a high tubular flow through the TAL may reduce Mg reabsorption at this segment (50).

Reduced Tubular Reabsorption. Because insulin has been implicated in enhancing Mg reabsorption at the TAL, insulin deficiency or resistance in the diabetic state can promote Mg wasting at this nephron segment (58). The expression of paracellin 1 in TAL, however, has not been shown to be increased in diabetic rats (66).

In the same diabetic rat model, Lee *et al.* (66) revealed that TRPM6 expression in the DCT is not reduced but rather enhanced. This is thought to be a compensatory mechanism for the increased Mg load that is delivered to the DCT or blunted activity of the TRPM6 channel in the diabetic state. Accordingly, despite the increase in TRPM6 expression, overall renal Mg wasting is observed.

Metabolic Disturbances

Various metabolic disturbances that are associated with diabetes also have been suggested to promote urinary Mg excretion (67–69).

Hypokalemia. At the TAL segment, hypokalemia may reduce $Na^+-K^+-2Cl^-$ co-transport activity, the associated potassium extrusion through the potassium channel ROMK, and resultant diminution of the favorable transmembrane voltage that is required for paracellular Mg reabsorption. In addition, there is evidence to suggest that cellular potassium depletion may diminish Mg reabsorption at the DCT by yet unclear mechanisms (67).

Hypophosphatemia. Both micropuncture studies in phosphate-depleted dogs and *in vitro* studies involving phosphate-depleted mouse DCT cells have demonstrated reduced Mg uptake (68,69). Phosphate-induced reduction in cellular uptake of Mg is believed to be a posttranslational effect because the alteration in Mg uptake could be observed within 30 min of phosphate depletion.

Metabolic Acidosis. In addition to its role in increasing serum ionized Mg concentration and, hence, ultrafilterable Mg load for renal excretion, metabolic acidosis has been suggested to enhance protonation of the Mg channel in the DCT and subsequent inhibition of cellular Mg uptake (70). More recently, Nijenhuis *et al.* showed (71) reduced expression of TRPM6 with induced chronic metabolic acidosis in mice.

Insulin Deficiency and/or Resistance. As previously discussed, insulin deficiency or resistance may exacerbate renal Mg wasting because insulin has been shown to have antimagnesiuric effects in both the TAL and the DCT (55,62).

Use of Diuretics

The common use of diuretics among patients with diabetes also may contribute to magnesiuria. The degree of magnesiuria is traditionally thought to be lower for thiazides compared with loop diuretics (72–74). This difference has been explained by the site of action of the two types of diuretics because a smaller amount of intraluminal Mg is available for wasting at the DCT compared with that at the loop of Henle. In addition, inhibition of the Na^+-Cl^- co-transporter by thiazides has been suggested to induce hyperpolarization of the DCT plasma membrane and, hence, a more favorable transmembrane electrical gradient for Mg reabsorption (67,75).

Despite these theoretical advantages of thiazides over loop diuretics, severe hypomagnesemia is observed more frequently with Gitelman's compared with Bartter's syndrome, two syndromes that have traditionally been equated to the administration of thiazides and furosemide, respectively. Recently, in support of this observation, reduced TRPM6 expression and enhanced magnesiuria were shown in mice given chronic thiazide therapy (76). Given these observations and the lack of good direct comparative data between the two classes of diuretics, it must be assumed that significant magnesiuria may occur with either.

Others

Finally, the more common use of antibiotics and antifungals such as aminoglycosides and amphotericin in patients with diabetes may also contribute to renal Mg wasting (77).

Management of Hypomagnesemia in Type 2 Diabetes

Because the literature suggests adverse outcomes in association with hypomagnesemia in patients with type 2 diabetes, measures to minimize this abnormality are warranted (Table 2).

Optimization of Gastrointestinal Absorption

Dietary Mg intake may be optimized with the help of a nutritionist. Poor dietary intake as a result of gastrointestinal autonomic dysfunction must be controlled. Lifestyle modification such as eating multiple small meals at a time instead of two or three large meals a day; tight glucose control; and the use of prokinetic medications such as metoclopramide, domperidone, or erythromycin to improve gastric motility are indicated in patients with diabetic gastroparesis associated with erratic blood sugar control (65). In intractable cases, pyloric botulinum toxin injection, enteric feeding, and gastric pacing may be explored (78–80). For those with severe and intermittent diarrhea alternating with constipation, a trial of soluble fiber, gluten and lactose restriction, and regular efforts to move the bowels are recommended. Other measures including cholestyramine, clonidine, somatostatin analog, supplemental pancreatic enzyme, and antibiotics such as metronidazole have been suggested (65).

Table 2. Suggested management of hypomagnesemia in patients with type 2 diabetes

Increase Mg intake
  dietary consult
  high Mg-containing food types
    soy products, legumes, and seeds such as almonds and cashews, whole grains, and fruits and vegetables
      such as spinach, okra, Swiss chard, dried apricots, and avocados
Control of diabetic gastroparesis
  eat multiple small meals instead of two to three large meals per day
  tight glucose control
  use of prokinetic medications to enhance gastric motility
  others: pyloric botulinum toxin injection, enteric feeding, gastric pacing
Oral Mg supplementation
  see Table 3
Decrease gastrointestinal loss (diarrhea)
  trial of soluble fiber
  regular effort to move bowels
  trials of gluten-free diet, lactose restriction
  others: cholestyramine, clonidine, somatostatin analog, supplemental pancreatic enzyme, and antibiotics such as
    metronidazole
Decrease renal Mg loss
  decrease filtered load
    use angiotensin-converting enzyme and/or angiotensin receptor blockers
    tight glycemic control
    avoid excessive volume replacement during periods of hyperglycemia
Increase renal reabsorption
  tight glycemic control; measures to decrease insulin resistance (exercise)
  replacement of phosphate and potassium as needed
  replacement of diuretic-induced magnesiuria (based on a 24-h urine collection)

Table 3. Common Mg salts used as oral supplements in the United States

Mg Salt	Elemental Mg (mg)	Comments
Chloride	64	Slow-Mag,[a] Purdue[b]: contains calcium
Citrate	100	Active Calcium,[a] Usana[b]: contains calcium, vitamins D_3 and K
Gluconate	27/tablet	Magonate,[a] Fleming[b]: contains calcium and phosphorus
	54/5 ml	
Oxide	241	MagOx400,[a] Blaine[b]: no added products
	362	Beelith,[a] Beach[b]: contains pyridoxine

[a]Brand name.
[b]Manufacturer/pharmaceutical company.

Minimization of Renal Mg Wasting

Tight glycemic control is recommended to minimize recurring renal Mg wasting in association with osmotic diuresis and metabolic acidosis. Excessive volume replacement after hyperglycemia-induced osmotic diuresis should be avoided. Associated hypophosphatemia and hypokalemia must be corrected. When indicated, a 24-h urinary Mg measurement may be considered to assess diuretic-induced renal Mg wasting and replacement. Finally, control of glomerular hyperfiltration with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers or both may offer additional benefits in reducing renal Mg wasting. When hypomagnesemia persists despite all measures, oral Mg supplementation is indicated (Table 3).

Target Serum Mg Levels

Although no study has ever documented an optimal serum Mg concentration in patients with diabetes, we speculate that a level between 2.0 and 2.5 mg/dl may be favorable. Our suggestion is based on our previous findings that patients who had serum Mg levels within this range had the least degree of renal function deterioration and best glycemic control (7). Although the correction of low serum Mg levels has never been proved to be protective against chronic diabetic complications, intervention is justified because hypomagnesemia has been linked to many adverse clinical outcomes but, to our knowledge, *never* physiologic benefits. In addition, Mg supplementation is inexpensive and, with the exception of diarrhea, a relatively benign medication. Nonetheless, close observation must be given to those with renal insufficiency.

Conclusions

Hypomagnesemia, defined herein as having low serum magnesium concentrations, is common among patients with type 2 diabetes. Contributory mechanisms most likely are multifactorial. Because available data suggest that adverse outcomes are associated with hypomagnesemia, it is prudent that routine surveillance for hypomagnesemia be done and the condition be treated whenever possible.

Disclosures

None.

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