In the name of GOD

magnesium and diabetes mellitus

Dr. P. Aghajanzadeh

Nephrologist

Assistant professor of GUMS

- ❖diabetes was reported to be the sixth leading cause of death listed on US death certificates in 2000

- ❖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.

Incidence of hypomagnesemia in patients with T2DM, implicated contributing factors, and associated complications. Hypomagnesemia occurs at an incidence of 13.5 to 47.7%.

What may be contributory:

- Poor dietary intake
- autonomic dysfunction
- altered insulin metabolism
- glomerular hyperfiltration
- osmotic diuresis
- recurrent metabolic acidosis,
- hypophosphatemia
- hypokalemia

Hypomagnesemia has been linked to:

- poor glycemic control
- coronary artery diseases
- hypertension
- diabetic retinopathy
- nephropathy
- neuropathy
- foot ulcerations

The increased incidence of hypomagnesemia among patients with type 2 diabetes presumably is multifactorial.

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
- ❑as a key component in various reactions that require kinases
- ❑an essential enzyme activator for neuromuscular excitability and cell permeability
- ❑ a regulator of ion channels and mitochondrial function
- ❑ a critical element in cellular proliferatio and apoptosis
- ❑an important factor in both cellular and humoral immune reactions

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.

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

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 T2 DM compared with 2.5 to 15% among cohort.

In terms of gender difference, ahigher incidence of hypomagnesemia in women compared with men, at a 2-to-1 ratio

In addition, men with diabetes may have higher ionized levels of Mg

Clinical Signs of Hypomagnesemia[1,8]

Neuromuscular

- Muscle tetany, tremors
- Seizure activity
- Ataxia

Cardiac

- Electrocardiographic changes
  - — Peaked T waves
  - — Mild ST-segment depression
- Arrhythmias
  - — Ventricular tachycardia
  - — Torsades de pointes
  - — Supraventricular tachycardia
  - — Atrial fibrillation

Electrolyte

- Hypokalemia
- Hypocalcemia

Hypomagnesemia and Diabetes: Cause and Effect

- Not only has hypomagnesemia been associated with type 2diabetes, but also numerous studies have reported an inverse relationship between glycemic control and serum Mg levels
- 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
- 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
- In patients with type 2 diabetes, oral Mg supplementation during a 16-wk period was suggested to improve insulin sensitivity and metabolic control .
- 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,

Hypomagnesemia and Adverse Clinical Associations in T2 DM

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

Available data suggest that low Mg levels may promote

- ✓ endothelial cell dysfunction and thrombogenesis via increased platelet aggregation and vascular calcifications.
- ✓ induction of proinflammatory and profibrogenic response
- ✓ reduction of protective enzymes against oxidative stress
- ✓ induction or augmentation of vasoconstriction and hypertension
- ✓ stimulation of aldosterone

Moreover, because Mg is crucial in DNA synthesis and repair, it is possible that Mg deficiency may interfere with normal cell growth and regulation of apoptosis.

Macrovascular complications

Cardiovascular.

- (ARIC), amulticenter, 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

Foot Ulcerations.

- Given the link between hypomagnesemiaand risk factors for the development of diabetic footulcers (e.g., polyneuropathy, platelet dysfunction), suggested that hypomagnesemiamay be associated with an increased risk of diabeticfoot ulcers. Indeed, they observed a higher incidence of hypomagnesemia among their patients with diabetic foot ulcers compared with those without the condition

Diabetic Retinopathy

- 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

Nephropathy.

a significant decrease in serum ionizened Mg in both the micro albuminuria and overt proteinuria group compared with the non micro albuminuric group.

Accordingly ,in a recent retrospective study, an association between lower serum Mg levels and a significantly faster rate of renal function deterioration in patients with type 2 diabetes was reported.Others.

Finally, there also are data to suggest the association between hypomagnesemia and other diabetic complications, including dyslipidemia and neurologic abnormalities

a better understanding of Mg metabolism and efforts to minimize hypomagnesemia inthe routine management of diabetes are warranted.

Journal of Diabetes and Metabolism

Yanagawa, J Diabetes Metab 2017, 8:11
DOI: 10.4172/2155-6156.1000772

Commentary Open Access

Is the Renoprotective Effect of SGLT2 Inhibitors due to their Beneficial Effect on Hypomagnesemia?

Tatsuo Yanagawa*

Department of Medicine, Neri

***Corresponding author:** Ta
+81-3-5988-2200; Fax: +81-3

8530, Japan, Tel:

Received date: October 23, 2

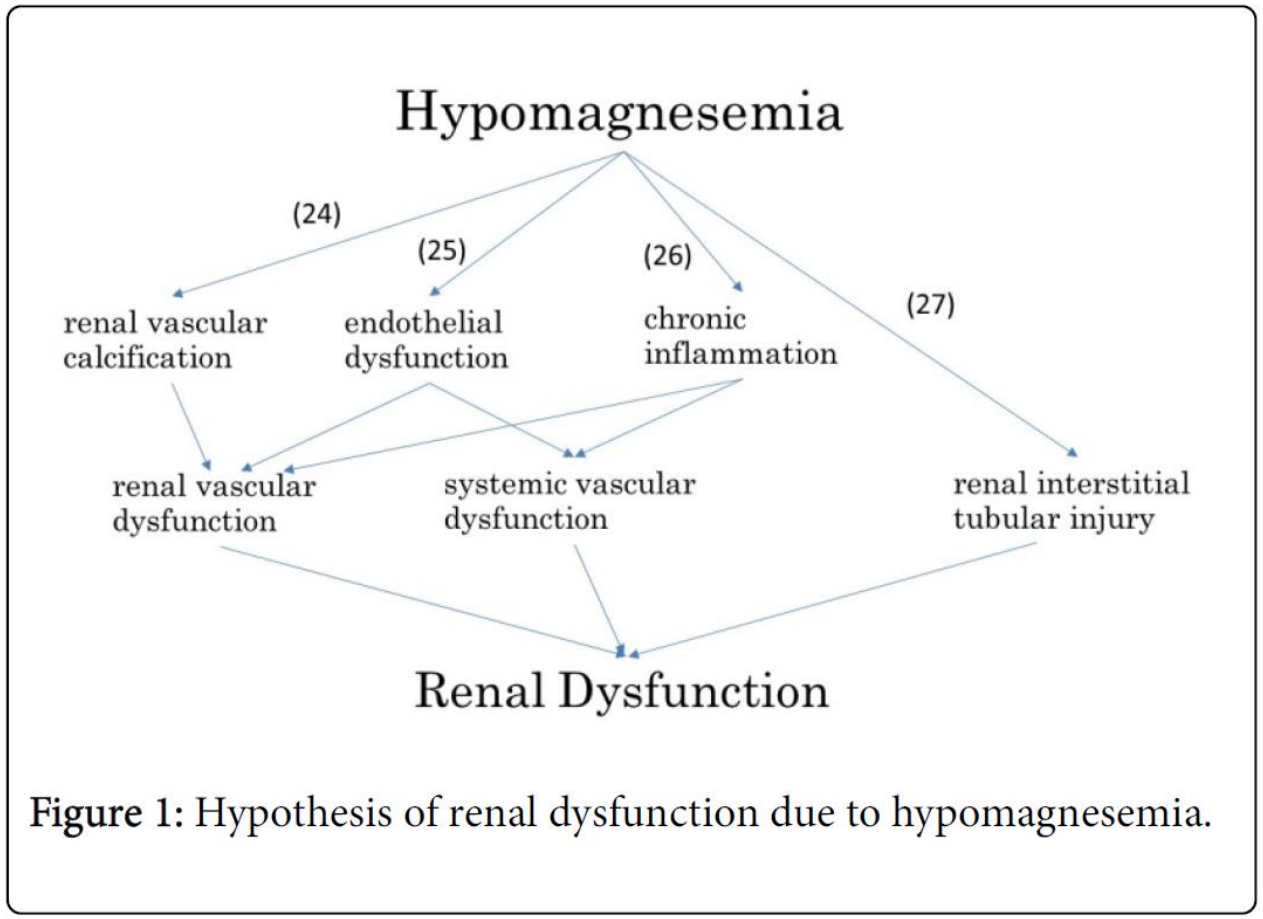


Figure 1: Hypothesis of renal dysfunction due to hypomagnesemia.

Normal Mg Metabolism: Gastrointestinal Metabolism

On an average American diet, 250 to 350 mg of Mg is consumed daily. 25% to 60% of dietary Mg is absorbed inthe gastrointestinal tract. Gastrointestinal absorption occurs predominantly in the small intestines via paracellular simple diffusion at high intraluminal concentrations and active transcellular uptakevia Mg-specific transporters at low concentrations Active intestinal Mg absorption is presumed to involve transient receptor potentialchannel melastatin 6 (TRPM6), which is expressed along the brush border membrane of the small intestine

Mutations of TRPM6 have been reported to be associated with hypomagnesemia with secondary hypocalcemia .

Normal Mg Metabolism; Renal Metabolism

Glomerular Filtration.

70 to 80% of plasmaMg is ultrafilterable in the **ionic** form (70 to 80%) and **complexed** with anions such as phosphate, citrate, and oxalate (20to 30%).

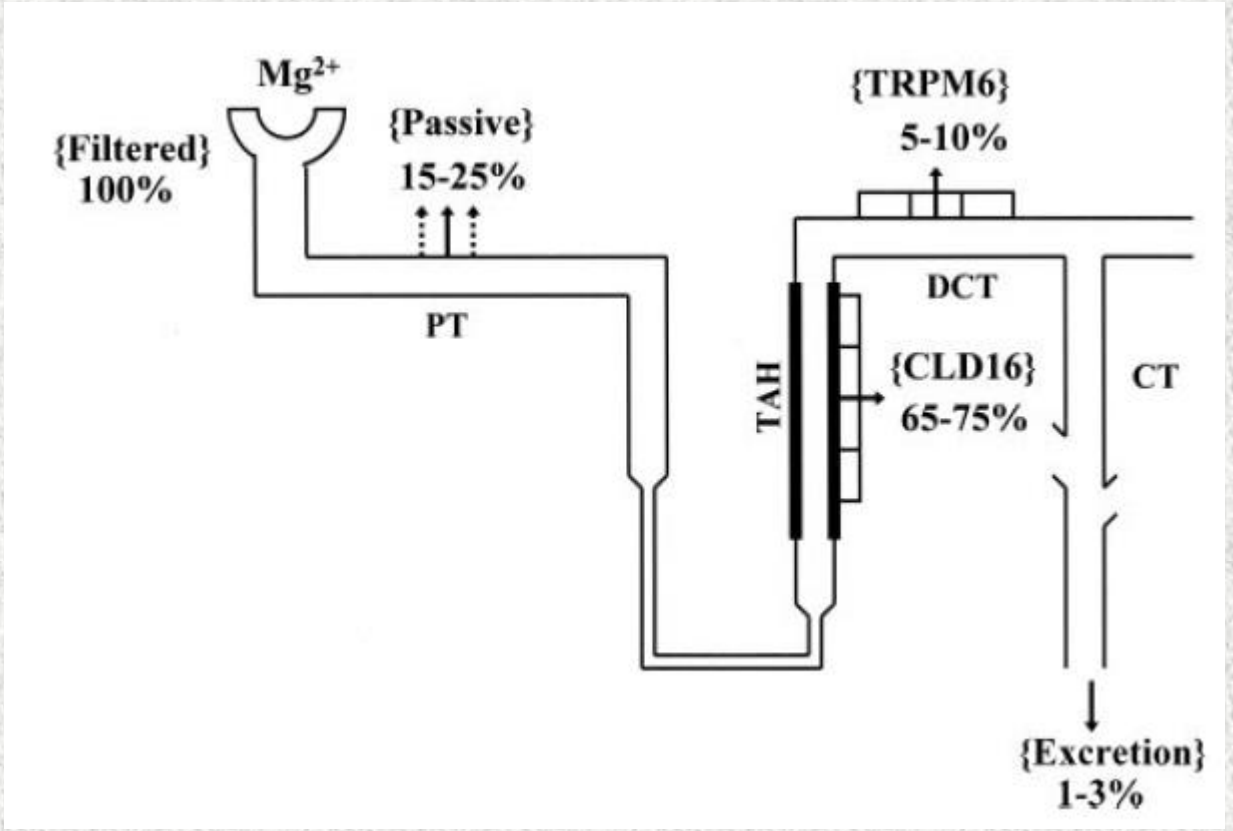
The ultrafilterability of Mg **depends on glomerulafiltration**, volume status, various metabolic states that would enhance the selection for ionized Mg (e.g., acidemia,reduced serum content of negatively charged species), and theintegrity of the glomerular basement membrane.

Proximal Tubules. Once Mg is filtered through the glomerulus***15 to 25%*** is reabsorbed in the proximal tubules Reabsorption at the proximal tubule is mainly passive and proportional to sodium and water reabsorption

Loop of Henle:65 to 75% of the Mg filteredload is reabsorbedvia the paracellular pathway in TAL .Paracellular Mg reabsorption at this nephron segmenthas been suggested to be facilitated by ***claudin 6***, also known as ***paracellin1.*** Paracellin 1 is a tight junction protein whose mutation is associated with severe hypomagnesemia with hypercalciuria and nephrolithiasis .

Parathyroid hormone,calcitonin ,glucagon, and ADH have been suggested toenhance Mg transport in the TAL via Camp

Insulin also has been implicated to play arole at this nephron segment by increasing the favorable transepithelial potential difference for Mg reabsorption .


Mg2+
{Filtered}
100%
{Passive}
15-25%
{TRPM6}
5-10%
DCT
PT
TAH
{CLD16}
65-75%
CT
{Excretion}
1-3%

Distal Convoluted Tubules.

DCTreabsorbs approximately **5 to 10%** of the filtered Mg via an **active** and regulated transcellular pathway. 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

Recently, Mg reabsorption at the DCT was shown to occur via **TRPM6.** It has been postulated that upon entry into the cells, Mg binds to divalent-binding proteins such asparvalbumin or calbindin-D28K for transport across the cell to the basolateral membrane, where Mg is taken into the interstitium by a basolateral Na2/Mg2 exchanger and/or ATP dependent Mg pump .

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 PTH In addition, the Ca2/Mg2 sensing receptoron the basolateral side may modulate hormone-stimulated Mg transport through G-protein coupling .

Finally, low dietary Mg intake and **estrogens** have been shown to upregulate renal TRP M6 expression and reduce urinary Mg excretion. Whether gastrointestinal Mg absorption via TRPM6 is reduced in the patient with diabetesis not known.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

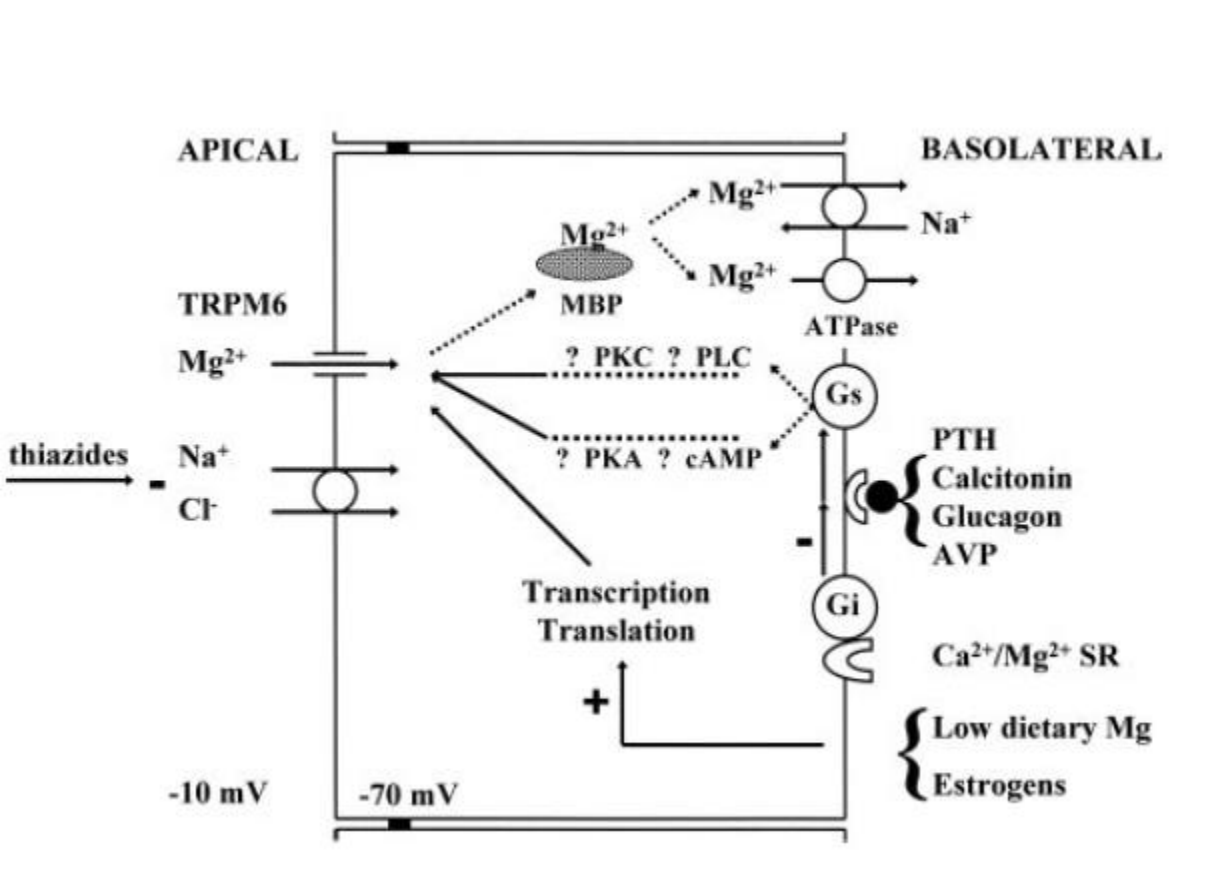

APICAL
BASOLATERAL
Mg2+
Mg2+
Na+
Mg2+
MBP
TRPM6
ATPase
Mg2+
? PKC ? PLC
Gs
thiazides
Na+
? PKA ? cAMP
PTH
Calcitonin
Glucagon
AVP
Cl-
Transcription
Translation
Gi
Ca2+/Mg2+ SR
Low dietary Mg
Estrogens
-10 mV
-70 mV

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

Causes of Hypomagnesemia[1,6,8]

Inadequate intake or excessive excretion

- Malnutrition
- Diarrhea
- Malabsorption

Renal loss

- Loop diuretics
- Parenteral fluid therapy
- Tubular disease
  - — Acute tubular necrosis
  - — Renal tubular acidosis
  - — Interstitial nephritis
  - — Postobstructive diuresis
  - — Drug injury
- Osmotic agents
  - — Mannitol
  - — Hyperglycemia
- Hypercalcemia
- Hypokalemia

Endocrine disease

- Diabetes mellitus
- Hyperthyroidism
- Hyperadrenocorticism

Redistribution

- Pancreatitis
- Sepsis
- Insulin therapy
- Catecholamine excess

Burns

Lactation

Reduced Tubular Reabsorption in T2 DM

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.

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 Hypokalemia.

At the TAL segment, hypokalemia may reduceNa-K-2Cl co-transport activity, the associated potassium extrusion through the potassium channel ROMK, and resultant diminution of the favorable trans membrane 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

Hypophosphatemia: Both micropuncture studies in phosphate-depleted dogs and in vitro studies involving phosphate depleted mouse DCT cells have demonstrated reduced Mg uptake.

Phosphate-induced reduction in cellular uptake of Mg is believed to be a post translational 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 . reduced expression of TRPM6 with induced chronic metabolic acidosis.

As previously discussed,insulin deficiency or resistance may exacerbate renal Mg wasting because insulin has been shown to have anti magnesiuric effects in both the TAL and the DCT

Use of Diuretics and others

The common use of diuretics among patients with diabetesalso may contribute to magnesiuria. The degree of magnesiuriais traditionally thought to be lower for thiazides compared with loop diuretics . In addition, in hibition 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.

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.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.

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

Target Serum Mg Levels

Although no study has ever documented an optimal serum Mg concentration in patients with diabetes

a level between 2.0 and 2.5 mg/dl may be favorable. within this range had the least degree of renal function deterioration and best glycemic control .

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

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.

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 54/5 ml	Magonate,[a] Fleming[b]: contains calcium and phosphorus
Oxide	241	MagOx400,[a] Blaine[b]: no added products
	362	Beelith,[a] Beach[b]: contains pyridoxine

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

Mini-Review

Hypomagnesemia in Patients with Type 2 Diabetes

Phuong-Chi T. Pham,* Phuong-Mai T. Pham,† Son V. Pham,‡ Jeffrey M. Miller,§ and Phuong-Thu T. Pham‖

*Nephrology and §Hematology/Oncology Division, Department of Medicine, Olive View-UCLA Medical Center, Sylmar, California; †Department of Medicine, Maine Medical Center, Lewiston, Maine; ‡Cardiology Division, Sacramento Veterans Administration Medical Center, Sacramento, California; ‖Kidney and Pancreas Transplantation, David Geffen School of Medicine at UCLA, Los Angeles, California

Clin J Am Soc Nephrol 2: 366–373, 2007. doi: 10.2215/CJN.02960906

Lisanne M.M. Gommers,[1] Joost G.J. Hoenderop,[1] René J.M. Bindels,[1] and Jeroen H.F. de Baaij[1,2]

Hypomagnesemia in Type 2 Diabetes: A Vicious Circle?

Diabetes 2016;65:3–13 | DOI: 10.2337/db15-1028

Any questions?

****

Thank you