

Magnesium: Why is it so important in clinical medicine ?

Nilrat Wannasilp, M.D.*

Abstract : Magnesium (Mg) is the second most plentiful intracellular cation. It has many important physiologic functions, including enzyme, membrane, calcium antagonist and structural functions. The serum contains Mg concentration less than 1 % of the total body Mg, and the remainder is mostly present in the soft tissue and bone. Consequently, assessing Mg status is quite difficult. At present, the majority of clinical laboratory information comes from the determination of the total Mg concentration in serum and 24- hour urinary excretion, but instrumentations to evaluate ionized Mg and intracellular Mg should be available in the near future. Disorders of Mg metabolism, especially hypomagnesemia (Mg deficiency), are frequently observed in clinical medicine. These may play important roles in the pathophysiology of many diseases or conditions, such as hypocalcemia, acute myocardial infarction and migraine. Also, Mg supplement may be a factor in the treatment of these conditions, but its routine use in emergency medicine is still controversial.

Key words : magnesium, clinical medicine

เรื่องย่อ : แมกนีเซียม : ทำไมจึงมีความสำคัญในเวชปฏิบัติทั่วไป
นิลรัตน์ วรรณศิลป์ พ.บ.*

*ภาควิชาพยาธิวิทยาคลินิก, คณะแพทยศาสตร์ศิริราชพยาบาล, มหาวิทยาลัยมหิดล, กรุงเทพมหานคร 10700.

สารศิริราช 2546; 55: 394-401.

แมกนีเซียมเป็นแร่ธาตุที่พบมากในเซลล์เป็นอันดับที่สอง มีหน้าที่สำคัญมากมายซึ่งเกี่ยวเนื่องกับเอนไซม์, ผนังเซลล์, การเป็นตัวขวางแคลเซียมเข้าออกเซลล์ และมีหน้าที่เกี่ยวกับโครงสร้างของสารในร่างกายนีรั่มประกอบด้วยแมกนีเซียมปริมาณความเข้มข้นน้อยกว่า 1% ของจำนวนแมกนีเซียมทั้งหมดของร่างกาย เนื่องจาก Mg ส่วนใหญ่จะถูกเก็บสะสมเป็นจำนวนมากในเนื้อเยื่ออ่อนและกระดูก จึงทำให้การประเมินความผิดปกติของแมกนีเซียมในร่างกายเป็นไปได้ยาก ปัจจุบันการตรวจที่นิยมใช้มากที่สุดได้แก่ การวัดระดับแมกนีเซียมทั้งหมดที่อยู่ในซีรั่มและการวัดปริมาณแมกนีเซียมในปัสสาวะที่เก็บ 24 ชั่วโมง แต่การตรวจทั้งสองวิธีไม่สามารถบอกความผิดปกติของปริมาณแมกนีเซียมในร่างกายได้อย่างถูกต้อง ส่วนการตรวจด้วยวิธีอื่นโดยการวัดไอออนไนซ์แมกนีเซียมและการวัดระดับแมกนีเซียมในเซลล์ยังอยู่ในระหว่างทำการศึกษาและยังไม่มีใช้ทั่วไป ความผิดปกติของระดับแมกนีเซียมในเลือดพบบ่อยในเวชปฏิบัติทั่วไปโดยเฉพาะภาวะที่มีระดับแมกนีเซียมต่ำในเลือด ซึ่งภาวะดังกล่าวอาจจะมีส่วนร่วมในการกำเนิดโรคหรือสภาวะหลาย ๆ อย่าง ดังเช่น ระดับแคลเซียมต่ำในเลือด, กล้ามเนื้อหัวใจขาดเลือดเฉียบพลันและไมเกรน ดังนั้นการรักษาด้วยการให้แมกนีเซียมอาจมีประโยชน์ในผู้ป่วยมากขึ้นเพื่อรักษาสภาวะดังกล่าว แต่การรักษาดังกล่าวยังไม่ได้ใช้เป็นมาตรฐาน และต้องการการศึกษาเพิ่มเติม

*Department of Clinical Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

INTRODUCTION

Currently, magnesium (Mg) is of interest to many clinicians and researchers. Why is it so important in clinical practice? Mg is the fourth electrolyte that is concentrated in the body and the second most abundant cation in the cell. Many studies

show that it may be related to a number of diseases and medical conditions. While its essential functions are well known (Table 1), there is still little information about its relationship with many diseases and conditions, especially cardiovascular disease.

Table 1. Functions of magnesium in the human body.

Enzyme function :

- Enzyme substrate : Kinases B = Hexokinase, Creatinine kinase, Protein kinase
- ATPases or GTPases : Na^+ , K^+ -ATPase, Ca^{2+} ATPase
- Cyclases : adenylate cyclase, guanylate cyclase
- Direct enzyme activation : Phosphofructokinase, Creatinine kinase, Adenylate cyclase, Na^+ , K^+ -ATPase, 5-phosphoribosyl-pyrophosphate synthetase

Membrane function :

- Cell adhesion
- Transmembrane electrolyte flux

Calcium antagonist :

- Muscle contraction/relaxation
- Neurotransmitter release
- Action potential conduction in nodal tissue

Structural function :

- Protein
- Polyribosomes
- Nucleic acids
- Multiple enzyme complexes
- Mitochondria

Magnesium distribution:

Mg is an element with an atomic number of 12 and a mass of 24.32 daltons. The normal human body contains about 1,000 mmol or 22.66 g of Mg. The distribution of Mg within the body is shown in Table 2. Serum contains less than 1% of total body Mg, of which 50% is found in bone. The normal serum Mg level ranges between 0.75 and 0.95 mmol/L (1.7-2.2 mg/dL, 1.5-1.9 meq/L). In the serum, Mg is present in three different states: ionized (55%), complexed to anions (15%), and bound to protein (30%). (Figure 1)

Magnesium nutrition :

Although the human requirement for Mg is still controversial, the recommended dietary allowance (RDA) of Mg for adults is 4.5 mg/kg/day. The daily requirement is higher in many conditions (pregnancy, lactation, following debilitating illness, those on high intakes of calcium, phosphate and high fat diet, and those under environmental stress). Cereal grains, nuts, legumes and chocolate are high in Mg; vegetables, fruits, meats and fish are intermediate; dairy products and beverages are low in Mg. Drinking water, especially hard water, is an important source. Modern food technology causes loss of Mg by refining or processing food.

Table 2. Distribution of magnesium in the adult human.

Tissue	% of total body magnesium
Serum	0.3
Red blood cells	0.5
Soft tissue	19.3
Muscle	27
Bone	52.9

**Figure 1.** Fractions of magnesium in serum.**Magnesium absorption and excretion:**

The majority of Mg absorption is in the ileum and colon, and the absorption rate is inversely proportional to the amount ingested. The major organ of Mg regulation is the kidney. Many factors, both hormonal (parathyroid hormone, calcitonin, glucagon and vasopressin) and nonhormonal (magnesium restriction, acid-base changes and potassium depletion) have an effect on renal reabsorption. In the plasma, Mg concentration controls its homeostasis by itself. For example, hypermagnesemia reduces loop transport but hypomagnesemia induces transport, whether there is magnesium depletion or not.

Assessment of magnesium status :

At the present, there are a lot of laboratory methods to evaluate Mg status both intracellular and extracellular Mg content (Table 3). However, there is

no simple, rapid and accurate laboratory test to indicate the total body Mg status. Even though intracellular Mg is more than 90%, serum total Mg concentration is still the only common method to be available now.

Many methods for the measurement of serum total Mg level have been used. Previously, historical tests were based on gravimetric, titrimetric and flame emission. Currently, they have no role in current clinical laboratory practice because of their poor accuracy, bad performance and time-consuming nature.

Second, many laboratories use atomic absorption spectroscopy. It has excellent specificity, precision and accuracy, so it has been established as a de facto reference method for Mg analysis in clinical practice. On the other hand, it is impractical for routine use because the equipment is so sophisticated and expensive. In addition, the methodology is

Table 3. Tests used in assessing magnesium status.**Serum magnesium concentration**

- Total magnesium
- Ultrafiltrable magnesium
- Ionized magnesium

Intracellular magnesium content

- Red cells
- Mononuclear blood cells
- Skeletal muscle

Physiologic test

- Metabolic balance studies
- 24-hour urinary excretion of magnesium
- Magnesium loading test

Intracellular free magnesium ion concentration

- Fluorescent dye
- Nuclear magnetic resonance spectroscopy

Others

- Magnesium balance
- Isotope studies
- Hair or tooth magnesium
- Functional assays

potentially hazardous, as it produces gases that are dangerous to the environment.

Third, enzymatic assays have been developed to examine Mg concentration in the blood. They are based on specific enzymes that involve in glycolysis and carbohydrate metabolism. There are many advantages (simplicity, specificity and good performance characteristics) but they have not yet gained widespread acceptance in routine laboratory practice, possibly because of other cations, heavy metals, proteins and lipaemia interference, and by the lack of readily available commercial kits.

Finally, photometric tests are currently the most commonly used method in routine measurement of Mg. Of these methods, xylydyl blue is the most widely use in many laboratories. It is automated available and has good precision and accuracy; however, interference by calcium remains controversial.

Although the total serum Mg concentration is a widespread method, it is not the best method to evaluate Mg status. About half of serum Mg is bound to proteins and anions so alteration of protein and

anion concentration affect serum total Mg concentration without necessarily affecting the physiologically active ionized fraction. In the last few years, ion-selective electrodes for Mg have been developed and several commercial analyzers for measurement of ionized Mg concentration are now available. Even though the instruments achieve within-run coefficient variation (CV) of approximately 3-5% and between-run CV of 12%, they do not use in routine clinical practice because they have high interference by calcium.

Nowadays, abundant intracellular Mg measurements have been developed in many laboratories by using red blood cell, mononuclear blood cells, platelet and skeletal muscle to evaluate. While they are reproducible, reliable, accurate and easy to perform, the techniques are still difficult, especially skeletal muscle Mg measurement; it is an invasive procedure and requires special expertise. They require more clinical evaluation.

Mg loading test has been used for assessing Mg status. Mg is infused intravenously into the body and 24-hour urine is been collected to measure Mg

excretion. In consequence, the method requires normal renal function and it may be of limited value for patients with poor renal function.

Other methods such as intracellular free Mg measurement, isotope studies, Mg balance test, hair or tooth Mg measurement and function assays have been used, but they need further investigation.

Hypomagnesemia:

Hypomagnesemia is defined as a serum Mg level below 1.7 mg/dL. The majority causes of hypomagnesemia are in Table 4. First, many gastrointestinal diseases may induce Mg loss, such as acute and chronic diarrhea, malabsorption syndrome and acute pancreatitis. The second common cause of hypomagnesemia is renal losses by chronic parenteral fluid therapy of volume expanded states.

Finally, Mg loss may occur during medical therapy. Many drugs involving diuretics, alcohol, aminoglycoside antibiotics, cisplatin, amphotericin B and cyclosporine have been reported to be associated with hypomagnesemia. Other conditions related to hypomagnesemia are phosphate depletion, hungry-bone syndrome, correction of chronic systemic acidosis, postobstructive nephropathy, renal transplantation, diuretic phase of acute renal failure and primary renal tubular magnesium wasting.

Clinical manifestations of hypomagnesemia have been shown in Table 5. Most of the symptoms and signs of moderate to severe hypomagnesemia are non-specific and they are usually associated with other ion abnormalities, such as hypocalcemia, hypokalemia and metabolic alkalosis.

Table 4. Causes of hypomagnesemia.

Gastrointestinal losses

- Prolonged nasogastric suction
- Acute and chronic diarrhea
- Malabsorption syndromes
- Steatorrhea
- Extensive bowel resection
- Primary intestinal hypomagnesemia
- Acute pancreatitis
- Severe malnutrition
- Intestinal fistula

Renal losses

- Chronic parenteral fluid therapy
- Volume expanded states
- Hypercalcemia and hypercalciuria
- Osmotic diuresis (diabetes, urea, mannitol)

Drugs

- Diuretics (thiazide or loop)
- Alcohol
- Aminoglycoside
- Antibiotics
- Cisplatin
- Amphotericin B
- Cyclosporine
- Foscarnet
- Pentamidine

Phosphate depletion

Hungry-bone syndrome

Correction of chronic systemic acidosis

Postobstructive nephropathy

Renal transplantation

Diuretic phase of acute renal failure

Primary renal tubular magnesium wasting

Table 5. Clinical manifestations of hypomagnesemia.**Neuromuscular**

- Trousseau and Chvostek signs
- Carpopedal spasm
- Seizures
- Vertigo and ataxia
- Muscular weakness
- Depression, psychosis

Metabolic

- Carbohydrate intolerance
- Hyperinsulinism
- Atherosclerosis

Cardiovascular

- Widening of QRS complex
- Prolongation of PR interval
- Inversion of T wave, U waves
- Severe ventricular arrhythmias
- Sensitivity to cardiac glycosides

Bone

- Osteoporosis and osteomalacia

Role of hypomagnesemia in pathophysiology of diseases and conditions:

As more knowledge about Mg function has been established, the list of diseases and conditions possibly affected by alteration of Mg metabolism has increased.

Hypokalemia is a common event in hypomagnesemic patients, appearing in 40-60% of cases. The relationship is due to underlying diseases that cause both Mg and potassium loss (diuretic therapy and diarrhea). Hypomagnesemia is associated with cellular Mg depletion, which may then lead to decrease in ATP activity and increase in the number of open potassium channels. Given the very high cell potassium concentration, these changes would promote potassium secretion from the cell into the lumen and enhance urinary losses. In the same way, hypokalemia in hypomagnesemic patients may contribute to the cardiac manifestation of hypomagnesemia.

Hypocalcemia may involve in development of clinical signs of severe hypomagnesemia, including tetany, positive Chvostek and Trousseau signs and generalized convulsions. Hypocalcemia

occurs in patients with severe hypomagnesemia by four mechanisms: parathyroid hormone resistance, reduction in parathyroid hormone secretion, vitamin D deficiency and vitamin D resistance. Additionally, there are many conditions in hypomagnesemic patients that can lower the total and ionized calcium, such as sepsis, hypoalbuminemia and stress.

Heart and cardiovascular disorders may occur in patients with prolonged hypomagnesemia. Two prospective studies report that people with hypomagnesemia may contribute to increase risk for development of cardiovascular artery disease. In the same manner, patients with acute myocardial infarction who have mild hypomagnesemia appear to have a two-to three-fold increase in the frequency of ventricular arrhythmias in the first 24 hours when compared to those with normal plasma magnesium levels. In congestive heart failure, many reports find that an increased incidence of hypomagnesemia has been found in these patients by many mechanisms (diuretic therapy, low Mg intake, hypophosphatemia, hypokalemia, chronic congestive heart failure and respiratory alkalosis). Also, hypomagnesemia may appear in patients with Torsade De pointes.

Intensive care unit patients may be at increased risk for reduction of serum Mg concentration. Hypomagnesemia is a common co-incidence of patients in intensive care unit, the percentage being as high as 60-65%. Many reports suggest that these patients have a high mortality rate when compared with ill normomagnesemic patients.

Acute asthma is associated with reduced intracellular Mg concentrations while plasma levels remain unchanged. This decline in intracellular Mg content appears regardless of the severity of the exacerbation and returns to normal values after control has been achieved.

Diabetic patients, especially type 2 diabetes mellitus, are at high risk to develop intracellular Mg depletion and have been associated with increased risk of cardiovascular artery disease. Decreased intracellular Mg might underlie the initial pathophysiologic events leading to insulin resistance and abnormality of platelet coagulation. In addition, Mg has one function like an antioxidant. When reduced intracellular Mg occurs, there is probably a decrease in antioxidant status too. The implication is the greater susceptibility to low density lipoprotein-cholesterol oxidation. The attendant risk of the development of premature coronary heart disease is discussed.

Cancers have been reported to be associated with hypomagnesemia. Reduction of serum Mg level is evident in about one third of leukemic patients, and decreased intracellular Mg content seems to be associated with the development of acute leukemia and malignant lymphoma. Many studies found that disturbances of Mg status may contribute to an underlying pathophysiological event in diseases like gastric cancer, breast cancer, colon cancer, bladder cancer and upper digestive tumors, but the mechanisms are still unknown and controversy.

Chronic renal failure may contribute to reduction of intracellular Mg levels. As a result,

Mg depletion has been implicated in various pathological conditions that occur to an increased extent in kidney disease, such as arterial hypertension, cardiac arrhythmias, thrombosis and atherosclerosis.

Other conditions that have been reported to be associated with hypomagnesemia are alcoholism, thalassemia and migraine; however, there is still no conclusion about their mechanisms.

Role of magnesium in future treatment of many diseases and conditions :

There has been considerable interest in Mg as a treatment for many diseases and conditions, including myocardial infarction, cardiac failure, arrhythmias, bronchial asthma, migraine, chronic renal failure, cancers and stroke, but the outcomes are still controversial. Further large prospective studies are necessary for this intervention in all emergency conditions. Although today the data, while biologically plausible, is still unproven, Mg is potentially a safe and rapid intervention.

CONCLUSION

All in all, Mg is a very important intracellular cation. It acts as cofactor of many essential enzymes, controlling of ion channels on cell membrane, calcium antagonist and stabilizing cell structures. Alteration in Mg concentration in the blood or the body, especially hypomagnesemia, may play an important role in pathogenesis of many diseases and conditions, such as hypokalemia, hypocalcemia, heart disease, diabetes mellitus and asthma. So, the assessment of Mg status and Mg supplement may be necessary in these patients, but their routine uses in clinical medicine are still controversial. Further investigations are required for these interventions in routine uses.

REFERENCES

1. Elin RJ. Magnesium: the fifth but forgotten electrolyte. *Am J Clin Pathol* 1994; **102**: 616-22.
2. Anonymous. Disorders of magnesium metabolism. *JIFCC* 1999; **11**: 10-18.
3. Weisinger JR, Bellorin-Font E. Magnesium and phosphorus. *Lancet* 1998; **352**: 391-96.
4. Ryan MF, Barbour H. Magnesium measurement in routine clinical practice. *Ann Clin Biochem* 1998; **35**: 449-59.
5. Agus ZS. Hypomagnesemia. *J Am Soc Nephrol* 1999; **10**: 1616-22.

6. Takaya J, Higashino H, Kotera F, Kobayashi Y. Intracellular magnesium of platelets in children with diabetes and obesity. *Metabolism* 2003; **52**: 468-71.
7. Soliman HM, Mercan D, Lobo SS. Development of ionized hypomagnesemia is associated with higher mortality rates. *Crit Care Med* 2003; **31**: 1082-87.
8. Anetor JI, Senjobi A, Ajoye OA, Agbedana EO. Decreased serum magnesium and zinc levels : atherogenic implications in type-2 diabetes mellitus in Nigerians. *Nutr Health* 2002; **16**: 291-300.
9. Zervas E, Papatheodorou G, Psathakis K. Reduced intracellular Mg concentrations in patients with acute asthma. *Chest* 2003; **123**: 113-18.
10. Sahin G, Ertem U, Duru F. High prevalence of chronic magnesium deficiency in T cell lymphoblastic leukemia and chronic zinc deficiency in children with acute lymphoblastic leukemia and malignant lymphoma. *Leu Lymphoma* 2000; **39**: 555-62.
11. Mooren FC. Magnesium status and gastric function: experimental and clinical data. *Magnes Res* 1999; **12**: 311-18.
12. Pasternak K, Przyszlak W. Magnesium in stomach cancer. *Magnes Res* 1999; **12**: 139-43.
13. Freng A, Daae LN, Engeland A. Malignant epithelial tumours in the upper digestive tract: a dietary and socio-medical case-control and survival study. *Eur J Clin Nutr* 1998; **52**: 271-78.
14. Michaud DS, Spiegelman D, Clinton SK. Prospective study of dietary supplements, macronutrients, micronutrients, and risk of bladder cancer in US men. *Am J Epidemiol* 2000; **152**: 1145-53.
15. Yang CY, Hung CF. Colon cancer mortality and total hardness levels in Taiwan's drinking water. *Arch Environ Contam Toxicol* 1998; **35**: 148-51.
16. Millionis HJ, Bourantas CL, Siamopoulos KC. Acid-base and electrolyte abnormalities in patients with acute leukemia. *Am J Hematol* 1999; **62**: 201-7.
17. Deheinzeln D, Negri EM, Tucci MR. Hypomagnesemia in critically ill cancer patients: a prospective study of predictive factors. *Braz J Med Biol Res* 2000; **33**: 1443-48.
18. Pedrozzi NE, Truttmann AC, Faraone R. Circulating ionized and total magnesium in end-stage kidney disease. *Nephron* 1998; **79**: 288-92.
19. Irish AB, Thompson CH, Kemp GJ. Intracellular free magnesium concentrations in skeletal muscle in chronic uraemia. *Nephron* 1997; **76**: 20-25.
20. Saha H, Hormoinen A, Nisula M. Serum ionized versus total magnesium in patients with chronic renal disease. *Nephron* 1998; **80**: 149-52.
21. Franceschi LDe, Cappellini MD, Graziadei G. The effect of dietary magnesium supplementation on the cellular abnormalities of erythrocytes in patients with β thalassemia intermedia. *Haematologica* 1998; **83**: 118-25.
22. Kaye P, Sullivan IO. The role of magnesium in the emergency department. *Emerg Med J* 2002; **19**: 288-91.
23. Muir KW. Magnesium in stroke treatment. *Postgrad Med J* 2002; **78**: 641-45.