

Assessment of magnesium status for diagnosis and therapy

Ronald J. Elin

Department of Pathology and Laboratory Medicine, School of Medicine,
University of Louisville, Louisville, USA

Correspondence: R.J. Elin, Department of Pathology and Laboratory Medicine, School of Medicine,
University of Louisville, 627 South Preston Street, Room 210, Louisville, KY 40202, USA
<rjelin01@gwise.louisville.edu>

Abstract. Magnesium is an essential element needed for health. Even though only 1% of the total body magnesium is present in blood, the serum magnesium concentration (SMC) is the predominant test used by medicine to assess magnesium status in patients. The traditional method to establish a reference interval for the SMC is flawed by the large number of “normal” individuals who have a subtle chronic negative magnesium balance due to a significant decrease in magnesium intake over the past century. Evidence-based medicine should be used to establish the appropriate lower limit of the reference interval for health and I recommend 0.85 mmol/L based on current literature. The decrease in magnesium in the diet has led to chronic latent magnesium deficiency in a large number of people since their SMC is still within the reference interval due to primarily the bone magnesium supplementing the SMC. These individuals need adjustment of their diet or magnesium supplementation to achieve a normal magnesium status for health.

Key words: magnesium, serum, reference interval

Magnesium is an important element for health and disease. Magnesium, the second most abundant intracellular cation, has been identified as a cofactor in over 300 enzymatic reactions involving energy metabolism and protein and nucleic acid synthesis. Approximately half of the total body magnesium is present in soft tissue, and the other half in bone. Less than 1% of the total body magnesium is present in blood. None the less, the majority of our information about this element comes from determination of magnesium in serum. In this review, I will explore the clinical and research laboratory tests available for the assessment of magnesium status, why we need an evidence-based reference interval for the serum magnesium concentration (SMC) and the concept of chronic latent magnesium deficiency.

Laboratory tests to assess magnesium status

Since approximately 99% of the total body magnesium is in bone and soft tissue, this makes clinical

laboratory assessment of magnesium status problematic [1]. Tests should be available to assess magnesium status in tissue and the state of magnesium. At present, the assessment of magnesium status in an individual is a challenge to the clinical laboratory. I would like to review the clinical and research laboratory tests that have been used to assess magnesium status (*table 1*).

The serum ionized (free) magnesium concentration has been available in the United States for over 15 years. At present, only the Nova electrode is available for clinical laboratories in the United States. In 1997, thiocyanate, which is increased in the blood of smokers, was documented to have a negative interference for the Nova ion-selective electrode for magnesium [2]. Even though there have been improvements to the electrode, a more recent study still shows interference by thiocyanate [3]. At present, only 105 clinical laboratories subscribe to the College of American Pathologists (CAP) proficiency testing program for ionized

Table 1. Laboratory tests to assess magnesium status.

Clinical laboratory tests
- Total serum Mg concentration
- Serum ionized Mg concentration
- Twenty-four hour excretion of Mg in urine
Research tests
- Mg retention test
- Total and free red blood cell Mg concentration
- Tissue Mg-muscle, bone, etc.
- Electron probe for total Mg in tissue
- NMR for free Mg in tissue
- Isotope studies

magnesium but 5,485 subscribe for the SMC [4]. This means less than 2% of clinical laboratories in the United States who use CAP proficiency testing (the majority of hospital-based laboratories) offer ionized magnesium. Thus, it seems like physicians have not found ionized magnesium to be of significant value for patient care in the United States. The 24-hour excretion of magnesium in the urine is offered by many hospitals and is of value to assess magnesium wasting by the kidney but is not a test to assess magnesium status.

I also list most of the research tests that have been used with varying success to assess magnesium status (*table 1*). By and large, these tests are not available to the practicing physician to assess magnesium status in their patients. Thus, we are left with the SMC as essentially the only test used by patient care physicians to assess magnesium status. What are the properties of this test and how can we improve interpretation of the results?

Serum magnesium concentration

At present, clinical medicine has identified the SMC as the preferable test to assess magnesium status which is related to the technology and the tests readily available in the clinical laboratory. Magnesium has been determined in serum far more frequently than in any other tissue. However, with the exception of interstitial fluid and bone, the SMC has not been shown to correlate with other tissue pools of magnesium. In a study of 14 patients, Alfrey *et al.* found an excellent correlation ($r = 0.96$) between bone and the SMC [5]. This study has not been repeated by other investigators to support this finding. Further, the SMC does not reflect the total body magnesium status. There are individuals with the SMC within the reference interval that

have a total body deficit of magnesium. This is especially likely when an individual has chronic latent magnesium deficiency, which I will describe in greater detail later in the paper. The reverse situation, a low SMC but normal magnesium body content, also occurs, but less frequently. This is usually seen when drugs are given to a patient which acutely increase the excretion of magnesium in urine, reducing the SMC. However, clinical medicine has chosen the SMC as the standard for the assessment of magnesium status, imperfect as it may be. I will describe some of the properties of the SMC and propose how to use this important test result more effectively for patient care.

Magnesium exists in serum in three states. Approximately one-third of the magnesium in serum is bound by protein; approximately 25% of the total SMC is bound to albumin and 8% to globulins [6]. For the two thirds of the SMC that is ultrafilterable, approximately 92% is free (61% of the total serum magnesium) and approximately 8% is complexed to phosphate, citrate and other compounds [7]. Albumin and SMCs are related linearly at high and low albumin concentrations. However, within the reference interval for albumin, the SMC is independent of the albumin concentration [6]. Since only the ionized magnesium is physiologically active, the SMC is a reasonable approximation of ionized magnesium but varies primarily with the albumin concentration.

The equilibrium among most tissue compartments (including serum) for magnesium is reached very slowly, if at all. Studies suggest that the biologic half-life for the majority of magnesium in the body is approximately 1,000 hours [8]. Thus, changes in the total body magnesium content and SMC normally occur very slowly over a period of months to years in the normal individual. This is evident by studies where oral magnesium supplementation is started but the SMC doesn't change for weeks to months [9].

The reference interval for serum magnesium was determined in a U.S. population of 15,820 individuals between the ages of 18-74 years as part of the NHANES I study. The results of this study identified the reference interval (central 95th percentile) as 0.75 mmol/L to 0.955 mmol/L with a mean concentration of 0.85 mmol/L [10]. This is a definitive study because of the large number of subjects and also because the magnesium was determined by atomic absorption. The assumption in any study to determine the reference interval is that the individuals have a "normal" concentration of the analyte

under study. However, a substantial number of adults in the United States fail to consume adequate magnesium in their diet which may lead to an SMC that is lower than that needed for health [11]. This would bias a traditional study to statistically determine the reference interval. Is there a better way to determine the reference (normal) interval for SMC?

Evidence-based reference interval for serum magnesium

I recommend an expert panel to establish an evidence-based reference interval for the SMC similar to that which was done many years ago for cholesterol and related lipids. In 1988, an expert panel reviewed the literature related to the serum cholesterol/related lipids and health/disease. The panel established reference intervals for cholesterol and related lipids that are still in place today [12]. We need a similar process to establish the reference interval for the SMC. As with cholesterol, many individuals who were considered “normal” had markedly elevated cholesterol based upon their diet, which skewed the upper limit of the reference interval beyond the level that was consistent with health. Since the intake of magnesium has fallen dramatically in the past century, primarily related to the processing of food, the majority of individuals have an intake below the recommended daily allowance (RDA) [11, 13]. Thus, the reference interval study that I cited before from NHANES I probably contained many individuals with an inadequate intake of magnesium over a prolonged period of time which had reduced their SMC below a concentration suitable for health. If an expert panel cannot be convened, and for the immediate future, I would recommend that the lower limit of the reference interval for serum magnesium be 0.85 mmol/L for health, the mean of the NHANES I reference interval study [10]. I would cite the following studies to support that recommendation.

In a study done in Europe, magnesium deficiency was determined clinically and compared with the SMC. These investigators found that for a SMC of 0.70 mmol/L, 90% of the individuals had clinical magnesium deficiency; at a cutoff of 0.75 mmol/L, 50% of individuals had clinical magnesium deficiency; at a cutoff of 0.80 mmol/L, 10% of individuals had clinical magnesium deficiency and at a cutoff of 0.90 mmol/L, only 1% of the individuals had clinical magnesium deficiency [14, 15]. Several studies have shown an inverse relationship between the SMC and the risk for type 2 diabetes mellitus. In a second

study, a cohort of 9,784 participants in the NHANES I study was followed for 18 years [16]. There were 690 participants who developed type 2 diabetes mellitus. Using an adjusted Cox’s regression, the authors showed that the hazard ratio was 1.20 with a SMC between 0.80 and 0.84 mmol/L and the hazard ratio was 1.51 when the SMC was < 0.80 mmol/L. The risk ratio began to increase when the SMC was < 0.85 mmol/L. In the third study, individuals between the ages of 20-65 were screened with a fasting blood glucose, a glucose tolerance test and a SMC and were excluded from the study if any of these tests were abnormal [17]. A total of 817 normal individuals were identified and reexamined 10 years later with the same tests. A Poisson regression model was used for data analysis. The results show that there was greater risk for an impaired fasting glucose concentration with a SMC < 0.85 mmol/L and an impaired glucose tolerance test with a SMC < 0.8 mmol/L. The above three studies support the hypothesis that our current reference interval for the SMC based on the statistics of a “normal” population is not providing what is optimum for health at the lower limit of the reference interval for magnesium. This is particularly true for type 2 diabetes mellitus where patients are frequently in the lower half of the reference interval for the SMC and have what I have chosen to call chronic latent magnesium deficiency, *i.e.* since the SMC is within the reference interval, the physician assumes no problem for magnesium. I will discuss this concept in greater detail.

Chronic latent magnesium deficiency

Several factors are needed to achieve and maintain magnesium balance. *Figure 1* depicts the factors needed for magnesium balance and lays the foundation for the etiology of chronic latent magnesium deficiency. This is chronic since it extends over years to a lifetime. It is latent since frequently the SMC is within the current reference interval, albeit at the lower end of the reference interval.

The normal individual has an adequate intake of magnesium, normal absorption of magnesium from the gastrointestinal tract and does not waste magnesium through excretion in the urine. However, a change in any one of these three entities that is chronic may lead to chronic latent magnesium deficiency. An inadequate intake of magnesium is the most likely culprit that leads to chronic latent magnesium deficiency. As I indicated before, a shift in eating habits in many parts of the world to

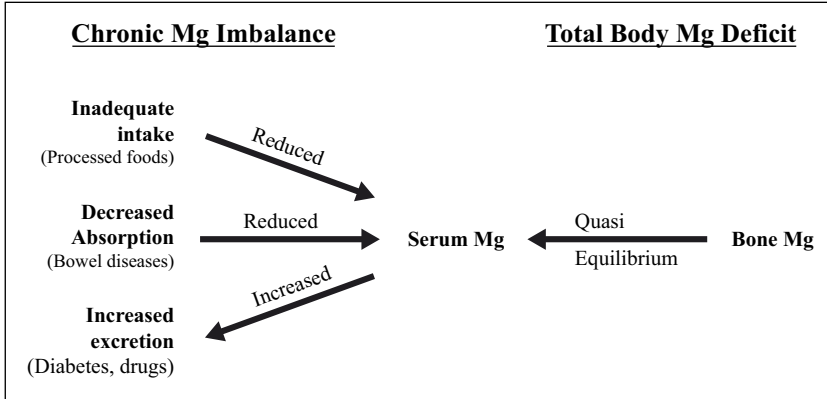


Figure 1. The etiology of chronic latent Mg deficiency.

a diet with a significant amount of processed and/or fast foods has significantly reduced magnesium intake [11, 13]. This has led to a subtle chronic magnesium imbalance that occurs over years or a lifetime. In the vast majority of individuals, this imbalance is not detected by measuring the SMC, since magnesium is slowly leached from bone to maintain the SMC within the reference interval [18]. The best evidence that magnesium has been taken from bone in a state of chronic latent magnesium deficiency is a study that shows a very significant negative correlation between ($r = -0.992$) between bone magnesium content and the magnesium retention test [19]. The magnesium retention test is viewed as the best assessment of magnesium deficiency [20]. If the bone magnesium is normal, implying normal magnesium status, the individual does not retain a significant amount of magnesium after intravenous administration, indicating that body pools have adequate magnesium, particularly bone. On the other hand, if a significant amount of the intravenous magnesium is retained and not excreted in the urine, it indicates magnesium deficiency. It is this equilibrium between bone and the SMC that facilitates the development of chronic latent magnesium deficiency in “normal” individuals. Certain disease entities do not permit the appropriate absorption of magnesium from the gastrointestinal tract and increase the probability for this entity. Chronic wasting of magnesium through the kidney into the urine is seen in common diseases such as diabetes mellitus and alcoholism and also a growing list of drugs that enhance magnesium excretion in the urine. Thus, chronic latent magnesium deficiency is prevalent in our population but can be identified and treated by

establishing an evidence-base reference interval for the SMC where the lower limit is adjusted to a value for health, approximately 0.85 mmol/L.

Disclosure

The author has no conflict of interest or financial support to disclose.

References

1. Elin RJ. Magnesium metabolism in health and disease. *DM* 1988; 34: 163-218.
2. Rehak NN, Cecco SA, Niemela JE, Elin RJ. Thiocyanate in smokers interferes with Nova magnesium ion-selective electrode. *Clin Chem* 1997; 43: 1595-600.
3. Abudu N, Miller JJ, Elin RJ. The effect of thiocyanate on the Nova ion-selective electrode for magnesium. *Clin Chem* 2006; 52 (Suppl.): A105.
4. College of American Pathologists. Participant Summary. AQ-C Survey p41 and C-C Survey p44, 2009.
5. Alfrey AC, Miller NL, Butkus D. Evaluation of body magnesium stores. *J Lab Clin Med* 1974; 84: 153-62.
6. Kroll MH, Elin RJ. Relationship between magnesium and protein concentrations in serum. *Clin Chem* 1985; 31: 244-6.
7. Speich M, Bousquet B, Nicolas G. Reference values for ionized, complexed, and protein-bound plasma magnesium in men and women. *Clin Chem* 1981; 27: 246-8.
8. Avioli LV, Berman M. Mg^{28} kinetics in man. *J Appl Physiol* 1966; 21: 1688-94.
9. Song Y, He K, Levitan EB, Manson JE, Liu S. Effects of oral magnesium supplementation on glycaemic control in Type 2 diabetes: a meta-analysis of randomized double-blind controlled trials. *Diabet Med* 2006; 23: 1050-6.

10. Lowenstein FW, Stanton MF. Serum magnesium levels in the United States, 1971-1974. *J Am Coll Nutr* 1986; 5: 399-414.
11. Ford ES, Mokdad AH. Dietary magnesium intake in a national sample of U.S. adults. *J Nutr* 2003; 133: 2879-82.
12. Expert Panel. Report of the National Cholesterol Education Program expert panel on detection, evaluation, and treatment of high blood cholesterol in adults. *Arch Intern Med* 1988; 148: 36-69.
13. Marier JR. Quantitative factors regarding magnesium status in the modern-day world. *Magnesium* 1982; 1: 3-15.
14. Von Ehrlich B. Magnesiummangelsyndrom in der interistischen praxis. *Magnes Bulletin* 1997; 19: 29-30.
15. Liebscher DH, Liebscher DE. About the misdiagnosis of magnesium deficiency. *J Am Coll Nutr* 2004; 23: 730S/731S.
16. Everett CJ, King DE. Serum magnesium and the development of diabetes. *Nutrition* 2006; 22: 679.
17. Guerrero-Romero F, Rascon-Pacheco RA, Rodriguez-Moran M, de la Pena J, Escobedo, Wachter, N. Hypomagnesaemia and risk for metabolic glucose disorders: a 10-year follow-up study. *Eur J Clin Invest* 2008; 38: 389-96.
18. Alfrey AC, Miller NL. Bone magnesium pools in uremia. *J Clin Invest* 1973; 52: 3019-27.
19. Cohen L, Laor A. Correlation between bone magnesium concentration and magnesium retention in the intravenous magnesium load test. *Magnes Res* 1990; 3: 271-4.
20. Ryzen E, Elbaum N, Singer FR, Rude RK. Parenteral magnesium tolerance testing in the evaluation of magnesium deficiency. *Magnesium* 1985; 4: 137-47.