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Interpreting Magnesium Status to Enhance Clinical Care – Key Indicators

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Abstract

Purpose of review—To update advances in identifying factors affecting magnesium (Mg) status that assist in providing improved evidence-based clinical decision-making for assessing Mg status.

Recent findings—Findings from recent cohort studies, small randomized control trials, and multiple meta-analyses reinforce earlier work that serum Mg concentrations, urinary Mg excretion, and Mg dietary intakes are inversely associated with cardiovascular disease, chronic kidney disease, and diabetes. These studies indicate that the reference range for serum Mg needs updating, and that individuals with serum Mg in the range of 0.75–0.85 mmol/L and displaying changes in other factors associated with a low Mg status may be Mg deficient. Individuals with serum Mg concentrations below this range most likely are Mg deficient, and above this range, are most likely Mg sufficient.

Summary—The combined determination of serum Mg concentration, 24-hr urinary Mg excretion, and dietary Mg intake is currently the most practical method to obtain a sound assessment of Mg status. The strong correlations of Mg deficiency with increased risk of several chronic diseases, some of which exist as co-morbidities, indicate that Mg status should be ascertained in subjects presenting such pathology.

Keywords

Magnesium status; hypomagnesmia; chronic disease; risk factors

INTRODUCTION

Magnesium (Mg) is a cofactor for over 600 enzymatic reactions vital to metabolic pathways including DNA, RNA, protein and adenosine-5′-triphosphate synthesis; cellular energy production and storage; glycolysis; and cellular second messenger systems. Because it has so many critical functions, body Mg is well regulated through three main mechanisms: (i) absorption through the gastrointestinal tract, (ii) renal excretion after filtration-reabsorption, and (iii) exchange from the large pool in bone [1]. During low intakes of Mg, the percent

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absorbed from the diet is increased, the amount excreted in the urine is decreased, and bone reserves are used. When dietary intakes are adequate, the opposite occurs.

The strong response of the body to maintain Mg homeostasis has made it difficult to establish status indicators for Mg. In addition, mild and moderate Mg deficiencies (subclinical Mg deficiency) are mostly asymptomatic [2*]. As a result, subclinical Mg deficiency has not been routinely recognized in healthy population groups. Nonetheless, relatively low Mg intakes, serum Mg concentrations, and urinary Mg excretions have been associated with critical health issues, including cardiovascular disease [3, 4, 5*, 6], type 2 diabetes [7*, 8, 9], pre-diabetes [10*], and chronic kidney disease [11, 12]. These associations often did not correlate with a Mg deficiency as defined by the currently designated serum clinical reference range. The lack of correlation raises the question about the ability to assess Mg status to determine the presence of subclinical Mg deficiency. The lack justifies a review of current research to determine whether there is an improved method for evaluating Mg status, and a need for a revised clinical reference range for serum Mg

Measures to assess Mg status

A review of Mg assessment measures and their utility are described in Table 1 and those with clinical utility are the focus of this article.

Serum Mg

A review of recent literature indicates that total serum Mg concentration is the predominant, but unreliable, clinical test used to assess Mg status. The reference interval used for total serum Mg concentration was determined by measuring Mg in 15,820 “healthy normal individuals” aged 18–74 years in the 1974 National Health and Nutrition Examination Survey 1 (NHANES 1). The central 95th percentile was established as the “normal” range for Mg, which resulted in a reference interval of 0.75–0.95 mmol/L [13]. This reference interval likely is not reflective of environmental conditions and eating habits of Americans today. For example, Mg intakes apparently have decreased because of such factors as lower amounts of Mg in processed foods and “fast foods” and a lower consumption of whole grains, and fruits and vegetables. In addition, over 99% of total body Mg (22 to 26 g for an adult) is extravascular; mostly in the bones (>50%), and <1% in the serum [1] [Figure 1]. Thus, serum Mg may not necessarily reflect true total body Mg content. This conclusion is supported by controlled metabolic unit studies with postmenopausal women that found serum Mg concentrations responded slowly (several weeks) with changes from deficiency to adequacy, or vice versa [14*]. Zhang and colleagues [15**] used a meta-analysis of 48 RCTs enrolling 2,131 subjects to quantify the overall responsiveness of serum Mg to oral Mg supplementation ranging from 197 to 994 mg/day for periods ranging from three weeks to five years (median 12 weeks). Significant dose and time responses of serum Mg concentration to oral Mg supplementation increased gradually until reaching a steady state at 300 mg/day after approximately 20 weeks (P-nonlinearity <0.001). High baseline serum Mg concentrations were associated with less or no changes in serum Mg. A recent extensive review found that serum Mg in relation with risk factors for chronic disease such as glucose intolerance, inflammation, and elevated blood pressure indicated that many individuals had what has been termed chronic latent Mg deficiency as defined by serum concentrations in

the range of 0.75–0.85 mmol/L [2*]. These findings indicate that many physicians may assume that patients have “normal” Mg status when they may actually have chronic or subclinical deficiency.

Dietary Mg

Dietary Mg also is used as a measure of Mg status. In the United States and Canada, Mg dietary reference intakes (DRIs) were set in 1997. For adults aged 19–30 years, and 31–70 years, respectively, recommended dietary allowances (RDAs) of 310 and 320 mg/d for women and 410 and 420 mg/d for men were set; estimated average requirements (EARs; average daily level of intake estimated to meet the requirements of 50% of healthy individuals) of 255 and 265 mg/d for women and 330 and 350 mg/d for men were set [16]. Controlled metabolic unit studies suggest that these DRIs need modification and that the DRIs vary with body weight [14*]. The studies indicated that the RDA and EAR may be 250 (or 3.57 mg/kg) and 175 mg/day (or 2.5 mg/kg), respectively, for a healthy 70-kg individual. In 2010, the average weights of American women and men were 166.2 and 195.5 (75.54 and 88.9 kg), respectively [17]. Basing the DRIs on body weight would result in an average EAR and RDA for women and men of 189 and 270 and 222 and 317 mg/day, respectively. Close to half of the US population has been shown to consume less than the daily requirement (1997 EAR) of Mg from foods [18*]. Table 2 provides a list of high Mg food sources.

The efficiency of a Mg uptake after ingestion is affected by its chemical form, when given as a supplement and by dietary factors that can enhance (lactose, fructose, and glucose) or inhibit absorption (fiber, free fatty acids, oxalate, phytate, and high levels of zinc). Also, net Mg absorption increases with increasing Mg intake; however fractional Mg absorption falls. Humans studies using diets ranging from low to high have found absorption to range from 35% to 70%. However, with normal intakes, 30% to 40% of dietary Mg is absorbed [16].

Urinary Mg

Although no standard has been set for urinary Mg excretion indicating a deficiency, controlled metabolic experiments indicate 40 to 80 mg (1.65 to 3.29 mmol) is the range of daily Mg excretion when Mg intakes are <250 mg/day, and 80 to 160 mg is the daily range when intakes are >250 mg/day independent of gender [14*]. However, it was found that urinary Mg excretion changed rapidly between these two ranges (within a few days) upon changing from below to equal or above the current RDA, or vice versa. This rapid change indicates that a single determination of 24-hour urinary Mg would be best used to support other Mg status indicators, or in the evaluation of Mg status of population groups. Analysis of datasets from subsets the Nurses’ Health Study I and II and the Health Professionals Follow-up Study found that for the population 24-hour urinary excretion of Mg, among other urinary biomarkers measured, was stable upon repeated measurements within one year. The investigators calculated intraclass correlation coefficients (ICC) of urinary magnesium in multiple 24-hour urine samples to evaluate reproducibility. They further calculated a reliability index (RI; the mean of a very large number of repeat measurements) to further evaluate reproducibility. For magnesium excretion the ICC was found to be ≥ 0.70 with an RI of ≥ 0.80. Thus these investigators suggest that biomarkers such as urinary magnesium

measured on several timepoints are potentially useful for the assessment of various nutritional and environmental exposures in epidemiologic studies [19**].

Mg status indicators and their association with cardiovascular diseases

In the vast majority of prospective and cross-sectional studies, serum, urinary, and dietary Mg have been inversely associated with hypertension and blood pressure. This is exemplified by a recent systematic review and meta-analysis of prospective cohort studies that found a dose-response between dietary Mg and hypertension with intakes below 250 mg/day by visual inspection of the displayed figure [20]. A longitudinal analysis for of heart failure diagnosis in the Jackson Heart Study cohort involving 4,916 African Americans free of heart failure but with other co-morbidities found the median gap from the baseline visit to initiation of heart failure was 1,837 days with 270 incident cases being reported. Participants in the first quartile of Mg intake (0.52 – 2.30 mg/day/kg body wt approx.181 mg/day) had an increased risk of heart failure hospitalization compared to those in the remaining quartiles (>2.30 mg/day/kg body wt) [HR of 0.66 and a 95% CI of 0.47 to 0.94]. In the Atherosclerosis Risk in Communities Study, a low serum Mg (<70 mmol/L) was associated with a 70% higher risk of incident heart failure [21]. An extensive review of cohort studies of cardiovascular disease outcomes found that the risk of mortality and morbidity of several cardiovascular diseases decreased as Mg status markers improved (dietary intake >250 mg/day; serum concentration >0.75 mmol/L; urinary excretion >100 mg/day) [2*].

Over 30 randomized controlled trials using a range of formulations and doses of oral Mg in normotensives and hypertensives provides a rich source of data on serum and urinary Mg with changes in blood pressure. As noted for the cohort studies, these studies similarly show increases in serum or urinary Mg with oral Mg supplementation along with variable results on blood pressure. In the meta-analysis by Zhang and colleagues [3], after a median dose of 368 mg/day for a median duration of 3 months in 2028 subjects, SBP was reduced by 2.0 mmHg (95% CI 0.43 to 3.58) and DBP by 1.78 mmHg (95% CI 0.73 to 2.82) with a noted rise of 0.05 mmol/L in serum Mg. A more targeted meta-analysis that included 11 studies (543 subjects) enrolling individuals with insulin resistance, prediabetes, or noncommunicable chronic disease found that Mg supplementation (365 – 450 mg/day) for a median of 3.6 months resulted in a mean reduction in SBP of 4.18 mmHg (standardized mean difference, −0.20; 95% CI −0.37 to −0.03) and 2.27 mmHg in DBP (−0.29; 95% CI −0.46 to −0.12) [22]. The authors of this meta-analysis concluded that the magnitude of blood pressure reduction is of great clinical significance when applied at the public health level.

Mg status indicators and their association with the metabolic syndrome and diabetes

Magnesium deficiency is not only a feature of diabetes but also frequently observed in individuals with prediabetes and/or the metabolic syndrome. Most recent support of this relationship is provided by the Canadian Health Measures Survey cycle 3 conducted between 2012 and 2013 that determined serum Mg concentrations in subjects aged 3–79 years. Type I or type 2 diabetes was associated with 0.04 to 0.07 mmol/L lower serum Mg compared to not having diabetes. Serum Mg concentration was negatively associated with diabetes, BMI, serum glucose, serum insulin, HbA1c, and HOMA-IR [23**]. This study

also found substantial proportions of the adult sex-age groups (9.5%–16.6%) and adolescents 12–19 years (15.8–21.8%) had serum Mg concentrations <0.75 mmol/L, currently accepted as an indication of Mg deficiency.

Another recent systematic review and meta-analysis of observational studies found a less robust association between serum Mg and the metabolic syndrome (mean difference: −0.19; 95% CI −0.36 to −0.03; P=0.023) [24*]. However, increased Mg intake was highly associated with a lower risk of the metabolic syndrome (OR: 0.73, 95% CI 0.62 to 0.86; P<0.001).

An analysis of data from 8,555 participants enrolled in the population-based Rotterdam Study found, in the fully adjusted statistical model, that participants with hypomagnesaemia (not defined) had an increased risk of developing diabetes over a median follow-up of 5.7 years (HR of 1.79 and a 95% CI of 1.16 to 2.77). Hypomagnesemic subjects were at risk for developing prediabetes over a median follow-up of 5.7 years, which was not statistically significant in fully adjusted models. A 0.1 mmol/L decrease in serum Mg concentrations was associated with an increased risk of both prediabetes and diabetes. This analysis also found that common genetic variants in magnesium-regulating genes influenced diabetes risk and that the risk was mediated through serum Mg [10*] with the authors suggesting a potential causal role of Mg in the development of diabetes.

Analysis of dietary Mg intake data from 25 prospective cohort studies involving 637,922 subjects with 26,828 incident cases of type 2 diabetes found, after adjusting for age and body mass index, the risk of developing diabetes was reduced by 8–13% per 100 mg/day increment in dietary Mg intake [7*].

Mg status indicators and their association with bone health

Mg totals about 1.0% and is in constant equilibrium with serum Mg and plays an important role in bone and mineral homeostasis. Deficient Mg can directly affect bone by altering the structure of apatite crystals. Mg deficiency is also associated with reductions of PTH and 1,25(OH_2) D levels and inflammation, all of which can lead to bone loss.

Both experimental and epidemiological studies suggest that both low and high serum Mg concentrations are associated with changes in bone health [25]. Postmenopausal women with osteoporosis are noted to have consistently lower serum Mg concentrations across studies than their healthy controls. Men, but not women, enrolled in the European Prospective Investigation into Cancer and Nutrition-Norfolk cohort showed significant inverse trends in fracture risk across serum Mg concentration groups for spine fractures (P=0.02) and total hip, spine, and wrist fractures (P=0.02). The mean serum Mg for men was 0.81 ± 0.12 mmol/L [26]. Similarly, for 2245 men aged 42–61 participating in the Kuopio Ischemic Heart Disease prospective cohort study found that low serum Mg levels with comparable dietary intakes were strongly and independently associated (HR 2.10, 0.74 mmol/L bottom quartile of serum Mg to top quartile, 0.89 mmol/L; 95% CI 1.30 to 3.41) with increased risk of total and femoral fractures [27].

The effect of Mg intake on bone indices such as bone mineral density (BMD) is unclear and the data are mixed. Magnesium intake was evaluated with respect to BMD and fractures, measured at multiple sites, in a systematic review of 24 studies that included both males and females (118,664 subjects 0.8 mos. to 67.7 yrs) and in an accompanying meta-analysis that included 12 studies. These authors found that high intakes of Mg (not defined) were not significantly associated with an increased risk of hip (summary effect size 1.92; 95% CI 0.81 to 4.55) and total fractures (1.01; 0.94 to 1.07). However, a high degree of heterogeneity was present in this small subgroup dataset. Additionally, they noted a positive and marginally significant correlation between Mg intake and femoral neck and total hip BMD based on 9 studies.

Mg status indicators and their association with chronic kidney disease

Hypomagnesemia has been shown to be an emerging risk factor for incident chronic kidney disease [11, 12]. Dietary intake of Mg was associated with a rapid decline in kidney function independent of multiple kidney disease risk factors as documented in The Healthy Aging in Neighborhoods of Diversity across the Life Span Study enrolling 3,720 healthy adults (estimated GFR >60 ml/min/1.73m^2). Magnesium intakes ranged from 46.9 mg/1000 kcal in tertile 1 to a high of 468.2 mg/1,000 kcal in tertile 3. After a median of 5 years of follow-up, participants in the lowest tertile [OR for tertile 1 vs 3: 2.02, 95% CI 1.05 to 3.86, p=0.02 in fully adjusted model) of dietary Mg intake had a 2-fold greater odds of rapid decline in kidney function [28**].

The finding that Mg affects kidney function decline suggests that a kidney function measurement may be useful in assessing Mg status. For example, urinary fibroblast growth factor-23 (FGF-23) might be such an indicator. FGF-23 **is a potent regulator of vitamin D and phosphate metabolism.** In a cross-sectional study which pooled three populations of young adults (n=1411) with normal kidney function and of African ancestry, but from diverse geographical regions, a linear regression analysis showed that after adjusting for covariates and calorie-adjusted dietary factors, a significant trend of increased serum FGF-23 levels occurred with decreasing quartiles of Mg intake (P<0.001) [29**].

Low serum Mg concentrations with FGF-23 dysregulation also have been deemed as a risk factor for cardiovascular mortality in diabetic patients with mild-to-moderate chronic kidney disease because these variables were associated with increased mitral valve calcification and intima media thickness [30*]. Additionally, decreased serum Mg and FGF-23 concentrations were significantly and independently associated with higher pulse pressure in pre-dialysis diabetic patients with chronic kidney disease [31].

Summary

Magnesium has been characterized as a shortfall nutrient of public health concern in America [18*]. Data from prospective cohort studies and small focused randomized controlled trials show strong correlation of Mg deficiency with increased risk of several chronic diseases, some of which exist as co-morbidities. The data are convincing that there may be a relationship, but we do not know the type of relationship. The papers linking low Mg to disease in this review are all associative data (except for blood pressure). What is

needed to advance the field are Mg supplementation studies to test whether the association is causal. However, a simple, rapid, and reliable single measurement to determine the presence of Mg deficiency is lacking. Each of the three most commonly used indicators of magnesium status has shortcomings. The serum reference range is questionable in individuals with Mg concentrations between 0.75 and 0.85 mmol/L as possibly deficient. Dietary Reference Intakes apparently need revision and likely change with body weight. Urinary Mg responds too quickly to changes in dietary Mg intakes. However, because each status indicator can be strengthened by the addition of one or both of the other indicators, a combination of all three indicators would be the most practical method to assess Mg status.

Conclusion

At present, a combined determination of serum Mg concentration and urinary Mg excretion along with a dietary Mg history seems to be the propitious choice to get a valid assessment of magnesium status. Magnesium deficiency should be considered as contributing to some chronic diseases and associated morbidities if subjects exhibit a combined serum Mg <0.85 mmol/L; urinary Mg excretion <80.0 mg/day; and/ Mg intakes <250 mg/day.

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Abbreviations

Mg	magnesium
RDA	recommended dietary allowance
DRI	dietary reference intake
EAR	estimated average requirement

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Key Points

- A simple, rapid, and accurate single measurement to assess total body Mg status is lacking.
- A combination of serum, urinary, and dietary Mg may the most practical method to assess Mg status at present.
- Improved, evidence based Mg DRIs and serum reference range are needed.
- Magnesium is a shortfall nutrient of public health concern.
- Assessment of Mg status is important because deficiency has an impact on multiple chronic diseases, morbidity and mortality

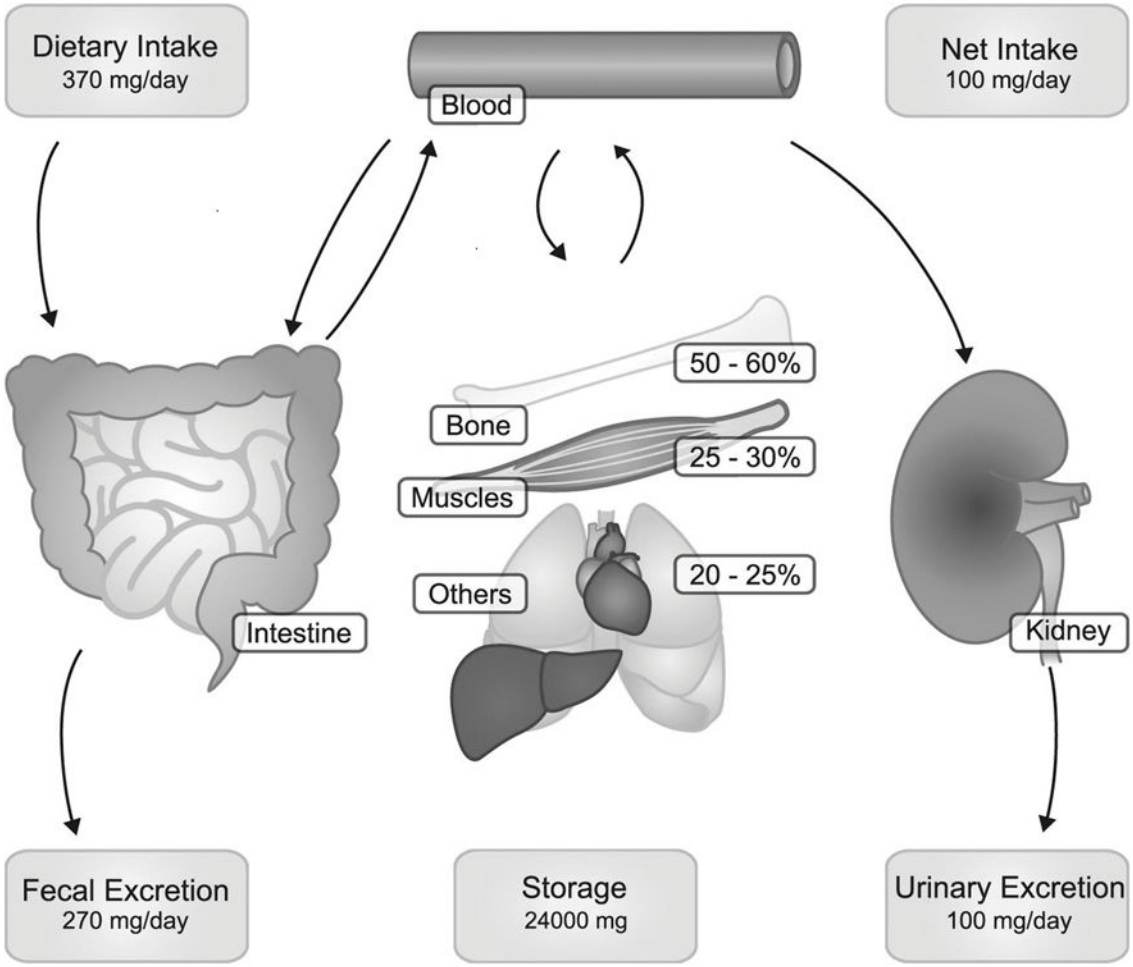

Figure 1.

Magnesium homoeostasis. Panels represent the daily amount of Mg^{2+} intake and excretion. Daily the intestines absorb ≈120 mg and secrete 20 mg of Mg^{2+}, resulting in a net absorption of 100 mg. In the kidney daily ≈2,400 mg Mg^{2+} is filtered by the glomerulus, of which 2,300 mg is reabsorbed along the kidney tubule. This results in a net excretion of 100 mg, which matches the intestinal absorption. Bone and muscle provide the most important Mg^{2+} stores. From de Baaji, Hoenderop, and Bindels, 2015 [1].

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Table 1

Magnesium assessment measures and their utility[1]

Biomarker	Type	Use	Utility	Factors to be considered	Assessment Methods
Dietary Mg	Exposure	Individual Population	Inadequate intake of dietary Mg contributes to etiology of Mg deficiency	Impacted by diets high in phytates, calcium, and phosphorus	Requires data on intake of phytates, calcium and possibly phosphorus as well as food preparation methods and extent of consumption of refined grains. Diet history and FFQ should be used to align with individuals; 24 hr recall and weighed or estimated diet records should be aligned with populations.
Serum / Plasma Mg Concentration	Exposure Status (deficiency or excess)	Individual Population	Responds to Mg restriction, wasting or supplementation. Generally not influenced by age or sex.	Feasible and inexpensive. Not reflective of total body stores. Impacted by time of day (circadian rhythm), inflammation, poor or compromised renal function, poorly controlled diabetes, drugs (diuretics, cancer therapies; PPIs). Hypoalbuminemia may lead to spuriously low magnesium values.	Assay Method of Choice: Atomic Absorption Spectrophotometry. Acceptable methods: Colorimetric is used by the majority of clinical laboratories; enzymatic also acceptable. NIST standard available Reference Range 0.75–0.95 mmol/L
24 hr Urinary Mg Excretion	Exposure Status (deficiency or excess)	Individual Population	Responds to Mg restriction, wasting or supplementation.	Considerable subject burden. Susceptible to incomplete collection Impacted by time of day (circadian rhythm), inflammation, poor or compromised renal function, poorly controlled diabetes, drugs (diuretics) In adults, appears to be an effective biomarker.	Assay Method of Choice: Atomic Absorption Spectrophotometry. In presence of hypomagnesemia urinary Mg excretion <12 mg (0.5 mmol) is consistent with intact renal response and urinary Mg >24 mg (1 mmol) excretion indicates abnormal renal wasting. Reference Range: 3.0–5.0 mmol/24 hr
Fractional Excretion of Mg (FEMg)	Exposure Status for deficiency	Individual	Used to distinguish between GI and renal Mg losses	Impacted by time of day (circadian rhythm), inflammation, poor or compromised renal function, poorly controlled diabetes, drugs (diuretics, cancer therapies).	FEMg = [uMg × sCr)/sMg × uCr×0.7] × 100. U=urine, s=serum, Cr = creatinine. FEMg >2% indicates inappropriate renal wasting. FEMg <2% indicates appropriate renal handling.
Red Cell Mg Concentration	Exposure Status (deficiency or excess)	Individual	Responds to Mg restriction, wasting or supplementation. May be more accurate than serum measures.	Care must be taken not to hemolyze blood sample Unknown if reflective of body stores.	Assay Method of Choice: Atomic Absorption Spectrophotometry. Reference Range 1.65–2.65 mmol/L Test is not commercially available
Blood mononuclear cell Mg concentration	Exposure status for deficiency	Individual	Has been used in experimental human Mg deficiency and in patient populations.	May be more accurate than serum measures.	Test is not commercially available.
Serum Ionized Mg concentration	Exposure (deficiency or excess)	Individual	Responds to severe Mg restriction, wasting or supplementation.	Ion selective electrode probes susceptible to interference by calcium, lipophilic cations and thiocyanate in the blood. Unknown if reflective of body stores	Ion selective electrodes can measure ionized Mg (70% of total Mg) in serum, plasma, and whole blood. Reference Range: 0.55–0.75 mmol/L.
Buccal cell Mg concentration	Exposure (deficiency or excess)	Individual	Relatively new. Few data from randomized trials	Unknown if reflective of body stores	Assay method yet to be validated. Commercial kits are available.

Biomarker	Type	Use	Utility	Factors to be considered	Assessment Methods
Mg Load Retention Test	Exposure (deficiency)	Individual	Based on 24-hr urine collection and ability to administer IV Mg Sulfate.	Invasive and cumbersome. Values correlate well with bone magnesium but have yet to be shown to correlate with other magnesium measures – such as serum or plasma blood levels.	Standard protocols exist. Based on amount of Mg retained post infusion of 15 mmol over 4 hour period. <20% retention – normal Mg status >20 and <50% - borderline deficient Mg status >50% - deficient Mg status

[1] Table compiled from Witkowski, Hubert, and Mazur, 2011 [13].

TABLE 2

Magnesium Content of Selected Foods[1]

Food	Magnesium mg/serving
Almonds, dry roasted, 1 ounce	80 (20% DV)
Spinach, boiled, ½ cup	78
Chocolate, dark, 70–85% cacao solids, 1 oz	65
Peanuts, oil roasted, ¼ cup	63
Oatmeal, regular and quick, cooked, 1 cup	63
Soymilk, plain or vanilla, 1 cup	61
Black beans, cooked, ½ cup	60
Peanut Butter, smooth, 2 TBSP	54
Edamame, shelled, cooked, ½ cup	50
Bread, whole wheat, 2 slices	48
Potato, baked with skin, 1 medium, 173 g	48
Avocado, cubed, 1 cup	44
Rice, brown, cooked, ½ cup	42
Soymilk, original and vanilla with added calcium, vitamins A&D, 1 cup	36
Milk, reduced fat, 2% milk fat, 1 cup	34
Cereal, cheerios, 1 cup	32
Banana, 1 medium, 118g	32
Yogurt, plain, low fat, 8 oz’	27
Kale, cooked, boiled, 1 cup	23 (6% DV)

[1]Source: USDA, National Nutrient Database for Standard Reference, Release 28 [19].

DV=Daily Value