# Perspective: The Case for an Evidence-Based Reference Interval for Serum Magnesium: The Time Has Come[1–5]

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## ABSTRACT

The 2015 Dietary Guidelines Advisory Committee indicated that magnesium was a shortfall nutrient that was underconsumed relative to the Estimated Average Requirement (EAR) for many Americans. Approximately 50% of Americans consume less than the EAR for magnesium, and some age groups consume substantially less. A growing body of literature from animal, epidemiologic, and clinical studies has demonstrated a varied pathologic role for magnesium deficiency that includes electrolyte, neurologic, musculoskeletal, and inflammatory disorders; osteoporosis; hypertension; cardiovascular diseases; metabolic syndrome; and diabetes. Studies have also demonstrated that magnesium deficiency is associated with several chronic diseases and that a reduced risk of these diseases is observed with higher magnesium intake or supplementation. Subclinical magnesium deficiency can exist despite the presentation of a normal status as defined within the current serum magnesium reference interval of 0.75–0.95 mmol/L. This reference interval was derived from data from NHANES I (1974), which was based on the distribution of serum magnesium in a normal population rather than clinical outcomes. What is needed is an evidenced-based serum magnesium reference interval that reflects optimal health and the current food environment and population. We present herein data from an array of scientific studies to support the perspective that subclinical deficiencies in magnesium exist, that they contribute to several chronic diseases, and that adopting a revised serum magnesium reference interval would improve clinical care and public health. *Adv Nutr* 2016;7:977–93.

Keywords: serum magnesium, plasma magnesium, magnesium deficiency, reference interval, chronic disease

## Introduction

The perspectives gathered in this article stem from a workshop on addressing an evidence-based reference interval for serum total magnesium concentration (STMC)[15] that was held in April 2015 in Lowell, Massachusetts. The objectives of this article are to *1*) gather and categorize studies that have used serum and/or urinary magnesium, *2*) evaluate whether these studies collectively support the need for an evidence-based re-evaluation of the clinical reference interval, *3*) determine

whether the magnesium biomarkers in serum and/or urine are consistent across population groups, and *4)* identify data gaps for serum or urinary magnesium in terms of population groups (specific age, sex, and ethnicity) that are necessary to inform a re-evaluation of the clinical reference interval for serum magnesium.

Approximately half (48%) of the US population has been shown to consume less than the daily requirement of magnesium from foods (1), partly because of the processing of food, a lower consumption of whole grains and fruits and vegetables than recommended, and a greater consumption of fast food that has a low magnesium content. The 2015 Dietary Guidelines Advisory Committee found magnesium to be underconsumed relative to the Estimated Average Requirement (EAR) and characterized it as a shortfall nutrient of public health concern (2). The European Food Safety Authority recently published a scientific opinion on dietary reference values for magnesium and found that "although the role of Mg in bone structure and physiology is well established, there are few quantitative data for using this relation for setting dietary reference values for magnesium" (3). Nevertheless, the impact of chronically low magnesium intake on serum magnesium concentrations and long-term health remains poorly studied; most trials have been of short duration, and most observational studies have lacked repeated serum measures.

Overt signs of clinical magnesium deficiency have not been routinely recognized in the healthy population. However, relatively low magnesium intake and/or status has been associated with critical health issues, such as but not limited to hypertension (4–9), cardiovascular disease (CVD) (10–14), type 2 diabetes (T2D) (15–18), and osteoporosis (19, 20). In most cases, risk was elevated at serum magnesium concentrations higher than the present clinical cutoff for deficiency, raising the question of potential subclinical deficiency and chronic latent magnesium deficiency and justifying a review of the current research to evaluate contemporary ideas on "healthy" or "normal" serum total magnesium values. Therefore, this perspective is oriented toward supporting a need for identifying a clinical reference interval of STMC that is needed for optimal health.

STMC is the predominant test used by healthcare providers to assess magnesium status. The current reference interval for STMC was determined by measuring serum magnesium in then-representative healthy normal individuals of NHANES I (1974) (21). The central 95th percentile of this measure in 15,820 apparently healthy individuals aged 18–74 y was defined as the normal range (**Figure 1**).

This set the reference interval for serum magnesium at 0.75–0.95 mmol/L. It is important to highlight that this reference interval was based on the distribution in a normal population—not the relation between serum magnesium and clinical outcomes. Re-evaluating this reference interval while also taking into account health outcomes is therefore justified (22). Physicians may be led to assume that patients have normal magnesium status when they may have chronic latent magnesium deficiency (23, 24). Complicating the picture further, the last time serum magnesium was measured
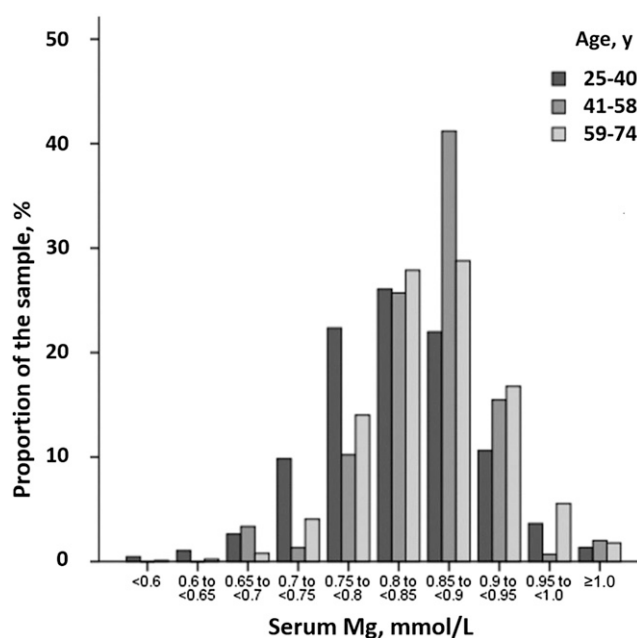


**FIGURE 1** Age-specific distributions of serum magnesium in US adults. Data were derived from NHANES I (1971–1975). Mg, magnesium.

in NHANES was >40 y ago, and given changes in the food supply, changes in population distribution, prevalence of diseases such as obesity and T2D, and so on, the current distribution of serum magnesium in the United States is effectively an unknown.

A simple, rapid, and accurate test to assess total body magnesium status is lacking. Although STMC is most commonly used to assess the status of patients, >99% of total body magnesium (22–26 g in adults) is extravascular, mostly in the bones (>50%), with only 0.3% in the serum (25). Thus, this parameter does not necessarily reflect the true total body magnesium content. The serum concentration of ionized magnesium, the biologically active form, may be more reflective of true magnesium status; however, clinical reliance on this measure remains controversial (26). Another noninvasive method is to analyze urinary magnesium excretion. Because renal magnesium excretion decreases in response to dietary deficiency, this can be an important parameter during the assessment of magnesium status (27). The combined determination of the STMC and urinary magnesium excretion are currently the most practical tests to assess magnesium status (28), but their reliability as biomarkers needs rigorous evaluation.

Although normal serum magnesium concentrations can be seen in the presence of intracellular magnesium deficiency, once serum magnesium declines, it is unlikely that the intracellular magnesium concentration remains normal. In addition, taking into account that magnesium homeostasis depends on the relation between intake and loss, a rational approach for a reliable magnesium biomarker should take into account the relation between intake, serum concentrations, and urinary concentrations. Available data suggest that serum and plasma magnesium concentrations,

RBC concentrations, and urinary magnesium excretion respond to dietary manipulation (29).

Discussions from the previously mentioned workshop on the critical evaluation of the clinical reference interval are summarized in the sections that follow along with their applicability in evaluating the STMC reference range. The perspectives presented in this review reflect a gathering of current literature that has measured serum total, urinary, and/or dietary magnesium in both healthy humans and in humans with various chronic diseases (osteoporosis, T2D, hypertension, CVD).

## What Have We Learned from Balance Data with Respect to Dietary Requirements and Status Indicators of Magnesium?

Because dietary intake of magnesium is often used to support the judgment of status for determining reference values, adequate and deficient intakes need to be based on data obtained from well-controlled studies with humans. The EAR and RDA set for magnesium in 1997 in the United States and Canada were based on highly variable balance data from only 34 men and women on self-selected diets (30). Since then, improved balance data have been reported that can be used to determine the Dietary Reference Intakes for magnesium. These include data from 27 tightly controlled metabolic ward studies (including 243 healthy men and women aged 19–77 y whose weight ranged from 46 to 136 kg) that found neutral magnesium balance, without considering surface or phlebotomy losses, occurred at an intake of 165 mg/d with a 95% prediction interval of 113–237 mg/d (31). With the use of the upper 95% value of 237 mg/d and considering that 98% is the upper interval level used for setting RDAs, the metabolic unit balance data indicated an RDA of ∼245 mg/d. Considering surface and phlebotomy losses in the balance studies would increase the RDA to 250 mg/d for a healthy 70-kg adult.

Body weight and environmental and dietary factors can have a marked effect on the magnesium requirement. These factors need to be considered if or when dietary magnesium intake is used to indicate magnesium status in the determination of reference values (31–38).

The balance data obtained from the metabolic unit studies of magnesium depletion and repletion also have provided additional information that may be useful for determining reference values. These studies determined changes in serum and urinary magnesium with changes from deficient to adequate magnesium intakes (39–42). These findings indicate that urinary magnesium is a relatively good indicator of magnesium intake, that urinary excretion <80 mg/d indicates a risk for a current dietary magnesium deficiency, and that urinary excretion 80–160 mg/d is associated with magnesium intakes >250 mg/d (**Figure 2**). However, the rapid change in urinary excretion with a change from deficient to adequate magnesium intake, or vice versa, indicates that urinary magnesium measurement alone is not a good indicator of status if dietary changes were recent or short term. In such cases, individuals excreting <80 mg/d could still be

magnesium adequate, whereas individuals excreting >80 mg/d could be magnesium deficient.

Serum magnesium does not respond as quickly or consistently as does urinary magnesium when magnesium deficiency is present based on results from metabolic unit studies (39–42). This indicates that those individuals with serum magnesium concentrations indicating adequacy actually could be in, or approaching, a chronic latent magnesium-deficient state caused by a less-than-adequate magnesium intake.

In conclusion, metabolic unit balance and depletion and repletion experiments indicate that serum magnesium concentrations <0.82 mmol/L (2.0 mg/dL) (i.e., higher than the current cutoff) with a urinary magnesium excretion of 40–80 mg/d, indicating magnesium intake of <250 mg/d, strongly suggest that an individual is magnesium deficient, thus potentially increasing the risk for some chronic diseases. In addition, these individuals should respond well to an increase in magnesium intake.

## Does Inflammation and Its Relation to Chronic Disease Help Inform a Reference Range for Serum Magnesium?

Many pathologic conditions involving low serum magnesium status have been associated with an increased inflammatory response and oxidative stress in both animals (43) and humans (34). This is well characterized by the activation of several leukocytes and macrophages as well as the release of numerous inflammatory cytokines and acute-phase proteins. Although low magnesium status may not be a direct cause of inflammatory diseases, insufficient magnesium has consistently been shown across multiple laboratories to increase chronic low-grade inflammation, which is thought to play a major role in chronic disease etiology. Animal studies limiting magnesium intake support data in humans confirming the biological plausibility behind low magnesium status and low-grade chronic inflammation (34), although the lack of dose-response randomized controlled trial (RCT) data makes it difficult to ascertain a direct effect. It is plausible that low magnesium status may be an indicator of other suboptimal dietary and lifestyle patterns that lead to low-grade chronic inflammation (e.g., inadequate intakes of fruits and vegetables).

However, most studies have indicated that increased dietary intakes of magnesium have been linked to a decrease in several markers of systemic inflammation and endothelial dysfunction such as, but not limited to, IL-6, TNF-α, soluble intracellular adhesion molecule 1, soluble vascular cell adhesion molecule 1, and C-reactive protein (CRP). A systematic review and meta-analysis of observational and experimental studies indicated an inverse association between magnesium intake and serum CRP (44). A recent RCT of 62 men and nonpregnant women (45) supported this finding and indicated that low serum magnesium status is correlated with higher serum CRP. Individuals who received magnesium chloride in this RCT had higher serum magnesium concentrations (0.86 ± 0.08 compared with 0.69 ± 0.16 mmol/L; $P = 0.002$) and lower serum CRP concentrations (4.8 ± 15.2

**FIGURE 2** Data derived from urinary magnesium excretion in 93 men and 150 women participating in 27 different tightly controlled metabolic unit studies in which dietary magnesium ranged from 84 to 598 mg (3.46–246 mmol/d). Diet, dietary; Mg, magnesium.
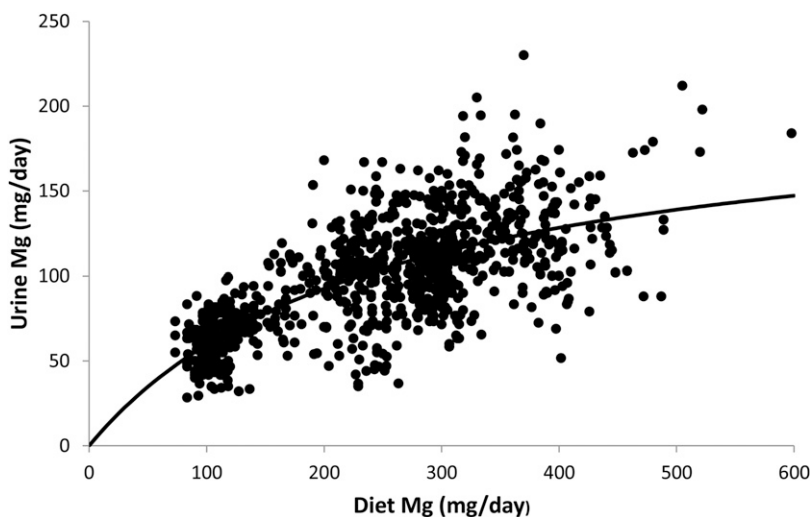
compared with $17.1 \pm 21.0$ nmol/L; $P = 0.01$) than participants in the control group. Two mechanisms have been proposed to explain the increase in inflammatory response caused by magnesium deficiency or insufficiency. First, reactive oxygen species are increased when an individual undergoes a state of magnesium deficiency, as measured by serum magnesium status. The increase in reactive oxygen species promotes membrane oxidation and NF-kB production. Second, the attenuation of the calcium channel-blocking effect of magnesium during magnesium deficit allows for increased calcium entry within immune-competent cells, stimulating an inflammatory response (46).

These studies support a role for magnesium in the inflammation-based etiology of many chronic diseases and suggest a causal role for magnesium in lowering certain markers of inflammation. However, more studies are needed if magnesium's role in inflammation can or should be used to support a revision of reference intervals, especially because many markers of inflammation do not yet have clinically useful reference intervals. Nevertheless, the relations demonstrated to date on the role of magnesium and inflammation suggest that this and accruing evidence could support a disease and/or optimal health-based re-evaluation of the current serum magnesium reference interval.

### Are Skeletal Studies Informative for Redefining the Reference Range for Serum Magnesium?

Magnesium consists of ~0.5–1.0% bone ash and plays an important role in bone and mineral homeostasis. Several animal studies have demonstrated that magnesium deficiency results in bone loss (47, 48). The small body of clinical evidence suggesting that long-term low dietary intakes of magnesium influence bone mass, bone turnover, bone-related hormones, and cytokine concentrations has been previously reviewed (37). There is growing evidence that magnesium may not only affect bone cell function and hydroxyapatite crystal formation but may also be an important factor in quantitative changes of the bone matrix that predict fragility. Magnesium has been evaluated with respect to bone health in a meta-analysis of

7 studies (49) and 6 case-control studies (50–55). In these studies, the association between serum magnesium concentrations in postmenopausal women with osteoporosis compared with a healthy control were examined. The 6 case-control studies were all included in the meta-analysis (49), which suggested that serum magnesium concentrations have an inverse relation with bone mineral density (BMD). Taken together, these studies suggest low serum magnesium is a plausible risk factor for osteoporosis among postmenopausal women. BMD is currently the only risk biomarker of osteoporosis considered valid by the FDA; however, other markers of bone turnover have also been used to assess the effect of serum magnesium status in relation to bone health and fracture risk (56, 57). 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 magnesium concentration groups for spine fractures ($P = 0.02$) and total hip, spine, and wrist fractures ($P = 0.02$). The mean serum magnesium for men was $0.81 \pm 0.12$ mmol/L (58).

Postmenopausal women with osteoporosis had consistently lower serum magnesium concentrations across studies than their healthy controls (49). In addition, RBC magnesium concentrations have been shown to be lower in postmenopausal women with osteoporosis than a healthy control (59). These data are consistent with other studies that have indicated that the dietary intake of magnesium is inversely associated with DXA bone status measurements (60). A recent analysis of the Women's Health Initiative Observational Study, which did not assess serum or urine magnesium, suggested that lower dietary magnesium intake is associated with lower BMD of the hip and whole body but not with an increased risk of fractures (61). Magnesium intake has been shown to have a positive association with BMD in both cross-sectional studies that used dietary recalls (20, 62–65) and clinical studies of supplemental intake (66–68).

The limited evidence to date, primarily in the form of case-control studies, points to an inverse relation between serum magnesium and osteoporosis, a relation further

supported by observational studies of dietary magnesium in bone health. The literature on magnesium in bone health is notably dwarfed by the vast literature on calcium, a mineral that often competes with magnesium; i.e., magnesium has been largely ignored. More data from trials and prospective observational studies will be needed to support an appropriate serum magnesium reference interval for older individuals, particularly for postmenopausal women, who represent the highest and largest risk group for osteoporosis and for whom serum magnesium is a plausible risk factor for osteoporosis.

## How Do Data from Studies in Healthy Individuals Inform a Reference Range for Serum Magnesium?

### Cross-sectional studies

*Serum magnesium.* To our knowledge, 35 cross-sectional studies or surveys have evaluated serum magnesium in healthy individuals, 4 of which were national health surveys. Table 1 presents the means and ranges of serum magnesium in these studies in addition to the cutoff and prevalence of hypomagnesemia. As noted earlier, NHANES I, which included 15,820 white and black men and women aged 1–74 y, is the only national study in the United States to our knowledge to have collected serum magnesium concentrations (21). Several other countries have included serum magnesium in their measures, including the 2006 Mexican National Health and Nutrition Survey, which consisted of a population of representative men and women aged >20 y (70), adolescents (71), and children (72). In addition, the China Health and Nutrition Survey initiated in 1989 collected blood samples in 2009 from 8511 participants aged ≥18 y from 228 communities across 9 provinces in China (73), and the 1998 Comprehensive Survey of Living Conditions of the People on Health and Welfare examined a subset of 62 Japanese adults aged 20–90 y (74). Table 1 presents a summary of these results.

Five studies were conducted exclusively in children aged <18 y (75–79). Two studies evaluated adults >65 y. The first of these studies compared residents living in nursing homes with those who were not (*n* = 345) to document serum magnesium and zinc and associated deficiency symptoms (80). In total, 33% of the seniors sampled were found to be hypomagnesemic. The second study, part of the Prospective Investigation of the Vasculature in Uppsala Seniors (81), evaluated 897 seniors to validate the Nordic Reference Interval Project for a battery of clinical chemistry tests. No individuals with T2D were studied in this population, but 80% of the seniors were on medications, predominantly for CVD. Serum magnesium for both men and women without CVD ranged from 0.70 to 0.96 mmol/L and was similar to those previously documented for the entire Nordic population.

Twelve studies evaluated participants with a BMI (in kg/m²) <25 (70, 74, 75, 77, 82–89), and 14 studies reported on participants with a BMI >25 (70, 81, 84–88, 90–96). In total, 9 of the 14 studies (64%) that enrolled participants with a BMI >25 demonstrated hypomagnesemia (<0.75 mmol/L) compared with 2 of the 12 studies (16%) that enrolled participants with a BMI <25. Sharifi et al. (94) found that the prevalence of magnesium deficiency (<0.70 mmol/L) in women with polycystic ovary disease was significantly higher than in women without the disease (13% compared with 0%; *P* = 0.02).

*Dietary magnesium.* In addition to measuring serum magnesium, 5 studies also collected information on dietary magnesium (70, 77, 88, 96, 97). One of these studies (88) evaluated concentrations of magnesium in the water in 3 different geographical regions in Serbia. Individuals in 2 soft-water (low concentration of dissolved calcium and magnesium) regions had lower concentrations of serum magnesium (0.72 ± 0.05 mmol/L) than the 1 hard-water (high concentration of dissolved calcium and magnesium) region (0.87 ± 0.09 mmol/L).

*Urinary magnesium.* Two large multinational population-based studies (98, 99) collected 24-h urinary magnesium along with other biomarkers of interest. Although neither collected serum magnesium concentrations, thereby limiting the inferences that can be made, these studies did supply useful dietary and associated risk-factor data. The INTERMAP Study (98) investigated the role of multiple dietary factors and urinary metabolites on blood pressure (BP) concentrations among 4680 middle-aged men and women in the United States, United Kingdom, China, and Japan. Mean dietary magnesium intake in 2194 US participants aged 49.1 ± 5.4 y was 148.2 ± 40 mg/1000 kcal, which is within the normal range (113–237 mg/d). Urinary magnesium was 4.25 ± 1.58 mmol/d (104 mg/d), above the deficiency cutoff cited earlier. In the WHO CARDIAC Study (99), which evaluated 24-h magnesium excretion and CVD factors in 4211 participants aged 48–56 y in 50 population samples from 22 countries, the reported magnesium:chromium ratio (mg:g) by quintile ranging from a low of 34.7 ± 12.1 to a high (fifth quintile) of 136.7 ± 44.9. magnesium:chromium ratios were found to be inversely associated with BMI, systolic and diastolic BP, and total cholesterol. The risk of hypertension was significantly higher only in the lowest magnesium:chromium ratio quintile (*P* < 0.001).

Collectively, these data provide serum magnesium and/or 24-h urinary concentrations across the spectrum of age groups for both men and women over a range of BMI measures and in multiple ethnic groups with diverse dietary patterns. Lacking are studies collecting both dietary data and serum and/or urinary magnesium data; such studies could help inform the biomarker use in assessing magnesium intake or its ability to improve a less-than-adequate magnesium status.

### RCTs

Table 2 shows basal circulating magnesium concentrations from 28 RCTs (7 of which were cross-over) that enrolled a total of 2106 healthy participants or participants with

**TABLE 1** Reference intervals of serum magnesium from nationally representative studies and surveys[1]

| Reference (country) | Mean serum magnesium, mmol/L | Range of serum magnesium, mmol/L | Prevalence of hypomagnesemia | Additional study findings |
|---|---|---|---|---|
| Lowenstein and Stanton (21) (United States) | 0.85 | 0.75–0.96 | Women: 21% (<0.8 mmol/L); men: 1.5% (<0.7 mmol/L) | NHANES I (1971–1975) reported 12 age categories; small sex differences were observed between the ages of 18 and 45 y, with men having higher concentrations than women; both white men and women had higher serum concentrations than black men and women of the same age; these differences were statistically significant in many age groups, particularly in young and middle-aged adults; low serum magnesium (<0.80 mmol/L) was associated with all-cause mortality (69) |
| Mejía-Rodríguez et al. (70) (Mexico) | 0.81 (median) | 0.70–0.95 (median) | Women: 36.3% (<0.75 mmol/L); men: 31% (<0.75 mmol/L) | 5410 adults representing ~59 million Mexican adults from the National Health and Nutrition Survey (2006) aged ≥20 y; 63.2% women; 70% overweight or obese |
| De la Cruz-Góngora et al. (71) (Mexico) | 0.79 (no difference by sex) | NR | Overall: 37.6%; females: 40%; males: 35.4% (<0.75 mmol/L) | 2447 adolescents representing ~17 million adolescents from the National Health and Nutrition Survey (2006); mean age: 15.1 y (range: 12–19 y); survey included 54% females, of which 35.4% were overweight or obese; 7.29 (7.7% females and 6.8% males) had a CRP >6 mg/dL; overall median daily magnesium intake was 235 mg/d; no significant associations were found for serum magnesium with sex, BMI (in kg/m²), CRP, or ethnicity |
| Morales-Ruán Mdel et al. (72) (Mexico) | 0.86 | 0.86–0.90 (<5 y); 0.82–0.87 (5–11 y) | Overall: 22.6%; aged 1–4 y: 12%; aged 5–11 y: 28.4% (<0.75 mmol/L) | 5060 children representing ~24 million children from the National Health and Nutrition Survey (2006); age range: 1–11 y; 49% females |
| Zhan et al. (73) (China) | Men: 0.95; women: 0.93 | 0.84–1.05 | NR | Samples collected from 8511 participants; significant interaction found with serum magnesium and sex and low serum ferritin (P < 0.001); prevalence of anemia decreased with increasing concentrations of serum magnesium |
| Akizawa et al. (74) (Japan) | 0.85 | 0.54–1.19 | NR | Participants from the 1998 Comprehensive Survey of Living Conditions of the People on Health and Welfare; distribution of serum magnesium was normal; daily magnesium intake (322 ± 147 mg/d) correlated with serum magnesium (0.28; P = 0.05) |

[1] CRP, C-reactive protein; NR, not reported.

CVD risk factors given either magnesium supplementation or a placebo in studies that lasted 28 d to 12 mo. These studies evaluated magnesium status via serum and/or urine and the impact of magnesium supplement or placebo upon biomarkers of insulin resistance, glycemic control, blood lipids, and/or inflammation.

Very few studies enrolled exclusively men or exclusively women. Only one study—the Trial of Hypertension Prevention, which was the largest of the studies—reported serum values separately for men, women, blacks, and whites (100). Data from 13 different countries are represented in this healthy RCT data set. The 20–39- and 40–59-y age groups were the predominant groups studied; 2 studies were identified with participants aged <18 y, and 4 studies enrolled participants ≥75 y. Serum and plasma magnesium was collected in 23 studies. Dietary data were collected in 5 of these studies, urinary data were collected in 4, and

3 studies collected all 3 status markers. No studies collected urinary magnesium data alone, but 2 collected urinary data along with dietary data.

Together, these population-based cross-sectional studies and clinical trials indicate that some 10–30% of a given population, considered healthy, may have serum magnesium concentrations below typically used cutoffs (<0.80 mmol/L). This points to several potential realities and questions. If, in fact, serum magnesium concentrations are clinically low in as much as a third of any given population, such a reality would warrant considerable attention and potential intervention, not to mention additional research (notably trials) on the causes of such a high incidence of hypomagnesemia and the potential effects of magnesium intake in reducing or preventing chronic disease. Of course, as highlighted elsewhere, the possibility remains that existing clinical cutoffs are too low. If so, the proportion of the

**TABLE 2** Serum and plasma magnesium concentrations reported at baseline in trials of healthy participants and those with risk factors for cardiovascular disease[1]

| | Healthy, no risk factors | Glucose-intolerant | Overweight or obese[2] | Elevated cholesterol | Hypomagnesemic | Blood pressure | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| | | | | | | Normotensive subjects | Hypertensive subjects |
| Numbers of studies (references) | 10 (100–109) | 9 (106, 110–117) | 15 (45, 100, 108, 110–114, 117–123) | 3 (103, 108, 109) | 10 (45, 104, 107, 110, 112, 113, 116–118, 122, 124) | 16 (45, 105, 106, 111, 112, 118, 121, 122, 124–129) | 14 (126, 130–143) |
| Range of serum and plasma magnesium, mmol/L | 0.61–0.87 | 0.56–0.89 | 0.79–0.94 | 0.82–0.88 | 0.56–0.74 | 0.53–1.17 | 0.62–1.01 |

[1] Some studies enrolled participants that may have presented with >1 risk factor and are referenced accordingly.
[2] BMI (in kg/m$^2$) >25.

population with suboptimal serum magnesium concentrations, along with any associated adverse health consequences, may be even higher.

## How Do Oral Magnesium Studies in Participants with Elevated BP Inform a Reference Range for Serum Magnesium?

BP is an extremely easy physiologic marker to measure, and hypertension is an established and reliable risk factor for CVD morbidity and mortality. Meta-analyses of clinical trials of oral magnesium therapy and BP have also shown varying results (4–8) depending on the meta-analysis inclusion and exclusion criteria. Overall, however, these meta-analyses have established a statistically significant effect of oral magnesium in lowering high BP. In a recent meta-analysis that investigated oral magnesium supplementation, Zhang et al. (9) showed a mean rise of 0.05 mmol/L in serum magnesium in 27 trials in a median time of 87 d and found significance (P < 0.001).

### Clinical studies

Our search of magnesium in BP and hypertension resulted in 80 studies (53 clinical trials and 6 cohort, 3 case-control, and 18 cross-sectional studies) (**Supplemental References**) that included measurements of serum and/or urinary magnesium, 2 of which were in adolescents (1 RCT in those aged 14–18 y and 1 cohort study in those aged 12–14 y). The remaining 78 studies were conducted in adults, of which 5 included some elderly participants aged ≥75 y. Our search returned no studies on young children or infants. Thus, there are considerable gaps in the data for the understanding of magnesium and BP in children, infants, teens, and the elderly. In the vast majority of prospective and cross-sectional studies, serum, urinary, and dietary magnesium were inversely associated with hypertension and BP, except in one study in teens. In general, these studies show that when urinary, serum, and/or dietary magnesium goes up, both systolic and diastolic BP go down.

### Intervention trials

Our search resulted in 53 publications that reported 65 human clinical trials of oral magnesium therapy for BP with measurements of serum and/or urinary magnesium (Supplemental References). Of these 65 trials, 44 were RCTs, 9 were non-RCTs, and 12 were noncontrolled trials. Of the 44 RCTs, 30 reported serum magnesium measurements. Table 2 shows the range of baseline serum and plasma magnesium reported in these 30 RCTs on normotensive and hypertensive participants.

This large number of clinical trials that used oral magnesium for BP in adults provides a rich source of data on serum and urinary magnesium with changes in BP during a stated supplemental oral magnesium dose. All of these studies, both those on normotensive as well as hypertensive participants, show increases in serum and urinary magnesium with oral magnesium supplementation along with variable results on BP (analyzed in the section that follows).

## How Do Cohort Studies of CVD Outcomes Inform a Reference Range for Serum Magnesium?

Magnesium is believed to be linked to CVD risk through a broad range of physiologic roles, several of which have been described in the previous sections; e.g., low circulating concentrations have been associated with impaired glucose homeostasis and insulin action, elevated BP, chronic inflammation, impaired vasomotor tone and peripheral blood flow, and electrocardiogram abnormalities (4, 15, 144, 145). To date, no RCT to our knowledge has explored whether magnesium supplementation is related to lower CVD risk. However, prospective observational studies in initially generally healthy populations have linked low circulating magnesium to a higher risk of CVD morbidity and mortality. Many of these observational studies were included in one or both of the 2 meta-analyses (10, 146) published in 2013. Del Gobbo et al. (10) estimated that per 0.2-mmol/L increment in circulating magnesium, the risk of total CVD was 30% lower (RR: 0.70; 95% CI: 0.56, 0.88), the risk of ischemic heart disease was 17% lower (RR: 0.83; 95% CI: 0.65, 1.05), and the risk of fatal ischemic heart disease (e.g., fatal myocardial infarction) was 39% lower (RR: 0.61; 95% CI: 0.37, 1.00). Results were similar, albeit slightly weaker, in the meta-analysis from Qu et al. (146) for total CVD events (RR: 0.91; 95% CI: 0.85, 0.97 per 0.05 mmol/L). The studies included in the meta-analyses and 4 additional

studies [2 nested case-control (147, 148) and 2 cohort (11, 149)] resulting from a recent literature search are summarized in **Figure 3** (**Supplemental Table 1** displays the CIs for this data set), which shows that the risk of mortality and morbidity of several cardiovascular diseases goes down as magnesium status markers rise. Two studies that reported the prevalence of low magnesium status (magnesium <0.73–0.80 mmol/L), as opposed to quantile-based analyses, observed that ~25% of the populations had low serum magnesium (149, 150). Across all of these prospective studies in initially healthy populations, a higher risk of CVD morbidity and mortality tended to begin to be observed at circulating magnesium circulations <0.75–0.85 mmol/L.

Compared with ischemic heart disease and stroke, there are far fewer prospective studies of other cardiac conditions such as atrial fibrillation and heart failure. In 2 studies, ARIC (Atherosclerosis Risk in Communities) (151) and the Framingham Heart Study Offspring (152), each of which included 18–20 y of follow-up, lower circulating magnesium (<0.76 and 0.73 mmol/L, respectively) was associated with a 30% and 50% higher risk, respectively, of incident atrial fibrillation. In ARIC, low serum magnesium (≤0.70 mmol/L)

was also associated with a 70% higher risk of incident heart failure (153).

Findings from ARIC are particularly informative when evaluating the serum magnesium interval optimal for CVD health because it includes a large (~16,000) population-based sample of blacks and whites and because participants experience many clinical CVD events over >25 y of follow-up. Serum magnesium measured at the baseline visit (1987–1989) followed a normal distribution, with 98% of individuals having serum magnesium concentrations between 0.6 and 1.0 mmol/L, and 11.3% were deemed hypomagnesemic (<0.75 mmol/L). Within ARIC, low serum magnesium has been linked to a greater risk of incident CVD-related risk factors, such as hypertension (163), diabetes (164), and chronic kidney disease (165). Furthermore, it has been linked to numerous CVD outcomes, including ischemic heart disease (157), sudden cardiac death (155), heart failure (153), atrial fibrillation (151), and ischemic stroke (156). Unfortunately, the published ARIC studies did not present serum magnesium in a uniform way in their statistical models (i.e., serum magnesium was variously modeled as quintiles, quartiles, and according to



**FIGURE 3** Risk estimates and corresponding risk and reference circulating magnesium concentrations from prospective studies of incident cardiovascular diseases. Estimated risks [from published ORs, RRs, or HRs (11, 147–162)] were derived from comparing the cutoff of circulating magnesium in cases to controls or the risk quantile compared with the reference quantile. The risk estimate at a given circulating magnesium concentration is connected to its corresponding reference magnesium concentration by a line for the following outcomes: atrial fibrillation (closed circles), coronary heart disease morbidity or mortality (closed squares), cardiovascular disease morbidity or mortality (open circles), heart failure (open squares), ischemic stroke (open diamonds), and sudden cardiac death (shaded circles). By way of example, for sudden cardiac death (shaded circle), 1 study (157) observed an RR of 0.23 at a circulating magnesium concentration >0.86 mmol/L relative to <0.78 mmol/L, which in this case was the reference concentration (RR = 1). Published and/or derived risk estimates (along with CIs) used to create this figure are shown in Supplemental Table 2. CHD, coronary heart disease; CVD, cardiovascular disease.
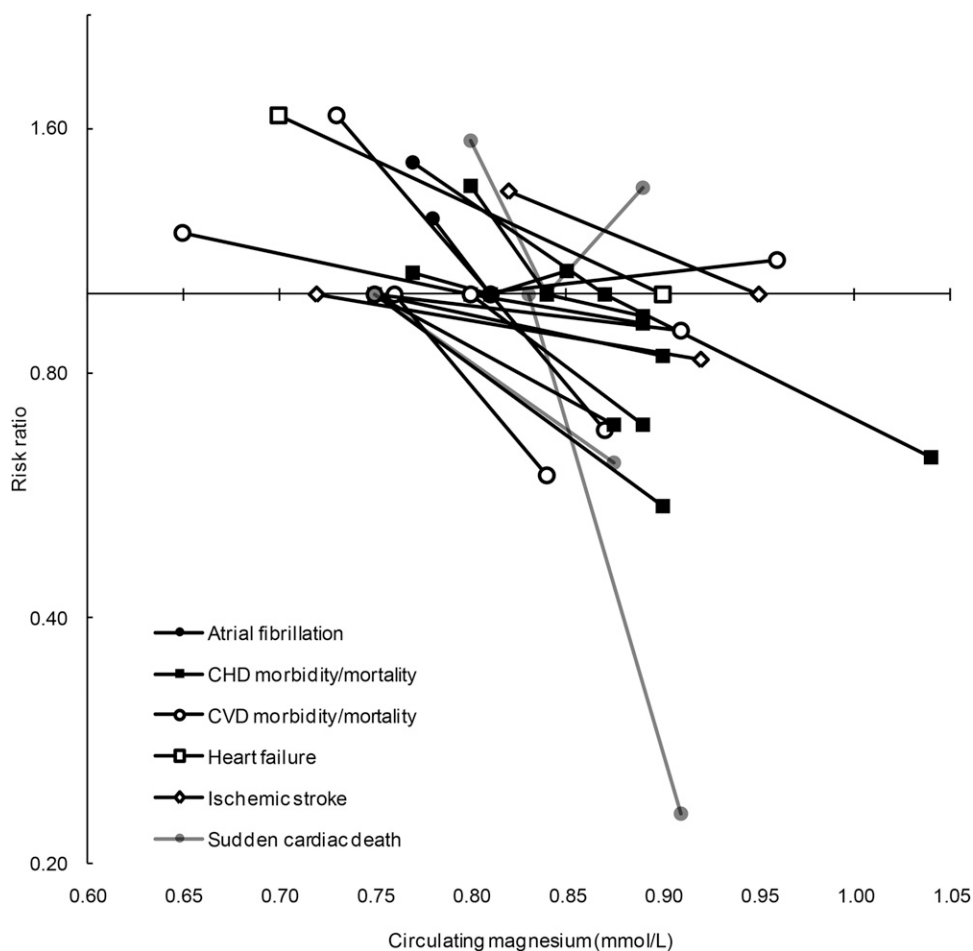
prespecified categories). However, when reviewing the totality of the data, it appears that the risk of CVD outcomes typically increases around serum magnesium concentrations ≤0.75 mmol/L. Although these findings are observational and based on a single study population, they are consistent with the wider body of evidence in suggesting that concentrations of serum magnesium >0.75 mmol/L may be associated with lower CVD risk. Whether magnesium supplementation to concentrations ≥0.75 mmol/L leads to lower CVD is unknown and awaits testing in an appropriately powered RCT.

## What Is the Clinical Evidence for Magnesium and T2D That Can Inform a Serum Reference Range for Magnesium?

Magnesium deficiency is frequently observed in individuals with T2D because of increased diuresis, a feature of uncontrolled diabetes (166). Among healthy individuals, reports from a 10-y (8735 person-years) follow-up study highlighted that serum magnesium concentrations <0.74 mmol/L predicted incident-impaired glucose tolerance and T2D (90). A longer follow-up of 15 y (11,905 person-years) corroborates the hypothesis that serum magnesium concentrations ≤0.74 mmol/L are related to the risk of developing glucose metabolic disorders (90) (**Figure 4**). These results strongly suggest that hypomagnesemia is not only a feature of diabetes but also a risk factor for the development of glucose and insulin disorders, thus supporting the idea that in addition to dietary magnesium intake, individuals with diabetes, as well as those at risk of developing the disease, may experience health benefits by increasing their consumption of magnesium. However, multiple conditions can modify the response to dietary and supplemental magnesium, masking their efficacy.

To define which diabetes populations might benefit from oral magnesium supplementation and to recognize gaps that require resolution before public health advocacy for the expansion of the use of magnesium supplements for the prevention of T2D, we searched evidence derived from RCTs that evaluated serum, urinary, or intracellular magnesium concentrations in adult humans. A total of 10 RCTs were identified (125, 126, 130, 131, 167–172) that enrolled 315 participants with T2D (mean duration of diabetes: 10.1 ± 4.3 y) who received magnesium supplementation (mean dose: 20.5 ± 8.2 mmol elemental magnesium/d) over 11.5 ± 5.9 wk. Between baseline and final conditions, serum magnesium concentrations showed a significant increase (0.73 ± 0.2 to 0.83 ± 0.1 mmol/L; $P < 0.005$) and fasting plasma glucose (FPG) concentrations a mild but significant decrease (10.6 ± 2.5 to 9.5 ± 2.1 mmol/L; $P < 0.01$) (**Supplemental Figure 1**).

By focusing on improving FPG as the critical outcome of magnesium supplementation and stratifying the study populations by age, length of diabetes, serum magnesium at baseline, and baseline FPG, **Supplemental Table 2** highlights that after magnesium supplementation, final FPG was significantly lower in participants with diabetes who had higher FPG and lower serum magnesium concentrations at baseline. This suggests that individuals with poorly controlled, untreated, or uncontrolled T2D and serum magnesium <0.74 mmol/L would likely benefit considerably from magnesium supplementation.

Among RCTs that have assessed urinary magnesium (125, 130, 162, 163, 165, 166, 171, 172), a total of 144 participants with T2D (mean duration of diabetes: 9.3 ± 5.1 y) were enrolled and received a mean dose of 24.4 ± 11.3 mmol elemental magnesium/d during a mean of 8.8 ± 4.4 wk. Between baseline and final conditions, serum (0.74 ± 0.3 to 0.80 ± 0.1 mmol/L; $P < 0.005$) and urinary (3.2 ± 1.5 to 4.3 ± 1.4 mmol/d; $P < 0.05$) magnesium significantly increased. It is important to highlight that serum magnesium concentrations of targeted populations at baseline were within normal reference values; however, supplementation was effective for decreasing FPG concentrations in those participants with T2D.

These data show that magnesium supplementation may benefit individuals with T2D, particularly among those with serum magnesium <0.74 mmol/L and FPG ≥7.4 mmol/L. Among the most important challenges in the field is the need for identifying a reliable biomarker of magnesium deficiency in the diabetic population. Evidence is currently insufficient for determining an appropriate cutoff of serum magnesium concentrations to establish hypomagnesemia in T2D; additional studies are required, and any future reference range should address disease states, including chronic diseases.

## Do Dose and Time Responses of Serum and Plasma Magnesium Biomarkers to Oral Magnesium Supplementation Support a Redefinition of the Serum Reference Range?

Based on RCT data, changes in serum and plasma magnesium concentrations in response to magnesium supplementation in certain doses and durations may provide useful information on the utility of serum and plasma magnesium in reflecting magnesium status. A previous meta-analysis of 22 intervention studies (up to September 2008) showed a 0.03-mmol/L elevation (95% CI: 0.01, 0.06) of circulating magnesium concentrations in response to magnesium intake (29) and that serum and urinary magnesium responded to dietary magnesium manipulation.

From a recently published meta-analysis (173), we found that 41 RCTs examined serum magnesium (29 RCTs) and plasma magnesium (12 RCTs) among 1388 and 506 participants, respectively. The median serum and plasma magnesium concentrations at baseline were similar among the magnesium supplementation and placebo groups for all included trials (serum magnesium: 0.785 compared with 0.79 mmol/L; plasma magnesium: 0.75 compared with 0.75 mmol/L). After magnesium supplementation at a median dose of 365 mg/d for a median duration of 12 wk, serum magnesium concentrations were significantly elevated by 0.05 mmol/L (95% CI: 0.02, 0.07; $P < 0.0001$) compared with placebo groups. Similarly, plasma magnesium was higher in magnesium groups than placebo groups after a

**FIGURE 4** Associations between the risk of developing impaired glucose tolerance (A) and type 2 diabetes (B) in relation to serum magnesium concentrations in individuals followed for ≤15 y. Poisson regression models were adjusted for age, sex, family history of diabetes, waist circumference, and HOMA-IR index. Mg, magnesium.
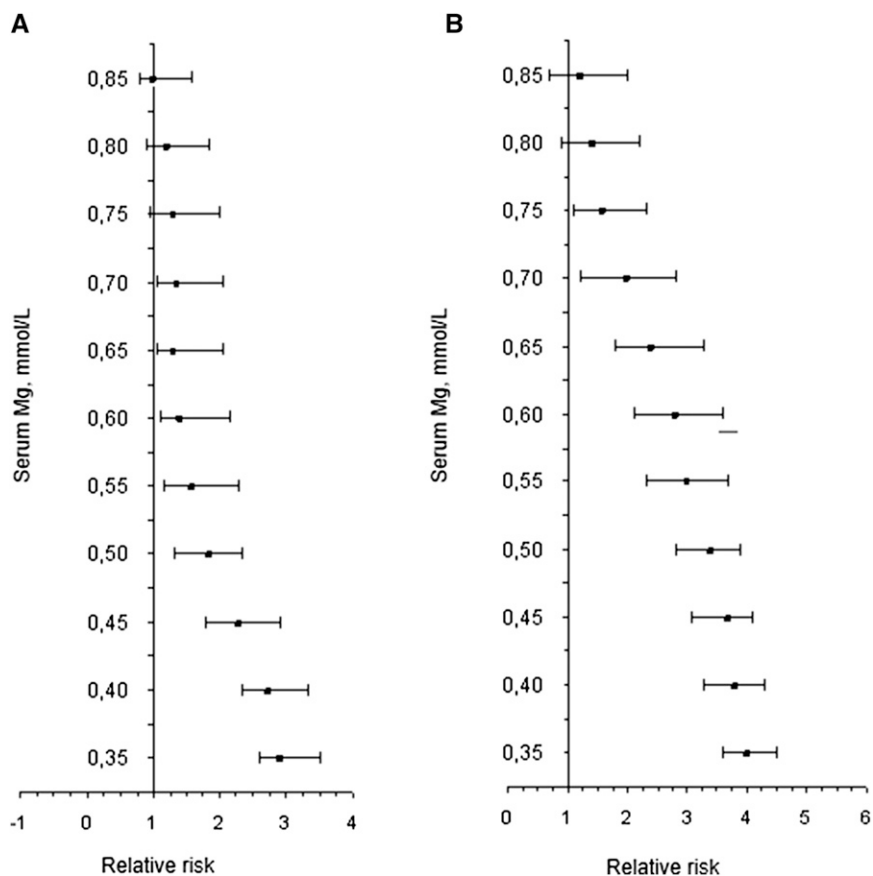
median duration of 2 mo (weighted mean difference: 0.03 mmol/L; 95% CI: 0.01, 0.05; $P < 0.0001$). Dose- and time-response analyses indicated that serum and plasma magnesium concentrations were elevated immediately after magnesium supplementation and gradually peaked at a dose of 500 mg/d (**Supplemental Figure 2**) over a duration of 25 wk (**Supplemental Figure 3**). In addition, serum and plasma magnesium changes did not significantly vary by age, sex, magnesium formulation (organic or inorganic magnesium supplements), cardiometabolic health status (participants free of or with diabetes, CVD, and/or hypertension), trial sample size, or trial quality ($P$-interaction > 0.05 for all).

This quantitative assessment of available RCT data shows similarly substantial dose and time responses of serum and plasma magnesium concentrations to oral magnesium supplementation. These results provide direct evidence that both serum and plasma magnesium are useful for their effectiveness in reflecting long-term magnesium status (i.e., 25 wk for serum and 15 wk for plasma magnesium measurements), although the sensitivity and specificity of serum and plasma magnesium concentrations in determining magnesium status need to be reliably calibrated in well-designed and rigorously conducted RCTs with the gold-standard measure of magnesium status, i.e., the magnesium loading test. In addition, further studies are needed to fully explore potential biological modifiers of serum and plasma magnesium concentrations.

## The Case for Transitioning STMC to an Evidence-Based Reference Interval

Modern medicine has chosen STMC to evaluate magnesium status, but it represents only ~0.3% of the total body magnesium content and is not in equilibrium with other body tissues except nominally with the bone. As noted earlier, the reference interval for STMC was determined in a US population as part of NHANES I with the use of atomic absorption spectrometry. The identified reference interval (central 95th percentile) was 0.75–0.95 mmol/L with a mean concentration of 0.85 mmol/L (21) and followed a normal Gaussian distribution curve.

### Can the clinical laboratory accurately and precisely measure STMC?

A reference system for accurately determining STMC has been established (174). The definitive method for magnesium is isotope dilution/MS as indicated by the National Institute of Standards and Technology. The clinical laboratory reference method for magnesium is flame atomic absorption spectrometry. Reference materials for magnesium are available from the National Institute of Standards and Technology. Standard reference material (SRM) 929 is a preparation of magnesium gluconate dihydrate, and SRM 3131a is a stock solution of magnesium at a concentration of 10 g/L and 10% $HNO_3$. Furthermore, SRM 909 is a human serum with certified values for many analytes, including magnesium.

Most clinical laboratories in the United States now use a colorimetric method (96.8%) for determining STMC. A few laboratories use an enzymatic method (3.2%), as indicated by the College of American Pathologists Proficiency Testing Survey. The 2015 survey set C-C (the first "C" indicating chemistry and the second "C" the third survey of the year) for magnesium report results from 4942 clinical laboratories with 5 separate challenges (175). The mean CV among all results was 4.94%, indicating excellent precision among methods. Furthermore, there was excellent agreement for the mean result among methods. Thus, we have in place today in clinical laboratories across the country an accurate and precise methodology for determining STMC.

### Is STMC a Valid Clinical Indicator of Magnesium Status?

Several factors are needed for humans to achieve and maintain magnesium balance. **Figure 5** depicts the factors needed for magnesium balance and lays the foundation for the etiology of chronic latent magnesium deficiency (23). It is chronic because it extends over years and often lasts a lifetime. It is latent because STMC is frequently within the reference interval, albeit at the lower end, and an individual is thus assessed as having normal magnesium status.

The normal individual in magnesium balance has an adequate intake of magnesium and normal absorption of magnesium from the gastrointestinal tract and does not waste magnesium through overexcretion in the urine. However, a change in any of these 3 entities that is chronic may lead to chronic latent magnesium deficiency. The considerable decrease in magnesium in the food supply is likely a major cause of chronic latent magnesium deficiency. 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 STMC because magnesium is slowly leeched from the bone to maintain STMC within the lower part of the reference interval. The best evidence that magnesium has been taken from the

bone in a state of chronic latent magnesium deficiency is a study that shows a very significant inverse correlation ($r = -0.992$; $P < 0.0001$) between bone magnesium content and the magnesium retention test (176). It is this equilibrium between the bone and STMC that facilitates the development of chronic latent magnesium deficiency in normal individuals. As noted earlier, postmenopausal women with low serum magnesium are at increased risk for osteoporosis.

STMC has been determined to be a valid biomarker for magnesium status. In an extensive review of the literature, Witkowski et al. (29) determined that there were 3 effective biomarkers of magnesium status: plasma and serum magnesium, RBC magnesium, and urinary magnesium. Although STMC is supplemented by bone magnesium during periods of magnesium deficiency, it is still a valid biomarker of magnesium status and essentially the only test used to assess magnesium status by clinical medicine at this time. The availability of a valid and reliable biomarker is essential for determining an evidence-based reference interval. Furthermore, the capacity of labs nationwide to measure serum magnesium accurately and precisely at a relatively low cost is advantageous in thinking about targeted screening for low magnesium concentrations.

### What is the impact of chronic latent magnesium deficiency on human health?

Studies have shown that humans need an STMC $\geq 0.85$ mmol/L for health (177). Thus, based on the study by Lowenstein and Stanton (21) and data from Table 1, $\geq 25\%$ of the people in the United States may have chronic latent magnesium deficiency. Decreased magnesium favors oxidation with an increase in free radicals and endothelial dysfunction (178, 179) as well as systemic inflammation, as noted earlier. Endothelial dysfunction with an increase in free radicals accelerates the atherosclerotic process and risk for CVD. As described previously, studies of CVD in humans (e.g., stroke, heart failure, atrial fibrillation, heart disease morbidity and
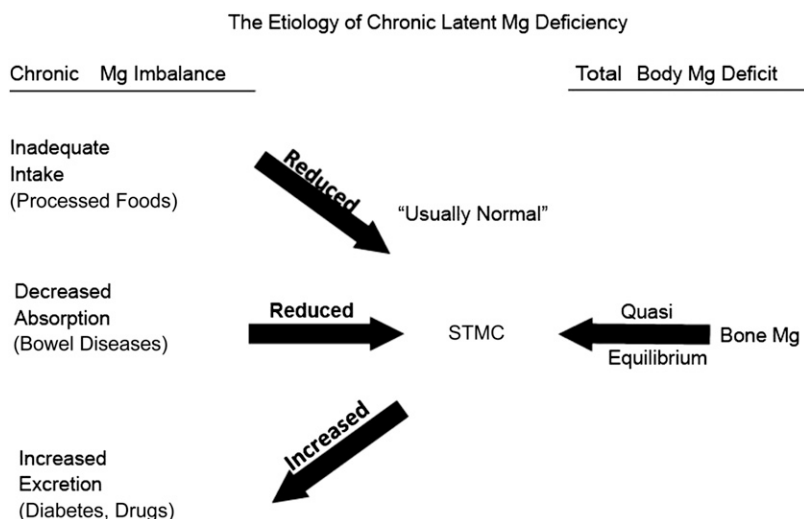


FIGURE 5 The etiology of chronic latent magnesium deficiency. Mg, magnesium; STMC, serum total magnesium concentration. Adapted from reference 23 with permission.

**Total Serum Mg Concentration for Assessment of Mg Status**

**Current Reference Interval**

| Symptomatic Hypomagnesemia | Asymptomatic Hypomagnesemia | Chronic Latent Magnesium Deficiency (CLMD) | Asymptomatic Hypermagnesemia | Symptomatic Hypermagnesemia |

0.500　　0.750　　0.850　0.955　　2.000

**Proposed Reference Interval for Health**

**Total Serum Magnesium Concentration (mmol/L)**
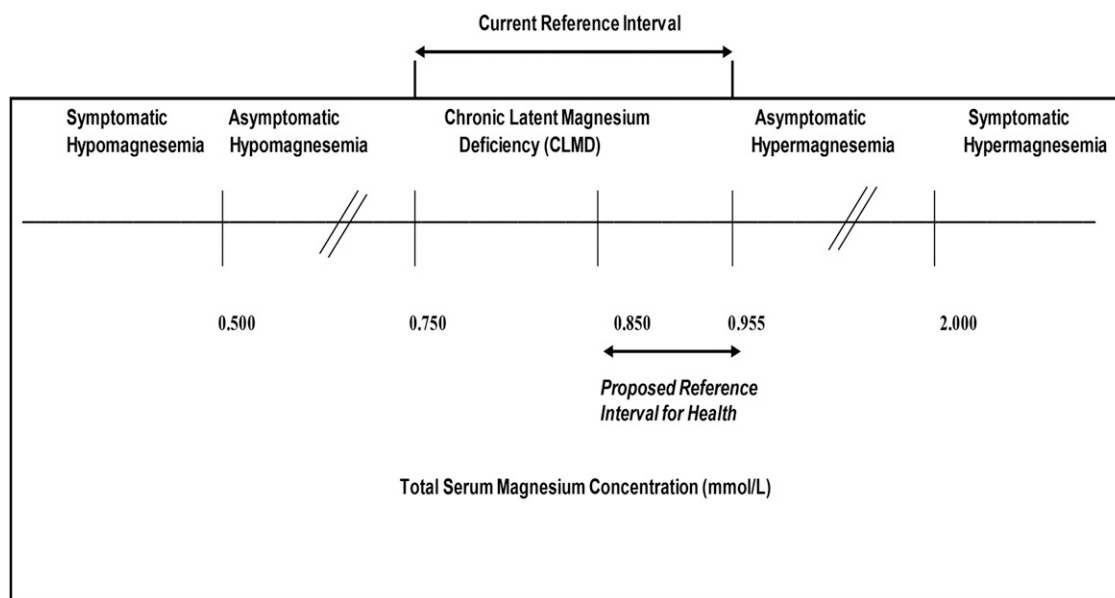
**FIGURE 6** Current and proposed clinical cut-offs of the serum total magnesium concentration for assessing magnesium status. Current reference range derived from reference 21.

mortality) support adverse risk at serum magnesium concentrations <0.80 mmol/L. Several animal studies have documented this relation (43, 180–183). Furthermore, based on this mechanism, there is an increased risk for T2D, which we also discussed previously. In addition, in clinical settings, serum magnesium concentrations of 0.75–1.0 mmol/L have been shown to prolong QTc intervals on electrocardiograms, increasing the risk of cardiac arrhythmias. A recent retrospective hospital chart review in 3200 participants (free of medications that would alter the electrocardiogram) demonstrated a mean QTc of 465.4 $\pm$ 1.1 ms with serum magnesium >1.0 mmol/L, whereas the mean serum magnesium of <1.0 mmol/L had a longer QTc that averaged 470.1 + 0.99 ms ($P < 0.001$) (184), suggesting an increased risk in vulnerable population groups even when serum STMC may be within or above the upper limit of the reference interval.

### What is needed to recognize chronic latent magnesium deficiency?

The model for approaching an evidence-based reference interval for STMC is similar to that done over many years for blood lipids, particularly cholesterol (185). The reference interval for the serum total cholesterol concentration was established with the use of normal individuals and conventional statistics. This was in part because the reference interval from hospital samples varied greatly, with some having an upper reference cutoff >300 mg/dL. An additional component of establishing the evidence-based reference interval for cholesterol was that the medical literature documented a direct relation between the serum total cholesterol concentration and risk of heart disease. A consensus

conference was held at the NIH that established the upper limit of the reference interval for serum total cholesterol of 200 mg/dL (185). We now recommend a similar consensus conference with subject experts to establish an evidence-based reference interval for STMC (Figure 5) that reflects the US population.

Based on the review of literature presented herein, we propose adopting an evidenced-based reference interval for STMC ≥0.85 mmol/L to reduce the risk of CVD, T2D, and other diseases (**Figure 6**). We further propose a program
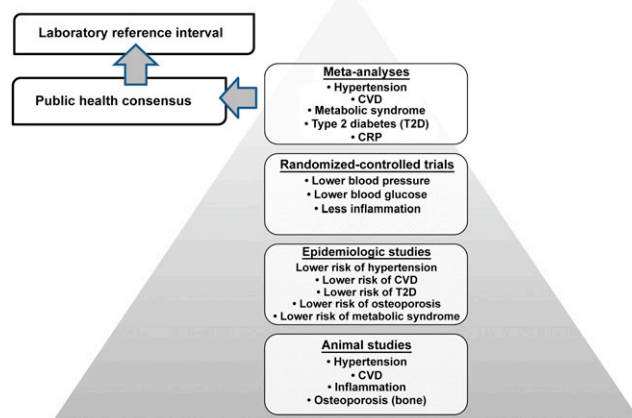


**FIGURE 7** Summary of the accumulated evidence base to inform a revised serum reference interval. CRP, C-reactive protein; CVD, cardiovascular disease; Mg, magnesium; T2D, type 2 diabetes.

similar to what was done for blood lipids to establish this evidenced-based STMC reference interval (**Figure 7**).

## Conclusions

Because magnesium has been deemed a shortfall nutrient for the US population, more research is urgently needed. The key to advancing the field of magnesium research is validating a biomarker that most reflects magnesium status whether based on dietary intake and urinary and/or serum magnesium concentrations in healthy individuals or individuals at risk for chronic diseases. Increased public health emphasis and educational messages on the importance of magnesium in the diet to foster optimal health are needed for all age groups. Systems are needed to monitor the impact of magnesium insufficiency and to address methods for improving the intake of magnesium in crops and packaged food products, especially for populations at high risk for magnesium deficiency. Furthermore, it has been >40 y since magnesium status was assessed in a nationally representative population-based sample. Contemporaneous measurement of serum magnesium in a nationally representative sample is urgently needed. The system used to determine the present magnesium reference interval was based on the distribution of magnesium in the population, not health outcomes. As detailed herein, a substantial body of evidence suggests that the current cutoff is too low.

We support the need for a timely re-evaluation of the conventional serum total magnesium reference interval based upon evidence from the literature linking magnesium to health outcomes. Implementing an evidence-based reference interval will allow institutions and health professionals to provide the necessary dietary and therapeutic interventions to increase magnesium concentrations, thereby stemming the tide of adverse health outcomes that may occur as a consequence of chronic latent magnesium deficiency.

## Acknowledgments

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