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LETTER TO THE EDITOR

Comment to "Recommendation on an updated standardization of serum magnesium reference ranges"

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Magnesium is an essential cofactor for > 600 enzymes and is required for DNA stability and protein synthesis [1]. To maintain stable intracellular magnesium levels, the serum magnesium concentration is tightly regulated by the interplay of intestinal uptake and renal excretion [1]. Rosanoff et al. recently reported the wide disparity among reference ranges for serum Mg^{2+} that are applied in different clinical centers [2]. By comparing 43 hospital laboratories, the authors describe that the cut-off value for hypomagnesemia may range between 0.58 mmol/L (1.4 mg/dL, 1.14 mEq/L) and 0.85 mmol/L (2.07 mg/dL, 1.7 mEq/L) depending on the hospital [2]. Consequently, patients with a relatively low serum Mg^{2+} concentration may be termed hypomagnesemic or normomagnesemic depending on the location and the type of the measurement. The analysis of Rosanoff et al. underlines the need for better consensus among clinical centers to achieve a uniform definition of hypomagnesemia and to increase the comparability of research studies.

In general, the reference range is defined as the 95% confidence interval in the general population [3]. Based on this definition, the NHANES I study defined the reference interval for serum magnesium at 0.75–0.95 mmol/L in the US population [4]. Indeed, recent large population studies independently demonstrate that the mean serum magnesium concentration in the general population is 0.81–0.85 mmol/L [5–7]. Rosanoff et al. propose the introduction of a novel reference range of serum magnesium of 0.85–0.96 mmol/L (2.06–2.33 mg/dL, 1.70–1.92 mEq/L), which would define the lower limit of the reference range as the upper estimate for the population mean (0.85 mmol/l) [2]. Consequently, approximately 50% of the general population would suddenly have to be considered hypomagnesemic. Not surprisingly, this proposed reference range is higher than in 41 of the 43 reported study centers

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[2]. Clinically, there is no evidence that would support such a high percentage of individuals with hypomagnesemia, let alone the need to correct serum magnesium level to a level above 0.85 mmol/l.

The proposal of a novel reference range of serum magnesium of 0.85–0.96 mmol/L is based on the claim that this range is optimal for health and supported by two narrative reviews of (partially) the same authors [8, 9]. We have two main issues with the introduction of this novel reference range: 1. the reference range is based on cohort studies that were not systematically reviewed nor quality assessed; 2. the health claims are not supported by randomized clinical trials with magnesium supplementation.

Cohort studies

Over the last decades, many cohort studies have demonstrated an inverse association of serum magnesium levels with cardiovascular disease, metabolic syndrome and other common disease [1, 8]. Although these studies may suggest a positive effect of magnesium on human health, association does not imply causality. Low serum magnesium levels can be caused by poor dietary habits and diabetes mellitus, which may introduce a significant bias in association studies. Indeed, we recently published a large cohort of patient studies in which low serum magnesium was associated with stroke [10]. However, when correcting for common cardiovascular risk factors, this association was completely lost [10]. A similar trend was present in a systematic review by Qu et al. demonstrating that six out of ten of the included studies failed to demonstrate a significant association between serum magnesium concentration and cardiovascular events [11]. In their meta-analysis, the reduced relative risk for cardiovascular disease was mainly dependent on cohort studies that did not control for HDL, LDL and triglycerides [11]. Altogether, these results demonstrate that observational studies should be interpreted with care. Moreover, there is the possibility of confounding factors: metabolic syndrome and hypomagnesaemia are both associated with mitochondrial disease [12]. We identified genetic factors that independently affect magnesium homeostasis and cardiovascular function [13]. A systematic review of the literature and meta-analysis of only high-quality studies controlling for known CVD risk factors is required. The narrative review of Costello et al. that was used to propose a novel reference range of serum magnesium of 0.85–0.96 mmol/L does not fulfill these criteria [8].

Randomized clinical trials

Although cohort studies can be indicative of a positive effect of magnesium on human health, randomized controlled clinical (interventional) trials are required to prove first and foremost causality, and whether correcting serum magnesium towards a specific target value is therapeutic or preventive. A systematic review and meta-analysis of the effect of intravenous magnesium supplementation on myocardial infarction demonstrates that magnesium is not beneficial [14]. Similar outcomes were shown for stroke, as intravenous Mg^{2+} supplementation did not improve mortality in patients with stroke [15]. Randomized controlled trials in people with type 2 diabetes, who often have hypomagnesemia, have never evaluated the effect of magnesium supplementation on hard clinical endpoints. Systematic reviews and meta-analyses on the effect of magnesium supplements on diabetes parameters (e.g., HOMA-IR, fasting glucose, HbA1c) did generally demonstrate beneficial results [16, 17]. Studies in rare diseases associated with hypomagnesemia, as is the case of Gitelman syndrome (GS), pointed out the possible consequences of hypomagnesemia. GS patients with severe hypomagnesemia had a higher insulin resistance index and a tendency toward higher BMI irrespective of the presence of severe hypokalemia, suggesting that magnesium depletion is the predominant contributor to insulin resistance [18]. However, the available studies are limited by short study durations and small sample sizes. Therefore, these studies are underpowered to determine to optimal serum magnesium range.

The serum magnesium level is subject to variation. It has been demonstrated that the serum magnesium level has a circadian rhythm and is sensitive to hormonal regulation by adrenergic signaling, insulin and aldosterone [19–22]. Consequently, serum magnesium may vary after a meal or exercise and may be dependent on the acid–base status at the time of measurement [23]. The proposed narrow reference range of 0.1 mmol/L will, therefore, inevitably result in difficulties in the assessment of the Mg^{2+} status of individual patients, as a patient will be considered hypomagnesemic, normomagnesemic or hypermagnesemic depending on the time of the measurement.

Altogether, there is currently no evidence to propose a reference range of 0.85–0.96 mmol/L. Nevertheless, we do encourage better consensus among clinical centers and a commonly agreed reference range. However, at this moment there is no evidence to differ from its 95% confidence interval, as usual, which would be 0.70–1.1 mmol/L.

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