



Recommendation on an updated standardization of serum magnesium reference ranges

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Abstract

Purpose Serum magnesium is the most frequently used laboratory test for evaluating clinical magnesium status. Hypomagnesemia (low magnesium status), which is associated with many chronic diseases, is diagnosed using the serum magnesium reference range. Currently, no international consensus for a magnesemia normal range exists. Two independent groups designated 0.85 mmol/L (2.07 mg/dL; 1.7 mEq/L) as the low cut-off point defining hypomagnesemia. MaGNet discussions revealed differences in serum magnesium reference ranges used by members' hospitals and laboratories, presenting an urgent need for standardization.

Methods We gathered and compared serum magnesium reference range values from our institutions, hospitals, and colleagues worldwide.

Results Serum magnesium levels designating “hypomagnesemia” differ widely. Of 43 collected values, only 2 met 0.85 mmol/L as the low cut-off point to define hypomagnesemia. The remainder had lower cut-off values, which may underestimate hypomagnesemia diagnosis in hospital, clinical, and research assessments. Current serum magnesium reference ranges stem from “normal” populations, which unknowingly include persons with chronic latent magnesium deficit (CLMD). Serum magnesium levels of patients with CLMD fall within widely used “normal” ranges, but their magnesium status is too low for long-term health. The lower serum magnesium reference (0.85 mmol/L) proposed specifically prevents the inclusion of patients with CLMD.

Conclusions Widely varying serum magnesium reference ranges render our use of this important medical tool imprecise, minimizing impacts of low magnesium status or hypomagnesemia as a marker of disease risk. To appropriately diagnose, increase awareness of, and manage magnesium status, it is critical to standardize lower reference values for serum magnesium at 0.85 mmol/L (2.07 mg/dL; 1.7 mEq/L).

Keywords Serum magnesium · Serum magnesium reference range · Chronic latent magnesium deficit · CLMD · Hypomagnesemia

Abbreviations

CLMD Chronic latent magnesium deficit
CVD Cardiovascular disease
MaGNet Magnesium global network

Introduction

Magnesium is essential for life. Although its homeostasis at the cellular, tissue, and organism levels seems to be well buffered, there is a widely distributed tendency for low magnesium status to be associated with the most common chronic diseases [1]. In the absence of a more selective, reliable, and easily testable biomarker, serum magnesium is the most frequently used laboratory test for evaluating clinical

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magnesium status. Researchers use serum magnesium reference ranges to designate hypo-, normo-, or hypermagnese-mic status, whereas hospitals and primary care physicians use serum magnesium values in deciding whether to admin-ister magnesium therapy. Consequently, the lower cutoff for serum magnesium reference value of a hospital or clinical laboratory determines the number of patients diagnosed as “hypomagnese-mic.”

Hypomagnese-mia has several clinical manifestations that vary from asymptomatic to severe. Overt symptoms present at ≤ 0.6 mmol/L [2] (Fig. 1). These clinical manifestations include metabolic issues (hypokalemia and hypocalcemia), neuromuscular-central nervous system symptoms (hyperex-citability, muscle weakness, tremors, seizures, tetany, head-aches, and fatigue), cardiovascular abnormalities (tachy-cardia, arrhythmias such as torsade de pointes, ventricular

fibrillation, mitral valve prolapse, cardiac ischemia, myo-cardial infarct, and hypertension), and endocrine abnormali-ties (insulin resistance and type 2 diabetes) [2, 3] (Table 1). Reported severe, overt symptoms of hypomagnese-mia also include the mimic of acute stroke [4], life-threatening arrhythmias [3], metabolic acidosis [5], and new-onset dia-betes following heart transplantation [6]. In intensive-care units, hypomagnese-mia is associated with higher mortality, the need for mechanical ventilation, and increased length of stay [7].

In addition to hypomagnese-mia presenting with overt disease states, patients can present with asymptomatic hypomagnese-mia or chronic latent magnesium deficit (CLMD) at serum Mg levels well above 0.6 mmol/L (Fig. 1). CLMD has been defined as a subclinical condition that ren-ders individuals more susceptible to disease. CLMD occurs

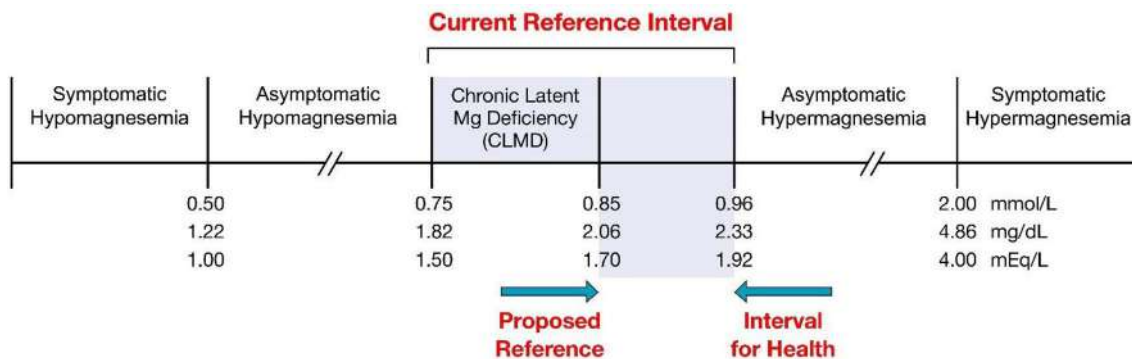


Fig. 1 Total serum magnesium concentration for assessment of mag-nesium status. *Conversion factor:* for mg/dL to mmol/L, multiply by 0.411; for mmol/L to mg/dL, multiply by 2.43; and for mmol/L to

mEq/L, divide by 0.5. Reproduced from Costello and Rosanoff [14], which was adapted from Costello et al. [12]

Table 1 Clinical manifestations of hypomagnese-mia. Adapted from Ehrenpreis et al. [2] and Ahmed et al. [3] with permission

System	Clinical manifestation
Neuromuscular/central nervous system	Positive Chvostek’s and Trousseau’s signs, tremor, fasciculations, tetany, headaches, seizures, fatigue, gener-alized fatigue, asthenia
Cardiovascular	Hyperexcitability, weakness, dysphagia, vertical nystagmus, apathy, delirium, coma
	Atherosclerotic vascular disease/coronary artery disease
	Arrhythmias (Torsades de pointes, PR prolongation, progressive QRS widening, and diminution of T-waves)
	Hypertension
Endocrine	Congestive heart failure
	Mitral valve prolapse, tachycardia, cardiac ischemia, myocardial infarct
	Altered glucose homeostasis/diabetic complications
Biochemical/other	Osteoporosis
	Insulin resistance and type 2 diabetes
	Hypokalemia
	Hypocalcemia
	Asthma
	Nephrolithiasis

with a small chronic negative magnesium balance, which may be attributed to decreased dietary intake, decreased gastrointestinal absorption, and/or increased renal loss [8]. The most common cause of CLMD worldwide is decreased magnesium dietary intake, since processed food and fast food tend to have low magnesium content [9, 10]. However, illness and drug use must also be taken into account. Over time, this negative magnesium balance causes the serum magnesium concentration to decrease. Since this is a subtle chronic process, some magnesium is depleted in bone to support the circulating serum magnesium pool [11]. Thus, patients with CLMD appear to have “normal” magnesium status, because their serum magnesium value falls within the traditionally normal reference ranges, but these patients are not in sufficient magnesium status for long-term health. The actual magnesium deficiency of the patient is latent—a fallacy of the reference interval as serum magnesium reference intervals have been established with “healthy” individuals, including many who unknowingly have CLMD [11]. This is the basis for updating the lower limit reference interval for the serum magnesium concentration.

Two groups of magnesium researchers, one in the United States [12] and one in Germany [13], have independently agreed on a serum magnesium value of 0.85 mmol/L as the low cut-off point to define hypomagnesemia, since serum magnesium values <0.85 mmol/L (2.07 mg/dL or 1.7 mEq/L) have been associated with an increased risk of various diseases (e.g., cardiovascular disease [CVD], metabolic), obesity, and aging.

In response to the COVID-19 pandemic, our international group of magnesium researchers (Magnesium Global Network [MaGNet]) began meeting in September 2020 to discuss the research. In these meetings, we discussed the serum magnesium reference ranges used by our institutions’ hospitals and laboratory service providers, and we discovered that they were far from uniform. We decided to gather these values to compare them with the suggested evidence-based serum magnesium reference for hypomagnesemia of 0.85 mmol/L [12, 13], and we present those findings here.

Materials and methods

We collected and evaluated the various serum magnesium reference range values of our institutions, including the laboratory methodology used to obtain those values when available. To expand our indicative database, we also gathered serum magnesium reference range values from colleagues around the world. Institutions were coded by country, and all contributed values were calculated to express commonly used alternate units of serum magnesium—milligrams per

deciliter (mg/dL), millimoles per liter (mmol/L), and milliequivalents per liter (mEq/L)—for each reported value. GraphPad Prism version 9 was used to tabulate data and create Fig. 2. The independently suggested evidence-based serum magnesium reference range of 0.85–0.95 mmol/L (2.07–2.3 mg/dL or 1.7–1.9 mEq/L) was added to Figure 2 for comparison.

Results

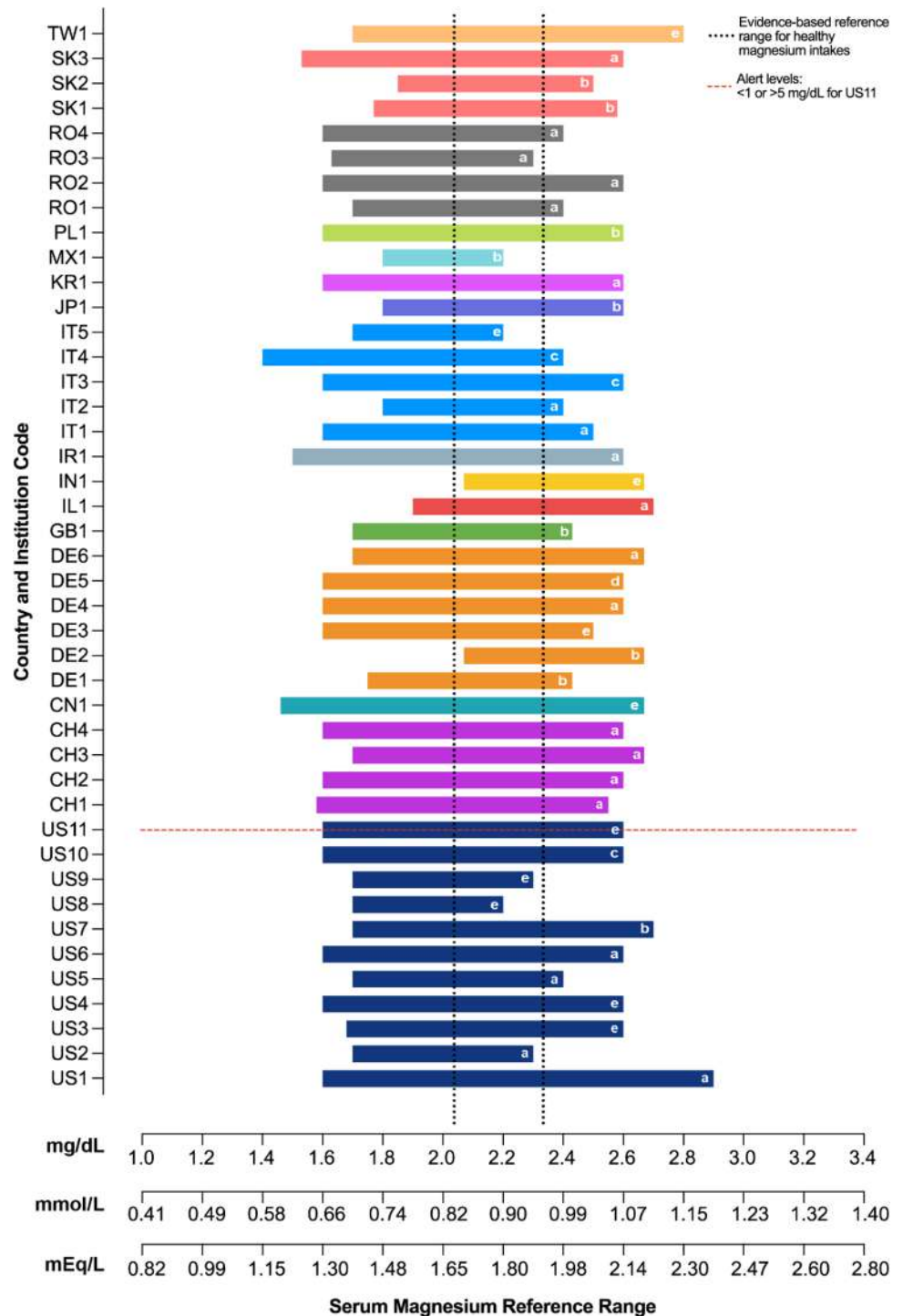
As shown in Fig. 2 and Table 2, the level of serum magnesium designating a patient as hypomagnesemic differs worldwide. Forty-three values were gathered from institutions in 16 different countries, including China, Germany, India, Iran, Israel, Italy, Japan, Korea, Mexico, Poland, Romania, Slovakia, Switzerland, Taiwan, the United Kingdom, and the United States. Of those 43 values, only 2 (5%) designated a low serum magnesium reference range cut-off value of 0.85 mmol/L. Forty-one values of the 43 institutions (95%) designated their low cutoff for definition of hypomagnesemia below and even well below this suggested standard, from 0.58 mmol/L for IT4 to 0.78 mmol/L for IL1. Most of the collected values (29 of 43; 67%) used colorimetric methodology, with 9 specifying xylydyl blue and 1 indicating calmagite as the colorimetric agent. Of the 43 values, 1 (2%) used atomic absorption spectroscopy and 3 (7%) used enzymatic methodology. Ten values (21%) did not report methodology. Figure 1 summarizes the definition of low and high magnesemia as proposed by previous works on magnesium reference range [14] and highlights how CLMD is currently included in the normal serum magnesium range (see Discussion).

Discussion

Such different serum magnesium reference range values render our current use of this medical tool imprecise, causing many hypomagnesemic patients to be deemed normomagnesemic and potentially minimizing the effects of low magnesium status in research.

When different cut-off values for hypomagnesemia are used, substantially different results can ensue. For instance, in one study at a Warsaw hospital, when a lower cut-off reference value of 0.65 mmol/L was used, 7% of 20,483 patients were deemed hypomagnesemic [15]. With the lower cut-off reference value of 0.75 mmol/L, 25% of this same patient cohort showed hypomagnesemia. Finally, with a lower cut-off reference value of 0.85 mmol/L, 60% were diagnosed as hypomagnesemic [15].

Fig. 2 Serum magnesium reference ranges from several institutions and laboratory service providers, gathered by magnesium researchers for the MaGNet Global Magnesium Project. Assessment methods are indicated with lowercase letters as follows: colorimetric (a), colorimetric/xylidyl blue (b), enzymatic assay (c), atomic absorption spectroscopy (d), and not reported (e). Colorimetric, photometric, and spectrophotometric designations of methodology are all classified under colorimetry. See Table 2 for full details



Clearly, the serum magnesium reference range used by a hospital, clinical, or research laboratory is crucial in the designation of low magnesium status. The present observational study's wide spectrum of serum reference interval values used in hospital and clinical laboratories around the world documents an urgent need for a consensus reference interval for serum magnesium concentration, specifically on the lower cut-off limit, since

low magnesium status is currently a common condition worldwide [16]. The evidence-based lower cut-off value of 0.85 mmol/L (2.07 mg/dL or 1.7 mEq/L) proposed by the US and German research groups [12, 13] specifically prevents the inclusion of individuals with CLMD [12], who usually fall into the lower half of the reference interval of <0.85 mmol/L (see Fig. 1).

Table 2 Working table of serum magnesium reference ranges for various hospitals and institutions

Institution code	Country	Institution	Serum magnesium reference range ^a			Method ^b	Researcher
			mg/dL	mmol/L	mEq/L		
CH1	Switzerland	Kantonsspital Aarau	1.58–2.55	0.65–1.05	1.3–2.1	Photometric	Anton Kraus
CH2	Switzerland	University Hospital, Zurich	1.6–2.6	0.66–1.07 (age dependent)	1.3–2.1	Photometric	Anton Kraus
CH3	Switzerland	Analytica Medizinische Lab, Zurich	1.7–2.67	0.7–1.10	1.4–2.2	Photometric	Anton Kraus
CH4	Switzerland	Laboratory of Dr. Risch	1.6–2.6	0.66–1.07 (age dependent)	1.3–2.1	Photometric	Anton Kraus
CN1	China	Zhangzhou Affiliated Hospital of Fujian Medical University, Zhangzhou	1.46–2.67	0.6–1.1	1.2–2.2	NR	Andrea Rosanoff [18]
DE1	Germany	Dr. Schottdorf Augsburg Laboratory	1.75–2.43	0.75–1.0	1.5–2.0	Photometric, colorimetric, xylidyl blue	Bodo von Ehrlich
DE2	Germany	Medical Office	2.07–2.67	0.85–1.1	1.7–2.2	Photometric, colorimetric, xylidyl blue	Bodo von Ehrlich
DE3	Germany	St. Elisabeth Hospitals Herne	1.6–2.5	0.66–1.03	1.3–2.06	NR	Klaus Kisters
DE4	Germany	Laboratory Enders, Stuttgart (https://www.labor-enders.de/analysenverzeichniss)	1.6–2.6	0.66–1.07	1.3–2.1	Colorimetric	Anton Kraus
DE5	Germany	Laboratory Amedes Holding, Hamburg (https://www.amedes-group.com)	1.6–2.6	0.66–1.07	1.3–2.1	Atomic absorption spectroscopy	Anton Kraus
DE6	Germany	Franziskus Hospital Bielefeld	1.7–2.67	0.7–1.1	1.4–2.2	Photometric	Oliver Micke
GB1	UK	UK Hospitals – National Health Service	1.7–2.43	0.7–1.00	1.4–2.0	Colorimetric, xylidyl blue	Rhian Touyz and Yee Pang Teoh
IL1	Israel	Chaim Sheba Medical Center	1.9–2.7	0.78–1.1	1.6–2.2	Photometric color test	Michael Shechter
IN1	India	Nirogyam Pathology Laboratory	2.07–2.67	0.85–1.1	1.7–2.2	NR	Oliver Micke
IR1	Iran	National Research Institute of Tuberculosis and Lung Diseases, Iran	1.5–2.6	0.62–1.07	1.2–2.1	Colorimetric	Guitti Pourdowlat and Shadi Baniyasi
IT1	Italy	University Hospital of Palermo, Italy	1.6–2.5	0.66–1.03	1.3–2.06	Colorimetric	Mario Barbagallo
IT2	Italy	Policlinico Gemelli, Rome	1.8–2.4	0.74–0.99	1.48–2.0	Colorimetric	Federica Wolf
IT3	Italy	Campus Biomedico, Rome	1.6–2.6	0.66–1.07	1.3–2.1	Enzymatic assay	Federica Wolf

Table 2 (continued)

Institution code	Country	Institution	Serum magnesium reference range ^a			Method ^b	Researcher
			mg/dL	mmol/L	mEq/L		
IT4	Italy	Clinical Pathology Laboratory at Sacco Hospital	1.4–2.4	0.58–0.99	1.15–2.0	Enzymatic assay (isocitrate dehydrogenase)	Jeanette Maier
IT5	Italy	Used UCSF (USA) ref range for study at Reggio Emilia Hospital	1.7–2.2	0.70–0.905 ^c	1.4–1.8	NR	Stefano Iotti and Lucia Merolle
JP1	Japan	Jikei University, Japan	1.8–2.6	0.74–1.07	1.48–2.14	Colorimetric, xylidyl blue	Ka Kahe and Kuni-nobu Yokota
KR1	Korea	Ajou University School of Medicine, South Korea	1.6–2.6	0.66–1.07	1.3–2.1	Colorimetric	Ka Kahe and Dae Jung Kim
MX1	Mexico		1.8–2.2	0.74–0.905	1.48–1.8	Colorimetric, xylidyl blue	Claudia Gamboa
PL1	Poland	Diagnostic Medical Laboratory "Synevo"	1.60–2.60 (age dependent)	0.66–1.07	1.3–2.1	Colorimetric, xylidyl blue; fasting	Jeanette Maier and Magdalena Maj-Zurawska
RO1	Romania	Fundeni Clinical Hospital Bucuresti	1.7–2.4 (adult patients)	0.70–0.99	1.40–1.98	Spectrophometric	Mihai Nechifor
RO2	Romania	Iasi Recovery Clinical Hospital BIOCLINICA St. Spiridon County Clinical Hospital Iasi	1.6–2.6 (> 12 y) 1.6–2.6 (> 14 y) 1.6–2.6 (no age specified)	0.66–1.07	1.36–2.14	Spectrophometric Colorimetric	Mihai Nechifor
RO3	Romania	Timis County Emergency Clinical Hospital, Timisoara	1.6–2.3 (no age specified)	0.66–0.95	1.36–1.90	Spectrophometric	Mihai Nechifor
RO4	Romania	Synevo network of private labs	1.6–2.4 (> 20 y)	0.66–0.99	1.36–1.98	Colorimetric	Mihai Nechifor
SK1	Slovakia	ICB, University Hospital Martin, Slovakia	1.77–2.58	0.73–1.06 (adult male)	1.46–2.1	Colorimetric, xylidyl blue	Martin Kolisek
SK2	Slovakia	ICB, University Hospital, Martin, Slovakia	1.87–2.5	0.77–1.03 (adult female)	1.5–2.06	Colorimetric, xylidyl blue	Martin Kolisek
SK3	Slovakia	Alpha Medical, Unilabs Group, Slovakia	1.53–2.6	0.63–1.07	1.26–2.14	Colorimetric	Martin Kolisek
TW1	Taiwan	Taichung Veterans General Hospital, Taichung, Taiwan	1.7–2.8	0.70–1.15	1.4–2.3	NR	Fu-Chou Cheng
US1	USA	Indiana University Hospital Pathology Laboratory	1.6–2.9	0.66–1.19	1.3–2.4	Colorimetric	Nana Gletsu-Miller and Taylor Wallace
US2	USA	University of Louisville, Louisville, KY	1.7–2.3	0.70–0.95	1.4–1.9	Colorimetric, calmagite	Ron Elin
US3	USA	Dartmouth	1.68–2.60	0.69–1.07	1.4–2.1	NR	Emily Campbell

Table 2 (continued)

Institution code	Country	Institution	Serum magnesium reference range ^a			Method ^b	Researcher
			mg/dL	mmol/L	mEq/L		
US4	USA	Medical University of South Carolina	1.6–2.6	0.66–1.07	1.3–2.1	NR	Emily Campbell
US5	USA	Clinical laboratories, Hawaii	1.7–2.4	0.70–0.99	1.4–1.98	Colorimetric	Andrea Rosanoff
US6	USA	Diagnostic laboratories, Hawaii	1.6–2.6	0.66–1.07	1.3–2.1	Colorimetric	Andrea Rosanoff
US7	USA	Clinical Laboratory, Indiana University School of Medicine Diabetes Center Translation Core	1.70–2.70	0.70–1.1	1.4–2.2	Colorimetric (xylydyl blue)	Yiqing Song
US8	USA	UCSF (https://www.ucsfhealth.org/medical-tests/magnesium-blood-test)	1.7–2.2 ^c	0.70–0.905 ^c	1.4–1.8 ^c	NR	Stefano Iotti
US9	USA	Mayo Clinical Laboratories (age > 17 y)	1.7–2.3 (age dependent)	0.70–0.95	1.4–1.9	NR	Stefano Iotti
US10	USA	National Institutes of Health Clinical Center	1.6–2.6	0.66–1.07	1.3–2.1	Enzymatic, assayed on Abbott Architect. Alert levels: < 1.0 or > 5.0 mg/dL	Rebecca Costello
US11	USA	Columbia University Presbyterian Hospital, New York	1.6–2.6	0.66–1.07	1.3–2.1	NR	Ka KaHe

These data were gathered by MaGNet for the Global Magnesium Project, 2020–2021

NR, not reported; UCSF, University of California, San Francisco

^aBolded values are those provided by the researchers. Nonbolded values are the respective conversions (*conversion factor*: for mg/dL to mmol/L, multiply by

0.4114; for mmol/L to mg/dL, multiply by 2.43; and for mmol/L to mEq/L, divide by 0.5)

^bIn Fig. 2, colorimetric, photometric, and spectrophotometric designations of methodology are all classified under colorimetry

^cThe published UCSF serum magnesium reference range reports 1.7–2.2 mg/dL (shown in bold here) converting to 0.85–1.1 mmol/L on their webpage. However, the correct conversion for 1.7–2.2 mg/dL is 0.70–0.905 mmol/L, not 0.85–1.1 mmol/L; possibly their reported value of 1.7–2.2 is mEq/L (rather than mg/dL), which converts to 0.85–1.1 mmol/L

Despite the central role of magnesium in maintaining proper immune, vascular, and pulmonary function, emerging evidence indicates that magnesemia is seldom assessed in patients [17]. Additionally, an evidence-based standard for the upper range of serum magnesium to differentiate between a “safe” and “hypermagnesemic” value is yet to be determined.

Conclusion

The 43 serum magnesium reference range values we collected from 16 countries varied widely, and all but 2 (DE2 and IN1) had a hypomagnesemic cut-off point well below that of the recommended 0.85 mmol/L (2.07 mg/dL or 1.7 mEq/L). Thus, the hypomagnesemic reference values in this informal collection indicate that physicians and researchers are vastly underestimating hypomagnesemia in their patients and institutions, interpreting as “normal” serum magnesium values that fall well below that recently

proposed to be safe for good health. It is critically important to appropriately identify, diagnose, and manage low magnesium status, which is often overlooked and may play a role in susceptibility to increasingly common chronic diseases (e.g., CVD, diabetes, and chronic obstructive pulmonary disease), among other conditions.

A consensus serum magnesium to define hypomagnesemia is suggested to be 0.85 mmol/L (2.07 mg/dL or 1.7 mEq/L). An evidence-based, standardized serum magnesium reference range for hypermagnesemia still needs to be determined. MaGNet researchers should continue gathering and monitoring new evidence to further update recommendations for guidelines that define the correct serum magnesium reference range to maintain health.

Disclosures

Christina West received financial support from CMER for her role in this work. She provides editorial consulting services to authors, nonprofit organizations, and publishers, but has no conflicts of interest that influenced or are relevant to this work. Anton Kraus is an employee of Verla-Pharm Arzneimittel.

Author contributions A.R.: conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; supervision; validation; visualization; roles/writing—original draft; writing—review and editing. C.W.: data curation; visualization; software; writing—review and editing. R.J.E., O.M., S.B., M.B., E.C., F.-C.C., R.B.C., C.G., F.G.-R., N.G.-M., B.v.E., S.I., K.K.H., D.J.K., K.K., M.K., A.K., J.A.M., M.M.-Z., L.M., M.N., G.P., M.S., Y.S., Y.P.T., R.M.T., T.C.W., K.Y., and F.W.: conceptualization; data curation; formal analysis; investigation; methodology; validation; visualization; writing—review and editing.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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