Serum magnesium: time for a standardized and evidence-based reference range

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Abstract. Magnesium deficiency can have serious health consequences. Low magnesium intake or low serum levels are risk factors for e.g. type 2 diabetes and cardiovascular diseases. Despite its scientifically recognized importance, too little attention is paid to magnesium in clinical practice. This may be due to the fact that there is no uniform and evidence-based reference range for serum magnesium as is the case for other electrolytes such as sodium and potassium. The serum magnesium concentration is also of a limited informative value, as it is maintained for a long time by releasing magnesium from body pools. A low serum magnesium is a definite sign of magnesium deficiency; however, values within the reference range do not rule out deficiencies. Nevertheless, serum magnesium should become part of routine diagnostics in order to be able to better detect deficiency states. For serum magnesium, a reference range of 0.75 to 0.95 mmol/L (1.82 to 2.31 mg/dL) can often be found. However, according to the current data situation, serum magnesium values of less than 0.85 mmol/L are associated with increased health risks. Therefore, the lower limit of the reference range should be raised to 0.85 mmol/L (2.07 mg/dL).

Key words: magnesium, magnesium deficiency, hypomagnesemia, reference range, diagnostics

Magnesium (Mg) is necessary as a cofactor for more than 600 enzyme reactions and it also acts as an activator for another 200 enzymes [1]. As a component of the Mg-ATP complex, Mg plays a role in practically all cellular processes [2]. Overall, around 80% of all metabolic reactions are dependent on Mg [3]. Therefore, Mg deficiency can be very multifaceted. Apart from the well-known muscle cramps, many other symptoms are possible, including headache, cardiac arrhythmias, hypertension, sleep disturbances, depression, complications in pregnancy, insulin resistance, impaired glucose tolerance, deficiency of active vitamin D and secondary electrolyte disorders (hypocalcemia, hypokalemia) [4]. Low Mg intake and a low Mg concentration in blood serum (serum Mg) are considered as risk factors for serious illnesses, including type 2 diabetes and cardiovascular diseases such as hypertension, coronary heart disease and sudden cardiac death [5-9]. Owing to a large number of studies in basic research and clinical research, the importance of Mg in science is recognized. However, Mg is still not valued enough in clinical practice. In the international literature, Mg is therefore referred to as the "forgotten" or

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"orphan" cation [1, 10, 11]. This may contribute to the fact that, in contrast to other electrolytes (sodium, potassium, calcium), serum Mg is not part of routine laboratory diagnostics and only rarely determined. In this respect, the limited informative value of serum Mg as a parameter for the Mg status could play a role. In addition, there is no uniform and evidence-based reference range for serum Mg to date. The objectives of this review are as follows:

- To work toward a uniform and evidence-based reference range for the serum Mg.
- To contribute to establishing serum Mg in routine laboratory diagnostics.

This would result in a faster and better diagnosis of the Mg deficiency. Therefore, symptoms of Mg deficiency, which can be serious, could be prevented. Furthermore, Mg deficiency often occurs as a concomitant phenomenon of illnesses and can aggravate the underlying illness. In addition, the risk for the development of a number of diseases could be reduced if Mg deficiency was recognized in good time and treated or avoided. The significance of serum Mg as a parameter for the Mg status will also be addressed in this review.

Materials and Methods

For this literature review, a literature search of "magnesium" in connection with the search terms "reference interval", "reference range", "diagnostics", "status", "serum", "plasma", "hypomagnesemia" and "deficiency" was carried out in the PubMed database with the following restrictions:
– period from January 1, 2000 to March 15, 2021;
– full text in English or German;
– study types: "meta-analysis", "systematic review", "review".

In addition, the reference lists of related articles were manually reviewed.

Informative value of the serum Mg is limited

A simple, fast, and reliable laboratory parameter for the Mg status is currently not available [12]. Functional biomarkers (*e.g.*, ferritin for iron status) have not yet been found for Mg [13]. The serum Mg, which is usually measured due to the lack of alternatives, has only limited informative value. The Mg concentration in blood serum can be maintained for a long time by reducing renal excretion and by the release of Mg from tissues (especially muscles and bones). Only when the Mg stores are exhausted, that is, in the case of an advanced deficiency, serum Mg will decrease. In addition, only 0.3% of the total body Mg can be found in the serum [3, 13]. Under the stress conditions that are often present when blood is drawn, Mg may be released quickly from intracellular stores. This can lead to an artificial increase in serum Mg, thereby masking low values. Thus, on the one hand, serum Mg values below the reference range (hypomagnesemia) are indicative of a Mg deficiency. On the other hand, values within the reference range do not rule out a (intracellular) Mg deficiency [3, 12-15]. In the special case of hypoalbuminemia (*e.g.*, in liver failure), there may be hypomagnesemia without a real Mg deficiency (pseudohypomagnesemia) as approximately 25% of the Mg in blood serum is bound to albumin. Therefore, a reduced albumin content is associated with a decreased serum Mg [12, 17]. A chronic latent Mg deficiency, which is often overlooked when only looking at the serum Mg, is already associated with increased disease risks [14, 16, 18]. Therefore, in clinical practice, a "normal" serum Mg should be interpreted with caution. Laboratory findings should be accompanied by a warning that values within the reference range do not rule out a Mg deficiency [15]. Mg deficiency that cannot be diagnosed based on serum Mg may be identified with the more sensitive Mg retention test [13, 19]. The low sensitivity of serum Mg is probably still little known among physicians. Usually, only values outside the specified reference ranges are taken into account when assessing laboratory results [15]. It should also be borne in mind that a Mg deficiency may already be well advanced when a laboratory diagnosis of hypomagnesemia is made [13]. Other laboratory parameters with a more informative value than the serum Mg are not available due to the high level of efforts involved in routine diagnostics (i.e., Mg retention test, Mg in lymphocytes or muscle, ionized Mg in serum) [14]. The Mg concentration in the

erythrocytes is also viewed critically as a parameter for Mg status [3].

What is required is a uniform and evidence-based reference range for all laboratories

There is currently no standardized reference range for serum Mg. The lower limit value is primarily under discussion. Internationally, a reference range of 0.75 to 0.95 mmol/L (1.82 to 2.31 mg/dL) is often given [16, 18, 20]. However, there are also reference ranges with significantly less lower limit values, for example, 0.70 to 1.10 mmol/L [21], 0.70 to 1.00 mmol/L [3] or 0.66 to 1.07 mmol/L, in specifications of laboratories in Germany [22, 23]. The reference range of 0.75 to 0.95 mmol/L was derived more than 40 years ago. This reference range represents the distribution of serum Mg values in the NHANES study (USA, $n = 15{,}820$) with an (apparently) healthy average population in the age of 1 to 74 [16, 24]. Accordingly, this reference range is not related to the risk of diseases; that is, it does not provide any information about which serum Mg would be reasonable from a health point of view [14, 16]. An American panel of experts is therefore calling for a reference range that suggests an optimal health status [16]. Epidemiological data indicate that the risk of a number of diseases increases with falling serum Mg, even within the reference range of 0.75 to 0.95 mmol/L [12, 16]. The German Society for Magnesium-Research e.V. had already proposed in 2000 that a lower limit value of 0.80 mmol/L should be set from a preventive point of view [17]. Current data suggest an increased risk of cardiovascular diseases, type 2 diabetes, and mortality from these diseases even with values below 0.75 to 0.85 mmol/L [16]. Therefore, a lower limit value of 0.85 mmol/L is stipulated internationally [14, 16, 18, 20]. The authors of this work agree with this requirement: The target value should be a serum Mg of $\geq$0.85 mmol/L. This adaptation of the reference range to the scientific evidence could significantly contribute to improve public health [16]. The lower limit of 0.85 mmol/L is supported by balance and metabolic studies, according to which a Mg deficiency must be expected in a range of >0.75 to 0.85 mmol/L. In these studies, there was no noticeable drop in serum Mg below the reference range, even with significantly reduced Mg intake via food. Nevertheless, the test subjects developed relevant pathophysiological changes (*e.g.* cardiac arrhythmias, impaired glucose tolerance) that reacted positively to Mg supplementation [12, 18, 20]. The upper limit of serum Mg is often given as 1.00 mmol/L [3] or 1.10 mmol/L [2, 21]. From the epidemiological studies that speak in favor of an increase in serum Mg, no upper limit value can be derived which, as a precaution, should not be exceeded. In contrast to hypomagnesemia, hypermagnesemia is rare due to the high renal excretion capacity for Mg. Hypermagnesemia usually is the result of severe renal insufficiency or excessive Mg intake, for example, in the form of Mg-containing antacids or laxatives [25, 26]. Hypermagnesemia remains asymptomatic up to a serum Mg of 2.00 mmol/L [2, 27, 28]. In patients with renal insufficiency, mild hypermagnesemia is associated with a survival benefit [29]. Overall, the question arises as to whether the previous upper limit value for serum Mg is of clinical relevance or should be increased moderately.

Serum Mg should be part of routine analysis

Similar to the other electrolytes (sodium, potassium, calcium), the serum Mg should be routinely determined in laboratory diagnostics. This would facilitate the detection of Mg deficiency despite the limited informative value of the serum Mg [1]. Studies show that relevant prevalence of hypomagnesemia can be expected in the average population, especially in risk groups. In an unselected German sample ($n = 16{,}017$), hypomagnesemia was found in 14.5% of the people when the lower limit of serum Mg was set at 0.76 mmol/L; at a limit of 0.80 mmol/L, the prevalence was 33.7% [30]. In typical risk groups, the prevalence was significantly higher, for example, in pregnant women (71.5%, limit value <0.76 mmol/L) [31] and elderly people (33.0%, limit value <0.76 mmol/L) [32] in Germany. The prevalence among

diabetics in Switzerland was 37.6% (limit value <0.75 mmol/L) [33]. Internationally, there was also a high prevalence in critically ill patients in intensive care units, for example, 52% (limit value <0.70 mmol/L) [34] or 61% (limit value <0.75 mmol/L) [35].

A meta-analysis of six cohort studies with a total of 1,550 patients revealed that hypomagnesemia in the critically ill patients admitted to the intensive care unit is associated with an increased mortality rate (RR = 1.90; 95% Cl: 1.48 to 2.44; $p < 0.001$), an increased need for artificial ventilation (RR = 1.65; 95% CI: 1.12 to 2.43; $p = 0.01$) and longer hospital stays (+4.1 days; 95% CI: 1.16-7.04; $p = 0.01$) [36]. Other meta-analyses came to similar conclusions [37]. These relationships should also be taken into account against the background of the current COVID-19 pandemic [38].

The strong correlation between poor Mg supply and the incidence of chronic diseases such as type 2 diabetes or cardiovascular diseases also suggests that Mg status should be determined and monitored in these patients [12].

Table 1. Instructions and recommendations for determination of serum magnesium.

General information:
• Serum is preferred as the sample material over plasma since anticoagulants can be contaminated with Mg or influence the analysis.
• Circadian rhythm and body position when taking blood can influence the serum magnesium.
• Recognizing and avoiding stressful situations when taking blood samples.
• Blood draw:
• If possible, avoid stoppage of blood flow or only allow brief flow restrictions (risk of hemolysis).
• Blood collection should be as gentle as possible. Aspiration systems have an advantage over vacuum systems.
Obtaining serum:
• No shaking or excessive cooling of whole blood.
• Ideally, centrifugation of the serum on site:
– Store the whole blood for at least 20 min and maximum 60 min before centrifugation (tubes should stand, not lie).
– Appropriate centrifugation (10 min at 2000 g with a free-swinging centrifuge).
– Carefully pipette the serum into the shipping container (do not pour over it as this would introduce erythrocytes).

Methodological aspects

The analytical method of choice is atomic absorption spectrometry. Photometric methods are acceptable and widely used [1, 12, 16]. The values are given in mmol/L or mg/dL (conversion: mmol/L = mg/dL x 0.4114). However, there is a note of caution: Hemolysis can cause incorrectly high serum Mg values and is a significant source of error [13] (*table 1*). In Germany, the costs for the determination of the serum Mg according to the fee schedule for doctors are low at €2.33 (simple fee rate) and €2.68 (permissible fee rate) and correspond to the costs for serum calcium [39].

Conclusions

The importance of an optimal Mg supply in prevention and therapy is scientifically recognized. In order to establish this importance in clinical practice, the determination of serum Mg should be established as part of the routine laboratory diagnostics analogous to other electrolytes. For this purpose, it is necessary to determine a uniform and evidence-based reference range for the serum Mg. The previously used lower limit values of the reference range are too low from a preventive perspective. According to international expert groups, a lower limit for serum Mg of 0.85 mmol/L is suggested. The measurement of serum Mg is inexpensive and should be part of the statutory health insurance obligation. In view of the limited informative value of the serum Mg (Mg deficiency can also be present with serum Mg values in the normal range), the diagnosis should focus not only on serum Mg, but also on Mg deficiency symptoms (see examples above) and anamnestic evidence (risk factors for Mg deficiency); examples of this are diseases (*e.g.* diabetes mellitus, inflammatory bowel disease), drugs (*e.g.* loop diuretics and thiazides, proton pump inhibitors, platinum compounds) and life conditions (*e.g.* pregnancy, high level of physical activity, chronic stress).

Key statements

- Magnesium deficiency can have serious health consequences. Furthermore, low magnesium intake and low serum magnesium are considered risk factors, for example, for type 2 diabetes mellitus and cardiovascular diseases.
- Serum magnesium is the only available parameter for the magnesium status in routine analysis but has only limited informative value. It should, therefore, be noted in the laboratory results that values within the reference range do not exclude the presence of a magnesium deficiency.
- In order to establish the great importance of Mg in clinical practice, serum Mg should be part of routine diagnostics.
- According to current data, an increase in the lower limit value for serum magnesium to 0.85 mmol/L (2.1 mg/dL) is required from a health point of view.
- A magnesium deficiency is best diagnosed on the basis of the magnesium deficiency symptoms and the anamnesis (risk factors for magnesium deficiency) in combination with the serum magnesium.

Disclosures

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