Review

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Improving diagnosis and treatment of hypomagnesemia

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Abstract: Magnesium is one of the most abundant cations in the body and acts as a cofactor in more than 600 biochemical reactions. Hypomagnesemia is a highly prevalent condition, especially in subjects with comorbid conditions, but has received less attention than other electrolyte disturbances. This review will discuss magnesium physiology, absorption, storage, distribution across the body, and kidney excretion. After reviewing the regulation of magnesium homeostasis, we will focus on the etiology and clinical presentation of hypomagnesemia. The role of laboratory medicine in hypomagnesemia will be the main purpose of this review, and we will discuss the laboratory tests and different samples and methods for its measurement. Although free magnesium is physiologically active, total serum magnesium is the most commonly used measurement in laboratory medicine and is apt for clinical purposes; however, it is not appropriately used, and many patients with hypomagnesemia remain undiagnosed and not treated. Using information technologies, laboratory medicine can largely improve the diagnosis and treatment of hypomagnesemia through the design and establishment of automatic demand management and result management interventions by acting in the first and last steps of the laboratory cycle, test requests, and actions taken after test results, to unmask patients with hypomagnesemia and improve the number of patients undergoing treatment.

Keywords: appropriateness; clinical laboratory; diagnosis; hypomagnesemia; magnesium

Introduction

Magnesium, an essential electrolyte and nutrient, is one of the most abundant cations in the human body. It acts as a cofactor in more than 600 enzyme systems regulating various biochemical reactions in the body [1].

Magnesium physiology cannot be separated from other minerals. In fact, magnesium also maintains the level of intracellular calcium and potassium; acts a signalling molecule; and regulates the synthesis, storage, and transport of adenosine triphosphate (ATP) [2].

Despite its crucial role in cell function, hypomagnesemia has received poor attention from physicians than other electrolyte disturbances [3]. This may be in part because symptoms related to hypomagnesemia are difficult to separate from other underlying disorders and metabolic diseases, resulting in hypomagnesemia to be evaluated as secondary in nature [4, 5] with symptoms appearing only when the level is too low. Furthermore, another reason may be that the exact role of magnesium in normal physiology is poorly understood [6].

Although more than 99 % of the total body magnesium is located in the intracellular space, intracellular magnesium measurement is not included in daily basis in the clinical laboratory, being measured in serum and/or plasma. Hypomagnesemia – considered when serum magnesium concentration is below 0.7 mmol/L [4] – is common, especially in subjects with comorbid conditions. The causes of hypomagnesemia can be broadly classified into four categories: gastrointestinal loss, renal loss, secondary to medications, and decreased intake [7]. The prevalence of hypomagnesemia depends on multiple factors and varies according to different healthcare scenarios: 2.7 % in the general population [8], approximately 10 % in hospitalized patients, most commonly in critically ill patients [9], 14.7 % in patients with chronic kidney disease [10], 30–80 % in persons with alcohol use disorder [11] and 10–60 % in patients with diabetes [12–16]. Mild deficiency can remain undetected because it
often presents non-specific symptoms, such as irritability, nervousness, mild anxiety, muscle contractions, weakness, fatigue, and digestive problems [17]. A more pronounced magnesium deficiency can cause more severe symptoms of neuromuscular, cardiac, or nervous disorders [18].

The biological relevance of magnesium is clear and has been known since ancient times; however, hypomagnesemia has been overlooked, and magnesium is still one of the forgotten tests in current laboratory medicine [6].

Beyond providing readers with a better understanding of magnesium homeostasis, as well as the etiology and pathophysiology of hypomagnesemia, as reported in previous reviews by experts on the subject [18–22], this review will focus on the importance of laboratory medicine in the diagnosis and assessment of hypomagnesemia, as well as its treatment.

**Physiology**

**Absorption**

**Dietary sources and recommended daily intake of magnesium**

Magnesium is widely distributed in plant and animal food and beverages. The richest dietary sources of magnesium are whole grain cereals, green vegetables, beans, nuts, and seafood [23]. In addition, water, both tap and bottled, can contribute significantly to the daily amount of ingested magnesium [24]. Magnesium consumption from water rich in magnesium may be taken into consideration as an alternative source of magnesium [25].

The United States Food and Nutrition Board recommends a daily magnesium intake of 420 mg for men and 320 mg for women to maintain constant serum magnesium levels [26].

**Intestinal absorption**

Intestinal magnesium absorption occurs predominantly in the small intestine and occurs via both passive and active pathways [27]. Passive transport is responsible for 80–90 % uptake and is attributed to a high luminal magnesium concentration, which is regulated by proteins comprising the tight junction, including claudins [28]. Lower concentrations of intestinal magnesium promote active transport in the distal small intestine and colon via the predominant magnesium transporters, members of the transient receptor potential melastatin (TRPM) family of cation channels [27], include TRPM6 and TRPM7.

Despite this process, the intestine seems to have a limited role in regulating the magnesium balance. In contrast to other minerals, intestinal magnesium absorption is poorly regulated and mainly depends on magnesium intake [29, 30]. TRPM6 and TRPM7 are highly sensitive to intracellular magnesium levels, causing the inhibition and saturation of active transport at higher magnesium concentrations, resulting in magnesium absorption being dominated by passive transport [31, 32]. In contrast to calcium, magnesium transport in the colon is independent of 1,25-dihydroxyvitamin D3 signalling [33].

Cyclin M (CNNM) belong to a family of proteins that function as magnesium-extruding transporters by stimulating sodium/magnesium exchange. The absorbed magnesium enters the bloodstream by exchanging intracellular magnesium with extracellular sodium, mediated by CNNM4 and CNNM2 at the basolateral membrane of cells [34, 35].

**Storage and distribution**

Approximately 99 % of total body magnesium is stored in bone, muscles, and non-muscular soft tissue [36] and less than 1 % is present in blood and extracellular fluids [37].

Plasma magnesium exists into three fractions; protein-bound (20–30 %), complexes with anions such as phosphates, sulfates, or bicarbonates and citrates (5–15 %), and free ionized cations (55–70 %) [38]. The magnesium concentration in erythrocytes is three times higher than in plasma [19].

**Excretion**

Renal excretion is the most important factor in magnesium homeostasis, and magnesium concentration is controlled by excretion in the urine.

Approximately 2,400 mg of magnesium in the plasma is filtered daily by the glomeruli under physiological conditions. Along the nephron, 90–95 % of the magnesium is reabsorbed, and the remaining is excreted in the urine. The major sites for reabsorption are the thick ascending limb of the loop of Henle and the distal convoluted tube [1, 6, 39].

The process at the thick ascending loop is facilitated by paracellin-1/claudin 16 and claudin 19, and that in the distal convoluted tube is mediated by the transporter TRPM6 and TRPM7 [40]. Reabsorption of magnesium in distal convoluted tube is crucial to the final balance of magnesium [41].

Studies in hypomagnesemic families have revealed over a dozen genes directly or indirectly involved in magnesium transport. Those can be classified into four groups: hypercalciuric hypomagnesemias (encompassing mutations in CLDN16, CLDN19, CASR, CLCNKB), Gitelman-like hypomagnesemias (CLCNKB, SLC12A3, BSND, KCNJ10, FYXD2,
HNF1B, PCBD1), mitochondrial hypomagnesemias (SARS2, MT-TI, Kearns–Sayre syndrome) and other hypomagnesemias (TRPM6, CNM2, EGF, EGFR, KCNA1, FAM111A) [42]. The physiology and homeostasis of magnesium is summarized in Figure 1.

**Regulation of magnesium homeostasis**

Approximately 24–76 % of the magnesium ingested in the diet is absorbed in the gut, and the magnesium that is not absorbed is eliminated with feces. When the intestinal magnesium concentration is low, active transport prevails primarily in the distal small intestine and colon [43].

The kidneys are the primary site of magnesium homeostasis and play a key role in regulating and maintaining the magnesium balance. The tubular reabsorption of magnesium is different from that of other ions because it is primarily conducted along the thick ascending loop of Henle rather than the proximal tubule [44], which only reabsorbs 10–25 % of the filtered load. Although the distal tubules reabsorb only 10 % of the filtered magnesium through the glomerulus, this amount is significant because it represents 60–70 % of the magnesium delivered to this segment from the loop of Henle. Because there is no indication of magnesium absorption beyond the distal tubule in the collecting ducts, the tubule segments comprising this portion of the nephron play a fine-tuning in determining the final urinary excretion of magnesium [45].

Magnesium absorption and excretion are influenced by different hormones: 1,25 dihydroxyvitamin D can stimulate intestinal magnesium absorption, estrogens are known to stimulate TRPM6 expression [39] and parathyroid hormone (PTH) is involved in magnesium reabsorption in the kidney, absorption in the intestine, and release from bone excretion [46].

**Hypomagnesemia – etiology**

The causes of hypomagnesemia are related to the setting of the patient and can be broadly classified into four categories (Figure 2): gastrointestinal loss, renal loss, secondary to medications, and decreased intake [7, 47].

**Gastrointestinal losses**

Common settings in which hypomagnesemia may be observed include acute or chronic diarrhea, malabsorption and steatorrhea, and small bowel bypass surgery. Hypomagnesemia has also been observed in acute pancreatitis. The hypomagnesemia mechanism is presumably similar to the mechanism partially responsible for hypocalcemia in acute pancreatitis: saponification of magnesium and calcium in necrotic fat [48] Furthermore, hypomagnesemia with secondary hypocalcemia can be produced by a familial disorder characterized by a selective defect in magnesium absorption (primary intestinal hypomagnesemia) [49].
Renal losses

Urinary magnesium loss can be caused by inherited or acquired disorders.

Expansion of the extracellular fluid volume by reducing sodium and water reabsorption can decrease passive magnesium transport.

Hypercalcemia can lead to mild hypomagnesemia, with various mechanisms that may contribute to the reduction in magnesium reabsorption [50]. It can induce hypomagnesemia by competition in transport, but also by its effect on the calcium-sensing receptor (CaRs) of the basolateral membrane, since its union inhibits renal outer medullary potassium channel (ROMK) and hinders paracellular reabsorption of magnesium, in addition to acting directly on claudins [51].

Primary renal magnesium wasting is an unusual disorder that may present sporadically or as a familial disease. Several hereditary disorders characterized by perturbations in renal magnesium reabsorption leading to hypomagnesemia have been described: Gitelman and Bartter syndrome, EAST (SeSAME) syndrome, familial hypomagnesemia with hypercalciuria and nephrocalcinosis, Na⁺/K⁺-ATPase mutations, voltage-gated potassium channels, hepatocyte nuclear factor-1-beta gene mutations, epidermal growth factor gene mutations, PCBD1 mutations, and cyclin M2 mutations [52–55].

Secondary to medications

Diuretic medications are a known cause of hypomagnesemia. The kidney plays a major role in magnesium reabsorption and secretion; thus, medications that affect the kidneys can cause hypomagnesemia. Thiazide diuretics are most likely the major cause of hypomagnesemia [58]. Loop diuretics, such as furosemide, have been associated with the development of hypomagnesemia [59]; however, there are studies that have found no association [60].

Hypomagnesemia, usually with hypocalcemia, has been described in case reports related to long-term proton pump inhibitors (PPIs) (usually for more than one year). The presumed mechanism involves a decrease in intestinal magnesium absorption by intestinal epithelial cells [61].

Nephrotoxic drugs may cause renal tubular dysfunction leading to urinary magnesium loss [62–64]. In addition, post-transplant patients who received solid organs showed a high incidence of hypomagnesemia. It is attributed to renal magnesium wasting and is primarily caused by calcineurin inhibitors such as tacrolimus and cyclosporine [65, 66].

Decreased intake

The 2001–2008 National Health and Nutrition Examination Survey (NHANES) showed that over 50% of the adult population did not consume the recommended magnesium intake regardless of their weight status [67]. The 2015–2020 Dietary Guideline for Americans particularly identified magnesium as one of the shortfall nutrients [68].
The main causes were alcohol use disorders, critically ill patients receiving total parenteral nutrition, and starvation. Hypomagnesemia is very common in alcoholic patients admitted to hospitals, and many other factors are thought to contribute to hypomagnesemia in these patients, including dietary deficiency, acute pancreatitis, and diarrhea [69]. In addition, hypomagnesemia is a secondary complication in critically ill patients and appears to be associated with a greater risk of mortality, sepsis, mechanical ventilation, and length of stay in patients admitted to the ICU [70].

The elderly tends to follow a diet that often is both quantitatively and qualitatively insufficient. Nevertheless, the origin of hypomagnesemia in the elderly is not only related to age malnutrition [71], but also could contribute diminished intestinal absorption, increased urinary output, and different drug interactions [72].

Finally, hypomagnesemia should be considered during starvation.

**Hypomagnesemia – clinical presentation**

The signs and symptoms of hypomagnesemia include mild tremors and generalized weakness to cardiac ischemia and death. Hypomagnesemia, while typically defined as serum magnesium below 0.7 mmol/L, with or without accompanying total body depletion, does not lead to clinically significant signs and symptoms until serum levels fall below 0.5 mmol/L [4].

The main clinical manifestations include neuromuscular (hyperexcitability, weakness, apathy, delirium, and coma), cardiovascular manifestations (widening of the QRS and peaking of T waves with moderate magnesium depletion, widening of the PR interval, diminution of T waves, and atrial and ventricular arrhythmias with severe depletion), and other electrolyte abnormalities, such as hypocalcemia, hypokalemia, metabolic alkalosis, and hypoparathyroidism [3, 47].

**Disorders related to hypomagnesemia**

Several studies have shown that chronic hypomagnesemia is frequently associated with other electrolyte abnormalities [73, 74].

Chronic magnesium deficiency is associated with many diseases [19].

In addition, magnesium deficiency has been linked to atherosclerosis, alterations in blood lipid levels, myocardial infarction, kidney stones, premenstrual syndrome, and psychiatric disorders [75–78]. The incidence of hypomagnesemia in patients with type 2 diabetes ranges widely from 13.5 to 47.7 % [79].

Magnesium deficiency increases the risk of numerous cardiovascular diseases [80]. Magnesium is involved in blood pressure regulation. Alterations in calcium and magnesium metabolism have been implicated in the pathogenesis of primary hypertension. In this context, it is important to reiterate that acute hypomagnesemia shows clear clinical signs and symptoms, and that its diagnosis is easy. However, subclinical or maintained magnesium deficiency is often underestimated [19].

Osteoporosis is the most common bone disease in humans and represents a major public health problem, particularly in women and older people. Magnesium deficiency may be a risk factor for osteoporosis [81].

Numerous studies have reported the involvement of magnesium in neurological diseases [82]. Studies have found that patients with cluster headaches and classic or common migraine, especially menstrual migraine, have low magnesium levels [83, 84]. An excellent review summarizes the recent literature on magnesium deficiency in this type of disease: chronic pain, migraine, stroke, epilepsy, Alzheimer’s, and Parkinson’s, as well as the common comorbid conditions of anxiety and depression [85].

Several epidemiological studies have demonstrated that a diet poor in magnesium increases the risk of developing cancer [86].

In summary, there are numerous diseases and clinical conditions related to low magnesium levels presented in Table 1.

**Treatment**

Supplementation with magnesium depends on the degree of hypomagnesemia and the presence and severity of the

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<th>Table 1: Diseases or clinical conditions related to low magnesium levels.</th>
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| Diabetes | Hypertension | Osteoporosis | Atherosclerosis | Alterations in blood lipids | Myocardial infarction | Kidneys stones | Premenstrual syndrome | Psychiatric disorders | Neurological diseases (chronic pain, migraine, stroke, epilepsy, Alzheimer’s, and Parkinson’s) | Increased risk of cancer |
symptoms. Hypomagnesemia management is based on the severity of patient symptoms, kidney function, and hemodynamic status.

Severe, symptomatic hypomagnesemia, or both should be treated with intravenous magnesium sulfate, administered slowly with clinical and hemodynamic monitoring [87].

In hemodynamically unstable patients, the dose is 1–2 g magnesium sulfate (8–16 mEq [4–8 mmol]) intravenous over 2–15 min. Repeat dose as needed up to 50 mEq (25 mmol) over 8–24 h. In hemodynamically stable patients, the dose is 1–2 g magnesium sulfate (8–16 mEq [4–8 mmol]) in 50–100 mL 5% dextrose in water given over 5–60 min followed by continuous infusion of 4–8 g magnesium sulfate (32–64 mEq [16–32 mmol]) slowly over 12–24 h. Repeat as necessary to maintain plasma magnesium >1 mg/dL (0.4 mmol/L or 0.8 mEq/L).

In pediatric patients, the dose is 25–50 mg/kg (0.2–0.4 mEq/kg) (with a maximum of 2 g (16 mEq)) [88–90].

Special attention should be paid to replacing magnesium in patients with abnormal kidney function to avoid hypermagnesemia. Studies recommend reducing the magnesium dose by 50 % and closely monitoring magnesium levels in these patients [88].

An overdose of intravenous magnesium may cause thirst, hypotension, drowsiness, muscle weakness, respiratory depression, cardiac arrhythmia, coma, and death [91].

Oral replacement therapy should be reserved for asymptomatic patients [88] if tolerable. Magnesium supplementation is well tolerated, but it can cause gastrointestinal symptoms, including diarrhea, nausea, and vomiting [92]. Although mild-to-moderate hypomagnesemia is typically asymptomatic, long-term deficiencies have been reported to be associated with a spectrum of adverse outcomes (increased risk of diabetes mellitus, various diabetic complications, arrhythmias, particularly congestive heart failure, more rapid progression of kidney disease, increased risk of fractures, higher mortality rates in critical patients) [3, 93–95]. Organic magnesium salts are generally better absorbed, usually followed by magnesium chloride, then magnesium oxide. Tendency to cause loose stools is likely inversely proportional to absorbability of the salts [96].

A daily dose of 800–1,600 mg (40–80 mEq [20–40 mmol]) can be used to treat moderate to severe hypomagnesemia. Patients with gastrointestinal disorders that are not easily correctable can be challenging to treat because oral magnesium preparations can cause diarrhea and potentially worsen the deficit. Oral preparations should be started at the lowest dose and only gradually increased. Magnesium oxide tends to cause more gastrointestinal intolerance than other oral preparations [97].

Therefore, the underlying cause of persistent hypomagnesemia should be addressed and treated. Restoration of magnesium is recommended, whereas alternative therapeutic regimens are recommended, if applicable. For example, potassium-sparing diuretics (amiloride) may be substituted in patients with hypomagnesemia due to renal loss related to thiazide diuretics [98]. In patients with hypomagnesemia due to PPIs, changing this drug to an alternative drug should be considered [99].

Regardless of treatment, patients who present with another electrolyte abnormality in addition to hypomagnesemia should be treated appropriately [6].

Laboratory medicine role in hypomagnesemia

The relevance of magnesium to body metabolism and the significant rates of hypomagnesemia are inconsistent with the potential serum magnesium test under request [100], which makes the evaluation of magnesium status more challenging [101]. Moreover, despite the under request of the so-called forgotten test [6], the only reported intervention to adjust the demand for serum magnesium (besides those from our research group, reported later) is to reduce, not increase, its request through a care provider order entry system [102]. Moreover, there has been no improvement in its use in clinical practice over the years, as magnesium appears to be one of the least investigated macrominerals compared to calcium or iron. A 25-year search for articles using the Web of Science showed a relatively flat research output on magnesium deficiency relative to calcium and iron [101].

These facts put the laboratory professionals in an important position first to try to find the best way for its measurement with the means we have at our disposal in laboratory medicine, what sample and what technology to choose, to achieve this purpose, and second to give the magnesium the place that it deserves in terms of the appropriateness of magnesium laboratory test requests in each situation that needs to be studied and its result utilization. As with any laboratory marker, the measurement of magnesium with no clinical correlate does not appear to be a meaningful approach. However, in the case of a patient with hypocalcemia or hypopotasemia, it is of utmost importance as those cannot be corrected without previously magnesium reposition.
Laboratory tests, samples, and methods for measurement

Total and free magnesium in serum/plasma

Free magnesium is the physiologically active fraction, and although its measurement is spreading in daily practice, total magnesium is still the most frequently used in laboratory medicine. Serum is the most commonly utilized sample, although plasma is widely used in urgent samples. Because extracellular magnesium concentrations are only 1% of the total magnesium in the body, intracellular magnesium levels also can be measured, to determine whether true deficiency exists [103].

Total serum magnesium levels have been reported to correlate with bone and interstitial fluid magnesium content [104], but not with total body magnesium levels [101, 105]; therefore, high serum magnesium test values could be seen in deficiency and low when there is excess magnesium in the body [80] but is considered sufficient for most clinical purposes [106].

As magnesium is mainly an intracellular element, its measurement in red blood cells could theoretically be of great interest, however in clinical routine, serum or plasma are the samples of choice [107].

Serum magnesium levels remained constant within very narrow limits. The reference values are 0.7–1.1 mmol/L [108]. In 15,820 adult individuals in the US, with the ion measured utilizing atomic absorption, the reference interval was identified as 0.75–0.95 mmol/L [109].

It is important to evaluate hemolysis and bilirubin [110] which can distort the levels.

Hypomagnesemia can be classified as mild (0.57–0.70 mmol/L), moderate (0.40–0.56 mmol/L), or severe (<0.40 mmol/L) [111]. As the physiologically active magnesium in plasma is free magnesium and the required technology for its evaluation might not be available in most clinical laboratories, some authors have proposed a formula for magnesium corrected per albumin [112].

Total magnesium in urine

Total magnesium can also be measured in the urine. Serum levels of magnesium are altered throughout the day due to the circadian rhythm of magnesium excretion, with higher levels in the morning hours and lower levels in the evening when maximum magnesium excretion is occurring [113]. Urine levels are used as a complement to total serum magnesium when investigating the source of hypomagnesemia [36]. Urinary magnesium excretion should be interpreted in conjunction with serum magnesium levels.

Though no standard has been set for urinary magnesium excretion indicating deficiency, controlled metabolic experiments indicate that 40–80 mg (1.65–3.29 mmol) is the range of daily magnesium excretion when magnesium intakes are <250 mg/day, and 80–160 mg is the daily range when intakes are >250 mg/day independent of gender [114]. The calculation of fractional excretion of magnesium (FEMg) (Figure 3) in patients with hypomagnesemia and normal renal function is useful for the diagnosis of hypomagnesemia, and values >3% indicate inappropriate renal wasting of magnesium [115]. The measurement of urinary magnesium would be meaningful in daily clinical practice when interest to evaluate the cause of hypomagnesemia [115].

In summary, in patients with hypomagnesemia, 24 h urine magnesium >24 mg/day or fractional excretion >3% indicates renal magnesium wasting, and lower values would suggest low magnesium intake or gastrointestinal losses, or both.

However, most laboratories avoid 24 h urine samples because collection is cumbersome and often inadequate. Some believe that it would be more appropriate to switch to the use of random urine, such as with albumin in the urine. The magnesium-creatinine ratio can be beneficial when assessing the cause of hypomagnesemia. The request for urinalysis is frequent in the laboratories, which provides the opportunity to determine magnesium in random urine in patients with low magnesium serum levels [116], and the reference ranges in adults are reported 0.04–0.12 mg/mg creatinine [117, 118].

Methods for measurement

Free magnesium measurement is performed using ion-selective electrodes [119] and is not commonly used in laboratory medicine in daily practice; neither is atomic absorption spectroscopy employed for total magnesium measurement, even though it is a reference method owing to its specificity and accuracy [106]. However, these methods are impractical and expensive in laboratory medicine.

\[
\text{FEMg} (%)= \left( \frac{\text{uMg} \times \text{sCr}}{\text{sMg} \times \text{uCr} \times 0.7} \right) \times 100
\]

FEMg: fractional magnesium excretion, u: urine, s: serum

Figure 3: Fractional excretion of magnesium (FEMg) calculation.
because they are not automated. Therefore, spectrophotometric methods for total magnesium are most commonly used, as they are easily automated, fast, and included in random-access analyzers, where analysis is performed on a collection of specimens sequentially, with each sample analyzed for a different selection of tests, allowing the measurement of variable numbers and types of analytes in each specimen.

Spectrophotometric methods are based on magnesium binding to metallochromic indicators, such as calmagite and methylthymol blue, xylidyl blue, chlorophosphonazo III, and arsenazo or formazan dye in dry chemistry methods, which generally form a colored complex with magnesium in alkaline solution measured at approximately 600 nm. Enzymatic assays can also be employed using an enzyme whose activity strictly depends on magnesium [106].

In the Unity Interlaboratory Program [120], which provides reports from more than 50,000 instruments in more than 90 countries, free magnesium measurement is not included, nor is total magnesium measured through atomic absorption spectrophotometry. Instead, the participants used colorimetric methods, with xylidyl blue as the most widely employed method.

Desirable quality specifications are based on biological parameters, with a median within-subject variation of 3.6% and a median between-subject variation of 6.4% for total serum magnesium. Therefore, for magnesium analysis, the desirable analytical imprecision was 1.8%, and the desirable bias was less than 1.8% [121]. For quality assessment schemes that use single-sample analysis, it is desirable that the acceptability criterion (total error) be 4.8%. Unfortunately, in general laboratory practice, state-of-the-art for magnesium assays fall far short of desirable performance based on biological variability considerations [120]. There is still considerable room for improvement in the existing methodology for magnesium measurements.

Laboratory medicine in improving the diagnosis and treatment of hypomagnesemia

The laboratory has evolved significantly in recent decades. The laboratory cycle established by Lundberg [122], and later improved in collaboration with Plebani and Laposata [123], already called the “Brain to brain laboratory loop,” evolved into a process of nine consecutive steps, including the pre- and post-analytical stages, for the selection of the test and the interpretation of the result and the consequent action [124].

Advances in technology have decreased the rate of analytical errors [125] and the number of errors in the pre- and post-analytical phases. As a result, the steps carried out within the laboratory walls — the “intra-laboratory” processes — are increasingly safe, especially in the analytical phase [126] and the risk to the patient has been reduced [123]. Conversely, the errors have significantly increased in the “extra-laboratory” processes, the first and last stages of the laboratory cycle [124, 127], test request and action taken when receiving tests results, and we must focus on reducing those rates through demand management (DM) and result management (RM) interventions to correct inappropriate test requests and improve test result utilization. As a consequence of this evolution of the laboratory cycle, parallel evolution in the laboratory model has occurred [128]. From the traditional laboratory, an auxiliary or support service in the overall patient care process that intervenes in the clinical decision, processing all the requested tests to corroborate or rule out the hypothesis suspected by the clinician. The leading laboratory model, already transformed into a key service in the overall process of patient care, focuses mainly on the pre-and post-analytical steps, and not only intervenes in the clinical decision, but also leads to clinical decisions. It manages not just DM interventions to correct over-request, but the under-request is also acted upon, and the last step of the laboratory cycle is also improved through RM interventions, ensuring that the laboratory results have been communicated, received, reviewed, and the correct action is taken [129–131]. Currently, DM and RM interventions that are crucial in improving the laboratory cycle are the main features of the leading laboratory model, and the outcome key process indicators (KPIs) that monitor DM and RM interventions are crucial to monitor its performance [128, 132].

Automatic laboratory DM and RM interventions to unmask and treat hypomagnesemia

General considerations

To design and establish the interventions, we followed our procedure to manage inappropriate requests for laboratory tests from detection to monitoring [133]. We decided to design and establish DM interventions to correct serum magnesium testing under-request, since re-envisioning it was a good target for such interventions given the risky consequences of a potential under-request [134]. Regarding the target population and trying to generate the greatest
impact with the least effort, we applied the Pareto principle (80% of outcomes result from 20% of all causes for any given event). Accordingly, we chose our main providers, the primary care (PC) and the emergency department (ED) for our DM interventions. The third step in our approach, after selecting the test and the population, is the generation of the idea, not just through our knowledge of laboratory testing but also through creative imagination, communication, and leadership [135]. Finally, in the design of the intervention, it is crucial to reach a consensus with the requesting physicians and their monitoring over time; the final design must be written with objectives, action plans, or strategic initiatives, and the indicators for its monitoring.

Moreover, the implementation of the DM intervention should always be established for a specific period and monitored through process and outcome indicators to decide whether to continue, stop, or redesign the intervention if necessary. The process indicators show an increase in test measurement [136] (in absolute numbers or as a relationship to a related or widely requested test [137–139]). The outcome indicators are especially important in DM interventions to correct under-request, that is, the magnesium test case, because we are increasing expenses by measuring an additional test. Outcome KPIs are based on the improvement generated by DM intervention in the patient, or healthcare organization, or both.

We strongly advocate DM interventions to correct laboratory tests under-request. One of the immediate consequences – as one is acting upon a “hole” in disease prevention – is improved disease diagnosis and monitoring. However, we acknowledge that legal matters in some regions may not allow for these practices. In such settings, we encourage our colleagues to include a relevant and short comment in the laboratory report instead of automatically registering and measuring the under-requested test. For example, in the case of a patient with hypocalcemia, the comment could be linked to serum calcium result, as follows: “We recommend the request and measurement of the total magnesium in the current sample, as hypomagnesemia could be the source of hypocalcemia, and could be acted upon”.

For the magnesium serum test, we also designed and established an RM intervention. RM interventions are also automated and based on LIS and patient databases, agree with clinicians, and consist of the addition of automatic comments in the laboratory report to encourage requesting clinicians the awareness of laboratory results crucial in clinical decision making, and accordingly to take the appropriate action.

There are more potential interventions possible to design and establish based, first on the situations in which hypomagnesemia is prevalent (Table 1), and second on new information technologies, such as artificial intelligence and machine learning, new predictive analytics tools that will change health care, and the practice of laboratory medicine [140].

The DM and RM interventions we will report are successful [100, 128, 130, 141, 142]. All are automated, as they are based on the Laboratory Information System (LIS) and the laboratory patient database, agreed with clinicians, and monitored monthly after its establishment through process and outcome indicators [133].

The DM and RM interventions presented below are summarized in Figure 4.

**DM interventions to correct hypomagnesemia based on patient serum calcium or potassium values [128, 130]**

A. **DM intervention rationale.** Calcium and magnesium derangements are associated with increased morbidity and mortality, and hypocalcemia and hypokalemia should raise suspicion of magnesium depletion.

B. **DM intervention design.** The LIS is configured to automatically add a serum magnesium test (if not requested by a clinician) when serum calcium or potassium levels, or both are <7.5 mg/dL and <2.5 mEq/L, respectively, in ED and PC patients.

C. **DM intervention monitoring.** KPIs can be used to monitor and assess the results of DM intervention (Table 2).

In ED patients, the rate of detection of hypomagnesemia was higher in patients with hypokalemia (39.8%) than in those with hypocalcemia (53.2%); however, in both cases, more than one hypomagnesemia case was identified for every two screened patients, resulting in a cost of 0.7 $ when prompted by hypocalcemia and 0.6 $ when hypokalaemia was present. However, in PC, we found only the opposite, and we had a lower detection rate for hypokalemia (13%) than for hypocalcemia (45%). What was astonishing is that since the establishment of the DM intervention to measure total serum magnesium during hypocalcemia, the percentage of ED patients with hypocalcemia that were readmitted to the ED in the first 30 days following initial hypocalcemia detection was reduced from 25 to 13%. A very interesting outcome indicator measured the improvement in the patient through our DM intervention.

Numerous ED patients with hypomagnesemia were identified through our DM intervention; subjects who would have otherwise not been diagnosed and were less likely to be readmitted to the ED. DM interventions should be established in each laboratory, as hypocalcemia is not corrected if magnesium deficiency is not treated [130].

It is of common knowledge that, as it happens with any laboratory marker, the measurement of magnesium without paying attention to the clinical picture is really not meaningful approach. However, in the case of a patient with hypocalcemia or hypopotasemia, it is of utmost importance as these facts could not be corrected without previously magnesium reposition.

**DM interventions to correct hypomagnesemia in patients with diabetes, hypertension, and age [100, 128, 141]**

A. **DM intervention rationale.** Magnesium deficiency is frequently associated with diabetes mellitus [52] and hypertension [143], and elderly patients have a multifactorial predisposition to hypomagnesemia [144].

B. **DM intervention design.** The LIS, through real time access to data in electronic medical record, automatically adds the serum magnesium test when sample availability in requests for PC patients with a diagnosis of diabetes and hypertension as codified by the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) [145], and patients over 65 years of age, and with no test measurement in the previous year.

C. **DM intervention monitoring.** (Table 2).

The rate of hypomagnesemia was higher in patients with diabetes (24 %) than in those with hypertension (8 %) and in
the elderly (12%). In the latter group, the detection rate was higher when subjects were institutionalized (15%) than when they were living at home (11%) [100]. This is relevant, since hypomagnesemia is related to poor control of diabetes, and periodic determination of magnesium levels and appropriate replacement of their levels is advised. However, magnesium is not included in diabetes guidelines [146]. It is also known that magnesium deficiency is associated with hypertension [143]. In addition, hypomagnesemia is frequent in elderly patients with cumbersome symptomatology that can be mistaken for old age [144].

**DM interventions to correct hypomagnesemia based on PPI treatment**

A. **DM intervention rationale.** Magnesium deficiency is frequently associated with chronic PPI treatment [147].

B. **DM intervention design.** The LIS automatically adds the serum magnesium test when sample availability in requests for PC patients on PPI chronic treatment and with no test measurement in the previous year.

C. **DM intervention monitoring.** (Table 2)

The detection rate of hypomagnesemia in the patient population was 10% [128].

In summary, DM intervention in patients receiving PPI treatment helps to identify patients automatically with hypomagnesemia at a very affordable cost. Given the considerable number of patients receiving PPI treatment [148], we recommend its establishment. In addition, the general practitioners could benefit from a system that alerts to this interaction between the drug and magnesium levels [149].

**RM intervention to increase the number of treatments in patients with hypomagnesemia**

A. **Rationale for RM intervention.** Through the revision of patient medical records, we observed that many patients with hypomagnesemia were not treated.

B. **RM intervention design.** The automated RM intervention is based on LIS and consisted of generating an automatic comment in the laboratory report, “Patient with hypomagnesemia, please consider treatment if clinically indicated” when plasma magnesium <1.5 mg/dL (<0.6 mmol/L). Our ED physicians established this plasma magnesium level as the threshold for treating hypomagnesemia.

C. **RM intervention monitoring.** We counted the number of patients with hypomagnesemia who were appropriately treated.

The RM intervention to correct the action taken after receiving the test results increased the number of treated patients; in fact, it augmented the rate of treatment. A revision of the patient’s medical records to investigate if they were treated in the ED or in the following month showed that the number of patients with hypomagnesemia that were appropriately treated increased significantly, from 15 to 75%, a dramatic improvement in the treatment of hypomagnesemia [130].

Acting only in the first step of the TTP – test request – might not be sufficient without intervening to improve clinician awareness of relevant laboratory information to impact patient care through RM interventions.

**Conclusions**

The key role that magnesium plays in healthcare system could be widely recognized; however, unfortunately, laboratory tests to identify magnesium disorders are not appropriately used, and many patients with hypomagnesemia remain undiagnosed and not treated.

Using information technologies, laboratory medicine can contribute to better informed and more personalized decision making by impacting the test ordering behaviour and ensuring that the tests relevant to the clinical suspicion or provided diagnosis are measured and acted upon. These interventions improved the diagnosis, follow-up, and treatment of magnesium disorders and likely improved the outcome of associated chronic diseases, such as diabetes and hypertension.

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**References**


56. Elliott C, Newman N, Madan A. Gentamicin e


59. Lo


68. Magne Res 2011;24:S92


74. Salinas et al.: Hypomagnesemia – diagnosis and treatment


80. Salinas et al.: Hypomagnesemia – diagnosis and treatment


145. ICD - ICD-10-CM – international classification of diseases, tenth revision, clinical modification [Internet]. https://www.cdc.gov/nchs/icd/icd10cm.htm [Accessed 13 Jan 2022].


