Opinion Paper

The underestimated problem of using serum magnesium measurements to exclude magnesium deficiency in adults; a health warning is needed for “normal” results

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Abstract

Background: A major use of serum magnesium measurements in clinical practice is to identify patients with deficiency. However, numerous studies have shown that magnesium deficiency is common and may be present in over 10% of hospitalized patients, as well as in the general population. An important cause for under diagnosis of deficiency is that serum magnesium, the most commonly used test, can be normal despite negative body stores. This article focuses on the limitations of “normal” magnesium results and highlights the importance of lifestyle or “modus vivendi” as a pragmatic means of identifying those individuals potentially at risk for negative body magnesium stores.

Methods: Researched peer reviewed articles on magnesium published between 1990 and 2008 in MEDLINE and EMBASE, using database keywords “magnesium, deficiency, diagnosis, treatment and hypomagnesaemia”. Bibliographies of retrieved articles have been searched and followed. We have also performed a manual search of each individual issue in which most of these reports have appeared.

Results: In 183 peer reviewed studies published from 1990 to 2008, magnesium deficiency was associated with increased prevalence and risk in 11 major conditions. Similarly, in 68 studies performed over the same period, magnesium deficiency was found to predict adverse events and a decreased risk of pathology was noted when supplementation or treatment was instituted.

Conclusions: The perception that “normal” serum magnesium excludes deficiency is common among clinicians. This perception is probably enforced by the common laboratory practice of highlighting only abnormal results. A health warning is therefore warranted regarding potential misuse of “normal” serum magnesium because restoration of magnesium stores in deficient patients is simple, tolerable, inexpensive and can be clinically beneficial.

Keywords: deficiency; diagnosis; life-style; limitation; magnesium.

Introduction

Magnesium is the fourth most abundant mineral in the body after calcium, potassium and sodium. It is biochemically regarded as a “chronic regulator” and physiologically as a “forgotten electrolyte” (1–5). Adequate magnesium stores are necessary for the function of hundreds of widely distributed kinases, a group of magnesium-dependent enzymes that catalyzes the transfer of a phosphate group to a recipient molecule in the process of phosphorylation. The underlying mechanism seems to be the same for all known kinases and necessitates the presence of magnesium. Kinases can only bind “ATP-Mg” molecules, cleaving the γ phosphate group which is subsequently transferred to the recipient molecule. Phosphorylation transforms (switches on) an inactive molecule into an active or “functional” one, which can then perform specific biological/biochemical tasks (or vice versa). In addition to the phosphorylation of small organic molecules, up to 30% of body proteins are activated by magnesium-dependent kinases.

Magnesium-dependent kinases are paramount in regulating the cell-cycle and growth, as well as apoptosis. It has also a vital role in signal transduction and the production and actions of second messengers, such as c-AMP, diacylglycerol, calmodulin and c-GMP. Central to all these intracellular functions is that each protein must be at the right place and work at the right time. Individual kinases regulate and control a particular subset of proteins in these highly complex systems within each cell.

Magnesium plays an important role in electrolyte homeostasis; being necessary for the activation of ATP/ATPase pumps, such as Na+/K+, Na+/Ca2+, Na+/Mg2+ and Mg2+/Ca2+ pumps. If deficient, this can result in a reduction in their efficacy and activities. Chronic magnesium deficiency with time may eventually lead to overt pathology and electrolyte disturbances, such as “refractory” hypokalaemia and/
or hypocalcaemia. Neither the former nor the latter can be corrected by potassium or calcium treatment alone, and magnesium replacement becomes essential for restoration of cellular function (6). It is essential to note that magnesium itself is an electrolyte and plays a major role in the homeostasis of other major electrolytes, namely Na⁺, K⁺ and Ca²⁺. Furthermore, magnesium is necessary for bone mineral density and strength, protein, carbohydrate and fat metabolism, energy transfer, storage, and use. About 150 magnesium-dependent kinases are linked to a wide variety of diseases. Therefore, it is not surprising that magnesium deficiency can potentially cause or exacerbate a wide range of disorders (1–5).

**Diagnosis of magnesium deficiency**

The diagnosis of magnesium deficiency is biochemical. However, even when magnesium deficiency is suspected, the diagnosis can still be missed since the routine practice is to assess serum magnesium concentrations, which can be normal despite whole body deficiency. This is not surprising because magnesium in the circulation does not represent total body magnesium, being only 1% or less of total body content. In addition, magnesium in serum is subdivided into three heterogeneous fractions: magnesium-bound to albumin (∼30%), a fraction loosely complexed with anions, such as phosphate, citrate and bicarbonate (∼20%) and a free ionised fraction. The latter represents ∼50% of total serum magnesium and is mistakenly regarded by some to be the biologically active moiety i.e., analogous to ionised calcium. However, unlike calcium the bulk of magnesium is intracellular, bound to numerous subcellular components, and these are the moieties which account for its biological role. Thus, it is intracellular bound magnesium which accounts for its primary biological role, and normal serum magnesium, total or ionised, must be interpreted with caution (7).

Dynamic studies involving the intravenous administration of an elemental magnesium load (as sulphate or chloride), followed by assessment of the amount of elemental magnesium excreted in the urine in the following 24 h, are valuable (8–12). Deficiency is present if ∼90% of the administered magnesium load is excreted in the urine. This is because a larger fraction of the given magnesium load is retained and therefore a smaller amount of the given dose appears in the urine. Such a procedure, though valuable, accurate and informative, is time consuming and rarely used in clinical practice. Also, it is contraindicated in individuals with renal impairment.

Low serum magnesium, with normal albumin in a fasting or random sample indicates deficiency and warrants supplementation. However, normal magnesium concentrations must not be used to exclude deficiency. In cases with a high index of suspicion, the only reliable biochemical test is the magnesium loading test, performed in patients with normal renal function, as it is the only physiological “gold standard test” within the capability of all routine hospital laboratories.

Although deficiency of other major minerals, such as calcium, sodium and potassium are commonly reflected in their serum concentrations, significant deficiency of body magnesium may not be associated with low serum concentrations. Since an alternative biomarker for magnesium, which is both practicable and accurate, is currently unavailable. It may be prudent that the patient’s lifestyle or “modus vivendi” is taken into account as a pragmatic means for identifying patients with potential risk of negative body magnesium stores, despite normal serum magnesium, and for whom further testing and/or supplementation may be beneficial.

**Role of “modus vivendi” in identifying patients with potential magnesium deficiency**

The main causes of magnesium deficiency are shown in Table 1. It may not be difficult to surmise potential magnesium deficiency from an individual’s “modus vivendi” as body stores are dependent on the balance between daily intake and renal loss. Approximately 30%–70% of dietary magnesium intake is absorbed by a healthy gut with a negative magnesium store, with high gastric acidity enhancing absorption (13, 14). The commonly recommended daily intake for adults is 320–400 mg/day or 6 mg/kg/body weight for both genders (13–15). An average healthy daily diet supplies ∼250 mg of magnesium (120 mg per 1000 calories) with green vegetables, cereals, fish and nuts being a rich source (Table 2). Refined grains and white flour are generally low in magnesium (13, 14).

Another important source is water (16), with some hard tap water containing 5–25 times more magnesium than soft water, averaging ∼6 mg/L. Local water suppliers can provide information regarding magnesium concentration in tap water in each location (e.g., postcode area in the UK). The content of magnesium in bottled water also varies greatly, from 0 to 126 mg/L (17). Carbonated tonic and soda water contain little or no magnesium. One gram of instant coffee granules release ∼5 mg of magnesium in hot water; the corresponding figure for tea is ∼0.6 mg (18). Unrefined sea salt is very rich in magnesium, present at ∼12% of the mass of sodium. However, because this makes raw sea-salt bitter, magnesium, as well as calcium, are removed, making purified table salt essentially ∼99% sodium chloride.

Significant magnesium deficiency has been reported in both self-caring elderly individuals, as well as in hospitalised

<table>
<thead>
<tr>
<th>Table 1 Factors contributing to chronic magnesium deficiency.</th>
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<tr>
<td>Age; elderly absorb less and lose more magnesium</td>
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<tr>
<td>Daily diet low in magnesium</td>
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<tr>
<td>Soft drinking water, bottled or hard water low in magnesium</td>
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<tr>
<td>Refined salt for cooking and in food</td>
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<tr>
<td>Regular alcohol intake esp. spirits</td>
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<tr>
<td>Malabsorption (also short bowel syndrome/intestinal surgery)</td>
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<td>Drugs such as diuretics</td>
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Table 2  Magnesium content in food.

| Magnesium-rich food contains >100 mg per measure. A measure is a cup of vegetables, grains, legumes or 2 oz (or 56 g) of nuts and seeds. Vegetables: Green and leafy e.g., spinach, seaweed and artichoke Fish: Halibut (4 oz) Grains: Barley, wheat, oat, bran (whole grain bread) Legumes: Soybean, adzuki and black bean Nuts: Almond, Brazil, cashews, pine, peanuts (peanut butter) Seeds: (Dried) Pumpkin, sunflower, watermelon Chocolate: Dark (2 oz) Intermediate values of magnesium are present in other vegetables, fruits, meats, dairy products and fish.

Norwegians (19). In a survey involving 37,000 Americans, 39% were found to ingest <70% of the recommended daily magnesium intake (20) and 10% of women over the age of 70 years consume <42% of the recommended dietary requirement. When dietary magnesium intake is poor, the kidney can compensate by increasing fractional reabsorption. However, prolonged periods of poor dietary intake will eventually lead to a decline in intracellular magnesium concentrations.

Another common cause of negative magnesium stores is excessive renal loss. Alcohol is a known cause, being a magnesium diuretic; even moderate amounts can produce magnesiuresis. Alcohol increases urinary magnesium loss above baseline by an average of 167% (range 90%–357%). This effect is rapid (21–23) and even occurs in individuals who already have a negative magnesium balance (22). Alcohol consumption has increased due to its being readily available and with low cost (24). Taken in moderate amounts, alcohol consumption is considered socially and culturally acceptable (taken as 2–4 units i.e., 16–32 g of alcohol a day, though there is no standard definition). It may be of interest to point out that spirits, such as gin, rum, brandy, cognac, vodka and whisky contain little or no magnesium; fermented apple ciders have 10–50 mg/L of magnesium, while beer and wine have concentrations ranging from ~30–250 mg/L. Although drinks, such as some ciders, beer and wine may be considered “magnesium-rich”, they cannot be recommended as a reliable source of magnesium. In addition, consumption of large volumes of magnesium rich beer and wine can have a significant laxative effect, potentially impeding bioavailability and absorption.

Therefore, it seems reasonable to suggest that a lifestyle associated with low dietary magnesium intake in food and drinking water, purified table salt for cooking and in food, coupled with moderate and regular consumption of alcoholic drinks that cause net renal magnesium loss, can lead to negative balance over time. Potential magnesium deficiency can further be compounded with malabsorption; medications, such as diuretics (loop and thiazide), proton pump inhibitors (omeprazole), tacrolimus, chemotherapeutic agents, such as cisplatin, cyclosporin and some phosphate-based drugs.

Clinical Features of magnesium deficiency

We reviewed peer reviewed articles on magnesium published in English between 1990 and 2008 in MEDLINE and EMBASE using database keywords “magnesium, deficiency, diagnosis, treatment and hypomagnesemia”. The bibliographies of retrieved articles were searched and reviewed. In addition, we also performed a manual search of each individual issue of the major clinical and biochemical journals in which most of these reports have appeared.

Clinically, magnesium deficiency may present acutely or with chronic latent manifestations. Clinical presentation of chronic magnesium deficiency may vary from vague and non-specific symptoms to causing and/or exacerbating the progression of wide range of diseases, such as cardiovascular pathology (CVS), primary hypertension and diabetes type 2.

Magnesium is a physiological calcium antagonist in skeletal and smooth muscle, promoting relaxation whereas calcium stimulates contraction. A high calcium/magnesium ratio caused by magnesium deficiency and/or high calcium intake may affect this finely regulated homeostatic balance and may be a factor in the increased risk of cardiovascular events in patients receiving calcium supplementation (25, 26). Magnesium deficiency is present in almost all patients with hypokalaemia and those with magnesium-dependent hypocalcaemia (27).

A growing body of literature has demonstrated a wide pathological role for magnesium deficiency. In 183 peer reviewed studies published from 1990 to 2008, magnesium deficiency was associated with increased risk and prevalence for the 11 conditions listed in Table 3 (irrespective of the nature, design, parameters, size and statistical approach of these studies). Such an inverse relationship was also demonstrable irrespective of the wide range of methods used to assess magnesium body stores. Because it would be difficult to be prescriptive (being outside the scope of this review), these references are indicated in Table 3 for each of these conditions.

Similarly, in 68 studies over the same period, magnesium deficiency was found to predict adverse events and a reduced risk of pathology was noted when supplementation or treatment was instituted. In a recent study (28), a direct aetiological link between magnesium deficiency, impaired glucose tolerance and CVS was demonstrated. In this study, 13 post-menopausal American women (12 Caucasian and 1 African-American) volunteered to reduce their dietary magnesium intake to approximately one-third of the recommended daily requirement (average 101 mg/day). In <3 months, five subjects had cardiac rhythm abnormalities and three exhibited atrial fibrillation or flutter that responded quickly to magnesium supplementation (28). Furthermore, impaired glucose homeostasis was found in 10 volunteers who underwent an intravenous glucose tolerance test (IV GTT). The clinical manifestation in these patients was reflected in reduced concentrations in red cell membranes, although serum concentrations remained within the reference range (28). This study,
Magnesium supplementation has low toxicity in people with normal renal function. However, deficiency may not be corrected through nutritional supplementation only. The most common therapeutic modalities are intravenous infusion in patients with depletion manifesting as significant hypomagnesaemia; and orally (occasionally subcutaneously) for individuals requiring long-term supplementation. Intravenous magnesium (up to \( \approx 30 \) mmol of elemental magnesium; \( 1 \) mmol \( \approx 24 \) mg) is given over a period of hours. A slow rate infusion is important because plasma concentrations above the normal range would reduce magnesium retention and increases urinary excretion with its potential misinterpretation. Magnesium body stores are considered repleted when \( >90\% \) of an elemental magnesium load is excreted in a 24-h urine. Other analytes which may be associated with magnesium deficiency are calcium, potassium, phosphate and vitamin D (31).

Common oral magnesium supplements exist in two forms: chelated and non-chelated. In the chelated form, magnesium is attached to organic radicals. In the non-chelated form, magnesium is in the form of sulphate, chloride or oxide. Magnesium attached to aminoacid radicals appears to be better tolerated. Generally, toxic concentrations are unlikely to occur in patients receiving the recommended oral magnesium supplement when renal function is normal. This is because magnesium excretion can exceed 100\% of the filtered load when the intake is above normal, achieved by reduced absorption from the gut plus minimal or no renal re-absorption coupled with active secretion.

It is of interest that net magnesium absorption rises with increasing intake. However, fractional absorption falls as magnesium intake increases (e.g., from 65\% at 40 mg intake to 11\% at 960 mg). Magnesium absorption from the gut is slow, with \( \approx 80\% \) of oral magnesium being absorbed within 6–7 h (32).

**Conclusions**

Serum magnesium is a useful test because low serum concentrations indicate significant deficiency warranting replacement. However, normal magnesium concentrations must not be used to exclude negative body stores. Modus vivendi has an important role in identifying at risk patients, such as adults living in areas with soft drinking water or hard water with low magnesium content, plus the other factors listed in Table 1, notably diet and diuretics. Magnesium status should always be considered in cases such as electrolyte disturbances (hypocalcaemia and/or hypokalaemia), arrhythmias, especially Torsades de Pointes, regular or excessive alcohol intake and muscular spasms/cramps in both normocalcaemic and hypocalcaemic patients. However, for the other conditions listed in Table 3, it is important that patients at risk in each category are identified.

The inaccuracy of serum magnesium as a biomarker of negative body stores, although well known among laboratorians, is not widely disseminated nor emphasised to clinicians. The perception that ‘normal’ serum magnesium excludes deficiency is not uncommon among clinicians, and this has contributed to under-diagnosis of chronic deficiency (Table 4). Based on literature in the last two decades, magnesium deficiency remains common and undervalued, warranting a proactive approach by the laboratory because restoration of magnesium stores is simple, tolerable, inexpensive and can be clinically beneficial.

Supplementary data associated with this article can be found in the online version at: http://www.reference-global.com/doi/suppl/10.1515/CCLM.2009.077.

**Acknowledgements**

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### Table 3

<table>
<thead>
<tr>
<th>Electrolytes (1–23):</th>
<th>Hypocalcaemia</th>
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<tbody>
<tr>
<td>CVS (24–152):</td>
<td>Ventricular arrhythmias esp. Torsades de Pointes, Cardiac conduction abnormalities – supraventricular tachycardias (SVTs), Abnormal vascular tone, congestive heart failure</td>
</tr>
<tr>
<td></td>
<td>Ischaemic heart disease, cardiac surgery, myocardial infarction</td>
</tr>
<tr>
<td>Hypertension (153–200):</td>
<td>Pre-eclampsia/eclampsia, primary hypertension</td>
</tr>
<tr>
<td>Diabetes (201–262):</td>
<td>Type 2 diabetes mellitus</td>
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<tr>
<td>Metabolic syndrome (263–269):</td>
<td>The Metabolic syndrome</td>
</tr>
<tr>
<td>Osteoporosis (270–309):</td>
<td>Bone mineral density and osteoporosis</td>
</tr>
<tr>
<td>Musculoskeletal (310–326):</td>
<td>Muscle weakness, fatigue, numbness, tingling, spasms/cramps/tetany, fibromyalgia</td>
</tr>
<tr>
<td>Neurological (327–352):</td>
<td>Irritability, depression, migraines, strokes, vertical and horizontal nystagmus</td>
</tr>
<tr>
<td>Cancer (353–361):</td>
<td>Colorectal</td>
</tr>
<tr>
<td>Alcoholics (362–383):</td>
<td>Exhibiting any of the described manifestations</td>
</tr>
<tr>
<td>Respiratory (384–431):</td>
<td>Asthma</td>
</tr>
</tbody>
</table>

The numbers between brackets are additional references published from 1990 to 2008 for each entity, see Supplemental data.

though small, is consistent with epidemiological surveys, supplementation trials and animal studies (29, 30).

### Table 4

<table>
<thead>
<tr>
<th>Take Home Message.</th>
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<tbody>
<tr>
<td>Magnesium deficiency is common</td>
</tr>
<tr>
<td>It is under diagnosed</td>
</tr>
<tr>
<td>It has clinical consequences</td>
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<tr>
<td>Treatment is straightforward and clinically beneficial</td>
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It is under diagnosed
ments and advice: Prof. A. Al-Din (Neurology), Dr. M. Galvin (Haematology), Dr. P. Gajjar (General practice and Palliative medicine); Dr. N. Haboubi (Chemical Pathology); Mr. D. Hutchinson (Surgery); Dr. T. Lench (General Practice); Dr. R. MacFaul (Paediatric); Mr. Y. Mashhour (Cardio-thoracic surgery); Dr. S. Smellie (Chemical pathology); Dr. D. Walls (Gastroenterology).

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References
