REVIEW ARTICLE

Magnesium Deficiency in clinical practice: An undervalued disorder

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Introduction

Magnesium is called "the chronic regulator" by biochemists and the "forgotten electrolyte" by physiologists. In living cells, magnesium (Mg^{++}) is the second most common intracellular mineral after potassium and the most abundant divalent intracellular cation. It is the 4th most plentiful mineral in the body after calcium (Ca^{++} sodium (Na^{++}) and potassium (K^{++}). An adult has approximately 1000 mmol of magnesium, 40% of which is intracellular and some 60% in bone and teeth with 1% or less is present in the extracellular fluid (ECF)/blood.

Magnesium is essential for the function of hundreds of the widely distributed kinases, a group of magnesium-dependent enzymes that catalyzes the transfer of a phosphate group and attaches it to the recipient molecule i.e. phosphorylation. In the presence of magnesium, kinases bind an ATP-molecule and cleave one phosphate group which is subsequently transferred to the recipient molecule. Phosphorylation transforms (switches on) an inactive molecule into an active or "functional" one which could then perform a specific biological/biochemical task (or vice versa).

In addition to the phosphorylation of small organic molecules, up to 30% of all body proteins are activated by magnesium-dependent Kinases. Up to 500 kinases exist within each cell and about 150 kinases are linked to a wide variety of diseases inclucling cancer. It is of interest to point out that 30% or more of current pharmaceutical research for new drugs is targeting kinases.

Magnesium-dependent kinases are also paramount in signal transduction, a highly organized cascade of biochemical events triggered by cell-surface or cytoplasmic receptor activation by a ligand/mitogen which ultimately results in an increase in levels of intracellular second messengers.

The production and actions of second messengers such as c-AMP in the protein-kinase A pathway; diacylglycerol and calmodulin in the protein-kinase C pathway and c-GMP in nitric oxide pathway involve numerous kinases. Central to all these intracellular functions is that each protein must be at the right place and works 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. Electrical transcellular gradient is maintained by the high intracellular concentration of K^{++} and Mg^{++} against a high concentration of Na^{++} and Ca^{++} extracellularly. A balanced concentration of these cations across cell membranes creates electrical voltage commonly referred to as electrical potential. Maintaining this gradient is vital for cellular action such as conductivity and contraction including cardiac muscle. This is achieved by continuous and relentless active transport of these major cations, against considerable gradient, namely an influx of both K^{++} and Mg^{++} from ECF into the cells and an efflux of intracellular Na^{++} and Ca^{++} to ECF. These processes require considerable energy (almost accountable for total body energy at rest) and involve specific ATP/ATPase pumps for paired electrolytes.

Magnesium is necessary for the activation of A*TP*/ATPase pumps and if deficient would cause impairment and reduction in their efficacy and activities. Impediment in cellular permeability would follow and can lead to reduction in intracellular K^{++} and Mg^{++}

associated with Na^{++} and Ca^{++} overload. Continuous decline in intracellular Mg^{++} would cause further impediment in ATPase pumps, exacerbating intracellular vs. ECF electrolytes imbalance.

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 later can be corrected by K^{++} or Ca^{++} treatment alone and Mg^{++} replacement becomes essential for restitution. It is therefore paramount to note that Mg^{++} itself is an electrolyte which plays a major role in the homeostasis of other major electrolytes. Furthermore, Mg^{++} is necessary for bone strength, protein, carbohydrate and fat metabolism, energy transfer, storage and use. It is not therefore surprising that Mg^{++} deficiency can lead to a wide range of diseases.

Magnesium ion-channels and homeostasis

Only in the last decade, two ion channels have been suggested as Mg^{++} transporters which appear to play a pivotal role in its homeostasis through the dual processes of its absorption from the gut and reabsorption by the kidneys. Ion channels conduct a particular ion after which it is named while excluding others e.g. Na^{+}, K^{+} and Ca^{++} cation channels and chloride (Cl^{-}) anion channel. Ion hydration energy (water shell surrounding each ion) and the charges at the binding sites by the ligand make the internal milieu within each channel favorable for conducting only a specific ion.

Magnesium ion has unique characteristics which are quite different from other biologically important cations. For example, the hydrated radius of Mg^{++} is ~ 400 times larger than its dehydrated radius, a much larger difference than that of Na++ and Ca ++ (~25 fold) or K++ (fourfold). Magnesium is the most "charge-dense" of all biological cations, holding the waters rigidly within hexa-coordinated hydration shell with affinity 10^{3}-10^{4} greater than do Ca^{++}, K^{++} or Na^{++}. These characteristics make magnesium biologically unique, molecularly obvious to proteins associated with its actions.

Recently, two dedicated ion channels specific for transporting Mg^{++} have been suggested. These belonged to the transient receptor potential melastatin (TRPM), a sub-family of the transient receptor potential proteins super-family involved in transporting other cellular cations such as Ca^{++}. The two proteins TRPM 6 and TRPM 7 have been suggested as unique transporters for Mg ++ and are termed chanzymes because they possess a channel and a kinase domain. They are differentially expressed, with TRPM 6 being found primarily in colon and renal distal tubules. Up-regulation of TRPM 6 occurs in response to reduction in intracellular Mg^{++}; this in turn enhances its absorption from the gut and its reabsorption by the kidneys and can therefore alter whole-body Mg^{++} homeostasis. TRPM 7 is ubiquitous, occurring in numerous organs (e.g. lung). These two chanzymes may therefore represent the first molecular mechanism specifically aimed at regulating body magnesium balance.

Causes of Magnesium Deficiency:

The main causes of Mg++ deficiency are outlined in Table 1. It may not be difficult to surmise potential magnesium deficiency from an individual's "modus Vivendi" because it is dependent on the balance between daily intake and renal loss. Approximately 30-70% of dietary Mg^{++} intake is absorbed by a healthy gut with negative Mg++ store and with high gastric acid level enhancing.

Age: elderly absorb less and lose more magnesium
Daily diet low in magnesium
Soft drinking water, bottle or hard water low in magnesium
Refined salt of cooking and in food
Regular alcohol intake such as spirits
Malabsorption
Drugs such as diuretics

Table 1: Factors contributing to chronic magnesium deficiency

The commonly recommended daily intake for adults is 320-400 mg/day (or 6 mg/KgBW for both sexes) and increases during pregnancy, lactation and regular strenuous exercise which increase Mg^{++} losses in urine and sweat. An average healthy daily diet supplies ~250 mg of magnesium (120 mg per 1000 calories) with green vegetables, cereals, fish and nuts are being a rich source (Table 2). Refined grains and white flour are generally low in Mg^{++}.

Magnesium-rich food contains> 100 mg per measure. *A measure is a cup of vegetable, grains, legumes and 2 oz (or 56 g) for nuts and seeds*.
Vegetable; 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
Seeds; (Dried) Pumpkin, Sunflower, watermelon
Chocolate; Dark (2 oz)
Intermediate values of magnesium are present in other vegetables, fruits, meats, dairy products and fish.

2: Magnesium content in foodTable

Another important source is water, with some hard tap water containing 5-25 times more magnesium than soil water which averages -6 mg/liter. The content of magnesium in bottled water varies greatly from 0 to

126 mg/liter, while carbonated tonic and soda water has little or no Mg++. One gram of instant coffee granules releases -5 mg of Mg++ in hot water; the corresponding figure for tea is -0.6 mg38. Unrefined sea salt is very rich in Mg++ occurring at -12% of Na++ mass, however because this makes raw sea-salt bitter, Mg^{++} (and Ca^{++}) are removed making purified table salt essentially -99% sodium chloride.

Significant Mg^{++} deficiency was found in both elderly self-caring in the community as well as in hospitalized Norwegians. In a consensus survey involving 37,000 Americans, 39% were found to ingest less than 70% of the recommended daily Mg^{++} intake and l0% of women over the age of 70 years consume less than 42% of the recommended dietary requirement. When dietary Mg^{++} intake is poor, the kidney can ameliorate such inadequacy by increasing fractional reabsorption from the filtered load, mainly in the loop of Henle. Normally, plasma Mg^{++} is filtered at the glomeruli apart from the fraction bound to albumin. Reabsorption of the filtered load can vary dependent on the body store, being lowest when body store are adequate to maximum in deficiency. Prolonged periods of poor dietary intake however would eventually lead to decline in intracellular Mg^{++} concentration.

Another common cause of negative Mg++ store is excessive renal loss. Alcohol increases urinary medium loss above normal baseline by an average of 167% (range 90-357%) and its effect is rapid and occurs even in individuals with an already negative Mg^{++} balance. It may be of interest to point out that spirits such as gin, rum, brandy, cognac, vodka and whisky contain little or no Mg^{++}; fermented apple ciders have 10-50 mg/l of Mg^{++}, while beer and wine have levels ranging from ~ 30-250 mg/1.

It appears reasonable therefore to suggest that a life-style associated with low dietary Mg^{++} intake in food and drinking water, purified table salt for cooking and in-food, coupled with moderate and regular consumption of alcoholic beverages which cause a net renal loss of Mg++ can additively lead to negative balance with time.

Magnesium deficiency can be further compounded with malabsorption and those receiving medications such as diuretics (loop and thiazide), proton pump inhibitors, tacrolimus, ciclosporin, omeprazole and some phosphate-based drugs.

Clinical Features of Magnesium Deficiency

We have researched peer reviewed articles on magnesium published in English between 1990 and 2008 in MIDLINE and EMBASE using database keywords "magnesium, deficiency, diagnosis, treatment and hypomagnesaemia". Bibliographies of retrieved articles have been searched and followed. We have also carried out a manual search of each individual issue of major clinical and biochemical journals in which most of these reports have appeared.

Clinically Mg++ deficiency may present acutely or with chronic latent manifestation. The clinical features include muscle weakness, muscle spasm, cramps (including night cramps), numbness, tingling, tetany, general fatigue, irritability, apathy and depression.

Magnesium is the physiological calcium antagonist on skeletal and smooth muscle, promoting relaxation while calcium stimulates contraction. A high Ca^{++} / Mg^{++} ratio caused by Mg^{++} deficiency and/or high Ca^{++} 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. Magnesium deficiency is implicated in almost all patients with hypokalaemia and those with magnesium-dependent hypocalcaemia.

A growing body of literature has demonstrated a wide pathological role for Mg^{++} deficiency. In 183 peer reviewed studies published from 1990 to 2008, Mg^{++} deficiency was associated with increased risk and prevalence in 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 Mg++ body store.

Electrolytes - Hypocalcaemia Hypokalaemia
CVS - Ventricular arrhythmias esp. Torsades de Pointes, Cardiac conduction abnormalities- SVTs, Abnormal vascular tone, Congestive cardiac failure ischemic heart disease, cardiac surgery, myocardial infarction
Hypertension - Pre-eclampsia/eclampsia, primary hypertension
Endocrine - Type II Diabetes Mellitus
Metabolic - The Metabolic syndrome
Bone - BMD and osteoporosis
Musculoskeletal - Muscle weakness, fatigue, numbness, tingling,
spasms/cramps/tetany, fibromyalgia
Neurological - Irritability, depression, migraines, vertical and horizontal nystagmus
Cancer - Colorectal
Alcoholics - Exhibiting any of the described manifestations
Respiratory - Asthma

Table 3: Conditions associated with magnesium deficiency.

Similarly, in 68 studies over the same period, Mg^{++} deficiency was found to predict adverse events and a reduced risk of pathology were noted when supplementation/treatment was instituted. In recent study

by Forrest *et al*, a direct etiological link between Mg^{++} deficiency, impaired glucose tolerance and CVS pathology was demonstrated. Thirteen postmenopausal American women (12 Caucasian and 1 African-American) volunteered to reduce their dietary Mg^{++} intake to ~ one third of the recommended daily requirement (~101 mg/day). In less than 3 months, 5 individuals had cardiac rhythm abnormalities and 3 exhibited atrial fibrillation/flutter that responded quickly to Mg^{++} supplementation. Impaired glucose homeostasis was found in 10 volunteers who underwent glucose tolerance test. This study, though limited in numbers, is consistent with epidemiological surveys, supplementation trials as well as animal studies.

However, the clinical impact of Mg^{++} therapy on those who had already developed overt pathology related to Mg^{++} deficiency is not uniform. Treatment with Mg^{++} was highly effective in reversing pathology in conditions such as electrolyte disturbances e.g. hypokalaemia (which is almost always associated with Mg^{++} deficiency) and refractory hypocalcaemia; neuromuscular hyperexcitability (e.g. spasms/cramps in normocalcaemic patients) and arrhythmia especially Torsades de Pointes. Magnesium therapy was also effective in patients with pre-eclampsia/eclampsia and alcoholics/regular drinkers with overt neuromuscular hyperexcitability, electrolytes, neurological or cardiac manifestations.

In some conditions however, a beneficial effect was noted in only some patients following Mg^{++} administration e.g. reduced frequency and/or severity of attacks such as migraine (~40% reduction), angina and atrial fibrillation. Restoring the body Mg^{++} store has also increased bone mineral density and reduced and/or ameliorated micro and macrovascular complications in patients with diabetes type 2, asthma, ischaemic heart disease, primary hypertension, mitral valve prolapse and post cardiopulmonary bypass when given before and after cardiothoracic surgery. The effect of therapy in post-myocardial infarction remained controversial and reduction in fracture risk has not been established either. A number of mechanism(s) by which Mg^{++} deficiency leads to these pathologies have been described.

Diagnosis of Magnesium Deficiency

The diagnosis of Mg^{++} deficiency is biochemical. However, even when Mg^{++} deficiency is suspected, the diagnosis can still be missed. This is because of the routine practice of relying on serum Mg^{++} which can be normaldespite significant deficiency. This is not surprising because Mg^{++} in the circulation does not represent total body Mg^{++}, being only 1% or less of total body content. Furthermore, Mg^{++} in serum is subdivided into three heterogeneous fractions namely magnesium-bound to albumin (~30%), a fraction loosely complexed with anions such as phosphate, citrate and bicarbonate (~20%) and a free ionized fraction. The later is ~50% of total serum Mg^{++} and mistakenly regarded by some to be biologically the active moiety i.e. analogous to ionized Ca^{++}. Unlike calcium however, the bulk of magnesium is intracellular, bound to numerous subcellular components and these are the moieties which account for its biological role. In other words, it is the intracellular bound magnesium which expresses its primary biological role and that normal serum magnesium, total or ionized must be interpreted with caution.

To overcome the limitations of serum Mg^{++} as a biomarker, methods to measure intracellular Mg^{++} have therefore been developed using accessible blood cells (platelets, red or white cells) or sublingual cells. These methods, though reliable in assessing body status, are technically unsuitable for routine use. New nanotechnological methods using dispersive X-ray microanalysis for non-invasive intracellular measurement of Mg^{++} have also been described.

Dynamic studies involving the administration of elemental magnesium load (as sulphate or chloride) intravenously followed by assessment of the amount of elemental Mg^{++} excreted in the urine in the following 24 hrs are recommended. Deficiency is considered present if <90% of Mg^{++} load is excreted in the urine. Such a procedure, though valuable, accurate and informative, is time consuming and understandably (but unfortunately) rarely used in clinical practice. Yet the test is safe in those without deficiency and therapeutic in deficient patients. It is however contra-indicated in individuals with renal impairment.

A pragmatic approach for assessing Mg^{++} status in clinical practice is to initially measure serum Mg^{++} in a fasting blood sample, taken without stasis and free from haemolysis. Separation of serum from cells should be carried out without delay. Low serum Mg^{++} (with normal albumin) indicates deficiency warranting supplementation. Low serum Mg^{++} in a random sample also indicates deficiency but normal Mg^{++} concentration in fasting or random samples must not be used to exclude deficiency. In cases with high index of suspicion, a Mg^{++} loading test may be considered if renal function is normal being the only physiological "gold standard test" within the capability of all routine hospital laboratories.

Therapeutic modalities for magnesium deficiency

Magnesium is a low-toxicity nutrient in individuals with normal renal function. Deficiency however may not be corrected through nutritional supplementation only. In patients with severe Mg^{++} deficiency, the effective method for restoring body store is repeated intravenous infusions given over a period of few weeks. Each dose (~30 mmol of elemental Mg^{++}; 1 mmol = 24 mg) is given over a period of at least 4hrs and preferably longer. This is important because plasma Mg^{++} concentration affects renal reabsorption threshold and abrupt elevation of plasma concentration above the normal range would reduce Mg^{++} retention and increases urinary excretion with its potential misinterpretation. Magnesium body stores are considered repleted when >90% of the elemental Mg^{++} load is excreted in the following 24hr urine. It may be prudent in these patients to monitor calcium, potassium phosphate and vitamin D which may be associated with magnesium deficiency.

Oral magnesium supplements are essentially three forms: chelated, non-chelated and enterically coated Mg^{++}. In the chelated forms, Mg^{++} is attached to organic radicals such as amino acids, citrate, acetate, aspartate, malate and lactate. In the non-chelated forms Mg^{++} is in the form of sulphate or chloride. The enteric-coated Mg^{++} contains a soluble-salt such as magnesium chloride.

Magnesium is absorbed from both the ileum and the colon. Monitoring, if deemed prudent should always be on a fasting sample. Generally however, toxic levels are unlikely to occur in patients on oral Mg^{++} supplement when renal function is normal. This is because Mg^{++} 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.

Of note, Mg^{++} supplements are widely available without prescription in health-food shops and supermarkets and can be problematic in patients with impaired renal function or those on medications such as some oral antibiotics and biphosphonates. Also note that magnesium in some antacids such as milk of magnesia (used as laxative too) can be absorbed. Although magnesium hydroxide in milk of magnesia is generally poorly absorbed, it can be converted to magnesium chloride by gastric acidity and if consumed in excess may even lead to hypermagnesaemia67(a table spoonful of milk of magnesis contains ~1.2 g Mg (OH).

It may be of interest to point out that net Mg^{++} 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). This curvi-linear function between absorption and intake of Mg^{++} suggests two simultaneous absorptive processes namely a hyperbolic mechanism that reaches an absorptive maximum superimposed on another linear function which absorb ~ 7% of ingested Mg^{++} endlessly. Absorption of Mg^{++} from a large single high dose may be therapeutically therefore less desirable than dividing the intended intake into smaller ones of ~ 120 mg each. Magnesium absorption from the gut is relatively slow with ~ 80% of oral Mg^{++} being absorbed within 6-7 hrs.

Conclusions

Negative Mg^{++} body store is more likely to occur in elderly patients living in areas with soft drinking water or hard water with low Mg^{++} content. Specifically, Mg^{++} status should be considered in cases such as electrolyte disturbances (hypocalcaemia and/or hypokalaemia), arrhythmia esp. Torsades de Pointes, regular/excessive alcohol intake, pre-eclampsia/eclampsia and muscular spasms/cramps in both normocalcaemic and hypocalcaemic patients. In other conditions however, it is important that patients at risk in each category are identified and on whom testing, including Mg^{++} loading test may be considered.

Magnesium deficiency is an under-diagnosed common condition and may therefore warrant more input by laboratorians to raise awareness, improve diagnosis and management of this insidious problem. This is paramount because physiological restitution of magnesium store is simple, tolerable, and inexpensive and can be clinically beneficial.