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Magnesium: A Mineral Essential for Health Yet Generally Underestimated or Even Ignored

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Abstract

Magnesium is the fourth most common mineral in the human body after calcium, potassium and sodium. Magnesium must be continuously replenished through foods and water intake because it is not synthesizable. Chronic inadequate intake of magnesium over long period of time can manifest as latent magnesium deficiency with symptoms such as muscle weakness, cramps, fatigue, neurological and cardiovascular dysfunctions, reduced bone mineralization and strength. Reports published by WHO have estimated that ~two thirds of Americans and French have magnesium intake below the recommended amounts but only a small numbers are overtly depleted. The authorities in Finland were concerned of the negative impact of geochemical magnesium deficiency in the eastern region of Finland and its adverse effect on heart health. A program was initiated to increase magnesium intake though supplementation; this has contributed to progressive fall of death rate due to heart-related issues. Restoring and sustaining adequate magnesium store are easy and inexpensive.

Some 40% of total body magnesium is intracellular and ~60% in bone and teeth with less than 1% in circulation. Intracellular magnesium deficiency may or may not be reflected as overt hypomagnesaemia making measurement of plasma/serum magnesium potentially misleading when "normal" plasma/serum concentration is "interpreted" to exclude deficiency.

In this review, the role of magnesium at cellular level, its homeostasis and major clinical conditions associated with magnesium deficiency in adults will be briefly discussed. Assessment of magnesium status and its potential deficiency by examining individual's "modus vivendi" and/or the use of laboratory tests will be highlighted. Finally, various therapeutic modalities and monitoring of treatment will be summarized.

Keywords: Magnesium; Mineral; Human health; Food

Background

The relationship between magnesium and health has been recognized some 400 years ago and well before magnesium was even identified as an element. The English summer in 1618 was exceptionally hot and dry. A farmer by the name of Henry Wicker in Epsom, Surrey dug out few wells in his farm to get water for his herd of cows. He noticed that his thirsty animals refused to drink this water because it had a tarty and bitter taste. However he noted that this water has the ability to rapidly heal scratches, sores and rashes both in animals and humans. Tried by others, the fame of this water was spread by the word of mouth. Londoners flocked to Epsom which became a Spa town, surpassing others more fashionable ones at the time such as Tunbridge wells in Kent for its water and salt. A physician (also a Botanist) with extensive practice in London by the name of Nehemiah Grew noted that the salt in this water had a laxative effect. This "mind-boggling" discovery was patented as a purging salt and a factory in London was established for world-wide marketing. In England this salt was (and still is) known as "Epsom Salt" and in continental Europe as "Salt Anglicum".

Late in the 17th century and thereafter, Epsom salt was one of the most popular medicinal drugs. The people who used it did not know exactly why it was so beneficial, but they did understand that in some way it was good for health and promoted longevity. Even now, it is surprising to know that there is an "Epsom Salt Council" in the UK whose members are wild about the goodness of "Epsom Salt". Currently, 13 wonderful ways have been described for the use of "Epsom Salt" by this council.

Epsom Salt is a magnesium salt (hydrated magnesium sulphate; $MgSO_4.7H_2O$). In 1755, the Scottish Chemist Joseph Black in Edinburgh identified magnesium as an element and the English chemist Sir Humphrey Davy was the first to isolate magnesium by electrolysis in 1808. The 19th century was the age of chemistry of magnesium; its biology however became clearer during the 20th century. The importance of magnesium in health remained overlooked or even ignored in the 21st century. This may be attributed to (a) the amorphous ramifications of magnesium deficiency causing a wide range of clinical manifestations and (b) the common and overuse of plasma/serum magnesium measurement when deficiency is suspected, the lack of understanding of the limitations of this test and it's often misinterpretation by health practitioners [1]. It is not therefore surprising that magnesium deficiency is not uncommon in the general population and even in some people with apparently healthy life style who may be deficient of such important mineral.

Magnesium, a Major But Under-recognized and Underestimated Mineral

Of the 90 naturally occurring elements in the planet earth, ~25 are considered to be essential for health in humans. Four of these 25 namely carbon, oxygen, hydrogen and nitrogen constitute ~97% of body building blocks. The other 21 elements accounting for ~3% of all elements in human's body, of which 8 are "anions" namely phosphorous, sulphur, chlorine, iodine, fluorine, boron, chromium and silicon; and 13 are metals "cations". Based on body contents and recommended daily allowance (RDA), only four metals are regarded as "majors"; these are calcium, potassium, sodium and magnesium; the other 9 are required in relatively much smaller amounts and are designated as "trace-metals"; these are iron, zinc, manganese, copper, selenium, molybdenum, cobalt, tin and vanadium.

Although calcium, potassium and sodium are readily recognizable as major minerals, magnesium is neither commonly known nor perceived as a major one, even by some health professionals despite its relatively high recommended daily allowance (RDA). For example, the RDA of magnesium is ~50% and ~25% that recommended for calcium and sodium respectively and ~26 times greater than that of iron, the top of all trace metals in terms of RDA. Sustaining magnesium balance is not only dependent on RDA but its absorption and retention in the body. Age is an important physiological factor because absorption of magnesium from the gut is reduced and its loss from the body in urine increases with age in both genders. Consequently, magnesium deficiency occurs more often in the elderly than in the young. Furthermore, the incidence is also likely to vary significantly from one area to another because of the large variation in magnesium contents in drinking water which can provide up to 30% of daily requirement.

Brief Note on the Biological Role of Magnesium at Cellular Level

The 19th century was the age of chemistry of magnesium; its biology however became clearer during the 20th century. Approximately 40% of magnesium is intracellular and some 60% in bone and teeth with 1% or less is present in the circulation [1].

It may be important to reiterate that although magnesium intake is in the form of elemental radical, in body fluids magnesium do not function nor operate biologically in this form i.e., "native chemical radicals" but as "hydrated-ions", enclosed within shells of water which confer and exert a profound influence on their electrochemical, biochemical and physiological roles.

Magnesium *in vivo* (Mg^{2+}) exhibits a rather unique or even peculiar characteristic in its ionic hydration form, being distinctly different from the other three major minerals namely Ca^{2+}, K^{+} and Na^{+}. Such difference is important to highlight because it illustrates the physical uniqueness of hydrated Mg^{2+} ion and its recognition at molecular level (Table 1).

Table 1 shows the massive and disproportionate increase in the Mg^{2+} atomic radius upon hydration compared with the other three major ions [2,3]. This is because Mg^{2+} is a highly "charge dense" ion compared not only with Na^{+}, K^{+} or Ca^{2+}, but all other cations, thus holding the waters' shell tightly by a factor of 10^{3}-10^{4}, rigidly within hexa-coordinated hydration shell. It was suggested that this unique characteristic makes the hydrated Mg^{2+} ion more recognisable for various molecular actions/transport.

Atomic Wt. radius (Est)	Ionic radius, picometer (Est)	Increase in hydrated
Na^{+} 23	102-116 pm ?	X25 fold
K^{+} 39	138-152 pm ?	X4 fold
Ca^{2+} 40	100-114 pm ?	X25 fold
Mg^{2+} 24	72-86 pm ?	X400 fold

Table 1: Changes in atomic radius on hydration (estimated).

Biologically, magnesium is regarded with justification as a "chronic regulator" and biochemically as a "forgotten electrolyte". The number of cells in an adult is ~37 trillion [4] and cellular biochemistry/physiology is complex. Biological processes carried out within each cell and between adjacent cells have to be orderly and function harmoniously and in synchrony using highly complex systems of neuroendocrine bio-communication. Individual living cell receives a large number of signals such as stimulation to grow, to divide, to initiate or stop the making of specific bio-components, to trigger an immune response et cetera. Each signal needs to be correctly transmitted, properly read, interpreted and clearly communicated both within individual cell and between adjacent cells in the first place. These processes are regulated by specific intracellular proteins/enzymes each dedicated to a specific biological task which may not be only sequential but require appropriate activation/initiation to start a process followed by deactivation/stoppage signal to terminate such task. Mitochondria within individual cell also generate its own energy utilizing a cascade of proteins/enzymes which drive this process. When a cell dysfunction, repairing processes is attempted and when fails, the dysfunctional cell commits orderly and voluntary suicide (i.e., apoptosis). Central to all these cellular processes is that each cellular component must be at the right place and function at the right time, both within and between cells.

The regulators of all the above examples of cellular functions are catalysed by some 500 enzymes known biochemically as Kinases which essentially coordinate, control and integrate such complex web of orderly processes. Kinases have a vital role in signal transduction and the production and actions of second messengers such as c-AMP, diacylglycerol, calmodulin and c-GMP. Kinases activate or inhibit individual protein/component, route them to a specific cellular location, or block their interaction with others (i.e., establishing an orderly production-line). To transmit their orders, kinases label specific location(s) within a corresponding protein/component with polar phosphate group (PO^{3-}) i.e., phosphorylation. The source of polar phosphate group is ATP and Kinases can only bind "Mg-ATP" complex, allowing it to cleave the γ phosphate group which is subsequently transferred to the recipient molecule. Phosphorylation is an ion-radical, electron-spin selective process [5-7] which transforms (switches on) an inactive molecule into an active or "functional" one which can then perform a specific biological/biochemical task (or vice versa). In addition to the phosphorylation of small organic molecules, up to 30% of functional body proteins are activated by magnesium-dependent kinases.

Physiologically, magnesium plays an important role in electrolyte homeostasis being necessary for the activation of ATP/ATPase pumps such as Na^{+}/K^{+} pump, Na^{+}/Ca^{++} , Na^{+}/Mg^{++} and Mg^{++}/Ca^{++} pumps which if deficient causes impairment and 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 later can be corrected by potassium or calcium treatment alone and magnesium replacement becomes essential for restitution. It is therefore paramount to note that magnesium itself is an electrolyte which plays a major role in the homeostasis of other major electrolytes, namely Na^+, K^+ and Ca^{++}. Furthermore, magnesium is necessary for bone mineral density and strength, protein, carbohydrate and fat metabolism, energy transfer, storage and use (i.e., bioenergetics, and oxidative energy metabolism). About 150 magnesium-dependent kinases are linked to a wide variety of diseases; it is not therefore surprising that magnesium deficiency can potentially cause/exacerbate a wide range of disorders [8-16].

Magnesium also encourages bone formation [12], directly and indirectly through its effect on bone hormones such as parathyroid and vitamin D. Magnesium plays a role in bone mineralization and its mechanical strength. Several studies have shown a positive relationship between dietary magnesium intake and bone mineral density (BMD). There is evidence to suggest that magnesium supplementation increases BMD over the course of one year but its impact on bone fractures is not yet known.

Finally, the underlying reaction mechanism seems to be the same for all known kinase. Up to 300 different kinases are present within a single cell; each devoted to a particular task, route individual component to a specific cellular location, or blocks their interaction with others (i.e., streamlining an orderly production-line). The dependence of Kinases on magnesium for their function has led to their nomenclature as "magnesium-dependent kinases". Magnesium deficiency if present impairs and if depleted impedes kinase's activity. Kinases are the largest superfamily of all enzymes in the human body to which ~one fifties of the ~24,000 human genes are dedicated to their encoding, highlighting their important role in regulating nearly all intracellular biological processes. The central role of these regulatory mechanisms in biochemistry/physiology is reflected in the worldwide publication of some 200,000 papers on these subjects over a period of only 18 months between March 2012 and July 2014.

Magnesium Homeostasis

Considering the many vital roles of magnesium, there was surprisingly lack of information regarding its homeostasis. Only in the last decade however two ion channels have been suggested as magnesium 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^{++} channels. 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 favourable for conducting only a specific ion. The two dedicated ion channels specifically aimed at transporting Mg^{++} belong 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 calcium by TPRM 3. Recently, TRPM 6 and TRPM 7 have been suggested as unique transporters for Mg^{++} termed chanzymes because they possess a channel and a kinase domain. These two chanzymes may therefore represent molecular mechanism aimed at regulating magnesium homeostasis at cellular level [2,17-22]. They are differentially expressed, with TRPM6 being found primarily in colon and renal distal tubules. Up-regulation of TRPM 6 occurs in response to reduction in intracellular magnesium; this in turn enhances magnesium absorption from the gut and its reabsorption by the kidneys and can therefore alter whole-body magnesium homeostasis. TRPM7 is ubiquitous, occurring in numerous organs (e.g. lung). These two chanzymes may therefore represent a molecular mechanism specifically aimed at regulating body magnesium balance [2,17-22].

Clinical Conditions Associated with Magnesium Deficiency in Adults

Magnesium deficiency is common in the general population as well as in hospitalized patients and can occur in individuals with an apparently healthy lifestyle. Latent magnesium deficiency is more common in the elderly, probably exacerbated by oestrogen which decline in women and men with age. Oestrogen influence body magnesium balance through its effect on TRPM6 which may help explaining the hypermagnesuria in the elderly in general and postmenopausal in particular. Magnesium deficiency is clinically under-diagnosed condition, yet surprisingly easy to treat [23-27].

We have researched peer reviewed articles on magnesium published in English between 1990 and April 2011 in MEDLINE and EMBASE and updated thereafter till April 2015 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 magnesium deficiency may present acutely or with chronic latent manifestations. Clinical presentation of chronic/latent 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 two.

Magnesium is a physiological calcium antagonist and natural calcium channel blocker and thereby essential for normal neurological and muscular function [28,29]. In skeletal and smooth muscle, magnesium promotes relaxation whilst 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 [30,31]. Magnesium deficiency is implicated/present in almost all patients with hypokalaemia and those with magnesium-dependent hypocalcaemia [32-38].

A growing body of literature has demonstrated a wide pathological role for magnesium deficiency. In 221 peer reviewed studies published from 1990 to April 2015, magnesium deficiency was associated with increased risk and prevalence in the eleven conditions listed in Table 2 (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.

Similarly, in 79 studies over the same period, magnesium deficiency was found to predict adverse events and a reduced risk of pathology were noted when supplementation/treatment was instituted. In a recent study [39] a direct aetiological link between magnesium deficiency, impaired glucose tolerance and CVS was demonstrated. In this study thirteen postmenopausal American women (12 Caucasian

and 1 African-American) volunteered to reduce their dietary magnesium intake to ~one third of the recommended daily requirement (average 101 mg/day). In less than three months, five subjects had cardiac rhythm abnormalities and three exhibited atrial fibrillation/flutter that responded quickly to magnesium supplementation. Impaired glucose homeostasis was found in 10 volunteers who underwent intravenous glucose tolerance test (IV GTT). The clinical manifestation was reflected in reduced levels in red-cell membranes; however, serum levels remained within reference range. This study, though small, is consistent with epidemiological surveys, supplementation trials and animal studies [40,41] (Table 2 and [1,11]).

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

Table 2: Conditions associated with magnesium deficiency.

"Modus Vivendi" and Its Role in Identifying Potential Magnesium Deficiency

Potential causes of magnesium deficiency are outlined in Table 3. It may not be difficult to surmise potential magnesium deficiency from an individual's life-style as body stores are dependent on the balance between daily intake and renal loss [21,42-44]. Approximately 30-70% of dietary magnesium intake is absorbed by a healthy gut with negative magnesium store and high gastric acidity enhancing absorption [21,28,42-46]. The commonly recommended daily intake for adults is 320-400 mg/day (or 6 mg/kg/body weight for both genders) [47] and increases during pregnancy, lactation and regular strenuous exercise [48-50] which increases magnesium 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 4). Refined grains and white flour are generally low in magnesium. Unrefined sea salt is very rich in magnesium occurring at ~12% of sodium mass, however because this makes raw sea-salt bitter, magnesium (and calcium) are removed making purified table salt essentially ~99% sodium chloride.

Another important source is water [51,52], with some (but not all) hard tap water containing more magnesium than soft water. Local water supplier can provide information regarding magnesium concentration in tap water to each location (e.g. postcode area in the UK). The bioavailability of magnesium in water is generally good at ~60%; however its absorption from water significantly decline with age [53,54].

The magnesium content in tap and/or bottle water varies greatly. Hardness of water is caused by dissolved calcium and magnesium and is usually expressed as the equivalent quantity of calcium carbonate in mg/l (e.g. a hardness of 100 mg/l would contain 40 mg/l of elemental Ca and/or Mg and 60 mg as carbonate). Water containing >200 mg/l equivalent calcium carbonate is considered hard; medium hardness is between 100-200 mg/l; moderately soft <100 mg/l and soft <50 mg/l calcium carbonate equivalent. Hardness above 200 mg/l results in scale deposition on heating if large amount of calcium carbonate is present because it is less soluble in hot water.

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 for cooking and in food
Pregnancy, lactation and regular strenuous exercise
Regular alcohol intake esp. spirits
Malabsorption (also short bowel syndrome/intestinal surgery)
Drugs such as diuretics

Table 3: Factors contributing to chronic magnesium deficiency.

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

Table 4: Magnesium content in food.

It may be important to point out that the ratio of calcium to magnesium in hard water varies. Hard water may in some cases have predominantly high concentration of calcium but low in magnesium or vice versa. Furthermore, the type of anion in the calcium salt is important. For example, hard water which is rich in calcium carbonate is usually regarded as "temporary hardness" because on heating, calcium carbonate precipitates. In other forms of hard waters, magnesium and/or calcium may combine with anions other than carbonate, such as sulphate and in this case water is referred to as "permanently hard" because these elements are not affected by heating. All naturally occurring magnesium salts unlike those of calcium, are relatively more soluble in both cold and heated water, including

magnesium carbonate. Although hard water is a general term which encompasses wide ratios of calcium to magnesium, the magnesium contents in most hard water (but not all) are 5-20 times more than in soft water and can potentially provide up to 30% of daily requirement.

The term soft water is straight forward because it is used to describe types of water that contain few calcium or magnesium ions. Soft Water usually comes from peat or igneous rock (volcanic rocks which make 95% of earth's crust after the cooling of magma); other sources are granite and sandstone. All such sedimentary rocks are usually low in calcium and magnesium. The magnesium content of soft drinking water is between 2-20 mg/l, average ~6 mg/l. The content of magnesium in bottled water varies from 0-126 mg/litre [55] while carbonated tonic and soda water contains little or no magnesium. One gram of instant coffee granules releases ~5 mg of magnesium in hot water; the corresponding figure for tea is ~0.6 mg [56].

Significant magnesium deficiency has been reported in both elderly self-caring in the community as well as in hospitalized Norwegians [57]. In a consensus survey involving 37,000 Americans, 39% were found to ingest less than 70% of the recommended daily magnesium intake and 10% of women over the age of 70 yrs consume less than 42% of the recommended dietary requirement [58-60]. When dietary magnesium intake is poor, the kidney can compensate by increasing fractional reabsorption to >99% of the filtered load, mainly in the loop of Henle with further reabsorption in the distal tubule. Normally, plasma magnesium is filtered at the glomeruli apart from the fraction bound to albumin. Reabsorption of the filtered load can vary depending on the body store, being lowest when body stores are adequate to maximum in deficiencies. Prolonged periods of poor dietary intake however would eventually lead to a decline in intracellular magnesium concentration.

Excessive renal loss is however a common cause of negative magnesium stores. Alcohol is a known cause, being magnesium diuretic as even moderate amounts produces magnesiuresis. Alcohol increases urinary magnesium loss above baseline by an average of 167% (range 90-357%) and its effect is rapid [61-66] and occurs even in individuals with an already negative magnesium balance. Alcohol consumption has increased with availability and cheaper cost [65,67] and in moderate amounts, is considered socially and culturally acceptable (taken as 2 to 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 levels 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. Furthermore, large consumption of magnesium rich beer and wine can have a laxative or even diarrheatic effect, potentially impeding bioavailability and absorption.

It appears reasonable therefore to suggest that a life-style associated with low dietary magnesium intake in food and drinking water, purified table salt for cooking and in-food, regular and strenuous exercise coupled with moderate and regular consumption of alcoholic drinks which cause a net renal magnesium loss can additively lead to negative balance over time. Magnesium deficiency can be further compounded with malabsorption and those receiving medications [68-72] such as diuretics (loop and thiazide), proton pump inhibitors, tacrolimus, chemotherapeutic agents such as cisplatin, ciclosporin, omeprazole, cetuximab and some phosphate-based drugs.

In summary, modus vivendi when carefully examined can determine the potential of latent magnesium deficiency which may be associated with a wide range of major pathologies. It is however a common practice for clinicians to rely more on laboratory tests in the diagnosis of magnesium deficiency.

Laboratory Tests and Assessment of Magnesium Deficiency

Assessment of magnesium status is biochemical. Serum magnesium is the most commonly requested test and is informative when magnesium is reduced indicating hypomagnesaemia. However, normal serum magnesium (commonly reported ~0.75 mmol/l to ~1.2 mmol/l) remained problematical because in patients suspected with magnesium deficiency serum concentration can be normal despite whole body deficiency [73-76]. This is not surprising because only 1% or less of body magnesium is in blood; 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 normal serum magnesium (total or ionized) must be interpreted with caution [76]. Low serum magnesium (with normal albumin) in a fasting or random sample confirms significant deficiency warranting supplementation. For this reason, the practicable, inexpensive and commonly used serum magnesium must be regarded as potentially flawed test, capable of identifying magnesium deficiency in some (range from 2.5 to 15%) but not all patients with deficiency and negative body stores. A fraction of bone magnesium appears to be on a surface limited pool, present either within the hydration shell or else on the crystal lattice. Based largely on animal studies, it has been speculated that this form of bone surface magnesium may represent a limited buffering capacity.

To exclude with confidence latent/chronic magnesium deficiency in cases with high index of suspicion albeit normal serum magnesium, a dynamic study namely magnesium loading test would be appropriate if renal function is normal. This procedure is probably the best physiological "gold standard test" within the capability of all routine hospital laboratories. It involves the administration of elemental magnesium load (as sulphate or chloride) intravenously followed by assessment of the amount of elemental magnesium excreted in the urine in the following 24 hrs [77-81]. A large fraction of the given magnesium load is retained and a smaller amount of the given dose appears in the urine in patients with latent magnesium deficiency. Such a procedure in the experience of one of us was valuable, accurate and informative, however, it is time consuming and (understandably) not commonly used in clinical practice. It is also contra-indicated in individuals with renal impairment.

Magnesium Loading Test

The loading test measures the body's retention of magnesium and therefore reflects the degree of deficiency [77-81]. Attention to details is however paramount for valid interpretation of data. Patient should empty their bladder immediately before the test. The test involves intravenous administration of 30 mmol of elemental magnesium (1 mmol=24 mg) in 500 ml 5% dextrose over a period of 8-12 hours. A slow rate infusion is important because plasma magnesium concentration affects the renal reabsorption threshold and abrupt elevation of plasma concentration above the normal range would reduce magnesium retention and increases urinary excretion with its

potential misinterpretation. Urine collection begins with the onset of magnesium infusion and continues over the next 24 hrs period, including a last void at end of this period.

Patients with adequate body magnesium stores retain less than 10% of the infused elemental magnesium load. Latent magnesium deficiency is considered present if less than 25 mmol of elemental magnesium are excreted in the 24 hrs collection. Repeat of magnesium loading test to check repletion can also be informative because average difference between two repeats is ~2%. Magnesium body stores are considered repleted when >90% of the elemental magnesium load is excreted in the following 24 hrs urine.

Magnesium loading test is contraindicated in patients with renal impediment, salt losing nephropathy, respiratory failure and medications which affect renal tubular function such as diuretics, cisplatin, ciclosporin, etc.

A number of studies attempted to simplify the magnesium loading test [82] by reducing the infused magnesium load to 0.1 mmol of elemental magnesium per kilogram body weight, reducing the infusion time to 1-2 hrs and collecting urine over shorter period of 12 hrs. Oral magnesium loading test was also described. However, although these modifications are simpler, their usage was limited and the 8-12 hour infusion of 30 mmol remained the standard test.

24-h Urinary Magnesium Excretion

Patients with magnesium deficiency, not on medications/alcoholic beverages and normal renal function, excrete small amounts of magnesium per day (usually <0.5 mmol or 12 mg). Considerable care and attention to completeness of 24-h urine collection is necessary [83].

Treatment Modalities in Patients with Magnesium Deficiency

Magnesium has low-toxicity in people with normal renal function. Deficiency however 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 [84]) for individuals requiring long-term supplementation. Aerosolized magnesium sulphate was also used in patients with acute asthma [85,86].

Intravenous magnesium (up to ~30 mmol of elemental magnesium; 1 mmol=24 mg) is given over a period of hours. A slow rate infusion is important because plasma magnesium concentration affects the renal reabsorption threshold and abrupt elevation of plasma concentration above the normal range can reduce magnesium retention. Magnesium body stores are considered repleted when >90% of the elemental magnesium load is excreted in the following 24 hrs urine (see magnesium loading test). On the other hand, persistent elevation in serum magnesium in samples taken longer than 24 hrs after treatment would be indicative of over-treatment. Other analytes which may be associated with magnesium deficiency are calcium, potassium, phosphate and vitamin D [87].

Common oral magnesium supplement exists in two forms-chelated and non-chelated. In the chelated forms, magnesium is attached to organic radicals; in the non-chelated forms magnesium is in the form of sulphate, chloride or oxide. Magnesium attached to organic/aminoacid radicals appears to be better tolerated with superior bioavailability [88,89] than the commonly available magnesium oxide. Generally over-treatment leading to significant hypermagnesaemia is unlikely to occur in patients on the recommended oral magnesium supplement. This is because when the intake exceeds daily requirement, absorption of magnesium from the gut is reduced and its excretion can exceed 100% of the filtered load caused by active renal secretion in the urine.

It may be of interest to point out 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 ~80% of oral magnesium being absorbed within 6-7 hrs [90]. Note also that calcium and magnesium competes for absorption, thus too much calcium in diet/medication can impede magnesium absorption. A ratio for calcium to magnesium of ~2:1 would allow adequate absorption of magnesium. However, high oral calcium intake or consumption of large amounts of calcium-rich products such as dairy foods which have a ratio of calcium to magnesium of ~10:1 can sufficiently alter the balance, potentially reducing magnesium absorption. Dosage regimen of oral magnesium should therefore take into account the degree of patients' magnesium deficiency in the first place, the basic chemical composition of oral magnesium supplement and its bioavailability plus other concurrent medications which can increase magnesium loss (e.g. diuretics, regular intake of spirits) and/or impede its absorption e.g. GI disorders. Sustained oral magnesium supplementation may be considered in individuals with life style below RDA intake.

Claims that Epsom salt can be absorbed through the skin are wide spread throughout the internet with numerous products which can be added to bath water, in oil, gel or lotions to be directly messaged to skin for "extra-relaxation, detoxification and exfoliation". However, no peer reviewed systematic or controlled studies could be found on this subject. In a widely quoted but rather limited, not peer-reviewed study involving 19 subjects (Waring R; School of Bioscience, Birmingham University, UK) who for one week bathed in water containing 1% Epsom salt at temperature of ~50°C for ~15 mins, 16 have increased their baseline serum magnesium concentration before the test by up to 40% and doubled their magnesium content in urine. However, in view of the dearth of scientifically peer-reviewed studies, transdermal absorption of magnesium should remain speculative.

Conclusion and Take-home Message

Magnesium deficiency is an underestimated multifactorial disorder, common particularly in the elderly. Magnesium deficiency can be associated with consequential morbidity and mortality especially in patients with other co-morbidities. Serum magnesium is a useful test because low serum concentration indicates significant deficiency warranting replacement. However, normal magnesium concentration 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 contents plus other factors listed in Table 2, notably diet and diuretics. The most informative laboratory investigation is magnesium loading test.

Magnesium deficiency should always be considered in cases such as electrolyte disturbances (hypocalcaemia and/or hypokalaemia), arrhythmia, regular/excessive alcohol intake 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 also identified. The limitations of serum magnesium, though well known among laboratorians is not widely disseminated nor emphasized to clinical practitioners. The perception that "normal" serum magnesium excludes deficiency has therefore contributed to the under-diagnosis of latent/chronic magnesium deficiency. Based on literature in the last two decades, magnesium deficiency remained common and undervalued, warranting a proactive approach because restoration of magnesium stores is simple, tolerable, and inexpensive and can be clinically beneficial.

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