UDK: 546.46:615.1
Review article
Received: 15 June 2013
Accepted: 18 September 2013

MAGNESIUM – MORE THAN A COMMON CATION

Ivana Čepelak[1], Slavica Dodig[2], Ognjen Čulić[3]

[1] Department of Medical Biochemistry and Hematology, Faculty of Pharmacy and Biochemistry, University of Zagreb, Croatia

[2] Department of Clinical Laboratory Diagnosis, Srebrnjak Children's Hospital, Zagreb, Croatia

[3] Faculty of Pharmacy and Biochemistry, University of Zagreb, Croatia

Summary

Magnesium is an essential biological cation, participating in whole spectrum of biological functions. It is an irreplaceable factor for more than 300 enzymatic reactions, including those that use ATP as chemical energy source. Only about 1% of whole body magnesium is present in plasma. Normal plasma concentrations are in a range: 0.75-1.00 mmol/L.

Concentrations lower or higher than in this interval are called hypomagnesemia and hypermagnesemia, respectively. Those are life treathening conditions. Hypomagnesemia requires quick i.v. supplementation with magnesium cation. In addition to hypoamgnesemia, we are nowadays aware of a common "invisible" deficit of magnesium in tissues. This is a result of changing nutrition habits causing an insufficient recommended daily uptake (>300mg daily). Large clinical studies have shown that magnesium status is negatively correlated with incidence and severity of diabetes type 2, metabolic syndrome, hypertension and some arrhythmias. Therefore, food supplementation with magnesium is one of positive therapeutic or prevention options. Future larger clinical studies are expected to provide information on usefulness of supplementation in some other common diseases and syndromes (e.g. migraine, fibromyalgia, coronary artery disease, chronic fatigue syndrome).

Keywords: magnesium; hypomgnesemia; hypermagnesemia; therapeutic applications of magnesium.

INTRODUCTION

The fact that magnesium (Mg) is essential for life was for the first time described in animals by Leroy in 1926 [1] and Kruse et al. in 1933 [2], while the first description of clinical depletion of Mg in humans was reported in 1934 by Hirschfelder & Haury [3]. However, studies of Mg began to gain increased attention only since 1950, after

descriptions of various pathological conditions related to Mg deficiency [4]. Such studies were additionally facilitated by advances in technology, i.e. the development of ever more sensitive and specific methods for determining Mg concentrations in different samples so that more and more information has become available on regulation and biological functions of Mg at molecular level.

SOURCES, RECOMMENDED ALLOWANCES AND MAGNESIUM DISTRIBUTION IN THE BODY

Intake of Mg in the body occurs via drinking water (approximately 30 mg/L in hard water) and food. Mg is abundant in green leafy vegatables (chlorophyll rich and containing Mg), seeds, leguminous plants, cereals, hazelnuts [5,6]. Fruit, vegetables, meat and fish contain small amounts of Mg, while this mineral is least present in dairy food [7]. Mg is reduced by as much as 85% in refined or processed food [8], which accounts for a high prevalence of low Mg intake in the body.

It is well known that the entire quantity of ingested Mg is not absorbed in the body but only, on average, 30-50% [9]. To maintain serum Mg concentration within the reference interval (0.75-1.0 mmol/L) – which is the basis of Mg biological functions, Recommended Dietary Allowance (RDA) values established in 1997 [10] for daily Mg intake are >300 mg (310-360 mg for women and 400-420 mg for men) and they have been adjusted for age, gender and nutritional status (*Table 1*).

Table 1. Recommended dietary allowances (USA 1997) and reference intakes (Germany, Austria, Switzerland, 2000) for magnesium (mg/day) (reprinted from ref. 10)

Age	Women (mg/day)	Men (mg/day)
1-3	80	80
4-8	130	130
9-13	240	240
14-18	360	410
19-30	310	400
31-50	320	420
51-70	320	420
>70	320	420
Pregnancy	+40	
Lactation	+40	

Mg absorption occurs mostly in the small intestine, i.e. in the jejunum and ileum and significantly less in the colon [6]. Considering numerous factors that affect the process of absorption, the absorbed proportion of Mg is as stated above, commonly from 30% to 50% or 24-75% depending on body stores and food content [11]. The absorbed Mg is then distributed mostly to various tissue cells and to a lesser extent extracellularly. It is excreted through stool and through the kidneys.

Regarding its presence in the body, Mg is the fourth most frequent cation (following calcium, sodium, and potassium) [12,13]. From average 25 g (or 1120 mmol) of Mg in the body of an adult individual, the highest proportion of Mg can be found in bones, followed by muscles and other soft tissue cells [5,13]. One portion (20-30%) of Mg in bones is replaceable and buffers acute changes in serum Mg concentration but this quantity is significantly reduced with years [14,15]. Extracellularly, <1.0% Mg is found in three different forms: free ionized Mg, Mg complexed with different ligands, and as protein-bound Mg (*Table 2*).

Table 2. Distribution and/or concentrations of magnesium in a healthy adult (modified according to ref. 10).

Tissue	% total body magnesium
Bone	60-65
Muscle	27
Other cells	6-7
Extracellular	<1
Serum	0.75-1.1 mmol/L (55% free; 13% complexes with citrate, phosphate, etc; 32% bound to proteins, primarily to albumin)
Cerebrospinal fluid	1.25 mmol/L (55% free, 45% complexed)
Sweat	0.3 mmol/L (in warm environment)

PHYSIOLOGICAL FUNCTIONS OF MAGNESIUM

Magnesium is, after calcium, the second most frequent cation in cells [12]. 90% Mg in cells is bound to different ligands (e.g., nucleic acids, adenosine triphosphate, ATP, ADP, citrates, negatively charged phospholipids, proteins, etc.), while 10% Mg is in a free form. A significant amount of Mg is found in mitochondria (they are considered the major intracellular repository for Mg), then in the nucleus, ribosomes and endoplasmic reticulum [10]. In cells, Mg has structural and dynamic roles as, for instance, stabilization of protein structure, of phosphate groups in lipids of cellular membranes, of negatively charged phosphates of nucleic acids, and acti-

vation or inhibition of many enzymes [12,16,17]. Magnesium is actually important for the catalytic activity of more than 300 enzymes (e.g., ATP-ase, phosphofructokinase, enolase, adenylate cyclase, creatine kinase, 5-phosphoribosyl pyrophosphate synthetase, DNA polymerase, etc.), particularly of those that catalyze energy metabolism reactions. These reactions involve the process of glycolysis, Krebs cycle, respiratory chains, pentose phosphate pathway, gluconeogenesis, urea cycle, etc. In regulating enzyme activity, Mg can act as an allosteric modulator or as a co-factor, most frequently in the form of the $Mg\text{-}ATP^{2-}$ complex [13,18]. Generation of a complex with ATP^{4-} is important to facilitate transphosphorylation reactions which are decisive for cell activation/deactivation. The complex is also involved in regulating the activity of ion channels that are significant for the transport of other electrolytes, e.g. potassium and calcium [19].

The biological role of Mg is rather heterogeneous. In addition to the above-mentioned structural and dynamic function, Mg – due to its relatively small atomic radius – easily competes with other divalent cations (particularly calcium) for specific binding sites on proteins [18,20,]. As an endogenous calcium antagonist, Mg is involved in, e.g., blockage of N-methyl-D aspartate (NMDA) receptor, inhibition of excitatory neurotransmitter release, blockage of Ca channels, and relaxation of vascular smooth muscle cells [21]. This characteristic, and that of binding to various ligands – particularly to ATP^{4-}, – is the basis for different physiological functions of Mg. Among other uses, Mg is essentially necessary for maintenance of normal neurological function and neurotransmitter release [6,8,13,22,23], muscular contractions/relaxations [6,9,24,25], regulation of vascular tonus and blood pressure [26,27, 28], of cardiac rhythm, [29,30,31], insulin signal transmission [32,33,34], parathormone secretion and activity [13,19,35], modulation of immunological functions [36,37], etc. It is therefore evident that tight regulation of Mg levels in blood /serum and Mg distribution to individual cell types are of vital importance.

MAGNESIUM HOMEOSTASIS

Although the importance of Mg in different physiological and biochemical processes is well known, direct hormonal control of Mg homeostasis has not been clearly described [38,39]. This is accounted for by Mg abundance in food during human evolution [10]. Indirect activity of hormones is mostly described at the level of intestinal absorption or renal tubular reabsorption. It is, actually, not known if hormone concentrations are under the influence of Mg status, which is the case when real hormonal control is present. The hormones in question are, e.g., calciotropic hormones (parathyreoid hormone, PTH, calcitonin and vitamin D) and, more rarely, insulin, glucagon, prostaglandins, epinephrine, aldosteron, etc. [40,41,42,43,44]. Mg

is, for instance, critical for maintenance of calcium homeostasis as it regulates PTH production and secretion, maintains adequate sensitivity of target tissues to PTH, is a cofactor of 1-alpha hydroxylase, an enzyme that participates in $1,25(OH)_2$ D_3 production, and also many calcium channels are dependent on Mg [45]. Besides its effect on calcium levels, Mg helps in regulation of other electrolytes (copper, zinc, potassium, sodium, etc.) so that the understanding of Mg homeostasis is important not only to understand disturbances in Mg levels but also for understanding and treatment of abnormalities of other electrolytes.

Magnesium homeostasis is controlled by dynamic interrelationships between intestinal absorption and by exchange with bones, but mostly by renal excretion [6,39,46].

Magnesium absorption

Mg absorption in the small intestine occurs primarily via non-saturable (passive) paracellular, and to a lesser extent by saturable (active) transcellular mechanisms [6,9,46,47,48].

The paracellular, passive mechanism involves absorption through small permeable spaces between epithelial cells (tight junction), and is responsible for 80-90% of Mg uptake in the body. This transport mechanism also includes some proteins from the claudin family (e.g., pracellin-1 or claudin-16) whose role is still at research stage [9,49]. Transcellular active transport to blood through the interior of intestinal epithelial cells is subject to tight regulation because ions must pass through apical and basolateral membrane. This mechanism includes specific channels (transient receptor potential channel melastatin - 6 and 7; TRPM-6 and 7) that are expressed on apical/luminal membrane of enterocytes [9,49,50,51]. It seems that the transport on basolateral membranes is associated with sodium gradient and corresponding activity of Na^+, K^+-ATPase [9].

Magnesium absorption in the intestines is generally dependent on the factors like the following: fiber rich food – phytates, organic acids, pH, Mg quantity, intestinal passage, meal volume and viscosity, vitamin D, calcium, phosphorus, polyphenols, oxalates, zinc, etc. [52,53,54,55,56].

Magnesium excretion

As serum Mg concentration is primarily controlled through urinary excretion, kidneys are considered the major regulators of Mg homeostasis. They have the ability to reduce Mg excretion to 0.5% of the filtered quantity in case of decreased serum concentrations, and to increase Mg excretion to 80% in case of elevated serum Mg concentrations [57,58].

Magnesium is filtered in glomerules (approximately 2400 mg/day), 90-95% of the filtered quantity is immediately reabsorbed, and only 3-5% is excreted, i.e. 100 mg/day [9,48]. To a lesser extent, reabsorption occurs via passive transport in proximal tubules (10-25%) [9], a significant proportion of 50-70% is reabsorbed in the thick ascending limb of the Henle's loop, and about 10% is reabsorbed in the distal part [6, 9, 59]. Magnesium reabsorption in the thick ascending limb of the Henle's loop occurs via passive paracellular pathway because of the electrochemical gradient that results in potassium exit through channels (renal outer medulla potassium channel, ROMK) in the apical cell membrane of the above-mentioned segment of the Henle's loop [60]. Reabsorption is at this stage further facilitated by claudin-16 (paracellin-1) and claudin-19 [50,61,62].

Ca^{2+}/Mg^{2+}- sensing receptor, CASR, that activates or inhibits Na^{+}-K^{+}-$2Cl^{-}$ co-transporter and ROMK channel on the apical side in conditions of hypomagnesemia or hypermagnesemia [63,64], is located on the basolateral cell membrane of the thick ascending limb of the Henle's loop and of the distal tubules.

Reabsorption in distal tubules is utilized to determine the final quantity of Mg that is to be excreted by urine. Reabsorption occurs via transcellular active mechanism that involves Mg entry into cells through the TRPM6 channel on the apical membrane (the role of TRPM7 channel is still investigated). It has been assumed that Mg exit from the cell on the basolateral membrane is facilitated, against concentration gradient, by the Na^{+}/Mg^{2+} dependent mechanism of exchange and/or Mg-ATPaze activity [64,65].

The processes of absorption and reabsorption are controlled by different regulatory factors. Thus, for instance, Mg intake through food and changes in TRPM6 expression play a role in regulating intestinal absorption [9]. Stimulation of absorption in the intestines with 1,25-dihydroxy vitamin D_3 ($(1,25(OH)_2D_{3)}$ was also described [66]. A regulatory factor of Mg reabsorption in kidneys is, e.g., epidermal growth factor (EGF) which regulates the activity of TRPM6 [67] whose expression is stimulated by estrogens [68].

Examination of Mg homeostasis at the level of cells themselves, i.e. Mg entry and exit from cells and its transport between cellular organelles via various pathways, carriers and exchangers, is in the focus of numerous studies that are currently underway. A reader is referred to an excellent review article by A.M Romani [12].

DISORDERS OF SERUM MAGNESIUM CONCENTRATIONS

Changes in serum Mg concentrations, related to reduced or increased levels outside the lower or upper limit of the reference interval (0.7-1.0 mmol/L), are termed hypomagnesemia and hypermagnesemia, respectively.

The occurrence of hypomagnesemia is more frequent, with the prevalence of 6.9% in general population and 7-11% among hospitalized patients [5, 69]. Hypomagnesemia in intensive care units ranges from 20% to 65% [70] and very frequently remains undetected. Some reports indicate a correlation between severe hypomagnesemia and increased mortality [71] so that it is recommended to monitor Mg concentration in severe patients.

Data on the prevalence of hypermagnesemia differ considerably and vary from 5.7% to 9.3% [13, 72]. Clinical findings related to serum Mg concentrations outside the reference interval are presented in *Table 3.*

Table 3. Clinical reports associated with altered magnesium concentrations (ref. 39).

Total Mg (mmol/L)	Report
<0.5	Tetany, convulsions, arrhythmias
0.5-0.7	Neuromuscular irritability
0.7-1.0	**Reference interval**
1.0-2.1	Typically without symptoms
2.1-2.9	Lethargy/listlessness, sleepiness, redness, nausea and vomiting, weakened reflexes of deep tendons
2.9-5.0	Drowsiness, weakened reflexes of deep tendons, hypotension, ECG changes
>5.0	Complete heart blockage, cardiac arrest, apnea, paralysis, coma

Symptoms of acute hypo- and hypermagnesemia partially overlap so that serum Mg concentration must be determined [6].

a) Hypomagnesemia

Hypomagnesemia and Mg deficiency in the body are the terms that are equally often used in practice, mostly referring to decreased serum Mg concentration. However, depletion of the total body Mg may be present with serum Mg concentrations being within the reference interval while, on the other hand, significant hypomagnesemia is possible without body Mg deficiency. In fact, the determination of the total serum Mg concentration is not the best method to evaluate Mg status in the body as there is very weak correlation between the levels of total serum Mg and total Mg status in the body.

Hypomagnesemia may be the consequence of decreased Mg intake, of Mg redistribution, and the consequence of extrarenal, renal and hereditary factors. Etiological factors of hypomagnesemia are summarily presented in *Table 4.*

Table 4. Etiology of hypomagnesemia (modified according to ref. 64*)*

Reduced Mg intake through food
Increased Mg loss via gastrointestinal tract: diarrhea, malabsorption, steathorrhea, small bowel bypass
Increased Mg excretion by kidneys: extracellular volume expansion, hypercalcemia, renal diseases, drugs (e.g. diuretics - thiazides, furosemide; amino glycoside antibiotics; cyclosporine; cisplatin inhibitors of proton pump, beta-adrenergic agonists, immunosuppressants, amphotericin B, foscarnet, etc.)
Hereditary causes: - Intestinal and renal: hypomagnesemia with secondary hypocalcemia (TRPM-6 mutations) - Renal: Bartter syndrome, Gitelman syndrome, familial hypomagnesemia with hypercalciuria and nephrocalcinose; autosomal dominant hypomagnesemia with hypocalciuria; isolated recessive hypomagnesemia, autosomal dominant hypocalcemia
Other etiologies: acute pancreatitis, alcohol induced tubular dysfunction, hungry bones syndrome, diabetes mellitus, enhanced sweating, increased requirements (pregnancy, growth)

Individuals with hypomagnesemia are often asymptomatic as Mg deficiency is usually secondary to other disease processes or drugs so that primary disease disguises Mg deficiency.

The signs and symptoms of hypomagnesemia depend more on the rapidity of decline in Mg levels than on serum Mg concentration itself [13], and they are usually not observed until serum Mg level drops below 0.5 mmol/L or lower. Clinical and biochemical manifestations of hypomagnesemia include the most frequent disorders of other electrolytes, disorders of cardiovascular, neuromuscular and central nervous system, complications due to Mg deficiency like hypertension, osteoporosis, glucose homeostasis disorder, atherosclerotic vascular disease and, e.g., migraine, asthma, etc.

Development of hypocalcemia in hypomagnesemia is associated with the role of Mg in the synthesis, secretion, and activity of parathormones on target tissues, and with the activity of $1,25(OH)_2D_3$. [73]. A significant proportion of individuals (40-60%) with hypomagnesemia also have hypopotassemia [72], and the mechanism involves the following: a) concurrent loss of Mg and potassium due to diarrhea or application of diuretics, and b) decline in the activity of Na^+, K^+-ATPase, that is, increase in the number of open potassium channels in the cells of the thick limb of the Henle's loop and collecting tubules [74, 75]. The hypopotassemia associated with hypomagnesemia is often refractory to potassium treatment so that Mg deficiency should also be corrected. Due to impaired electrical activity, myocardial

contractility and vascular tonus, cardiovascular disorders include, for instance, hypertension, dysrhythmias, ECG changes (e.g., prolonged QT interval, prolonged PR interval), atherogenic dyslipidemia, oxidative stress, impaired coagulation process, aggravated inflammatory problems, etc. [76,77,78].

Neuromuscular disorders, or neuromuscular hyperexcitability, are frequent in individuals with hypomagnesemia and involve, e.g., tetany, spontaneous carpal-pedal spasm, vertigo, ataxia, muscular weakness, convulsions, nystagmus, and psychiatric disorders like depression and psychosis, etc. [77,79]. The mechanism of the development of neuromuscular disorders is related to decreased axon stimulation threshold and increase in nerve conduction velocity due to reduced Mg concentration. Besides, as Mg participates in neurotransmitter (glutamate) release at neuromuscular junctions [80] and thus inhibits the calcium entry into presynaptic nerve terminals, enhanced calcium entry occurs in the situation of Mg deficiency and consequently of increased neurotransmitter release, which results in enhanced neuromuscular activity. Hypocalcemia is often concurrent with hypomagnesemia and it further contributes to neurological signs.

In case of inherited types of hypomagnesemia, whose molecular mechanisms have been discovered during the past ten years, they involve gene mutations for different proteins - channels, carriers, transporters [9,48,49], some of which are presented in *Table 5.*

Table 5. Some proteins of molecular magnesium homeostasis are related to hereditary hypomagnesemia.

Protein	Gene	Function	Comorbidity
Claudin-16 (ili paracellin-1) Claudin-19	*CLDN16* *CLDN19*	Allowability of paracellular permeability	Familial hypomagnesemia with hypercalciuria and nephrocalcinosis
NCCT	*SLC12A3*	(Na^+ Cl^- cotransporter)	Gitelman syndrome
TRPM-6	*TRPM6*	Selective Mg channel	Hypomagnesemia with secondary hypocalcemia
Na^+, K^+ -ATPase gamma subunit	*FXYD2*	Altered kinetics of Na^+ i K^+ exchange	Isolated dominant hypomagnesemia with hypocalciuria
EGF	*EGF*	Enhanced TRPM-6 activity	Isolated recessive hypomagnesemia
NKCC, Barttin, CIC Kb, ROMK	*SLC12A1,BSND, CLCNKB, KCNJ1*	Na+, K+ -cotransporter, Barttin, CIC-Kb-channel, ROMK-K-channel	Bartter syndrome

Hypomagnesemia therapy includes oral Mg replacement in food or food supplements in mild cases [39, 81] while intravenous replacement is applied in severe hypomagnesemia, most frequently in the form of Mg- sulfate [8, 82].

b) Hypermagnesemia

Hypermagnesemia is a condition where serum Mg concentration is >1.0 mmol/L. Mild hypermagnesemia is quite common in hospitalized patients and is usually not associated with clinical symptoms. Significant hypermagnesemia is related to different neuromuscular and cardiovascular disorders, and very severe hypermagnesemia may result in a coma.

One of the causes of hypermagnesemia is increased oral, rectal or parenteral intake of high Mg doses as, e.g., Mg supplementation in the form of magnesium salts or Mg-containing drugs (antacides, laxatives, purgatives), in some therapeutic approaches involving intravenous Mg application (e.g., torsade de pointes therapy of specific types of arrhythmia or convulsions in patients with eclampsia). Another cause is renal function impairment (acute and chronic diseases, rhabdomyolysis) because kidneys are the main organ that maintains Mg homeostasis (normal Mg concentration is maintained until glomerular filtration rate drops below 30 mL/min [13]. In such cases, renal compensatory mechanisms to maintain Mg homeostasis become inadequate and hypermagnesemia develops. Other causes include Mg redistribution to cells and, e.g., lithium therapy, familial hypocalciuric hypercalcemia, theophylline toxicity, etc. [39,83,84].

Signs and symptoms of hypermagnesemia occur at different Mg concentrations but they usually occur when serum concentrations are >2.0 mmol/L [13]. However, cases with very high serum Mg concentrations, i.e. 13.0 mmol/L [85], 17.0 mmol/L [86], 21.5 and 22. 5 mmol/L, have been described in the literature [87].

Clinical manifestations of hypermagnesemia include the most frequent neuromuscular and cardiovascular disorders (Mg is cardiotoxic in serum concentrations >3 mmol/L), nausea, and vomiting (*Table 6*).

Table 6. Clinical manifestations of hypermagnesemia (reprinted from *ref.13)*

Neuromuscular manifestations: confusion, lethargy, respiratory depression, absent tendon reflexes, paralytic ileus, bladder paralysis, muscle weakness/paralysis
Cardiovascular manifestations: hypotension, bradycardia, inhibition of AV and intraventricular conduction, heart block, cardiac arrest
Others: nausea, vomiting

With regard to biochemistry disorders, hyperpotassemia and hypocalcemia also occur in addition to hypermagnesemia [13,39].

Hypermagnesemia therapy involves discontinued Mg application and Ca-gluconate administration, while severe types of hypermagnesemia may even require hemodialysis [7].

CLINICAL ASPECTS

Physiological function of Mg in the body are numerous and varied (modulation of transport functions, of enzymatic activities, energy metabolism, synthesis of proteins and nucleic acids, etc.). It is, therefore, not surprising that Mg deficiency is involved in pathogenesis of a large number of pathological conditions (*Table 7*), with concurrent accumulation of data on the benefits of supplementing Mg as a pharmacological compound.

Table 7. Literature review of some pathological conditions related to magnesium deficiency

Pathological condition	References
Diabetes mellitus	24, 28, 88, 89,90,91,
Metabolic syndrome	92,93,94,95,
Cardiovascular diseases	10, 24, 48, 77, 96,97,
Arrhythmias	98, 99, 100, 101,
Hypertension	28, 98, 102, 103, 104, 105, 106,
Acute myocardial infarction	13,98, 107,108,109,
Atherosclerosis	13, 98, 110,111
Cerebrovascular disorders	71, 112,113,114,115,116,117,118
Headache (migraine)	119,120,121
Neuromuscular disorders	6,13,77,122,123,124,
Osteoporosis	13, 125,126,127,128
Asthma	13,77,129,130,131,
Preeclampsia/eclampsia	6,77, 132,133,134,135,
Malignant diseases	6,71,136,137,
Fibromyalgia	138,139
Cataract	140,141,
Pheochromocytoma	142,143,
Allergies	8, 144, 145, 146, 147,148,
Oxidative stress	149,150,
Drug application	6, 151,152,153,154,155,156

Early recognition of disorders of Mg metabolism (and its consideration with changes in other electrolytes) and their correction are necessary to avoid complications related to cardiac arrhythmia, hypocalcemia, etc. It is therefore necessary to frequently determine Mg in serum and possibly start Mg supplementation. Currently, different methodological approaches are available to estimate Mg status: methods for determination of total serum Mg concentration [6, 13, 77, 157], of ionized Mg form in whole blood, serum or plasma [13,48, 158], methods for Mg determination in erythrocytes [159], leukocytes [160], and skeletal muscle cells [25, 77, 161]. Magnesium may also be measured in urine, saliva, hair, and teeth [6,159]. In some clinical conditions, physiological tests are used as, e.g., Mg balance test, Mg excretion in 24-h urine, Mg loading test, Mg tolerance test [13, 162]. Recently, dry chemistry methods have also been developed for determination of ionized Mg for point-of-care testing [163]. Furthermore, for determination of ionized Mg concentration in the cell cytosol, the procedures with different metalochromatic or fluorescent dyes are used, as well as Mg-selective electrodes, and nuclear magnetic resonance and isotope testing [13, 48] which are mostly limited to scientific investigations.

Regarding therapy, Mg is usually administered in case of constipation [164] and dyspepsia [82]. According to reports by Guerera MP, et al. [82] and Geiger H, et al. [98] from 2012, indications for therapeutic applications of Mg (it has shown to be highly effective when applied intravenously) are primary reduction of the risk for eclampsia in preeclamptic women, arrhythmias (torsade de pointes in patients with long QT syndrome and digoxin induced arrhythmia), and severe asthma and migraine attacks.

Favorable effects of Mg have been observed in the control of glycemia in type 2 diabetes, improved efficacy of antihypertensive therapy, reduction in the frequency of muscular cramps, favorable effects on some risk factors of atherosclerosis, prevention of osteoporosis, of renal stone recurrence, of stroke, etc.

Although oral Mg supplementation is generally well tolerated, the following side-effects have been observed: nausea, vomiting, diarrhea, whereas large amounts of magnesium may result in hypotension, muscular weakness and coma. Mg must not be administered as therapy to patients with any type of renal dysfunction.

CONCLUSION

It is well known that Mg is the essential element for human health. However, due to increasing intake of Mg-deficient processed food, Mg deficiency may be expected to develop into a significant public health problem. It is not uncommon that hypomagnesemia is already a relatively frequent disorder which is, moreover,

often not recognized/not diagnosed because Mg concentration is seldom routinely determined. Actually, the evaluation of the Mg status is made difficult by the fact that most Mg is stored in tissues so that serum Mg levels are not representative. Generally accepted attitude is, however, that physicians should request Mg concentration measurement regardless of this difficulty, particularly in patients with the risk of possible hypomagnesemia.

As the low Mg intake may result in various, even severe, diseases, or contribute to complications that accompany different illnesses, it is necessary that researchers have thorough knowledge of those conditions in order to be able to assess symptoms related to Mg deficiency. In this regard, the application of novel analytical procedures in determining total and ionized Mg in different body fluids and cells, numerous clinical observations, and molecular genetic studies will certainly contribute to elucidation of the Mg role in terms of physiology and pathophysiology and particularly with regard to Mg deficiency treatment.

References

[1] *Leroy J*. Necessite du magnesiuma pour la croissance de la souris. C R Soc Biol. 1926;94:431-3.

[2] *Kruse HD*, *Schmidt MM*, *McCollum*, *EV*. Studies on magnesium deficiency in animals. IV: reaction to galvanic stimuli following magnesium deprivation Am J Physiol. 1933;105:635-42.

[3] *Hirschfelder AD*, *Haury VG*. Clinical manifestations of high and low plasma magnesium: dangers of epsom salt purgation in nephritis. J Am Med Ass. 1934;102:1138-41.

[4] *Flink EB*. magnesium deficiency syndrome in man. J Am Med Ass. 1956;160:1406-9.

[5] *Fox C*, *Ramsoomair D*, *Carter C*. Magnesium: its proven and potential clinical significance. South Med J. 2001;94:1195-201.

[6] *Jahnen-Dechnet W*, *Kettler M*. Magnesium basics. Clin Kidney J. 2012;5(Suppl 1):i3-i14.

[7] *Elin RJ*. Magnesium metabolism in health and disease. Dis Mon 1988;34:161-218.

[8] *Fawcet T WJ*, *Haxby EJ*, *Male DA*. Magnesium: physiology and pharmacology. Br J Anesth. 1999;83:302-20.

[9] *de Baaij JHF*, *Hoenderop JGJ*, *Bindels JM*. Regulation of magnesium balance: lessons learned from human genetic disease. Clin Kidney J. 2012;5(Suppl 1):i15-i24.

[10] *Vorman J*. Magnesium. nutrition and metabolism. Molecular Aspects of Medicine. 2003;24:27-37.

[11] *Schweigel M*, *Martens H*. Magnesium transport in gastrointestinal tract. Front Biosci. 2000;5:D666.D677.

[12] *Romani AMP*. Cellular magnesium homeostasis. Arch Biochem Biophys. 2011;512:1-23.

[13] *Swaminathan R*. Magnesium Metabolism and its Disorders. Clin Biochem Rev. 2003;24:47-66.

[14] *Alfrey AC, Miller NL*. Bone magnesium pools in uremia. J Clin Invest. 1973;52:3019-27.

[15] *Maquire ME, Cawan JA*. Magnesium Chemistry and Biochemistry. Biometals. 2002;15:203-10.

[16] *Cowan JA*. Metal Activation of Enzymes in Nucleic Acid Biochemistry. Chem Rev. 1998;98:1067-88.

[17] *Piovesan D*, *Profiti G*, *Martelli PL*, *Casadio R*. The human „magnesome": detecting magnesium binding sites on human proteins. BMC Bioinformatics. 2012;13(Suppl 14)1-8.

[18] *Wolf FI, Trapani V.* Cell (patho)physiology of magnesium. Clin Sci. 2008;114:27-35.

[19] Rude RK, Singer FR, Gruber HE. Skeletal and Hormonal Effects of Magnesium Deficiency. J Am Coll Nutr. 2009;28:131-41.

[20] *Romani A*, *Maquire ME*. Hormonal regulation of Mg2+ transport and homeostasis in eukaryotic cells. Biometals. 2002;15:271-83.

[21] *Ovbiagle B*, *Kidwell CS*, *Starkman S*, *Saver JL*. Neuroprotective agents for the treatment of acute ischemic stroke. Curr Neurol Neurosci Rep. 2003;3:9-20.

[22] *Cunningham J*, *Rodriguez M*, *Messa P*. Magnesium in Chronic Kidney Disease Stages 3 and 4 and in Dialysis Patients. Clin Kidney J. 2012;5(suppl 1):i39-i51.

[23] *Mauskop A*, *Altura BM*. Role of magnesium in the pathogenesis and treatment of migraines.Clin Neurosci. 1998;5:24-7.

[24] *Faryadi Q*. The Magnificent Effect of Magnesium to Human Health: a Critical Review. Int J Appl Sci and Toxicol. 2012;2:118-26.

[25] *Angelo EK, Singer HA, Rembold CM*. Magnesium relaxes arterial smooth muscle by decreasing intracellular Ca^{2+} without changing intracellular Mg^{2+}. J Clin Invest. 1992;89:1988-94.

[26] *Sontia B*, *Zouyz RM*. Role of magnesium in hypertension. Arch Biochem Biophys. 2007;458:33-9.

[27] *Yogi A*, *Callera GE*, *Antunes TT*, et al. Vascular biology of magnesium and its transporters in hypertension. Mages Res. 2010;23:S207-15.

[28] *Cunha AR*, *Umbelino B*, *Correia ML*, et al. Magnesium and Vascular Changes in Hypertension. Int J of Hypertension. 2012;Article ID 754250; doi:10.1155/2012/754250.

[29] *Byrd RP*, *Roy TM*. Magnesium: its proven and potential clinical significance. South Med J. 2003;96:104-14.

[30] *Sueta CA*, *Patterson JH*, *Adams KF*. Aniarrhytmic action of pharmacological administration of magnesium in heart failure: a critical review of new data. Magnes Res. 1995;8:389-401.

[31] *Ohtsuka S*, *Yamaguchi I*. Magnesium in congestive heart failure. Clin Calcium. 2005;15:181-6.

[32] *Barbagallo M, Dominguez Lj*. Magnesium metabolism in type 2 diabetes mellitus, metabolic syndrome and insulin resistance. Arch Biochem Biophys. 2007;458:40-7.

[33] *Takaya J*, *Higashino H*, *Kobayashi Y*. Intracellular magnesium and insulin resistance. Magnes Res. 2004;17:126-36.

[34] *Rumawas ME*, *McKeown NM*, *Rogers G*, et al. Magnesium Intake is Related to Improved Insulin Homeostasis in the Framingham Offspring Cohort. J Am Coll Nutr. 2006;25:486-92.

[35] *Buckle RM*, *Care AD*, *Cooper CW*, et al. The influence of plasma magnesium concentration on parathyroid hormone secretion. J Endocrinol. 1968;42:529-34.

[36] *Weglicki WB*, *Phillips TM*. Pathobiology of magnesium deficiency: a cytokine/neurogenic inflammation hypothesis. Am J Physiol. 1992;263:R734-R737.

[37] *Weglicki WB*, *Phillips TM*, *Freedman AM*, et al. Magnesium deficiency elevates circulating levels of inflammatory cytokines and endothelin. Mol Cell Biochem. 1992;110:169-73.

[38] *Zopf JM*, *Murray PT.* Hypomagnesemia and hypermagnesemia. Rev Endoc Metab Disord. 2003;4:195-206

[39] *Wu J*, *Carter A*. Magnesium: the forgotten electrolyte. Aust Prescr. 2007;30:102-5.

[40] *Bailly C*, *Roinel N*, *Amiel C*. Stimulation by glucagon and PTH Ca and Mg reapsorption in the superficial distal tubule of the rat kidney. Pflugers Arch. 1985;403.28-34.

[41] *Poujelol P*, *Touvay C*, *Roinel N*, et al. Stimulation of renal magnesium reapsorption bay calcitonin in the rat. Am J Physiol Renal Fluid Electrolyte Physiol. 1980;239:F524-F532.

[42] *Bailly C*, *Amiel C.* Effect of glucagon on magnesium renal reabsorption in the rat. Pflugers Arch. 1982;392:360–5.

[43] *Vetter T*, *Lohse MJ*. Magnesium and the parathyroid. Curr Opin Nephrol Hypertens. 2002;11:403-10.

[44] *Dai LJ*, *Ritchie G*, *Kerstan D*, et al. Magnesium Transport in Renal Distal Convoluted Tubule. Physiol Reviews. 2001;1:51-84.

[45] *Zofkova I*, *Kancheva RL*. The relationship between magnesium and calciotropic hormones. Magnes Res. 1995;8:77-84.

[46] *Saris NEL*, *Mervaala E*, *Karppanen H*, et al. Magnesium: An update on physiological, clinical and analytical aspects. Clin Chim Acta. 2000;294:1-26.

[47] *Kayne Lh*, *Lee DB*. Intestinal magnesium aposrption. Miner Electrolyite Metab. 1993;19:210-7.

[48] *Alexander RT*, *Hoenderop JG*, *Bindels RJ*. Molecular Determinants of magnesium homeostasis: Insight from human disease. J Am Soc Nephrol. 2008;19:1451-6.

[49] *Konrad M*, *Schlingmann KP*, *Gudermann T*. Insights into the molecular nature of magnesium homeostasis. am J Physiol Renal Physiol. 2004;286:F599-F605.

[50] *Amasheh S, Fromm M, Gunzel D*. Claudins of intestine and nephron – a correlation of molecular tight junction structure and barrier function. Acta Physiol (Oxf). 2011;201:133-40.

[51] *Wong V, Goodenough DA*. Paracellular channels. Science. 1999;285:62.

[52] *Hardwick LL, Jones MR, Brautbar N,* et al. Magnesium absorption: mechanisms and the influence of vitamin D, calcium and phosphate. J Nutr. 1991;121:13-23.

[53] *Lindberg JS, Zobitz MM, Poindexter JR* , et al. Magnesium bioavailability from magnesium citrate and magnesium oxide. J Am Coll Nutr. 1990;9:48-55.

[54] *Brink EJ, Beynen AC*. Nutrition and magnesium absorption: a review. Prog Food Nut Sci 1992;16:125-62.

[55] *Scholz-Ahrens KE, Schrezenmeir J.* Inulin, oligofructose and mineral metabolism -experimental data and mechanism. Br J Nutr. 2002;87:(Suppl 2):S179-S186.

[56] *Spencer H, Norris C, Williams D*. Inhibitory effects of zinc on magnesium balance and magnesium absorption in man. J Am Coll Nutr. 1994;13:479-84.

[57] *Steele TH, Wens f, Evenson MA*, et al. The contribution of thechronically diseased kidney to magnesium homeostasis in man. J Lab Clin Med. 1968;71: 455–63.

[58] *Quamme GA*. Renal magnesium handling: new insights in understanding old problems. Kidney Int 1997;52:1180–95.

[59] *de Rouffignac C, Quamme G*. Renal magnesium handling and its hormonal control. Physiol Rev. 1994;74:305-22.

[60] *Di Stefano A, Roinel N, de Rouffignac C,* et al. Transepithelial Ca2+ and Mg2+ transport in the cortical thick ascending limb of Henle's loop of the mouse is a voltage-dependent process. Ren Physiol Biochem. 1993;16:157–66.

[61] *Hou J, Renigunta A, Konrad M,* et al. Claudin-16 and claudin-19 interact and form a cation-selcitive tight junction complex. J Clin Invest. 2008;118:619-28.

[62] *Simon DB, Lu Y, Choate KA,* et al. Paracellin-1, a renal tight junction protein required for paracellular Mg2+ resorption. Science. 1999;285:103–6.

[63] *Brown EM,* MacLeod RJ. Extracellular calcium sensing and extracellular calcium signaling. Physiol Rev. 2001,81:239–97.

[64] *Naderi ASA,* Reilly R. Hereditary etiologies of hypomagnesemia. Nature Clin Pract Nephr. 2008;4:80-89.

[65] *Voets T, Nilius B, Hoefs S,* et al. TRPM6 forms the Mg2+ influx channel involved in intestinal and renal Mg2+absorption. J Biol Chem. 2004;279:19–25.

[66] *Schmulen AC, Lerman M, Pak CY*, et al. Effect of 1,25 $(OH)_2D_3$ on jejunal absorption of magnesium in patients with chronic renal disease. Am J Physiol. 1980;238:G349-G352.

[67] *Ikari A, Okude C, Sawada H,* et al. TRPM6 expression and cell proliferation are upregulated by phosphorilation of ERK1/2 in renal epithelial cells. Biochem Biophys Res Commun. 2008;369:1129-33.

[68] *Mc Nait P, Christiansen C, Transbol I*. effect of menopause and estrogen substitutional therapy on magnesium metabolism. Miner Electrolyte Metab. 1984;10:84-7.

[69] *Wong ET, Rude RK, Singer FR*. A high prevalence of hypomagnesemia in hospotalized patients. Am J Clin Pathol. 1983;79:348-52.

[70] *Noronha JL, Matuschak GM*. Magnesium in critical illness: metabolism, assessment and treatment. Intensive Care Med. 2002;28:667-79.

[71] *Chernow B, Bamberger S, Stoiko M*, et al. Hypomagnesemia in patients in postoperative intensive care. Chest. 1989;95:391-7.

[72] *Whang R, Ryder KW*. Frequency of hypomagnesemia and hypermagnesemia. J Am Med Assoc. 1990;263:3063-4.

[73] *Agus ZS*. Hypomagnesaemia. J Am Soc Nephrol. 1999;10:1616-22.

[74] *Whang R, Whang DD, Ryan MP*. Refractory potassium depletion: A consequence of magnesium deficiency. Arch Intern Med. 1992;152 :40-5.

[75] *Huang C-L, Kuo E*. Mechanism of hypokaliemia in magnesium Deficiency. J Am Soc Nephrol. 2007;18:2649-52.

[76] *Liao F, Folsom AR*, Brancati FL. Is low magnesium concentration a risk factor for coronary heart disease? The Atherosclerosis Risk in Communities (ARIC) Study. Am Heart J. 1998;136:480–90.

[77] *Tong GM, Rude RK*. Magnesium deficiency in critical illness. J Intensive Care Med. 2005;20:3-17.

[78] *Kasaoka S, Tsuruta R, Nakashima K*, et al. Effect of intravenous magnesium sulfate on cardiac arrhythmias in critically ill patients with low serum ionized magnesium. Jpn Circ J. 1996;60:871-5.

[79] *Wacker WE, Moore FD, Ulmer DD*, et al. Normocalcemic magnesium deficiency tetany. J Am Med Assoc. 1962;180:161-3.

[80] *Jenkinson DH*. The nature of the antagonism between calcium and magnesium ions at the neuromuscular junction. J Physiol. 1957;138:434-4.

[81] *Mathers TW, Beckstrand RL*. Oral magnesium supplementation in adults with coronary heart disease or coronary heart disease risk. J Am Acad Nurse Pract. 2009;21:651-7.

[82] *Guerera MP, Volpe SL, Mao JJ*. Therapeutic Uses of Magnesium. Am Family Phis. 2009;80:157-62.

[83] *Topf JM, Murray PT*. Hypomagnesemia and hypermagnesemia. Rev Endoc Metab Disord. 2003; 4:195-206.

[84] *Onishi S, Yashino S*. Chatartic-induced fatal hypermagnesemia in the elderly. Intern Med. 2006;45:207-10.

[85] *Oren S, Rapaport, Zlotnik M*, et al. Extreme hypermagnesemia due to ingestion of Dead Sea water. Nephron. 1987;47:199-201.

[86] *Huey CG, Chan KM, Eong ET*. Los Angeles County – university of Southern California Medical center clinical pathology case conference: extreme hypermagnesemia in a neonate. Clin Chem. 1995;41:615-8.

[87] *Ali A, Walentik C, Mantych GJ*, et al. Iatrogenic acute hypermagnesemia after total parenteral nutrition infusion mimicking septic shock syndrome: two case reports. Pediatrics. 2003;112:e70-e72.

[88] *Pham PC, Pham PM, Pham SV*, et al. Hypomagnesemia in patients with type 2 diabetes. Clin J Am Soc Nephrol. 2007;2:366-73.

[89] *Barbagallo M, Dominguez LJ*. Magnesium metabolism in type 2 diabetes mellitus, metabolic syndrome and insulin resistance. Arch Biochem Biophys. 2007;458:40–7.

[90] *Larsson SC, Wolk A*. Magnesium intake and risk of type 2 diabetes: a meta-analysis. J Intern Med. 2007;262:208–14.

[91] *Tosiello L*. Hypomagnesemia and diabetes mellitus: a review of clinical implications. Arch Intern Med. 1996;156:1143-8.

[92] *Belin RJ, He K*. Magnesium physiology and pathogenic mechanisms that contribute to development of metabolic syndrome. Magnes Res. 2007;20:107-29.

[93] *Guerrero-Romero F, Rodriguez-Moran M*. Hypomagnesemia, oxidative stress, inflammation, and metabolic syndrome. Diabetes Metab Res Rev. 2006;22:471–6.

[94] *Lelovics Z*. Relation between calcium and magnesium intake and obesity. Asia Pac J Clin Nutr. 2004;13:S144.

[95] *Guerero-Romero F, Bermudes-Pena C, Rodriguez-Moran M*. Severe hypomagnesemia and low – grade inflammation in metabolic syndrome. Magnes Res. 2011;24:45-53.

[96] *Yogi A, Callera GE, Antunes TT*, et al. Vascular biology of magnesium and its transporters in hypertension. Magnes Res. 2010;23:207-15.

[97] *Gums JG*. Magnesium in cardiovascular and other disorders. Am J Health Syst Pharm. 2004; 61:1569-76.

[98] *Geiger H, Wanner C*. Magnesium in disease. Clin Kidney J. 2012;5(suppl 1):i25-i38.

[99] *Millane TA, Ward DE, Camm AJ*. Is hypomagnesemia arrhythmogenic? Clin Cardiol. 1992;15:103-8.

[100] *Agus MSD, Agus ZS*. Cardiovascular actions of magnesium. Crit Care Clin. 2001;17:175-86.

[101] *Parika H, Toivonen L, Naukharinen V*, et al. Decreases by magnesium QT dispersion and venricular arrhytmias in patients with acute myocardial infarction. Eu Heart J. 1999;20:111-20.

[102] *Itoh K, Kawasaki K, Nakamura K*. The effects of high oral magnesium supplementation on blood pressure, serum lipids and related variables in apparently healthy japanese subjects. British J Nutrition. 1997,78:737-50.

[103] *Guerrero-Romero F, Rodriguez-Morian M*. The effect of lowering blood pressure by magnesium supplementation in diabetic hypertensive adults with low serum magnesium levels: a randomized, double-blind, placebo-controlled clinical trial. J Human Hypertens. 2009;23:245–51.

[104] *Laurant P, Touyz RM*. Physiological and pathophysiological role of magnesium in the cardiovascular system: implications in hypertension. J Hypertens. 2000;18:1177-91.

[105] *Corica F*, *Allegra A*, *Ientile R*, et al. Magnesium concentrations in plasma, erythrocytes, and platelets in hypertensive and normotensive obese patients. Am J Hypertens. 1997;10:1311-3.

[106] *Touyz RM*. Magnesium and hypertension. Curr Opin Nephrol Hypertens. 2006;15:141-4.

[107] *Antman EM*. Magnesium in acute myocardial infartction: overview of available evidence. Am Heart J. 1996;132:487-95.

[108] *Reffelmann T*, *Kloner RA*. The "no-reflow" phenomenon: basic science and clinical correlates. Heart. 2002;87:162-8.

[109] *Woods KL*, *Abrams K*. The importance of effect mechanism in the design and interpretation of clinical trials: the role of magnesium in acute myocardial infarction. Prog Cardiovasc Dis. 2002;44:267-74.

[110] *Rayssiguier Y*, *Noe L*, *Etienne J*, et al. Effect of magnesium deficiency on postheparin lipase activity and tissue lipoprotein lipase in the rat. Lipids. 1991; 26:182-6.

[111] *Nozue T*, *Ide N*, *Okabe H*, et al. Correlation of serum HDL-cholesterol and LCAT levels with the fraction of ionized magnesium in children. Magnes Res. 1999;12:297-301.

[112] *Gupta VH*. Intravenous Magnesium for Neuroprotection in Acute Stroke: Clinical Hope Versus Basic Neuropharmacology. Stroke. 2004;35:2758-9.

[113] *Auer RN*. Non-pharmacologic (physiologic) neuroprotection in the treatment of brain ischemia. Ann N Y Acad Sci. 2001;939:271-82.

[114] *Ginsberg, MD*. Neuroprotection for ischemic stroke: past, present and future. Neuropharmacology. 2008;55:363–89.

[115] *Muir KW*. Magnesium in stroke treatment. Postgrad Med J. 2002;78:641-5.

[116] *Larsson SC*, *Orsini N*, *Wolk A*. Dietary magnesium intake and risk of stroke; a meta-analysis of prospective studies. Am J Clin Nutr. doi:10.3945/ajcn.111.022376

[117] *Meloni BP*, *Zhu H*, *Knuckey NW*. Is magnesium neuroprotective following global and focal cerebral ischaemia? A review of published studies. Magnes Res. 2006;19:123-37.

[118] *Meloni BP*, *Campbell K*, *Zhu H*, et al. In search of clinical neuroprotection after brain ischaemia: the case for mild hypothemia (35 degrees C) and magnesium. Stroke. 2009;40:2236-40.

[119] *Mauskop A*, *Altura BM*. Role of magnesium in the pathogenesis and treatment of migraines. Clin Neurosci. 1998;5:24-7.

[120] *Trauninger A*, *Pfund Z*, *Koszegi T*, et al. Oral magnesium load test in patients with migraine. Headache. 2002;42:114-9.

[121] *Mauskop A*, *Varughese J*. Why all migraine patients should be treated with magnesium. J Neural Transm. 2012;119:575-9.

[122] *Rude RK*. Magnesium deficiency: a cause of heterogeneous disease in humans. J Bone Miner Res. 1998;13:749-58.

[123] *Simini B*. Magnesium sulphate for tetanus. Lancet. 2006;368:1398-9.

[124] *Durlach J, Bac P, Durlach V*, et al. Neurotic, neuromuscular and autonomic nervous form of magnesium imbalance. Magnes Res. 1997;10:169-95.

[125] *Sojka JE, Weaver CM*. Magnesium supplementation and osteoporosis. Nutr Rev. 1995;53:71-4.

[126] *Abbott L, Nadler J, Rude RK*. Magnesium deficiency in alcoholism: Possible contribution to osteoporosis and cardiovascular disease in alcoholics. Alcoholism: Clin Exp Res. 1994;18:1076–82.

[127] *Rude RK, Gruber HE*. Magnesium deficiency and osteoporosis: animal and human obsevationsJNutr Biochem. 2004;15:710-6.

[128] *Rude RK, Singer FR, Gruber HE*. Skeletal and hormonal effects of magnesium deficiency. J Am Coll Nutr. 2009;28:131-41.

[129] *Zervas E, Papatheodorou G, Psathakis K*, et al. Reduced intracellular magnesium concentrations in patients with acute asthma. Chest. 2003;123:113-8.

[130] *Cheuk DK, Chau TC, Lee SL*. A meta-analysis on intravenous magnesium sulphate for treating acute asthma. Arch Dis Child. 2005;90:74-7.

[131] *McLean RM*. Magnesium and its therapeutic uses; a review. Am J Med. 1994;96:63-76.

[132] *Turner JA*. Diagnosis and managament of pre-eclampsia: an update. Int J Womens Health. 2010;2:327-7.

[133] Nimodipine Study Group, *Belfort MA, Anthony J, Saade GR*, et al. A comparison of magnesium sulfate and nimodipine for the prevention of eclampsia. N Engl J Med. 2003;348:304-11.

[134] *Lowe SA, Brown MA, Dekker DA*, et al. Guidelines for the managament of hypertensive disorders of pregnancy 2008. Aust N Z J Obstet Gynecol. 2009;49:242-6.

[135] *Lew M, Klonis E*. Emergency managament of eclampsia and severe pre-eclampsia. Emerg Med (Fermantle). 2003;15:361-8.

[136] *Castiglioni S, Maier JA*. Magnesium and cancer: a dangerous liason. Magnes Res. 2011;24:S92-100.

[137] *Cittadini A*. Magnesium and neoplasia: from carcinogenesis to tumor growth and progression or treatment. Arch Biochem Biophys. 2007;458:24-32.

[138] *Sakarya ST, Akyol Y, Bedir A*, et al. The relationship between serum antioxidant vitamins, magnesium levels, and clinical parameters in patients with primary fibromyalgia syndrome. Clin Rheumatol. 2011;30:1039-43.

[139] *Kim YS, Kim KM, Lee DJ*, et al. Women with fibromyalgia have lower levels of calcium, magnesium, iron and manganese in hair mineral analysis. J Korean Med Sci. 2011;26:1253-7.

[140] *Nagai N, Fukuhata T, Ito Y*. Effect of Magnesium Deficiency on Intracellular ATP Levels in Human Lens Epithelila Cells. Biol Pharm Bull. 2007;30:6-10.

[141] *Agarwal R, Iezhitsa I, Agarwal P*, et al. Magnesium deficiency: does it have a role to play in cataractogenesis? Exp Eye Res. 2012; doi10.106/j.exer.2012.05.008.

[142] *Morton A*. Magnesium sulphate for pheochromocytoma crisis. Emerg Med Australs. 2007;19:482.

[143] *Bryskin R, Weldon BC*. Dexmedetomidine and magnesium sulphate in the perioperative managament of child undergoing laparoscopic resection of bilateral pheochromocytomas. J Clin Anesth. 2010;22:126-9.

[144] *Blach J, Nowacki W, Mazur A*. Magnesium in skin allergy. Postepy Hig Med Dosw. 2007;61:548-5.

[145] *Skotnicki AB, Jablonski MJ, Musiat J*, et al. The role of magnesium in pathogenesis and therapy of bronchial asthma. Przegl Lek. 1997,54:630-3.

[146] *Rosenlund H, Magnusson J, Kull I*, et al. Antioxidant intake and allergic disease in children. Clin Exp Allergy. 2012;42:1491-500.

[147] *Mathew R, Altura BM*. The role of magnesium in lung diseases: asthma, allergy and pulmonary hypertension. Magnes Trace Elem. 1991-1992,10:220-8.

[148] *Durlach J*. Magnesium and allergy: experimental and clinical relationship between magnesium and hypersensitivity. Rev Franc Allergol. 1975;15:133-46.

[149] *Weglicki WB, Mak IT, Kramer JH*, et al. Role of free radicals and substance P in magnesium deficiency. Cardiovasc Res. 1996;31:677-82.

[150] *Mak IT, Stafford R, Weglicki WB*. Loss of red blood cell glutathione during Mg deficiency: prevention by vitamin E, D-propranolol, and chloroquine. Am J Physiol. 1994;267:C1366-C1370.

[151] *Wazny LD, Brophy DF*. Amiloride for prevention of amphotericin B-induced hypokalemia and hypomagnesemia. Ann Pharmacother. 2000;34:94-7.

[152] *Lajer H, Daugaard G*. Cisplatin and hypomagnesemia. Cancer Treat Rev. 1999;25.47-58.

[153] *Broeren MA, Geerdink EA, Vader HL*, et al. Hypomagnesemia induced by several proton.pump inhibitors. Ann Intern Med. 2009;151:755-6.

[154] *Florentin M, Elisaf MS*. Proton pump inhibitor – induced hypomagnesemia: A new challenge. World J Nephrol. 2012;1:151-4.

[155] *Ryan MP*. Diuretics and potassium/magnesium depletion: directions for treatment. Am J Med. 1987;82(Suppl 3A):38-47.

[156] *Thompson CB, June CH, Sullivan KM*, et al. Association between cyclosporin neurotoxicity and hypomagnesemia. Lancet. 1984;2:1116-20.

[157] *Touyz RM*. Magnesium in clinical medicine. Front Biosci. 2004;9:1278-93.

[158] *Maj-Zurawska M*. Clinical findings on human blood with the KONE ISE for Mg^{2+}. Scand J Clin Lab Invest (Suppl). 1994;317:69-76.

[159] *Witkowski M, Hubert J, Mazur A*. Methods of assessment of magnesium status in humans: systematic review. Magnes Res. 2011;24:163-80.

[160] *Martin BJ, Lyon Td, Walker W*, et al. Mononuclear blood cell magnesium in older subjects: evaluation of its use in clinical practice. Ann Clin Biochem. 1993;30(pt1):23-7.

[161] *Kisters K, Krefting ER, Barenbrock M*, et al. Na^+ and Mg^{2+} contents in smooth muscle cells in spontaneously hypertensive rats. Am J Hypertens. 1999;12:648-52.

[162] *Ryzen E, Elbaum N, Singer FR*, et al. Parenteral magnesium tolerance testing in the evaluation of magnesium deficiency. Magnesium. 1985;4:137-47.

[163] *Zhang W*. Point of Care Testing. of Ionized Magnesium in Blood with Potentiometric Sensors – opportunities and Challenges. Am J Biomed Sci. 2011;34:301-12.

[164] *Ramkumar D*, Rao SS. Efficacy and safety of traditional medical therapies for chronic constipation: systematic review. Am J Gastroenterol. 2005,100:936-71.

Sažetak

Magnezij – više od običnog kationa

Magnezij je kation koji je vrlo bitan, nezamjenjiv, za brojne aspekte biologije stanice. Ta se tvrdnja najbolje zrcali u činjenici da je nezamjenjivi kofaktor za više od 300 enzimskih reakcija, uključujući najveći broj onih koje upotrebljavaju ATP kao izvor energije. Samo oko 1% ukupnog magnezija u organizmu čovjeka nalazi se u plazmi. Normalne koncentracije kreću se od 0.75 do 1.00 mmol/L.

Smanjena, odnosno povećana, koncentracija magnezija u plazmi naziva se hipomagnezijemija, odnosno hipermagnezijemija. Hipomagnezijemija može biti za život opasno stanje koje treba brzo sanirati povećanim (i.v.) unosom magnezija. Danas je poznato da, uz kliničku hipomagnezijemiju, vrlo često postoji i „nevidljiv" deficit magnezija u tkivima. Najčešće se javlja kao posljedica moderne prehrane, koja često ne zadovoljava dnevne preporučene doze (> 300mg dnevno). Kliničke studije pokazuju da su bolesti poput metaboličkog sindroma, dijabetesa tipa 2, nekih aritmija te hipertenzije, u pogledu pojavnosti i težine obolijevanja, u obrnutoj korelaciji s magnezijskim statusom organizma. Stoga je dodavanje magnezija prehrani jedna od mogućnosti pozitivnog utjecaja na spomenute bolesti. Od budućih kliničkih studija očekuje se jasna procjena opravdanosti magnezija kao dodatka prehrani i u nekim drugim bolestima i sindromima (migrena, fibromijalgija, bolest koronarnih arterija, kronični sindrom umora).

Ključne riječi: magnezij; hipomagnezijemija; hipermagnezijemija; terapijske aplikacije magnezija.

Corresponding author:
Ivana Čepelak
E-mail: ivcepelak@gmail.com