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BIOLOGICAL ROLE OF MAGNESIUM IN HEALTH, DISEASE AND EXERCISE

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Abstract

There is an enormous amount of data concerning the role of magnesium in health, disease and exercise capacity. More than 350 enzymes, in addition to those involved in metabolic cycles, appear to require and to be regulated by magnesium. Furthermore, magnesium affects many cellular functions, including transport of potassium and calcium ions, signal transduction, hormone secretion, energy metabolism and cell proliferation. However, the diagnosis of magnesium status is still under debate mostly due to the lack of functional biomarkers of body magnesium stores. It seems likely that magnesium deficiency contributes to the development of hypertension, type 2 diabetes and various cardiac diseases. At least in 20% of the population daily magnesium intake is suboptimal. Highly active subjects and especially elite sportsmen are at greater risk of magnesium deficiency due to ion losses in sweat and urine. Data concerning magnesium effects on exercise capacity are equivocal. A beneficial effect of magnesium supplementation on strength and endurance has been recognized in some studies. Concomitantly, the lack of effects of dietary magnesium intake on performance has also been demonstrated. However, assuming increased magnesium losses due to intensive physical activity, magnesium supplementation may be useful, at least in athletes with suboptimal magnesium intake. This is especially true for female athletes, who frequently do not consume adequate energy relatively to expenditure.

Key words: magnesium, muscle contraction, deficiency, health risk, exercise capacity

Introduction

The essential character of magnesium for humans has been acknowledged since the 1920's and since then an enormous amount of investigation have focused on the role of magnesium in health and disease (1). It is well documented that more than 350 enzymes, in addition to those involved in metabolic cycles, appear to require and be regulated by magnesium (2). In addition, magnesium affect many cellular functions, including transport of potassium and calcium ions, and modulates signal transduction, hormone secretion, energy metabolism and cell proliferation (3, 4).

However, the diagnosis of magnesium status is still under debate mostly due to the lack of functional biomarkers of body magnesium stores (5-8).

On the other hand, in developed countries marginal primary magnesium deficit is not uncommon and affects 15-20% of the population and is now believed to contribute to many diseases (metabolic syndrome, type 2 diabetes, myocardial infraction, hypertension) and its role as a therapeutic agent has been tested in numerous clinical trials (9-12).

Despite the above mentioned indispensability of magnesium in metabolic processes, the mechanism of its homeostasis, turnover and precise role in myocardium, striated muscle, in the regulation of insulin sensitivity and nervous system action is still subject of intensive research.

Magnesium distribution and turnover in the body

The total magnesium content in the human body is 20-28 g. About 60% of total magnesium builds up the bone structure, and the remaining about 40% is in other tissues (13). Blood and interstitial fluid magnesium makes up about 1% of its total body content (14). Magnesium concentration in body fluids and erythrocytes according to Durlach (15) is presented in Table 1.

At present it is well documented that magnesium undergoes constant exchange between different body compartments. According to Feillet-Coudray el al. (16) in healthy women exchangeable magnesium pools represents 11-12% of total body magnesium

Table 1. Physiological concentration in body fluids and erythrocytes (according to 15)

	Magnesium concentration($mmol \cdot l^{-1}$)
Plasma	0.88 ± 0.05
Sweat	0.25-0.29
Saliva	approx. 0.44
Cerebro-spinal fluid	1.03-1.24
Seminal fluid	approx. 4.4
Erythrocytes	2.30 ± 0.24

on the basis of multicompartmental analysis. Additionally, research has demonstrated that 25% of total magnesium exchanges rapidly from the plasma compartment with two extraplasmatic pools (17) One of the extraplasmatic compartments contains 80% of the exchangeable magnesium with a transport rate approximately 48 $mg \cdot h^{-1}$, the second – exchanges 179 mg of magnesium per hour (18).

These data highlight why the determination of plasma magnesium is not a reliable measure of magnesium status in the body.

Determination of magnesium status

As was mentioned earlier, so far there is no simple method to determine magnesium body stores and to recognize magnesium deficiency. Due to ion exchange between different compartments plasma magnesium does not reflect magnesium status. Moreover, total plasma magnesium undergoes circadian changes, which markedly differ with respect to sex (19). In males the highest plasma magnesium levels were observed in the afternoon, and the lowest – in the morning. In females two peaks were noted – in the afternoon and again at night, but the lowest levels were observed in the evening and in the morning. Thus, it is difficult to recognize which plasma magnesium levels reflect true ion status.

On the other hand, it is well known that total plasma magnesium is composed of three fractions – ionized (or free) magnesium, protein bound magnesium and a complex bound fraction. Külpmann and Gerlach (20) have demonstrated that total and ionized magnesium were correlated only in marked hypermagnesemia and poorly correlated in slight hypermagnesemia or in hypomagnesemia and the relationship was dependent on plasma protein concentration. Additionally, Ising et al. and Newhouse et al. (21, 22) have noted that ionized magnesium undergoes circadian rhythm and biological variability accounts for almost half of the variability in ionized magnesium levels. Thus, neither total nor ionized plasma magnesium seems to be a reliable index of magnesium status.

Feillet-Coudray et al. and Coudray et al. (23, 24) have indicated that the determination of the rapidly exchangeable magnesium pool using Mg isotopes is a reliable index of magnesium status since it responds to the fluctuation in dietary magnesium.

Rudziński et al. (25) proposed a magnesium loading test and magnesium determination in daily urine as a good measure of magnesium status. However, the drawback of this method is prolonged (8 h) intravenous magnesium infusion. The authors proposed a modification of the test by diminishing an Mg^{+2} dose and shorter infusion (4 h), but even then the method is too complicated to be applied in routine practice. Similarly, Walti et al. (26) used intravenous Mg^{26} infusion and determination of urinary magnesium excretion as an indicator of marginal magnesium deficiency.

Moreover, the above mentioned methods are complicated, time-consuming and do not seem to be useful in clinical practice.

Since almost 99% of the body magnesium is inside the cells, Malon et al. (27) have proposed the determination of ionized magnesium in erythrocytes as an index of magnesium status due to its response to both hyper-and hypomagnesemia and this method is simpler than the magnesium load test or the determination of exchangeable magnesium pool.

Magnesium homeostasis

Regulation of the total body magnesium balance principally resides within the kidney that tightly matches the intestinal absorption of magnesium (28). In the kidney approximately 80% of the total plasma magnesium is ultrafiltrated across the glomerular membrane and subsequently reabsorbed in consecutive segments of the nephron. Approximately 10 to 20% of Mg^{+2} is reabsorbed in proximal tubules, the remaining 50-70% in the loop of Henle.

Until recently the mechanisms of magnesium transport in the kidney and intestine were obscure. However, at present research has documented that two members of transient receptor potential family (TRP) named TRPM6 and TRPM7 contribute to Mg^{+2} epithelial transport and are prime targets for hormonal control of magnesium flux from the urine or intestinal lumen to the blood (29).

However, it should be stressed that Mg^{+2} homeostasis is tightly coordinated with calcium (Ca^{+2}) balance and regulated in concert by parathyroid glands, bone, kidney and intestine. Under conditions of both calcium and magnesium deprivation their intestinal absorption and kidney reabsorption increase (30-32). If depletion continues, then the bone store assists in maintaining appropriate plasma levels by exchanging part of its content with the extracellular fluid. The Ca^{+2} - sensing receptor (CaSR) represents the molecular mechanism by which parathyroid glands detect changes in the ionized calcium and magnesium levels and modulate PTH secretion (33, 34). In addition to the effects of both cations on PTH secretion, this hormone in turn regulates directly the calcium and magnesium balance by modulation of bone resorption, renal reabsorption, and indirectly Ca^{+2} and Mg^{+2} intestinal absorption by stimulation of vitamin D synthesis.

Dietary magnesium – absorption and interactions

In human nutrition whole grain products are the main source of dietary magnesium (35). However, the highest magnesium content has been found in legumes, soya beans, in rice, and chocolate (13). Hard mineral

waters (magnesium content approx. 110 mg·l^{-1}) are also an important source of magnesium (36, 37).

Magnesium absorption from the diet occurs mainly from ileum and colon and is tightly regulated by ion intraluminal content (32, 38, 39). At low intraluminal concentrations magnesium is absorbed primarily via the active transcellular, saturable route, and, with rising concentrations, via the paracellular pathway, yelding a curvilinear function for total absorption, however, total magnesium absorption increases proportionally with increasing dietary Mg^{+2+} (40).

However, intestinal magnesium absorption is also subject to complicated interactions with other dietary components especially calcium and phosphorus (41, 42).

Moreover, fiber, phytic acid and oxalate are potent inhibitors of intestinal Mg^{+2} absorption (43-47). On the other hand, research has demonstrated that non-digestible, but fermentable oligosaccharides (NOD - gums, pectin, inulin, lactulose, oligofructose) improve mineral absorption (48-51).

The increased absorption of minerals, including magnesium after NOD consumption takes place in the cecum and colon but not in the small intestine (52). The precise mechanism of their action in not fully understood and probably includes NOD fermentation, elevation of bifidobacteria content and production of short-chain fatty acids resulting in pH decrease and increase in mineral solubilization. The NODs probably also act at the villus level increasing the villus crypt height, number of epithelial cells per crypt and at the cellular level affecting expression of mineral transporting proteins.

However, at present our knowledge concerning dietary Mg^{+2} effects and its bioavailability on cation content in different tissues is limited. In the rat Zimmermann et al. (53) have revealed that magnesium deficiency (70 ppm daily magnesium) brings about the elevation in serum and heart ionized Mg^{+2} in comparison with a high magnesium diet (9000 ppm). In contrast, magnesium deficiency depressed skeletal muscle magnesium content in contrast to high magnesium diet. Both low and high magnesium diets lowered liver cation content. Additionally, total magnesium in the heart and skeletal muscle was positively and significantly correlated with total calcium content. The above data indicated that soft tissues may have regulatory mechanisms that compensate the deficiency in dietary magnesium whereas calcium seems to play a substantial role in the regulation of tissue Mg^{+2} stores.

Energy shuttling and magnesium

It is well recognized that in the cell ATP is bound to Mg^{+2} and exclusively in this form contributes to energy-requiring processes. (54). Intracellular magnesium regulates ADP phosphorylation and also adenine nucleotide synthesis in the pentose phosphate pathway (55). Moreover, phosphorylated glycolytic intermediate concentrations were also strongly dependent on both Mg^{+2} and Mg-ATP levels (56). Furthermore, Mg^{+2} has been found to contribute to the regulation of a key glycolytic enzyme – phosphofructokinase, allosterically inhibited by high concentrations of magnesium (57). Additionally, magnesium affects mitochondrial $F_1 F_0$ - ATP-ase activity, the most abundant source of ATP synthesis in humans (58, 59).

Summing up, magnesium is indispensable in energy provision in different ATP-generating systems.

Magnesium and muscle contraction

Magnesium plays a vital role in the regulation of contraction in smooth, cardiac and striated muscle and its role in muscle contraction is still a matter of intensive studies.

Smooth muscle

NMR studies have revealed that the Mg^{+2} concentration in smooth muscle is highly conserved within a limited range (60).

It is well documented that myogenic tone of cerebral vessels is strongly dependent on plasma Mg^{+2} concentrations and magnesium is believed to play an important role in the autoregulation of cerebral blood flow (61, 62). Collectively, these studies suggest that a decreased content of magnesium will increase cerebrovascular tone and may induce vasospasmic responses.

A recent study has demonstrated that in isolated canine basilar arteries low to medium magnesium induces contractions due to elevation in calcium concentration (63). Interestingly, the low magnesium effect increasing contractile tension was impaired by pretreatment of the arteries with genistein - an inhibitor of tyrosine kinase and with specific inhibitors of mitogen activated protein kinase (MAPK). The above data suggest that low magnesium disturbs several signaling pathways in canine basilateral arteries.

In addition, magnesium removal has been found to impair the regulatory role of endothelium in isolated femoral arteries of normotensive rats (64). After removal of magnesium from the external medium the noradrenaline-induced contraction was markedly augmented. On the other hand, after removal of endothelium noradrenaline effect was enhanced exclusively in magnesium-free solution. Thus, it has been suggested that magnesium plays an important role in the regulation endothelium-dependent vessel response to noradrenaline.

The precise mechanism of magnesium action in the regulation of blood vessel tone has not been fully elucidated, however it probably includes both Ca^{+2}

antagonism as well as the stimulation of nitric oxide synthase activity and promotes nitric oxide synthesis (65-67).

It has been also demonstrated that magnesium elicits a potent relaxing action in isolated rabbit tracheal strips (68). When potassium chloride was used as a constrictor agent Mg^{+2} caused a full relaxation of the tracheal muscle, but acetylcholine contraction was abolished in 55%. Based on the knowledge that both potassium chloride and acetylcholine cause Ca^{+2} mobilization, it was postulated that magnesium inhibits calcium flux by blocking calcium channels in the cells.

Cardiac muscle

Even small changes in intracellular free Mg^{+2} may have important effects on cardiac excitability and contractility, however, the mechanism of magnesium action has not been fully elucidated.

Research has demonstrated that magnesium deficiency induces an increase in intracellular calcium and promotes the imbalance of sodium and potassium in cardiomyocytes (69, 70). The force of contraction of papillary muscle in Mg^{+2} deficient medium was about 1.6 times greater than that of control (71). The opposing effects of Mg^{+2} and Ca^{+2} on myocardial contractility are probably due to the competition between both cations for the same binding sites on key contractile proteins such as troponin C, myosin and actin (72, 73). However, Zhu et al. (74) have indicated that Ca^{+2} and Mg^{+2} effects on myosin ATP-ase were different and Mg^{+2} was essential to maintain the conformation of myosin in cardiac muscle, whereas Ca^{+2} was likely to play a regulatory function.

However, magnesium action in the heart is not limited to the regulation of contractility. In vitro studies have revealed anti-infract magnesium action in isolated rat and rabbit hearts, probably due to promotion of adenosine synthesis or to Mg^{+2} action on adenosine receptors (75-77). Magnesium deficiency has been found to induce cardiac fibrogenesis in the rat probably due to augmented both circulating and cardiac angiotensin II levels and elevated rennin activity (78).

Skeletal muscle

In striated muscles, similarly to smooth and cardiac muscle, Mg^{+2} seems to play a pivotal role in the regulation of muscle contraction, however, not all details of its action are fully elucidated. In isolated sarcoplasmic vesicles it has been shown that magnesium as Mg-ATP complex increases Ca^{+2} - release channel sensitivity, thus contributing to the initiation of muscle contraction (79). This finding was further supported by Blazev and Lamb (80) who demonstrated that in rat skinned muscle fibres depolarization-induced Ca^{+2} release is modulated by the concentration of ATP as well as by free magnesium. Additionally, Mg^{+2} seems to activate the opening of Ca^{+2}-dependent K+ channels - essential for neuronal activity and modulation of muscle contraction (81). Recent data have indicated that the role of Mg^{+2} in excitation-contraction coupling is due to its interaction with the calcium - sensitive ryanodine receptor (RYR) (82). In the resting muscle RYR activation by Ca^{+2} is strongly inhibited by Mg^{+2} preventing uncontrolled Ca^{+2} - induced Ca^{+2} release between periods of activation. Physiological Ca^{+2} release and initiation of contraction is falicitated by a decrease in the affinity for Mg^{+2} binding to RYR (83).

Considering all the above mentioned effects of magnesium in smooth, cardiac and striated muscle it becomes clear that despite counteracting calcium action, magnesium plays an independent and important role in the regulation of excitation-contraction coupling.

Health risk of magnesium deficiency

Osteoporosis

As was mentioned earlier magnesium is an essential component of the bone. In addition, magnesium is required for the synthesis of calcitriol, the active form of vitamin D and normal calcium transport and utilization (84). Recent data have indicated that magnesium deficiency increases osteoclast number and potentiates bone resorption (85). There is a wealth of animal and human studies indicating that magnesium deficiency contributes to decreased bone density and subsequent osteoporosis (886-88). On the other hand, in menopausal females magnesium supplementation has been noted to improve bone density and to prevent fractures (89).

Diabetes

Early animal data have demonstrated insulinomimetic effects of magnesium and stabilization of post-meal blood glucose in diabetic rats after magnesium supplementation in the drinking water (90). The effect of prolonged magnesium treatment on glucose disposal was also tested in normal and diabetic rats (91). In normal animals magnesium did not affect glucose utilization. In contrast, in diabetic animals magnesium induced a small increase in the glycolytic pathway.

However, in humans research data concerning magnesium effects on glucose disposal are equivocal. Lal et al. (92) did not observe any effect of oral magnesium supplementation on glucose metabolism in patients with type 2 diabetes. On the contrary, Rodriguez-Moran (93) and Guerrero-Romero (94) noticed an improvement in insulin sensitivity expressed as HOMA-IR in hypomagnesemic subjects with type 2 diabetes in response to magnesium treatment.

It should be stressed that hypomagnesemia is observed in approximately 40% of diabetic subjects (95) probably due to decreased cation absorption, re-

absorption and depressed influx into the cells (96-98). Thus, it could not be excluded that beneficial effects of magnesium supplementation on glucose homeostasis were observed exclusively in subjects with low magnesium body stores.

On the other hand, numerous data have indicated that there is a close link between magnesium status, insulin resistance and diabetes (99). Epidemiological studies have indicated a significant inverse association between magnesium intake and type 2 diabetes risk in the USA population (100). Similarly, a potential link between magnesium intake and diabetes was noted in Indigenous Australians and elderly Taiwanese (101, 102). An inverse association between dietary magnesium intake, plasma ion level and fasting insulin was observed in obese children, suggesting a possible link between magnesium status and insulin resistance (103, 104).

Magnesium status and plasma lipoproteins

Magnesium is a controlling factor in cholesterol biosynthesis and is necessary for the activity of lipoprotein lipase (LPL) and lecithin cholesterol acyltransferase (LCAT) which lowers triacylglycerol levels and raises HDL-cholesterol concentrations (105).

In diabetic rats magnesium treatment decreased elevated total cholesterol and triacylglycerol levels (106). A similar effect of magnesium supplementation was noted in mice lacking LDL-receptor and fed a high-cholesterol diet together with lesser atherogenic changes at the aortic sinus (107). Magnesium supplementation in apparently healthy subjects resulted in elevation of LCAT activity and HDL-cholesterol concentrations (108).

Thus, it seems feasible that magnesium status may contribute to disturbances in lipoprotein metabolism observed in type 2 diabetes and may improve the lipoprotein profile in healthy subjects.

Cardiovascular effects of magnesium status

Magnesium deficiency is recognized as a cause of disturbances in cardiovascular system function. In animals ECG changes, arrhythmias, valvular malformations, endocardial fibrosis, intima hypertophy, hyperplasia, calcification and edema have been found accompanying magnesium deficiency (109). On the other hand, magnesium infusion decreases systemic vascular resistance and decreases mean blood pressure in sheep (110). A considerable number of experimental, epidemiological and clinical studies are now available which point to an important role of Mg^{+2} deficiency in the etiology for cardiovascular pathology in humans such as ischemic heart disease, congestive heart failure, sudden cardiac death, arrhythmia, hypertension and mitral valve prolapse (11, 111-113). Thus, a wealth of clinical studies have focused on either oral magnesium supplementation in prevention of cardiovascular disease or i.v. infusion in incidents of cardiac dysfunction (114-117).

Magnesium and exercise capacity

Lukaski et al. (118) have noted than in university athletes maximal oxygen uptake significantly correlated with plasma magnesium levels and suggested that magnesium may facilitate oxygen delivery to working muscle. In addition, it has been found that dietary magnesium depletion brings about the elevation in oxygen uptake and heart rate during submaximal exercise in postmenopausal women (119).

On the contrary, magnesium supplementation (varied from 250 mg to 540 $mg \cdot day^{-1}$) has improved muscle strength and endurance, but decreased oxygen consumption, ventilation and heart rate (for review see 120, 121).

However, it is worth noting that Weller et al. (122) and Finstad et al. (123) have not observed any beneficial effects of magnesium supplements on both anaerobic and aerobic physical performance in subjects with low to normal plasma magnesium levels.

Thus, it seems that experimental data concerning magnesium supplementation and physical capacity are equivocal. This may be due to the lack of specific biomarkers of magnesium status and poor diagnostic value of plasma magnesium determination mentioned earlier.

On the other hand, it is well recognized that during intensive physical activity as in high performance sports magnesium body stores may be depleted due to urinary and sweat losses (124). Thus, a significant decrease in plasma magnesium has been observed in response to 25-km and marathon running (125, 126) (Table 2).

Table 2. Recommended magnesium dietary intake and magnesium losses insedentary subjects (13)

Recommended dietary intake	
females	300 mg/day
males	370 mg/day
Excretion	
urine	60-200 mg/24 h
sweat	15 mg/24 h
faeces	1-2 % of total losses

Moreover, there is evidence that dietary magnesium intake in sportsmen may be suboptimal, especially in female athletes (127-129). Nuviala et al. (130) have reported that no group of female athletes (karate, handball, basketball and running) reached the minimal recommended magnesium intake of 280 $mg \cdot day^{-1}$. Similarly low magnesium daily intake has been found

in female volleyball players, mostly due to inadequate energy intake (131).

Thus, magnesium supplementation may be useful at least in athletes with low magnesium daily intake (132). Daily magnesium supplementation in physically active subjects should not exceed 10 $mg \cdot kg^{-1}$ body mass, because excessive magnesium intake has several adverse effects such as muscle weakness, bradycardia, diahrrea, vomiting, hypotension, and insomia (133).

In summary, despite the substantial role of magnesium in the regulation of many metabolic processes (generation of energy, muscle contraction, lipoprotein profile, insulin action) so far there is no reliable method evaluating magnesium status. In general, magnesium daily intake is suboptimal in about 20% of the population. However, highly active subjects and especially elite athletes are at greater risk of magnesium deficiency due to ion losses in sweat and urine. Although data concerning exercise capacity and magnesium status are equivocal, magnesium supplementation may be useful to prevent potential magnesium deficiency.

References

1. Durlach J, Pages N, Bac P. et al. Magnesium research: from the beginning to today. *Magnes Res* 2004; 17: 163-8.
2. Romani AM, Scarpa A. Regulation of cellular magnesium. *Front Biosci* 2000; 5: D720-D34.
3. Saris NE, Mervaala E, Karppanen H. et al. Magnesium. An update on physiological, clinical and analytical aspects. *Clin Chim Acta* 2000; 294: 1-26.
4. Matsuoka H. Aldosterone and magnesium. *Clin Calcium* 2005; 15: 187-91.
5. Durlach J. Present and future of magnesium research. *J Jap Soc Magnesium Res* 1993; 12: 113-35.
6. Spatling L, Classen HG, Kulpmann WR. et al. Diagnosing magnesium deficiency. Current recommendations of the society for magnesium research. *Fortschr Med Orig* 2000; 118: 49-53.
7. Liebscher DH, Liebscher DE. About the misdiagnosis of magnesium deficiency. *J Am Coll Nutr* 2004; 23: S730-S1.
8. Franz KB. A functional biological maker is needed for diagnosing magnesium deficiency. *J Am Coll Nutr* 2004; 23: S738-S41.
9. Durlach J. Recommended dietary amounts of magnesium: Mg RDA. *Magnes Res* 1989; 2: 195-203.
10. Touyz RM. Magnesium in clinical medicine. *Front Biosci* 2004; 9: 1278-93.
11. Gums JG. Magnesium in cardiovascular and other disorders. *Am J Health Syst Pharm* 2004; 61: 1569-76.
12. Murakami K, Okubo H, Sasaki S. Effect of dietary factors on incidence of type 2 diabetes: a systematic review of cohort studies. *J Nutr Sci Vitaminol* 2005; 51: 292-310.
13. Panczenko-Kresowska B, Ziemlański S. Składniki mineralne–ich znaczenie w żywieniu człowieka. In: Ziemlański S. red. Normy żywienia człowieka. Fizjologiczne podstawy. PWZL, Warszawa, 349-62.
14. Quamme GA. Magnesium homeostasis and renal magnsium handling. *Miner Electrolyte Metab* 1993; 19: 218-25.
15. Durlach J. Magnesium in clinical practice. Warsaw, PZWL: 1991 (in Polish).
16. Feillet-Coudray C, Coudray C, Tressol JC. et al. Exchangeable magnesium pool masses in healthy women: effects o magnesium suplementation. *Am J Clin Nutr* 2002; 75: 72-8.
17. Feillet-Coudray C, Coudray C, Gueux E. et al. A new approach to evaluate magnesium ststus: determination of exchangeable Mg pool masses using Mg stable isotope. *Magnes Res* 2002; 15: 191-8.
18. Sabatier M, Pont F, Arnaud MJ. et al. A compartmental model of magnesium metablism in healthy men based on two stable isotope tracers. *Am J Physiol Regul Integr Comp Physiol* 2003; 285: R656-R63.
19. Szyszka A, Brocki Z, Mrozikiewicz A. et al. Circadian changes in levels of magnesium in serum of healthy individuals. *Pol Tyg Lek* 1992; 47: 1078-9.
20. Külpmann WR, Gerlach M. Realtionship between ionized and total magnesium in serum. *Scand J Clin Lab Invest* 1996; 56: 251-8.
21. Ising H, Bertschat F, Gunther T. et al. Measurement o free magnesium in blood, serum and plasma with an ion-sensitive electrode. *Eur J Clin Chem Clin Biochem* 1995; 33: 365-71.
22. Newhouse IJ, Johnson KP, Montelpare WJ. et al. Variability within individuals of plasma ionic magnesium concentrations. *BMC Physiology* 2002; 2: 1-7.
23. Feillet-Coudray C, Coudray C, Brule F. et al. Exchangeable magnesium pool masses reflect the magnesium status of rats. *J Nutr* 2000; 130: 2306-11.
24. Coudray C, Feillet-Coudray C, Rambeau M. et al. Stable isotopes in studies of intestinal absorption, exchangeable pools and mineral status: the example of magnesium. *J Trace Elem Med Biol* 2005; 19: 97-103.
25. Rudziński J, Walasek L, Jurga M. Diagnostics of latent magnesium deficiency in human organism using modified magnesium loading test. *J Elementol* 2002; 7: 35-47.
26. Wälti MK, Walczyk T, Zimmermann MB. et al. Urinary excretion of an intravenous 26Mg dose as an indicator of marginal magnesium deficiency in adults. *Eur J Clin Nutr* 2006; 60: 147-54.
27. Malon A, Brockmann C, Fijalkowska-Morawska J. et al. Ionized magnesium in erythrocytes–the best magnesium parameter to observe hypo-or hypermagnesemia. *Clin Chim Acta* 2004; 349: 67-73.
28. Hoenderop JG, Bindels RJ. Epithelial Ca^{2+} and Mg^{2+} channels in health and disease. *J Am Soc Nephrol* 2005; 16: 15-26.
29. Schlingmann KP, Gudermann T. A critical role of TRPM channel-kinase for human magnesium transport. *J Physiol* 2005; 566: 301-8.
30. Dai LJ, Ritchie G, Kerstan D. et al. Magnesium transport in the renal distal convoluted tubule. *Physiol Rev* 2001; 81: 51-84.
31. Hoenderop JG, Nilius B, Bindels RJ. Molecular mechanism of active Ca2+ reabsorption in the distal nephron. *Annu Rev Physiol* 2002; 64: 529-49.
32. Konrad M, Schlingmann KP, Gudermann T. Insights into the molecular nature of magnesium homeostasis. *Am J Physiol Renal Physiol* 2004; 286: F599-F605.
33. Brown EM, Gamba G, Riccardi D. et al. Cloning and characterization of an extracellular Ca^{2+} sensing receptor from bovine parathyraid. *Nature* 1993; 366: 575-80.
34. Brown EM, MacLeod RJ. Extracellular calcium sensing and extracellular calcium signaling. *Physiol Rev* 2001; 81: 239-97.
35. Lopez HW, Leenhardt F, Remesy C. New data on the bioavailability of bread magnesium. *Magnes Res* 2004; 17: 335-40.
36. Verhas M, de la Gueronniere V, Grognet JM. et al. Magnesium bioavailability from mineral water. A study in adult men. Eur *J Clin Nutr* 2002; 56: 442-7.
37. Sabatier M, Arnaud MJ, Kastenmayer P. et al. Meal effect on magnesium bioavailability from mineral water in healthy women. *Am J Clin Nutr* 2002; 75: 65-71.
38. Schweigel M, Martens H. Magnesium transport in the gastrointestinal tract. *Front Biosci* 2000; 5: D666-D77.
39. Fawcett WJ, Haxby EJ, Male DA. Magnesium: physiology and pharmacology. *Br J Anaesth* 1999; 83: 302-320.
40. Hardwick LL, Jones MR, Buddington RK. et al. Comparison

of calcium and magnesium absorption: in vivo and in vitro studies. *Am J Physiol* 1990; 259: G720-6.
41. Hardwick LL, Jons MR, Brautbar N. et al. Magnesium absorption: mechanisms and the influence of vitamin D, calcium and phosphate. *J Nutr* 1991; 121:13-23.
42. Celotti F, Bignamini A. Dietary calcium and mineral/vitamin supplementation: a controversial problem. *J Int Med Res* 1999; 27: 1-14.
43. Watkins DW, Jahangeer S, Floor MK. et al. Magnesium an calcium absorption in Fischer-344 rats influenced by changes in dietary fibre (wheat bran), fat and calcium. *Magnes Res* 1992; 5: 15-21.
44. Knudsen E, Sandstrom B, Solgaard P. Zinc, copper and magnesium absorption from a fibre-rich diet. *J Trace Elem Med Bio* 1996; 10: 68-76.
45. Rimbach G, Pallauf J. Effect of dietary phytate on magnesium bioavailability and liver oxidant status in growing rats. *Food Chem Toxicol* 1999; 37: 37-45.
46. Bohn T, Davidsson L, Walczyk T. et al. Phytic acid added to white-wheat bread inhibits fractional apparent magnesium absorption in human. *Am J Clin Nutr* 2004; 79: 418-23.
47. Bohn T, Davidsson L, Walczyk T. et al. Fractional magnesium absorption in significantly lower in human subjects from a meal served with an oxalate-rich vegetable, spinach, as compared with a meal served with kale, a vegetable with a low oxalate content. *Br J Nutr* 2004; 91: 601-6.
48. Greger JL. Nondigestible carbohydrates and mineral bioavailability. *J Nutr* 1999; 129: S1434-S5.
49. Tahiri M, Tressol JC, Arnaud J. et al. Five-week intake of short-chain fructo-oligosaccharides increases intestinal absorption and status of magnesium in postmenopausal women. *J Bone Miner Res* 2001; 16: 2152-60.
50. Coudray C, Demigné C, Rayssiguier Y. Effects of dietary fibers on magnesium absorption in animals and humans. *J Nutr* 2003; 133: 1-4.
51. Coudray C, Rambeau M, Feillet-Coudray C. et al. Dietary insulin intake and age can significantly affect intestinal absorption of calcium and magnesium in rats: a stable isotope approach. *Nutr J* 2005; 4:1-8.
52. Scholz-Ahrens KE, Schaafsma G, van den Heuvel E. et al. Efects of prebiotics on mineral metabolism. *Am J Clin Nutr* 2001; 73: S459-S64.
53. Zimmermann P, Weiss U, Classen HG. et al. The impact of diets with different magnesium content on magnesium and calcium in serum and tissues of the rat. *Life Sci* 2000; 67: 949-58.
54. Jiang L, Mao XA. NMR evidence for Mg(II) binding to N1 of ATP. *Spectrochim Acta A Mol Biomol Spectrosc* 2001; 57: 1711-6.
55. Page S, Salem M, Laughlin MR. Intracellular Mg2+ regulates ADP phosphorylation and adenine nucleotide synthesis in human erythrocytes. *Am J Physiol* 1998; 274: E920-E7.
56. Laughlin MR, Thompson D. The regulatory role for magnesium in glycolytic flux of the human erythrocyte. *J Bio Chem* 1996; 271: 28977-83.
57. Buckwitz D, Jacobasch G, Gerth C. Phosphofructokinase from plasmodium berghei. Influence of Mg^{2+}, ATP and Mg^{2+}-complexed ATP. *Biochem J* 1990; 267: 353-7.
58. Weber J, Hammond ST, Wilke-Mounts S. et al. Mg^{2+} coordination in catalytic sites of F1-ATPase. *Biochemistry* 1998; 37: 608-14.
59. Vinogradov AD. Steady-state and pre-steady-state kinetics of the mitochondrial F_1F_0 ATPase: is ATP synthase a reversible molecular machine? *J Exp Biol* 2000; 203: 41-9.
60. Nakayama S, Clark JF. Smooth muscle and NMR review: an overview of smooth muscle metabolism. *Mol Cell Biochem* 2003; 244: 17-30.
61. Altura BM, Altura BT, Carella A. et al. Mg^{2+} and Ca^{2+} interaction in contractility of vascular smmoth muscle: Mg^{2+} vs organic calcium channel blockers on on myogenic tone and against-induced responsiveness of blood vessels. *Can J Physiol Pharmacol* 1987; 338: R7-R9.
62. Altura BT, Altura BM. The role of magnesium in etiology of strakes and cerebrovasospasm. *Magnesium* 1982; 1: 241-65.
63. Yang Z, Wang J, Zheng T. et al. Low $[Mg^{2+}]0$ induces contraction of cerebral arteries: roles of tyrosine and mitogen-activated proein kinase. *Am J Physiol Heatr Circ Physiol* 2000; 279: H185-H94.
64. Miyagawa K, Dohi Y, Kojima M. et al. Magnesium removal impairs the regulatory role of rat endothelium. *Hypertens Res* 2000; 23: 669-75.
65. Teragawa H, Matsuura H, Chayama K. et al. Mechanisms responsible for vasodilation upon magnesium infusion in vivo: clinical evience. *Magnes Res* 2002; 15: 241-6.
66. Volpe MA, Carneiro JJ, Magna LA. et al. The role of magnesium in the endothelial dysfunction caused by global ischemia followed by reperfusion: in vitro study of canine coronary arteries. *Scand Cardiovasc J* 2003; 37: 288-96.
67. Maier JA, Bernardini D, Rayssiguier Y. et al. Hihg concentractions of magnesium modulate vascular endothelial cell behaviour in vitro. *Biochim Biophys Acta* 2004; 1689: 6-12.
68. Gourgoulianis KI, Chatziparasidis G, Chatziefthimiou A. et al. Magnesium as a relaxing factor of airway smooth muscles. *J Aerosol Med* 2001; 14: 301-7.
69. Kurabayashi M. Role of magnesium in cardiac metabolism. *Clin Calcium* 2005; 15: 77-83.
70. Iezhitsa IN. Potassium and magnesium depletions in congestive heart failure-pathophysiology, consequences and replenishment. *Clin Calcium* 2005; 15: 123-33.
71. Manju L, Nair RR. Reduction of perifusate magnesium alters inotropic response of papillary muscle to ion channel modulators. *Magnes Res* 2005; 18: 1699.
72. Finley N, Dvoretsky A, Rosevear PR. Magnesium-calcium exchange in cardiac troponin C bound to cardiac troponin I. *J Mol Cell Cardiol* 2001; 32: 1439-46.
73. Smith GA, Vandenberg JI, Freestone NS. et al. The effect of Mg^{2+} on cardiac muscle function: Is CaATP the substrate for priming myofibril cross-bridge formation and Ca^{2+} reuptake by the sarcoplasmic reticulum? *Biochem J* 2001; 354: 539-51.
74. Zhu B, Wan CM, Liu RT. et al. Effects of Ca^{2+} and Mg^{2+} on the enzymatic properties of cardiac muscle myosin. *Space Med Med Eng* 2002; 15: 355-8.
75. Mallet RT, Sun J, Fan WL. et al. Magnesium activated adenosine formation in intact perfused heart: predominance of ecto 5'-nucleotidase during hypermagnesemia. *Biochim Biophys Acta* 1996; 1290: 165-76.
76. Matsusaka T, Hasebe N, Jin YT. et al. Magnesium reducs myocardial infarct size via enhancement of adenosine mechanism in rabbits. *Cardiovasc Res* 2002; 54: 568-75.
77. Ebrahimi S, Faghihi M, Keshavarz M. et al. Anti-infartc effects of magnesium is not mediated by adenosine A1 receptors in rat globally ischemic isolated hearts. *Clin Exp Pharmacol Physiol* 2004; 31: 868-72.
78. Sapna S, Ranjith SK, Shivakumar K. Cardiac fibrogenesis in magnesium deficiency: a role for circulating angiotensin II and aldosterone. *Am J Physiol Heart Circ Physiol* 2006.
79. Rousseau E, Pinkos J, Savaria D. Functional sensitivity of the native skeletal Ca^{2+}-relase channel to divalent cations and the Mg-ATP complex. *Can J Physiol Pharmacol* 1992; 70: 394-402.
80. Blazev R, Lamb GD. Low ATP and elevated Mg^{2+} reduce depolarization-induced Ca^{2+} relase in rat skinned skeletal muscle fibres. *J Physiol* 1999; 520: 203-15.
81. Shi J, Krishnamoorthy G, Yang Y. et al. Mechanism of magnesium activation of calcium-activated potassium channels. *Nature* 2002; 418: 876-80.
82. Duke AM, Hopkins PM, Steele DS. Mg^{2+} dependence of halothane-induced Ca^{2+} release from the sarcoplasmic reticulum in rat skeletal muscle. *J Physiol* 2003; 551: 447-54.
83. Haarmann CS, Dulhunty AF, Laver DR. Regulation of skeletal ryanodine receptors by dihydropyridine receptor II-III loop C-region peptides: relief of Mg^{2+} inhibition. *Biochem J* 2005; 387: 429-36.
84. Abraham GE, Facn MD. The importance of magnesium in

the management of primary postmenopausal osteoporosis. *J Nutr Med* 1991; 2: 165-78.
85. Rude RK, Gruber HE, Wei LY. et al. Immunolocalization of RANKL is increased and OPG decreased during dietary magnesium deficiency in the rat. *Nutr Metab* 2005; 2: 24.
86. Gruber HE, Rude RK, Wei L. et al. Magnesium deficiency: effect on bone mineral density in the mouse appendicular skeleton. *BMC Musculoskeletal Disord* 2003; 4: 7.
87. Stendig-Lindberg G, Koeller W, Bauer A. et al. Prolonged magnesium deficiency causes osteoporosis in the rat. *J Am Coll Nutr* 2004; 23: S704-S11.
88. Rude RK, Gruber HE. Magnesium deficiency and osteoporosis: animal and human observations. *J Nutr Biochem* 2004; 15: 710-6.
89. Sojka JE, Weaver CM. Magnesium supplementation and osteoporosis. *Nutr Rev* 1995; 53: 71-4.
90. Rossetti L, Giaccari A, Klein-Robbenaar E. et al. Insulinomimetic properties of trace elements and characterization of their in vivo mode of action. *Diabetes* 1990; 39: 1243-50.
91. Matsuda M, Mandarino L, DeFronzo RA. Synergistic interaction of magnesium and vanadate on glucose metabolism in diabetic rats. *Metabolism* 1999; 48: 725-31.
92. Lal J, Vasudev K, Kela AK. et al. Effect of oral magnesium supplementation on the lipid profile and blood glucose of patients with type 2 diabetes mellitus. *J Assoc Physicians India* 2003; 51: 37-42.
93. Rodriguez-Moran M, Guerrero-Romero F. Oral magnesium supplementation improves insulin sensitivity and metabolic control in type 2 diabetic subjects: a randomized double-blind controlled trial. *Diabetes Care* 2003; 26: 1147-52.
94. Guerrero-Romero F, Tamez-Perez HE, Gonzalez-Gonzalez et. al. Oral magnesium supplementation improves insulin sensitivity in non-diabetic subjects with insulin resistance. A double-blind placebo-controlled randomized trial. *Diabetes Metab* 2004; 30: 253-8.
95. Wälti MK, Zimmermann MB, Spinas GA. et al. Low plasma magnesium in type 2 diabetes. *Swiss Med Wkly* 2003; 133: 289-92.
96. Skibniewska A, Pasternak K. Magnez a cukrzyca. *Biul Magnezol* 2002; 7: 216-26.
97. Wälti MK, Zimmermann MB, Walczyk T. et al. Measurement of magnesium absorption and retention in type 2 diabetic patients with the use of stable isotopes. *Am J Clin Nutr* 2003; 78: 448-53.
98. Cefaratti C, McKinnis A, Romani A. Altered Mg^{2+} transport across liver plasma membrane from streptozotocin-treated rats. *Mol Cell Biochem* 2004; 262: 145-54.
99. Takaya J, Higashino H, Kobayashi Y. Intracellular magnesium and insulin resistance. *Magnes Res* 2004; 17: 126-36.
100. Lopez-Ridaura R, Willett WC, Rimm EB. et al. Magnesium intake and risk of type 2 diabetes in men and women. *Diabetes Care* 2004; 27: 134-40.
101. Longstreet DA, Heath DL, Vink R. A potential link between magnesium intake and diabetes in Indigenous Australians. *Med J Aust* 2005; 183: 219-20.
102. Wang JL, Shaw NS, Yeh HY. et al. Magnesium status and association with diabetes in the Taiwanese elderly. *Asia Pac J Clin Nutr* 2005; 14: 263-9.
103. Takaya J, Higashino H, Kotera F. et al. Intracellular magnesium of platelets in children with diabetes and obesity. *Metabolism* 2003; 52: 468-71.
104. Huerta MG, Roemmich JN, Kington ML. et al. Magnesium deficiency is associated with insulin resistance in obese children. *Diabetes Care* 2005; 28: 1175-81.
105. Inoue I. Lipid metabolism and magnesium. *Clin Calcium* 2005; 15: 65-76.
106. Baydas B, Karagoz S, Meral I. Effects of oral zinc and magnesium supplementation on serum thyroid hormone and lipid levels in experimentally induced diabetic rats. *Biol Trace Elem Res* 2002; 88: 247-53.
107. Coben H, Sherer Y, Shaish A. et al. Atherogenesis inhibition induced by magnesium-chloride fortification of drinking water. *Biol Trace Elem Res* 2002; 90: 251-9.
108. Itoh K, Kawasaka T, Nakamura M. The effects of high oral magnesium suppementation on blood pressure, serum lipids and related variables in apparently healthy Japanese subjects. *Br J Nutr* 1997; 78: 737-50.
109. Seelig MS. Cardiovascular consequences of magnesium deficiency and loss: pathogenesis, prevalence and manifestations. Magnesium and chloride loss in refractory potassium repletion. *Int Am J Cardiol* 1989; 63: G4-G21.
110. Zheng D, Upton RN, Ludbrook GL. et al. Acute cardiovascular effects of magnesium and their relationship to systemic and myocardial magnesium concentrations after short infusion in awake sheep. *J Pharmacol Exp Ther* 2001; 297: 1176-83.
111. Chakraborti S, Chakraborti T, Mandal M. et al. Protective role of magnesium in cardiovascular diseases: a review. *Mol Cell Biochem* 2002; 238: 163-79.
112. Rosanoff A. Magnesium and hypertension. *Clin Calcium* 2005; 15: 255-60.
113. Bobkowski W, Nowak A, Durlach J. The importance of magnesium status in the pathophysiology of mitral valve prolapse. *Magnes Res* 2005; 18: 35-52.
114. Piotrowski AA, Kalus JS. Magnesium for the treatment and prevention of atrial tachyarrhythmias. *Pharmacotherapy* 2004; 24: 879-95.
115. Shiga T, Wajima Z, Inoue T. et al. Magnesium prophylaxis for arrhythmias after cardiac surgery: a meta-analysis of randomized controlled trials. *Am J Med* 2004; 117: 325-33.
116. Somberg JC, Cao W, Cyetanovic I. et al. The effect of magnesium sulfate on action potential duration and cardiac arrhythmias. *Am J Ther* 2005; 12: 218-22.
117. Tsuji A, Araki K, Maeyama K. et al. Effectiveness of oral magnesium in a patient with ventricular tachycardia due to hypomagnesemia. *J Cardiovasc Pharmacol Ther* 2005; 10: 205-8.
118. Lukaski HC, Bolonchuk WW, Klavay LM. et al. Maximal oxygen consumption as related to magnesium, copper, and zinc nutriture. *Am J Clin Nutr* 1983; 37: 407-15.
119. Lukaski HC, Nielsen FH. Dietary magnesium depletion affects metabolic responses during submaximal exercise in postmenopausal women. *J Nutr* 2002; 132: 930-5.
120. Lukaski HC. Magnesium, zinc and chromium nutrition and athletic performance. *Can J Appl Physiol* 2001; 26: S13-S22.
121. Lukaski HC. Vitamin and mineral status: effects on physical performance. *Nutrition* 2004; 20: 632-44.
122. Weller E, Bachert P, Meinck HM. et al. Lack of effect of oral Mg-supplementation on Mg in serum, blood cells, and calf muscle. *Med Sci Sports Exerc* 1998; 30: 1584-91.
123. Finstad EW, Newhouse IJ, Lukaski HC. et al. The effects of magnesium supplementation on exercise performance. *Med Sci Sports Exerc* 2001; 33: 493-8.
124. Rayssiguier Y, Guezennec CY, Durlach J. New experimental and clinical data on the relationship between magnesium and sport. *Magnesium Res* 1990; 3: 93-102.
125. Casoni I, Guglielmini C, Graziano L. et al. Changes of magnesium concentrations in endurance athletes. *Int J Sports Med* 1990; 11: 234-7.
126. Buchman AL, Keen C, Commisso J. et al. The effect of a marathon run on plasma and urine mineral and metal concentrations. *J Am Coll Nutr* 1998; 17: 124-7.
127. Pate RR, Sargent RG, Baldwin C. et al. Dietary intake of wo-

men runners. *Int J Sports Med* 1990; 11: 461-6.
128. Lukaski HC. Micronutrients (magnesium, zinc, and copper): Are mineral supplements needed for athletes? *Int J Sport Nutr* 1995; 5: S74-S83.
129. Lukaski HC. Magnesium, zinc, and chromium nutriture and physical activity. *Am J Clin Nutr* 2000; 72: S585-S93.
130. Nuviala RJ, Lapieza MG, Bernal E. Magnesium, zinc, and copper status in women involved in different sports. *Int J Sport Nutr* 1999; 9: 295-309.
131. Papadopoulou SK, Papadopoulou SD, Gallos GK. Macro- and micro-nutrient intake of adolescent greek female volleyball players. *Int J Sport Nutr Exerc Metab* 2002; 12: 73-80.
132. Clarkson PM. Micronutrients and exercise: Anti-oxidants and minerals. *J Sports Sci* 1995; 13: S11-S24.
133. Podlewski JK, Podlewska-Chwalibogowska A. Drugs in contemporary practice. Split Trading, Warsaw, 1999: 360-1. (in Polish)

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