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Public Health Perspective on Magnesium

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Abstract

Magnesium is a cofactor in more than 300 enzymes, it plays a vital role in energy metabolism, homeostasis of electrolites, and bone metabolism, and regulates a number of fundamental functions such as muscle contraction, neuromuscular conduction, glycemic control, and blood pressure. Magnesium deficiency has been associated with a wide range of diseases, from cardiovascular diseases, hypertension, diabetes, to anxiety and other mental disorders, migraine and osteoporosis, and especially worrying is subclinical form which is estimated to affect up to 30% of the population. Recommended dietary intake of magnesium is 300 mg and 350 mg per day for adult males and females, respectively. While highly abundant in a variety of foods, especially green leafy vegetables, nuts and seeds, water is the main contributor to magnesium daily intake. Water has been the focus of a number of public health interventions aiming to improve magnesium status of populations, especially in Israel and Australia. Supplements are becoming a more important contributor to the total magnesium intake, especially among physically active individuals. Public awareness of the health benefits gained from physical activity is improving, and more individuals decide to engage in (recreational) physical activity. Even though physical activity increases the risk of magnesium deficiency, misuse of supplements due to lack of knowledge and misinformation shared on social networks can have a detrimental effect on individual's health and physical performance.

Keywords: magnesium, deficiency, public health, water, physical activity

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Introduction

Magnesium (Mg) is an important cation and essential mineral with numerous functions in the body[1,2]. It is a crucial factor for over 300 enzymatic reactions including DNA, RNA, protein and adenosine-triphosphate (ATP) synthesis, cellular energy production and storage, glycolysis and cellular second messenger systems. Magnesium regulates cellular ion channels, transporters and signaling, which is especially important for calcium, potassium and sodium balance[1-4]. This effect is probably most evident with muscle cramps, the main symptom of Mg deficiency. Muscle contracts when depolarization of skeletal muscle cell occurs with sodium/calcium exchange across the membrane. After muscle contraction calcium pump, via ATPase, which is Mg dependant, transports calcium ions to sarcoplasmic reticulum for storage. In case of Mg deficiency, prolonged retention of calcium manifests itself as muscle cramps and fatigue[5-7].

Mg's functions are closely interrelated with other electrolytes. For example, sodium, potassium and chloride create positive gradient for the paracellular permeability and enable cations like Mg and calcium to enter the cell. Mg is involved in sodium and potassium balance, evident through occurrence of hypokalemia and hypokalcemia with Mg deficiency[8].

Change in Mg homeostasis in the body may result in a deficiency which has been implicated in several clinical conditions[9], including cardiovascular disease[10], diabetes[11], essential hypertension[12,13], anxiety disorders[14], migraine[15], and osteoporosis[16]. For all essential nutrients, focus is always on their recommended intake, absorption, possible deficiency or excessive intake and their aftermath on the public health. Even though severe Mg deficiency is considered to be rare, growing number of research supports the idea that Mg deficiency is an important risk factor for many non-communicable and cronic inflammatory diseases[1-4,10,17,18]. In average 10 to 15% of body's Mg is lost by sweat[7]. Therefore, athletes and physically active people are considered to be at higher risk of Mg deficiency in comparison to other population groups[19].

Magnesium Body Homeostasis

Following calcium, sodium and potassium, Mg is the fourth most abundant cation in the body and the second most abundant intracellular cation. There are at least three body pools of Mg in humans. About 60% of body Mg is found in bones, 40% is found in soft tissues, mostly muscles, where Mg preforms most of its essential functions and blood, which contains about 1% of Mg[1,2,20] (Table 1).

Table 1. **Distribution of magnesium in healthy adults (prepared according to 4,7)**

Tissue	% total body Mg
Bones	60-65
Muscles	27
Other cells	6-7
Extracellular	< 1
Serum	*0.75 – 1.1 mmol/L*
Cerebrospinal fluid	*1.25 mmol/L*
Sweat	*0.3 mmol/L (in warm environment)*

On average, Mg reserves in a healthy adult weighing 70 kg is 24 g[5,19]. 90% of Mg is mainly bound to nucleic acids, ATP, negatively charged phospholipids and proteins, acting as a structural stabilizator and/or enzyme activator/inhibitor (ATPase, phosphofructokinase, adenylate cyclase, DNA polymerase, ect.) and about 10% is in free form[4,21-23].

Magnesium can be absorbed by passive paracellular diffusion and active transport in all parts of the intestine, with a maximum absorption in distal jejunum and ileum. 80 – 90% is absorbed by the tight-junction passive diffusion[1,4]. Importantly, only free Mg can be absorbed via the paracellular pathway. The amount of Mg in food appears to be the main determinant when it comes to absorption[2], i.e. the more Mg is consumed the less is absorbed. For example, the highest absorption is achieved at a very low dietary intake (40 mg/day) while consumption of Mg near the recommended intake (around 300 mg/day) will result in 30–50 % absorption[20]. Availability of Mg will regulate absorption mechanism; higher availability means that 90% of Mg will be absorbed via passive diffusion while low availability activates active transport via TRPM6 found in the colon[1]. TRPM6 is a divalent cation channel that is tightly regulated by intracellular Mg2+ concentrations. After absorption through basolateral side of intestinal cell Mg is delivered to blood via Na+-dependent Na+/Mg2+ exchanger[1]. Absorption is also dependent on the intake of antinutrients, like fiber rich food – phytates, organic acids, polyols, calcium, phosphorus, polyphenols, oxalates, zinc, etc.[24].

Besides intestinal absorption, bone stores and kidneys coordinate Mg homeostasis[1,2,20,23,25]. With a normal serum Mg concentration of 1.8 to 2.3 mg/dL and normal glomerular filtration rate, 70% of circulating Mg (2400 mg) is filtered by glomeruli. Only 100 mg of Mg is excreted, while the remaining 2300 mg is reabsorbed along the kidney tubules by several coordinated transport processes. Only 30% of the filtered Mg is reabsorbed by the proximal tubule[1,2]. Besides urinary excretion, surface loss (through sweat) can be a significant contributor to Mg deficiency, especially when dietary consumption does not meet the recommendations[1].

Changes in Mg homeostasis are generally recognized as hypermagnesemia or hypomagnesemia, the latter being more prevalent. Change in any of the aforementioned mechanisms of Mg body homeostasis will result in (pre)clinical deficiency[26]. Clinical diagnosis of Mg deficiency is not simple, as symptoms associated with Mg deficiency are unspecific, and generally confounded by low consumption of other nutrients. Some of the most common symptoms include fatigue, muscle spasms, weakness, constipation, and depression[23,26]. On the other hand, hypermagnesemia caused by some kidney disease or excessive oral ingestion (usually through supplementation) may cause nausea, vomiting or diarrhea, lethargy or headaches[23].

Dietary Sources and Recommendations

Ever since Mg deficiency has been first described in year 1969,[3,27] dietary recommendations for Mg changed. Table 2 shows current recommendations for all population groups.

Though only 10% of Mg is excreted, given its immense importance in all, but especially musco-sceletal functions, one's diet is the main source of Mg. Mg is ubiquitous in commonly available foods, but especially good sources are green leafy vegetables, grains, nuts, beans, peas, and seeds (Table 3). Water, both tap and bottled, despite variable content of Mg also represent important source of Mg[2].

Table 2. **The magnesium Dietary Reference Values (AI, UL)[28]**

Life stage group	Adequate intake (AI) mg/day	Tolerable Upper Intake Level (UL) mg/day[a]
Infants		
7 – 11 months	80	ND
Children		
1 – 2 years	170	ND
3 years	230	ND
4 – 9 years	230	250
10 – 17 years		
Female	250	250
Male	300	250
Adults		
≥18 years	300	250
Female	350	250
Male	300	250
Pregnancy	300	250
Lactation		

[a] The UL applies to readily dissociable Mg salts (e.g., chloride, sulphate, aspartate, lactate) and compounds like MgO in food supplements, water or added to foods; does not include Mg naturally present in foods and beverages

Today, dietary supplements represent another important source of Mg, usually in a form of aspartate, chelate, citrate, chloride, gluconate, lactate, or oxide[2]. The most common form of supplemental Mg are granules (intended for an instant, direct effect) or as effervescent tablets, usualy in combination with vitamins B, i.e. vitamin B6 (Hermes Biolectra® Magnezij Direkt 300 mg; Diethpharm® Magnesium night; Natural Wealth® Magnezij direkt 375 mg + B + C; Natural Wealth® Magnezij Sport Direkt +B6 +C +L-karnitin; etc.). Vitamin B6 facilitates the cellular uptake of Mg by limiting its excretion and increasing its effectivnes, i.e. in ratio 10:1 vitamin B6 was found to provide faster relief of Mg-deficiency symptoms[30]. The Tolerable Upper Intake Level (UL) is set at 250 mg of supplementary Mg for adults and children older than 9 years[28].

Water as a Contributor to Magnesium Intake

Water intake is essential for life and body functions, like metabolism, substrate transport across membranes, cellular homeostasis, temperature regulation and circulatory function[31,32]. Water requirements vary between individuals and environmental conditions, but European Food Safety Authority set the adequate total water intakes for females at 2.0 L/day and 2.5 L/day for males in 2010[33]. Given the amount of water consumed daily (**Table 4**), it represents the main source of Mg. We still lack strong evidence regarding consumption and contribution of drinking water to the overall Mg and other mineral intake, as well as specific analysis for vulnerable population groups, just as it was outlined in the World Health Organization expert report from 2009[34]. An additional aspect that needs attention is that drinking water is not consumed as water *per se* but as a part of beverages and incorporated into foodstuffs[34], which represents another major research challenge[34,36].

According to the EFSA Comprehensive European Food Consumption Database[37] average consumption of drinking water, both bottled and unbottled, in Europe is 756.59 g/day, and 1214.52 g/day in Croatia. Drinking water mainly comes from groundwater sources[36] on which public water supply relies. According to the WHO, residents in Italy, Iceland, Austria, Denmark and Lithuania consume close to 90% of their water from groundwater sources, whereas people in France, Sweden and Finland consume up to 50%, similarly to the Netherlands and Germany, at 50–70%. The contribution of groundwater to water supply in the United Kingdom ranges from 30% to 35%, while only 15% in Norway[34]. Data for Croatia are in line with other EU countries[37] (Table 4).

Geological site of a spring will determine Mg's content in water (Table 5). On average, Mg's content in ground water is around 50 mg/L[38], differing significantly between soft and hard water[38,39]. For example, based on the recommended consumption of 2.0 L of water/day/adult, for those living in the city of Zagreb tap water would contribute with only 40 mg of Mg to their daily consumption, since Mg concentration is only 21.8 mg/L[36].

Water supply is becoming a major issue, so many countries rely on bottled water[34,40]. Consumption of bottled

Table 3. **Magnesium content in selected foods[29]**

Food	Magnesium content (mg/100g)	Food	Magnesium content (mg/100g)
Swiss chard	65 mg	Kale	20 mg
Spinach	56 mg	Brussels sprouts	19 mg
Bananas	42 mg	Peas	27 mg
Almonds	260 mg	Sweet corn	46 mg
Walnut	380 mg	Wheat bran	520 mg
Beans, white	180 mg	Sesame seeds	354 mg
Wheat bran	520 mg	Figs, dried	92 mg
Wholegrain bread, graham	93 mg	Dates, dried	59 mg

Table 4. **Drinking water intake in Croatia, g/day, per consumer[37]**

	Drinking water (g/day)			
	Bottled water		Unbottled water	
	Natural mineral water		Tap water	Well water
	Carbonated natural mineral water	Still natural mineral water		
Mean	240.08	248.63	1092.54	903.47
Standard deviation	244.52	423.66	682.02	587.52
Median	166.67	333.33	1072.73	816.67

Table 5. **Electrolyte content (mg/L) of some bottled waters from Croatian market**

Bottled water, Natural mineral water	Mg^{2+} (mg/L)	Na^{2+} (mg/L)	Ca^{2+} (mg/L)	K^{+} (mg/L)	HCO_3^- (mg/L)	Cl^- (mg/L)	SO_4^{2-} (mg/L)	F^- (mg/L)
Carbonated natural mineral water								
Mg Mivela (slightly carbonated)	343.9	121.0	23.8	9.9	2037.5	14.2	0.9	0.4
Mg Mivela (carbonated)	343.0	131.9	22.1	9.5	2064.8	14.4	<0.3	0.4
Kalnička	23.0	650.0	62.0	8.0	1410.0	350.0	-	-
Sarajevski Kiseljak	41.3	598.0	248.5	16.8	1805.6	95.7	490.0	-
Lipički studenac	26.4	101.0	72.5	13.3	493.0	51.2	31.3	1.2
Jamnica	43.0	805.0	114.0	27.1	2246.0	262.0	116.1	0.9
Donat Mg	1000.0	1500.0	390.0	-	7500.0	75.0	2200.0	-
Radenska	82.0	480.0	190.0	75.0	2700.0	58.0	97.0	0.5
Average	*237.8*	*548.4*	*140.4*	*22.8*	*2532.1*	*115.1*	*489.2*	*0.7*
Standard deviation	*336.9*	*469.8*	*128.5*	*23.9*	*2111.1*	*123.3*	*856.5*	*0.4*
Min	*23.0*	*101.0*	*22.1*	*8.0*	*493.0*	*14.2*	*0.9*	*0.4*
Max	*1000.0*	*1500.0*	*390.0*	*75.0*	*7500.0*	*350.0*	*2200.0*	*1.2*
Still natural mineral water								
Radenska	20.0	7.4	59.0	0.8	280.0	4.4	<1	>0.20
Jana	32.0	1.8	63.8	0.6	381.0	2.9	7.2	0.02
Studena	26.8	11.4	79.0	1.1	400.0	4.1	3.3	0.21
Santa	7.7	1.9	0.4	67.9	242.8	2.90	7.30	1.92
Kala	19.0	7.0	87.0	-	378.0	-	11.0	-
Sveti Rok	9.9	1.2	47.6	0.3	189.1	1.7	2.3	0.02
Cetina	1.2	1.9	76.2	0.4	238.5	3.3	3.42	0.038
Average	*16.7*	*4.7*	*58.9*	*11.9*	*301.3*	*3.2*	*5.75*	*0.44*
Standard deviation	*11.0*	*4.0*	*29.1*	*27.5*	*84.1*	*1.0*	*3.33*	*0.83*
Min	*1.2*	*1.2*	*0.4*	*0.3*	*189.1*	*1.7*	*2.30*	*0.02*
Max	*32.0*	*11.4*	*87.0*	*67.9*	*400.0*	*4.4*	*11.00*	*1.92*

water has been growing steadily for the past 30 years, and it is now the most dynamic sector of the entire food and beverage industry globally[34]. Like tap water, bottled water has variable Mg concentrations, as shown in Table 5. Bottled waters on the Croatian market have an Mg content from 23 to 1000 mg/L for carbonated and from 1.16 to 32.0 mg/L for still water. Though some of these types of water may cause symptoms of hypermagnesiemia, it should be noted that they are advertised as constipation relievers.

Magnesium Deficiency as a Public Health Issue

Public health significance of water as the main source of Mg is nicely summarized in the WHO's expert report[34]. In light of the environmental crisis, the importance of safe and sufficient water supply has never been stronger[41]. Estimated 17% of the world's population uses water from unprotected and remote sources, 32% from some form of protected source and 51% from some sort of centralized (piped) system to the dwelling or plot[34]. In response to increasing global and local water scarcity, there is the increasing use of sources such as recovered/

recycled waters, harvested rainwater and desalinated waters[34], with Australia and Israel being the world's leaders in water technology.

Some countries, like Israel who is one of the world's leader in water destilation, even have their own Ministry of Health program to restore concentrations of Mg in tap water to 30 mg/L. By doing that and encouraging people to consume tap water they are hoping to increase dietary Mg consumption and have positive impact on public health[42]. Other than Mg consumption, there is a number of policies or public health campaigns across the world that focus on promoting water consumption. For example, Australia's 2015 ACT School Food and Drink Policy was working to ensure water is the easiest choice available, including the installation of two water refill stations in each public school[43]. The Hungarian Aqua Promoting Programme in the Young (HAPPY) provides free availability of mineral water in the classrooms[44].

DiNicolantonio et al.[10] estimated the prevalence of Mg deficiency in the developing countries to be 15–20 %. Recent data indicates that around 10–30 % of the population has subclinical Mg deficiency[10]. People who drink hard water in comparison to those drinking soft water tend to have lower blood pressure and lower risk of cardiovascular diseases, including heart attacks and strokes[10]. Meta-analysis of 11 prospective cohort studies found an inverse relation between circulating levels of Mg and incidence of coronary heart diseases, hypertension and type 2 diabetes[18]. Cross-sectional study by Sun et al.[45] concluded that dietary Mg consumption was inversely associated with the risk of depression. Despite growing number of research, consensus opinion is that more well designed, controlled and long-term studies are needed to confirm this inverse relation[17,45,46].

Physicaly Active Individuals in Focus

The overall percentage of insufficient physicaly active adults in 2016 was 27.5% based on the data from 168 countries, and this trend had only marginaly dropped in comparison to 2001[47]. However, the trend is positive in men (25.5% vs 23.4% of inactive men in 2001 and 2016, respectively)[47]. People are becoming more aware of health benefits physical activity has, especially in well-developed countries. This is reflected in the steady rise of people who regulary engage in some sort of physical activity. For example, in the US, the total number of visits to the gym grew by 45 %, from 4.6 billion in 2010 to 6.7 billion in 2019[48]. In 2018, the estimated value of the entire physical activity economy was $828.2 billion globally[49].

Physically active individuals are at increased risk of Mg deficiency due to increased needs and loss[50,51]. Physical activity regulates Mg distribution and utilization[52], translocating Mg from plazma to adipocites and skeletal muscle. The amount of translocated Mg depends on the level of energy expenditure and ATP synthesis. With long-term endurance activity serum Mg is likely to shift to erythrocytes or muscles to support the activity and contrary, short-term activity may result in elevation of serum Mg levels[51-53]. Post-activity, Mg will be distributed from bones, tissue or muscles so plazma levels could be restored[7]. In other words, exercise leads to a temporary redistribution, not Mg deficiency[19]. However, long-tern Mg deficiency observed as low plasma consentrations, during prolonged strenuous activity increases Mg reqirements[6,19,54].

Prolonged periods of physical activity may cause increased mineral loss through perspiration and excretion[52,53]. Mg excretion by urine increases after physical activity due to elevated levels of lactic acid[19]. Surface losses through sweat can be a significant contributor factor for Mg deficiency especially under "extreme" conditions (heat, interval exercise, stress). Mg loss in sweat varies[1], from only 3.4 mg/L in hot dry environment to 12-60 mg/L in hot humid environment[6]. Another study found concentrations of 7.3 mg/L Mg in male sweat after exercising. That concentration decreased to 4.1 mg/l after 10 days of acclimation[1,54]. On the other hand, an average person in non-hot or humid environment loses less than 5 mg of Mg per day[1]. Still, sweat losses are not taken into consideration when Mg recommendations (Table 2) for physicaly active individuals were set[53]. Yet, studies consistently show that young and elite athletes consume less Mg then recommended[56-60].

Partially, this may be due to general shift in diet quality, nutrient-dense foods (fruits, vegetables, whole grains, etc.) are changed for energy-dense foods, including sports drinks and sodas[51]. In general, athletes with restricted energy intake or athletes that are on specific dietary programs, which eliminate one or several food groups[19]. This indicates the need for sports nutrition counseling especially when it comes to younger and elite athletes. Restricted energy intake is usually associated with sports which require weight control, like combat sports, wrestling, dance, gymnastics, etc.[51]. Athletes and active individuals should take additional 10 to 20 % Mg of the recommendation for their gender and age group. For male athletes consumption under 260 mg/day, and 220 mg/day for female athletes, may impact the performance ability[6,51]. Supplementary Mg was studied as a potential ergogenic aid[19,52,61]. Review by Zang et al.[51] concluded that exercise performance may be compromised in Mg deficient individuals. However, when vitamin and mineral status is adequate, studies fail to provide supporting evidence backing up supplementation's role on athletic performance[54].

Even thouh rates of supplement use vary greatly across countries[62], gym attendees tend to use a variety of supplements more often - in European countries estimated 30 % to 70 % of gym attendees use supplements[63]. This practice poses a number of health risks, mainly due to the lack of knowledge about potential side effects and consequences of supplement use, especially long-term use[64], as well as disinformation shared by unprofessionals through social networks[63,65,66].

Conclusion

As the fourth most abundant cation in the body, Mg plays a number of vital roles on cellular metabolism and the overall health. Its deficiency, despite its high abundance in a variety of foods, and especially water, affects up to one third of population globally. Magnesium deficiency has been associated with hypertension, cardiovascular diseases, including heart attacks and stroke, diabetes, osteoporosis, to mention some. Around the globe, public health interventions focused on Mg content in water are aiming to overcome the burden of Mg deficiency, particularly efficiently in Israel and Australia. Tap water in Croatia has low Mg content, but contributes to the total daily water intake with around 40 %. Unlike still bottled waters, most of the bottled carbonated waters on Croatia's market contain significant amounts of Mg. Physically active individuals stand out as a population group at a particularly high risk of Mg deficiency. As public awareness of health benefits of physical activity improves, more people engage in various forms of physical activity, which is especially evident in the number of gym attendees. This group is particularly prone to supplement use but highly vulnerable to their improper use, due to lack of knowledge about the side-effects, and misinformation shared through social media. More effort should be put in improving public knowledge on water as the most important Mg source, rising awareness on population groups at risk of Mg deficiency as well as on dangers of improper Mg supplementation.

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MAGNEZIJ IZ PERSPEKTIVE JAVNOG ZDRAVSTVA

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Sažetak

Magnezij je kofaktor za više od 300 enzima koji ima ključnu ulogu u energetskom metabolizmu, homeostazi elektrolita, metabolizmu kostiju te regulira brojne fiziološke procese kao što su kontrakcija mišića, neuromuskulatorne funkcije, kontrola glikemije i krvnog tlaka. Deficit magnezija predstavlja čimbenik rizika za cijeli niz zdravstvenih problema, od kardiovaskularnih bolesti, hipertenzije, dijabetesa, do anksioznosti i drugih mentalnih poremećaja, migrena i osteoporoze. Posebice zabrinjava subklinički oblik deficita magnezija za koji se procjenjuje kako pogađa do 30 % populacije. Preporučeni unos magnezija za odrasle osobe je 300 mg za žene i 350 mg za muškarce. Iako je široko rasprostranjen u hrani, posebice tamno zelenom lisnatom povrću, orašastim plodovima i sjemenkama, najveći doprinos dnevnom unosu magnezija dolazi iz vode. Upravo je voda u fokusu javnozdravstvenih intervencija koje imaju za cilj poboljšati status magnezija u populaciji, posebice u Izraelu i Australiji. Dodaci prehrani postaju sve važniji izvor magnezija, posebice među tjelesno aktivim osobama. S porastom svijest javnosti o zdravstvenim dobrobitima fizičke aktivnosti raste i broj (rekreativno) tjelesno aktivnih osoba. Iako rizik od deficita magnezija raste s fizičkom aktivnošću, pogrešno uzimanje dodataka prehrani uslijed nedostatnog znanja i dezinformacija koje se dijele na društvenim mrežama, povećava se mogućnost za negativne posljedice na zdravlje i tjelesnu sposobnost.

Ključne riječi: magnezij, deficit, javno zdravlje, voda, fizička aktivnost