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MAGNESIUM: ITS ROLE IN NUTRITION AND CARCINOGENESIS

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ABSTRACT

Magnesium (Mg^{2+}) plays a key role in many essential cellular processes such as intermediary metabolism, DNA replication and repair, transporting potassium and calcium ions, cell proliferation together with signalling transduction. Dietary sources rich in magnesium are whole and unrefined grains, seeds, cocoa, nuts, almonds and green leafy vegetables. Hard water is also considered to be an important source of magnesium beneficial to human health. The daily dietary intake of magnesium is however frequently found to be below that recommended in Western countries. Indeed, it is recognised that magnesium deficiency may lead to many disorders of the human body, where for instance magnesium depletion is believed to play an important role in the aetiology of the following; cardiovascular disease (including thrombosis, atherosclerosis, ishaemic heart disease, myocardial infarction, hypertension, arrhythmias and congestive heart failure in human), as well as diabetes mellitus, gastrointestinal (GI) tract disease, liver cirrhosis and diseases of the thyroid and parathyroid glands. Insufficient dietary intake of magnesium may also significantly affect the development and exacerbation of ADHD (Attention Deficit-Hyperactivity Disorder) symptoms in children. The known links between magnesium and carcinogenesis still remain unclear and complex, with conflicting results being reported from many experimental, epidemiological and clinical studies; further knowledge is thus required. Mg^{2+} ions are enzyme cofactors involved in DNA repair mechanisms that maintain genomic stability and fidelity. Any magnesium deficiencies could thereby cause a dysfunction of these systems to occur leading to DNA mutations. Magnesium deficiency may also be associated with inflammation and increased levels of free radicals where both inflammatory mediators and free radicals so arising could cause oxidative DNA damage and therefore tumour formation. The presented review article now provides a summary discussion of the various research performed concerning the impact that low magnesium intake has on tumour incidence; this includes impairment of magnesium homeostasis frequently observed in tumour cells, the influence of magnesium depletion on the progression of existing tumours and the occurrence of hypo-magnesaemia when patients are treated with certain anticancer drugs.

Key words*: magnesium, magnesium deficiency, carcinogenesis, tumours*

STRESZCZENIE

Magnez odgrywa kluczową rolę w wielu procesach komórkowych, takich jak metabolizm energii, replikacja i naprawa DNA, transport jonów potasu i wapnia, proliferacja komórek, a także transdukcja sygnału. Pełne ziarna zbóż, kakao, orzechy, migdały, zielone warzywa liściaste są dobrym źródłem magnezu. Twarda woda jest również uważana za ważne źródło magnezu, które pozytywnie wpływa na zdrowie człowieka. Dzienne spożycie magnezu w krajach zachodnich często jest poniżej zalecanej dawki. Niedobór magnezu może prowadzić do wielu zaburzeń w organizmie człowieka. Uważa się, że deficyt jonów Mg^{2+} może odgrywać ważną rolę w etiologii wielu chorób, takich jak choroby sercowo-naczyniowe (zakrzepica, miażdżyca tętnic, choroba niedokrwienna serca, zawał mięśnia sercowego, nadciśnienie, zaburzenia rytmu serca, zastoinowa niewydolność serca), cukrzyca, choroby układu pokarmowego, marskość wątroby, choroby tarczycy i przytarczyc. Niewystarczające spożycie magnezu może mieć znaczący wpływ na rozwój i pogłębienie objawów ADHD u dzieci. Rola magnezu w procesie kancerogenezy jest skomplikowana. Mimo stosunkowo dużej liczby badań aktualny stan wiedzy na temat zależności pomiędzy poziomem magnezu, a kancerogenezą jest ciągle niewystarczający i niespójny. Jony magnezu pełnią funkcję kofaktorów enzymów zaangażowanych w mechanizmy naprawcze DNA, które odpowiedzialne są za utrzymywanie stabilności genomu i wierności replikacji. W związku z tym niedobór magnezu może przyczyniać się do wadliwego działania tych systemów i występowania mutacji DNA. Ponadto, w badaniach na zwierzętach obserwowano korelację pomiędzy obniżonym stężeniem magnezu, a stanem zapalnym i wzrostem poziomu wolnych rodników. Zarówno mediatory zapalne jak i wolne rodniki przyczyniają się do generowania uszkodzeń oksydacyjnych DNA, których następstwem może być powstawanie nowotworów. W artykule omówiono niektóre aspekty badań dotyczących wpływu niskiego spożycia magnezu na częstość występowania nowotworów, zaburzonej homeostazy magnezu obserwowanej w komórkach

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nowotworowych, wpływu niedoboru magnezu na progresję istniejących nowotworów oraz występowania hipomagnezemii w trakcie leczenia pacjentów niektórymi lekami przeciwnowotworowymi.

Słowa kluczowe*: magnez, niedobór magnezu, karcynogeneza, nowotwory*

INTRODUCTION

The Mg^{2+} ion is vital to many cellular processes [42]. After potassium, Mg^{2+} is the second most prevalent cation in the intracellular fluid and the fourth most common in the human body (i.e. after calcium, potassium and sodium). Its importance in regulating large number of biochemical reactions has been long established [43, 54]. Magnesium activates many enzymes, crucially among which are those that perform hydrolysis and phosphate group transfer [7]. ATP hydrolysis to ADP is the most significant catalytic role of magnesium in cell energy metabolism [1]. Mg^{2+} is complexed with ATP, ADP and GTP, necessary for the activity of enzymes involved in phosphate group transfer such as glucokinase, phosphofructokinase, phosphoglycerate kinase and pyruvate kinase [6]. In fact all reactions involving ATP require the presence of Mg^{2+} ions [38, 49]. This ion also plays an important role in the synthesis of nucleic acids and proteins [1, 6], and is vital for maintaining genomic stability, through ensuring the fidelity of DNA replication and repair processes. More than half of the magnesium found in the cell nucleus is closely associated with nucleic acids and free nucleotides [38], and it is observed that DNA molecules adopt a more packed structure in the presence of Mg^{2+}. In addition, magnesium has a critical role in modulating cell cycle progression, cell proliferation, differentiation and apoptosis [29]. Furthermore, Mg^{2+}cations frequently modulate ion transport by pumps, carriers and ion-channels. In this manner Mg^{2+} may thus be a modulator of signal transduction and cytosolic concentrations of electrolytes such as Ca^{2+} and K^{+} [7, 46].

The adult human body contains approximately 21–28 g of magnesium [44] of which around 60–65% is mineralised in bones, whereas 33–34% is found in muscles and soft tissue [52]. Only 1% of magnesium is present in blood plasma and erythrocytes [44] where the latter contain three times more than the former. About 10% of magnesium is free and the rest (90%) being bound, mainly to nucleic acids, ATP, negatively charged phospholipids and proteins. The highest magnesium concentrations were found in microsomes containing ribosomes, endoplasmic reticulum, mitochondria and nuclei [52].

MAGNESIUM IN HUMAN NUTRITION

It would appear that mineral malnutrition, including magnesium deficiency, is nowadays quite common; the daily intake of magnesium in most industrialised countries is insufficient and does not meet the current recommended daily allowance (RDA). The effects of magnesium deficiency become especially acute when demand increases for example, during pregnancy, lactation, expended effort or a rise of body growth. In Poland, the recommended RDA for dietary magnesium is at least 300 mg for adult non-pregnant women and 370 mg for adult men; the average adult RDA in western societies being about 350 mg [19]. The actual magnesium requirement depends on levels of general activity (metabolic demand), type of work, lifestyle and possible disease.

Dietary sources rich in magnesium are: cocoa, nuts, almonds, whole seeds, unground grains, legumes and green leafy vegetables [44]. The green parts of plants are particularly rich in magnesium because it constitutes the prosthetic ion in chlorophyll. Another source is considered to be hard water, which has been shown to benefit human health in some parts of the world [14]. For example, some hard water can provide up to 100 mg of magnesium daily. Moreover, in areas where there is high consumption of hard water, these might actually supply the RDA of magnesium [50]. A study by *Madej* et al. [31] showed that the contribution of drinking water to magnesium intake was low (4%) amongst the elderly from the Warsaw region. Another study demonstrated that tap water, used by women for preparing beverages and/or meals, contributed 3.8% to the total magnesium dietary intake [24]. A survey of 18-26 years old students from Warsaw universities demonstrated that magnesium intake from bottled waters was about 8% of the RDA [16].

The bioavailability of magnesium depends largely on the form of the foodstuff. In fresh, unprocessed fruits and vegetables or in unrefined whole grains, magnesium is present at much higher concentrations compared to processed food. In the latter, magnesium is greatly reduced through procedural losses during production and thus little becomes absorbed by the human body. Another reason for lower magnesium intake through foodstuffs could be that the essential nutrient content in soil is depleted [19]. In addition, the mineral content (including magnesium) in the edible parts of plants are usually lower in the new high-yielding varieties of

cereals and some vegetables than their established counterparts. Modern cultivars, with rapid rates of growth and high yield of the edible parts, are genetically unable to achieve high concentrations of minerals; this being described as a genetic dilution effect [13, 19]. It is also seen that agricultural and food production techniques often lead to reduced magnesium levels in vegetables and meat. The preference for high-calorie foods that are micronutrient poor, frequently contributes to the negative balance of magnesium. Besides, magnesium deficiency may be the result of several adverse nutritional habits; the most important being:

- Drinking coffee and strong tea, especially in large amounts, leading to increased magnesium excretion;
- An excessive fat intake from foodstuffs with a high fat content such as fatty meat, which reduces magnesium absorption;
- A rapid or/and prolonged period of losing weight i.e. adopting a low-protein and high fibre diet can decrease intestinal magnesium absorption for those trying to lose weight;
- Excessive drinking of alcoholic beverages that both interfere with absorption and increase the excretion/removal of magnesium;
- Consuming too much food containing phosphates which are able to bind magnesium;
- Eating a high-calcium diet or taking calcium supplements over long periods; calcium reducing magnesium absorption. Magnesium is however well absorbed if the amount of calcium in foods is twice the level of magnesium [23, 52].

A negative magnesium balance also occurs in individuals exposed to chronic stress, people with increased urinary losses (through magnesium wasting genetic disorders) and patients treated with certain medicines such as diuretics, amino-glycoside antibiotics or sedatives and cytostatic drugs [52].

The Mg^{2+} ion is quite difficult to assimilate. On average, only 30% of the supplied element is absorbed, of which 10% occurs by passive diffusion. In cases of significant magnesium deficiency, 70-80% of magnesium available from foodstuffs can be absorbed. Magnesium absorption is improved when this element is supplied in the form of small doses i.e. spread over several meals. In humans, magnesium absorption ranges from about 75% for diets containing a small amounts of magnesium to 23% for those with high magnesium [23]. Magnesium is better absorbed as a food component than in the form of oral magnesium supplements. The assimilation of magnesium is facilitated by an acidic environment, diets rich in animal proteins, unsaturated fats, vitamin B6, vitamin D, sodium, lactose and secretion of insulin and parathyroid hormone [23]. Conversely, the bioavailability of magnesium from foodstuffs is reduced by the presence of phytate, fibre, oxalic acid, saturated fatty acids, an excess of phosphate or Ca^{2+} [44].

Mg^{2+} are absorbed mainly in the ileum and jejunum [52]. This process of absorption is the sum of two mechanisms: one of them being passive diffusion and the other is facilitated diffusion. The latter process depends on the metabolic energy supply and the concentration of Mg^{2+} ions. Magnesium absorption occurs in parallel with water absorption and is dependent on the extent of Mg^{2+} ion dissociation [23].

MAGNESIUM DEFICENCY IN HUMANS

High amounts of magnesium are especially required for cells from metabolically intensive working organs such as brain, heart and muscle. The normal function of these organs are thus particularly sensitive to any magnesium deficiency; a strong likelihood of this arising is indicated by observing the following symptoms: permanent weakness, fatigability, impaired concentration and attention, increased stress susceptibility, trembling and tingling of the hands, calf muscle cramps, trembling eyelids, mental and physical hyperactivity, restlessness, anxiety and irritability, irregular heartbeat, heart palpitations, headaches [23].

A magnesium deficit is more pronounced in older individuals, when gastrointestinal and renal mechanisms for magnesium conservation invariably become inefficient. It is also found that children, athletes, people who physically work hard or people living in very hot climates (i.e. loss of magnesium through sweat) are particularly vulnerable to magnesium deficiencies.

It is believed that magnesium depletion plays an important role in the aetiology of many disorders, such as cardiovascular disease (thrombosis, atherosclerosis, ischemic heart disease, myocardial infarction, hypertension, arrhythmias and congestive heart failure in human), diabetes mellitus, diseases of the gastrointestinal tract, liver cirrhosis, thyroid and parathyroid disease [7]. There is also a correlation between a chronic deficiency of certain minerals and the occurrence of ADHD. Insufficient dietary intake of magnesium may significantly affect the development of and in enlarging the symptoms of ADHD in children [27].

MAGNESIUM AND CARCINOGENESIS

The role of magnesium in cancer formation is complex. Numerous studies have focused on the effect of magnesium deficiency on tumour incidence, where an unbalanced magnesium homeostasis is frequently observed in tumour cells and that either magnesium

deficiency or supplementation can affect the progression of existing tumours.

It has been found that magnesium could impact carcinogenesis by two mechanisms [56]. Experimental and clinical data have suggested that magnesium deficiency might be associated with inflammation and/or increased levels of free radicals. Magnesium-deficient animals show an increased susceptibility to *in vivo* oxidative stress and their tissues are more susceptible to *in vitro* peroxidation [41]. Both inflammatory mediators and free radicals might lead to oxidative DNA damage and thereby cancer formation [6].

Magnesium is also known to stabilise the structure of nucleic acids and is a vital co-factor of enzymes involved in DNA replication, repair and gene expression [1]. DNA repair mechanisms are responsible for maintenance of genomic stability and fidelity, thus any magnesium deficiency may contribute to defects in these systems and the appearance of DNA mutations. Accumulation of genomic alterations may thereby lead to tumour-genesis [56].

Some studies have demonstrated that magnesium homeostasis is impaired in neoplastic cells in which the cation is accumulated in tumours which behave as magnesium traps. Neoplastic cells show extremely high affinities for magnesium even when cultured at low magnesium concentration [6]. The tendency of neoplastic cells to accumulate magnesium could be related to abnormal sodium-dependent magnesium extrusion. Another reason may be the over-expression of transient receptor potential melastatin 7 (TRPM7) [6]. This TRPM7 is an ubiquitously expressed ion channel, that plays a central role in magnesium homeostasis as well as in magnesium uptake mechanisms [43].

Furthermore, serum magnesium concentrations were frequently found to be decreased in patients with solid neoplasias, independent of therapy, with the decrease being correlated with the stage of malignancy [45]. These results suggest that in neoplastic disease, the magnesium requirement is increased, not only in tumour tissue, but also in erythrocytes. The increase in erythrocyte magnesium content may be related to various changes in the erythrocyte membrane, facilitating intracellular magnesium transport to the tumour. The concomitant decrease in serum magnesium may therefore be due to enhanced uptake of magnesium by erythrocytes from the extracellular pool. Such alterations in magnesium distribution may, by these means, play an important role in neoplastic development and genetic instability [20].

Low magnesium levels limit endothelial cells proliferation, migration and differentiation *in vitro* [3]. This finding is supported by other studies where, for instance, in cases of magnesium depletion, mice with *Lewis* lung carcinoma develop less vascularised tumours [34]. Another study on mice with xenografted solid tumours (*Lewis* lung carcinoma, 16/C mammary adenocarcinoma or C38 colon adenocarcinoma) showed that mice with nutritionally-induced magnesium deficiency exhibit significant growth reduction of primary solid tumours compared to magnesium-sufficient controls. According to the authors, a low magnesium content reduces the number of cells engaged in the S phase of the cell cycle [37]. It is suggested that magnesium deficiency inhibits tumour cell proliferation and neoangiogenesis [55].

There is also convincing evidence from other animal studies that magnesium could exert a protective effect in the early stages of carcinogenesis [6]. Magnesium inhibits lead and nickel-induced lung tumours in mice, nickel-induced carcinogenesis in the rat kidney and 3-methylcholantrene-induced fibro-sarcomas in rats [25, 39, 40]. It has also been reported that magnesium supplementation reduces the incidence of experimentally induced colon cancer in animals which might be related to a decrease of colonic epithelial cell proliferation [47, 53]. Other studies demonstrate that a diet poor in magnesium increases the incidences of thymic tumours and leukaemias [5, 20]. Animals with nutritionally-induced magnesium deficiency showed an increased vulnerability *in vivo* to oxidative stress and their tissues were more susceptible to *in vitro* peroxidation. Increased radical-related damage of nucleic acids, proteins and lipids may thus lead to many cellular perturbations and development of cancer [41].

Magnesium appears to be protective at the early stages of carcinogenesis; however, it promotes the growth of existing tumours at later stages [6]. Magnesium deficiency seems to favour invasion and metastatic colonisation [37].

The availability of magnesium may affect metastatisation in two ways. It seems that a low magnesium content stimulates the first stage of angiogenesis by synthesis of vascular endothelial growth factor (VEGF) and formation of a pro-inflammatory environment. In contrast, decreased magnesium availability inhibits the second step of angiogenesis; both endothelial cell proliferation and migration [56].

Magnesium deficiency has thus been proposed as a risk factor for some type of human cancer. Several epidemiological studies have demonstrated that a magnesium-rich diet may reduce the occurrence of colon cancer [18, 29, 30, 51]. Another study revealed no correlation between dietary intake of magnesium, potassium, sodium, calcium, phosphorus, iron, or water-soluble vitamins with bladder cancer risk [35]. The results of a case-control study demonstrated a correlation between low dietary magnesium and increased risk of lung cancer [33]. The observed effect was more pronounced amongst the elderly, current smokers, drinkers and those with a late-stage disease. In contrast, a prospective study has not supported these earlier findings [32] and in fact

showed no significant associations between total Ca, Mg, Fe, Cu, Se, and Zn intakes and lung cancer risk. Minerals supplementation also did not affect lung cancer risk. Paradoxically, it was observed that magnesium intake may increase lung cancer risk. This discrepancy may be due to difficulties in correctly evaluating dietary composition and the fact that smoking is a very strong risk factor for lung cancer [32].

Several studies have investigated the possible relationship between magnesium availability in drinking water and a risk of some type of cancers. An epidemiological study demonstrated that drinking water rich in magnesium reduced the risk of liver cancer [50], nevertheless the regional vs. global nature of this link was not determined nor were its possible biochemical mechanisms explored. As a probable explanation of these results, the effect of alcohol was considered; as alcohol consumption both harms the liver and reduces magnesium concentrations in the body [50]. Another study suggested a significant protective effect of magnesium intake from drinking water on the risk of ovarian cancer mortality [9]; similar findings being observed for prostate cancer [60]. A decreased risk of oesophageal cancer was demonstrated in a case-control study when magnesium levels in drinking water were elevated [61]. Moreover, a significant inverse relationship between calcium and magnesium concentrations in water with the occurrence of breast cancer has been reported [57]. Conversely, a subsequent study showed no correlation between magnesium levels in water and colonic cancer [59], which in turn contradict the results from prospective studies that show a diet rich in magnesium reducing the occurrence of colonic cancer [18, 29, 51]. One study has found that there is a strong inverse relationship between water hardness and pancreatic cancer risk [58], however, another study did not demonstrate any significant relationships between dietary intake of magnesium or iron with the risk of contracting pancreatic cancer in men [26]. Only a moderately low risk associated with total magnesium intake was observed amongst overweight individuals. These observations were similar to a further study, which reported a strong association between dietary magnesium intake and colorectal cancer amongst those who were overweight [51].

A matched case-control study investigated the relationship between nitrate exposure in drinking water and the risk of death from rectal cancer [8], where levels of magnesium or calcium in drinking water were tested to see if they could change the effect of nitrates on rectal cancer risk; results however indicated that magnesium had no effect on the correlation between nitrate exposure and higher risk of rectal cancer. In contrast, another study demonstrated a significant trend in an increased risk of colon cancer mortality with raised nitrate levels in drinking water, where magnesium was seen to influence this relationship [10]. Nitrate exposure in drinking water was found not to be associated with a higher mortality risk from brain cancer and magnesium intake via drinking water did not modify this particular relationship [21].

The link between trihalomethanes (TTHM) levels in public water supplies and the risk of pancreatic cancer has been also investigated [11]. Here, it was shown that magnesium in drinking water influenced the correlation between TTHM exposure and pancreatic cancer risk. In another study, magnesium modified the effects of TTHM exposure on the risk of developing rectal cancer [28].

It has been suggested that a high serum Ca : Mg ratio might be a risk factor for postmenopausal breast cancer [43]. The metabolism of magnesium is closely linked with that of calcium and the biochemical antagonism between both ions makes it important to treat together, the principal aspects of this competitive behaviour [2]. Magnesium and calcium ions control an important and diverse range of cellular processes. Magnesium levels directly affect transient receptor potential melastatin 7 (TRPM7) related to Ca^{2+} influx besides calcium–adenosine triphosphatase (Ca–ATP) levels. An imbalance of Ca/Mg intake may impair DNA repair, cell proliferation and differentiation. These disturbances could so lead to cancer formation [43].

Hypo-magnesaemia is observed in chemotherapy, especially in the treatment of tumours with cisplatin or when used in combination with 5-fluorouracil as well in radiotherapy [12, 17, 22]. Cisplatin is known to cause renal tubular damage thus impairing magnesium conservation which lead to the clinical syndromes of magnesium deficiency [62]. Some studies however indicate that magnesium supplementation during chemotherapy with cisplatin/paclitaxel in patients with ovarian cancer provides renal protection with no apparent reduction of anti-tumour effects [4]. Hypomagnesaemia was also observed during treatments with the anti-epidermal growth factor receptor (EGFR) antibody (cetuximab) [48, 55]. Cetuximab causes a reversible inhibition of magnesium reabsorption in the renal distal convoluted tubule [36, 55]. Despite this, it is not clear whether or not supplementation should be used on patients with hypo-magnesaemia. Some authors have also suggested that hypo-magnesaemia may be beneficial in cancer therapy by sensitising neoplastic cells to chemotherapy or radiotherapy treatments [6].

CONCLUSIONS

Dietary factors are considered to account for approximately 30% of cancer mortality in the Western World [15]. After tobacco, diet is the second preventable cause

of cancer. Magnesium is an essential micronutrient, which vitally impacts on numerous enzymatic processes in the cell and more attention should be paid for having an adequate content of this element in diet.

Magnesium deficiencies tend to increase tumour incidence in animals and humans where this element affects tumour growth, angiogenesis and metastatisation. However, despite decades of clinical and epidemiological investigation, more precise knowledge on its role in carcinogenesis is still lacking or is inconsistent. More studies should be undertaken to elucidate the contribution that magnesium makes on the different stages of tumour formation and development.

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