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METAL IONS

EFFECT OF MAGNESIUM SUPPLEMENTATION ON MAGNESIUM, CALCIUM, ZINC, IRON AND COPPER BALANCE IN RATS

R. Olкdzka, D. Skrajnowska

Department of Bromatology, Medical University of Warsaw.

Introduction

In recent years, there has been a dramatic increase in the demand for preparations to add vitamins, micro- and macronutrients, "energy" supplements etc. to our everyday diet. A time-consuming life-style makes following a well-balanced diet difficult, people tend to consume food that does not provide sufficient calories while the use of artificial fertilizers deprives many foodstuffs of their nutritional value (Bednarek, Lipicski, 1994; Harling, Van Delft, 1998). The easiest solution would be to maintain appropriate nutritional status by adoption of a proper diet, but tempted by advertisements people are eager to reach for commercially available nutritional supplements. Some of these must be actually taken at certain stages in our lives, including folic acid, vitamin C, vitamin D, calcium or magnesium (Meyer et al., 2000). However, it remains to be answered whether the supply of high doses of single nutrients does not affect the homeostasis of the body and its normal physiological functions. For example, it is well known that high doses of vitamin C are related to enhanced formation of urinary calculi while excessive magnesium intake may "wash" calcium out of the body. On the other hand, the actual bioavailability of foodstuffs, especially of micro- and macronutrients is affected by a number of factors, including the degree of tissue saturation, the size of tissue stores (deficiency or excess of particular elements), the presence of competitive ions and of substances either inhibiting or facilitating their absorption, stress, and associated hormone secretion, consumption of coffee, tea or alcohol, or coexisting disease (Princi et al., 1997; Creedon et al., 1999; Hunt, Roughead, 2000). As a result, dietary intakes may be inadequate to meet the requirements of the body. In such circumstances, the need for dietary supplements cannot be questioned, but they should be used with caution, bearing in mind their potential adverse effects.

Aim of the study

Hypomagnesemia is a common nutritional and metabolic disorder (Durlach et al., 1998; Wojtasik et al., 1999). According to the World Health Organization, the recommended dietary allowance is 5–6 mg Mg/kg/24h (Durlach et al., 1998). A long-term supply of one element is likely to affect the levels of other macro- and micronutrients. The aim of the present study was to determine, using an animal model, the effect of oral supplementation with magnesium given in doses of 2.5; 5.0; 10.0 and 20.0 mg Mg/kg/24h to rats fed a standard diet, on the retention of magnesium, calcium, zinc, iron and copper during the period of magnesium intake and after its discontinuation.

Experimental part

Male Wistar rats, age 4–5 weeks, body weight 60–70 g were used in the study. They were fed the LSM laboratory chow and given demineralized water *ad libitum.* The animals were divided into five groups (4 study groups and a control group). For 4 weeks, the animals were given by an intragastric tube a suspension of magnesium carbonate in 2% arabic gum in the amounts equivalent to 2.5 mg Mg/kg/24h (group 1), 5.0 mg Mg/kg/24h (group 2), 10.0 mg Mg/kg/24h (group 3) and 20.0 mg Mg/kg/24h (group 4), while the recommended daily allowance was 5.0 mg Mg/kg/24h (Griffith & Farris, 1942). Over the following 4 weeks the experiment was continued, but the animals did not receive magnesium. Control animals were given 2% arabic gum. During the course of the experiment the animals were housed in metabolic cages (2 animals per cage), at 2, 4 and 6 weeks or at 2, 4, 6 and 8 weeks, i.e. three or four times. For 36 hours, urine and feces were quantitatively collected from each pair of rats and subjected to magnesium and iron balance studies. The balance was calculated as the apparent retention rate according to the following formula: intake – (fecal excretion + urinary excretion) x 100% intake. Simultaneously, laboratory chow (standard diet) intake and body weigh gain were monitored. The element contents were measured by the ASA atomic spectrometry method.

Discussion

The apparent retention rate of magnesium was the highest compared to controls in study groups 2, 3 and 4 at week 2 of the experiment (Table 1). After 28 days of intake no significant differences were observed. The excess of magnesium following multiple dosing is probably removed mainly via the kidneys and the gastrointes-

TABLE 1. APPARENT RETENTION RATES OF MAGNESIUM AND ZINC (%).

Study groups	Experimental Weeks			
	Week 2	Week 4	Week 6	Week 8
Apparent Retention Rates of Magnesium (%)				
Control	45.30 ± 7.88	53.04 ± 15.97	11.53 ± 2.76	52.23 ± 10.07
Study group 1	51.98 ±11.41	56.87 ± 9.03	13.03 ± 3.69	40.50 ± 10.52
Study group 2	58.92 ± 10.99*	47.68 ± 12.66	33.43 ± 7.18*	37.60 ± 2.36
Study group 3	55.41 ± 8.82*	57.33 ± 8.41	35.57 ± 10.80*	40.04 ± 4.35
Study group 4	60.74 ± 9.66*	60.87 ± 12.33	52.08 ± 10.54*	47.50 ± 5.76
Apparent Retention Rates of Zinc (%)				
Control	21.63 ± 8.52	22.12 ± 11.77	20.14 ± 5.75	25.13 ± 7.38
Study group 1	21.10 ± 6.13	37.21 ± 9.45*	28.60 ± 8.03	26.93 ± 3.42
Study group 2	35.12 ± 11.06*	18.60 ± 5.97	34.16 ± 10.83*	31.77 ± 10.26
Study group 3	38.80 ± 11.67*	56.12 ± 12.67*	36.74 ± 8.45*	40.87 ± 7.16
Study group 4	30.78 ± 7.78	39.17 ± 9.22*	45.22 ± 11.37*	43.50 ± 2.0*

* A statistically significant difference compared to control ($p \leq 0.05$).

tinal tract, and as a result of hormonal regulation (Kuhn et al., 1992; Miura et al., 1999). After a 14-day interval in magnesium supplementation, i.e. at 6 weeks of the experiment another short-lasting increase in the apparent retention rate of magnesium was observed in the same study groups. At 8 weeks of the experiment, however, there were no differences found in the magnesium retention between the study groups and controls.

Magnesium doses used did not ultimately effect any permanent change in the apparent retention rate of magnesium, although they produced some disturbances in the retention of calcium. In our study, the effect of magnesium supplementation was investigated in animals fed a well-balanced diet with adequate content of magnesium and other nutrients (a standard laboratory chow — LSM granules). In these conditions, at 28 days of supplementation, a statistically significant decrease in the apparent retention rate of calcium was observed in the group receiving the highest dose of magnesium, i.e. 20.0 mg Mg/kg/h. Although at the other doses there were no changes in the calcium retention during the period of magnesium intake, at the end of the experiment, at 4 weeks following discontinuation of the magnesium supplementation, a significant decrease in the apparent retention rate of calcium was observed in all study groups (Table 2). That probably reflected a sustained competition for the intestinal absorption between magnesium and calcium. A long-term supply of dietary calcium is known to produce reduced absorption and retention in the rat (Smith et al., 1992; Miura et al., 1999) as a result of formation of insoluble calcium–magnesium–phosphorus complexes in the gut. That effect, however, is related to the diet content of phosphorus. Our study demonstrated that also prolonged intake of magnesium supplements for no apparent medical indications disturbs long-term calcium metabolism.

Our study also revealed that magnesium supplemented in the dosage described considerably modified iron retention. In the initial period of magnesium intake (week 2) a significant decrease in the apparent retention rate of iron was noted only in the group receiving 20.0 mg Mg/kg/24h. On the other hand, in the fourth week of magnesium supplementation the apparent retention rate was found to fall for iron in all study groups, while in group 3 the apparent retention rate of iron became negative. Even after a 4-week interval in magnesium supplementation (week 8), negative apparent retention rates of iron were observed in all study groups. The disturbed iron homeostasis persisted for a long time after magnesium discontinuation, which reflected the body's inability to rapidly adapt to changed magnesium intake. In the experimental conditions described, the excretion of iron with the feces and urine was excessive while the retention of iron was markedly decreased. It is known that the homeostasis of iron is controlled predominantly by intestinal absorption, mainly in the duodenum. Although there are many identified factors which affect the absorption, magnesium has not been clearly confirmed to influence the intestinal absorption of iron. In a reverse experimental system, M. Kimura & K. Yokoi (1996) investigated tissue retention of iron in the conditions of dietary magnesium deficiency. They found that magnesium deficit may lead to inefficient utilization of iron and its storage in the tissues, enhanced by administration of oral iron supplements. Our results confirm the interaction of magnesium and iron. Dietary magnesium supplements also produce disturbances in iron metabolism, which persist even after a 4-week interval in magnesium supplementation.

Our study reveals that magnesium supplemented at the doses of 5.0; 10.0 and 20.0 mg Mg/kg/24h exercises a beneficial effect on zinc retention (Table 1). The effect

TABLE 2. APPARENT RETENTION RATES OF CALCIUM, IRON AND COPPER (%).

Study groups	Experimental Weeks		
	Week 2	Week 4	Week 8
Apparent Retention Rates of Calcium (%)			
Control	74.33 ± 8.94	65.25 ± 10.13	43.37 ± 6.07
Study group 1	79.75 ± 5.22	67.65 ± 6.49	17.60 ± 6.14*
Study group 2	78.73 ± 5.57	60.13 ± 7.43	25.30 ± 4.85*
Study group 3	66.30 ± 13.52	55.62 ± 17.31	20.43 ± 5.71*
Study group 4	67. 61 ± 10.27	37.46 ± 10.01*	22.10 ± 4.32*
Apparent Retention Rates of Iron (%)			
Control	49.71 ± 3.81	53.56 ± 8.56	43.93 ± 11.83
Study group 1	48.49 ± 7.79	41.95 ± 9.39*	–103.1 ± 17.21*
Study group 2	53.23 ± 11.98	40.60 ± 7.84*	–16.73 ± 3.95*
Study group 3	46.23 ± 6.52	–22.64 ± 7.61*	–24.83 ± 7.39*
Study group 4	33.35 ± 9.30*	–37.04 ± 11.26*	–26.70 ± 1.22*
Apparent Retention Rates of Copper (%)			
Control	36.20 ± 8.02	27.43 ± 5.64	56.43 ± 11.91
Study group 1	42.34 ± 6.29	36.33 ± 8.84	–14.66 ± 3.43*
Study group 2	40.12 ± 9.20	24.07 ± 6.92	7.53 ± 1.36*
Study group 3	35.11 ± 8.26	30.62 ± 10.13	21.00 ± 3.74*
Study group 4	27.74 ± 7.53*	29.54 ± 8.37	–11.93 ± 4.20*

* A statistically significant difference compared to control ($p \leq 0.05$).

persisted even in the initial period (week 4) after magnesium supplementation was discontinued, which confirms strong synergy between the two ions. The effects of long-term magnesium intake, such as a positively increased zinc balance are observed long after discontinuation of the supplementation (up to 8 weeks in study group 4). Zinc is absorbed in the small intestine, the process being affected also by the presence of Fe, Cu, Mg, Co and P cations, and excreted by the kidneys and with feces (Solomons, Ruz, 1997; Salguiero et al., 2000). With zinc deficit, iron is known to play a compensatory role. In our study, after 4 weeks of continuous magnesium intake, irrespective of the dose used, unlike calcium and iron ions, zinc excretion with feces was significantly reduced, which may indicate the enhanced absorption of zinc. Many studies have confirmed a competitive action of zinc with respect to iron, copper and cadmium, achieved by binding to similar sites in the gut. Additionally, it is possible that zinc reduces iron binding to ferritin and in this way affects iron metabolism.

A 2-week supplementation with magnesium significantly decreased the apparent retention rate of copper compared to controls at a dose 20.0 mg mg/kg/24h (Table 2). However, at 28 days after discontinuation of supplementation in all doses used a significant decrease in the apparent retention rate of copper was observed.

Summing up, the findings reveal that multiple-dose magnesium intake in the doses described produced several disturbances in the retention of the investigated elements, especially of iron, both during magnesium supplementation and after its discontinuation.

Conclusions

Multiple-dose magnesium intake in nearly all doses used lowers the apparent retention rate for iron. The changes were observed over almost entire study period, i.e. both during magnesium supplementation and after its discontinuation. Compared to its effect on iron, magnesium intake in the doses described slightly differently affects the apparent retention of calcium and copper. In all study groups, with the exception of the group with the highest magnesium intake, the reduced retention rates for calcium and copper became obvious only after magnesium supplementation had been discontinued. On the other hand, the apparent retention rate for zinc remained increased compared to controls during the entire period of magnesium intake and in the initial period after the discontinuation. Magnesium retention, on the other hand, was increased exclusively in the initial period of supplementation.

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