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COMBINED EFFECT OF DIVERSIFIED Fe(III) CONTENT IN THE DIET AND Cr(III) SUPPLEMENTATION ON THE MAGNESIUM STATUS IN RATS*

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Abstract

Fe(III) and Cr(III) are transported by the same protein – transferrin, and they may have competitive effect on the absorption and transport to tissues. However, this effect may depend on relative proportions of these elements in a diet or in a body. As the status of iron and magnesium is disrupted in diabetes, the use of Cr(III) to support the treatment of this disease may further affect the content of these elements in the body. The aim of the study was to investigate the combined effect of diversified Fe(III) supply in a diet and simultaneous Cr(III) supplementation on the Mg status in rats.The assessment was based on a two-factor (2x3) experiment conducted on 54 female Wistar rats. The animals were randomly divided into 9 groups and for six weeks they were fed semi-purified diets (AIN-93) with different Fe(III) content: deficient – 5 mg kg^{-1} (10% RDA), recommended – 45 mg kg^{-1} (100% RDA) and high – 180 mg kg^{-1} (400% RDA), which was factor A. The diets were supplemented with Cr(III) at doses of 1, 50 and 500 mg kg^{-1} of the diet, which served as factor B. Iron(III) citrate was the source of Fe(III). Cr(III) was supplied in a complex of Cr(III) with propionic acid (Cr3). The Mg content in the liver, kidneys, spleen, heart and femur was analysed by atomic absorption spectrometry (AAS). The Fe(III) deficit in the diet (10% RDA) increased the Mg content in the liver, kidneys and heart. The high Fe(III) supply (400% RDA) increased Mg saturation in the femur, as compared with the Fe(III) control group, i.e. 45 mg kg^{-1} of the diet. Regardless of the Fe(III) supply, Cr(III) supplementation decreased the Mg content in the liver, kidneys and spleen, but increased it in the heart. The research proved that the diversified Fe(III) content in the diet, individually and in combination with Cr(III) supplementation, affected the Mg status in healthy rats.

Keywords: iron, chromium(III), magnesium, deficiency, overload, supplementation, rats.

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INTRODUCTION

Minerals often compete with each other for absorption in the intestine and distribution in tissues and organs (Kim et al. 2011). The deficiency or excess of some elements disturbs the metabolism of other minerals and results in changes of mineral concentrations in the blood and tissues (Kim et al. 2011).

Iron is an essential trace element for growth and health, as it is involved in many crucial biological processes (Hentze et al. 2004). Being a haemoglobin component in erythrocyte protein, it transfers oxygen from the lungs to tissues (Auerbach et al. 2016). Being a myoglobin component, i.e. a protein that provides oxygen to muscles, iron supports metabolism. Iron is also necessary for the growth, development, normal cellular functioning and synthesis of some hormones and connective tissues (Auerbach et a. 2016).

Iron deficiency is one of the most prevalent nutritional deficiencies in humans all over the world (Xiao et al. 2016). Kassebaum et al. (2014) estimated that over 30% of the world population is anaemic, mostly due to iron deficiency, which is caused by an inadequate iron intake and absorption in the body (Naigamwalla et al. 2012). Iron deficiency decreases the oxygen transport capacity, energy production and cellular proliferation (Gkouvatsos et al. 2012).

Iron is naturally present in many foods; it is added to some food products and it is available as a dietary supplement. The bioavailability and absorption of iron from the daily diet are affected by the presence and type of iron absorption promoters and inhibitors in the diet and by an individual iron status (Duque et al. 2014). Iron supplements have been widely used to overcome iron deficiency (Xiao et al. 2016).

Adults with normal intestinal function are at a very low risk of iron overload from dietary sources. However, excessive intake of more than 20 mg kg^{-1} of iron from supplements or medicines can lead to upset stomach, constipation, nausea, abdominal pain, vomiting and fainting, especially if food is not taken at the same time (Duque et al. 2014).

Some groups are at risk of iron overload (Munoz et al. 2011). Individuals with hereditary haemochromatosis, which predisposes them to the absorption of excessive amounts of dietary iron, are at a higher risk (Bacon et al. 2011).

Haemochromatosis is a disease caused by some mutation in the haemochromatosis (HFE) gene (Bacon et al. 2011). About 1 in 10 of white people carries the most common HFE mutation (C282Y), but only 4.4 out of 1,000 white people are homozygous for the mutation and have haemochromatosis (Whitlock et al. 2006). The American Association for the Study of Liver Diseases recommends that treatment of haemochromatosis should include the avoidance of iron and vitamin C supplements (Bacon et al. 2011).

On the other hand, many studies have shown that Cr(III) supplementation improved insulin sensitivity and blood glucose levels in animals and

humans suffering from impaired glucose tolerance, insulin resistance and diabetes (Tang et al. 2015, Sharma et al. 2011). This suggests that Cr(III) may increase the use of energy nutrients by influencing the activity of insulin receptors, and thus accelerate the loss of body weight and affect the body composition (Kurył et al. 2005). For these reasons, in recent years, Cr(III) supplements have become very popular therapeutics in diabetes and they have been used as agents aiding weight loss.

Fe(III) and Cr(III) are transported by the same protein – transferrin. It is believed that there may be a competitive effect between these elements on the absorption and transport to tissues (Quarles et al. 2011, Vincent, Love 2012). However, the effect may depend on relative proportions of these components in the diet or in the body.

Magnesium is the second most abundant intracellular cation and the fourth most abundant cation in the body. This element is a cofactor of numerous enzymes and plays an essential role in a wide range of fundamental cellular reactions. Over 300 enzymes are dependent on magnesium. This role is achieved through two important properties of magnesium – the ability to form chelates with important intracellular anionic-ligands, especially ATP, and the ability to compete with calcium for binding sites on proteins and membranes. Magnesium is essential for the synthesis of nucleic acids and proteins, for intermediary metabolism and for specific actions in different organs such as the neuromuscular and cardiovascular systems. It affects myocardial contractility by influencing the intracellular Ca concentration and the electrical activity of myocardial cells and the specialised cardiac conduction system by influencing the movement of ions such as Na, K and Ca across the sarcolemmal membrane. This element may also affect the vascular smooth muscle tone. Magnesium has a key role in many other important biological processes such as cellular energy metabolism, cell replication and protein synthesis (Swaminathan 2003).

Both iron and magnesium are considered essential minerals and are recommended for a balanced diet. The aim of the study was to investigate the combined effect of diversified Fe(III) content in the diet and Cr(III) supplementation on the Mg status in rats.

MATERIAL AND METHODS

Chemicals

The chromium(III) complex with propionic acid, known as Cr3, in the form of nitrate salt (chemical formula $[Cr_3O(O_2CCH_2CH_3)_6(H_2O)_3]NO_3$) was synthesised in the laboratory of the Department of Product Ecology, Poznań University of Economics, Poland, following the method described by Earnshaw et al. (1966). The AAS method (AAS-3 spectrometer with BC correction,

Zeiss, Germany) revealed 21% of elemental Cr in the Cr3. Iron(III) citrate (reagent grade, 16.6% Fe) was purchased from Sigma-Aldrich, Poland.

Animals and diets

54 six-week-old female Wistar rats were obtained from the Department of Toxicology, Poznań University of Medical Sciences, Poland. After five-day adaptation to laboratory conditions, the rats were divided into 9 groups of approximately equal initial mean body weight, i.e. 130.5 g. The animals were housed in single cages, at controlled temperature, photoperiod and air humidity (19-22°C, 12-h light/dark cycle, 55-60% of ambient air humidity). For 6 weeks all the groups were fed semi-purified AIN-93M diets (Reeves 1997), modified according to the two-factor experimental design.

Healthy female rats were divided into 9 experimental groups (6 animals in each) with different Fe(III) content: deficient – 5 mg kg^{-1} (10% RDA), recommended (adequate) – 45 mg kg^{-1} (100% RDA) and high (overload) – 180 mg kg^{-1} (400% RDA). Their diets were supplemented with Cr(III) at doses of 1, 50 and 500 mg kg^{-1} of the diet. The study was conducted according to the following pattern:

group 1 (control, C1) – Fe 45 mg kg^{-1}, Cr 1 mg kg^{-1};

group 2 (C50) – Fe 45 mg kg^{-1}, Cr 50 mg kg^{-1};

group 3 (C500) – Fe 45 mg kg^{-1}, Cr 500 mg kg^{-1};

group 4 (D1) – Fe 5 mg kg^{-1}, Cr 1 mg kg^{-1};

group 5 (D50) – Fe 5 mg kg^{-1}, Cr 50 mg kg^{-1};

group 6 (D500) – Fe 5 mg kg^{-1}, Cr 500 mg kg^{-1};

group 7 (H1) – Fe 180 mg kg^{-1}, Cr 1 mg kg^{-1};

group 8 (H50) – Fe 180 mg kg^{-1}, Cr 50 mg kg^{-1};

group 9 (H500) – Fe 180 mg kg^{-1}, Cr 500 mg kg^{-1};

The rats were allowed free access to food and distilled water throughout the experiment. The feed intake was measured daily, while body weight gains were monitored weekly. At the end of the experiment, after 12-hour starvation, the rats were euthanised by asphyxiation with CO_2. Blood was collected into tubes, tissue samples (liver, kidneys, heart, spleen, pancreas, ovaries) were harvested, weighed and frozen.

The study was conducted at the Department of Human Nutrition and Hygiene (Poznań, Poland) and was approved by the Animals Bioethics Committee of Poznań (No. 60/2013).

Methods

The Mg content in the tissue samples under analysis was determined by flame atomic absorption spectrometry (F-AAS), using an AAS-3 spectrometer (with BC, Carl-Zeiss, Germany), after prior digestion in a Microwave Digestion System (MARS-5, CEM, USA).

The tissues (liver, kidney, spleen, heart and femur) (0.5-1.5 g) were digested with 5 ml of SpectraPure HNO_3 concentrated at 65% (Merck) in Teflon pressure vessels. Thereafter, having diluted the samples to the measuring range with a 0.5% solution of $LaCl_3$ (Merck), the Mg concentration in the mineral solution was measured with the flame AAS method (F-AAS).

Statistical analysis

The results are shown as mean ± SD. The experimental data were assessed with a two-way analysis of variance (ANOVA), followed by a *post-hoc* Tukey test, which was used to compare the data between the groups. A p value of less than 0.05 was considered statistically significant. The data were analysed using Statistica 12.0 software (StatSoft, Tulsa, USA).

RESULTS

Table 1 shows the effects of diversified Fe(III) content in the diet and Cr3 supplementation on the tissular Mg content in female healthy rats.

Both experimental factors (individually and in combination) influenced the Mg content in the liver, kidneys, spleen and femur. The highest Mg content was found in the liver of the rats fed the Fe(III)-deficient 5 mg kg^{-1} diet (820.77 ± 54.52 μg g^{-1} d.m.), and it was significantly higher (10.4%) than in the group of rats fed diets with the recommended Fe(III) content 45 mg kg^{-1} diet (743.46 ± 80.76 μg g^{-1} d.m.) and high Fe(III) content 180 mg kg^{-1} diet (750.23 ± 119,46 μg g^{-1} d.m.). However, there were no significant differences in the Mg content in the liver between the rats fed the diet with high Fe(III) content (180 mg kg^{-1} diet) and the control group.

It was observed that the diet supplemented with Cr(III) at a dose of 50 mg kg^{-1} diet (742.91 ± 84.67 μg g^{-1} d.m.) and 500 mg kg^{-1} diet (741.31 ± ± 99.15 μg g^{-1} d.m.) significantly decreased the Mg content in the liver by 10.52% and 10.71%, respectively, as compared with the control group for Cr(III), i.e. 1 mg kg^{-1} diet (830.24 ± 71.87 μg g^{-1} d.m.).

There was also significant interaction between the factors under investigation in their influence on the hepatic Mg content. The lowest Mg content in the liver was found when the rats were fed with high Fe(III) 180 mg kg^{-1} diet and Cr(III) 500 mg kg^{-1} (663.50 ± 40.27 μg g^{-1} d.m.). This was significantly lower than the Mg level in the liver of animals fed diets with 180 mg kg^{-1} Fe(III) and Cr(III) at the recommended level of 1 mg kg^{-1} (881.20 ± 103.44 μg g^{-1} d.m.) and with deficient Fe(III) at all Cr(III) supplementation levels, respectively: recommended (806.40 ± 33.12 μg g^{-1} d.m.), supplemented with 50 mg Cr(III) (815.05 ± 80.84 μg g^{-1} d.m.) and 500 mg Cr(III) per kg diet (840.87 ± ± 41.25 μg g^{-1} d.m.) as well as in the control group with the recommended Fe(III) 45 mg kg^{-1} and Cr(III) 1 mg kg^{-1} diet (803.12 ± 32.94 μg g^{-1} d.m.).

Table 1

Combined effects of diversified Fe(III) content in the diet and Cr(III) supplementation on the Mg content in the tissues of rats

Experimental factor		Level factor (mg kg^{-1} diet)		Mg content in tissues (mean ± SD)				
				liver	kidney	spleen	heart	femur
				(μg g^{-1} d.m.)				
Factor A content Fe(III) in diet		5		820.77 ± 54.52^{a}	779.91 ± 132.70^{a}	1048.34 ± 118.27^{a}	1077.72 ± 112.14^{a}	4.19 ± 0.29^{a}
		45 (control)		743.46 ± 80.76^{b}	672.69 ± 124.48^{b}	1157.90 ± 78.81^{b}	1015.44 ± 100.05^{ab}	3.93 ± 0.23^{b}
		180		750.23 ± 119.46^{b}	768.15 ± 116.24^{ab}	1033.43 ± 84.35^{a}	970.56 ± 79.51^{b}	4.37 ± 0.27^{a}
Factor B content Cr(III) in diet		1 (control)		830.24 ± 71.87^{a}	786.16 ± 128.02^{a}	1132.39 ± 105.60^{a}	1008.17 ± 86.85	4.18 ± 0.22
		50		742.91 ± 84.67^{b}	758.95 ± 126.32^{ab}	1070.74 ± 99.18^{ab}	1015.82 ± 113.93	4.15 ± 0.31
		500		741.31 ± 99.15^{b}	670.20 ± 118.62^{b}	1036.53 ± 105.39^{b}	1039.74 ± 119.25	4.16 ± 0.41
Interactions (AxB)	group	Fe(III)	Cr(III)					
	D1	5	1	806.40 ± 33.12^{bc}	843.80 ± 124.22	1161.46 ± 95.05^{b}	1038.77±133.11	4.05±0.15^{ab}
	D50	5	50	815.05 ± 80.84^{bc}	791.86 ± 127.16	1006.15 ± 73.57^{ab}	1053.24 ± 132.42	4.16 ± 0.19^{ab}
	D500	5	500	840.87 ± 41.25^{bc}	704.08 ± 127.69	977.39 ± 97.89^{a}	1141.15 ± 32.95	4.35 ± 0.42^{b}
	C1	45	1	803.12 ± 32.94^{bc}	748.62 ± 122.35	1187.37 ± 97.56^{bd}	991.81 ± 65.45	4.08 ± 0.18^{ab}
	C50	45	50	707.70 ± 65.03^{ab}	642.96 ± 108.32	1168.82 ± 80.29^{bcd}	1033.41 ± 104.95	3.92 ± 0.21^{ab}
	C500	45	500	719.57 ± 101.85^{ab}	625.50 ± 124.26	1117.50 ± 44.80^{abcd}	1024.69 ± 137.34	3.80 ± 0.24^{a}
	H1	180	1	881.20 ± 103.44^{bc}	766.05 ± 138.42	1048.35 ± 79.06^{abcd}	993.95 ± 51.40	4.39 ± 0.17^{b}
	H50	180	50	705.99 ± 65.14^{ab}	842.04 ± 24.97	1037.27 ± 60.78^{abcd}	964.34 ± 104.98	4.38 ± 0.35^{b}
	H500	180	500	663.50 ± 40.27^{a}	681.99 ± 108.81	1014.68 ± 116.36^{abc}	953.39 ± 85.80	4.33 ± 0.32^{b}

The data are shown as mean ± SD. The values in the same column which are not marked with the same superscript letter differ significantly (two-way analysis of variance, $p < 0.05$).

There were no statistically significant differences in the other groups. However, a trend was observed in the groups with the recommended and high Fe(III) intake and there was an increase in the Cr(III) content in the diet, which reduced Mg levels in the rat liver. However, these trends were not observed in the Fe(III)-deficient groups.

It was found that the Fe(III) content in the diet significantly affected the Mg content in the kidneys, regardless of a dose of Cr(III). The Fe(III)-deficient diet (5 mg kg^{-1} diet) resulted in a significant increase in the Mg level in the kidneys, which was 16% higher than in the control group.

Cr(III) supplementation at a dose of 500 mg kg^{-1} diet resulted in a significant decrease in the Mg content in the kidneys, which was 15% lower than in the control group with the Cr(III) content of 1 mg kg^{-1} diet. The statistical analysis did not show any significant interaction effect of the factors under study on the kidney Mg content.

Both the deficit and the high dose of Fe(III) in the diet caused a significant decrease in the Mg content in the spleen, which was respectively 9% and 11% lower than in the control group.

The increase in the Cr(III) supply in the diet decreased the Mg content in the spleen. The supplementation of Cr(III) at 500 mg kg^{-1} diet decreased the Mg content in the spleen by 9%, as compared with the control group. There was no interaction effect of the experimental factors on this parameter.

The increase in the Fe(III) content in the diet decreased the Mg content in the heart. However, Cr3 supplementation did not affect the Mg content in the heart. Also, there were no significant interaction effects of the experimental factors on this parameter.

Both the deficit and the oversupply of Fe(III) caused an increase in the Mg content in the femur, which was respectively 7% and 11% higher than in the control group. However, Cr3 supplementation did not affect the Mg level in the femur. On the other hand, the experimental factors significantly affected this parameter. The lowest femur Mg content was found in the rats fed the diet with Fe(III) at the recommended level (45 mg kg^{-1} diet) and Cr(III) at 500 mg kg^{-1} (3.80 ± 0.24 μg g^{-1} d.m.). It was significantly lower than in the high Fe(III) supply groups at all Cr levels as well as in the group with Fe(III) deficiency and Cr(III) at a dose of 500 mg kg^{-1}.

DISCUSSION

Some trace elements may be involved in the pathogenesis of diet-dependent diseases. Iron deficiency is one of the leading risk factors of disability and death worldwide, affecting an estimated 2 billion people. Iron deficiency anaemia is a common nutritional problem, especially in developing countries. Nutritional iron deficiency arises when physiological requirements cannot be

met by iron absorption from the diet. Dietary iron bioavailability is low in populations consuming monotonous, plant-based diets (Zimmermman, Hurrel 2007). The primary strategies for correcting Fe deficiency in these populations are dietary modification or diversification to improve the Fe intake and bioavailability, Fe supplementation and Fe fortification of foods, and biofortification by plant breeding (Zimmermman, Hurrel 2007, Zielińska-Dawidziak et al. 2012).

The interaction between Fe and other elements has been well investigated in studies on animals and humans. It may occur directly or indirectly. Direct interactions are usually competitive phenomena, which take place during intestinal absorption or tissue utilisation, whilst indirect interactions take place when the mineral is involved in the metabolism of another mineral, in a way that the deficiency or overload of one mineral causes impaired function of the other (Vaz et al. 2010).

Diabetes mellitus is a group of metabolic diseases characterised by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. Some studies proved that Cr(III) supplementation improved insulin sensitivity and blood glucose levels in animals and humans suffering from impaired glucose tolerance, insulin resistance and diabetes (Sharma et al. 2011, Tang et al. 2015). The relationship between diabetes and trace minerals is complex, with no clear cause-and-effect relationship (Akhuemokhan et al. 2013). Several studies have reported that the imbalance of some essential metals might adversely affect pancreatic islets and cause the development of diabetes (Khan, Awan, 2014). Metal ions are known to play an essential role in living systems, both in their growth and in metabolism. Impaired metabolism of trace elements is observed in diabetic patients (Khan, Awan 2014). Altered metabolism of Cr(III), Cu(II), Fe(III), Mg(II), and Zn(II) has been reported in type 2 diabetes mellitus (Khan et al. 2015). There is a lot of evidence that the metabolism of several trace elements is altered in diabetes mellitus and that these nutrients might have specific roles in the pathogenesis and progress of this disease (Khan, Awan 2014).

Fe(III) and Cr(III) are transported by the same protein – transferrin. It is believed that there may be competitive effect of these elements on the absorption and transport to tissues (Quarles et al. 2011, Vincent, Love 2012). Mg metabolic disorders are observed in a variety of diseases, such as diabetes, renal and gastrointestinal disease, cardiovascular and neurological disorders (Zheltova et al. 2017). So far, there have been no studies on the combined effect of different Fe(III) levels in the diet and Cr(III) supplementation on tissular Mg levels in rats.

There have been reports on the interaction between Mg and Fe (Sampaio et al. 2014). However, the mechanisms of this interaction have not been investigated. Vaz et al. (2010) found that Fe deficiency decreased intestinal Mg absorption, whereas supplementation with inulin-type fructans re-established Mg absorption to levels comparable with those in a non-deficient

control group. In comparison with control groups, Mg levels were reduced in the bones of Fe-deficient rats. It is suggested that increased bone Mg mobilisation might have occurred to allow the erythrocyte survival in Fe-deficient rats (Vaz et al. 2010).

Magnesium may be utilised better in some processes that require iron when it is deficient. This speculation is further strengthened by the fact that the magnesium content in the liver remains unchanged. As the liver is a storage organ for iron, it will store adequate amounts of iron for cellular metabolism even when the element is deficient. It is also possible that iron deficiency affects magnesium absorption and transportation, reducing the magnesium content in these tissues (Oladiji 2003).

Oladiji (2003) observed that iron deficiency decreased the Mg content in the kidneys, heart, lungs and brain, but not in the liver. Furthermore, Fe deficiency negatively affected the absorption of Mg and Zn in male Wistar rats (Vaz et al. 2010). However, Mg deficiency increased the iron content in different tissues. It was also confirmed by Kim et al. (2011), who reported that Mg deficiency increased the content of Fe, Cu and Zn in the liver of male rats. It has been suggested that Mg deficiency leads to increased fragility and destruction of erythrocytes (Sanchez-Morito et al. 2000). Studies have shown that magnesium deficiency can lead to anaemia as the lack of magnesium causes the red-blood cell (erythrocyte) membrane to become more fragile and easily damaged. On the other hand, magnesium provides protection from damage caused by iron overload, reducing haemolysis and the release of free iron (Shi et al. 2008).

As far as the effect of Cr(III) supplementation on the Mg content in the organism is concerned, Krejpcio et al. (2009) reported that supplementary Cr(III) at a dose of 5 mg kg^{-1} did not affect Mg metabolic indices in Wistar rats. Supplementary doses of Cr3 (10-100 mg of Cr kg^{-1} of body mass) given for 4 weeks did not affect the Mg status in the healthy female Wistar rats (Staniek, Krejpcio 2017). Sirirat et al. (2012) found that NanoCrPic supplementation at doses of 0, 500 and 3,000 ppb improved the utilisation of Zn, Fe and Ca and they decreased the Zn, Fe and Ca content in chicken excreta. Prescha et al. (2014) reported that the addition of Cr(III) to a fibre-free diet and to diets with cellulose or pectin did not change the Zn, Mg and P content in the femur or the Cr, Fe, and Zn content in the muscles of rats. However, addition of pectin or cellulose to the diets, especially with Cr, increased the Zn content in the liver and kidneys and changed the Mg and Ca levels in these tissues. Król et al. (2013) reported that Cr3 supplementation disturbed mineral homeostasis in the organs of rats fed a high-fructose diet. Cr3 given for 4 weeks at doses of 1 and 5 mg kg^{-1} b.w. per day increased hepatic Mg, Cu and Cr levels, but it did not influence the tissular content of Ca, Fe or Zn.

CONCLUSIONS

The diversified content of Fe(III) in the diet and Cr(III) supplementation, individually and in combination, influenced on the Mg status in healthy rats.

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