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The combined effects of Cr(III) propionate complex supplementation and iron excess on copper and zinc status in rats

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ABSTRACT

It is suggested that both iron overload and chromium(III) deficiency may be risk factors of diabetes. It seems that both Fe and Cr(III) metabolism as well as copper and zinc metabolism are interrelated. However, the direction of these changes may depend on mutual proportions of these elements in the diet and organism. The aim of the study was to evaluate the combined effects of Cr(III) supplementation with Fe excess on the Cu and Zn status in female rats. Thirty-six healthy rats were divided into 6 experimental groups with different Fe levels in the diet. Groups marked with C (control) contained Fe at the recommended level (45 mg kg^{-1}). The excess groups (E) contained Fe at 180 mg kg^{-1}. At the same time the animals were supplemented with Cr(III) of doses 1, 50 and 500 mg kg^{-1} of diet. The Cr, Fe, Cu and Zn dietary and tissular contents were measured with the AAS method.The excess Fe in the diet significantly decreased the Cu content in the liver and kidneys, but it increased the spleen Cu level. The Cr(III) supplementary did not affect the tissular Cu levels, regardless of Fe supply with diet. The experimental factors did not have significant interactional effect on the Cu status parameters under study.The Fe excess in the diet reduced the renal and splenic Zn content, but increased the heart Zn content. The Cr(III) supplementation decreased the Zn content in the kidneys. The Zn content in the liver and spleen tended to decrease as the Cr(III) supply in the diet increased. There was no significant interactional effect of Cr(III) supplementation and the Fe excessive supply in diet on the parameters of Zn metabolism in Wistar rats.

Iron oversupply disturbed the rat's Cu and Zn status. However, Cr(III) supplementation did not affect the tissular levels of these elements, except the kidney Zn content. Simultaneous supplementation with the Cr(III) propionate complex did not deepen changes in tissular Cu and Zn levels caused by the Fe excess in the diet.

1. Introduction

Some metals are one of the food components. They are essential for health and proper bodily functions. Minerals are not synthesized, so they should be delivered at the adequate amounts to the body [1]. The bioavailability and tissular deposition of trace elements depend on their chemical form, diet components, age, and physiological state of the organism, and element interactions [2]. In relation with the food fortification with Fe compounds and uncontrolled dietary Fe supplementation, in order to eliminate deficiencies of this element, the certain groups of the population may be exposed to the opposite effect of these actions, i.e. Fe overload. Nowadays, the market offers a wide range of easily accessible supplements of minerals. Recently there has been growing interest in iron overload/excess and its health consequences. Iron can have negative effect when it accumulates in the organism in excess. Fe, Cu, Zn and Cr(III) are trace elements, whose balance is essential for proper bodily functions [3]. It seems that the metabolism of these elements is interrelated and they may interact with each other. They may act direct or indirect role in the development many diseases, e.g. anaemia, diabetes, depression. Disturbances in Fe homeostasis are associated to a broad spectrum of metabolic and neurodegenerative diseases [4]. The Fe content in the body largely depends on the efficiency of its absorption and request. Iron absorption disturbances underlie various disorders of the homeostasis of this element [5]. One of them is increased Fe absorption despite the adequate or increased Fe content, which may be caused by primary Fe loading disorders or hemochromatosis [5]. Iron generates reactive oxygen species (ROS) and acts as an oxidant. Most evidence supports the hypothesis that Fe overload causes overproduction of free radicals. Thus, it contributes to tissue damage and increases oxidative stress [1,6]. Fe oversupply might be related with the aetiology of some chronic diseases, such as diabetes [7,8], cardiovascular disease [4,9,10] and cancer [11].

Both Fe overload and insufficient Cr(III) supply were suggested as possible risk factors of carbohydrate metabolism disturbance, which may lead to development of diabetes [7,12–14].

Interactions between Fe and Cr(III) may indicate the fact that

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transferrin, the Fe transport protein, is the molecular agent responsible for Cr(III) transport to target tissues [15]. It is suggested that at high levels Cr or Fe may act as antagonist due to the fact that metal binding sites are divided between Fe(III) and Cr(III) ions [16–18]. Studies showed that the physiologically correct concentration of chromium ions did not influence the binding of Fe(III) at physiological concentrations to transferrin, but Fe(III) oversupply reduced the Cr(III) ability to bind to transferrin [17,19]. Iron also influences in the metabolism of other trace elements such as Cu and Zn.

Iron is a very important element required for the synthesis of haemoglobin and myoglobin, which is involved in the transport of oxygen and which affects with insulin sensitivity [7]. Some reports showed a positive correlation between serum ferritin concentration and Fe deposition in tissues, which increased linearly with the duration of diabetes [1,20]. Cooksey et al. [21] noticed the long-lasting reversible and beneficial effect of the low-Fe diet on carbohydrate metabolism in the ob/ob mice. Many studies reported that Fe overload may cause insulin resistance and diabetes [1,7,10,22–25]. One of the proposed mechanisms is oxidative stress induced by increased iron storage in the liver and β-cells, leading to cell damage and insulin resistance, causing insulin deficiency [21] and disturbing glucose metabolism [6,14]. Another hypothesis suggests that insulin may facilitate Fe accumulation by redistribution of transferrin receptors to the cell surface as well as cellular uptake and stimulation of ferritin synthesis [10,14,26].

Cu is also involved in the production of haemoglobin, melanin and myelin. This element also enables for proper thyroid function. Cu is responsible for the function of many critical enzymes, like superoxide dismutase (SOD), cytochrome c oxidase, lysyl oxidase as well as tyrosinase. It can act both as antioxidant and as a pro-oxidant [27].

In turn, zinc has a structural, catalytic and control function. It is responsible for immunological reactions, apoptosis and ageing of the organism. Zinc is also engaged in the activity of many enzymes and proteins, such as metabolic enzymes, transcription factors and cell signalling proteins [28]. Both Cu and Zn are components of superoxide dismutase (Cu-Zn SOD), so their levels can significantly affect the oxidative potential in cells.

Chromium(III) improves the parameters of glucose metabolism, especially in patients with diabetes. Insufficient Cr(III) intake was implied as a possible risk factor of the development of diabetes [12,13]. Despite the fact that since 2014 the European Food Safety Authority (EFSA) [29] has not longer considered Cr(III) an essential element for animals and humans, it is still a very popular component of dietary supplements.

Cr(III) and Zn ions have been postulated as an attractive nutritional intervention approach in the therapy of diabetes [30]. On the contrary, some essential trace elements play a certain role in the pathogenesis and development of type 2 diabetes. For example, it is high Fe level and dysregulation of Cu homeostasis [25]. For these reasons, it is important to support the appropriate mineral dietary balance between Fe, Cr(III), Cu and Zn [27]. Dietary habits and adequate doses of supplements may be significant in the treatment or reduction of risk some diseases e.g. diabetes [16].

In view of these facts, Cr(III) supplementation was hypothesized to soothe changes in the Cu and Zn status caused by Fe excess in the diet. Therefore, the combined effects of dietary Cr(III) propionate complex supplementation and Fe oversupply on the Cu and Zn metabolism in animal model were studied.

2. Material and methods

2.1. Test chemicals

The Cr(III) propionate complex (Cr3) was prepared according to the procedure by described Earnshaw et al. [31,32]. Iron(III) citrate was purchased from Sigma Aldrich (USA).

2.2. Animals and diets

This research was conducted using in a factorial design, with three different Cr(III) concentration levels in the diet (1, 50, and 500 mg kg^{-1}, respectively) and two different concentration levels of Fe in the diet [recommended (C) – 45 mg kg^{-1} and excess (E) – 180 mg kg^{-1}]. The experiment was carried out on 36 healthy female Wistar rats, according to the procedure described in detail by Staniek & Wójciak [31]. All procedures involving rats were in accordance with the ethical standards or practice of the institution at which the experiment were conducted. The study was accepted by the Local Animals Bioethics Committee (No. 60/2013).

The thirty-six rats were divided into 6 experimental groups (6 animals in each) with different Fe levels in the diet. The groups marked with C (control) contained Fe at the recommended level (45 mg kg^{-1} – 100% RDA). The excess (oversupply) groups (E) contained a 4 times higher Fe level in the diet (180 mg kg^{-1} – 400% RDA). At the same time the animals were supplemented with Cr(III) at doses of 1, 50 and 500 mg kg^{-1} of diet. The experiment was carried out according to the following group scheme: C1 – control (Fe 45 mg kg^{-1}, Cr 1 mg kg^{-1}); C50 (Fe 45 mg kg^{-1}, Cr 50 mg kg^{-1}); C500 (Fe 45 mg kg^{-1}, Cr 500 mg kg^{-1}); E1 (Fe 180 mg kg^{-1}, Cr 1 mg kg^{-1}); E50 (Fe 180 mg kg^{-1}, Cr 50 mg kg^{-1}); E500 (Fe 180 mg kg^{-1}, Cr 500 mg kg^{-1}).

2.3. Laboratory analyses

The chemical composition of the experimental diets was presented in detail in the previous paper [31]. The diet and tissue samples for mineral analyses were digested with concentrated 65% spectra pure nitric acid (Merck) in a Microwave Digestion System (MARS-5, CEM, USA).

The tissues (liver, kidney, heart, spleen and femur) (0.5–1.5 g) were digested with 5 ml concentrated 65% spectra pure nitric acid (Merck) in Teflon pressure vessels. Thereafter, having diluted the samples to the measuring range of the selected element in deionised H_2O, the concentrations of selected elements in the mineral solution were measured.

The concentration of Cu, Zn and Fe in mineralized samples was determined with F-AAS (Zeiss AAS-3, with BC, Germany). The concentration of Cr was measured by means of GF-AAS (AAS-5 EA with BC, Jenoptic, Germany). The accuracy of Zn, Cu and Fe measurements was ensured by simultaneous analysis of certified reference material (Pig Kidney BCR No. 186, Brussels), while the accuracy of Cr analysis was ensured using mussel tissue certified reference material (ERM®-CE278). The average recoveries of certified levels were as follows: Zn – 98%, Cu – 101%, Fe – 98% and Cr – 101%.

2.4. Statistical analysis

The data are showed as mean ± SD. Statistica version 12.0 for Windows (StatSoft, Poland) used for statistical analysis. The significance of the main effects and interaction of experimental factors was determined with two-way analysis of variance (ANOVA/MANOVA). Differences between the mean values of multiple groups were analyzed by means of one-way ANOVA and parametric Tukey's post hoc test. The results were statistically significant at $p < 0.05$.

3. Results

Table 1 shows the main effects of different Fe(III) and Cr(III) levels in the diet on the tissular Cu and Zn contents in female rats. The Fe excess in the diet significantly reduced the content of Cu in the liver ($p < 0.01$) by 16% and kidneys ($p < 0.01$) by 32%, but increased the spleen Cu level ($p < 0.001$) by 76% in comparison with the control Fe level in the diet. However, it did not cause significant changes in the content of this element in the heart and femur (Table 1). The Cr(III) supplementary did not affect the tissular Cu levels regardless of Fe

Table 1
The main effects of Fe(III) excess and Cr(III) supplementation on the Cu and Zn content in rats' tissues (mean ± SD).

Parameters	Main effects					
	Factor B Cr(III) level in diet			Factor A Fe(III) level in diet		
	1 vs. 50 vs. 500 (mg kg^{-1} diet)		*p*-Value	Adequate vs. excess (mg kg^{-1} diet)		*p*-Value
Cu content in liver (μg g^{-1} d.m.)	1 (control)	27.93 ± 3.11	NS	45 (control)	29.23 ± 3.49^{b}	$p < 0.01$
	50	27.69 ± 5.81		180 (excess)	24.64 ± 3.85^{a}	
	500	24.82 ± 3.42				
Cu content in kidney (μg g^{-1} d.m.)	1	45.45 ± 12.82	NS	45	48.38 ± 11.10^{b}	$p < 0.01$
	50	40.71 ± 8.61		180	32.78 ± 9.41^{a}	
	500	34.25 ± 14.66				
Cu content in spleen (μg g^{-1} d.m.)	1	10.41 ± 3.72	NS	45	6.61 ± 1.06^{b}	$p < 0.001$
	50	7.76 ± 1.90		180	11.60 ± 2.38^{a}	
	500	9.77 ± 3.31				
Cu content in heart (μg g^{-1} d.m.)	1	21.57 ± 1.49	NS	45	20.41 ± 2.80	NS
	50	19.32 ± 2.88		180	20.68 ± 2.08	
	500	20.76 ± 2.32				
Cu content in femur (μg g^{-1} d.m.)	1	3.83 ± 0.44	NS	45	4.02 ± 0.40	NS
	50	3.79 ± 0.29		180	3.74 ± 0.36	
	500	3.97 ± 0.46				
Zn content in liver (μg g^{-1} d.m.)	1	120.45 ± 8.47	NS	45	114.20 ± 10.80	NS
	50	115.74 ± 16.65		180	118.33 ± 14.33	
	500	113.36 ± 10.94				
Zn content in kidney (μg g^{-1} d.m.)	1	105.54 ± 19.09^{b}	$p < 0.001$	45	107.35 ± 13.21^{b}	$p < 0.01$
	50	101.54 ± 8.16^{b}		180	90.22 ± 16.23^{a}	
	500	88.78 ± 19.38^{a}				
Zn content in spleen (μg g^{-1} d.m.)	1	88.13 ± 10.71	NS	45	87.62 ± 9.13^{b}	$p < 0.05$
	50	84.33 ± 7.74		180	80.46 ± 8.72^{a}	
	500	79.68 ± 9.26				
Zn content in heart (μg g^{-1} d.m.)	1	68.73 ± 6.77	NS	45	63.29 ± 7.67^{a}	$p < 0.05$
	50	63.18 ± 8.43		180	70.07 ± 7.69^{b}	
	500	69.13 ± 8.77				
Zn content in femur (μg g^{-1} d.m.)	1	314.69 ± 15.52	NS	45	322.18 ± 24.71	NS
	50	319.41 ± 19.67		180	309.80 ± 14.51	
	500	312.64 ± 26.70				

The values with different superscript letters are significant differently (two-way analysis of variance, $p < 0.05$). d.m.: dry mass; NS: no significant effect.

supply in the diet. However, the Cu content in the liver and kidneys tended to decrease gradually along with the Cr(III) dose pattern in the diet, but these changes were not statistically significant (Table 1).

The experimental factors did not have significant interactional effect of on the rat's Cu level parameters (Fig. 1). However, it was observed some tends that the rats supplemented with Cr(III) in combination with Fe oversupply had lower Cu levels in most analyzed tissues (except the spleen) than the animals given Cr(III) and Fe at the control level, respectively (Fig. 1).

Regarding the influence of the main experimental factors on tissular Zn levels, the Fe excess in the diet was found to decrease the renal Zn level by 16% ($p < 0.01$) and the splenic Zn level by 8% ($p < 0.05$), but it increased the heart Zn content by 11% ($p < 0.05$). However, the concentration of Cu in the liver and femur was unaffected by Cr(III) supplementation. The Cr(III) supplementation decreased the Zn content in the kidneys ($p < 0.001$), but this effect was significant only at the highest dose (500 mg kg^{-1} of diet). The Zn content in the liver and spleen tended to decrease along with the increase in the Cr(III) supply in the diet, but these changes were not statistically significant. There was no significant interaction effect of Cr(III) supplementation and excessive Fe supply in the diet on the parameters of Zn metabolism in Wistar rats (Fig. 2).

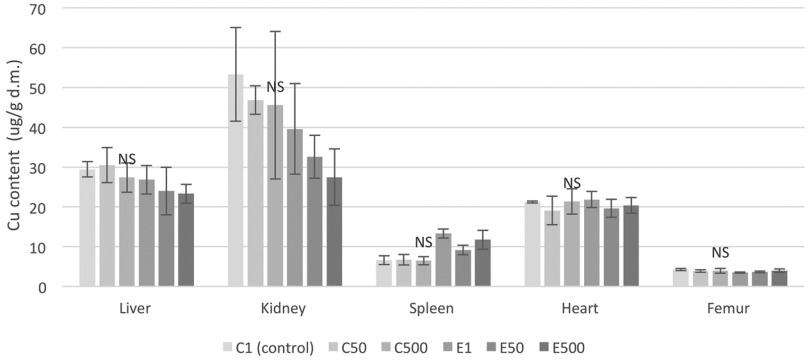

Fig. 1. The combined effects of different Fe(III) levels in the diet and Cr(III) supplementation on the Cu content in rats' tissues (mean ± SD). NS – no significant effect; d.m. – dry mass; *C – Fe control groups (45 mg kg^{-1} diet); E – excessive Fe level groups (180 mg kg^{-1} diet); supplemented with Cr(III) at doses of 1, 50 and 500 mg kg^{-1}, respectively.

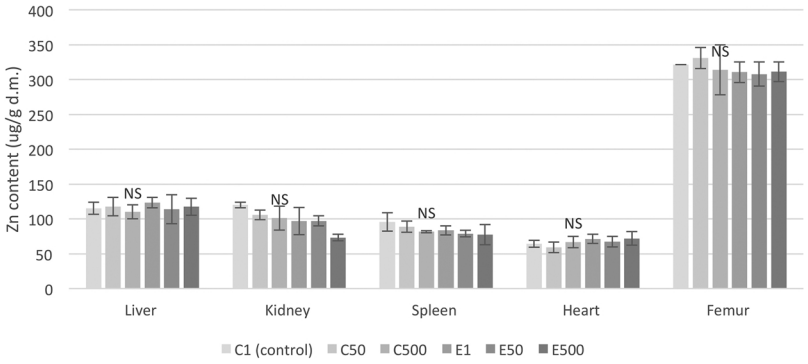

Fig. 2. The combined effects of different Fe(III) levels in the diet and Cr(III) supplementation on the Zn content in the tissues of rats (mean ± SD). NS – no significant effect; d.m. – dry mass; *C – Fe control groups (45 mg kg^{-1} diet); E – excessive Fe level groups (180 mg kg^{-1} diet); supplemented with Cr(III) at doses of 1, 50 and 500 mg kg^{-1}, respectively.

4. Discussion

Iron can have negative effect when it accumulates in excess in the organism. Fe overload induces disturbances in the status of some elements, such as Zn, Cu or Cr(III), which was confirmed by many authors [31,33–35]. One of genetic disorders which involves dysregulation of Fe absorption is hereditary haemochromatosis (HH). It is suggested that abnormal Fe absorption and metabolism may affect the levels of other important minerals [34]. Recent studies showed that the absorption of Fe, Cu, and Zn takes place by means of a subtle control system in which special transport proteins are operative for each element. Some transporters engaged in Fe, Zn, and Cu metabolism may also be involved in the absorption of other trace elements such as Cr(III) [17,18,36]. The interactions between Fe, Cu, and Zn are complicated and the molecular mechanisms underlying these interplays are not fully known [37]. Imbalance in the concentrations of these elements can lead to deficiency or overload disorders, which may increase the risk of some diseases [8,36]. The Fe status can influence the process of some metabolic diseases, such as obesity, type 2 diabetes, atherosclerosis and non-alcoholic fatty liver disease [8]. The Fe overload can respond on tissues involved in glucose and lipid metabolism, such as the liver, muscle, pancreatic β cells, and adipose tissue [8,10]. An imbalance of homoeostatic mechanisms, which includes interactions between Fe and ferritin, transferrin, insulin, and hepcidin, as well as adipokines and proinflammatory molecules causes damage of these organs [8].

On the other hand, there is no data on the effect of the combined administration of Cr and Fe compounds on tissular Cu and Zn levels. It seems that at high concentrations either Cr or Fe may operate as antagonists. Due to the fact that the metal binding sites in transferrin are divided between Fe(III) and Cr(III) ions [16–18], Fe(III) excess reduces the Cr(III) ability to bind to transferrin [17,19]. In this study the Fe(III) excess decreased the Cr concentrations in the female rats' serum, liver and kidneys. However, the Cr(III) supplementation increased the Cr levels in the liver and kidneys, but did not change most of the biochemical, haematological and tissular indices of Fe metabolism. Moreover, there was interaction between Cr(III) and Fe levels in the diet. The supplementation with the Cr3 complex increased the kidney Fe level in the groups with Fe oversupply, as compared with those with the recommended Fe level in the diet [31].

Cr(III) is perceived to be a relatively non-toxic element. Furthermore, it is widely used as an essential trace element in animal and human nutrition. The results of our earlier studies revealed that the Cr3 complex was a relatively safe compound. It was characterized by low acute toxicity (the LD_{50} dose > 2000 mg kg^{-1} body weight (b.w.) when administered orally to rats [38]. It had low genotoxic and teratogenic effect on female rats [39,40]. Some studies showed that Cr(III) supplementation with the organic complex affected Cu and Zn levels [13,40–43]. The results of this research and our previous studies confirmed that the Cr3 complex affected on Cu and Zn metabolism in rats [40,41].

The results of our previous studies demonstrated that the Cr3 complex at doses of 200 and 1000 mg Cr kg^{-1} diet (equivalent to 20 and 100 mg Cr kg^{-1} b.w. per day) increased the Cu accumulation in the liver and spleen as well as the renal Zn level during the four-week experiment on female rats [41]. The supplementation of pregnant rats with the Cr3 complex at doses of 100 mg Cr kg^{-1} diet (7.2 mg Cr kg^{-1} b.w day^{-1}) increased the maternal hepatic and renal Cr contents and reduced the liver Cu and Zn contents. The maternal Fe status and foetal Fe and Cr levels were unaffected by Cr(III) supplementation, but the foetal liver Zn content increased, whereas the kidney Cu level reduced [40]. Sahin et al. [44] noted an increase in the Zn concentration in the kidneys of different generations of rabbits (pregnant, offspring, and young rabbits) after $CrCl_3$ administration at doses 220 or 400 ppb. Ścibior and Zaporowska [45] found an increase in the liver Fe level and kidney Zn content after a 12-week treatment with V (sodium metavanadate) and Cr(III) (chromium chloride). However, it did not change the Cr and Cu contents in liver and kidney in male Wistar rats. The increase in kidney Zn level induced by Cr(III) alone and in combination with V suggests interaction between these elements. The increase may also have been induced by metallothionein synthesis. Yasutake and Hirayama [46] showed that Fe overload increased the hepatic metallothionein level but reduced its renal concentration in Wistar rats

Zinc is an essential element with beneficial antioxidative, anti-inflammatory, and apoptotic properties. The liver has a relevant role in supporting Zn homeostasis. Zn deficiency causes many of metabolic disturbances, including insulin resistance, hepatic encephalopathy as well hepatic steatosis [47]. Trace elements like Zn and Cr(III) play beneficial role in insulin transduction. Zn stimulates insulin signal cascade and prevents β-cell damage by cytokines. Both Cr(III) and Zn supplementation have beneficial effects on metabolic parameters in diabetic patients [48,49]. Sadri et al. [16] observed that the combined administration of Zn-Cr, Leu-Zn, Leu-Cr, and Leu-Zn-Cr resulted in a better lipid profile than each nutritional supplement given alone. However, they did not note a response in the glucose concentration and area under the 2-h blood glucose response curve (glucose AUC). Some reports suggested that supplementary Cr(III) affected the status of other metals, with a synergistic effect on the Zn content but an antagonist effect on the Fe and Cu contents [41,50].

In this study the Cr(III) supplementation reduced the Zn content in the kidneys but did not change the tissular Cu levels of female rats. Moreover, the study showed that the Fe excess resulted in a marked decrease in the hepatic and renal Cu as well as the renal and splenic Zn contents. This result is consistent with the observations made by Yanagisawa et al. [51] on male Sprague–Dawley rats and by Suliburska et al. [52] on male Wistar rats. However, simultaneous supplementation with the Cr(III) propionate complex did not deepen changes in the tissular Cu and Zn levels caused by the Fe oversupply in the diet.

The Fe oversupply in the diet might limit Zn absorption in the intestine [46]. It may result from the antagonistic action of Fe in the process of Zn absorption because the mechanisms responsible for the absorption of Fe and Zn are similar [51,53]. Yasutake and Hirayma [46] observed that Zn concentrations in the plasma, liver and kidney

indicated a transient but significant reduction at the beginning of the high Fe intake. Later these parameters returned to the control values three-week experiment. In this study the renal, splenic and cardiac Zn contents decreased, too. In turn, Vayenas et al. [33] noticed that the Fe overload in rats fed orally or by intraperitoneal (i.p.) or intravenous (i.v.) injection of polymaltose Fe resulted in increased absorption from the intestine and increased liver and spleen concentrations of Fe and Zn, but not Cu. However, there were no changes in the male Wistar rats' brain Fe, Zn, and Cu contents for a period of 4 months.

Arredondo et al. [54] evaluated the effects of increasing concentrations of Cu, Fe, and Zn on the Cu and Fe uptake in *Caco-2* cells. The in vitro experiment showed that metals with similar chemical properties and uptake may be competitive in aqueous solutions and at higher uptake amounts. The results of these interactions may depend on the relative contents of nutrients [54]. They noted that Zn and Cu inhibited the Fe uptake, and while Fe lowered the Cu uptake, but did not influence the Zn uptake. When these elements were given jointly (1: 1: 1 ratio), the Cu or Fe uptake was inhibited by about 40% [54]. Also, Rashed [55] observed that Zn lowered the Fe uptake in a concentration-dependent manner in human epithelial *Caco-2*TC7 cell-line. The Zn inhibition of the Fe uptake appeared when the Fe:Zn ratio was 1:100.

Herrera et al. [56] found that serum Fe and Zn levels were decreased, but the serum Cu level did not differ between hypotransferrinemic mice (hpx) and wild type (wt) mice, at four months of experiment. They noticed that the hpx mouse tissue element imbalances were most noticeable for Fe, and much less visible defects were observed for Cu and Zn in certain tissues at different ages. The tissular Fe levels increased with the hpx mice's age. They were greater in the hpx mice of all ages than in the wild type (wt) mice, except the splenic Fe content. The liver Cu level and the liver, heart and pancreas Zn contents decreased, while the spleen and lung Cu levels increased with the hpx mice's age, as compared with wt mice. Like in hpx mice, Hjv-deficient mice progress hepcidin deficiency and Fe overload. Herrera et al. [56] noticed that the hepatic Fe concentrations in hypotransferrinemic (hpx), Hjv-deficient, as well hpx Hjv-deficient mice were higher than wild type mice (wt). However, there were no significant changes in the Cu or Zn levels in these mice.

Fe excess interferes with Cu utilization [57]. Experiments on rodents showed that high Fe intake developed Cu deficiency in these animals [58,59]. There were disturbances in the tissular distribution of Cu in mice fed a high Fe diet, which lead Cu depletion in organism [58]. Mice C57BL/6 consuming high Fe diets were anaemic, and characterized lower Cu levels in the liver and their serum ceruloplasmin activity was reduced after of five weeks of experiment [58]. Similarly, Ha et al. [59] found that dietary Cu disturbed Fe balance during Fe deficiency and Fe overload in Sprague-Dawley rats. During a five-week experiment the high Fe diet decreased the serum and tissular Cu levels and ceruloplasmin concentration. This is confirmed by the results of this study. It may have been caused by ceruloplasmin (CP), which is the main Cu transport protein in Fe homeostasis. It has been confirmed in patients and animals with aceruloplasminemia, which characterized with hepatic iron overload [60]. However, higher Cu levels in the high Fe diet increased the serum and liver Fe concentrations and transferrin saturation, but lowered the spleen Fe level in male rats [59].

The data obtained by Tinkov et al. [61] show that the chronic consumption of Fe and Cu with drinking water increased the concentrations of these elements in the liver of rats kept on standard (STD) and high-fat (HFD) diets. The combined administration of Fe and Cu in water given to rats fed the STD and HFD diets increased the hepatic Fe level by 29% and 35%, respectively. Tinkov et al. [61] noticed that the treatment of Wistar rats with Fe and Cu in a mixture independently of the diet did not change the animal's liver Cu level.

Kim et al. [62] found that the polycystic ovary syndrome (PCOS) patients had higher serum Fe levels and hepcidin concentrations than the control subjects. These findings were confirmed by Chen et al. [63], who studied whether PCOS changed Fe, Zn, Cu and Cr levels in female BALB/c mice and if Cr supplementation affected these changes during a four-week experiment. The researchers observed that the PCOS mice were characterized by higher Fe and Zn levels, but lower Cr and Cu contents, except the serum Cu concentration. The Cr(III) supplementation increased the concentrations of this element in the serum and tissues. It also increased the liver and muscle Cu levels and the fat and bone Zn levels, but decreased the Fe concentrations in the serum, liver and bone [63].

5. Conclusion

The Fe oversupply disturbed the Cu and Zn status in the female Wistar rats. However, Cr(III) supplementation did not affect the tissular levels of these elements, except the kidney Zn content. Simultaneous supplementation with the Cr(III) propionate complex did not deepen changes in the tissular Cu and Zn levels caused by the Fe excess in the diet. Further investigation is required to explain interactions and relationships between these elements and their transporters.

Conflict of interest

None declared.

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