Journal of Trace Elements in Medicine and Biology 41 (2017) 41–53

Contents lists available at ScienceDirect

Journal of Trace Elements in Medicine and Biology

journal homepage: www.elsevier.com/locate/jtemb

Review

Interactions of iron with manganese, zinc, chromium, and selenium as related to prophylaxis and treatment of iron deficiency

Geir Bjørklund[a,*], Jan Aaseth[b,c], Anatoly V. Skalny[d,e,f,g], Joanna Suliburska[h], Margarita G. Skalnaya[d], Alexandr A. Nikonorov[e,i], Alexey A. Tinkov[d,e,f,i]

[a] Council for Nutritional and Environmental Medicine, Mo i Rana, Norway
[b] Department of Public Health, Hedmark University of Applied Sciences, Elverum, Norway
[c] Department of Research, Innlandet Hospital Trust, Brumunddal, Norway
[d] RUDN University, Moscow, Russia
[e] Orenburg State University, Orenburg, Russia
[f] Yaroslavl State University, Yaroslavl, Russia
[g] All-Russian Research Institute of Medicinal and Aromatic Plants, Moscow, Russia
[h] Poznan University of Life Sciences, Poznan, Poland
[i] Orenburg State Medical University, Orenburg, Russia

ARTICLE INFO

Article history:
Received 29 September 2016
Received in revised form 21 January 2017
Accepted 7 February 2017

Keywords:
Iron
Iron deficiency
Zinc
Manganese
Chromium
Selenium

ABSTRACT

Iron (Fe) deficiency is considered as the most common nutritional deficiency. Iron deficiency is usually associated with low Fe intake, blood loss, diseases, poor absorption, gastrointestinal parasites, or increased physiological demands as in pregnancy. Nutritional Fe deficiency is usually treated with Fe tablets, sometimes with Fe-containing multimineral tablets. Trace element interactions may have a significant impact on Fe status. Existing data demonstrate a tight interaction between manganese (Mn) and Fe, especially in Fe-deficient state. The influence of Mn on Fe homeostasis may be mediated through its influence on Fe absorption, circulating transporters like transferrin, and regulatory proteins. The existing data demonstrate that the influence of zinc (Zn) on Fe status may be related to their competition for metal transporters. Moreover, Zn may be involved in regulation of hepcidin production. At the same time, human data on the interplay between Fe and Zn especially in terms of Fe-deficiency and supplementation are contradictory, demonstrating both positive and negative influence of Zn on Fe status. Numerous data also demonstrate the possibility of competition between Fe and chromium (Cr) for transferrin binding. At the same time, human data on the interaction between these metals are contradictory. Therefore, while managing hypoferremia and Fe-deficiency anemia, it is recommended to assess the level of other trace elements in parallel with indices of Fe homeostasis. It is supposed that simultaneous correction of trace element status in Fe deficiency may help to decrease possible antagonistic or increase synergistic interactions.

Contents

* Corresponding author at: Council for Nutritional and Environmental Medicine, Toften 24, NO-8610 Mo i Rana, Norway.
E-mail address: bjorklund@conem.org (G. Bjørklund).

http://dx.doi.org/10.1016/j.jtemb.2017.02.005
0946-672X/

1. Introduction

Iron (Fe) is an essential trace element for most life on the Earth, including human beings. The adult human body contains 3–5 g Fe. About 75% of this is found in hemoglobin (Hb), myoglobin and Fe-containing enzymes such as catalase and peroxidase enzymes. The other 25% of the body Fe is stored in the bone marrow, liver, and spleen. Iron is also necessary for the functioning of various cellular mechanisms, including DNA synthesis, enzymatic processes, and mitochondrial energy generation [1].

About 30% of the world's population has anemia [2], and about 50% of these cases are due to Fe deficiency [3], which is also considered to be the most common nutritional deficiency. However, the prevalence of Fe deficiency anemia varies highly between different countries and different parts of the world [2].

The human body needs a dietary intake of about 20 mg Fe daily for the production of red blood cells and cellular metabolism [4]. The average intake of dietary Fe in the US is 16–18 mg/day for men, 12 mg/day in pre- and postmenopausal women, and about 15 mg/day in pregnant women [5]. The body lose about 1–2 mg Fe daily due to skin desquamation, sweating, and urinary excretion [4]. In a typical Western diet, less than 20% of available Fe is absorbed. The bioavailability of Fe from a vegetarian diet is only 10% while it is 18% from a mixed diet [5].

A growing child has almost the same need for Fe as an adult, but it eats less and has a significantly greater risk of Fe deficiency than adults have. In babies and young children (aged 0–15 years), rapid growth decreases Fe stores that have accumulated during gestation, which can lead to an absolute Fe deficiency [6]. Especially at risk are infants that are born preterm, with low birthweight, or if the mother had Fe deficiency [3,7,8]. Even full-term infants may be at risk if they do not receive adequate amounts of solid foods that are rich in bioavailable Fe when they are 6–9 months old [9]. After childhood, adolescent girls are especially at risk to develop Fe deficiency caused by menstrual Fe losses [10].

The absorption of Fe is regulated by a small peptide hepcidin, which is mainly secreted by hepatocytes [11]. Hepcidin binds to the Fe export protein ferroportin in enterocyte, macrophage, and hepatocyte membranes. The ferroportin-hepcidin complex is internalized and degraded. The result is reduced export of Fe from enterocytes and macrophages into the circulation, which leads to decreased plasma Fe levels. Iron overload upregulates the production of hepcidin, and Fe deficiency down-regulate it. The bone morphogenetic protein (BMP), mutated hemochromatosis (HFE [human factors engineering]) protein, transferrin receptor 2 (TfR2), and hemojuvelin (HJV) are essential activation regulators of the hepcidin synthesis. Lack of or mutations in the genes for these proteins, for example, the HFE mutation, C282Y, in primary hemochromatosis reduces the synthesis of hepcidin. Iron regulatory proteins (IRP) can bind to Fe-responsive sequences (IRE) in ferritin mRNA and transferrin receptor mRNA and regulate protein synthesis. In mammalian cells, the intracellular Fe homeostasis is mainly controlled by two cytoplasmic RNA-binding proteins (IRP1 and IRP2). Dietary calcium (Ca) may also inhibit Fe absorption [12,13]. Phytates (in cereals and beans) and tannins (in tea) reduce the absorption of non-heme Fe [14,15]. The copper (Cu) protein hephaestin is also essential for Fe absorption, explaining that Cu deficiency may cause microcytic anemia.

Iron deficiency occurs when Fe losses or requirements exceed absorption and is often multifactorial. It is crucial to determine the underlying causes of the Fe deficiency, rather than just treating it with Fe supplements. Among factors that can cause Fe deficiency is increased physiological demands, *e.g.*, during pregnancy and growth. Gastrointestinal disorders like ulcerative colitis and Crohn's disease, and gastric bypass (bariatric) surgery increase the risk of Fe deficiency [16–20].

The present paper discusses the interactions between Fe and other trace elements included in multimineral supplements, viz. manganese (Mn), zinc (Zn), and chromium (Cr), and focuses on interactions in Fe deficiency. Interactions with selenium (Se) are only briefly summarized. The present paper covers especially aspects of interactions that have not been highlighted in previous reviews.

2. Iron supplementation

Dietary Fe is present in two different forms (heme and non-heme): Heme iron is bound to Hb and myoglobin and is present in animal food sources such as meat, poultry, and seafood [21]. Non-heme Fe (ferric iron, Fe^{3+}) is present in cereal and vegetable food sources [21]. Iron bound to Hb and myoglobin (heme Fe) is better absorbed than non-heme Fe. Heme Fe contributes to 10–15% of the total Fe intake but accounts for more than 40% of total absorbed Fe due to its higher absorption rate [22].

A standard treatment in cases of minor to moderate Fe deficiency is supplementation with a Fe salt, *e.g.* ferrous sulfate, at a dose corresponding to 60 mg of iron daily [23].

Daily Fe supplementation during pregnancy significantly reduces the risk of anemia at term [24]. A preventive supplement of 15 mg daily is often prescribed [5]. The dietary demand of other minerals are also increased during pregnancy, and a multimineral tablet with Fe (15 mg), usually enriched with Zn, Cu, Mn, Cr, Se, and folate, may be a preferred supplement [25,26].

At the same time, earlier data demonstrate that trace elements interaction may have a significant impact on Fe status. In particular, Cu plays an important role in Fe metabolism [27–29]. Ceruloplasmin is the major Cu-transporting protein in the blood. Also, it plays a role in Fe metabolism. Copper deficiency is associated with a reduced absorption of Fe. Anemia is a clinical sign of Cu deficiency. In Fe-deficient animals, Cu accumulates in the liver. Adequate Cu is required for normal Fe metabolism and red blood cell formation [28]. The interaction between Fe and Cu has been extensively

reviewed previously [29–31], and is therefore not further discussed in this paper.

In both humans and animals, the intestinal absorption of lead (Pb) and cadmium (Cd) increases in case of Fe deficiency [32]. Thus, Fe deficiency in young children may increase the risk of Pb poisoning [33].

3. Interactions between iron and manganese

Manganese (Mn) is an essential trace element required for normal metabolism of lipids, carbohydrates, and proteins through its cofactor role in certain enzymes [34]. Manganese is also involved in reproduction and growth, immunity, energy homeostasis, antioxidant defense and other processes [35]. At the same time, excessive Mn intake may result in metal toxicity [36]. A multimineral tablet may contain 2 mg Mn.

The existing data demonstrate that the interaction between Fe and Mn occurs due to similarities in absorption and transport mechanisms [37].

3.1. Studies in cell lines

The pioneer study on the role of DMT-1 in metal transport demonstrated that this protein mediates active transport of a broad range of metals including Mn [38]. Moreover, it is supposed that the affinity of DMT1 to Mn is higher than that of Fe [39,40]. Incubation of Caco2 cells in the presence of 500 μM Mn significantly decreased acid-stimulated Fe uptake by DMT1 [41]. Moreover, Mn exposure (100 μM for 24 and 48 h) also resulted in upregulation of DMT1 expression in choroidal epithelia of the blood–cerebrospinal fluid barrier [42]. The role of DMT1 in Mn transport was also studied in various non-mammalian species [43]. At the same time, a study on A549 cell line demonstrated that DMT1 is not the predominant Mn transporter in pulmonary cells [44]. Thus, DMT1 may not be the key to explaining Fe-Mn interaction.

It has also been noted that Mn exposure significantly increases the level ferroportin (Fpn) being the Fe exporter in the basolateral membrane of the enterocytes. Moreover, Fpn has been shown to transport Mn in terms of metal overload (100, 250, or 500 μM for 6 h) [45]. It has also been demonstrated that Fpn-mediated Mn export in *Xenopus laevis* oocytes was partially inhibited by treatment with 100 μM Fe, Co, or Ni [46]. In another study using *Xenopus* oocytes, ferroportin-stimulated efflux of Mn was also demonstrated. However, Mn efflux was not inhibited by hepcidin [47], a key regulator of Fe homeostasis. It is notable that treatment with 10, 50, or 100 μM Mn for 16–24 h had no effect on *Fpn* gene expression in J774 cells [48].

An early study indicated that Mn forms a specific complex with transferrin [49], a key part of Fe delivery system [50]. Later studies demonstrated that Mn binds to both Fe-binding sites in Tf molecule [51,52] and the oxidation state of Mn determines metal affinity to endogenous ligands during its transport across the blood-brain barrier [53]. It has also been shown that Mn^{3+} is transported to target cells by the Tf mechanism similarly to Fe^{3+}, [54]. It is notable that the results of *in vitro* study demonstrated that ceruloplasmin might take part in Mn binding to apoTf [55,56]. Apparently, Mn^{2+} should be oxidized to Mn^{3+} before interaction with Tf [57].

In addition to Fe transport mechanisms, Mn also interferes with the system of Fe regulatory proteins (IRP), acting as the regulatory system of Fe metabolism [58,59]. In particular, it has been demonstrated that moderate Mn exposure (10 and 50 μM) resulted in decreased IRP binding activity, whereas high-level Mn exposure (200 μM) increased IRP binding in incubated PC12 cells [60]. A Later study from these authors demonstrated that Mn-exposed (1, 10, 50, and 200 μM for 12, 24, 36, and 48 h) neuronal PC12 cells are characterized by altered dynamics of IRP-1 binding and the intracellular abundance of IRP-2 [61]. At the same time, a later study showed that Mn-induced (150 or 300 μM) alteration of Fe homeostasis in GABAergic AF5 cells predominantly occurs through modulation of IRP2, and only to a lesser extent of IRP1 [62]. A detailed study of the effect of non-ferrous metals on IRP binding demonstrated that Mn has as high affinity as Fe to the fourth labile position of Fe-S cluster in IRP1 [63].

An investigation using cultured hepatocytes demonstrated that Mn treatment (100 μM $MnCl_2$) results in increased hepcidin levels [64]. Taking into account the role of hepcidin in Fe homeostasis, the author proposes that Mn exposure, especially in Fe-deficient state, may aggravate Fe deficiency [64].

3.2. Studies in laboratory animals

The results of *in vivo* studies involving laboratory animals confirmed these results of in vitro studies partially. Numerous investigations using laboratory rodents was performed to assess the role of DMT1 in Mn transport in various tissues. An *in vivo* investigation using developing rats indicated that Mn exposure through milk during lactation was associated with enhanced DMT1 expression in the brain of the newborn [65]. Manganese uptake by olfactory epithelium was also DMT1-mediated being upregulated during Fe-deficiency anemia [66]. However, a recent study demonstrated that DMT1 is essential for the transport of Fe, but not for Mn transport in a mouse model lacking intestinal DMT1 [67]. These data correspond to the earlier finding that Mn transport across the blood-brain barrier is not mediated by DMT1 [68]. Therefore, the animal studies are in agreement with *in vitro* experiments being indicative of the insignificant role of DMT1 in mediating the complex interaction between Mn and Fe *in vivo*.

The involvement of Fpn in Mn transport was also confirmed by an observation of impaired Mn metabolism in Fpn-deficient mice [69,70]. Interestingly, this group of researchers indicated enhanced Mn absorption in mice with HFE deficiency, whereas no significant alteration of tissue Mn distribution was observed after metal injection or instillation [71]. However, another study on $HFE^{-/-}$ mice being characterized by increased ferroportin expression showed that liver mitochondria contained significantly lower Mn and elevated Fe levels as compared to wild-type controls [72]. In a rat model of Mn-induced parkinsonism, Mn exposure (IP injection of 5, 15, and 20 mg/kg $MnCl_2$ for 16 weeks) was associated with increased expression of DMT1 and decreased expression of Fpn1 in the *substantia nigra* ultimately leading to iron overload [73].

Laboratory rodent experiments also demonstrated that transferrin serves as the major Mn carrier in plasma independently of the route of Mn administration [74]. Correspondingly, studies using hypotransferrinemic mice showed that normal levels of transferrin are required for proper body distribution of Mn [75]. In contrast, an *in vivo* investigation in *hpx* mice, a model of inherited transferrin deficiency, demonstrated that transferrin does not have a primary role in Mn distribution [76]. The observed contradiction may be related to different sources of Mn in these studies, *i.e.* subcutaneous injection [75] and diet [76]. It has also been hypothesized that Tf may be essential for manganese distribution in the case of Mn deficiency or overload [76]. Also, Mn-Tf has been shown to compete with Fe-Tf for the binding site of the receptor on lactating mouse mammary gland cells [77]. However, it is questionable whether such competition may have a significant impact on Fe metabolism due to the much lower concentration of Mn in comparison to Fe.

Animal studies demonstrated the interplay between Mn and Fe status (Table 1). It has been demonstrated that dietary Fe-deficiency in rats increases the rate of Mn accumulation in liver and elevates the susceptibility to Mn toxicity in rats [78]. These data are in agreement with the later results obtained by Wessling-Resnick and the

Table 1
Experimental data on the interaction between manganese (Mn) and iron (Fe).

Objects	Conditions	Factors	Effects	References
Rats	Fe-deficiency	47 mg/100 g $FeSO_4 \cdot 7H_2O$ in diet + 15 mg/kg $MnCl_2 \cdot 4H_2O$ ip	↑ liver Mn	[78]
Rats 21 d	Fe deficiency	20–25 ppm Fe diet + 22.5Ci ^{54}Mn/kg iv injection/intratracheal instillation	↑ RBC Mn ↔ plasma Mn	[79]
Rats 21 d	Fe overload	+ 10000 ppm Fe + 1.5 ml $^{54}MnCl_2$ (10 μCi/ml) intratracheal instillation + 0.5 ml $^{54}MnCl_2$ (30 μCi/ml) iv	↓ lung Mn absorption	[80]
Rats	Fe overload	+ 3% w/w carbonyl iron in diet	↔ liver Mn ↑ spleen Mn	[81]
Rats	Fe overload	+ polymaltose Fe ip	↔ liver Mn ↑ spleen Mn	[81]
Rats	Fe overload	+ polymaltose Fe iv	↑ liver Mn ↑ spleen Mn	[81]
Rats 7–8 w	Fe-adequate	+ 6 mg/kg/day Mn ip	↓ plasma Fe ↑ CSF Fe	[82]

ip – intraperitoneally; iv – intravenously; ↑ – significant increase; ↓ – significant decrease; ↔ – no significant changes.

collaborators, who have demonstrated that Fe deficiency increases pulmonary Mn absorption [79], whereas its excess has the opposite effect [80]. It is interesting that Fe supplementation by intraperitoneal (IP) or intravenous (IV) injection resulted in increased Fe and Mn content in rat's liver and spleen [81]. Chronic Mn exposure through IP injections of $MnCl_2$ for 30 days resulted in a 32% decrease in plasma Fe, whereas Fe excess in cerebrospinal fluid [82]. High intake of Fe resulted in decreased absorption of Mn in calves [83]. Therefore, both Mn and Fe overload may have a significant negative effect on each other.

3.3. Human studies

Human studies also demonstrated certain interactions between Mn and Fe, especially in the Fe-deficient state (Tables 2–5). In particular, an examination of infants with Fe deficiency detected significantly increased levels of blood Mn, whereas Fe supplementation therapy for 1–6 months significantly improved Fe status and decreased Mn concentrations [84]. These data correspond to the results of the earlier assessment of Mn status in adults [85] and children [86] with Fe deficiency anemia. A large Korean National Health and Nutritional Examination Survey (KNHANES) 2008 demonstrated that blood Mn concentration was significantly higher in the low ferritin groups of both men and women as compared to the normal ferritin groups' values [87]. Similar data were obtained during HUNT 2 study. In particular, low ferritin group was characterized by elevated blood Mn levels. Moreover, serum ferritin was the main determinant of blood Mn levels [88]. The results of these observational studies are in agreement with the case report of a 5-year-old girl with manganism who had concurrent Fe deficiency [89]. It has also been demonstrated that genetic variants in Fe metabolism genes significantly alter Mn status through their influence on Mn absorption, distribution, and excretion [90].

Additional data on the interaction between Mn and Fe were obtained in persons occupationally exposed to Mn. In particular, it has been demonstrated that the increased Mn content in biosamples from welders is associated with lower plasma and erythrocyte Fe content [91]. At the same time, a recent investigation of 241 welders observed Fe deficiency only in few persons. No significant association between blood Mn and serum ferritin was found [92]. However, another examination of male welders revealed significant elevation of both Fe and Mn concentration in serum in parallel with increased transferrin levels and decreased transferrin receptor levels. Moreover, in the current investigation, serum Mn was inversely associated with transferrin levels. At the same time, only transferrin receptor levels were significantly decreased in female examinees [93]. Correspondingly, Mn alloy production workers were characterized by the lower concentrations of serum soluble transferrin receptor as compared to unexposed controls, suggesting that Mn exposure is associated with higher intracellular Fe concentrations [94]. Although the data obtained provide only a mechanistic link to Fe-Mn interaction, the differential effect of Mn exposure on various markers of Fe status are of particular interest. Hypothetically, these contradictions may be related to multiple factors including the different Fe status of the examinees at the moment of investigation and the exposition dose of Mn.

It has been shown that Fe supplementation failed to affect Mn status in healthy pregnant women [95]. At the same time, the rate of Mn absorption in healthy young women was maximal in those with low serum ferritin concentrations and vice versa. Moreover, the highest half-life of Mn was detected in persons with high ferritin levels consuming a low-Mn diet [96], being in agreement with the supposition that Tf may play a significant role in Mn distribution in Mn-deficient state [76]. It is interesting that dietary heme and non-heme Fe differentially affect Mn status. In particular, increasing consumption of non-heme Fe negatively affected the level of Mn, whereas no such effect was observed in the case of heme Fe [97]. The results of a 124-day supplementation study demonstrated that supplementation of 15 mg/day Mn did not affect Fe status in healthy women. However, combined administration of Mn and Fe resulted in a significant decrease in serum Mn levels as compared to both Fe- and Mn-treated values [98].

Conclusively, the reviewed experimental and clinical data indicate a possible association between Mn and Fe metabolism in the human organism. Special attention to this interaction should be paid in the case of Fe deficiency. In particular, excessive intake of Mn in a Fe-deficient state may result not only in aggravation of Fe deficiency but also in potentiation of Mn toxicity [99].

Generally, data from cell culture studies demonstrate that Mn-induced modulation of hepcidin and IRE/IRP with subsequent regulation of transport protein (DMT1, Fpn) expression may underlie impaired Fe status. Moreover, these transporters are also capable of Mn transport. However, it seems unlikely that direct competition for transport proteins may mediate antagonistic effects between Fe and Mn. Similarly, competition for Tf binding observed *in vitro* may not have a significant impact on Fe status *in vivo* due to the difference in concentrations of Fe and Mn in tissues. The existing data from exposed and non-exposed organisms (laboratory animals and humans) demonstrate that the doses of metals as well as their ratios in the diet and in the organism, may significantly affect

Table 2
Human data on the interplay between manganese (Mn) and iron (Fe) in children.

Objects	Conditions	Factors	Effects	References
Infants 6 mo – 2 yo	Fe deficiency	Fe deficiency	↑ blood Mn	[84]
Infants 6 mo – 2 yo	Fe deficiency	+ 6 mg/kg Fe	↓ blood Mn * * as compared to pretreatment values	[84]
Children 1–6 yo	Fe deficiency anemia	Fe deficiency anemia	↑ whole blood Mn	[86]
5-year-old girl	Manganism	↑ whole blood Mn ↑ serum Mn ↑ liver Mn	↑ Hb ↓ MCV ↓ serum Fe ↑ TIBC	[89]

↑ – significant increase; ↓ – significant decrease; ↔ – no significant changes; MCV – mean corpuscular volume; TIBC – total iron-binding capacity.

Table 3
Human data on the interplay between manganese (Mn) and iron (Fe) in adults.

Objects	Conditions	Factors	Effects	References
Patients	Fe deficiency anemia	Fe deficiency anemia	↑ blood Mn	[85]
Patients	Fe deficiency anemia	160–240 mg/day Fe	↓ blood Mn * * as compared to pretreatment values ↔ blood Mn * as compared to control values	[85]
Adults	Fe deficiency	Ferritin <15 μg/L	↑ blood Mn	[87]

↑ – significant increase; ↓ – significant decrease; ↔ – no significant changes.

Table 4
The interplay between manganese (Mn) and iron (Fe) in women.

Objects	Conditions	Factors	Effects	References
Women 20–55 yo	Fe deficiency	Ferritin < 12 μg/L	↑ whole blood Mn	[88]
Pregnant women 20–35 yo	Fe adequate	+ 100 mg/day $FeSO_4$	↔ blood Mn	[95]
Women 20–45 yo	Low ferritin	+ 0.7 mg/d Mn	↑ Mn absorption * * as compared to high ferritin group	[96]
Women 20–45 yo	High ferritin	+ 0.7 mg/d Mn	↑ Mn half-life * * as compared to low ferritin group	[96]
Women ~24 yo	Fe-adequate	non-heme Fe consumption	↓ serum Mn ↑ urine Mn	[97]
Women ~24 yo	Fe-adequate	heme Fe consumption	↔ serum Mn ↔ urine Mn	[97]
Women ~24 yo	Fe-adequate	+15 mg/day Mn	↔ Ht ↔ ferritin ↔ transferrin ↔ serum Fe	[98]
Women ~24 yo	Fe-adequate	+15 mg/day Mn	↔ Ht * ↔ ferritin * ↔ transferrin * ↔ serum Fe * * as compared to placebo	[98]
Women ~24 yo	Fe-adequate	+ 60 mg Fe fumarate	↑ serum Mn * * as compared to placebo ↔ serum Mn * * as compared to Mn-treated	[98]
Women ~24 yo	Fe-adequate	+ 60 mg Fe fumarate + 15 mg/day Mn	↓ serum Mn * * as compared to Fe- and Mn-treated	[98]

↑ – significant increase; ↓ – significant decrease; ↔ – no significant changes; Ht – hematocrit.

the regulatory mechanisms of Fe metabolism. Therefore, additional studies involving both humans and cellular and animal models are required for estimation of the intimate mechanisms of Fe-Mn interaction at different exposure levels (deficiency, physiological range, overload).

4. Interactions between iron and zinc

Zinc is an essential trace element involved in multiple cellular functions. It possesses antioxidant, anti-inflammatory, immunostimulatory [100], anticancer [101] and neuroprotective [102]

Table 5
The interplay between manganese (Mn) and iron (Fe) in workers.

Objects	Conditions	Factors	Effects	References
Welders	Mn exposure	↑ saliva Mn ↑ plasma Mn ↑ RBC Mn ↑ urine Mn ↑ hair Mn	↑ saliva Fe ↑ plasma Fe ↑ RBC Fe ↑ urine Fe ↑ hair Fe ↑ transferrin ↑ saliva transferrin receptor	[91]
Male welders 19–54 yo	Mn exposure	↑ serum Mn	↑ serum Fe ↔ ferritin ↑ transferrin ↓ transferrin receptor	[93]
Female welders 19–54 yo	Mn exposure	↑ serum Mn	↔ serum Fe ↔ ferritin ↔ transferrin ↓ transferrin receptor	[93]
Mn alloy production workers 27–62 yo	Mn exposure	↑ blood Mn ↑ urine Mn	↔ serum Fe ↔ urine Fe ↔ ferritin ↔ TIBC ↔ transferrin saturation ↑ transferrin receptor	[94]

↑ – significant increase; ↓ – significant decrease; ↔ – no significant changes; TIBC – total iron-binding capacity; RBC – red blood cells.

effects. Zinc deficiency is a worldwide problem with nearly 25% of people worldwide at risk of Zn deficiency [103]. Due to the involvement of Zn in multiple cellular processes its deficiency is associated with various pathologic states [104]. Despite its essentiality, excessive Zn intake may be associated with toxicity [105]. Therefore, the risks and benefits of Zn supplementation should always be taken into account while developing strategies for supplementation [103].

The interplay between Zn and Fe was documented several decades ago [106]. The social and health impact of this interaction in the third world countries has also underlined [107]. At the same time, the character and mechanisms of such interaction especially in the case of Fe deficiency are unclear.

4.1. Studies in cell lines

The Zn transport in the organism is mediated by two families of transport proteins: zinc transporters (ZnT) and Zrt- and Irt-like proteins (Zip). Detailed information on the function of Zn transporters is provided elsewhere [108,109]. It is notable that certain Zn transporters may also be involved in Fe homeostasis [110]. In particular, it has been proposed that Zip-14 [111,112] and Zip-8 [113] may act as Fe transporters. At the same time, previous studies indicate that Zn being a divalent ion (Zn^{2+}) also may be transported by DMT1 [38]. However, the affinity of DMT1 to Zn ions is rather low as compared to Fe, cobalt, cadmium, and Mn [114]. The low affinity of DMT-1 to Zn ions indicates that Zn competition for DMT-1 cannot be the main mechanism for the interaction between these two metals. However, Zn is capable of regulating DMT1 functioning. It has been demonstrated that Zn supplementation (50 μM) increases the apical membrane abundance of DMT1 in Fe or Zn-deficient Caco-2 cells [112]. These data are in agreement with the earlier indication of a Zn-induced increase in DMT-1 protein and mRNA levels and pH-dependent Fe uptake [115]. Furthermore, ferroportin (IREG-1), the main basolateral exporter of Fe, also possesses affinity to Zn [47]. Moreover, Zn treatment (50 or 100 μM for 24 h) also stimulates transepithelial Fe transfer due to increased IREG-1 mRNA expression [115]. Earlier studies indicated that the influence of Zn on Fe regulatory proteins (IRP) is a key system for Fe homeostasis regulation in mammals [116]. In particular, it has been shown that Zn interferes with the Fe-responsive element (IRE)-binding activity of IRP1 [117]. In turn, Zn-deficient Swiss 3T3 cells were characterized by an increased IRE-binding activity of IRP2, whereas the activity of IRP1 was decreased [118].

Hepcidin, a key regulator of Fe metabolism functions to decrease access to body iron stores through its sequestration in macrophages [119]. The existing data indicate that this systemic regulator of Fe homeostasis is also affected by Zn. In particular, it has been shown that Zn treatment (100 μM $ZnSO_4$) significantly increases hepcidin expression through its activation of metal response element (MRE)-binding transcription factor-1 [120]. At the same time, Graham et al. (2012) propose that Zn deficiency increases hepcidin expression and vice versa Zn supplementation may downregulate hepcidin production following by increased Fe absorption [121].

Finally, the competition studies using Caco-2 cells indicated that incubation of cells with the increasing doses of Zn (0.5–100 μM $ZnSO_4$) significantly affected Fe uptake [122]. Another study demonstrated a dose-dependent inhibition of Fe absorption by Zn (incubation with 50 μM ^{65}Zn for 2 h) in Caco-2 cell line. At the same time, Fe marginally increased Zn intake into the cells [123].

4.2. Studies in experimental animals

Animal experiments also provide additional data on the association between Zn and Fe metabolism (Table 6). A detailed study by Kelleher and Lönnerdal indicate that the effect of Zn supplementation in suckling rat is age-dependent. In particular, in early infancy (10th postnatal day) Zn supplementation significantly increased DMT1, hephaestin, and hepcidin mRNA levels. In contrast, at the 20th postnatal day, Zn supplementation significantly decreased hephaestin and hepcidin mRNA levels [124]. Simultaneous administration of Zn and Fe in Fe-deficient rats effectively increased serum Fe, and hippocampal ferritin content [125].

Previous data indicate that rats exposed to dietary Fe deficiency were characterized by low blood Zn content [126]. It has also been demonstrated that dietary Fe deficiency is associated with significantly lower liver Zn content and 50% higher Zip14 mRNA levels [127]. Oppositely, dietary Fe overload resulted in increased liver Zn content and Zip5 expression along with depressed Zip6, Zip7, Zip10 expression [127]. Moreover, long-term intake of high Zn diet was associated with Fe deficiency anemia in rats [128]. Another experiment demonstrated a higher rate of Fe retention in offspring of dams fed a Zn-deficient diet [129]. Oppositely, the results of another experimental study indicate that Zn absorption is not affected

Table 6
The interplay between zinc (Zn) and iron (Fe) in laboratory rats.

Objects	Conditions	Factors	Effects	References
Rats 10 d	Fe-adequate	+ 750 μg Zn as $ZnSO_4$	↓ Whole body Fe retention ↑ Intestine Fe retention ↑ DMT1 mRNA ↑ hephaestin mRNA ↑ hepcidin mRNA	[124]
Rats 20 d	Fe-adequate	+ 750 μg Zn as $ZnSO_4$	↓ Muscle Fe ↓ hephaestin mRNA ↓ hepcidin mRNA	[124]
Rats 19–20 d	Fe-deficiency	+ Zn (12 mg added/kg) + Fe (245 mg/kg diet)	↑ serum Fe * ↑ hippocampal ferritin * * as compared to Fe only	[125]
Rats	Fe deficiency	Fe deficiency	↓blood Zn ↔ tissue Zn	[126]
Rats 21 d	Fe deficiency	Fe deficiency	↓ liver Zn content ↑ Zip14 mRNA	[127]
Rats 21 d	Fe overload	dietary Fe overload	↑ liver Zn content ↑ Zip5 mRNA ↓ Zip6 ↓ Zip7 ↓ Zip10	[127]
Rats 6 w	Fe-adequate	high Zn diet (0.2% Zn)	↓ serum Zn ↓ Hb ↓ Ht ↓ MCV ↓ MCH ↓ MCHC ↑ Reticulocytes	[128]
Rats	Fe adequate	Zn-deficiency	↑ Fe retention	[129]
Rats	Fe deficiency	Fe deficiency	↔ Zn absorption	[130]
Rats	Fe deficiency Fe-adequate	Perfusion with Fe	↓ Zn absorption	[130]

↑ – significant increase; ↓ – significant decrease; ↔ – no significant changes; DMT1–divalent metal transporter; Hb – hemoglobin; MCH – mean corpuscular hemoglobin; MCHC – mean corpuscular hemoglobin concentration; MCV – mean corpuscular volume; Ht – hematocrit.

significantly in Fe-deficient rats [130]. Finally, it has been noted that Zn deficiency results in decreased plasma erythropoietin concentration in rats [131,132], and thus may have a significant impact on the development of Fe deficiency anemia.

4.3. Human studies

Human data on the interplay between Fe and Zn, especially regarding Fe-deficiency and Fe supplementation, are contradictory (Tables 7–9). Children with Fe-deficiency anemia were characterized by significantly lowered Zn values of serum [133] and hair [134] as compared to the healthy controls, whereas no significant changes in whole blood Zn levels were observed in children with Fe deficiency [135,136].

A randomized, placebo-controlled, double-blind trial involving Peruvian children with Fe-deficiency anemia indicated a significant effect of the addition of Zn to Fe supplementation on indices of Fe status as well as on duration of diarrhea [137]. Correspondingly, treatment of Fe deficiency with a combination of Fe, Zn, and vitamin A was more effective than administration of Fe alone or a combination of Fe and vitamin A [138]. Simultaneous treatment of Fe-deficient pregnant women with a combination of Fe and Zn significantly improved hematological parameters and Fe status, whereas administration of Fe alone did not possess a comparable effect [139]. However, simultaneous supplementation of pregnant Peruvian women with Fe and Zn had a lower effect on serum Fe and ferritin than obtained with Fe alone. Moreover, women treated with Fe were characterized by lowered serum Zn levels compared to controls [140]. A negative influence of prenatal Fe supplementation on serum Zn was confirmed by the same group of researchers [141]. Some of these observations in pregnant women have also been reproduced in lactating women. In particular, supplementation with 60 mg ferrous sulfate at 7–9 wk of lactation resulted in lower fractional Zn absorption as compared to the control values [142]. Iron supplementation has been shown to decrease Zn absorption in a dose-dependent manner in ileostomy patients [143]. These data are in agreement with the results of the earlier study by Crofton et al. who reported that Zn supplementation could impair Fe absorption [144]. It has also been reported that a fivefold excess of Zn to Fe decreased Fe absorption from an aqueous solution but not from a hamburger meal [145].

An early study demonstrated that Fe fortification at the currently used fortification levels of weaning cereal, wheat bread, and infant formula did not have a significant negative impact on Zn absorption [146]. Similar data were obtained during the investigation of the effect of consumption of Fe-fortified food in infants [147]. Sodium-Fe-EDTA as a food fortificant for bread did not significantly influence the Zn retention [148]. Furthermore, a 3-months Fe treatment (30 mg/kg/day as ferrous sulfate before meal) in 1-year old infants did not alter serum Zn levels [149]. No significant effect of prior Fe supplementation was observed on Zn absorption in breastfed infants [150]. An examination of pregnant women from 16 weeks of gestation to term demonstrated that Fe supplementation did not affect fractional Zn absorption and exchangeable Zn pool [151]. Moreover, two months of supplementation with 20 mg of $ZnSO_4$ between meals in non-anemic adult Chilean women did not have a significant effect on Fe absorption and Fe status [152].

Multiple studies have demonstrated that the Zn-to-Fe (or vice versa) molar ratio in the diet is crucial for the character of interaction between Fe and Zn during absorption. It has been shown that high doses of Zn even at a molar ratio of 1:1 inhibited Fe bioavailability by 56% [153]. Correspondingly, Zn supplementation in a molar ratio 20:1 Zn to Fe simultaneously with Fe significantly depressed Fe absorption. However, no such effect was observed when Zn was administered 30 or 60 min before Fe [154]. In turn, previous human experiment indicated that administration of Zn

Table 7
Interaction between zinc (Zn) and iron (Fe) status in human children.

Objects	Conditions	Factors	Effects	References
Infants 9 mo	Fe-adequate	Fe-fortified meals	↔ Zn absorption	[147]
Infants 18–27 wk	Fe-adequate	+ Sodium-Fe-EDTA fortified products	↔ Zn absorption * * as compared to $FeSO_4$	[148]
Breastfed infants	Fe adequate	+ 1 mg/kg/day Fe	↔ Zn absorption	[150]
1-year old	Fe adequate	+ 30 mg/day Fe as $FeSO_4$	↔ serum Zn	[149]
Children	Fe-deficiency anemia	Fe-deficiency anemia	↓ serum Zn	[133]
Children 1–4 yo	Fe-deficiency anemia	Fe-deficiency anemia	↓ serum Zn ↓ hair Zn	[134]
Children ~ 7 yo	Fe-deficiency anemia Fe deficiency	Fe-deficiency anemia	↔ serum Zn ↔ serum Zn	[135]
Children ~ 76 yo	Fe-deficiency anemia	Fe-deficiency anemia	↔ serum Zn	[136]
Children 6 mo – 6 yo	Fe deficiency anemia	+ 4 mg/kg/d $FeSO_4$ + 5 mg/d oral $ZnSO_4$	↔ serum Zn * ↔ ferritin * ↔ blood count * * as compared to Fe only	[187]
Children 6–35 mo	Fe deficiency	+ 0.7 mg/kg/day Zn + 3 mg/kg/day Fe	↑ Hb * ↑ ferritin * ↓ diarrhea * * as compared to Fe only	[137]

↑ – significant increase; ↓ – significant decrease; ↔ – no significant changes; Hb – hemoglobin.

Table 8
Interaction between zinc (Zn) and iron (Fe) status in human adults.

Objects	Conditions	Factors	Effects	References
Ileostomy patients 55 yo	Fe-adequate	+ 100/400 mg Fe as Fe gluconate	↓ Zn absorption (dose-dependent)	[143]
Male volunteers 26–46 y	Fe-adequate	+ 842 μmol Fe + 344 μmol Zn	↔ plasma Fe * * as compared to Fe only	[144]
Male volunteers 26–46 y	Fe-adequate	+ 421 μmol Fe + 421/1048 μmol Zn	↓ plasma Fe * * as compared to Fe only	[144]
Volunteers 19–50 yo	Fe-adequate	+ 15/45 mg Zn + 3 mg Fe (solution)	↓ Fe absorption	[145]
Volunteers 19–50 yo	Fe-adequate	+ 15/45 mg Zn + 3 mg Fe (meal)	↔ Fe absorption	[145]
Volunteers	Fe-adequate	Fe fortification: 200 or 500 mg Fe/kg (weaning cereal), 65 mg Fe/kg (white wheat flour) and 12 mg Fe/l (infant formula)	↔ Zn absorption	[146]

↑ – significant increase; ↓ – significant decrease; ↔ – no significant changes; Hb – hemoglobin.

sulfate and Fe sulfate in a ratio of 1:1 slightly inhibited Zn absorption, whereas Fe/Zn ratio of 2:1 and 3:1 possessed more expressed effect on Zn absorption [155]. The importance of Zn/Fe ratio for metal interaction during their absorption has been recently demonstrated in perfused jejunal loops. In particular, Fe did not inhibit Zn absorption at Fe:Zn ratio below 2:1 in non-Fe-deficient rats, whereas at higher ratios a significant decrease was observed. Oppositely, in Fe-deficient rats at Fe/Zn ratio of 2:1 no alteration of Zn absorption was found [156].

In sum, the quoted data indicate that depending on a number of factors Zn may increase or decrease Fe absorption and retention and vice versa. Generally, the *in vivo* studies involving laboratory animals and humans demonstrating a mutual positive interaction between Zn and Fe are in agreement with *in vitro* studies on cell cultures. In particular, the mechanisms of such interaction may involve Zn-induced modulation of hepcidin and IRE/IRP signaling, resulting in upregulation of DMT1 and Fpn expression and subsequent increase in Fe absorption. However, certain supplementation studies have revealed a negative interaction between Fe and Zn. These findings are also supported by *in vitro* investigations demonstrating possible up-regulation of hepcidin by Zn treatment ultimately leading to decreased Fe absorption and iron sequestration. In turn, increased iron uptake was shown to differentially affect the level of zinc transporters, resulting in impaired Zn handling. Therefore, both *in vivo* and *in vitro* studies demonstrate that the mechanisms mediating Fe-Zn interaction are strongly dependent on the level of metals and their ratios. In addition to modulation of Fe absorption, other mechanisms may also link Zn deficiency or excess to anemia [157].

5. Interactions between iron and chromium

Chromium occurs in two oxidation states Cr (III) and Cr (VI) which are considered as biologically and environmentally relevant [158]. Cr (III) is the most stable form in biological systems and is regarded as an essential nutrient that influences carbohydrate, lipid, and protein metabolism by enhancing insulin action. Multimineral tablets may contain up to 50 μg Cr, in the trivalent form. Trivalent Cr exhibits low toxicity in animals, which may result from its poor transport across cellular membranes. In contrast, Cr(VI) is very toxic and has a high ability to enter cells, inducing a wide variety of injuries such as DNA damage, chromosomal aberrations, alterations in the epigenome, and microsatellite instability [159]. Symptoms of Cr deficiency is mainly related to its role in the glucose metabolism and include glucose intolerance, increased circulating glucose and insulin, and may be complicated by neuropathy [158,160].

Chromium is present in the diet in both its inorganic form and in the form of organic complexes. The absorption of Cr is low, ranging between 0.4 and 3.0% and the bioavailability of Cr from

Table 9
Interaction between zinc (Zn) and iron (Fe) status in women.

Objects	Conditions	Factors	Effects	References
Women 15–45 years	Fe deficiency anemia	60 mg/day Fe + 15 mg/day Zn + 200000 IU vitamin A	↑ Hb * * as compared to Fe only or Fe + vitamin A	[138]
Pregnant women 20–38 yo (~21 wk gestation)	Fe deficiency	+ Fe citrate 100 mg/day + mg/day β-alanyl-L-histidinate Zn	↑ Hb * ↑ RBC * ↑ Ht * ↑ Reticulocytes * ↑ TIBC * * as compared to initial values	[139]
Pregnant women (18 – 35 y) 30–36 wk gestation	Fe-adequate	+ 60 mg/day Fe as $FeSO_4$ + 250 mg folate + 15 mg Zn as $ZnSO_4$	↑ ferritin * * as compared to controls ↓ serum iron * * as compared to Fe only	[140]
Pregnant women (18 – 35 y) 30–36 wk gestation	Fe-adequate	+ 60 mg/day Fe as $FeSO_4$ + 250 mg folate + 15 mg Zn as $ZnSO_4$	↓ Zn absorption * * as compared to Fe only and control values	[141]
Lactating women (7–9 wk lactation) ~33 yo	Fe-adequate	+ 60 mg/day Fe as $FeSO_4$	↔ serum Zn * ↓ fractional Zn absorption * * as compared to no-Fe values	[142]
Pregnant women (16 wk gestation) 18–40 yo	Fe-adequate	+ 100 mg/day Fe as Fe gluconate	↔ plasma Zn ↔ exchangeable Zn pool ↔ urinary Zn excretion ↔ Zn absorption	[151]
Women 35–45 yo	Fe-adequate	+ 20 mg/day Zn as $ZnSO_4$	↔ serum Fe * ↔ ferritin * ↔ TIBC * ↔ body Fe * ↔ blood count * * as compared to placebo	[152]

↑ – significant increase; ↓ – significant decrease; ↔ – no significant changes; Hb – hemoglobin; Ht – hematocrit; RBC – red blood cells.

organic complexes is higher than from its inorganic form [161,162]. Chromium is absorbed in the intestinal mucosa. Absorbed Cr is transported to tissues bound to transferrin and to a lesser extent to albumin. Transferrin possesses two binding sites with different affinities for Fe as a function of pH. It has been shown that Cr binds exclusively to one of these sites [158,162]. The antagonism between Cr and Fe in binding to transferrin might cause the increase in hematological parameters (Hb, hematocrit, erythrocytes and mean erythrocyte volume) reported in Cr deficiency [161].

5.1. Studies in cell lines and experimental animals

In vitro studies have shown that Cr reduces Fe binding to transferrin [163]. In animal studies, it was found that high doses of Cr (1 mg/kg/day for 45 days) significantly reduced transferrin saturation by Fe, depleted tissue Fe storage, and decreased Hb [164]. Because Cr inhibits Fe binding to transferrin, it is suggested that Cr supplements intake can impair Fe transport and utilization also in human. In some studies in adults supplemented with Cr picolinate reported 20–30% decreases in serum ferritin concentrations [165,166]. Chromium supplementation decreased Fe concentration in serum, liver, and bone in mice with polycystic ovary syndrome [167].

In contrast, in other experiments, no changes in iron tissue content were observed in rats after Cr supplementation [168–170]. Some investigators found that Cr supplementation had no effect on Fe balance in buffalo calves or rainbow trout [171,172]. Antagonism between Fe and Cr in diabetes was also observed in the animal studies. Król and Krejpcio found increased Fe concentration in the liver of rats with STZ induced diabetes as compared to the control group. Unexpectedly, this elevated Fe level in liver was reduced by Cr propionate supplementation (dietary 10 or 50 mg/kg of Cr propionate for five weeks) [173]. Accordingly, a previous study of our group demonstrated a significant decrease in adipose tissue Cr content in animals fed Fe sulfate [174].

However, some results indicated that Fe deficiency anemia is associated with decreased level of Cr in the body which may suggest synergism between Cr and Fe in the condition of Fe deficiency [175]. However, results of several studies are not consistent with this observation.

5.2. Summary of observations in humans

Randomized controlled studies did not find any significant influence of Cr supplementation (200 and 924 μg per day) on Fe status in women or men [163,176].

However, a decrease in Cr concentration in patients with type 2 diabetes may be associated with increased Fe levels, although other studies did not confirm these results [160,177]. It is suggested that many factors (*e.g.*, nutritional status, diseases, subjects, diet) may influence the Cr-Fe interactions in the organism. However, it is apparent that the interactions between Fe and Cr, *e.g.*, in the cases of siderosis with diabetes, is yet not fully understood.

Therefore, both experimental and clinical studies demonstrate that interaction between Cr and Fe may take place in the organism. However, the particular character of such interaction as well as the underlying mechanisms are still unclear. Additional *in vitro* and *in vivo* studies are required to characterize the biological interaction between Fe and Cr under various exposure regimens and metal ratios.

6. Iron overload, selenium, and antioxidants

Before multimineral supplementation with Fe is prescribed it is crucial to assess indices of Fe homeostasis since the asthenia of Fe overload in some cases has been interpreted as a symptom of Fe deficiency [178]. Iron overload may be due to increased Fe absorption as in *primary hemochromatosis*, or it may be *secondary* to blood transfusions or inappropriate ingestion of Fe. The autosomal recessive disease known as *primary* hemochromatosis is more common than previously thought, and the first symptom is often patient

weakness. Hereditary hemochromatosis is particularly prevalent in Northern Europe and is rare in Africa and Asia. The disease is related to a gene mutation on the short arm of chromosome 6 (the *HFE* gene, which is linked to the HLA locus), in Europe often the C282Y mutation [179]. The allele frequency, *i.e.* the occurrence of the C282Y mutation in the population, is highest in Ireland, by 9.7%, while other European countries have allele frequencies in the range of 1–4% [180]. Patients with this disease are treated by frequent phlebotomy and avoidance of medical Fe-intake. Secondary hemochromatosis or *siderosis* may happen secondary to prolonged ingestion of medicinal Fe or Fe-rich food combined with sour beer brewed in iron kettles [181]. Siderosis is also a complication of anemias due to genetically 5deranged erythropoiesis requiring frequent blood transfusions, *e.g.* the thalassaemias. Hemochromatosis usually requires specialized chelation therapy [182] to avoid complications such as siderosis resulting *e.g.* in cardiomyopathy.

The oxidative stress accompanying the massive Fe accumulation in siderosis is considered to be a causative factor in the development of complications such as cardiomyopathy and liver cancer [182–184]. Although several transition metals react with physiological occurrences of H_2O_2 to form the extremely toxic hydroxyl radical $HO^{\cdot}$, most attention has been paid to the role of Fe excesses and the Fenton reaction *in vivo* [185]:

$$Fe(II) + H_2O_2 \rightarrow HO^{\bullet} + Fe(III)$$

Hydrogen peroxide, as well as superoxide radicals, are continuously formed under non-pathological conditions in aerobic cells. However, under physiological conditions, the concentrations of these reactive oxygen species (ROS) are kept extremely low due to the activity of antioxidative enzyme systems including the superoxide dismutases (Cu,Zn-SOD, and Mn-SOD) and the glutathione peroxidases (GPx), the latter enzyme containing Se. Thus, an adequate daily intake of Se protects against deleterious effects of ROS, *e.g.*, oxygen radicals resulting from Fe deposits. A multimineral tablet usually contains about 50 μg Se, in addition to adequate amounts of the antioxidative components vitamin C (ascorbate) and vitamin E. Here, it should be noted that ferric complexes, *e.g.* like Fe-transferrin, react very slowly with H_2O_2 compared to ferrous forms of Fe. Reducing agents can thereby stimulate the Fenton reaction. This may occur with simultaneous overdosing with ascorbate and Fe:

$$Fe(III) + \text{ascorbate}^{-} \rightarrow Fe(II) + \text{semidehydroascorbate}$$

Hence, whereas vitamin C in reasonable doses acts as an antioxidant, the same vitamin in megadoses (>1000 mg/day) may be harmful by acting as a prooxidant, especially in subjects with Fe overload [186].

7. Perspectives

The existing data demonstrate multiple forms of interactions between Fe and Mn, Zn, Cr, and also with antioxidants and Se. Previous reviews have given extensive discussions on Fe-Cu-interactions [29]. These interactions may have a significant impact on Fe status in the case of Fe deficiency. Therefore, while managing hypoferremia and Fe-deficiency anemia, it seems recommendable to assess the status of other trace elements such as Cu, Mn, Zn and Se in parallel with indices of Fe homeostasis. We suppose that simultaneous adequate correction of complete trace element status in Fe deficiency may help to alleviate the condition of the patient. Furthermore, it is important to monitor the effect of supplementation to avoid Fe excess. A personalized approach to the assessment of trace elements status in Fe deficiency and its correction may significantly improve Fe homeostasis more efficiently than supplementation with Fe alone. Admittedly, this can only be recommended for affluent countries. At the same time, further studies are required to investigate additional mechanisms of interaction between Fe and other essential trace elements.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

The authors are thankful to an anonymous reviewer who provided helpful comments to improve the manuscript.

References

[1] G.J. Anderson, G.D. McLaren, Iron Physiology and Pathophysiology in Humans, Humana Press, New York, 2012.
[2] N.J. Kassebaum, R. Jasrasaria, M. Naghavi, S.K. Wulf, N. Johns, R. Lozano, M. Regan, D. Weatherall, D.P. Chou, T.P. Eisele, S.R. Flaxman, R.L. Pullan, S.J. Brooker, C.J. Murray, A systematic analysis of global anemia burden from 1990 to 2010, Blood 123 (2014) 615–624.
[3] World Health Organization, Iron Deficiency Anaemia: Assessment, Prevention, and Control. A Guide for Programme Managers, World Health Organization, Genève, 2001.
[4] A.U. Steinbicker, M.U. Muckenthaler, Out of balance—systemic iron homeostasis in iron-related disorders, Nutrients 5 (2013) 3034–3061.
[5] Food and Nutrition Board, Institute of medicine, iron, in: Food and Nutrition Board, Institute of Medicine, Dietary Reference Intakes for Vitamin A, Vitamin K, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc, National Academy Press, Washington, 2001, pp. 290–393.
[6] F. Pizarro, R. Yip, P.R. Dallman, M. Olivares, E. Hertrampf, T. Walter, Iron status with different infant feeding regimens: relevance to screening and prevention of iron deficiency, J. Pediatr. 118 (1991) 687–692.
[7] M.M. Black, A.M. Quigg, K.M. Hurley, M.R. Pepper, Iron deficiency and iron-deficiency anemia in the first two years of life: strategies to prevent loss of developmental potential, Nutr. Rev. 69 (Suppl. 1) (2011) S64–S70.
[8] M. Domellöf, Iron requirements in infancy, Ann. Nutr. Metab. 59 (2011) 59–63.
[9] P.J. Aggett, Iron, in: J.W. Erdman, I.A. Macdonald, S.H. Zeisel (Eds.), Present Knowledge in Nutrition, tenth ed., Wiley-Blackwell, Washington, 2012, pp. 506–520.
[10] L.J. Harvey, C.N. Armah, J.R. Dainty, R.J. Foxall, D. John Lewis, N.J. Langford, S.J. Fairweather-Tait, Impact of menstrual blood loss and diet on iron deficiency among women in the UK, Br. J. Nutr. 94 (2005) 557–564.
[11] C. Pigeon, G. Ilyin, B. Courselaud, P. Leroyer, B. Turlin, P. Brissot, O. Loréal, A new mouse liver-specific gene encoding a protein homologous to human antimicrobial peptide hepcidin, is overexpressed during iron overload, J. Biol. Chem. 276 (2001) 7811–7819.
[12] L. Hallberg, L. Rossander-Hulten, M. Brune, A. Gleerup, Calcium and iron absorption: mechanism of action and nutritional importance, Eur. J. Clin. Nutr. 46 (1992) 317–327.
[13] B. Lönnerdal, Calcium and iron absorption-mechanisms and public health relevance, Int. J. Vitam. Nutr. Res. 80 (2010) 293–299.
[14] P.B. Disler, S.R. Lynch, R.W. Charlton, J.D. Torrance, T.H. Bothwell, R.B. Walker, F. Mayet, The effect of tea on iron absorption, Gut 16 (1975) 193–200.
[15] L. Hallberg, Wheat fiber, phytates and iron absorption, Scand. J. Gastroenterol. (Suppl. 129) (1987) 73–79.
[16] R.D. Bloomberg, A. Fleishman, J.E. Nalle, D.M. Herron, S. Kini, Nutritional deficiencies following bariatric surgery: what have we learned? Obes. Surg. 15 (2005) 145–154.
[17] C. Gasche, A. Berstad, R. Befrits, C. Beglinger, A. Dignass, K. Erichsen, F. Gomollon, H. Hjortswang, I. Koutroubakis, S. Kulnigg, B. Oldenburg, D. Rampton, O. Schroeder, J. Stein, S. Travis, G. Van Assche, Guidelines on the diagnosis and management of iron deficiency and anemia in inflammatory bowel diseases, Inflamm. Bowel Dis. 13 (2007) 1545–1553.
[18] F. Bermejo, S. Garcia-Lopez, A guide to diagnosis of iron deficiency and iron deficiency anemia in digestive diseases, World J. Gastroenterol. 15 (2009) 4638–4643.
[19] U.D. Bayraktar, S. Bayraktar, Treatment of iron deficiency anemia associated with gastrointestinal tract diseases, World J. Gastroenterol. 16 (2010) 2720–2725.
[20] K.A. Gudzune, M.M. Huizinga, H.Y. Chang, V. Asamoah, M. Gadgil, J.M. Clark, Screening and diagnosis of micronutrient deficiencies before and after bariatric surgery, Obes. Surg. 23 (2013) 1581–1589.
[21] J.M. McDermid, B. Lönnerdal, Iron, Adv. Nutr. 3 (2012) 532–533.
[22] R. Hurrell, I. Egli, Iron bioavailability and dietary reference values, Am. J. Clin. Nutr. 91 (2010) 1461S–1467S.
[23] M.B. Zimmermann, R.F. Hurrell, Nutritional iron deficiency, Lancet 370 (2007) 511–520.

[24] A.G. Cantor, C. Bougatsos, T. Dana, I. Blazina, M. McDonagh, Routine iron supplementation and screening for iron deficiency anemia in pregnancy: a systematic review for the U.S. preventive services task force, Ann. Intern. Med. 162 (2015) 566–576.
[25] J. Aaseth, Y. Thomassen, D.G. Ellingsen, G. Støa-Birketvedt, Prophylactic iron supplementation in pregnant women in Norway, J. Trace Elem. Med. Biol. 15 (2001) 167–174.
[26] H.N. Moussa, S. Hosseini Nasab, Z.A. Haidar, S.C. Blackwell, B.M. Sibai, Folic acid supplementation: what is new? Fetal, obstetric, long-term benefits and risks, Future Sci. OA 2 (2016) FSO116, http://dx.doi.org/10.4155/fsoa-2015-0015.
[27] C.D. Vulpe, Y.M. Kuo, T.L. Murphy, L. Cowley, C. Askwith, N. Libina, J. Gitschier, G.J. Anderson, Hephaestin a ceruloplasmin homologue implicated in intestinal iron transport, is defective in the sla mouse, Nat. Genet. 21 (1999) 195–199.
[28] J.R. Turnlund, Copper, in: M.E. Shils, M. Shike, A.C. Ross, B. Caballero, R.J. Cousins (Eds.), Modern Nutrition in Health and Disease, tenth ed., Lippincott Williams & Wilkins, Philadelphia, 2006, pp. 286–299.
[29] J.F. Collins, J.R. Prohaska, M.D. Knutson, Metabolic crossroads of iron and copper, Nutr. Rev. 68 (2010) 133–147.
[30] P.L. Fox, The copper-iron chronicles: the story of an intimate relationship, Biometals 16 (2003) 9–40.
[31] P. Sharp, The molecular basis of copper and iron interactions, Proc. Nutr. Soc. 63 (2004) 563–569.
[32] B. Elsenhans, H. Janser, W. Windisch, K. Schümann, Does lead use the intestinal absorptive pathways of iron? Impact of iron status on murine ^{210}Pb and ^{59}Fe absorption in duodenum and ileum *in vivo*, Toxicology 284 (2011) 7–11.
[33] F. Shah, T.G. Kazi, H.I. Afridi, J.A. Baig, S. Khan, N.F. Kolachi, S.K. Wadhwa, A.Q. Shah, Environmental exposure of lead and iron deficit anemia in children age ranged 1–5 years: a cross sectional study, Sci. Total Environ. 408 (2010) 5325–5330.
[34] J.L. Aschner, M. Aschner, Nutritional aspects of manganese homeostasis, Mol. Asp. Med. 26 (2005) 353–362.
[35] D.S. Avila, R.L. Puntel, M. Aschner, Manganese in health and disease, Met. Ions Life Sci. 13 (2013) 199–227, http://dx.doi.org/10.1007/978-94-007-7500-8_7.
[36] J. Crossgrove, W. Zheng, Manganese toxicity upon overexposure, NMR Biomed. 17 (2004) 544–553.
[37] J.A. Roth, M.D. Garrick, Iron interactions and other biological reactions mediating the physiological and toxic actions of manganese, Biochem. Pharmacol. 66 (2003) 1–13.
[38] H. Gunshin, B. Mackenzie, U.V. Berger, Y. Gunshin, M.F. Romero, W.F. Boron, S. Nussberger, J.L. Gollan, M.A. Hediger, Cloning and characterization of a mammalian proton-coupled metal-ion transporter, Nature 388 (1997) 482–488.
[39] M.D. Garrick, K.G. Dolan, An expression system for a transporter of iron and other metals, Methods Mol. Biol. 196 (2002) 147–154.
[40] M.D. Garrick, S.T. Singleton, F. Vargas, H.C. Kuo, L. Zhao, M. Knöpfel, T. Davidson, M. Costa, P. Paradkar, J.A. Roth, L.M. Garrick, DMT1: which metals does it transport? Biol. Res. 39 (2006) 79–85.
[41] D.I. Bannon, R. Abounader, P.S. Lees, J.P. Bressler, Effect of DMT1 knockdown on iron cadmium, and lead uptake in Caco-2 cells, Am. J. Physiol. Cell Physiol. 284 (2003) C44–C50.
[42] X. Wang, G.J. Li, W. Zheng, Upregulation of DMT1 expression in choroidal epithelia of the blood—CSF barrier following manganese exposure in vitro, Brain Res. 1097 (2006) 1–10.
[43] C. Au, A. Benedetto, M. Aschner, Manganese transport in eukaryotes: the role of DMT1, Neurotoxicology 29 (2008) 569–576.
[44] E.A. Heilig, K.J. Thompson, R.M. Molina, A.R. Ivanov, J.D. Brain, M. Wessling-Resnick, Manganese and iron transport across pulmonary epithelium, Am. J. Physiol. Lung Cell. Mol. Physiol. 290 (2006) L1247–L1259.
[45] Z. Yin, H. Jiang, E.S. Lee, M. Ni, K.M. Erikson, D. Milatovic, A.B. Bowman, M. Aschner, Ferroportin is a manganese-responsive protein that decreases manganese cytotoxicity and accumulation, J. Neurochem. 112 (2010) 1190–1198.
[46] M.S. Madejczyk, N. Ballatori, The iron transporter ferroportin can also function as a manganese exporter, Biochim. Biophys. Acta 1818 (2012) 651–657.
[47] C.J. Mitchell, A. Shawki, T. Ganz, E. Nemeth, B. Mackenzie, Functional properties of human ferroportin, a cellular iron exporter reactive also with cobalt and zinc, Am. J. Physiol. Cell Physiol. 306 (2014) C450–C459.
[48] B.Y. Park, J. Chung, Effects of various metal ions on the gene expression of iron exporter ferroportin-1 in J774 macrophages, Nutr. Res. Pract. 2 (2008) 317–321.
[49] P. Aisen, R. Aasa, A.G. Redfield, The chromium manganese, and cobalt complexes of transferrin, J. Biol. Chem. 244 (1969) 4628–4633.
[50] K. Gkouvatsos, G. Papanikolaou, K. Pantopoulos, Regulation of iron transport and the role of transferrin, Biochim. Biophys. Acta 1820 (2012) 188–202.
[51] W.R. Harris, Y. Chen, Electron paramagnetic resonance and difference ultraviolet studies of Mn2+ binding to serum transferrin, J. Inorg. Biochem. 54 (1994) 1–19.
[52] J.B. Vincent, S. Love, The binding and transport of alternative metals by transferrin, Biochim. Biophys. Acta 1820 (2012) 362–378.
[53] M. Aschner, K.E. Vrana, W. Zheng, Manganese uptake and distribution in the central nervous system (CNS), Neurotoxicology 20 (1998) 173–180.
[54] T.E. Gunter, B. Gerstner, K.K. Gunter, J. Malecki, R. Gelein, W.M. Valentine, M. Aschner, D.I. Yule, Manganese transport via the transferrin mechanism, Neurotoxicology 34 (2013) 118–127.
[55] A.A. Moshtaghi, A. Badiei, T. Hasanzadeh, Role of ceruloplasmin and ethanolamine in manganese binding to human serum apo-transferrin, Iran. J. Sci. Technol. B 21 (1997) 157–168.
[56] N.E. Hellman, J.D. Gitlin, Ceruloplasmin metabolism and function, Annu. Rev. Nutr. 22 (2002) 439–458.
[57] J.W. Critchfield, C.L. Keen, Manganese+ 2 exhibits dynamic binding to multiple ligands in human plasma, Metabolism 41 (1992) 1087–1092.
[58] J.A. Roth, M.D. Garrick, Iron interactions and other biological reactions mediating the physiological and toxic actions of manganese, Biochem. Pharmacol. 66 (2003) 1–13.
[59] K. Pantopoulos, Iron metabolism and the IRE/IRP regulatory system: an update, Ann. N. Y. Acad. Sci. 1012 (2004) 1–13.
[60] C.L. Kwik-Uribe, S. Reaney, Z. Zhu, D. Smith, Alteratio ns in cellular IRP-dependent iron regulation by *in vitro* manganese exposure in undifferentiated PC12 cells, Brain Res. 973 (2003) 1–15.
[61] C. Kwik-Uribe, D.R. Smith, Temporal responses in the disruption of iron regulation by manganese, J. Neurosci. Res. 83 (2006) 1601–1610.
[62] D.R. Crooks, M.C. Ghosh, M. Braun-Sommargren, T.A. Rouault, D.R. Smith, Manganese targets m-aconitase and activates iron regulatory protein 2 in AF5 GABAergic cells, J. Neurosci. Res. 85 (2007) 1797–1809.
[63] S. Oshiro, K. Nozawa, M. Hori, C. Zhang, Y. Hashimoto, S. Kitajima, K.I. Kawamura, Modulation of iron regulatory protein-1 by various metals, Biochem. Biophys. Res. Commun. 290 (2002) 213–218.
[64] T.B. Bartnikas, Known and potential roles of transferrin in iron biology, Biometals 25 (2012) 677–686.
[65] S.J. Garcia, K. Gellein, T. Syversen, M. Aschner, A manganese-enhanced diet alters brain metals and transporters in the developing rat, Toxicol. Sci. 92 (2006) 516–525.
[66] K. Thompson, R.M. Molina, T. Donaghey, J.E. Schwob, J.D. Brain, M. Wessling-Resnick, Olfactory uptake of manganese requires DMT1 and is enhanced by anemia, FASEB J. 21 (2007) 223–230.
[67] A. Shawki, S.R. Anthony, Y. Nose, M.A. Engevik, E.J. Niespodzany, T. Barrientos, H. Öhrvik, R.T. Worrell, D.J. Thiele, B. Mackenzie, Intestinal DMT1 is critical for iron absorption in the mouse but is not required for the absorption of copper or manganese, Am. J. Physiol. Gastrointest. Liver Physiol. 309 (2015) G635–G647, http://dx.doi.org/10.1152/ajpgi.00160.2015.
[68] J.S. Crossgrove, R.A. Yokel, Manganese distribution across the blood–brain barrier III. The divalent metal transporter-1 is not the major mechanism mediating brain manganese uptake, Neurotoxicology 25 (2004) 451–460.
[69] Y.A. Seo, M. Wessling-Resnick, Ferroportin deficiency impairs manganese metabolism in flatiron mice, FASEB J. 29 (2015) 2726–2733.
[70] Y.A. Seo, J.A. Elkhader, M. Wessling-Resnick, Distribution of manganese and other biometals in flatiron mice, Biometals 29 (2016) 147–155.
[71] J. Kim, P.D. Buckett, M. Wessling-Resnick, Absorption of manganese and iron in a mouse model of hemochromatosis, PLoS One 8 (2013) e64944, http://dx.doi.org/10.1371/journal.pone.0064944.
[72] H.A. Jouihan, P.A. Cobine, R.C. Cooksey, E.A. Hoagland, S. Boudina, E.D. Abel, D.R. Winge, D.A. McClain, Iron-mediated inhibition of mitochondrial manganese uptake mediates mitochondrial dysfunction in a mouse model of hemochromatosis, Mol. Med. 14 (2008) 98–108.
[73] L. Pang, J. Wang, W. Huang, S. Guo, A study of divalent metal transporter 1 and ferroportin 1 in brain of rats with manganese-induced parkinsonism (in Chinese), Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi 33 (2015) 250–254.
[74] L. Davidsson, B. Lönnerdal, B. Sandström, C. Kunz, C.L. Keen, Identification of transferrin as the major plasma carrier protein for manganese introduced orally or intravenously or after *in vitro* addition in the rat, J. Nutr. 119 (1989) 1461–1464.
[75] T.K. Dickinson, A.G. Devenyi, J.R. Connor, Distribution of injected iron 59 and manganese 54 in hypotransferrinemic mice, J. Lab. Clin. Med. 128 (1996) 270–278.
[76] C. Herrera, M.A. Pettiglio, T.B. Bartnikas, Investigating the role of transferrin in the distribution of iron manganese, copper, and zinc, J. Biol. Inorg. Chem. 19 (2014) 869–877.
[77] D. Moutafchiev, L. Sirakov, P. Bontchev, The competition between transferrins labeled with 59Fe 65Zn, and 54 Mn for the binding sites on lactating mouse mammary gland cells, Biol. Trace Elem. Res. 61 (1998) 181–191.
[78] S.V. Chandra, G.S. Shukla, Role of iron deficiency in inducing susceptibility to manganese toxicity, Arch. Toxicol. 35 (1976) 319–323.
[79] E. Heilig, R. Molina, T. Donaghey, J.D. Brain, M. Wessling-Resnick, Pharmacokinetics of pulmonary manganese absorption: evidence for increased susceptibility to manganese loading in iron-deficient rats, Am. J. Physiol. Lung Cell. Mol. Physiol. 288 (2005) L887–L893.
[80] K. Thompson, R. Molina, T. Donaghey, J.D. Brain, M. Wessling-Resnick, The influence of high iron diet on rat lung manganese absorption, Toxicol. Appl. Pharmacol. 210 (2006) 17–23.
[81] D.V. Vayenas, M. Repanti, A. Vassilopoulos, D.A. Papanastasiou, Influence of iron overload on manganese, zinc, and copper concentration in rat tissues *in vivo*: study of liver, spleen, and brain, Int. J. Clin. Lab. Res. 28 (1998) 183–186.

[82] W. Zheng, Q. Zhao, V. Slavkovich, M. Aschner, J.H. Graziano, Alteration of iron homeostasis following chronic exposure to manganese in rats, Brain Res. 833 (1999) 125–132.
[83] S.L. Hansen, M.S. Ashwell, A.J. Moeser, R.S. Fry, M.D. Knutson, J.W. Spears, High dietary iron reduces transporters involved in iron and manganese metabolism and increases intestinal permeability in calves, J. Dairy Sci. 93 (2010) 656–665.
[84] S. Park, C.S. Sim, H. Lee, Y. Kim, Blood manganese concentration is elevated in infants with iron deficiency, Biol. Trace Elem. Res. 155 (2013) 184–189.
[85] Y. Kim, J.K. Park, Y. Choi, C.I. Yoo, C.R. Lee, H. Lee, J.H. Lee, S.R. Kim, T.H. Jeong, C.S. Yoon, J.H. Park, Blood manganese concentration is elevated in iron deficiency anemia patients, whereas globus pallidus signal intensity is minimally affected, Neurotoxicology 26 (2005) 107–111.
[86] E.A. Smith, P. Newland, K.G. Bestwick, N. Ahmed, Increased whole blood manganese concentrations observed in children with iron deficiency anaemia, J. Trace Elem. Med. Biol. 27 (2013) 65–69.
[87] Y. Kim, B.K. Lee, Iron deficiency increases blood manganese level in the Korean general population according to KNHANES 2008, Neurotoxicology 32 (2011) 247–254.
[88] H.M. Meltzer, A.L. Brantsæter, B. Borch-Iohnsen, D.G. Ellingsen, J. Alexander, Y. Thomassen, H. Stigum, T.A. Ydersbond, Low iron stores are related to higher blood concentrations of manganese, cobalt and cadmium in non-smoking Norwegian women in the HUNT 2 study, Environ. Res. 110 (2010) 497–504.
[89] P. Brna, K. Gordon, J.M. Dooley, V. Price, Manganese toxicity in a child with iron deficiency and polycythemia, J. Child Neurol. 26 (2011) 891–894.
[90] B. Claus Henn, J. Kim, M. Wessling-Resnick, M.M. Téllez-Rojo, I. Jayawardene, A.S. Ettinger, M. Hernández-Avila, J. Schwartz, D.C. Christiani, H. Hu, R.O. Wright, Associations of iron metabolism genes with blood manganese levels: a population-based study with validation data from animal models, Environ. Health 10 (2011) 97, http://dx.doi.org/10.1186/1476-069X-10-97.
[91] D.M. Cowan, Q. Fan, Y. Zou, X. Shi, J. Chen, M. Aschner, F.S. Rosenthal, W. Zheng, Manganese exposure among smelting workers: blood manganese-iron ratio as a novel tool for manganese exposure assessment, Biomarkers 14 (2009) 3–16.
[92] B. Pesch, T. Weiss, B. Kendzia, J. Henry, M. Lehnert, A. Lotz, E. Heinze, H.U. Käfferlein, R. Van Gelder, M. Berges, J.U. Hahn, M. Mattenklott, E. Punkenburg, A. Hartwig, J.U. Hahn, Levels and predictors of airborne and internal exposure to manganese and iron among welders, J. Expo. Sci. Environ. Epidemiol. 22 (2012) 291–298.
[93] L. Lu, L.L. Zhang, G.J. Li, W. Guo, W. Liang, W. Zheng, Alteration of serum concentrations of manganese, iron, ferritin, and transferrin receptor following exposure to welding fumes among career welders, Neurotoxicology 26 (2005) 257–265.
[94] D.G. Ellingsen, E. Haug, R.J. Ulvik, Y. Thomassen, Iron status in manganese alloy production workers, J. Appl. Toxicol. 23 (2003) 239–247.
[95] K. Tholin, B. Sandström, R. Palm, G. Hallmans, Changes in blood manganese levels during pregnancy in iron supplemented and non supplemented women, J. Trace Elem. Med. Biol. 9 (1995) 13–17.
[96] J.W. Finley, Manganese absorption and retention by young women is associated with serum ferritin concentration, Am. J. Clin. Nutr. 70 (1999) 37–43.
[97] C.D. Davis, E.A. Malecki, J.L. Greger, Interactions among dietary manganese heme iron, and nonheme iron in women, Am. J. Clin. Nutr. 56 (1992) 926–932.
[98] C.D. Davis, J.L. Greger, Longitudinal changes of manganese-dependent superoxide dismutase and other indexes of manganese and iron status in women, Am. J. Clin. Nutr. 55 (1992) 747–752.
[99] K.M. Erikson, T. Syversen, J.L. Aschner, M. Aschner, Interactions between excessive manganese exposures and dietary iron-deficiency in neurodegeneration, Environ. Toxicol. Pharmacol. 19 (2005) 415–421.
[100] A.S. Prasad, Clinical immunological, anti-inflammatory and antioxidant roles of zinc, Exp. Gerontol. 43 (2008) 370–377.
[101] A.S. Prasad, O. Kucuk, Zinc in cancer prevention, Cancer Metastasis Rev. 21 (2002) 291–295.
[102] C.W. Levenson, Zinc supplementation: neuroprotective or neurotoxic? Nutr. Rev. 63 (2005) 122–125.
[103] W. Maret, H.H. Sandstead, Zinc requirements and the risks and benefits of zinc supplementation, J. Trace Elem. Med. Biol. 20 (2006) 3–18.
[104] A.S. Prasad, Discovery of human zinc deficiency: its impact on human health and disease, Adv. Nutr. 4 (2013) 176–190.
[105] L.M. Plum, L. Rink, H. Haase, The essential toxin: impact of zinc on human health, Int. J. Environ. Res. Publ. Health 7 (2010) 1342–1365.
[106] E.J. Underwood, Trace Elements in Human and Animal Nutrition, 4th ed., Academic Press, New York, 1977.
[107] N.W. Solomons, M. Ruz, Zinc and iron interaction: concepts and perspectives in the developing world, Nutr. Res. 17 (1997) 177–185.
[108] R.J. Cousins, J.P. Liuzzi, L.A. Lichten, Mammalian zinc transport trafficking, and signals, J. Biol. Chem. 281 (2006) 24085–24089.
[109] M. Murakami, T. Hirano, Intracellular zinc homeostasis and zinc signaling, Cancer Sci. 99 (2008) 1515–1522.
[110] M.D. Garrick, Human iron transporters, Genes Nutr. 6 (2011) 45–54.
[111] J.P. Liuzzi, F. Aydemir, H. Nam, M.D. Knutson, R.J. Cousins, Zip14 (Slc39a14) mediates non-transferrin-bound iron uptake into cells, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 13612–13617.
[112] V. Iyengar, R. Pullakhandam, K.M. Nair, Coordinate expression and localization of iron and zinc transporters explain iron-zinc interactions during uptake in Caco-2 cells: implications for iron uptake at the enterocyte, J. Nutr. Biochem. 23 (2012) 1146–1154.
[113] C.Y. Wang, S. Jenkitkasemwong, S. Duarte, B.K. Sparkman, A. Shawki, B. Mackenzie, M.D. Knutson, ZIP8 is an iron and zinc transporter whose cell-surface expression is up-regulated by cellular iron loading, J. Biol. Chem. 287 (2012) 34032–34043.
[114] A.C. Illing, A. Shawki, C.L. Cunningham, B. Mackenzie, Substrate profile and metal-ion selectivity of human divalent metal-ion transporter-1, J. Biol. Chem. 287 (2012) 30485–30496.
[115] S. Yamaji, J. Tennant, S. Tandy, M. Williams, S.K. Singh Srai, P. Sharp, Zinc regulates the function and expression of the iron transporters DMT1 and IREG1 in human intestinal Caco-2 cells, FEBS Lett. 507 (2001) 137–141.
[116] T.A. Rouault, The role of iron regulatory proteins in mammalian iron homeostasis and disease, Nature Chem. Biol. 2 (2006) 406–414.
[117] A. Martelli, J.M. Moulis, Zinc and cadmium specifically interfere with RNA-binding activity of human iron regulatory protein 1, J. Inorg. Biochem. 98 (2004) 1413–1420.
[118] B.J. Niles, M.S. Clegg, L.A. Hanna, S.S. Chou, T.Y. Momma, H. Hong, C.L. Keen, Zinc deficiency-induced iron accumulation a consequence of alterations in iron regulatory protein-binding activity, iron transporters, and iron storage proteins, J. Biol. Chem. 283 (2008) 5168–5177.
[119] T. Ganz, Hepcidin a key regulator of iron metabolism and mediator of anemia of inflammation, Blood 102 (2003) 783–788.
[120] S. Balesaria, B. Ramesh, H. McArdle, H.K. Bayele, S.K. Srai, Divalent metal-dependent regulation of hepcidin expression by MTF-1, FEBS Lett. 584 (2010) 719–725.
[121] R.D. Graham, M. Knez, R.M. Welch, How much nutritional iron deficiency in humans globally is due to an underlying zinc deficiency? Adv. Agron. 115 (2012) 1–40.
[122] M. Arredondo, R. Martinez, M.T. Nunez, M. Ruz, M. Olivares, Inhibition of iron and copper uptake by iron, copper and zinc, Biol. Res. 39 (2006) 95–102.
[123] V. Iyengar, R. Pullakhandam, K.M. Nair, Iron-zinc interaction during uptake in human intestinal Caco-2 cell line: kinetic analyses and possible mechanism, Indian J. Biochem. Biophys. 46 (2009) 299–306.
[124] S.L. Kelleher, B. Lönnerdal, Zinc supplementation reduces iron absorption through age-dependent changes in small intestine iron transporter expression in suckling rat pups, J. Nutr. 136 (2006) C1185–C1191.
[125] S. Shoham, M.B. Youdim, The effects of iron deficiency and iron and zinc supplementation on rat hippocampus ferritin, J. Neural Transm. (Vienna) 109 (2002) 1241–1256.
[126] K. Yokoi, M. Kimura, Y. Itokawa, Effect of dietary iron deficiency on mineral levels in tissues of rats, Biol. Trace Elem. Res. 29 (1991) 257–265.
[127] H. Nam, M.D. Knutson, Effect of dietary iron deficiency and overload on the expression of ZIP metal-ion transporters in rat liver, Biometals 25 (2012) 115–124.
[128] H. Yanagisawa, Y. Miyakoshi, K. Kobayashi, K. Sakae, I. Kawasaki, Y. Suzuki, J. Tamura, Long-term intake of a high zinc diet causes iron deficiency anemia accompanied by reticulocytosis and extra-medullary erythropoiesis, Toxicol. Lett. 191 (2009) 15–19.
[129] J.M. Rogers, B. Lönnerdal, L.S. Hurley, C.L. Keen, Iron and zinc concentrations and 59Fe retention in developing fetuses of zinc-deficient rats, J. Nutr. 117 (1987) 1875–1882.
[130] A.E. Gómez-Ayala, F. Lisbona, I. López-Aliaga, I. Pallarés, M. Barrionuevo, S. Hartiti, M.C. Rodríguez-Matas, M.S. Campos, The absorption of iron calcium, phosphorus, magnesium, copper and zinc in the jejunum-ileum of control and iron-deficient rats, Lab. Anim. 32 (1998) 72–79.
[131] A. Konomi, K. Yokoi, Zinc deficiency decreases plasma erythropoietin concentration in rats, Biol. Trace Elem. Res. 107 (2005) 289–292.
[132] A. Konomi, K. Yokoi, Changes of erythropoietin concentrations in plasma and kidney induced by zinc deficiency in rats, FASEB J. 24 (Suppl) (2010) 718.2.
[133] A. Ece, B.S. Uyanik, A. Işcan, P. Ertan, M.R. Yiğitoğlu, Increased serum copper and decreased serum zinc levels in children with iron deficiency anemia, Biol. Trace Elem. Res. 59 (1997) 31–39.
[134] M.K. Gürgöze, A. Ölçücü, A.D. Aygün, E. Taşkin, M. Kiliç, Serum and hair levels of zinc selenium, iron, and copper in children with iron-deficiency anemia, Biol. Trace Elem. Res. 111 (2006) 23–29.
[135] S. Turgut, A. Polat, M. Inan, G. Turgut, G. Emmungil, M. Bican, T.Y. Karakus, O. Genc, Interaction between anemia and blood levels of iron zinc, copper, cadmium and lead in children, Indian J. Pediatr. 74 (2007) 827–830.
[136] A.A. Hegazy, M.M. Zaher, M.A. Abd El-Hafez, A.A. Morsy, R.A. Saleh, Relation between anemia and blood levels of lead, copper, zinc and iron among children, BMC Res. Notes 3 (2010) 133, http://dx.doi.org/10.1186/1756-0500-3-133.
[137] K. Alarcon, P.W. Kolsteren, A.M. Prada, A.M. Chian, R.E. Velarde, I.L. Pecho, T.F. Hoeree, Effects of separate delivery of zinc or zinc and vitamin A on hemoglobin response growth, and diarrhea in young Peruvian children receiving iron therapy for anemia, Am. J. Clin. Nutr. 80 (2004) 1276–1282.
[138] P. Kolsteren, S.R. Rahman, K. Hilderbrand, A. Diniz, Treatment for iron deficiency anaemia with a combined supplementation of iron vitamin A and zinc in women of Dinajpur, Bangladesh, Eur. J. Clin. Nutr. 53 (1999) 102–106.
[139] S. Nishiyama, K. Kiwaki, Y. Miyazaki, T. Hasuda, Zinc and IGF-I concentrations in pregnant women with anemia before and after supplementation with iron and/or zinc, J. Am. Coll. Nutr. 18 (1999) 261–267.

[140] K.O. O'Brien, N. Zavaleta, L.E. Caulfield, D.X. Yang, S.A. Abrams, Influence of prenatal iron and zinc supplements on supplemental iron absorption red blood cell iron incorporation, and iron status in pregnant Peruvian women, Am. J. Clin. Nutr. 69 (1999) 509–515.
[141] K.O. O'Brien, N. Zavaleta, L.E. Caulfield, J. Wen, S.A. Abrams, Prenatal iron supplements impair zinc absorption in pregnant Peruvian women, J. Nutr. 130 (2000) 2251–2255.
[142] C.S. Chung, D.A. Nagey, C. Veillon, K.Y. Patterson, R.T. Jackson, P.B. Moser-Veillon, A single 60-mg iron dose decreases zinc absorption in lactating women, J. Nutr. 132 (2002) 1903–1905.
[143] F.J. Troost, R.J. Brummer, J.R. Dainty, J.A. Hoogewerff, V.J. Bull, W.H. Saris, Iron supplements inhibit zinc but not copper absorption *in vivo* in ileostomy subjects, Am. J. Clin. Nutr. 78 (2003) 1018–1023.
[144] R.W. Crofton, D. Gvozdanovic, S. Gvozdanovic, C.C. Khin, P.W. Brunt, N.A. Mowat, P.J. Aggett, Inorganic zinc and the intestinal absorption of ferrous iron, Am. J. Clin. Nutr. 50 (1989) 141–144.
[145] L. Rossander-Hulten, M. Brune, B. Sandström, B. Lönnerdal, L. Hallberg, Competitive inhibition of iron absorption by manganese and zinc in humans, Am. J. Clin. Nutr. 54 (1991) 152–156.
[146] L. Davidson, A. Almgren, B. Sandström, R.F. Hurrell, Zinc absorption in adult humans: the effect of iron fortification, Br. J. Nutr. 74 (1995) 417–425.
[147] S.J. Fairweather-Tait, S.G. Wharf, T.E. Fox, Zinc absorption in infants fed iron-fortified weaning food, Am. J. Clin. Nutr. 62 (1995) 785–789.
[148] L. Davidsson, P. Kastenmayer, R.F. Hurrell, Sodium iron EDTA [NaFe (III) EDTA] as a food fortificant: the effect on the absorption and retention of zinc and calcium in women, Am. J. Clin. Nutr. 60 (1994) 231–237.
[149] R. Yip, J.D. Reeves, B. Lönnerdal, C.L. Keen, P. Dallman, Does iron supplementation compromise zinc nutrition in healthy infants? Am. J. Clin. Nutr. 42 (1985) 683–687.
[150] M. Domellöf, O. Hernell, S.A. Abrams, Z. Chen, B. Lönnerdal, Iron supplementation does not affect copper and zinc absorption in breastfed infants, Am. J. Clin. Nutr. 89 (2009) 185–190.
[151] L.J. Harvey, J.R. Dainty, W.J. Hollands, V.J. Bull, J.A. Hoogewerff, R.J. Foxall, L. McAnena, J.J. Strain, S.J. Fairweather-Tait, Effect of high-dose iron supplements on fractional zinc absorption and status in pregnant women, Am. J. Clin. Nutr. 85 (2007) 131–136.
[152] D.L. de Romaña, M. Ruz, F. Pizarro, L. Landeta, M.A. Olivares, Supplementation with zinc between meals has no effect on subsequent iron absorption or on iron status of Chilean women, Nutrition 24 (2008) 957–963.
[153] M. Olivares, F. Pizarro, M. Ruz, New insights about iron bioavailability inhibition by zinc, Nutrition 23 (2007) 292–295.
[154] M. Olivares, F. Pizarro, D. Gaitán, M. Ruz, Acute inhibition of iron absorption by zinc, Nutr. Res. 27 (2007) 279–282.
[155] N.W. Solomons, R.A. Jacob, Studies on the bioavailability of zinc in humans: effects of heme and nonheme iron on the absorption of zinc, Am. J. Clin. Nutr. 34 (1981) 475–482.
[156] J.M. Pérès, F. Bureau, D. Neuville, P. Arhan, D. Bouglé, Inhibition of zinc absorption by iron depends on their ratio, J. Trace Elem. Med. Biol. 15 (2001) 237–241.
[157] M. Olivares, E. Hertrampf, R. Uauy, Copper and zinc interactions in anemia: a public health perspective, in: K. Kraemer, M.B. Zimmermann (Eds.), Nutritional Anemia, Sight and Life Press, Basel, 2007, pp. 99–109.
[158] J.B. Vincent, The Bioinorganic Chemistry of Chromium, John Wiley & Sons, Chichester, 2013.
[159] H. San, J. Brokato, M. Costa, Oral chromium exposure and toxicity, Curr. Environ. Health Rep. 2 (2015) 295–303.
[160] T.G. Kazi, H.I. Afridi, N. Kazi, M.K. Jamali, M.B. Arain, N. Jalbani, G.A. Kandhro, Copper chromium, manganese, iron, nickel, and zinc levels in biological samples of diabetes mellitus patients, Biol. Trace Elem. Res. 122 (2008) 1–18.
[161] A. Pechova, L. Pavlata, Chromium as a essential nutrient: a review, Vet. Med. (Praha) 52 (2007) 1–18.
[162] N. Laschinsky, K. Kottwitz, B. Freund, B. Dresow, R. Fischer, P. Nielsen, Bioavailability of chromium(III)-supplements in rats and humans, Biometals 25 (2012) 1051–1060.
[163] A.A. Moshtaghie, M. Ani, M.R. Bazrafshan, Comparative binding study of aluminum and chromium to human transferrin, Biol. Trace Elem. Res. 32 (1992) 39–46.
[164] M. Ani, A.A. Moshtaghie, The effect of chromium on parameters related to iron metabolism, Biol. Trace Elem. Res. 32 (1992) 57–64.
[165] H.C. Lukaski, W.W. Bolonchuk, W.A. Siders, D.B. Milne, Chromium supplementation and resistance training: effects on body composition, strength, and trace element status of men, Am. J. Clin. Nutr. 63 (1996) 954–965.
[166] S.G. Boyd, B.E. Boone, A.R. Smith, J. Conners, G.L. Dohm, Combined dietary chromium picolinate and an exercise program leads to a reduction in serum cholesterol and insulin in college-aged subjects, J. Nutr. Biochem. 9 (1998) 471–475.
[167] T.S. Chen, Y.T. Chen, C.H. Liu, C.C. Sun, F.C. Mao, Effect of chromium supplementation on element distribution in a mouse model of polycystic ovary syndrome, Biol. Trace Elem. Res. 168 (2015) 472–480.
[168] A. Prescha, M. Krzysik, K. Zablocka-Slowinska, H. Grajeta, Effects of exposure to dietary chromium on tissue mineral contents in rats fed diets with fiber, Biol. Trace Elem. Res. 159 (2014) 325–331.
[169] A. Dogukan, N. Sahin, M. Tuzcu, V. Juturu, C. Orhan, M. Onderci, J. Komorowski, K. Sahin, The effects of chromium histidinate on mineral status of serum and tissue in fat-fed and streptozotocin-treated type II diabetic rats, Biol. Trace Elem. Res. 131 (2009) 124–132.
[170] E. Król, Z. Krejpcio, Dietary chromium(III) propionate complex supplementation affects tissue mineral levels in rats fed high-fructose diet, J. Elem. 18 (2013) 91–98, http://dx.doi.org/10.5601/jelem.2013.18.1.07.
[171] M. Kumar, H. Kaur, A. Tyagi, V. Mani, R. Sarma, G. Chandra, V.K. Sharma, Assessment of chromium content of feedstuffs their estimated requirement, and effects of dietary chromium supplementation on nutrient utilization growth performance, and mineral balance in summer-exposed Buffalo Calves (Bubalus bubalis), Biol. Trace Elem. Res. 155 (2013) 29–37.
[172] F.Z. Kucukbay, H. Yazlak, N. Sahin, M.N. Cakmak, Effects of dietary chromium picolinate supplementation on serum glucose, cholesterol and minerals of rainbow trout (Oncorhynchus mykiss), Acquaint Int. 14 (2006) 259–266.
[173] E. Krol, Z. Krejpcio, Evaluation of anti-diabetic potential of chromium(III) propionate complex in high-fat diet fed and STZ injected rats, Food Chem. Toxicol. 49 (2011) 3217–3223.
[174] A.A. Tinkov, V.S. Polyakova, A.A. Nikonorov, Chronic administration of iron and copper potentiates adipogenic effect of high fat diet in Wistar rats, Biometals 26 (2013) 447–463.
[175] M.G. Angelova, T.V. Petkova-Marinova, M.V. Pogorielov, A.N. Loboda, V.N. Nedkova-Kolarova, A.N. Bozhinova, Trace element status (iron, zinc, copper, chromium, cobalt, and nickel) in iron-deficiency anaemia of children under 3 years, Anemia 2014 (2014) 718089, http://dx.doi.org/10.1155/2014/718089.
[176] W.W. Campbell, J.L. Beard, L.J. Joseph, S.L. Davey, W.J. Evans, Chromium picolinate supplementation and resistive training by older men: effects on iron status and hematological indices, Am. J. Clin. Nutr. 66 (1997) 944–949.
[177] M. Basaki, M. Saeb, S. Nazifi, H.A. Shamsaei, Zinc copper, iron, and chromium concentrations in young patients with type 2 diabetes mellitus, Biol. Trace Elem. Res. 148 (2012) 161–164.
[178] M.A. Van Bokhoven, C.T. van Deursen, D.W. Swinkels, Diagnosis and management of hereditary haemochromatosis, BMJ 342 (2011) c7251.
[179] J.K. Olynyk, D.J. Cullen, S. Aquilia, E. Rossi, L. Summerville, L.W. Powell, A population-based study of the clinical expression of the hemochromatosis gene, N. Engl. J. Med. 341 (1990) 718–724.
[180] S. Distante, K.J. Robson, J. Graham-Campbell, A. Arnaiz-Villena, P. Brissot, M. Worwood, The origin and spread of the HFE-C282Y haemochromatosis mutation, Hum. Genet. 115 (2004) 269–279.
[181] V. Gordeuk, R.D. Boyd, G. Brittenham, Dietary iron overload persists in rural sub-Saharan Africa, Lancet 327 (1986) 1310–1313.
[182] Chelation Therapy in the Treatment of Metal Intoxication, in: J. Aaseth, G. Crisponi, O. Andersen (Eds.), Academic Press, London, 2016.
[183] R.G. Stevens, D.Y. Jones, M.S. Micozzi, P.R. Taylor, Body iron stores and the risk of cancer, N. Eng. J. Med. 319 (1988) 1047–1052.
[184] J. Aaseth, T.P. Flaten, O. Andersen, Hereditary iron and copper deposition: diagnostics, pathogenesis, and therapeutics, Scand. J. Gastroenterol. 42 (2007) 673–681.
[185] B. Halliwell, S. Chirico, Lipid peroxidation: its mechanism measurement, and significance, Am. J. Clin. Nutr. 57 (1993) 715S–724S.
[186] V. Herbert, S. Shaw, E. Jayatilleke, Vitamin C-driven free radical generation from iron, J. Nutr. 126 (1996) 1213S.
[187] M. Gülsan, B. Malbora, Z. Avci, N. Bayraktar, I. Bozkaya, N. Ozbek, Effects of zinc sulfate supplementation in treatment of iron deficiency anemia, Turk. J. Haematol. 30 (2013) 144–1452.