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A Concise Review: Influence of Mineral Nutrients on Non-Haem Iron Uptake

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Abstract: There are two types of iron in foods: haem iron and non-haem iron. Iron Deficiency Anaemia (IDA) affects those lived in developing countries as well as developed countries. A number of factors influence non-haem iron uptake including mineral nutrients.

Key words: Non-haem iron, haem iron, mineral nutrients, macrominerals, microminerals

INTRODUCTION

Dietary iron: Despite the fact that iron is the most abundant metal, both in terms of cosmic abundance and in the earth's crust (Carpinteri and Manuello, 2011) iron deficiency is the commonest cause of anaemia especially in developing countries. Iron is a vital micronutrient for the formation of red blood cell and mostly stored in the haemoglobin (Bolanle, 2005). Haemoglobin functions as an oxygen carrier in the body. Persistent low levels of haemoglobin is a risk factor for postpartum depression in new mothers (Corwin *et al*., 2003) and can lead to cardiac arrest in patients with kidney diseases (Fort *et al*., 2010). There is an estimate that 25% of the world population is affected by iron deficiency and >90% of affected individuals live in developing countries (Monajemzadeh and Zarkesh, 2009).

There are two main types of iron available in foods: haem iron and non-haem iron. Haem iron is present in meat and its products (around 20-30% being absorbed) and non-haem iron which can be obtained from vegetables sources and generally has much lower bioavailability ranging from 1- 8% (Philip and Greenwood, 2000; Krishnamurthy *et al*., 2007; Yokoi *et al*., 2009). In developing countries and third world countries where large numbers of poor people might not be averse to eating meat, non-haem iron is the most important source of dietary iron (Chiplonkar and Agte, 2006). Unlike haem iron, non-haem iron uptake is regulated and it needs to compete with many complexing ligands in the intestinal lumen to be absorbed. However, haem iron is absorbed as a porphyrin-iron complex, a separate pathway from non-haem iron absorption and is generally not influenced by dietary factors of iron absorption (Yanatori *et al*., 2010).

An important consideration with respect to adequate intake of iron for human consumption is the availability of iron-containing foods. The absorption of non-haem iron is highly variable and depends on the nature of meal. Factors influencing dietary iron absorption is as given (Rossander-Hulton *et al*., 1991):

Haem iron absorption:
- Amount of haem iron, especially as meat
- Content of calcium in meal
- Food preparation (time, temperature)

Non-haem iron absorption:
- Iron status of subjects
- Amount of potentially available non-haem iron
- Balance between enhancers and inhibitors factors:
  Enhancers:
  - Ascorbate
  - Meat/fish
  - Fermented foods

  Inhibitors:
  - Phytate
  - Iron-binding
  - Soy protein
  - Calcium
  - Polyphenols

Although, iron is widely distributed in foods inappropriate food combinations can compromise its absorption. *In vitro* and *in vivo* studies reveal that various factors including mineral nutrients also known as dietary minerals influence bioavailability of non-haem iron (Navas-Carretero *et al*., 2008). The iron status of an individual along with the balance between absorption facilitators and inhibitors determines the bioavailability of iron from individual foods or from meals (Lynch, 2005). Table 1 shows the recommended intakes for dietary iron in the different age groups by country.

Table 1: Recommended intakes of dietary iron (mg)

			Malaysia RNI (%)			
Groups	Age	UK RNI	10	15	Can RNI	US RDA
Infants	Up to 6 months	4.3	a	a	0.3	6
	6 months to 1 year	7.8	9	6	7	10
Children	1-3	6.9	6	4	6	10
	4-6	6.1	6	4	8	10
	7-10	8.7	9	6	8	10
Males	11-14	11.3	15	10	10	12
	15-18	11.3	19	12	10	12
	19-24	8.7	14	9	9	10
	25-50	8.7	14	9	9	10
	51+	8.7	14	9	9	10
Females	11-14	14.8	14 (nm)	9 (nm)	13	15
	-	-	33 (m)	22 (m)	-	-
	15-18	14.8	31	21	12	15
	19-24	14.8	29	20	13	15
	25-50	14.8	29	20	13	15
	51+	8.7	11	8	8	10
Pregnant	-	No increment	29 (1st trimester)	20 (1st trimester)	10+	30
	-	-	b (2nd trimester)	b (2nd trimester)		
	-	-	b (3rd trimester)	b (3rd trimester)		
Lactating	1st 6 months	No increment	15	10	No increment	15
	2nd 6 months	No increment	15 (nm)	10 (nm)	No increment	15
	-	-	32 (m)	21 (m)	-	-

UK RNI = United Kingdom Reference Nutrient Intake; Malaysia RNI = Malaysia Recommended Nutrient Intake; US RDA = Untied States Recommended Dietary Allowance; Can RNI = Canadian Recommended Nutrient Intake; a: No recommendations. Neonatal iron stores are sufficient to meet iron requirement for first 6 months in full-term infants. Premature infants and low birth weight infants require additional iron; b: Iron supplements in table form recommended for all pregnant women. In the non-anaemic pregnant woman, daily supplements of 100 mg iron given during second half of pregnancy are adequate. In anaemic women, higher doses are usually required. nm: non-menstruating, m: menstruating

Thus, the aim of this review study is to review the influence of nine common but important mineral nutrients; namely macro-minerals and micro-minerals on non-haem iron uptake.

MINERAL NUTRIENTS AND THEIR PHYSIOLOGICAL FUNCTIONS

Microminerals

Calcium: Calcium is the most abundant mineral in the body and is mostly stored in the hard tissue of the bones and teeth. Calcium is also important for many other bodily functions such as muscle contraction and exocytosis. Calcium is also essential for nerve conduction, the regulation of enzyme activity and the formation of cell membranes (Emkey and Emkey, 2012).

Milk and other dairy products are the primary sources of dietary calcium. The effect of calcium on iron uptake has been carried out by *in vitro* and *in vivo* studies (Chattipakorn *et al*., 2011; Gaitan *et al*., 2012). Calcium had an intriguing effect on iron uptake and is reported to have the same inhibition effect on both non-haem and haem iron (Hallberg, 1998). A transport study done in Caco-2 cells by Gaitan *et al*. (2012) found that the administration of calcium and iron at a molar ratios between 500 and 1000:1 increased iron uptake across the apical membrane, decreased iron transport across the basolateral membrane but had no effect on the net absorption of non-haem iron.

At typical supplementary doses, calcium is believed not to have an inhibition effect on iron absorption (Gaitan *et al*., 2012).

A study done by Shawki and Mackenzie (2010) in Xenopus oocytes found that calcium ion blocked the Fe (III) evoked currents and inhibited $^{55}Fe^{2+}$ uptake in a non-competitive manner ($K_i \approx 20$ mM). DMT1 does not mediate calcium transport because the DMT1-induced $^{45}Ca^{2+}$ uptake was not inhibited by a saturating concentration (100 μM) of Fe^{2+}.

Magnesium: Magnesium is the eighth most abundant element in the earth's crust but does not occur uncombined (Dobrzanski *et al*., 2009). Magnesium plays an important role in a wide range of biochemical and physiological processes, particularly the body's metabolism including muscle tension, the regulation of blood pressure and bone cell function (Touyz, 2004).

Although, it was postulated that the alkaline earth metal ions such as Barium ion (Ba^{2+}), Strontium ion (Sr^{2+}), and Magnesium ion (Mg^{2+}) inhibited DMT1-mediated iron-transport activity (Shawki and Mackenzie, 2010), there is no recorded evidence that magnesium inhibits non-haem iron uptake.

Sodium: Sodium chloride is vital for human health. Sodium ions are responsible facilitating transmission of electrical signals in the nervous system and regulate the water balance between body cells and body fluids (Doyle and Glass, 2010). Absorbability of iron from foods are varies widely depending on the type of sodium compounds presence in the meals. A study conducted by Fisher and colleagues on the effect of high sodium ions on iron uptake by the halotolerant alga Dunaliella showed that high salt affects neither the affinity nor the rate of iron uptake (Pick, 2004). A study conducted by Fidler *et al*. (2003) on iron absorption from fish sauce and soy sauce fortified with sodium iron EDTA also found no significant different between NaFeEDTA and $FeSO_4$-fortified fish sauce (3.3 and 3.1%, respectively) and soy sauce (6.1 and 5.6%, respectively).

Potassium: Potassium can be found in many plants and is essential for proper function of all cells, tissues and organs in the human body (Soetan *et al*., 2010). Potassium is required for maintaining a normal water balance between the cells and body fluids. Potassium is crucial to heart function and plays a key role in skeletal and smooth muscle contraction making it important for normal digestive and muscular function (Haddy *et al*., 2006).

Potassium plays a role on haem iron uptake where cells exposed to K^+ depletion or with cytosol acidification had a lower haem iron uptake than control cells (Arredondo *et al*., 2008). A study conducted by Musilkova and Kovar (2001) showed that there was an increase in iron uptake by HeLa and K562 cells when calcium and potassium were added into the medium. However, there is no recorded evidence that potassium had an effect on non-haem iron uptake.

Trace minerals

Copper: Copper is important for red blood cell formation, manufacturing collagen and central nervous system function. Copper is a trace element present in all tissues and is required for cellular respiration, peptide amidation, neurotransmitter biosynthesis, pigment formation and connective tissue strength (Desai and Kaler, 2008; Goez *et al*., 2011). Copper is a cofactor for numerous enzymes and plays an important role in central nervous system development but are toxic in excess (Cox and Moore, 2002; Madsen and Gitlin, 2007).

The effect of dietary Copper Deficiency (CuD) has been shown to cause iron deficiency anaemia in rats (Reeves and DeMars, 2004). In their study, iron absorption in CuD rats was determined by feeding diets labelled with ^{59}Fe and using Whole Body Counting (WBC) to assess the amount retained over time. Symptoms of iron deficiency anaemia appeared within 2 weeks of first feeding weanling rats a diet deficient in copper (Johnson and Saari, 1991; Reeves and DeMars, 2004). Yu and Wessling-Resnick (1998) have shown that copper deficiency reduced uptake of non-haem iron suggesting possible impairment of reductase activity. The reduction of iron by ferrireductase is a critical step prior to DMT1 transport across the apical membrane of enterocytes.

A study done by Jiang and Collins in HEK-293 cells to evaluate whether DMT1 (the main iron transporter) can transport copper by inducing DMT1 overexpression with a Doxycycline (DOX) found that ^{64}Cu uptake was not different from untreated cells. However, a significant increase in copper uptake was noted (~5 fold) when cells were treated with DOX in the presence of an iron chelator (as compared to DOX only treated cells). It is thus concluded that under control conditions, DMT1 does not transport copper however, DMT1 may be involved in copper transport under low-iron conditions.

In another study by Han and Wessling-Resnick (2002) on copper-repleted cells, increased iron uptake was displayed across the cell monolayer. Furthermore, Northern blot analysis revealed that expression of DMT1, Iron regulator protein (Ireg1) and Hephaestin (Heph) was upregulated by copper supplementation.

Iodine: Iodine is present naturally in soil and seawater (Fuge, 2007). The availability of iodine in foods differs by geographical location. Iodine forms part of the thyroid hormones deficiency may cause goiter, slowed metabolism, mental retardation in infants and children whose mothers were iodine deficient during pregnancy and cretinism (Zimmermann, 2009). In 1990s, iodised salt was made available to protect against Iodine Deficiency Disorders (IDD). The fortification of salt with iodine has been a global success story but there are also other micronutrient supplementation schemes that have yet to reach vulnerable populations sufficiently (Muller and Krawinkel, 2005). Some children born to iodine-deficient mothers can also be iron deficient. High prevalence of iron, vitamin A and iodine deficiencies affect more than a third of the world's population (Self *et al*., 2012). To overcome iron and iodine deficiencies around the globe, a microencapsulation method has been developed to coat iodine through surface coating and prevent interaction between the minerals (Li, 2009). Specifically, ferrous fumarate (a more stable form and pleasing flavour of iron) was microencapsulated into a form of salt grain-sized premix and then added into iodised salt. The earlier process involved fluidised-bed agglomeration followed by lipid coating (Li *et al*., 2011).

At present, there is no recorded evidence of adverse interactions between iodine and iron partly because iodine is actively taken up via the Na^+/I^- symporter on the apical surface of enterocytes (Nicola *et al*., 2009) whereas DMT1 mediates iron uptake in the intestine (Mackenzie and Garrick, 2005).

Selenium: Selenium is an essential trace element in human and animals (Rayman and Rayman, 2002) for the efficient and effective operation of many aspects of the immune system (Arthur *et al*., 2003). Incorporation of selenium into proteins as a designated selenoproteins acts as cofactor for an antioxidant enzyme. Plant foods are the major dietary sources of selenium. Selenium occurs in staple foods such as corn, wheat and soybean as selenomethionine, the organic selenium analogue of the amino acid methionine (Schrauzer, 2001, 2003). Animal and human studies suggest that there is a correlation between selenium deficiency and anaemia (Zimmermann *et al*., 2000; Semba *et al*., 2006, 2009). Several studies have showed that iron supplementation has no influence on selenium level in serum (Yetgin *et al*., 1992; McAnulty *et al*., 2003) and selenium supplementation has no effect on the iron status in healthy individuals (Neve and Vertongen, 1988). Furthermore, there is no recorded evidence that selenium influences the main iron transporter DMT1.

Zinc: Zinc is an essential dietary trace metal required by the human body for a number of physiological and biochemical functions. Zinc is essential for growth and development, proliferation, differentiation and apoptosis, neurogenesis, synaptogenesis, neuronal growth and neurotransmission (Fraker and King, 2004). The best sources of zinc are oysters (richest source), red meats, poultry, cheese, shrimp, crab and other shellfish. The body absorbs 20-40% of the zinc present in food. Zinc from animal foods like red meat, fish and poultry is more readily absorbed by the body than zinc from plant foods (Walingo, 2009). Recommendations for dietary zinc intake are based on average daily intake of populations from several countries and range from 4.7-18.6 mg day^{-1} (Nishiyama *et al*., 1999). Bioavailability of zinc is influenced by other food constituents. Dietary fibre, particularly phytates, calcium, iron and pharmacological intakes of folic acid can interfere with zinc absorption (Hunt, 2003; Oberleas, 1996; Viadel *et al*., 2006; Simmer *et al*., 1987). The amount of zinc needed daily is about 2-3 mg in adults, i.e., only 0.1% of the total zinc pool is renewed daily, in agreement with a biological half-life of approximately 280 days for zinc (Wastney *et al*., 1996).

A study conducted by Thumser *et al*. (2010) showed mixed-type (non-competitive) inhibition of iron uptake by zinc with calculated K_i values of 141 and 236 μM Zn^{2+}, in the absence and presence of ascorbate, respectively (Thumser *et al*., 2010). Moreover, zinc was able to significantly increase DMT1 levels for the whole cells and membrane levels ($p \leq 0.05$) but had no effect on the expression of Ireg1 in $CaCO_2$ TC7 cells (Rashed, 2012). Increasing zinc concentration will probably lead to the cells becoming depleted in iron and will indirectly increase expression of DMT1. This study also showed that Ireg1 is not only affected by iron but also by other metals in the medium (Rashed, 2012).

Manganese: Manganese is a trace element found in a variety of food includes cereals, vegetables and nuts (Gow *et al*., 2010). In the body, manganese functions as an enzyme activator (responsible for the utilization of several key nutrients including biotin, thiamin, ascorbate and choline) and a component of metalloenzymes (an enzyme that contains a metal ion in its structure) (Aschner and Aschner, 2005). The study done by Rossander-Hulten *et al*. (1991) showed that manganese inhibited iron absorption both in solutions and in a hamburger meal (Rossander-Hulten *et al*., 1991). Iron transport in the Loops of Henle (LH) can be reduced by the addition of copper or manganese to the luminal perfusate suggesting that these ions may compete with iron for a common transport pathway (Wareing *et al*., 2000).

CONCLUSION

In this concise review, the effect of nine common but important mineral nutrients on iron uptake will be discussed. Some biological functions of these minerals are also mentioned in this review.

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