Bioavailability of Dietary Iron in Human : An Updated Overview

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Introduction

Of the human nutritional deficiencies iron deficiency is considered to be the most common throughout the world[1]. Iron deficiency is the commonest cause of anaemia, espcially in children and women of child bearing age. According to Royston[2] about half of the non-pregnant women and nearly two-thirds of the pregnant women in developing countries could be considered anaemic.

In many developing countries iron deficiency has been ascribed to the presence of low bioavailable iron in the diet together with the exaggerated need for iron due to intestinal infestation and gestation.[1,3]. A wealth of information about iron absorption from various foods and complex interacting nature in meals has made it possible to predict realistic measures against iron deficiency[3]. It is therefore important to study the bioavailability of iron encompassing such aspects as to how the various dietary factors affect its abosrption resulting deficiency. The present review highlights the various factors in food enhance or inhibit iron absorption affecting its bioavailability.

Measurement of Iron Absorption

Basically iron absorption is assessed by iron balance study and by measuring erythrocytic incorporation of iron[5]. Chemical balance techniques used earlier is now replaced by radio isotopic technique where iron absorption is measured on account of erythrocytic incorporation of iron after placing the subject on biosynthetically labelled food (intrinsic tag). It is assumed that 90% of iron is incorporated into RBC within 10-14 days in normal subjects[6].

In another method, a trace amount of radio iron 1 to 10 mcci is allowed to ingest as a drink with various standard meals followed by scientific count of 4 hours and 14-20 days later to get an index of iron absorption[5].

Later on extrinsic tag technique considered a valid and better method in which a small amount of inorganic radio iron (0.001 to 0.5 mcg) is used that equillibrates with the exchangeable non-heme iron pool of a meal. It was observed that simultaneous administration of intrinsic and extrinsic tracer would give a constant identical ratio (1.10) of iron absorption in different food and in different subjects[5].

Subsequently in-vitro techniques have been developed to predict bioavailability of iron[7,8]. Besides this, more than one method is now practised for correct estimation of iron absorption.

Site and Mechanism of Iron Absorption

Aside from a small amount of iron that absorbs in the stomach, most of the absorption takes place in the duodenum and upper jejunum[9].

A multifaceted iron absorption system developed in man involves solubilization through interactions between free iron and food component, motility effect, mucosal uptake of various forms of iron, mucosal processing of iron and finally the movement of iron from the mucosal cell to the body interior (transfer)[9].

There are atleast three pathways of mucosal iron absorption involving iron salts, transferring bound iron and heme iron. Iron salts are absorbed in the upper duodenum

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where the acid pH foster iron solubility. The presence of mucosal transferring in the gut lumen provides a second pathway in which non-heme iron is chelated by transport protein and enters the mucosal cell via transferrin receptor system. The release of iron from this transferring iron receptor complex may be mediated by a fall in pH since an acid labile binding site loses its iron first.

Heme iron is absorbed intact by a special receptor in presence of heme oxidase.[9] Iron from these three different pathways appears to enter a common pool within the mucous cell.

Pool Concept of Bioavailability of Iron

When an inorganic radio-iron tracer is added to a meal, an isotopic exchange between the tracer and all the native iron probably occurs. This forms a common pool of ionic exchange from which absorption takes place[4]. There are two possible iron pools namely heme and non-heme iron pool[5]. Hence the quantity of bioavailable non-heme iron is influenced by many factors, the difference in bioavailability of iron in different single foods may be considered as due to the difference in the relative size of pool of exchange. Thus, the bioavailability of iron in a meal might be the effect of all the food items and their constituents, increasing or decreasing non-heme iron absorption.

Factors Influencing Iron Absorption

The greater percentage of dietary iron is non-heme amonst 100% in meals that exclude any form of animal tissue. Unlike heme iron non-heme iron absorption is greatly influenced by the variety of ligands present in the diet (table-1).

1. Specific Human Factors

Iron Status

Iron absorption is related to iron need of the body[4]. The iron deficient subjects tend to absorb more iron than iron-replete subjects. However, a marked subject to subject variation was observed based on which the reference dose of radio iron has been proposed. Under standardized conditions the ratio of iron absorption from test food to a standardized reference dose of ferrous ascorbate (3 mg Fe S 04 + 30 mg ascorbic acid) can give an index of relative bioavailability of non-heme iron in different subject[10]. It is stated that in a fasting subjects (10-12 hours) of borderline iron deficiency, the absorption of reference dose was 40% and it is proposed that the bioavailability of non-heme iron in a meal be expressed corresponding to a 40% absorption from reference dose[4,10].

Pregnanacy

Daily iron requirement increased from 0.8 mg in early pregnancy to 4 to 7 mg in the second and third trimesters with a consequent increase in iron absorption[11]. In one study it was observed that mean absorption during the period 8-16 weeks was 8.14%, during 28-32 weeks it was 31% and in 36-39 weeks it was 32.8%[11].

Disease state

It was observed that iron absorption decreased in febrile conditions while it showed a slight increment in hemolytic syndromes[5]. Iron absorption is impaired in giardiasis and in other intesfinal disorders and also in children with Protein Energy Malnutrition (PEM)[12].

2. Intestinal factors

The amount of iron available for asborption depends on[9].

a) adequacy of gastric secretions,

b) the amount of iron supplied through diet.

c) the chemical nature of iron,

d) the composition and consistency of the meal and

e) the influences of the ligands.

Gastric secretions help absorption of iron[13]. However, controversy exists about gastroferrin secretion which might inhibit iron absorption. Usually as the amount of iron in the diet increases, the proportions of absorption falls but the absolute amount increases. Simple ferrous salts are found to be better absorbed than complex one[11].

Protein and Carbohydrate food

The effects of protein on iron absorption depends on the nature of protein in the diet, its amount and the nature of food with which it is mixed[14]. It is now well established that protein present in meat and fish is a potential enhancer, and the promoting effect is dose related. This meat effect for iron absorption has not yet been well defined. According to Layrisse et al[15] cysteine would be the single most common amino acid found in protein to increase iron absorption in humans. They

Table 1. *Factors affecting Fe absorption*

	Factors	**Absorption** increase	decrease
INTESTINAL SPECIFIC	Dietary Fe content	Fe replete diet	Fe deficient diet
	Chemical form of Fe	Fe 2 + Heme Fe	Fe 3+
	Dietary constituents	Fructose, cysteine, ascorbic, cytric, succinic, malic acids	starch, phytate, oxalate, fibre polyphenol phosvitin con-albumin
	Intestinal secretion	HCL, proteolytic enzymes	Achlorohydria
	Intestinal motility	reduced	increased (e.g. diarrhoea)
	Complexing agents,		EDTA* Gastroferrin (?)
	Fe status of the body	Fe deficiency	Fe overload
	Erythropoiesis	blood loss, haemolysis, pregnancy.	Aplastic anaemia
HUMAN	Increased Fe turnover due to other causes	Thalassemia, sideroblastic anaemia	Endotoxin
	Others	Idiopathic haemochromatosis	PEM, Giardiasis

* Ethylenediaminetetraacetate.

Source: Bernat, I.[5] (modified)

also observed the strong effect of cysteine on iron absorption at doses of 50 to 100 gm of protein.

The phosphoprotein of egg has an inhibitory effect on iron absorption and the milk protein (casein) has a similar effect on iron absorption may also be due to the presence of phosphoprotein[5]. Unlike cow's milk, iron in human milk is well absorbed as high as 49%[16].

Recent study has shown that protein equivalent quantities of soy protein, whey protein and casein are even stronger inhibitors than egg protein[17].

The low absorption of iron from cereals has been traditionally attributed to the presence of phytate and fibre. Cooking of cereals produces a greater absorptive surface and therefore, a higher capacity to absorb cations[18]. However, the additional depressing effect of cooked starch on iron absorption observed by Rozo et al[18] deserves further investigation.

Ascorbic acid

Synthetic ascorbic acid and fruit juice containing a high content of ascorbic acid markedly increases non-heme iron absorption[19]. However, ascorbic acid has no effect on the absorption of heme iron. The enhancing effect of ascorbic acid is attributed to its reducing effect and/or chelating property with ferric iron at acid p[11] that remains soluble in an alkaline millieu of the small intestine[20]. Ascorbic acid simultaneously consumed with other foods enhances iron absorption 3-6 fold and the effect is dose-related[19,20]. Recently, the detailed physiological role of ascorbic acid on iron absorption from different meals have been investigated based on which Hallberg et al[19] suggested that 50 gm of ascorbic acid in any form (crystalline or native) would increase iron absorption to approximately the same extent as an addition of 90-100 gm of meat or as doubling of iron content of the meal by iron fortification with Fe S04. Cooking and baking can destroy ascorbic acid and thus effects of iron absorption.

Calcium, phosphorus and cadmium

Monsen and cook[22] observed that only when calcium and phosphorus salts added simultaneously to a meal (semisynthetic), a significant inhibition of iron absorption took place. However, ferric orthophosphate and iron pyrophosphate have low bioavailability and iron fortification with these seems to be ineffective. The phosphorus present in vegetables, mostly in the forms of phytate have a strong inhibitory effect on iron absorption[23]. Cadmium reduced absorption of iron salts by about half in both normal and iron deficient subjects[24].

Organic acids and polyphenols

Low molecular weight organic acids such as citric acid., malic acid, tartaric acid have been found to be potential enhancers of iron absorpiton even in small quantities[23]. The vegetables associated with moderate or good iron bioavailability contain appreciable amount of one or more of these organic acids. However, tannic and oxalic acid exert a moderately depressing effect on iron absorption[23,25].

Phytate

It is now well established that sodium phytate and foods with high phytate content such as bran decrease iron absorption in man. Simpson et al[26] demonstrated that whole bran had a marked decreasing effect on iron absorption while dephytinized bran (either by endogenous phytate or by washing with HCL) significantly increase iron absorption.

A recent study shows that various nuts such as walnuts, almounds, peanuts, hazelnuts. brazilnuts etc. have a strong inhibitory role on iron absorption which might be due to the presence of phytate, polyphenolic compounds and protein content within[27].

Fibre

Iron-binding experiments carried-out in-vitro suggests that fibre is an inhibitory substance of iron absorption, although there is little evidence in human[28]. According to Vahowny et al[29] fibre helps to increase goblet cells in the villi column secretion of which acts as a rate limiting diffusion barrier for iron absorption. Cook et al[30] found modest inhibitory effect of fibre on iron absorption. However, among various forms of fibre, only hemicellulose and lignin have inhibitory effect on iron absorption[23].

Chemicals and alcohols

Cycloheximine impairs iron absorption, possibly by interferring synthesis of carrier protein while phenobarbitol found to increase absorption. Alcohol increases iron absorption in subjects with normal gastric secretion[11].

Iron bioavailability in meals

Table-2 shows the bioavailability of iron in Thai meals. This study demonstrate the marked influence of the composition of the meals on the bioavailability of non-heme iron.

Bioavailability of iron in the whole diet based on nutrient density

Hallberg[4] formulated that bioavailability of iron would be the amount of iron absorbed (in mg) from a meal per unit of energy (1000 kcal) by subjects who are borderline iron deficient (i.e. 40% of reference doses of iron).

The study revealed that the average bioavailable nutrient density of the diet was 0.9 mg of iron/1000 kcal and taking energy intake of 2675 kcal/person/day the iron absorption at a state of borderline iron deficiency was estimated as 2.4 mg/day. The bioavailable nutrient density of menustruating women was estimated in the same way (1.7 mg/1000 kcal). To meet the iron requirement in 90% of women of childbearing age, 2.2 mg of iron must be absorbed daily. If the average energy intake is about 2000 kcal, the average bioavailable nutrient density must reach 1.1 mg of iron/1000 kcal.

Regulation of iron absorption

The regulation of iron absorption is

Table 2. *Bioavailability of iron in some Thai diets**

Meal Composition	Iron content	Absorption			Bioavailable nutrient density
	Non-heme (mg)	Non-Heme (mg)	%	Total	mg of iron/ 1000 kcal
Basal meal (rice, veg., spices)	1.5	0.16	10.7	0.16	0.47
Basal mealt fish	1.9	0.29	15.3	0.29	0.75

* Published absorption figures calcuated to correspond to 40% reference dose absorption. Heme iron absorption calculated to 25%[4].

multifactorial. Charlton and Bothwell[26] hypothesized that iron content of individual tissues might be in itself a regulatory factor for iron absorption. A labile pool of iron available to transferrin is assumed to be present in all body tissues. Since iron uptake from transferrin is determined by the requirements of the erythroid marrow, each tissue supplies iron to transferrin in proportion to its labile iron pool. Therefore, a decrease in tissue iron content would results in an increased entrance of iron from the gut, while an acute rise in plasma iron turnover due to enhanced erythropoietic activity would cause an increased iron absorption.

On the basis of various observation, Hubers[9] proposed a functional model for iron absorption. This proposition is based on the generalization that the mucosa has a certain capacity to absorb iron which is determined by previous exposure to available iron in the lumen by internal iron stores, and under certain circumstances (in the presence of placenta or due to abnormal erythropoiesis), influenced by the transferrin receptor mass within the body. It is also hypothesized that only when the internal iron supply to the erythroic marrow of placenta is inadequate to saturate receptors, a signal for increased iron procurement dictates an increased absorption. There is however, still a great deal of uncertainty as to what signal the mucosal cell provides to increase or to decrease iron absorption[9].

Discussion

It is evident From the present review that iron availability in the body depends on many factors either endogenous to food or exogenous. Though, the recent advancement of regulation of iron absorption and its molecular basis was outlined[9], the controversy still exists. However, knowledge about bioavailability of dietary iron has increased rapidly that may help to design meals to maximize iron bioavailability. The new pool concept facilitate to incorporate its idea into meal planning. It demonstrated how to increase iron absorption not only by increasing iron content of the diet, but also by evaluating the quantitative effect of inhibitors of non-heme iron absorption and the interaction of inhibitors and enhancers. Research in these areas is thus crucial to find effective ways and means of improving the bioavailability of dietary iron and hence iron nutrition to all.

Summary

Absorbtion of dietary iron vary from meal to meal which is modified by its composition (bioavailability). The absorption of heme iron is always greater than non-heme iron. Absorption of non-heme iron is affected by many factors while only bioavailability factor of heme iron may be the amount of meat in the meal. Meat, fish, poultry and low molecular weight organic acids viz., ascorbic acid, citric acid, tartartic acid and malic acid are demonstrated as enhancers of iron absorption. Synthetic complexing agents (e.g., EDTA) as well as specific complexing agents endogenous to food exert inhibition of non-heme iron. The purified form of these substances or synergism in foods may act to reduce absorption. Polyphenolic compounds present specially in tea and coffee also inhibit absorption of non-heme iron to a great extent.

The generalization that iron of plant origin have low bioavailability may not true for vegetables but for legumens and cereals.

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