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IRON ABSORPTION; NATURE, AND NURTURE INTERACTIONS

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Abstract

Background: Iron deficiency anemia (IDA) is a global health concern, particularly affecting women and children. Both genetic and dietary factors contribute to iron absorption and status. Understanding these interactions is vital for effective prevention strategies. **Methods:** This narrative review examined literature from Scopus-indexed journals (2005–2024) to explore the influence of TMPRSS6 gene polymorphisms—particularly rs855791 and rs4820268—and dietary components (enhancers and inhibitors) on iron absorption. **Results:** Genetic variations in TMPRSS6, especially rs855791, are associated with increased hepcidin levels, leading to decreased iron absorption and lower hemoglobin. On the dietary side, ascorbic acid and meat proteins significantly enhance non-heme iron uptake, while phytates, polyphenols, and calcium inhibit it. Food processing techniques such as fermentation and germination can reduce inhibitor effects and improve iron bioavailability. **Conclusion:** Iron absorption is influenced by both inherited genetic variations and modifiable dietary practices. A combined understanding of these nature and nurture factors is essential to develop personalized and population-based nutritional strategies to prevent and manage IDA effectively.

Keywords: Iron Deficiency Anemia; TMPRSS6 gene polymorphisms; iron bioavailability

Introduction

Iron deficiency has previously been hypothesized to influence dietary and/or other environmental factors. An iron deficiency is the most common and widespread nutritional disorder in the world, and it is also the most prevalent single-nutrient deficiency in developed and developing countries. Based on WHO estimates, worldwide, 1.6–2 billion people are anemic. [1] Infants, children, adolescents, and women of childbearing age, especially pregnant women, have the highest prevalence of iron deficiency. In Indonesia, iron deficiency anemia is still a common public health problem[2], with prevalence among under-five children being 28.1%, schoolchildren (5–12 years old) being 29%, pregnant women being 37.1%, girl adolescents (13–18 years old) being 22.7%, and women of reproductive age being 22.7%, respectively.[3,4] Iron deficiency is the impact of inadequate intakes of dietary iron, poor absorption, excessive losses, or a combination of these factors.[5,6] Iron deficiency for at least half of the cases of anemia has possible causes, including genetic, infectious, and other nutritional deficiencies.[7,8] Ensuring that sufficient dietary iron can be absorbed and utilized by the body is a major barrier to achieving the reduction of iron deficiency around the world.

Nature; Gene *TMPRSS6* polymorphism and Iron Deficiency Anemia

Matriptase-2 also called *TMPRSS6* is a type II plasma membrane serine protease (TTSP). Structurally matriptase-2 contains (1) a short 54-aaN-terminal cytoplasmic domain, (2) a membrane spanning region, (3) an SEA (sea urchin sperm protein, enteropeptidase and arginine) domain, (4) 2 CUB [Cls/Clr, urchin embryonic growth factor, and bone morphogenetic protein (BMP)-1] domains, (5) three LDLa (low-density-lipoprotein receptor, class A) domains, (6) and a trypsin-like serine protease domain containing the catalytic triad

of histidine, aspartate, and serine residues. Matriptase-2 accommodates glycine, serine, alanine, isoleucine, or arginine in the P1 _ position. In human, TMPRSS6 is located in chromosome 22q12.3 has 18 exons that encodes a liver specific serine protease which hydrolysis various proteins, including type 1 collagen, fibronectin, fibrinogen and with lesser efficiency, urokinase type plasminogen based on The National Center for Biotechnology Information (NCBI). TMPRSS6 is hydrolytic enzymes and secreted soluble protein.[9]

Severe mutations in the protease domain of matriptase-2 causing premature termination and leading to an iron deficiency phenotype.[9]

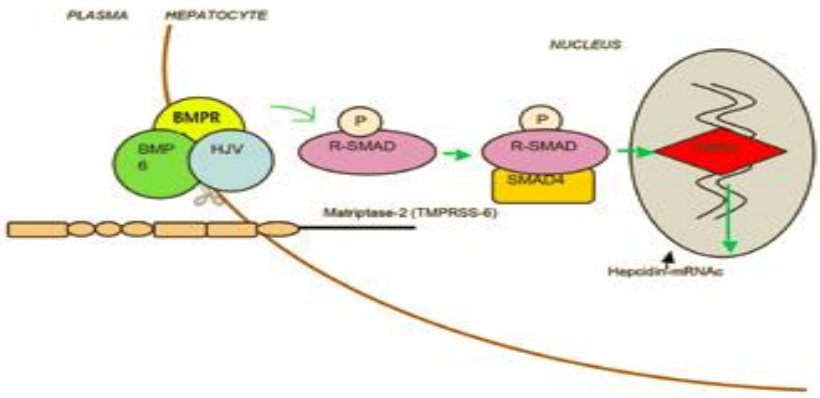

Figure. 1 Systematic Model of Hepcidin Regulation by Matriptase-2[10]

The identification of hemojuvelin as key substrate for Metatripse-2 can stimulate Matriptase-2 expressed by *TMPRSS6* to manage hepcidin-regulated iron homeostasis. Mutation in gene TMPRSS6 can influence that gene translate different protein and disturb pair process with hemojuvelin and loss catalyctic domain of Matriptase-2 and can lead to an increase in hepcidin expression in the liver, reduced dietary iron absorption, and severe microcytic anemia[11] Matriptase-2 prevent hepcidin overexpression by degrading hemojuvelin, which acts as a co-receptor for bone morphogenetic protein (BMP) to promote HAMP gene expression. In Matriptase-2 deficiency, high level of hemojuvelin enhances the BMP signaling pathway, leading to overexpression of hepcidin. Cleavage of hemojuvelin

results in loss from the hepatocyte cell surface and the loss of hemojuvelin to act as a coreceptor for BMPs. Nevertheless, BMPs can still upregulate hepcidin expression directly through the BMP receptors in the absence of hemojuvelin. Likewise, inflammatory cytokines such as IL-6 are able to upregulate hepcidin expression in the absence of hemojuvelin. It remains to be determined if matriptase-2-mediated cleavage products of hemojuvelin can act as a soluble antagonist for the binding of BMPs to the cognate receptor in the same manner as soluble hemojuvelin. [9]

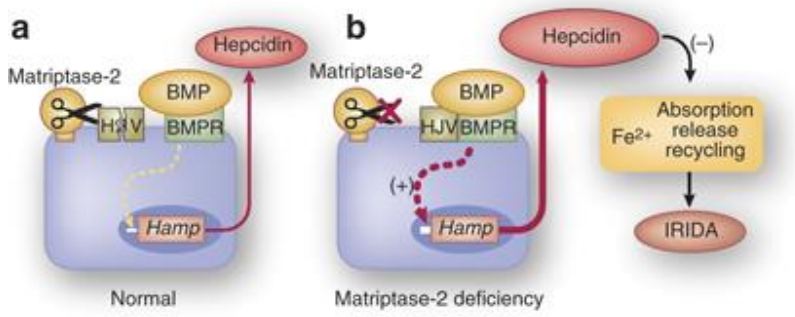

Figure. 2 Working Model of Matriptase-2 Regulation of Iron Homeostasis (A), And in Matriptase-2 Deficiency (b)[12]

Hepcidin inhibits iron absorption, release, and recycling, thereby causing Iron Refractory Iron Deficiency Anemia (IRIDA).[13] Hepcidin binds to ferroportin and causes its internalization and degradation in endolysosomes, what in turn blocks the iron transport via ferroportin. When iron stores are adequate or high, increased hepcidin expression inhibit intestinal iron absorption, release of recycled iron from macrophages and its transport across the placenta. [14]

Location of Polymorphism in the Gene called Single Nucleotide Polymorphism (SNP). Gene TMPRSS6 has 8 differences minor allele frequencies SNPs such as rs855791, rs4820268, rs2111833, rs142312, rs228921, rs228918, rs228919, and rs 575620. [15] Among these SNPs, SNP rs855791 has the strongest association with red blood cell indices and iron parameters in general population.[13] The SNP rs855791 is the polymorphism most associated with Iron and hematology parameters and located in exon 17 and in position 357922882. Based on NCBI, rs855791 identifies T>C substitution in position 2207 (correspondent to a complementary A>G change), resulting missense valine (V) to alanine (A) change in position 736, nearby catalytic and binding sites of Metriptase-2. Valine is non-polar amino acid and

prefers to hydrophobic cores. While, Alanine is probably the dullest amino acid, it is not particularly hydrophobic and it is non-polar. Those are very non-reactive amino acid and have a role in substrate recognition. The human database indicates V at the 736 positions as the "wild type" amino acid of Metriptase-2. Mutation type in SNP rs855791 is A/G Transition Substitution, and has primer GCGTGGCGTCACCTGGTAGCGATAG**[A/G]**CCTCGCTGCACAGGTCCTGTGGGAT (SNPedia).

The second strongest SNP is rs4820268 located in exon 13 and leads to a synonymous change (missense) Aspartate (D) to Asparagine (N) at nucleotide position 521. Aspartate and asparagine being charged and polar, and prefer to be on the surface of protein. Those are quite frequently involved in protein active or binding sites. Based on NCBI rs4820268 identifies G>A and considered the G allele is minor allele on the forward strand and C allele in the reverse allele and has primer CCCTACCTTCCTGGCACTGCTCTTC**[A/G]**TCGCTGCCGTTGAGACAATAGGCT

Some study both in human study and in animal study shown the strong association between TMPRSS polymorphism and Iron Deficiency Anemia. Study from Gan show, both polymorphism from TMPRSS6 rs855791 and rs4820268 were significant associated with lower hemoglobin concentration (P≤0.0013), plasma ferritin (P≤0.0058), iron overload risk (P≤ 0.0068).[11] Other study done by Sung-Nan Pei shown people who has CC (homozygote dominant) has protective role against from iron deficiency anemia (OR= 0.4) among woman at reproductive age.[13]

Variant rs855791 in exon 17 showed the strongest association with serum iron levels, confirming results from a Genome-wide Association Study (GWAS).[16] Other study said change in the serine protease domain of TMPRSS6 SNP rs855791 effected decrease hemoglobin concentration 0.13 g/dL per copy allele.[17] Similar result show each A allele which is the minor allele on the reserve strand was associated with 0.11 g/dL lower Hemoglobin concentration, reduction serum ferritin concentration 3.71 µg/L, and increasing 0.02 mg/dL serum transferrin receptor concentration among overall population (Cucasian, Asian, and mixed) and they found that the risk allele frequencies of rs855791 and rs4820268 as high as 63% in the Asian population.[15]

Nurture; Factor Influencing Iron Absorption

Iron absorption is influenced by various external factors, including dietary components, meal composition, and overall nutritional status. Understanding these "nurture" of dietary characteristic factors is crucial for optimizing iron bioavailability and preventing iron deficiency.[18] Understanding the nurture factors affecting iron absorption is essential for developing dietary strategies to prevent and treat iron deficiency anemia.[19] By optimizing meal composition and timing, and considering the interactions between various dietary components, it is possible to enhance iron bioavailability and improve overall iron status.

Iron Bioavailability

The amount of absorbable iron provided thus depends on both the amount of iron added to the fortified food and the bioavailability of that iron when the fortified food is consumed as part of a mixed diet.[20] In a food menu with a large portion of animal sources, the bioavailability of iron is high. On the other hand, a diet consisting mostly of vegetable sources, the bioavailability of iron is low. Bioavailability of iron in food consumption in its calculation determined by heme and non-heme iron, enhancers, and inhibitors absorption of iron from food.[21]

a. Enhancers

Ascorbic Acid

One of the dietary components that really helps the absorption of non-heme iron is ascorbic acid. Ascorbic acid is the only predominant absorption enhancer in vegetarian diets, and iron absorption from vegetarian and vegan food can be excellent optimized by the inclusion of ascorbic acid–containing vegetables.[22] Add fruits and vegetables containing ascorbic acid and or organic acid into daily diet will increase two to three times of iron absorption[23]. The content of ascorbic acid can reduce ferric iron becomes ferrous in the small intestine so that easily absorbed by inhibiting the formation of hemosiderin. Iron absorption in non-heme form increased fourfold in the presence of ascorbic acid.[24] To increase iron absorption, WHO recommend that the content of ascorbic acid in daily diet at least 25 mg or more when consuming food with high inhibitors.[23] When taken with tea, ascorbic acid

prevents the development of an iron-tannin complex, hence counteracting the tea's inhibitory effect on iron absorption. The dose-response relationship obtained from a semi-synthetic meal containing 4.1 mg iron and ascorbic acid in doses ranging from 25 to 1000 mg is best described by a steep linear response up to a 7.5 molar ratio of ascorbic acid to iron, followed by a less pronounced linear dose-response for molar ratios above 7.5. At the 7.5 molar ratio the increase in iron absorption was about 3-fold.[25]

Protein/Muscle Tissue

In addition to ascorbic acid, protein is one of the enhancers of iron absorption in the body by releasing peptides during the digestive process of food so that the iron-peptide bonds will prevent precipitation, polymerization, or binding of water-insoluble components so that they can release iron easily into the intestinal mucosa. Beside that protein also can stimulate secretion of gastric acid by meat, solubilization of iron, and binding the iron by undigested protein fragments.[26] Two amino acids, Asparagine and glycine had the greatest impact increasing iron absorption by a significant amount ($p< 0.001$) more than serine or ascorbic acid. When any of the other amino acids were combined with iron, there was no statistically significant increase in iron absorption.[27] Nonheme iron absorption is helped by meat, fish, and poultry. The component in meat that boosts non-heme iron absorption has yet to be discovered. Evidence suggests that peptides high in the amino acid cysteine may help with non-heme iron absorption. Meat aids iron absorption in two ways: it enhances non-heme iron absorption and offers easily absorbed heme iron.[25] When compared to a base meal without meat, 75 g of meat boosted nonheme iron absorption by 2.5 times.[28] Some study found adding meat in complete diet will improve iron absorption by 30 – 50%.[29] In the other hand, protein from egg source and plant-protein sources has inhibitor effect on iron absorption.[30]

b. Inhibitors

Phytate

In contrast to enhancers, inhibitors are also one of the factors that affect the bioavailability of iron by inhibiting the release of iron into the intestinal mucosa. Phytates are a phosphate and mineral storage form found in grains, seeds, nuts, vegetables, and fruit. Phytates severely inhibit iron absorption in a dose-dependent manner, and even tiny levels

of phytate (about 2 - 10 mg/meal), given 2 and 250 mg of phytate will inhibit iron absorption by 18 – 82%. Phytic acid will form a complex compound of phytate-mineral-protein so that it can and makes them unavailable due to its chelating property and humans do not have an endogenous enzyme system that can catalyze the hydrolysis of the phytate molecule.[25,29,31] In vitro solubility of iron from these meals decreased from 7.9 to 1.52 per cent as phytate content increased from 0.3-1.3 g/d.[32] This theory is proven by research conducted on pregnant women, it was found that the absorption of iron in all pregnant women is inhibited due to the presence of phytate in their diet.[33] Another result found in previous study is the removal of polyphenol and phytic acid from dephytinized porridge enhanced absorption by 2.6 times (P 0.001).[34] Milling, heat treatment, soaking, germination, and fermentation are some of the food processing and preparation processes that can be used to remove or degrade phytate to variable degrees.[29] Soaking cereals like pearl millet with endogenous or exogenous phytase enhanced iron and zinc solubility in vitro by 2–23% but soaking and cooking together have been demonstrated more effective than soaking for a short period of time in reducing phytic acid. Germination can reduce the amount of phytic acid in a plant by up to 40%.[31] About 90% of the phytic acid in cereal grains is removed during milling.[35] The effectiveness of fermentation in reducing phytate levels can be seen in the results of a study conducted by Anam et al, this study found the longer the fermentation *tempe kara benguk*, the lower the phytic acid content and the higher the dissolved protein content. [36] When the protein was substantially enzyme hydrolyzed and phytate destroyed, will increase iron absorption 19-fold.[29] Ascorbic acid, meat, fish, and poultry can all help to mitigate the effects of phytate.[25] A phytate-rich low-vitamin C meal with a small amount of meat (≥50 g) dramatically increases nonheme-iron absorption.[37]

One of the important components of edible plant is dietary fiber that is difficult to digest and absorb in small intestine. Small effect found on intestinal iron absorption as result from soluble fiber, but insoluble fiber give inhibitor effect of mineral bioavailability.[30] Bran and hemicellulose found can reduce iron absorption, but pectin, guar gum, and cellulose have no effect.[38] Dietary fiber can reduce luminal pH and increase the ability of bacteria composition in the gut environment so that it can increase iron absorption and indirectly increase iron biomarkers, but further clinical trials are still needed.[39] Interaction between prebiotic and

soluble fibers will promote heme iron absorption through prebiotics fermentation by beneficial microorganism but it has no effect on non-heme absorption. [30,39]

Polyphenol

The second inhibitor that can significantly inhibit iron absorption is polyphenol.[40] During digestion, phenolic compounds are released from food or beverages, and they can interact with iron in the intestinal lumen, rendering it inaccessible for absorption. Although all major forms of food polyphenols have been shown to significantly reduce dietary non-heme iron absorption, it should be emphasized that long-term consumption of polyphenol compounds has been linked to iron depletion or deficiency in people with low iron reserves. The content of polyphenols as much as 20 - 50 mg can reduce iron absorption by 50 - 70% while the total content of polyphenols as much as 200 - 400 mg can reduce absorption up to 90%.[41] Polyphenols can be found in a variety of plant foods and beverages, including vegetables, fruit, some cereals and legumes, tea, coffee, and wine, in varying levels.[29] The polyphenol content in 50 - 20 mg of beans can reduce iron absorption by 15 - 45%, chocolate reduces as much as 70%, herbs/black tea or red wine reduces iron absorption by 60 - 80% regardless of the strength of the tea.[34] Tea drinking in the intervals between meals reduces non-heme iron absorption by 62% (simultaneous consumption of tea and iron) to 30% (interval 0.5 hour) to 21% (interval 1 hour) to 10% and 15% (interval respectively 2 and 3 hours.[25] The inhibitory effect of polyphenols in tea can be reduced by spraying ferric sodium EDTA because Fe(III)-EDTA is better absorbed, since it prevents iron from binding to these inhibitor compounds. By the addition of Fe: EDTA in a molar ratio ≥1 : 2, it is possible to produce an iron fortified tea without the formation of off-flavours.[42]

Calcium

Calcium, both as a salt and in dairy products, inhibits heme and non-heme iron absorption significantly by regulating enterocyte iron transporter proteins.[30] Initially, the inhibitory impact was thought to occur during the transfer of iron over the basolateral membrane from the enterocyte to the plasma because absorption of both forms of iron is equally blocked, suggesting roles for the serosa exporter ferroportin (FPN) and hephaestin

and recently, it was proposed that the inhibition occurs at the initial uptake into the enterocytes.[29,43] Calcium affects iron absorption but sometimes does not affect iron status level in the blood due to the luminal event where the binding between iron and calcium will affect iron uptake through DMT1 and it occurs short duration and there also may be compensatory mechanisms[44]. The dose-effect relationship between the amount of calcium administered and the degree of iron absorption inhibition has been reported no effect of calcium on iron absorption is seen when < 40 mg Ca is present in a meal and it had effect of amount ≥ 100 mg calcium inhibits both heme and non-heme iron absorption by 50%.[25,45] Other study found that nonheme iron absorption was reduced by 49.6% on average when calcium doses of 1000 mg were given. The absorption of 5 mg heme iron was reduced by 37.7% when given an 800 mg calcium dosage.[43]

Zinc and Oxalic Acid

Zinc has close related with activity of the enzyme matriptase-2, matriptase-2 is an enzyme that plays a role in the amount of hepcidin secretion in the circulation so that it can inhibit the absorption of iron in the small intestine so that it is at risk of suffering from iron deficiency anemia. Iron metabolism and absorption are affected by zinc levels via decrease in DMT1 and FPN1 expression. This might have physiological significance and a metabolic benefit. As a result of their similar physio-chemical characteristics, iron and zinc are known to compete with different metabolic proteins. It is known that zinc is an antioxidant while iron is a pro-oxidant. Direct zinc modulation of iron metabolism may reflect changing tissue iron requirements associated with growth at various periods of life.[46] Kondaiah's review conclude that zinc have marginal negative impact on iron status especially on ferritin serum and only give impact when in liquid but no such effect when in the meal.[46]

Oxalic acid will inhibit iron absorption with producing insoluble ferrous oxalate when iron is in the ferrous form such as in ascorbic-acid rich foods or heme iron but had no impact on ferric uptake in non-heme iron foods.[30,47] his is in line with the results of the Bonsmann study which found that there was no effect of adding 1.26 mg of dissolved potassium oxalate on iron absorption.[47]

CONCLUSION

Iron deficiency has previously been hypothesized to influence dietary and/or other environmental factors, but several discoveries have indicated that there is genetic contribution to the development of iron deficiency. *TMPRSS6* polymorphism can influence iron concentration in blood by controlling the hepcidin concentration through cleave the hemojuvelin. Hepcidin is negative regulator of intestinal iron absorption and removal by macrophages and hepatocytes, excess of hepcidin is a major contributor to the pathogenesis of anemia in inflammatory processes. In addition to the host related factor, namely the TMPRSS6 gene polymorphism, other factors that greatly influence iron absorption are the balance between consumption of enhancers and inhibitors, the type of iron food sources consumed, and the treatment (pre-processing and cooking treatment) carried out.

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