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Renal Anemia and Iron Metabolism

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Abstract

Normal iron metabolism is essential for effective hemoglobin (Hb) production in the management of renal anemia. Considering that studies regarding the optimal Hb levels predated the creation of the iron management indices found in the treatment guidelines for hemodialysis (HD) patients, an increase in the Hb levels caused by intravenous iron supplementation has been used as an iron management index. However, no consideration was given to iron metabolism or the long-term safety of intravenous iron supplementation. Although iron is a vital trace element in humans, it can also be toxic, and its metabolism is carefully controlled, with several factors affecting it. Considering that the details regarding the mechanisms underlying iron metabolism have been elucidated recently, a study regarding iron management that is safe and considers iron metabolism status effective for Hb production in patients with renal anemia is warranted. This study presents information regarding iron metabolism in patients on HD, the factors that influence iron metabolism in such patients, and the problems with existing treatment guidelines in Japan, apart from discussing the optimal iron levels and optimal Hb production indices.

Renal anemia occurs as the kidneys lose their ability to produce erythropoietin (EPO), and it is the most frequently observed complication in patients on hemodialysis (HD). EPO inhibits the apoptosis of erythroid progenitor cells and

promotes their proliferation and differentiation, helping in hematopoiesis and iron absorption for the process of hemoglobin (Hb) synthesis. The treatment is, therefore, mainly based on the administration of erythropoiesis-stimulating agents (ESAs) and the regulation of iron stores. It is, thus, crucial to maintain the optimal iron levels for hematopoiesis to adequately demonstrate the efficacy of ESAs.

Iron is not only involved in Hb synthesis but also in other processes, such as oxidoreduction reactions, cell proliferation, and apoptosis, and it is a vital trace element for the body. However, if free iron (such as non-transferrin-bound iron and the labile iron pool) is present in even the smallest quantities, it produces extremely toxic hydroxyl radicals through the Fenton's reaction. In the body, iron is bound to transferrin in the blood and is stored as ferritin within cells, maintaining the iron levels while suppressing free iron as much as possible and strictly controlling iron absorption from the intestines and iron storage in the body to avoid iron excess or deficiency. However, the impaired intestinal iron absorption of patients on HD has been assumed to be caused by multiple causes, and nonphysiological intravenous iron supplementation has been usually recommended to increase Hb. However, intravenous iron has been linked to oxidative stress and susceptibility to infection [1–4].

Today, various factors surrounding iron metabolism have been identified, and research is being conducted to elucidate iron metabolism and the harmful effects of iron, although none are large-scale intervention trials. However, it is necessary to reconsider what the safest and most effective iron levels are for patients on dialysis, with consideration for their iron metabolism.

Iron Management Standards and Guidelines

Globally, in treatment guidelines, serum ferritin levels and transferrin saturation (TSAT) are generally accepted iron management criteria for patients receiving dialysis. Serum ferritin is ferritin that has leaked from cells into the blood. Although serum ferritin levels are a useful index of iron reserves within the body, they can increase because of inflammation [5]. Moreover, although TSAT demonstrates the amount of available iron, this level fluctuates throughout the day and is influenced by nutritional condition [6] and inflammation [7]. Accordingly, no absolute benchmark exists, and a combination of these 2 tests is used to estimate the iron reserves within the body and iron metabolism.

To increase Hb and decrease ESA for HD patients, the Kidney Disease: Improving Global Outcomes iron supplementation guidelines recommend that intravenous iron should be administered if TSAT is ≤30% and the serum

ferritin level is ≤500 ng/mL [8]. In contrast, the Japanese Society for Dialysis Therapy (JSDT) guidelines, which were revised in 2015 and have a lower iron management standard than Europe and the US in the interest of avoiding the risk of iron excess, recommend iron supplementation therapy for patients in whom it is not possible to maintain the target Hb levels if TSAT is <20% and serum ferritin level is <100 ng/mL. The JSDT guidelines further propose that iron supplementation be administered if TSAT is <20% or the serum ferritin level is <100 ng/mL, provided this be conducted only in cases where no conditions that could decrease the iron utilization rate are observed. Based on the ferrugination findings in the liver and because of the risk of infection, they also added a note stating that "iron supplementation is not recommended if such supplementation increases serum ferritin levels to ≥300 ng/mL." [9]. However, these findings formed the basis for using Hb increase and ESA decrease as indices, and no consideration was given to the long-term safety. Furthermore, as iron supplementation had mainly been carried out intravenously, these do not necessarily reflect the physiological iron volume adjustment mechanism of subjects. In an older DRIVE study, it was reported that even in a situation of iron excess, intravenous administration was effective in increasing Hb levels and decreasing ESA levels [10]. However, with intravenous administration, this reportedly induces highly toxic labile plasma iron [11, 12] or oxidative-stress markers malondialdehyde, advanced oxidation protein product, and 8-OHdG [3, 13, 14]. Oral administration was included in the latest revision of the JSDT guidelines because of its high level of safety. As oral iron administration relies on the physiological ability of the organism to absorb iron, it becomes essential to consider iron metabolism and determine iron deficiency. Reportedly, the Hb content of reticulocytes, the percentage of hypochromic erythrocytes, and soluble transferrin receptor are more useful for detecting iron deficiency than serum ferritin levels or TSAT [15, 16], and it is presumed that the detection of iron deficiency using these markers can be one way of assessing the optimum iron levels. In the future, studies that investigate the optimal iron levels considering the long-term patient safety and iron metabolism are warranted.

Hematopoiesis and Iron Metabolism

The body contains approximately 4–5 g of iron, of which approximately 70% exists in the reticuloendothelial system in Hb, bone marrow, and reticuloendothelial macrophages and up to 30% is stored as ferritin in the liver and spleen; the rest is stored as myoglobin in the muscles. In the absence of any

active pathway for iron elimination, physiological iron elimination in the body is limited to loss through the shedding of skin cells and gastrointestinal mucosal cells, implying that 1–2 mg is absorbed and lost each day in a semi-closed system.

Hb is produced in the bone marrow, where iron, mediated by transferrin receptor 1, is combined with heme protein during erythropoiesis as erythroblasts differentiate into reticulocytes. Because supplemental iron for increasing blood Hb can be administered in doses of 25–30 mg/day, or 6–8 times that of the normal serum iron levels, iron is considered to be metabolized quickly in the body, and a steady supply of iron to the blood is considered vital for Hb production. Approximately, 90% iron is provided by reticuloendothelial macrophages in the recycling of old red blood cells, and the rest comes from food and stored iron.

The main regulator of iron metabolism is hepcidin, which is a peptide produced in the liver and was discovered in the year 2000. Although the transmembrane protein ferroportin (FPN) is solely responsible for transporting iron from liver cells, intestinal epithelia, and reticuloendothelial macrophages, hepcidin initially binds to FPN and the resulting complex is broken down in the lysosomes. The iron remains stored inside the macrophages for 2–3 days while FPN is resynthesized, and no iron is released into the circulation (Fig. 1). TfR2 in liver cells is assumed to detect serum iron and regulate hepcidin expression. Hepcidin synthesis is inhibited in response to hematopoiesis or hypoxia. However, it is upregulated in response to stored iron or inflammation [17], resulting in the FPN decomposition, which disrupts the extracellular transport of iron, locking the iron stores inside cells. Hence, even if a sufficient amount of iron exists in the body, the supply of recycled iron from the reticuloendothelial system and exported iron from storage to the blood is suppressed, resulting in an iron deficiency state required to synthesize Hb.

Therefore, although the administration of iron tablets during iron excess or inflammation can temporarily increase the Hb level, it will have an adverse impact on iron metabolism. Reportedly, serum ferritin and hepcidin levels are positively correlated [18, 19], in addition to the fact that there is no standard at this stage regarding the assessment of hepcidin and there is no easy way to measure hepcidin levels in clinical practice. When considering iron metabolism, we are left with the option of estimating hepcidin levels by using serum ferritin levels as a marker. Recently, erythroferrone was identified as an upstream regulator of hepcidin synthesis. Erythroferrone is produced in erythroblasts in response to stress that requires hematopoiesis, and it is considered that the suppression of hepcidin production promotes the supply of iron, resulting in the promotion of Hb synthesis [20, 21].

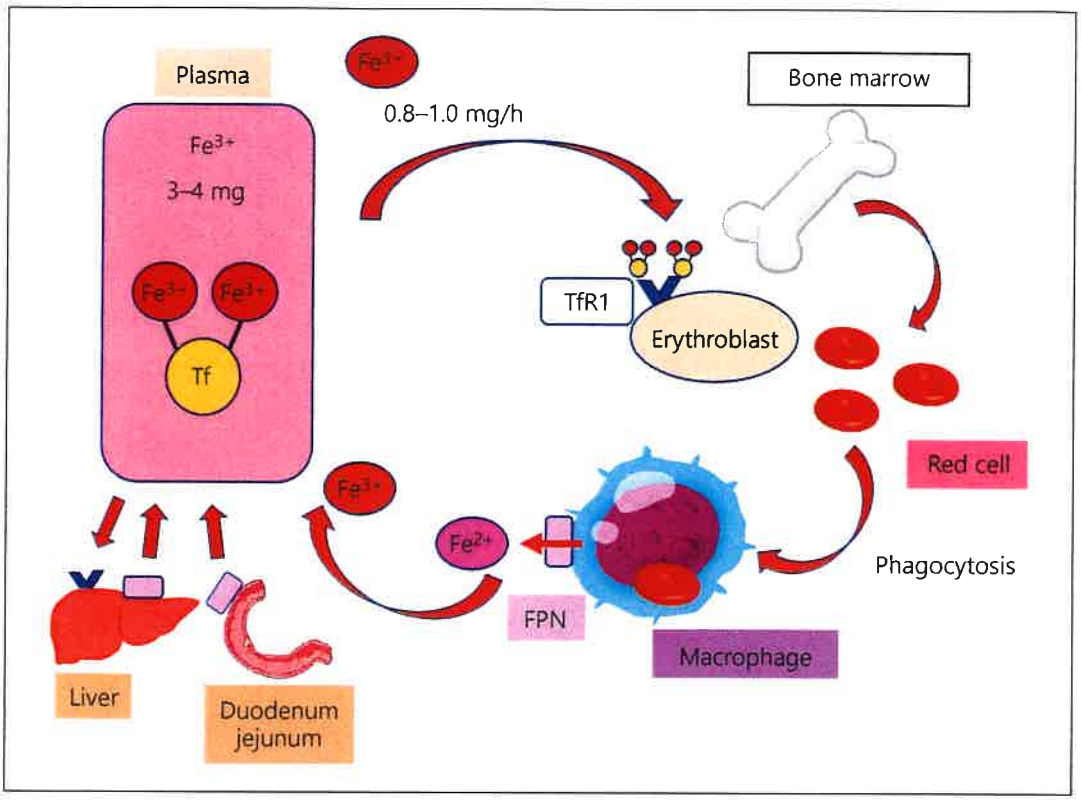

Fig. 1. The supply of iron through recycled iron in the reticuloendothelial system, iron reserve, and diet. Iron required for hematopoiesis is 0.8–1.0 mg/h, 90% of which comes from the reticuloendothelial system. Tf, transferrin; TfR, transferrin receptor; FPN, ferroportin.

Iron Absorption and Mucosal Block

Iron is absorbed into the body mainly through the duodenal epithelium and the upper jejunum. Reportedly, approximately 12% iron in the diet is usually absorbed, whereas approximately 30% is absorbed in a state of iron deficiency. With regard to non-heme iron in the diet, ferric (Fe^{3+}) is decreased into ferrous (Fe^{2+}) catalyzed by the duodenal cytochrome b in the intestinal epithelium, and Fe^{2+} will be absorbed into cells through divalent metal transporter 1. Conversely, heme iron is taken up through heme carrier protein. When necessary, iron is released into the blood through FPN in the blood. Therefore, an increase in hepcidin suppresses iron absorption in the intestines (Fig. 2).

Furthermore, an increase in iron in the intestinal cells suppresses the expressions of duodenal cytochrome b and DMT1 through the action of iron-responsive element/iron-regulatory proteins, which in turn suppresses the intercellular iron absorption in the intestines. This control mechanism for iron absorption is referred to as a "mucosal block" and is considered the physiological function that prevents iron excess in the body.

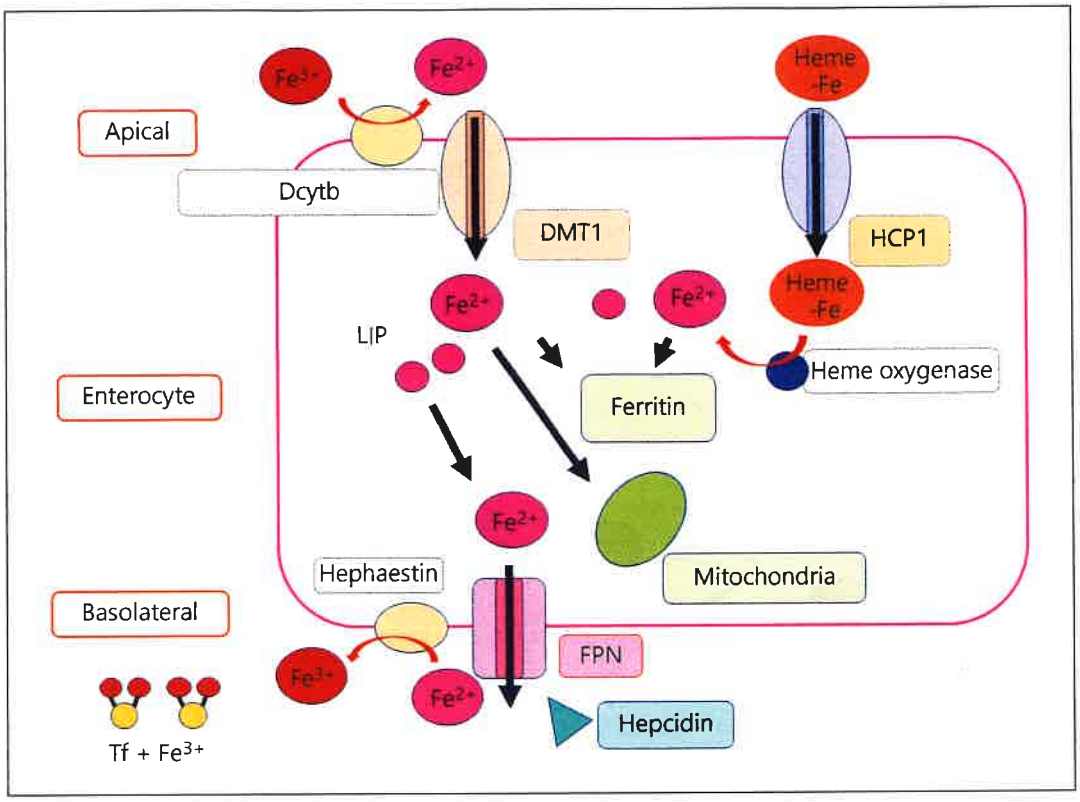

Fig. 2. Iron absorption in the intestinal epithelium. Non-heme iron, Fe^{3+} is decreased into Fe^{2+} in the intestinal epithelium when catalyzed by Dcytb, and Fe^{2+} will be taken up into cells through DMT1. Conversely, heme iron is absorbed through HCP1. Iron absorbed into cells is released into the blood through FPN in the blood, while the excess is stored in ferritin. DMT1, divalent metal transporter 1; HCP, heme carrier protein; FPN, ferroportin; Tf, transferrin; LIP, labile iron pool; Dcytb, duodenal cytochrome b.

However, one study reported that in a group where the average serum ferritin level was approximately 600 ng/mL, ferric citrate, which was administered as a phosphate binder (containing iron), increased serum ferritin levels and TSAT in addition to Hb [22]. In this particular group, hepcidin levels were evidently high, suggesting the presence of absorbed iron, which obviously could not be controlled by hepcidin. As demonstrated in reports regarding diet-derived excess iron [23, 24], including the example of the Bantu people, oral intake is not always safe, meaning that it is essential to consider the possibility of iron overdose.

Iron Metabolism and Patients on Hemodialysis

Iron absorption tests using radioactive isotopes conducted on patients on HD who do not take ESAs indicate a negative correlation between serum ferritin levels and iron absorption. Although >20% iron was absorbed when the serum

ferritin level was <30 ng/mL, it decreased to 2.52% when the serum ferritin level was 96 ng/mL. If this is considered as a linear approximation, then iron absorption becomes 0% when the serum ferritin level is approximately 60 ng/mL [25]. Although increased iron absorption when the serum ferritin level is <30 ng/mL could be interpreted as a state of iron deficiency, iron stores are sufficient when the serum ferritin level reaches 60 ng/mL, suggesting that iron is only absorbed through the intestines as a maintenance dose. The study also suggested a similar relationship between serum ferritin levels and iron absorption through the intestines in healthy adults.

Although some reports have stated that hepcidin levels increase in response to proinflammatory cytokines, such as interleukin 6 and interferon-alpha, in patients on dialysis in a state of chronic inflammation [26–28], other studies have suggested that hepcidin and serum ferritin levels (for which a positive correlation is indicated) are similar in healthy subjects and patients on dialysis [18, 29]. This finding indicates no significant difference between the response of hepcidin to iron levels in the body in healthy adults and patients on dialysis in whom inflammation has been brought under control. Although the serum ferritin levels for iron deficiency in healthy adults are <12–30 ng/mL [30, 31], the values mentioned in the JSDT guidelines' iron management criteria are completely different.

Some studies have reported cases of chronic kidney disease where hepcidin levels increased as the disease progressed; however, this effect was not attributed to failing clearance accompanying decreases in the glomerular filtration rate, but rather to decreasing hematopoietic potential and/or increasing ferritin levels [29, 32]. Hence, it can be presumed that after HD is instituted, serum ferritin and hepcidin levels will decrease as hematopoietic potential recovers as a consequence of ESA therapy and the alleviation of uremia [29]. Some reports indicate that hepcidin is removed by HD; there is a possibility that iron metabolism is affected by the HD process itself [26, 33, 34].

ESA and Iron Metabolism

According to a 2012 statistical survey conducted by the JSDT, ESA is administered to >90% HD patients. The currently available ESA can be roughly categorized into the following 3 types: recombinant human erythropoietin (rHuEPO), darbepoetin alfa (DA), and continuous erythropoietin receptor activator (CERA), which is a newer ESA with a long half-life. In addition, the impact of each type of ESA on iron metabolism has been investigated. Reportedly, ESA works on erythroid progenitor cells in the bone marrow and promotes

proliferation and differentiation into red blood cells while inhibiting hepcidin. According to Shoji et al. [35], although no significant reduction in hepcidin was observed after rHuEPO administration, after DA administration, a significant decline from the baseline of 46.44 ± 31.88 ng/mL was observed on day 3 of administration, reaching a low of 10.55 ± 6.89 ng/mL on day 5 [35]. Furthermore, Onuma et al. [36] reported that after DA administration, hepcidin levels declined from 20.2 ± 27.8 to 9.8 ± 18.1 ng/mL (days 5–6), whereas after CERA administration, it exhibited a greater decline than DA, changing from 29.7 ± 48.1 to 5.7 ± 13.1 ng/mL (days 5–6). Although the duration of the recovery period was 7 days in the DA group, it was 14 days in the CERA group. With regard to TSAT, while the DA group demonstrated a mild decline, the CERA group exhibited a greater decline, suggesting that a larger amount of iron is required for CERA administration than with DA [36]. In addition, a report suggests a negative correlation between the ESA administration dose and hepcidin levels [29]. On the basis of these reports, there is a possibility that the amount of iron required to synthesize Hb effectively depends on the ESA type and dosage.

Studies Regarding Optimal Levels of Iron and Hb Levels

Although it is considered that the key to treating renal anemia is to maintain an optimal balance of iron and hepcidin, it is still debatable as to what those levels are for dialysis patients.

We, therefore, conducted a retrospective study regarding the correlation between Hb, serum ferritin levels, and TSAT to investigate the optimal iron level for patients on HD. We enrolled 208 patients on maintenance HD who received rHuEPO treatment. We set the Hb level of ≥10 g/dL as the endpoint, as the target Hb level in the JSDT guidelines at the time was 10–11 g/dL. The receiver operating characteristic curve analysis revealed that the cutoff point was a serum ferritin level of <90 ng/mL (sensitivity, 69.1%; specificity, 72.1%) with a TSAT of ≥20% (sensitivity, 77.6%; specificity, 48.8%). Moreover, the logistic regression model analysis revealed that the odds ratio was highest at 46.75 (95% CI 10.89–200.70; $p < 0.001$) with a serum ferritin level of <90 ng/mL and a TSAT of ≥20% when the reference group had a serum ferritin level of ≥90 ng/mL and a TSAT of <20% [19]. This study demonstrated that serum ferritin levels have a greater impact on Hb than TSAT, and regarding iron levels, the best level was a serum ferritin level at <90 ng/mL with TSAT of ≥20%. Furthermore, another study regarding iron levels and Hb using JSDT data from over 140,000 patients also showed that Hb level was high with s-ft

<100 ng/mL and TSAT ≥20% [37], which was in line with our results. In addition, our study demonstrated a significantly positive correlation between hepcidin levels and serum ferritin levels (r = 0.78 [95% CI 0.72–0.83; p < 0.001]), and that the level of hepcidin, in a condition corresponding to when the serum ferritin level was 90 ng/mL, was approximately 30 ng/mL, which was measured using the quantitative method of liquid chromatography coupled with tandem mass spectrometry. As it is reported that the hepcidin levels of healthy adults measured using the same method were somewhere between 20 and 30 ng/mL [18, 26], this result would seem to be appropriate.

Notably, a study regarding oral iron supplementation for patients on HD reported a negative correlation between the rate of Hb improvement and the average levels of serum ferritin/hepcidin, which were 33.5 ± 24.2 and 32.8 ± 38.3 ng/mL, respectively, in a group with a lower response rate [38]. The results of this study suggest that when serum ferritin and hepcidin levels are both ≥30 ng/mL, the influence of iron deficiency on anemia is minimal. We believe that this also supports the results of our study.

Conclusion

Although it is essential to control iron stores for Hb production in patients on HD, the current guidelines do not consider physiological iron metabolism and long-term safety.

Iron levels are strictly controlled in the body, and research thus far suggests that it is better for iron delivery for hematopoiesis to be managed at decreased body iron levels because patients on HD whose inflammation is under control have iron levels in their bodies that are similar to those found in healthy adults but are at risk of increased iron retention.

One-size-fits-all iron supplementation can lead to high serum ferritin and hepcidin levels and pose a risk of negatively affecting iron metabolism. Presumably, the optimum amount of iron in a patient is that which can supply the blood with the exact quantity of iron needed for Hb production, an amount less than that indicated by the JSDT guidelines, and it was suggested that the optimal iron level might be nearer to a state of iron deficiency.

It is also possible that the amount of iron required for Hb synthesis varies according to the dose and type of ESA used, and it is possible that iron supplementation should be precisely managed in line with the condition and therapeutic situation of each patient to prevent iron deficiency and maintain proper iron metabolism. Now that oral iron supplementation (which the body's mecha-

nisms for regulating iron levels depend on) has been reexamined, further studies based on metabolism are required.

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