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Review

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Chronic Renal Failure, Anemia, and Parenteral Iron Treatment: From Bench to Bedside

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Abstract

Anemia is one of the common chronic renal failure (CRF) complications. Reduced renal erythropoietin (EPO) production and a shortened life span of erythrocytes due to uremic environment and iron deficiency are the main causes of anemia in patients with CRF. Correcting of iron deficiency constitutes the basis for the treatment of anemia in patients with CRF. Iron replacement can be done orally or intravenously. The seriousness of anemia and iron deficiency, tolerance of tablet use, response to previous treatments, and the presence of a ready vascular access determine the manner in which iron treatment is done. New generation parenteral iron preparations have complex carbohydrate structures that strongly bind to iron and reduce plasma free iron release. New generation iron molecules correct iron deficiency without causing an inflammatory process. The point that should be kept in mind is that new formulations may have a side effect profile that has not yet been experienced, in addition to various advantages. When using new iron molecules, precaution measures should be taken with regard to the development of arrhythmia, unstable angina, and hypophosphatemia.

Keywords: Chronic renal insufficiency, iron deficiency anemia, iron carboxymaltose

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INTRODUCTION

Anemia is one of the common complications of chronic renal failure (CRF). The reduction of renal erythropoietin (EPO) production and shortening of the erythrocyte life due to uremic environment and iron deficiency are the main causes of anemia. Anemia due to CRF occurs when the glomerular filtration rate (GFR) is approximately 60 mL/min/1.73m^2, and the frequency increases when the GFR drops below 30 mL/min/1.73m^2. In the American National Health and Nutrition Survey that included approximately 15.000 patients, the anemia prevalence was 1% in patients with GFR ≈60 ml/min/1.73m^2, 9% in patients with GFR ≈30 mL/min/1.73 m^2, and in patients with end-stage renal disease (ESRD), it increased up to 67% (1). Almost 90% of patients who receive kidney replacement therapy are anemic (2). In the Turkish Society of Nephrology Registry 2016 Report, the hemoglobin level of 70% of patients undergoing hemodialysis in Turkey was reported to be less than 12 gr/dL (3). El-Achkar et al. (4) reported that anemia develops earlier and that it is more severe in diabetic patients with CRF than in non-diabetic patients with CRF.

The purpose of this review is to evaluate iron deficiency and the parenteral iron preparations commonly used in clinical practice in terms of cellular and systemic effects.

As stated in the Kidney Disease Improving Global Outcomes (KDIGO) 2012 guideline, the evaluation of anemia begins when the hemoglobin level of patients with CRF is <12 g/dL in women and 13 g/dL in men (5). If anemia is not treated in ESRD, the hemoglobin level drops to approximately 8 g/dL without an additional factor such as hemolysis or bleeding. Lower hemoglobin levels bring into question the presence of a second

etiology, except renal failure. In patients with CRF, anemia is often normocytic normochromic as in other chronic diseases. Anemia is the basis of most of the symptoms associated with decreased renal function, whereas it is also associated with a decreased quality of life, increased hospitalization frequency and mortality in patients with CRF (6). Anemia was considered to be a defined risk factor for the development of left ventricular hypertrophy in patients with CRF who did or did not receive renal replacement therapy; it was also found to be associated with the development of heart failure and poor cardiac outcomes (7, 8). In one of these studies, Astor et al. (7) found that anemia was a risk factor independent from renal function and hypertension in the increase of left ventricular diameter in a 9-year follow-up in non-dialysis patients with CRF. It has been emphasized in various studies that, in addition to its negative effects on cardiac functions, anemia is an important factor in the development of ESRD and kidney function loss. In a recent study including 415 patients with CRF and left ventricular hypertrophy, the loss of renal function was found to be faster in patients with anemia than in patients who were not anemic (GFR decline rate -2.66 vs. -1.05 mL/min /1.73m^2/year) (9). The adverse effects of anemia in patients with CRF are summarized in Table 1.

As it is undesirable for hemoglobin levels to be low (<10 g/dL) in CRF, very high hemoglobin levels (>13 g/dL) are not beneficial in terms of survival. Various studies attempted to answer the question, "What is the optimal hemoglobin level in CRF patients?"; in a meta-analysis conducted by Jing Z, et al. (10), it was stated that a safe hemoglobin target should be 10-12 gr/dL in patients with all CRF stages. It was found that the frequency of cardiovascular events, stroke, and hospitalization increased in patients with targeted hemoglobin levels above these levels, especially above 13 g/dL (11). It was also reported that high hemoglobin levels in dialysis patients possessed a risk for inadequate dialysis, hyperphosphatemia, hyperkalemia, and thrombosis in arteriovenous fistula (5).

Table 1. Anemia in chronic renal failure and some adverse effects

• Malaise, fatigue, adynamia
•Dyspnea, insomnia, headache, decrease in mental acuity
•Sexual dysfunction and reduced quality of life
•Development and worsening of left ventricular hypertrophy
•Worsening of heart failure symptoms
•Cardiac perfusion deterioration and predisposition to cardiac ischemia
•Acceleration in the development of end-stage renal failure
•An increase in the frequency of hospitalization and overall mortality
•Complications associated with blood transfusion (viral infection, reactive autoantibody development, allergic reactions, hemolysis, iron accumulation, etc.)

CRF and Iron Deficiency Anemia

Iron deficiency is the most common improvable cause of anemia in patients with CRF. In the survey on anemia management (ESAM) including 8100 patients from 11 European countries, the frequency of iron deficiency in dialysis patients was reported to be 31.7% (12); in the pre-dialysis CRF patients (PRESAM), it was reported to be 61% (13). An inadequate food intake, deterioration of iron absorption and loss from the gastrointestinal, and recurrent venous puncture are the main causes of iron deficiency in CRF (Table 2). In the 2018 update, Fishbane reported the annual loss of iron in a hemodialysis patient to be 2000 mg (14).

Absolute iron deficiency (transferrin saturation [TSAT] <20% and ferritin <100 ng/dL) is defined as the complete depletion of iron stores in the bone marrow, spleen, and liver, whereas *functional iron deficiency* is a state in which there is insufficient iron incorporation into erythroid precursors in the face of apparently adequate body iron stores (15) (Table 3). Functional iron deficiency is characterized by low TSAT (<20%) and high ferritin levels. Failure to incorporate stored iron to the erythroid precursors may be due to the existing inflammation or EPO deficiency. When evaluating anemia in patients with CRF, it is helpful to know the level of C-reactive protein (CRP), in addition to the iron indicators. In a patient with anemia, the elevation of ferritin accompanied by CRP throws doubt on the presence of an active inflammatory event such as dialysis insufficiency, infection, malignancy, or rheumatic disease. In such a case, functional iron deficiency is mentioned, and the underlying inflammatory condition should be resolved for the treatment of anemia. Other iron indicators that provide information about the iron status in the body include the percentage of hypochromic erythrocyte and reticulocyte hemoglobin content, but the use of these markers is not as widespread as the measurement of TSAT and

Table 2. Causes of iron deficiency in chronic renal failure

Inadequate intake with food
• Anorexia due to uremia and poor nutrition from animal foods
Inadequate absorption from the gastrointestinal tract
• Use of a proton pump inhibitor, histamine-2 blocker, and calcium containing phosphorous binder
• Chronic inflammation and suppression of iron absorption by hepcidin
• Bacterial overgrowth in the bowel of immunocompromised patients
Gastrointestinal bleeding
• Platelet dysfunction
• Anticoagulant and antiaggregant use
• Peptic ulcer, malignancy, arteriovenous malformations, diverticula, etc.
Recurrent vascular access
Increased iron need
• Use of an erythropoiesis-stimulating agent

serum ferritin, and the number of studies based on these assays in patient management is extremely low. In the guidelines, it is recommended that the hypochromic erythrocyte percentage should be <6 and reticulocyte hemoglobin content should be ≥30 pg before the use of an erythropoiesis-stimulating agent (ESA) in patients with CRF (16).

In patients with CRF, knowing the type and cause of iron deficiency is important for the treatment, but often the differentiation of both conditions is done according to the response of anemia to the treatment (iron and/or ESA, retrospectively). In some patients, there is no adequate response to the treatment due to the underlying inflammatory condition; high doses of iron and ESA are required (17).

Because of uremic toxins in CRF, the synthesis of inflammatory markers and adhesion molecules increases (18). A high level of inflammation is associated with increased mortality and insufficient response to anemia treatment (19). Hepcidin is a hormone with systemic effects, whose synthesis and function is activated by inflammatory cytokines that are made from hepatocytes, particularly the interleukin (IL)-6 (20). Hepcidin inhibits the intestinal absorption of iron. In addition, it inhibits the transfer of iron stored in the reticuloendothelial system into the plasma via ferroportin. As a result, iron cannot be presented to the erythroid precursors, and anemia develops (21). Increased inflammation and hepcidin that restrains the iron presentation to the bone marrow play an important role in the development of chronic anemia in CKD (22).

Table 3. Types of iron deficiency

	Absolute Iron Deficiency	Functional Iron Deficiency
Serum TSAT	<20%	<20%
Serum ferritin	<100 ng/dL	≥100 ng/dL
Serum C-reactive protein	Low	Normal-high

TSAT: Transferrin Saturation

Table 4. Recommended Iron Targets in Chronic Renal Failure

	EBPG	NICE	KDIGO
Serum ferritin	100-500 ng/dL	200-500 ng/dL	500-800 ng/dL
Serum TSAT	30%-50%	>20%	>30%

TSAT: Transferrin Saturation; EBPG: European Best Practice Guideline (2013); NICE: National Institute for Health and Clinical Excellence (2014); KDIGO: Kidney Disease Improving Global Outcomes (2012)

CRF, Iron Targets, and the Route of Administration

In the KDIGO 2012 guide, iron replacement is recommended if TSAT is less than 30% and ferritin level is less than 500 ng/dL in adult CKD patients with anemia (5). In the European Good Clinical Practice 2013 and UK National Institute of Health 2014 guidelines, it is recommended to keep the TSAT above 20% and the ferritin level between 200 and 500 ng/dl in patients with CRF (21-24) (Table 4). In the Dialysis Patients' Response to Intravenous Iron With Elevated Ferritin (DRIVE) trial conducted by Coyne et al. (25), it was indicated that in the anemia treatment, the ESA response is better when the parenteral iron supplementation in hemodialysis patients with anemia is continued (Hb <11 g/dL), when TSAT is low (<25%) but ferritin levels range between 500 and 1200 ng/dL, and that the desired hemoglobin levels are reached in a shorter time without any side effects. The necessity of continuing iron supplementation in the hepcidin-mediated functional iron deficiency anemia was understood well with this study (25). One of the most comprehensive studies as a resource to the guidelines that examined the relationship between iron indicators and all mortality was conducted by Kalantar-Zadeh et al. (26). Approximately 60,000 hemodialysis patients from the American database were included in the study, and the relationship between the serum ferritin and TSAT levels and overall mortality was evaluated. In the patients with the serum ferritin level 200-800 ng/dL and TSAT 30%-50%,

Table 5. Common parenteral iron preparations

Preparation	FDA Approval Date	Molecular Weight (kDa)	Maximum Dose at a Time	Half Life (hour)	Test Dose Requirement	Antigenic Property	Application Time Iron dextran
(High-molecular weight) Iron dextran	1996	265	20 mg/kg	72-96	Yes	High	6 hours
(Low-molecular weight)	1991	165	20 mg/kg	48-72	Yes	High	6 hours
Iron gluconate	1999	289-440	125 mg	1	No	Low	15 minutes
Iron sucrose	2000	30-100	7 mg/kg*	6	No	Low	3.5 hours
Iron carboxymaltose	2013	150	15 mg/kg**	16	No	Low	15 minutes
Iron isomaltoside	-	150	20 mg/kg	24-96	No	Low	30 dk

*It is recommended not to exceed 100 mg/day.
**It is recommended not to exceed 750-1000 mg/day.

the overall mortality risk was determined to be the lowest. In the same study, there was an increase in the risk of death in patients with the serum ferritin level >1000 ng/dL (26). It was stated in the guidelines that if the serum ferritin level exceeds 500 ng/dL, the maintenance iron dose should be re-evaluated to avoid iron accumulation (14). Hemochromatosis, cirrhosis of the liver, and endocrine disorders such as diabetes mellitus can be seen as a result of iron accumulation. For this reason, a continuous high-dose iron overload should be avoided in patients by referring to the results of the DRIVE study.

Iron replacement may be oral or intravenous. The severity of anemia and iron deficiency, tolerability of the patient to the use of the tablet, the response to previous treatments, and whether there is a vascular access determine the manner in which iron therapy is performed. According to the KDIGO 2012 anemia management guideline, in Stage 5 CRF hemodialysis patients, the intravenous route should be preferred as an iron replacement route. The availability of vascular access for intravenous iron administration in hemodialysis patients and the applicability of iron therapy during hemodialysis sessions are important factors in choosing the intravenous route for iron replacement. It was evaluated in several studies that preferring intravenous iron replacement rather than oral showed better results; in these studies, a better increase in hemoglobin levels and less need for ESA with intravenous iron replacement compared to the oral route was observed (27, 28).

In patients with ESRD who were not undergoing hemodialysis, there is no consensus on how to perform iron replacement. In recent years, the studies showing intravenous iron therapy leading to kidney damage by oxidative stress and lipid peroxidation of kidney damage led to the emergence of concerns in clinicians on parenteral iron use in patients with valuable remaining kidney functions (29). On the other hand, the limitations in the use of oral iron preparations in daily practice, as mentioned above, cause the intravenous route to be the preferred iron replacement route also in patient groups that do not undergo dialysis. Adverse effects of oral iron preparations on the gastrointestinal tract (constipation, gas distension, dyspepsia, nausea), inadequate adaptation of the patients to the use of tablets, insufficient iron absorption from the intestines, and increased iron use in bone marrow due to erythropoiesis that accelerated during the ESA use, and failure of oral iron supplementation to adequately replace the needed dose may be considered as the limitations of oral iron treatment. It is stated that these problems are experienced in approximately one in three patients (10%-40%) (30).

An equation for calculating iron deficiency in relation to the body weight has been developed to overcome iron deficiency and to fill the iron stores in the body:

[Iron deficit (mg): (13-Hgb)×Body weightx2.145+500**]** In daily practice, frequently, approximately 1000 mg of iron is empirically administered without calculation. Some studies have reported that this dose is sufficient to correct anemia (31, 32). Sometimes a second 500-1000 mg dose may be needed to replace the iron depot 2-4 weeks after the first dose.

Parenteral Iron, Inflammation, Endothelial Damage, and Kidney Survival

The first parenteral iron therapy in the literature was reported by Heath et al. in 1932 (33). In this report, neutral iron was applied to patients with anemia mixed with ammonium citrate; symptoms such as palpitations, hot flashes, and nausea and vomiting occurred in patients who received iron at extremely low doses of 8 mg/day. Patients who received iron at doses of 48-80 mg showed significantly more severe reactions. With reports about toxic reactions caused by parenteral administration of the iron hydroxide salt, Nissim et al. (34) applied iron in combination with a carbohydrate, saccharide, and reported that such treatment was safer. Since then, iron is applied in a compound form with a carbohydrate unit such as dextran, gluconate, sucrose, and maltose (35). All of the current iron preparations consist of an iron oxyhydroxide core and a carbohydrate sheath around it, basically as the molecular structure. The carbohydrate sheath may be a dextran polymer, sucrose, gluconate, or maltose. This molecular structure mimics ferritin, which is responsible for storing iron in the liver, spleen, and bone marrow. The iron-carbohydrate component makes the molecular weight of the drug. Iron compounds containing dextran and maltose have the highest molecular weight and contain sucrose and gluconate at the lowest level. Molecular weight plays a major role in the pharmacokinetics of the preparation by affecting the rate of drug metabolism. The main factor determining the effectiveness of parenteral iron preparations is the dose of iron given; pharmacokinetic properties do not determine efficacy. Preparations with a great molecular size are largely removed from plasma by the reticuloendothelial system (RES) macrophages and stored; free iron releases into the circulation are at the minimum level. Iron preparations with a smaller molecular size are metabolized in the plasma, causing high levels of free iron in the plasma by rapidly saturating transferrin even at low doses. The iron-carbohydrate component is also important in terms of the molecular size and antigenicity. High-molecular-weight preparations can be administered at higher doses at a time; low-molecular-weight preparations are administered at lower doses at a time as they cause excessive free iron entry into the plasma (36). The dextran transport of the carbohydrate sheath may cause allergic reactions to the component.

In patients with CRF and iron deficiency, intravenous iron supplementation has become almost a standard treatment approach, especially in patients undergoing dialysis, due to the frequent deterioration of the intestinal iron absorption and poor compliance to oral iron preparations (37) (Table 5). With intravenous administration of iron, utilization is increased by skipping the inhibitory effect of hepcidin on iron absorption.

While intravenous iron use provides a faster rise in hemoglobin levels compared to the oral route and the use of a lower dose of ESA, the most important concern, in return, is its contribution to the inflammatory environment present in patients with CRF with the production of oxidative stress, lipid peroxidation, and free oxygen radicals (38). The number of major studies investigating the toxic effects of iron on oxidative stress and kidneys has increased in the last decade; the most interesting studies were done by Agarwal et al. (29). In an article published in 2004, the effects of iron therapy on oxidative stress and kidney injury in patients with CRF were examined; in patients with Stage CRF 3-4, after intravenous administration of 100 mg iron sucrose, an increase in the serum lipid peroxidation marker malondialdehyde (MDA) and transient proteinuria indicating renal injury was determined (29). After this research, the idea that the endothelial damage and the remaining kidney functions will be adversely affected by iron therapy has led the clinicians to develop a number of reservations against intravenous iron therapy and to conduct new research. However, in another short-term clinical study on hemodialysis patients, it was shown that 100 mg/day iron sucrose had no additional adverse effect on oxidative stress and erythrocyte deformability (39). In another study conducted by Agarwal et al. (40), the toxic effect of recurrent iron infusions on renal function was investigated in patients with CKD and iron deficiency, and it was observed that intravenous iron sucrose increased the protein leakage in the urine. In a prospective study conducted by the same researcher group Randomized Trial to Evaluate IV and Oral Iron in Chronic Kidney Disease (REVOKE), the effects of intravenous and oral iron therapy on the decrease in GFR, cardiovascular event, and frequency of infectious event that required hospitalization were investigated in patients with Stage 3-4 CKD and iron deficiency anemia in a 2-year observation. While the reduction rate of GFR was similar in both groups, the frequency of cardiovascular events and hospitalization due to infection were found to be increased with intravenous iron therapy compared to oral iron therapy (41).

Cellular and Systemic Toxicity of Free Iron in the Plasma

The free circulation of iron, which plays an essential role in many cellular physiological events in the organism, causes cellular toxicity in the plasma. While free iron circulating in the plasma is reduced by the Fenton reaction, it causes the formation of high-grade reactive oxygen radicals (superoxide O_2^- and hydroxyl radical HO^-), resulting in redox reactions (42). Therefore, iron is transported to the required location in the plasma by binding to the transferrin and is presented to the cells through the transferrin receptor. The fraction that is not bounded to transferrin (free iron, labile iron, redox active) is responsible for the oxidative stress and cellular damage. The free iron in the circulation causes activation of cytokines and increase in oxidative products (43). While the free iron in the plasma was caused by iron gluconate mostly, this is followed by iron sucrose and iron dextran. The clinical significance of this condition is that the more stable iron compounds can be administered at a higher dose at a time, while more labile forms such as iron gluconate and sucrose (which result in a high amount of free iron in the plasma after administration) can be given in much smaller amounts at one time.

Zager et al. (44) examined the pro-oxidant and cytotoxic properties of different parenteral iron formulations (dextran, sucrose, and gluconate) in human and rat proximal tubule cells *in vitro*; they reported that all agents caused similar levels of lipid peroxidation, whereas the maximum cell death was observed in the sucrose, gluconate, and dextran group, respectively. In another study conducted by Pai et al. (45) in chronic hemodialysis patients, it was found that iron sucrose and iron gluconate caused a much higher amount of free iron in the plasma compared to iron dextran. In a study involving patients with ESRD undergoing hemodialysis and healthy volunteers by the same group of investigators, iron sucrose caused much higher levels of free labile iron in both healthy adults and dialysis patients compared to iron dextran (43). In another *in vitro* study evaluating free labile iron fractions of different iron preparations (high- and low-molecular-weight dextran, sucrose, and gluconate), the maximum free iron was determined in iron gluconate, iron sucrose, low-molecular-weight iron dextran, and high-molecular-weight iron dextran groups, respectively (46).

In a comprehensive study conducted by Toblli et al. (47), all iron formulations (iron carboxymaltose, high-molecular and low-molecular weight iron dextran, iron gluconate, iron sucrose) were applied to rats for hemodynamic effects and development of oxidative stress; inflammatory parameters such as IL-6 and tumor necrosis factor (TNF)-alpha were studied from serum and MDA form the tissue homogenates. The histopathology of the liver, heart, and kidney tissues of rats was examined for the toxic effects of different iron molecules. The simultaneous introduction of all iron preparations used in daily practice in this experimental study enabled comparisons between the molecules. The main characteristics that differentiated this study from other studies were the evaluation of both biochemical and histomorphological toxicity findings and notation of the real creatinine clearance and proteinuria levels of rats during the study. In this study, inflammatory indicators were highest in the iron gluconate group, followed by dextran, sucrose, and carboxymaltose, respectively. The higher TNF-alpha and IL-6 levels found in the iron dextran group than in the iron sucrose group were linked to the antigenic structure of dextran. When the iron formulations were evaluated in terms of renal functions, the highest increase in proteinuria was observed in rats that were given iron gluconate, and no statistically significant difference was found in other groups. Again, in terms of creatinine clearance, the most decrease in clearance was observed in rats that were applied iron gluconate during the follow-up period, but no difference was found between other formulations. Oxidative stress markers evaluated in tissue homogenates were again the highest in the iron gluconate group. Almost an equal amount of oxidative end products was observed in the carboxymaltose group and the control group (47).

It is understood that iron formulations (iron gluconate and iron sucrose), which are small in size, lead to more free iron in the plasma, cause oxidative damage, increase inflammation, and cause more cellular and systemic toxicity. Therefore, they can be administered in limited doses at a time.

Iron carboxymaltose and iron isomaltoside, which belong to new parenteral iron preparations, significantly reduce the iron release to plasma by strongly binding iron to their complex carbohydrate structures, and they are caught from plasma by RES cells. The carbohydrate parts are metabolized in the cell by glycolysis to introduce iron cores for use. Since free iron is minimalized, these formulations offer the opportunity to be applied at high doses at a time. Since the new iron formulations do not contain dextran, their immunogenic potential is also low.

Beshara et al. (48) recorded the distribution of radiolabeled iron polymaltose in the body by positron emission tomography following intravenous administration, and they observed that the iron concentrates mostly in the liver, spleen, and bone marrow. In a review of the experimental studies with radioactive-labeled iron carboxymaltose, Funk et al. (36) showed that iron carboxymaltose was taken from the plasma by macrophages shortly after parenteral administration and presented to the bone marrow, and they reported that after 14 days, iron was distributed at 76% in the erythrocytes, which are the target cells, 11% in the liver, 2% in the spleen, and 1% in the kidneys.

The Effect of Iron Carboxymaltose on Inflammation, Renal Damage, and General Mortality

In a prospective study conducted by Prats et al. (49), the effects of iron carboxymaltose on the CRP, IL-6, intracellular adhesion molecule (ICAM), and vascular adhesion molecule (VCAM) levels in 47 pre-dialysis patients with iron deficiency anemia were evaluated. Iron carboxymaltose was given in a single dose of 15mg/kg (max 1000mg); no effects were observed in the parameters reflecting inflammation and endothelial functions at the 60th minute, 3rd week, and 3rd month following administration. While hemoglobin levels were significantly improved with iron carboxymaltose, no pro-inflammatory response was detected in the acute or subacute period (49).

In a multicentric randomized controlled trial (FIND CKD), including approximately 350 CRF patients who were not undergoing dialysis, the treatment of parenteral iron carboxymaltose was compared with oral iron treatment for their effect on the renal function. Study groups were designed as the first two of the study groups being low- (100-200 ng/dL) and high- (400-600 ng/dL) ferritin-level-targeted iron carboxymaltose groups, whereas the third group was given oral iron treatment (ferric sulfate). At the end of the 56-week follow-up, ferritin values targeted with iron carboxymaltose were achieved, and no adverse effects were found in the predicted GFR in patients receiving a low and high dose of iron carboxymaltose (50).

In a multicenter Randomized evaluation of efficacy and safety of ferric carboxymaltose in patients with iron deficiency anaemia and impaired renal function (REPAIR-IDA) study including 2584 non-dialysis CRF patients (mainly Stage 3-4) with iron deficiency anemia, the efficacy (change in the hemoglobin level) and safety (overall mortality, nonfatal myocardial infarction, nonfatal stroke, unstable angina, congestive heart failure, arrhythmia, blood pressure change) of iron carboxymaltose were compared with iron sucrose; the patients receiving iron carboxymaltose (750 mg twice a day, total 1500 mg on the day 0 and the day 7) and patients receiving iron sucrose (200 mg 5 times a day between Days 0 and 14, total 1000 mg) were followed for 120 days, and determined efficiency and safety parameters were evaluated. In terms of efficacy, the percentage of patients with increased levels of hemoglobin of 1 g/dL was found to be higher in the group of iron carboxymaltose (48.6% vs. 41%), but it should be noted that in the iron carboxymaltose group, higher doses of iron (1500 mg vs. 1000 mg) were given. There were no statistically significant differences between the two groups in terms of safety endpoints; it was noted that in the group of patients receiving iron carboxymaltose, more arrhythmia and unstable angina pectoris were observed during the follow-up (51).

In terms of its molecular structure, iron carboxymaltose has the advantage of applicability at a high dose at a time; the most significant adverse effect reported is a temporary asymptomatic hypophosphatemia, which becomes evident at the 2nd week after the administration, resolving spontaneously at 6-12 weeks (52). While mild (<2 mg/dL) hypophosphatemia is generally asymptomatic, in the case of severe hypophosphatemia (<0.6 mg/dL), the development of weakness, bone and joint pain, impaired consciousness, arrhythmia, and heart failure have been mentioned. In studies not including patients with CRF, the incidence of hypophosphatemia after iron carboxymaltose was reported to be 41%-70% (53-54). The main mechanism in hypophosphatemia following iron administration is the loss of renal phosphate induced by the fibroblast growth factor 23 (FGF23). FGF23 is a peptide with a phosphaturic effect made from osteocytes and the C-terminal, and its intact fragments are present in the plasma. It acts with its intact part in target organs. In healthy adults, the FGF23 synthesis increases from osteocytes in the case of iron deficiency, but as its disintegration increases simultaneously, the level of active hormone in the plasma does not change (55). While the carbohydrate structure of iron carboxymaltose increases the production of FGF23 in osteocytes, it selectively inhibits the breakdown of FGF23. Ultimately, the net effect is the increase of the intact FGF23 fragment (active peptide) in the plasma. This effect is specific to carboxymaltose.

The most comprehensive study evaluating the effect of iron carboxymaltose on phosphorus homeostasis was performed by Wolf et al. (56) in women with iron deficiency due to uterine bleeding. In the study, one group (n=34) was given 15 mg/

kg (max. 1000 mg) iron carboxymaltose at a time, and the other group (n=35) received 15 mg/kg iron dextran in a single dose; serum phosphorus, the FGF23 level, and fractional phosphorus excretion were recorded during the 5-week follow-up period. While no significant changes were observed in the level of intact FGF23 (active hormone) during the follow-up period in patients who were given iron dextran, the level of intact FGF23 in the patients who received iron carboxymaltose was determined to be elevated from the 1st day, peaked on the 7th day, and returned to the basal levels at the 5th week. Parallel with the intact FGF23 level, the serum phosphorus level was found to be at its lowest levels between 7 and 14 days, in patients applied iron carboxymaltose. While the serum phosphorus level decreased to less than 2 mg/dL in 10 patients in the iron carboxymaltose group, no hypophosphatemia was observed in the iron dextran group. Since FGF23 inhibited the production of 1,25 (OH) vitamin D in the kidney, a moderate decrease in serum calcium levels (mean 0.4 mg/dL) was observed in patients receiving iron carboxymaltose on Day 7 (56). Therefore, it is understood that serum phosphorus and calcium levels should be monitored before and after the treatment in patients who received iron carboxymaltose due to iron deficiency.

CONCLUSION

Iron replacement is important for an effective treatment of anemia in patients with CRF. Although the patient's compliance with the oral or parenteral supplementation of iron and the choice of the clinician are determinative, new iron molecules replace iron deficiency in a short time, providing an important advantage to the patient and the physician. It should be kept in mind that while new formulations lead to a variety of advantages, they can have side effects not experienced yet. When using new iron molecules precaution measures should be taken against the development of arrhythmia, unstable angina, and hypophosphatemia; especially in patients with a body weight <66 kg, the dose should be kept lower (51).

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