ORIGINAL RESEARCH

# Oral Versus Intravenous Iron Supplementation for the Treatment of Iron Deficiency Anemia in Patients on Maintenance Hemodialysis—Effect on Fibroblast Growth Factor-23 Metabolism

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**Objective:** Iron administration affects serum levels of intact (I-) fibroblast growth factor-23 (FGF23) and its cleavage product C-terminal (C-) FGF23 in iron-deficient patients on maintenance hemodialysis (MHD). The objective of this study was to compare the effect of oral or intravenous iron administration on serum levels of I-FGF23 and C-FGF23 in iron-deficient patients on MHD.

**Design and Methods:** A prospective randomized study.

**Subjects:** Participants on MHD with severe iron deficiency (n = 61).

**Intervention:** Participants were randomized to receive oral iron (50 mg of sodium ferrous citrate daily; oral group, n = 29) or intravenous iron (40 mg of saccharated ferric oxide weekly; IV group, n = 32).

**Main Outcome Measure:** Changes in I-FGF23 and C-FGF23 after 10 weeks of treatment.

**Results:** Iron supplementation significantly increased hemoglobin, mean corpuscular volume, ferritin, and transferrin saturation rate, and decreased erythropoiesis-stimulating agent dose and erythropoiesis-stimulating agent resistance index value. Serum phosphate, calcium, and intact parathyroid hormone levels did not change significantly during the study. I-FGF23 levels increased significantly in the IV group and did not change in the oral group, whereas C-FGF23 levels were significantly reduced in both groups. Serum interleukin-6 and tumor necrosis factor-$\alpha$ levels were increased in both groups. Multiple regression analysis indicated the relationship between iron or erythropoiesis and FGF23 metabolism.

**Conclusion:** Iron administration to patients on MHD with severe iron deficiency decreased C-FGF23 levels, whereas intravenous iron increased I-FGF23 levels though oral iron did not. If the target of chronic kidney disease-mineral and bone disorder therapy is reducing I-FGF23 levels, we suggest the use of oral iron.



## Introduction

MINERAL AND BONE disorders in chronic kidney disease (CKD) have recently emerged as the major cause of CKD-associated cardiovascular disease. It has been postulated that several factors affect their pathogenesis, including hyperphosphatemia, vitamin D deficiency, and secondary hyperparathyroidism. One of the mechanisms involved that contributes to cardiovascular disease is an increase in fibroblast growth factor 23 (FGF23), a bone-derived hormone.[1] CKD is the most common cause of elevated FGF23, and FGF23 levels were extremely high in patients with end-stage kidney disease.[2] In animal models, intramyocardial or intravenous injection of FGF23 in wild-type mice has resulted in left ventricular hypertrophy.[3,4] In the clinical setting, high FGF23 levels are strongly associated with greater risks of CKD progression, cardiovascular events, and mortality.[1,5–8]

Lowering FGF23 levels might attenuate these complications, although FGF23 levels are already up to 1000-fold above normal. It has been established that iron deficiency is associated with the increase in FGF23 levels and is a common complication in renal anemia with the use of erythropoiesis-stimulating agent (ESA) therapy. Thus, iron administration is indicated for these conditions.

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Although iron supplementation might attenuate the increase in FGF23 in patients on maintenance hemodialysis (MHD), results regarding the effect of iron administration on FGF23 metabolism are divergent, possibly because of the different routes of administration and/or different iron preparations trialed.[9,10]

It has been established that iron may play an important role in the metabolism of FGF23. In the bloodstream, the FGF23 protein circulates in distinct forms: a full-length mature form (intact FGF23 [I-FGF23]) and cleaved shorter forms (C-terminal FGF23 [C-FGF23]) that mainly arise from proteolytic cleavage of I-FGF23.[8] Iron has been shown to affect FGF23 expression in osteocytes and osteoblasts, whereas some iron preparations might affect the cleavage step of I-FGF23.[8]

From the point of view of FGF23 metabolism, the most appropriate route for iron supplementation in patients on MHD with ESA therapy has not yet been determined. We therefore examined the relation between iron administration route and FGF23 metabolism in the setting of a randomized, controlled, open-label single center study, comparing the effect on I-FGF23 and C-FGF23 levels as well as iron metabolism in patients with severe iron deficiency receiving either oral (oral group) or intravenous (IV group) iron.

## Materials and Methods

### Study Population and Design

This study was a prospective, open-label interventional study. We enrolled 119 participants with CKD who underwent MHD in Meiwa Hospital. Among these 119 participants, 70 had absolute iron deficiency, which was defined as a serum ferritin <50 ng/mL and transferrin saturation rate (TSAT) < 20% according to the 2015 Japanese Society for Dialysis Therapy Guidelines for Renal Anemia in Chronic Kidney Disease (2015 JSDT anemia guideline).[11] These 70 participants were arbitrarily randomized into 2 groups: an oral iron group (oral group, n = 35) and an intravenous iron group (IV group, n = 35). The oral group received a daily dose of sodium ferrous citrate (Ferromia; Eisai Co., Ltd., Tokyo, Japan) containing 50 mg of iron, and the IV group received a 40 mg dose of saccharated ferric oxide (Fesin; Nichi-iko Pharmaceutical, Co., Ltd., Toyama, Japan) weekly or the equivalent fortnightly. Two weeks before the start of this study, iron supplementation was discontinued. The study period involved 10-week of iron administration in both groups. Iron supplementation was halted if the serum ferritin level was >100 ng/mL in considering 2015 JSDT anemia guideline, which recommend iron therapy if the serum ferritin level is < 100 ng/mL and TSAT is <20%. Two patients, one was oral group and the other was IV group, were not received ESA but did not show any difference in anemia, iron, and chronic kidney disease-mineral and bone disorder (CKD-MBD) parameters.

Exclusion criteria included malignancy, infection (C-reactive protein [CRP] >3.0 mg/dL), gastrointestinal bleeding, chronic virus infection (hepatitis C or human immunodeficiency virus), and secondary hyperparathyroidism (intact parathyroid hormone [iPTH] ≧500 pg/mL). Accordingly, 9 participants were excluded from the study as follows: human immunodeficiency virus infection (n = 1), secondary hyperparathyroidism (n = 1), infection (n = 2), gastrointestinal bleeding (n = 2), withdrawal due to intolerance to oral iron (n = 1), and death (n = 2). Sixty-one participants were included in the final analysis.

Administration of ESA was maintained during the study as follows: epoetin alfa (EPO) was administered 1–3 times a week, darbepoetin-α (DA) was administered once a week, and continuous erythropoietin receptor activator (CERA) was administered twice a month. One patient in the oral group and one patient in the IV group received no ESA. The dose of ESA administered was not changed unless hemoglobin (Hb) was >12.0 g/dL, in which case it was reduced. In the IV group, saccharated ferric oxide was administered at the next dialysis session after administration of EPO or DA, and in 2 consecutive dialysis sessions after CERA administration every other week.

Phosphate binders, active vitamin D supplements, and cinacalcet were modified as appropriate to control calcium, phosphorus, and iPTH according to the 2012 Japanese Society for Dialysis Therapy Guidelines for the Management of Chronic Kidney Disease-Mineral and Bone Disorder.[12]

The study complied with the ethical principles laid out in the Declaration of Helsinki (amended in 2000) and Good Clinical Practice. All participants provided written informed consent, as required by the institutional committee on human research, and this committee approved the study protocol (Meiwa Hospital, No. 27-8). This study is registered with the University Hospital Medical Information Network (UMIN), No 000017119.

### Measurements and Assays

Blood samples were obtained before dialysis sessions at the start and the end of the study. Hematological and iron-related parameters were measured using standard methods. Iron parameters were analyzed within at least 7-day intervals after iron administration in the oral and IV groups, respectively. I-FGF23 and C-FGF23 levels were determined using 2 sandwich ELISA kits (Kainos Laboratories, Tokyo, Japan and Immutopics International, San Clemente, CA, USA, respectively). Serum hepcidin levels were measured using liquid chromatography coupled with tandem mass spectroscopy with reversed phase extraction (Medical Care Proteomics Biotechnology Co. Ltd., Ishikawa, Japan). Soluble transferrin receptor (sTfR) levels were measured with an ELISA kit (BioVendor Laboratory Medicine, Inc., Czech Republic). Interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) levels were measured with an ELISA kit (Thermo Fisher Scientific, MA, USA).