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IRON THERAPIES FOR IRON DEFICIENCY IN CHRONIC KIDNEY DISEASE: A LITERATURE REVIEW

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Abstract : Chronic kidney disease is a condition when kidney function fails gradually due to kidney damage. One of the causes of anemia in CKD is iron deficiency. Conventional oral iron treatment is not effective to treat iron deficiency anemia due to poor absorption and various side effects. Newer oral iron therapies with better tolerability and offer the potential to normalize iron without the need for intravenous iron. To review the currently available status oral iron therapies and summarizes the latest clinical trial evidence for their use. We researched Google Scholar and PubMed using keyword "iron" OR "ferri" OR "Ferro" OR "iron therapy" AND "Iron deficiency" AND "renal insufficiency, chronic" OR "chronic kidney disease" OR "kidney failure, chronic" OR "chronic renal disease" of last ten years. Total 8 articles recorded the identification stage by the criteria for inclusion. The articles are randomized controlled trials. Total 2.674 patients CKD of various types with or without anemia, age range 18-72 years were treated with oral iron therapies (ferric citrate, ferrous sulfate, sucroferric oxyhydroxide, ferric carboxymaltose) with varying doses. The most side effects of the therapies are gastrointestinal intolerance. Oral iron therapies are considered safe but drug development is still needed to minimize side effects.

Keywords: iron deficiency;iron treatment;chronic kidney disease.

INTRODUCTION

Chronic Kidney Disease is a chronic condition decline in kidney function that takes for months to years. Chronic disease affects up to 13% of adults and the most common complication is anemia and markedly increases the risk of early cardiovascular events and death. A common complication of CKD is iron deficiency. Iron deficiency is an important factor in the pathogenesis of anemia in patients with chronic disease not dependent on dialysis (ND-CKD). Iron deficiency affects 60% of men and 70% of women with ND-CKD. Anemia is a condition in which the level of hemoglobin in the blood is reduced. Anemia can be caused by a variety of pathological and physiological reactions. Iron deficiency anemia is anemia caused by reduced levels of iron needed for Hb synthesis (Block et al., 2015); Kapoh et al., 2021).

Identification of iron deficiency requires prompt assessment of diet, obvious or hidden causes of blood loss, and drugs that may interfere with iron absorption, and iron supplementation in most cases. Clinical practice guidelines recommend that levels of people with CKD and anemia with hemoglobin, 13.0 g/dL for men, and 12.0 g/dL for women are treated with iron rather than erythropoiesis-stimulating agents (ESAs) to increase hemoglobin if saturation is present transferrin (TSAT) 30% and serum ferritin level 500 mcg/L. However, ESAs themselves have a considerable side (Macdougall et al., 2017).

Iron therapy is the first choice of therapy for anemia in CKD patients diagnosed with iron deficiency, and in some patients with normal Hb levels without epoetin therapy. Combination of iron and epoetin therapy is required to stimulate iron deficiency. The principle of iron deficiency treatment is to find out the causative factors, overcome and provide therapy with iron preparations that are given orally and parenterally. Oral therapy is safer, cheaper, and has the same efficacy as parenteral therapy (KDIGO, 2013; NKF KDOQi, 2006; (Kapoh et al., 2021).

The most commonly used supplements but offer oral therapy is not very effective. However, ferrous sulfate has been shown to be relatively effective in increasing iron and hemoglobin concentrations in individuals with CKD and does not require dialysis, but the effect of oral iron supplementation on FGF23 is less clear, especially in patients with Chronic Kidney Disease. In addition to sulfate, citrate can also be used. However, it is not clear whether iron citrate is more effective in reducing FGF23 in CKD patients by increasing circulation to restrict absorption of phosphate when compared to ferrous sulfate (Womack et al., 2020).

MATERIALS AND METHODS

This study is a literature review study using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) method in CKD (chronic kidney disease) patients who were given oral iron therapy to determine iron status based on

parameters of changes in iron status values.

This research article was searched on PubMed and Google Scholar with a limitation of the last 10 years and then collected in Microsoft Excel. We conducted an electronic literature search on Google scholar and PubMed. The keywords used are "iron" OR "ferri" OR "Ferro" OR "iron therapy" AND "Iron deficiency" AND "renal insufficiency, chronic" OR "chronic kidney disease" OR "kidney failure, chronic" OR "chronic renal disease".

The inclusion criteria in this study were oral iron therapy in CKD patients who had anemia due to iron deficiency. There are no restrictions on age, gender, ethics, race and country. All articles are RCTs (randomized controlled trial) in English and Indonesian.

RESULTS AND DISCUSSION

This review uses the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) method. The inclusion criteria for this type of article are RCT (randomized controlled trial), oral iron administration in CKD patients with iron deficiency and the search limitation of the last ten years. A search for "iron deficiency, iron treatment, chronic kidney disease" total 3358 returns 997 articles on Google Scholar, 2361 on PubMed. The study results that have been obtained and screened based on inclusion and exclusion criteria. Then remove duplication (n: 3304), title screening (n:280), abstract screening (n: 81), then the full text screening used as the final result is 8 articles.

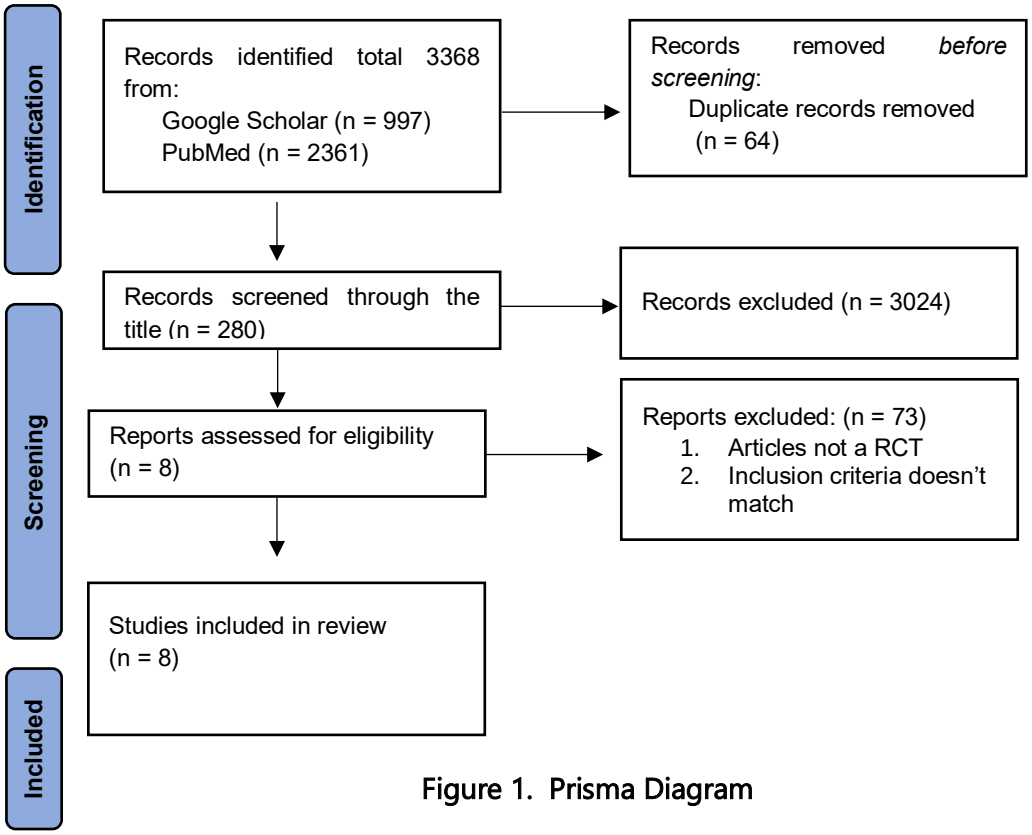

Figure 1. Prisma Diagram

Table 1. Study Characteristics

No	Author	Tittle	Location	Year
1	Rabeca Womack *et al.*	Effect of Ferric Citrate versus Ferrous Sulfate on Iron and Phosphate Parameters in Patients with Iron Deficiency and CKD	United States	2020
2	Iain C. Macdougall *et al.*	Erythropoietic response to oral iron in patients with nondialysis-dependent chronic kidney disease in the FIND-CKD trial	Denmark	2017
3	(Fishbane et al., 2017)	Effects of Ferric Citrate in Patients with NondialysisDependent CKD and Iron Deficiency Anemia	United States	2017
4	Geoffrey A. Block *et al.*	A 12-Week, Double-Blind, Placebo-Controlled Trial of FerricCitrate for the Treatment of Iron Deficiency Anemia andReduction of Serum Phosphate in Patients With CKD Stages 3-5	United States	2015
5	(Iguchi et al., 2018)	Effect of ferric citrate hydrate on FGF23 and PTH levels in patients with non-dialysis dependent chronic kidney disease with normophosphatemia and iron deficiency	Japan	2017
6	(Ketteler et al., 2019)	Effects of sucroferric oxyhydroxide and sevelamer carbonate on chronic kidney disease mineral bone	United Kingdom	2018

		disorder parameters in dialysis patients		
7	(Wüthrich et al., 2013)	Randomized Clinical Trial of the Iron-Based Phosphate Binder PA21 in Hemodialysis Patients	United States	2013
8	(Onken et al., 2014)	Ferric carboxymaltose in patients with iron deficiency anemia and impaired renal function: the REPAIR-IDA trial	United Kingdom	2013

Table 1. shows the results of this research literature review which includes a journal biography (title, author, study location, and year of publication). From the results of the literature search, it was found that 8 articles were used in this study.

Table 2. Subject Characteristics

No	Study	Population	Female/Male (treatment)	Traetment	Side Effect	Outcome
1.	Rabeca Womack *et al.* 2020	60 adults with moderate to severe CKD and iron deficiency	20/10 (ferric citrate) 29/11 (ferrous sulfate)	Ferric citrate 2 g trhee times a day with meals, n=30 Ferrous sulfate 325 mg three times a day, n =30 For 12 weeks	The most commonly reported side effects are change in stool color (n=24), constipation (n=20), diarrhea (n=14)	Treatment with ferric citrate for 12 weeks resulted in a greater mean incrase in TSAT and also increased hepcidin cencentrations more than ferrous sulfate
2.	Iain C. Macdougall *et al.* 2017	308 patients	Not reported	Oral iron 200 mg elemental iron/day	Frequent gastrointestinal side-effects	Oral iron theraphy for four weeks reported 21.6% patients showed

						hemoglobin (Hb) increase 1g/dL.
3.	(Fishbane et al., 2017)	234 adults with nondialysis-dependent CKD and iron deficiency anemia	76/41 (ferric citrate) 71/45 (placebo)	Oral ferric citrate (n=117) Placebo (n=117)	Gastrointestinal effects were most common, with diarrhea and constipation in patients treated with both ferric citrate and placebo. None of the deaths or serious adverse effects were thought to be drug-related.	Increase Hb concentration 1.0 g/dl or more in 16 weeks. Treatment with ferric citrate safe and efficacious for iron deficiency anemia patients with NDD-CKD.
4.	Geoffrey A. Block *et al.* 2015	149 patients with GFR < 60 mL/min/1.73 $m^{2,}$ iron deficiency anemia, and serum phosphate levels ≥ 4.0 to 6.0 mg/dl. IV iron or erythropoiesis-stimulating agents were prohibited.	50/22 (ferric citrate) 43/26 (placebo)	Ferric citrate 210 mg or placebo for 12 weeks	Most side effects were gastrointestinal, with discolored feces (n=24), diarrhea (n=15), constipation (n=14)	Ferric citrate treatment increased Hb levels, repletes iron stores, and reduces serum phosphate levels, urinary phosphates excretion, and FGF-23 in patients with CKD stages 3 to 5 and iron deficiency anemia.
5.	(Iguchi et al., 2018)	40 patients were included with 17 patients in the	Not reported	FCH-group 250 mg with each meal, SFC-group 50	Not reported	In FCH-group serum intact-PTH levels decreased,

		FCH-group, 14 patients in the SFC-group, and 9 patinets in thecontrol-group.		mg once a day for 12 weeks		FGF23 levels not decrease. Except in patients whose eGFR declined, FCH-group decreased CFGF23 levels.
6.	(Ketteler et al., 2019)	1059 patients	737/322	Sucroferric oxyhydroxide 1-3 g/day (n=710) Sevelamer 2.4-14.4 g/day (n=349) For 24 weeks	Not reported	Treatment with sucroferric oxyhydroxide or sevelamer significantly reduced serum FGF23.
7.	Rudolf P. (Wüthrich et al., 2013)	154 patients	46/80 (PA21) 10/14 (sevelamer-HCl)	PA21 with dosage 1.25, 5.0, 7.5, 10.0, or 12.5 g/d Sebelamer-HCl 4.8 g/d For 6 weeks	Most side effects reported were hypophosphatemia (n=23), discolored feces (n=15), and hyperphosphatemia (n=10).	Treatment with PA21 significanly reduces serum phosphorus in hemodialysis patinets with 5 to 12.5 g/d dosage
8	(Onken et al., 2014)	2584 patients were randomized treated with FCM group and iron sucrose-group	810 females (FCM) 818 females (iron sucrose)	FCM 750 mg in one week Iron sucrose 200 mg administered in up to five infusions in 14 days	The most common adverse effects were nausea, hypertension, flushing, dizziness and dysgeusia.	Treatment with FCM group increased Hb 1.13 g/dl and 0.92 g/dl with iron sucrose. FCM group are safe and effective alternative to multiple lower dose iron sucrose infusions in iron deficiency

anemia patients with NDD-CKD

Table 2. shows the results of the literature review of this study covering the authors, population, gender of participants, treatment, side effects, and the conclusion.

CKD patients with or without anemia, aged 18-72 years were given oral iron therapy (ferric citrate, ferrous sulfate, sucroferric oxyhydroxide, ferric carboxymaltose) with varying doses. The dose of administration varies according to the research that has been done. According to *Rabeca et al* who used Ferric citrate at a dose of 2 g three times a day with meals and ferrous sulfate 325 mg three times a day for 12 weeks, with the results of therapy using ferric citrate reported to increase TSAT and hepcidin more than ferrous sulfate. According to *Markus et al* who used sucroferric oxyhydroxide 1-3 g/day reported that this therapy can significantly reduce serum FGF23 levels, and there was a history of hyperphosphatemia and prescription of stable doses of phosphate binders for 1 month before screening. Study by *Jane et al* using ferric carboxymaltose at a dose of 750 mg for one week can increase Hb levels to 1.13 g/dl. In this study, there were side effects caused by the use of oral iron therapy, the most patients experienced gastrointestinal intolerance. *Iain et al* in their study gave oral iron therapy 200 mg elemental iron/day proven to increase hemoglobin levels for four weeks in 21.6% of the participants. *Steven et al* explained that in the oral therapy group, ferric citrate can increase hemoglobin concentrations of 1.0 g/dl or more in 16 weeks and this therapy is safe and effective in NDD-CKD patients with iron deficiency anemia. *Geoffrey et al's* study used ferric citrate to increase hemoglobin levels, replete iron stores, and suppress serum phosphate levels, urinary phosphate excretion, and suppress FGF23 serum levels in grade 3 to 5 CKD patients with iron deficiency anemia. *Akira et al's* study found that FCH-group can reduce intact PTH serum levels. A different study was conducted by *Rudolf et al* performed PA21 administration with varying dosage of 1.25, 5.0, 7.5, 10.0, or 12.5 g/d in patients whose receiving vitamin D or calcimimetics had to be on a constant dose for a least 1 month before screening and during the study, therapy with PA21 5 to 12.5 g/dl dose can significantly suppressing serum phosphorus in hemodialysis patients.

Oral iron therapy can increase hemoglobin levels in the body and suppress FGF23 serum levels. The most side effects of therapies were gastrointestinal problems. Oral iron therapies are considered safe but drug development is still needed to minimize side effects.

DISCUSSION

This study was conducted to determine the efficacy of iron therapy in CKD patients with iron deficiency anemia. Iron deficiency anemia is a condition where the total amount of iron in the body is less than normal due to reduced iron supply for erythropoiesis and results in low Hb formation. If the iron content in the body is low, it will inhibit the formation of red blood cells in the bone marrow so that the Hb level decreases below normal limits. Various studies have proven that iron supplements can increase Hb. Iron supplementation is beneficial because it can improve Hb status in a short time. several factors that can affect iron administration therapy, namely, patient compliance, diseases that can interfere with iron absorption, supplementation doses, and empty body iron reserves (Wahtini, 2019).

The principle of giving iron therapy in iron deficiency anemia is knowing the causative factors and overcoming and providing replacement therapy with iron preparations. In the case of iron deficiency anemia, after identifying the cause of the disease and treating it, iron replacement therapy is needed to improve Hb levels and rebuild iron stores in the body. Administration of iron can be prepared in two ways: oral and parenteral (Gunadi D, 2020).

Oral treatment of iron deficiency anemia is clearly cheaper than parenteral treatment. From a practical point of view, oral therapy is the first line to replace iron stores because it allows a normal absorption mechanism, and thus can prevent complications and risks of iron overload. Iron given by oral therapy must meet the requirements that each tablet or capsule contains 50-100 mg of elemental iron which is easily released in an acidic environment, is easily absorbed, and has less side effects. There are four irons that can be given orally, namely Ferric Citrate, ferrous sulfate, sucroferric oxyhydroxide, ferric carboxymaltose.

One way to overcome the weakness of oral iron therapy can be overcome by using parenteral iron therapy. In a meta-analysis study when compared oral iron therapy with intravenous therapy, intravenous therapy was more effective than iron therapy. Parenteral iron therapy is given if there are indications such as malabsorption, lack of tolerance for oral administration, and the patient is uncooperative and requires a rapid increase in Hb (Kapoh et al., 2021).

CONCLUSIONS

Oral administration of iron therapy can increase hemoglobin levels, and suppress serum FGF23 levels in CKD patients with iron deficiency anemia. The most side effects are gastrointestinal problems. Oral iron therapies are considered safe but drug

development is still needed to minimize side effects.

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