Journal of Nephrology
https://doi.org/10.1007/s40620-020-00885-z

EDITORIAL

Transforming the frail and elderly patient into an Iron Man: how to attenuate arterial calcification and improve cardiovascular outcomes in chronic kidney disease

Mario Cozzolino[1] · **Paola Ciceri**[2]

An article in the September issue of *The Clinical Journal of the American Society of Nephrology* described a study whose results demonstrated that, compared to ferrous sulfate, treatment with ferric citrate for 12 weeks had produced a greater mean increase in transferrin saturation and ferritin concentrations in individuals with moderate to severe chronic kidney disease and iron deficiency [1].

Why are these results important for nephrologists?

Chronic kidney disease patients have a higher burden of cardiovascular morbidity and mortality compared to other chronic diseases due to several of the risk factors which are consequences of renal function impairment. What deserves attention from a public health point of view is the fact that the majority of chronic kidney disease patients have a significantly higher incidence of all cardiovascular co-morbidities even before progressing to end stage renal disease. It is therefore clear that finding strategies to improve cardiovascular outcomes in chronic kidney disease patients is worth every effort.

Of the many therapeutic approaches nephrologists can employ, ferric citrate appears to represent an important option. Its uniqueness lies in its approval as both a phosphate binder (since 2014, in the United States and Japan) and for the treatment of iron deficiency anemia in chronic kidney disease patients not on dialysis (since 2017, in the United States, and 2020, in Japan). Ferric citrate has been found to be capable of treating mineral metabolism and anemia, two of the main conditions that need to be corrected in chronic kidney disease patients. The available evidence strongly supports the rationale of a likely effect of iron citrate on cardiovascular outcomes (Fig. 1). Yet, although its efficacy has been demonstrated in the treatment of three different surrogate outcomes (phosphate load, vascular calcification, and anemia), data are lacking that conclusively demonstrate the effect ferric citrate has on cardiac function.

Studies on animal models have shown that iron-based phosphate binders are able to reduce vascular calcification. Of these, ferric citrate has demonstrated its efficacy in preventing tunica media calcification development caused by reduced intestinal absorption of phosphate. In addition, in vitro studies demonstrate a direct effect of ferric citrate in reducing calcium deposition in high-phosphate treated vascular smooth muscle cells. The action of ferric citrate is independent of the activity of the phosphate binder and directly targets vascular calcification pathways such as apoptosis, autophagy, simil-osteoblastic trans-differentiation and extracellular matrix osteo-chondrogenic shift [2]. Ferric citrate in vitro is a powerful anti-calcification agent, not only because it can prevent calcification, but because it is also able to block the progression of calcification by reverting pathways that have been modified by high phosphate. These effects are obtained at an in vitro concentration in the same order of magnitude as the blood-iron concentration achieved in patients after an i.v. dose of iron. Although the translation from studies on cells to clinical application is always difficult and is never risk-free, the in vitro studies and in vivo experimental research on animals indicate that the effect of ferric citrate on vascular calcification in chronic kidney disease patients deserves to be evaluated. Full elucidation of the efficacy of ferric citrate in counteracting calcification, a major independent risk factor for incident cardiovascular disease and overall mortality in chronic kidney disease patients, is propaedeutic to clinical trials for the evaluation of the effect that ferric citrate has on cardiovascular outcomes.

✉ Mario Cozzolino
mario.cozzolino@unimi.it

[1] Department of Health Sciences, Division of Nephrology and Dialysis, ASST Santi Paolo e Carlo, University of Milan, Milan, Italy

[2] Renal Research Laboratory, Department of Nephrology, Dialysis and Renal Transplant, Fondazione Ca' Granda IRCCS, Ospedale Maggiore Policlinico, Milan, Italy

Published online: 02 January 2021

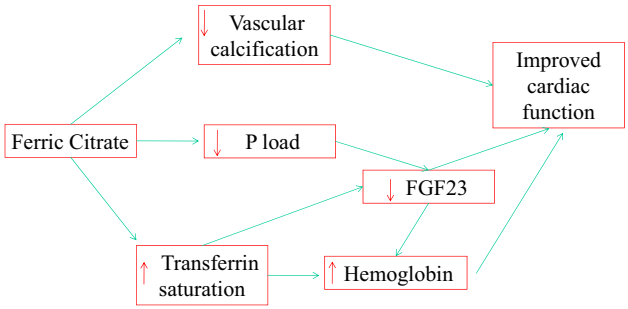

Fig. 1 Ferric citrate reduces vascular calcification in vitro, decreases phosphate (P) load and FGF23 levels, and increases transferrin saturation, reducing FGF23 and increasing hemoglobin in chronic kidney disease. These effects have the potential to improve cardiac function in chronic kidney disease

Ferric citrate decreases phosphate load in chronic kidney disease patients as its approval as a phosphate binder indicates. In vivo studies demonstrate that administrating ferric citrate to treat hyperphosphatemia has a protective action against fibrosis and ultimately renal dysfunction. Interestingly, the beneficial effect of ferric citrate on kidney function results from an attenuation of oxidative stress and inflammation and the lowering of fibroblast growth factor 23 (FGF23) levels [3]. Moreover, in an in vivo model of progressive chronic kidney disease, ferric citrate significantly reduced FGF23 levels, preserved renal function and improved cardiac function [4]. Although this occurred in an animal model, it is important evidence that the effect of ferric citrate on mineral metabolism is linked to cardiovascular outcomes, owing in part to the hypothesized independence of the ferric citrate cardiac effect from kidney disease progression.

In the chronic kidney disease milieu, excessive circulating FGF23 is a strong predictor of cardiovascular diseases, including cardiac hypertrophy, and death. In the last decade a link between iron metabolism and FGF23 regulation was found independently of phosphate metabolism. This relationship is relevant, as anemia is a classic co-morbidity and is associated with adverse outcomes. The FGF23 metabolism is complex, encompassing both the intact and cleaved forms, whose ratios and relative quantities differ depending on whether an iron deficiency is found in a healthy individual or in one with chronic kidney disease [5]. Interestingly, a direct effect of ferric citrate in correcting the increase in FGF23 levels induced by iron deficiency has been demonstrated when serum phosphate levels are normal. A further step in elucidating the contribution of iron deficiency anemia in modulating FGF23 levels is a recent study in an animal model of chronic kidney disease, which demonstrated that even without phosphate control, anemia correction can decrease FGF23 levels, thereby providing evidence for the hypothesis that management of iron utilization in chronic kidney disease patients is capable of modifying their mineral metabolism [6]. Thus, an increase in FGF23 levels in chronic kidney disease might be considered the junction between mineral metabolism impairment and iron deficiency anemia. In this respect, the action of ferric citrate in decreasing FGF23 levels may be the result of its double action, its ability to control both hyperphosphatemia and iron deficiency in chronic kidney disease. This modulation of FGF23 levels seems to be beneficial since a 30% reduction of this hormone in the EVOLVE trial was associated with a reduction in both adverse vascular outcomes and all-cause mortality [7].

Anemia in chronic kidney disease has been associated with an increased risk of morbidity and mortality, and the more severe the anemia becomes, the greater the risk is. Ferric citrate has recently been demonstrated to be safe and efficacious in increasing transferrin saturation, serum ferritin and hemoglobin in non dialysis-dependent chronic kidney disease patients with iron deficiency anemia [8].

In their recent study, Womack et al. [1] enrolled 60 patients with moderate to severe chronic kidney disease (eGFR 15–45 ml/min per 1.73 m^2) and iron deficiency (transferrin saturation $\leq 30\%$ and ferritin ≤ 300 ng/ml), dividing them into two groups: those taking 2 g of ferric citrate thrice daily with meals, (n = 30); those taking 325 mg of ferrous sulfate thrice daily (n = 30) for 3 months. The authors observed an 8% increase in transferrin saturation and in ferritin (difference in mean change, 37 ng/ml) in chronic kidney disease patients treated with ferric citrate compared to those treated with ferrous sulfate. Treatment with ferric citrate also resulted in a greater increase in hepcidin, without changes in hemoglobin and FGF23 levels.

Despite this evidence and despite the demonstrated safety profile of ferric citrate [9], no trials evaluating the effect of ferric citrate on cardiovascular outcomes have yet been performed, even though anemia seems to accelerate the progression of heart disease and increase the risk of death in chronic kidney disease patients.

In conclusion, ferric citrate has demonstrated its positive effects on many outcomes closely connected to cardiovascular conditions such as vascular calcification, phosphate load, FGF23 levels and iron deficiency anemia. Thus, in our opinion, there is a strong scientific and clinically supported rationale for designing a phase-3 controlled, randomized clinical trial to evaluate the impact of ferric citrate on cardiovascular outcomes and on survival in chronic kidney disease patients.

References

1. Womack R, Berru F, Panwar B, Gutiérrez OM (2020) Effect of ferric citrate versus ferrous sulfate on iron and phosphate parameters

in patients with iron deficiency and CKD: a randomized trial. Clin J Am Soc Nephrol 15(9):1251–1258. https://doi.org/10.2215/CJN.15291219
2. Ciceri P, Falleni M, Tosi D, Martinelli C, Cannizzo S, Marchetti G et al (2019) Therapeutic effect of iron citrate in blocking calcium deposition in high Pi-calcified VSMC: role of autophagy and apoptosis. Int J Mol Sci. https://doi.org/10.3390/ijms20235925
3. Jing W, Nunes ACF, Farzaneh T, Khazaeli M, Lau WL, Vaziri ND (2018) Phosphate binder, ferric citrate, attenuates anemia, renal dysfunction, oxidative stress, inflammation, and fibrosis in 5/6 nephrectomized CKD rats. J Pharmacol Exp Ther 367(1):129–137. https://doi.org/10.1124/jpet.118.249961
4. Francis C, Courbon G, Gerber C, Neuburg S, Wang X, Dussold C et al (2019) Ferric citrate reduces fibroblast growth factor 23 levels and improves renal and cardiac function in a mouse model of chronic kidney disease. Kidney Int 96(6):1346–1358. https://doi.org/10.1016/j.kint.2019.07.026
5. Edmonston D, Wolf M (2020) FGF23 at the crossroads of phosphate, iron economy and erythropoiesis. Nat Rev Nephrol 16(1):7–19. https://doi.org/10.1038/s41581-019-0189-5
6. Noonan ML, Clinkenbeard EL, Ni P, Swallow EA, Tippen SP, Agoro R et al (2020) Erythropoietin and a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHDi) lowers FGF23 in a model of chronic kidney disease (CKD). Physiol Rep 8(11):e14434. https://doi.org/10.14814/phy2.14434
7. Moe SM, Chertow GM, Parfrey PS, Kubo Y, Block GA, Correa-Rotter R et al (2015) Cinacalcet, fibroblast growth factor-23, and cardiovascular disease in hemodialysis: the evaluation of cinacalcet HCl therapy to lower cardiovascular events (EVOLVE) Trial. Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) Trial Investigators. Circulation 132(1):27–39. https://doi.org/10.1161/CIRCULATIONAHA.114.013876
8. Fishbane S, Block GA, Loram L, Neylan J, Pergola PE, Uhlig K et al (2017) Effects of ferric citrate in patients with nondialysis-dependent CKD and iron deficiency anemia. J Am Soc Nephrol 28(6):1851–1858. https://doi.org/10.1681/ASN.2016101053
9. Block GA, Block MS, Smits G, Mehta R, Isakova T, Wolf M et al (2019) A pilot randomized trial of ferric citrate coordination complex for the treatment of advanced CKD. J Am Soc Nephrol 30(8):1495–1504. https://doi.org/10.1681/ASN.2018101016