**Protocol title:**

Pilot Pragmatic Clinical Trial of Oral Iron Therapy in Children with CKD (Fetch-CKD)

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**Introduction**

Anemia complicates CKD in about 50% of children before they reach ESRD[1]. Erythropoietin (Epo) axis dysfunction and hepcidin activation are the two key drivers of renal anemia. Hepcidin, a hormone that prevents iron egress from cells, is elevated in children with CKD[2] and leads to iron sequestration and unavailability for erythropoiesis[3]. Therapeutic iron supplementation is being used to address low levels of circulating iron, but it further stimulates hepcidin[4] and has potential for iron overload and toxicity[5,6]. Conversely, hepcidin blockade improves anemia and skeletal growth in experimental CKD without exogenous iron supplementation[7]. Specific treatment targets are being developed in adult CKD patients to guide iron therapy[8]. In children with CKD not receiving erythrocyte stimulating agents (ESAs), iron status targets are based on expert opinions[9,10], and the adequacy of these targets with relation to clinically relevant outcomes have never been tested. Currently, iron therapy is 2-3 times more frequent than ESAs in children with mild to moderate CKD[11]. While we know that iron aggravates acute kidney injury[12], no studies have examined the effects of iron therapy on renal function, statural growth, body composition, appetite and food intake, executive function, and quality of life in pediatric CKD.

Our preclinical preliminary data indicate that achieving "normal" serum iron and hemoglobin (Hb) by oral iron supplementation in juvenile mice with CKD may have adverse effects on their growth, bone health, and kidney function. Conversely, low iron diet was well tolerated in juvenile experimental CKD and improved uremia *without compromising linear growth*. These data call into question the conventional goals of iron therapy in pediatric CKD, and highlight the urgent need for clinical trials examining iron therapy in children with CKD.

**Study outline**

This pilot study will compare the effects of a 3-month course of oral iron sulfate, 3-6 mg/kg/day, vs. no iron therapy, in children with CKD stages 2-4, anemia and functional iron deficiency as defined by the 2012 KDIGO guidelines[10] (endorsed by KDOQI[9]). Forty children with predialysis CKD, mild anemia, low TSAT and serum ferritin, not treated with ESAs or iron for the past 3 months will be enrolled. Children will be randomized and evaluated at study entry, in 6 weeks and at the conclusion of the study in 12 weeks.

**Study hypothesis:** while 3 months of iron therapy will normalize TSAT and improve hemoglobin, children in both iron therapy and no iron therapy groups will have comparable nutritional status, quality of life, muscle strength, and parameters of growth hormone-IGF1 axis. We also postulate that iron therapy will increase serum hepcidin. Thus, this study is expected to provide a preliminary evidence that current TSAT and serum ferritin thresholds for iron therapy initiation can be safely lowered in children with CKD. This pilot study will set a stage for future well-powered clinical trials to test the effects of iron therapy for CKD-anemia on disease progression, statural growth, executive function, and neurocognitive development in children with CKD.

**Study objectives:**

**1.** Determine the effects of oral iron therapy on iron status (transferrin saturation, serum ferritin, serum iron, TIBC, serum hepcidin), hemoglobin and other erythroid parameters, systemic inflammation, and oxidative stress in children with CKD-anemia, as well as changes in growth hormone-IGF1 axis. Attaining this objective will allow us to generate data about the efficacy of oral iron therapy in children with anemia of CKD. This is particularly important because hepcidin suppresses iron absorption and enhances iron sequestration, and therefore the efficacy of oral iron therapy has been questioned in pediatric CKD.

**2.** Establish short-term effects of oral iron therapy, in comparison with no iron therapy, on muscle strength, quality of life, and eating behavior in children with mild anemia of CKD. Comprehensive clinical and laboratory evaluation will be conducted at enrollment and at the conclusion of the study. The tolerance of oral iron will be evaluated via a standardized questionnaire. Adherence to iron therapy will be supported by monitoring pharmacy refill rates and assessed by self-recall. Comparisons will be made within (study entry vs. study exit) and between the groups.

**Clinical equipoise and scientific premise**

Anemia is one of the most common and significant complications of CKD in children, associated with poor quality of life, increased morbidity and mortality[13]. In many ESA-naïve children with pre-dialysis CKD iron appears to be unavailable for erythropoiesis even when iron stores are adequate[14]. Elevated serum hepcidin has been recently identified as a major cause of iron sequestration in CKD[15,16].

The clinical approach to the correction of iron imbalance in CKD has been similar to that in children with iron deficiency anemia. However, iron-deficiency anemia and anemia of CKD have different pathophysiology, because the former is associated with low, while the latter with high hepcidin. Recent advances in our understanding of iron metabolism in CKD call into question the traditional approach to iron therapy in children

with CKD. Iron deficiency anemia in children without CKD is associated with fatigue, decreased exercise capacity[17], poor and distorted appetite[18], and impaired growth and neurocognitive development[19], among other symptoms. Many if not all of these symptoms can be also seen in children with CKD, with or without anemia. One of the conventional goals of iron therapy is alleviation of the above symptoms. However, it has not been tested whether functional iron deficiency (defined as TSAT<20%[9]) is indeed associated with these symptoms in children with CKD, independent of kidney function. Furthermore, the efficacy of recommended iron therapy regimen in children with CKD on the parameters of iron status has not been established. Finally, it is not known whether iron therapy or its withholding would have any effects on clinically relevant and patient-centered outcomes, such as appetite / eating behavior, fatigue and physical activity, muscle strength, and quality of life.

It is also assumed that the benefits of correcting iron status and anemia overweigh the potential side effects that may arise from pro-oxidative and pro-inflammatory actions of iron. This is especially alarming because a number of studies have demonstrated that dietary iron restriction and iron chelation significantly delayed progression of experimental CKD[20-24].

**Risk/benefit assessment.** While oral iron supplementation is currently part of clinical practice guidelines for children meeting the inclusion criteria for this trial, the evidence supporting these recommendations is very weak (category D)[9,10]. Specifically, the current recommendations on when to begin iron therapy in children with CKD, what doses of oral iron to use, and for how long, are all based solely on expert opinions not supported by studies. Conversely, there are published studies demonstrating benefits of iron restriction in chronic kidney disease[20-24]. In an animal model of juvenile CKD, we have observed deterioration of kidney function in mice treated with oral iron to correct anemia[25]. The purpose of this pilot trial is to demonstrate that short-term iron withholding will not be associated with negative outcomes in children with the initial stages of anemia, which are asymptomatic. Because we do not expect any detectable symptomatology related to iron supplementation or iron restriction in this pilot trial, we will be using special methodologies to detect early changes in muscle strength, physical activity and eating behavior. The patient population that we target in this trial is not always treated with iron by the nephrologists, and these children are usually clinically monitored every 3-6 months and remain stable whether treated with iron or not. Therefore, the risk level for this pilot trial is very low.

**Table 1. Inclusion and Exclusion Criteria.**

| **Inclusion Criteria** | **Rationale** |
|---|---|
| ***Enrollment criteria*** | |
| 1-21 years old | Infants < 1 year old have different iron requirements |
| GFR < 90 ml/min/1.73 $m^2$ by bedside Schwartz formula [height (cm) *0.413 / serum creatinine (mg/dL)] | Stage I CKD (eGFR ≥ 90 ml/min/1.73$m^2$) is usually not associated with anemia of CKD |
| Hb ≥ 9.0 at the previous clinic visit | Withholding Iron / Epo therapy may not be safe in children with Hgb<9 g/dL. |
| Hb <11.5 g/dL in children <5 years<br>Hb <12.0 g/dL in children 5-12 years<br>Hb <12.5 g/dL in children12-15 yrs and females >15 yrs.<br>Hb <13.5 g/dL in males >15 years<br>(at the previous clinic visit) | These thresholds are 0.5 g/dL above the KDIGO / KDOQI definition of anemia in children with CKD |
| Participant and parent/guardian capable of providing informed consent and assent (assessed by provider) | Ethical and legal concerns |
| ***Randomization criteria*** | |
| TSAT ≤ 20% AND | Inclusion of children meeting KDIGO / KDOQI criteria for the initiation of iron therapy |
| Serum ferritin ≤ 100 ng/mL | |
| **Exclusion Criteria** | **Rationale** |
| Hb < 9 g/dL at the enrollment visit | Exclusion of children with moderate to severe anemia |
| TSAT < 5% at the enrollment visit | Exclusion of children who may have significant whole body iron deficiency |
| Serum ferritin < 10 ng/mL at the enrollment visit | |
| Iron therapy (including iron-based phosphate binders) or ESA therapy within 3 months prior to enrollment | Recent iron / ESA therapy may affect the response to study intervention |
| Blood transfusion within 4 months prior to enrollment | RBC lifespan ~120 days |
| Plans to relocate out of the area in the next 3 months | May be difficult to come for a follow up visit |
| Children on hemodialysis | IV iron may be preferred in hemodialysis patients |
| Rapidly deteriorating kidney function or expectation for transplantation or dialysis in less than 3 months | These children may not be able to complete the study |
| Unwillingness to provide informed consent | Ethical and legal concerns |
| Pregnancy and breast-feeding | Special iron requirements in pregnancy and lactation |

**Screening, Enrollment, Randomization, and Retention:**

Patients will be consented for study participation at routine visits to pediatric nephrology clinic. Study coordinators will prescreen clinic schedules and identify eligible patients with CKD fulfilling study entry criteria. Eligible families will receive information by mail and/or by phone about the study. They will be approached by pediatric nephrologists and/or research coordinators during their clinic visits, study participation offered, and informed consent obtained. Clinical and research blood samples will be collected via single venipuncture; and muscle strength measured. Enrolled families will be explained, that based on their laboratory evaluation at the current visit, the may be offered iron therapy. Should the randomization criteria be met, the family will receive a call about starting vs. withholding iron therapy. If randomization criteria are not met at a current clinic visit, same procedure will be repeated at the next clinic visit. Given small sample size, we will be using a covariate adaptive randomization to assure the balance between important covariates among study groups.

Retention in the study is always a concern in clinical trials. This pragmatic trial is designed in a way that retention is equivalent to the compliance with routine clinic visits. The proposed studies are not especially burdensome (muscle strength assessment and two short questionnaires). There will be no separate venipunctures for the study, and no separate study visits, as all study-related activities will take place at the routine clinic visits. Contact will be maintained between visits by phone calls to all subjects.

**Intervention:** Oral iron will be prescribed in the form of immediate-release iron sulfate, 3-6 mg/kg/day of elemental iron to children with body weight ≤43 kg, and 65 mg of elemental iron (325 mg of iron sulfate) per day to children with body weight >43 kg. Families will be instructed to administer iron sulfate with water or juice on an empty stomach. Subjects will be educated about food interaction with iron, including food items that decrease iron absorption: cereals, dietary fiber, tea, coffee, eggs, and milk. Subjects will be advised to consume these items as far apart from iron as possible. Medication pick- up from the pharmacy / medication delivery will be verified by phone. Families will be encouraged to use ancillary devices to help with medication adherence: pillbox, cell phone reminders, written medication administration schedule. Adherence will be enforced by phone calls.

Families will be instructed to call pediatric nephrology / study coordinators about possible side effects of iron sulfate, including constipation, darkening of stools, epigastric pain, gastrointestinal irritation, nausea, stomach cramps, vomiting, dental discoloration (for children receiving liquid preparations), diarrhea, heartburn, urine discoloration. Clinicians and / or study team will inquire about these side effects at the 6-week phone call. Formal Tolerability Questionnaire will be administered at the completion of the study. Patients whose hemoglobin falls below 7.0 g/dL at 6 weeks laboratory checkup or at any other point throughout the study period will be withdrawn from the study.

**Study measures and outcomes**

**Table 2. Study measures.**

| **Visit 1.** *Enrollment* | **Interim assessment**** *(6 wks)* | **Visit 2.** *Study exit (12 weeks)* |
|---|---|---|
| Demographics*, HGS, CEBQ, PROMIS, blood, actigraphy, BIA | Blood** | HGS, CEBQ, PROMIS, TQ, adherence, blood, actigraphy, BIA, exit survey |

HSG: handgrip strength, CEBQ: Children's Eating Behavior Questionnaire, PROMIS: Patient-Reported Outcomes Measurement Information System (Fatigue and Physical Activity short forms; child and proxy versions), TQ: Tolerability Questionnaire. BIA: bioelectrical impedance assessment. All biomarkers will be measured at visits 1 and 2.

* Including age/date of birth, sex, race, ethnicity, family history of anemia, CKD diagnosis and vintage, full anthropometrics, routine labs etc.

** Blood draw at 6 weeks will be performed for clinical indications only at the location convenient for the family. No clinic / study visit will be required.

CEBQ 'Food avoidant' sub-scales:

- Satiety responsiveness
- Slowness in eating
- Emotional under-eating
- Food fussiness

**Outcomes:**

***Aim 1.*** Primary outcome: change in *TSAT*. Fasting blood sample will be obtained and subjects will be instructed not to take iron sulfate in the morning on the day of the blood draw. The degree of sample hemolysis, if present, will be semi-quantified and recorded after serum separation. Modification of the automated AAII-25 colorimetric method is a widely accepted standard method used by clinical laboratories[26,27]. Serum iron is very stable and levels are not affected by freeze-thaw cycles.

Secondary outcomes: changes in serum ferritin, serum iron, hemoglobin, reticulocyte hemoglobin content, / reticulocyte hemoglobin equivalent, hepcidin (Intrinsic ELISA) – visit 2 will be compared to visit 1 (Table 2) within and between the study groups.

***Aim 2.*** Primary outcome: change in *muscle strength*. Digital handgrip dynamometer (Takei Digital Grip Strength Dynamometer, Creative Health Products) will be used for handgrip strength measurements. Normative grip strength charts for children are available[28]. Children will be instructed to apply as much handgrip pressure as possible using their non-dominant hand. The measurements will be repeated three times, and the highest value will be used for analyses. In addition to muscle strength, the changes in *skeletal muscle mass* and lean/fat mass ratio will be assessed using the bioelectrical impedance assessment (BIA).

Secondary outcomes: change in appetite / *eating behavior* will be assessed using the widely accepted and validated Children's Eating Behavior Questionnaire (CEBQ)[29,30]. Change in *quality of life* will be assessed in the fatigue, and physical activity domains using the NIH-recommended Patient-Reported Outcomes Measurement Information System (PROMIS) questionnaires (child and parental versions)[31,32]. Physical activity will be also objectively assessed by actigraphy before and after iron therapy; *change in sedentary time* will be one of the secondary outcomes.

**Other study variables:** Inflammation will be assessed using high sensitivity CRP, plasma IL-6 and TNF-alpha. Growth hormone, IGF1, and total FGF23 will be measured by ELISA. All biochemical studies will be performed based on the enrollment and study exit samples. Tolerability Questionnaire (TQ) will be conducted at the end of the study, and will collect information about gastrointestinal symptoms, and other side effects related to iron sulfate to evaluate iron therapy tolerance and possible side effects. Medication adherence will be assessed at Visit 2 via a 90- and a 7-day recall of missed doses. We will also conduct an open-ended exit questionnaire to assess possible dietary changes, dietary supplement use throughout the study and to illicit the participants' feedback about their experience while being in the study.

**Sample size and power**

The power analysis of equivalence was performed for the primary outcome of the 2nd objective (muscle strength). While no studies on the effect of iron therapy on muscle strength in children are available, Nakagawa et al. reported the association of increased serum ferritin with impaired muscle strength in adult hemodialysis patients[33]. Absolute handgrip strength measured in kg varied widely in this study depending on serum ferritin, within 2-3-fold range. In our proposed study, we will use the relative measure of handgrip strength, normalized for age and sex as SDS[34]. Tenbrock et al. measured handgrip SDS in children with CKD[35]. Based on the Tenbrock's et al. data, we expect standard deviation of our primary outcome (handgrip strength SDS) to be close to 1.0 in both groups, and based on the cited studies[33,35] we set our equivalence limit d at 1.0. This limit is about 40% lower than the difference observed by Tenbrock et al. in handgrip strength SDS between children with CKD and healthy children. Under these assumptions, 18 subjects per group will be required to demonstrate equivalence of iron therapy to no iron therapy with 80% power and significance level of $\alpha$=5%[36]. Importantly, no definitive answer about the effects of oral iron in children with CKD is expected from this pilot trial. Our goal is rather to determine the clinically meaningful equivalence limit / effect size of muscle strength and other outcomes of iron therapy and use these data to design a well-powered trial in the future.

**Statistical analysis**

This is a pilot clinical trial, which will test equivalence of oral iron therapy vs. no iron therapy in children with CKD and mild anemia and / or iron deficiency with regard to the outcomes of interest. The study will test the hypothesis that the effects of these two approaches are close enough so that one cannot be considered superior or inferior to the other. The two one-sided test (TOST) procedure will be used to test the equivalence of outcomes[37]. T-test will be used for within group comparisons of the effects of iron before vs. three months after the initiation of iron therapy. Assistance of PCEN Learning Health Systems Core will be used for statistical analyses.

**Anticipated results:** Upon completion of this trial, we expect to demonstrate that oral iron sulfate effectively elevates serum iron and transferrin saturation, and improves hemoglobin, while also elevating hepcidin in children with CKD. We also expect that deleterious effects of hepcidin and sequestered iron will counteract the possible benefits of improved hemoglobin, resulting in a net absence of patient-centered benefits. Of course, iron therapy is and will remain essential in a subset of children with CKD and ESRD, especially those on hemodialysis and treated with ESAs. Our proposed study, however, will help to understand whether introduction of iron therapy can be safely postponed in certain children with CKD, thus eliminating the possible negative sequelae of excess iron supplementation.

**Adverse events and subject termination/dropout.**

While adverse events will be very unlikely in this short-term trial, subjects will be closely monitored by their nephrologists and by the study team. As part of standard of care, signs and symptoms of anemia will be discussed with participating families at enrollment and randomization, and they will be instructed to call their pediatric nephrologist in case of developing fatigue, weakness, palpitations, lightheadedness, poor appetite. This will be assessed by the nephrologists and if clinically warranted a standard of care laboratory evaluation will be arranged. In addition, all patients will have their complete blood count checked 6 weeks after randomization. If children in no iron therapy group develop severe anemia (defined in this trial as hemoglobin < 7 g/dL) or require red blood cell transfusion, their study participation will be terminated and anemia management continued as deemed appropriate by the primary nephrologist. In addition, all subjects will complete an investigator-assisted Tolerability Questionnaire at the conclusion of the study, where the information about expected and unexpected side effects of iron therapy and anemia will be systematically collected. This will provide valuable information for safety monitoring in the future larger well powered trial.

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