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A Randomized Trial of Intravenous Iron Supplementation and Exercise on Exercise Capacity in Iron-Deficient Nonanemic Patients With CKD

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Introduction: Patients with chronic kidney disease (CKD) are often iron deficient, even when not anemic. This trial evaluated whether iron supplementation enhances exercise capacity of nonanemic patients with CKD who have iron-deficiency.

Methods: Prospective, multicenter double-blind randomized controlled trial of nondialysis patients with CKD and iron-deficiency but without anemia (Hemoglobin [Hb] >110 g/l). Patients were assigned 1:1 to intravenous (IV) iron therapy, or placebo. An 8-week exercise program commenced at week 4. The primary outcome was the mean between-group difference in 6-minute walk test (6MWT) at 4 weeks. Secondary outcomes included 6MWT at 12 weeks, transferrin saturation (TSAT), serum ferritin (SF), Hb, renal function, muscle strength, functional capacity, quality of life, and adverse events at baseline, 4 weeks, and at 12 weeks. Mean between-group differences were analyzed using analysis of covariance models.

Results: Among 75 randomized patients, mean (SD) age for iron therapy ($n = 37$) versus placebo ($n = 38$) was 54 (16) versus 61 (12) years; estimated glomerular filtration rate (eGFR) (34 [12] vs. 35 [11] ml/min per 1.73 m^2], TSAT (23 [12] vs. 21 [6])%; SF (57 [64] vs. 62 [33]) μg/l; Hb (122.4 [9.2] vs. 127 [13.2] g/l); 6MWT (384 [95] vs. 469 [142] meters) at baseline, respectively. No significant mean between-group difference was observed in 6MWT distance at 4 weeks. There were significant increases in SF and TSAT at 4 and 12 weeks ($P < 0.02$), and Hb at 12 weeks ($P = 0.009$). There were no between-group differences in other secondary outcomes and no adverse events attributable to iron therapy.

Conclusion: This trial did not demonstrate beneficial effects of IV iron therapy on exercise capacity at 4 weeks. A larger study is needed to confirm if IV iron is beneficial in nondialysis patients with CKD who are iron-deficient.

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Iron is central to oxygen uptake, transport, storage, and metabolism in both skeletal and cardiac muscle.[1,2] Skeletal muscle accounts for 10% to 15% of total iron body iron content, where iron is fundamental for oxygen storage in myoglobin, oxidative metabolism, and energy production by iron-containing mitochondrial enzymes.[3]

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Studies in both animals and healthy individuals[4,5] have shown that iron-deficiency results in reduced mitochondrial enzyme activity, leading to lower energy production through oxidative phosphorylation. These abnormalities are restored following iron repletion.[4,6,7] This phenomenon has been studied in patients with heart failure treated with IV iron exhibiting improved exercise capacity and patient-reported outcomes[8-10] as early as 4 weeks and lasting up to 24 weeks after treatment compared to those receiving placebo. These findings persisted up to 12 months post therapy[11] and the effects were evident without any significant change in Hb, suggesting that the effects were mediated via improvements in cardiac and/or skeletal muscle function following iron repletion.

Studies have identified skeletal muscle mitochondrial dysfunction in CKD, which may contribute to skeletal muscle dysfunction.[12-14] It has been suggested that iron-deficiency contributes to mitochondrial dysfunction and reduced energy production in cardiac and/or skeletal muscle of patients with CKD, and importantly may contribute to the reduced exercise capacity, physical function, and fatigue commonly reported in this population.[15,16] There is a dearth of studies exploring the effect of iron repletion on cardiac or skeletal muscle metabolism in nonanemic patients with CKD.[17] A recent trial in nondialysis-dependent kidney patients who were iron-deficient but not anemic reported no significant improvements in exercise capacity or patient-reported outcomes at 4 or 12 weeks following iron repletion.[18]

Exercise training for patients with CKD has been shown to be beneficial for improving exercise capacity[19]; however, the limited training responses observed in some patients remain unexplained.[20] It is possible that combining exercise training with iron therapy could target disease-related derangements in the oxygen transport chain and result in enhanced physiological adaptations to exercise in patients with CKD.[20]

In this trial, we examined whether a strategy of IV iron therapy in patients with stages 3–4 CKD who were iron-deficient (SF <100 μg/l and/or TSAT $\leq 20\%$) but *not* anemic (Hb 110–150 g/l) leads to improvements in exercise capacity, physical function, and fatigue; and explored the effects of combined exercise training and iron therapy.

Objectives

Primary Objective

To assess the effect of IV iron therapy compared to placebo on exercise capacity, measured by the distance walked during the 6MWT at 4 weeks post iron infusion.

Secondary Objectives

To assess the effect of IV iron therapy compared to placebo on exercise capacity (6MWT) at 12 weeks, iron status (ferritin, TSAT) and Hb, kidney function (urea, creatinine, and eGFR), Volume of Oxygen consumption VO_2 peak test (in a subset of participants), isokinetic dynamometry (muscle strength of knee extensors), functional capacity (sit-to-stand 60), quality of life (Kidney Disease Quality of Life 36 questionnaire, KDQOL-36), the Work and Social Adjustment Scale (WSAS), the Chalder Fatigue questionnaire, and adverse events at 4 and 12 weeks. Skeletal muscle phosphocreatine recovery half-time on magnetic resonance imaging spectroscopy ($n = 40$ patients at baseline and week 4), muscle metabolism (at baseline and at 4 weeks), the impact of iron therapy on iron regulatory genes (*HFE, TMPRSS6*), and a qualitative exploration of participant experience were assessed as part of the study but are not reported here.

METHODS

This was an investigator-led multicenter double-blind randomized placebo-controlled trial of patients with stages 3 to 4 CKD and iron-deficiency, but without anemia, aged 18 or over. The study design, flow of participants through the trial and methods have previously been reported.[21] The trial was funded by Kidney Research UK and supported by an unrestricted grant from Vifor (with donation of ferric carboxymaltose for the trial). Brent Ethics Committee approved the protocol (19/LO/0128) and the study was prospectively registered (EudraCT: 2018-000144-25 on 28/01/2019).

Adults with established nondialysis-dependent CKD stages 3 to 4 who had an SF of less than 100 μg/l and/or a TSAT of less than 20% but no anemia (defined in this study as a Hb 110–150 g/l for both males and females) were eligible to participate. Full eligibility criteria are provided in the protocol paper.[21]

Randomization, Treatment, and Follow-Up

Patients were randomized within 4 weeks after meeting screening requirements and were assigned in a 1:1 ratio using a secure web-based service supported by King's Clinical Trials Unit. Randomization used an approach based on randomly varying block sizes. Randomization was stratified by a single binary variable, defined by whether patients had a screening ferritin >50 μg/l or ≤ 50 μg/l, with planned capping so that a maximum of 35 patients had a screening ferritin >50 μg/l.

Participants were randomized to receive either 1000 mg ferric carboxymaltose (Ferinject, CSL Vifor, Switzerland) in 100 ml normal saline or 100 ml normal saline placebo only as a one-off infusion at the baseline visit. Patients were blinded to the treatment that they received, and all outcome assessments were performed by blinded research assistants who were

unaware of group allocation. All participants were offered 8 weeks of exercise training between week 4 and week 12 assessment visits.

The exercise training program has been reported previously.[21] Briefly, participants were assessed at 4 weeks and offered three 1-hour sessions of exercise training each week for 8 consecutive weeks, concentrating on large muscle groups of the lower limbs. The intervention was delivered by trained physiotherapy assistants, on an individual basis, in a hospital gym. Due to COVID-19 related restrictions on trial visits, and related patient concerns about traveling and attending hospital, some patients were offered the option of completing these sessions of exercise training at home via an online kidney-specific exercise platform, called Kidney Beam[22] https://beamfeelgood.com/onDemand/list/kidney-disease that was freely available on any technological device via the Internet. Each participant was provided with a heart rate monitor for use during the 8-week exercise training program, written guidance on how to access the platform, and exercise recording sheets.

Study Schedule

Full trial schedule has been reported previously.[21] Briefly, eligible participants were invited to attend a baseline visit, with follow-up at 4 weeks (±4 days) and 12 weeks (±14 days) after treatment. Assessments included 6MWT distance, eGFR, biochemical profile, full blood count, SF, TSAT, C-reactive protein, and urinary protein-to-creatinine ratio. Knee extensor isokinetic and isometric muscle strength was measured bilaterally using a Biodex S4 Isokinetic System Pro dynamometer (Mirion Technologies), physical function was assessed by the sit-to-stand 60 test,[23] and peak aerobic capacity (VO_2 peak) was measured in a subset of participants. Patient-reported outcome measures included the Chalder Fatigue questionnaire, the WSAS and the Kidney Disease Quality of Life Short-Form 1.3 questionnaire.

Trial End Points

The primary end point was the 6MWT distance at 4 weeks which was selected to provide clinical relevance. Studies that have evaluated the clinically meaningful change in the distance walked on the 6MWT in patients with heart failure[24,25] suggested a distance between 32 m and 45 m. Estimations from the FAIR-HF study[9] and a study in patients with CKD[26] suggested a clinically meaningful improvement in 6MWT of up to 40 m which was selected to inform the sample size of our study. The estimated sample size to detect a difference of 40 m with a SD of 56 m (derived from the higher SD reported by Tang *et al.*[26]) at 80% power and 5% alpha was 62 participants. We aimed to recruit at least 70 patients to enable dropouts and ensure that 4-week primary outcome data were collected for at least 62 patients.

Secondary endpoints included exercise capacity (6MWT) at 12 weeks; and ferritin, TSAT and Hb, urea, creatinine, eGFR, VO_2 peak test (in a subset of participants), muscle strength, sit-to-stand 60, KDQOL-36 questionnaire, the WSAS questionnaire, the Chalder Fatigue questionnaire, and adverse events at 4 and 12 weeks.

Serious adverse events were identified and documented at routine visits, based on participant reports, and primary or secondary care reports. In addition, episodes of infection requiring hospitalization and other infection episodes and cases of vascular access thrombosis were documented. Hb, SF, platelet levels, and other laboratory measurements detailed above were monitored.

Qualitative exploration of participant experience, phosphocreatine recovery half-time on magnetic resonance imaging spectroscopy, muscle metabolism, and the impact of iron therapy on iron regulatory genes (*HFE, TMPRSS6*) were measured as part of the study but are not reported here.

Statistical Analyses

A full description of the statistical analysis plan, including COVID-19 considerations, is reported elsewhere.[21] All data were analyzed in accordance with an intention-to-treat principle. For the primary outcome, the difference in means for distance walked during 6MWT (meters) at 4 weeks (primary outcome) between patients randomized to IV iron therapy and placebo were analyzed using an analysis of covariance model, using baseline 6MWT distance and the binary stratification variable SF (defined as whether baseline SF is over 50 μg/l) as covariates. The analysis of covariance were also performed for the 6MWT distance (meters) at 12 weeks, and for the other secondary end points. In each case, the baseline value of the variables and the binary stratification factor were used as covariates. All analyses were undertaken in R and Stata version 17 (IBM Corp. Released 2017, IBM SPSS Statistics for Windows, Version 25.0, Armonk, NY). We investigated whether any impact of COVID-19 break on the primary end point and 12 week's end points in a sensitivity analysis.

Data Monitoring and Quality Assurance

The trial was coordinated by a trial management group. A trial steering committee was established to oversee the conduct and progress of the trial. An independent

data monitoring committee monitored patient safety and treatment efficacy data.

RESULTS

Baseline Characteristics of Randomized Participants

The baseline characteristics of the full trial population are published elsewhere.[21] Briefly, 75 participants were randomized including 32 (43%) males. The mean (SD) age was 57 (14) years. The characteristics of the 2 groups of the trial were similar at baseline, although there was a 7-year age difference between treatment group ($n = 38$; mean [SD] age 54 [16] years) and placebo group ($n = 37$; mean [SD] age 61[12] years). There was a larger proportion of comorbidities in the treatment group, than in the placebo group. There was a larger proportion of females in the placebo group compared to the IV iron group (65% vs. 50%), and there was a difference in the mean (SD) baseline distance covered during the 6MWT (384 [195] meters in the treatment group vs. 469 [142] meters in placebo treated patients, Table 1). Overall, about half of patients (49%) were recruited before the COVID-19 break and similarly in each arm (47% and 51% in IV Iron and placebo, respectively). A CONSORT diagram is included as Supplementary Figure S1.

Primary End Point: 6MWT

At 4 weeks, the mean change from baseline in 6MWT was -4 (71) meters in 31 patients who received IV iron compared to 14 (37) meters in 31 patients who received placebo ($P = 0.261$) (Table 2).

Exercise Training

Exercise training, as per prescribed training protocol, was achieved by 16 of the 23 (70%) participants in the iron therapy group and by 16 of the 20 (80%) participants in the control group before the 12-week assessment.

Secondary Outcomes

At 12 weeks, the mean change from baseline in 6MWT was 44 (103) meters for 22 patients who received IV iron compared to 20 (45) meters for 20 patients who received placebo ($P = 0.338$) (Table 2). There was a statistically significant difference for SF and TSAT at both 4 weeks ($P < 0.001$ and $P < 0.001$, respectively) and 12 weeks ($P < 0.001$ and $P = 0.001$, respectively) from baseline, with greater increases in the treatment group (Table 3). There was no statistically significant difference in Hb at 4 weeks ($P = 0.66$); however, there was a statistically significant difference at 12 weeks ($P < 0.001$). Kidney function as assessed by serum creatinine and eGFR were similar in both study arms with no significant difference between iron therapy and placebo at 4 and 12 weeks. Proteinuria did not change with time or with IV iron treatment (Table 3). There were no significant differences in adverse events between study arms (Supplementary Table S1).

There were no significant differences between groups at 4 or 12 weeks in VO_2 peak test (in a subset of participants), muscle strength, sit-to-stand 60, KDQOL-36 questionnaire, the WSAS questionnaire, or the Chalder Fatigue questionnaire scores (Table 4) and there were no significant differences between the 2 groups at 4 or 12 weeks for muscle strength (Supplementary Table S2).

In a sensitivity analysis, there was no association between the primary end point and the before or after COVID-19 break status. In the after-break group, the 4 weeks 6MWT average was 19 m greater than in the before-break (432 m and 413 m, respectively). Two-thirds of patients completing their 12 weeks follow-up were recruited after the break. The 12 weeks 6MWT average was 88 m less in the after-break compared to the before-break (421 m and 509 m respectively); however, given the small sample size, there was no evidence of significant association ($P = 0.100$).

In exploratory analyses, when compared with baseline values, there was a greater than 25 m increase in 6MWT observed in 8 of 31 (26%) patients at 4 weeks and 10 of 22 (45%) at 12 weeks among those who received treatment compared with 7 of 31 (23% at 4 weeks) and 7 of 20 (35% at 12 weeks) among patients who received placebo, respectively. Similarly, a greater than 25 m increase in 6MWT was observed in 10 of 23 (43%) patients who received treatment versus 4 of 20 (20%) patients who received placebo between 4 and 12 weeks. A greater than 25 m increase in 6MWT was observed in 8 of 16 (50%) patients who received treatment and exercise training per protocol versus 4 of 16 (25%) patients who received placebo and exercise training per protocol between 4 and 12 weeks. Baseline characteristics for the participants included in these exploratory analyses were broadly representative of the study population as a whole, with a higher baseline 6MWT distance observed in the placebo group of 454 (160) m versus 379 (220) m in the treatment group (See Supplementary Table S3).

DISCUSSION

The Iron and Muscle Trial investigated whether a single dose of 1000 mg of IV iron (ferric carboxymaltose [Ferinject]) improves exercise capacity in comparison to placebo at 4 weeks after IV iron therapy in nonanemic patients with CKD who have iron-deficiency. Our study also explored the additional value of an 8-week exercise training regime between 4 and 12 weeks.

Table 1. Baseline demographic data; total number of available data (N_d), mean (SD) and ranges [Min, Max], number (n) or percentage (%) for all patients and for the 2 randomized groups

Variable	n	Overall $N = 75$	n	IV iron $n = 38$	n	Placebo $n = 37$
Age (yr)	75	57 (14), [23, 81]	38	54 (16), [23, 81]	37	61 (12), [29, 78]
Sex	75		38		37	
Male		32 (43%)		19 (50%)		13 (35%)
Female		43 (57%)		19 (50%)		24 (65%)
Ethnicity	75		38		37	
White		42 (56%)		20 (53%)		22 (59%)
Asian		15 (20%)		9 (24%)		6 (16%)
Black		16 (21%)		7 (18%)		9 (24%)
Mixed		1 (1.3%)		1 (2.6%)		0 (0%)
Other		1 (1.3%)		1 (2.6%)		0 (0%)
Smoker	71		35		36	
Yes: current smoker		6 (8.5%)		3 (8.6%)		3 (8.3%)
Yes: previous smoker		12 (17%)		5 (14%)		7 (19%)
Non		53 (75%)		27 (77%)		26 (72%)
Height (cm)	72	166 (11), [142, 193]	36	168 (12), [146, 193]	36	164 (10), [142, 185]
Weight (kg)	72	84 (18), [58, 151]	36	83 (20), [58, 151]	36	84 (16), [60, 129]
Waist circumference (cm)	72	105 (15), [73, 150]	36	103 (17), [73, 150]	36	107 (14), [79, 140]
Hip circumference (cm)	72	112 (13), [83, 147]	36	110 (14), [83, 147]	36	114 (11), [97, 140]
Body mass index (kg/m^2)	72	31 (7), [20, 54]	36	30 (7), [21, 54]	36	31 (6), [20, 47]
Hb (g/dl)	71	124.8 (116), [109, 157]	35	122.4 (92) [109, 141]	36	127.1 (12), [110, 157]
SF (µg/l)	69	59 (45), [11, 340]	36	57 (54), [11, 340]	33	62 (33), [18, 182]
TSAT %	70	22 (10), [3, 55]	35	23 (12), [7, 55]	35	21 (6), [3, 34]
Urea (mmol/l)	66	11.6 (5.4), [4.0, 33.0]	34	12.4 (6.3), [5.0, 33.0]	32	10.7 (4.0), [4.0, 20.0]
Serum creatinine (mg/dl)	72	1.98 (0.80), [0.96, 3.81]	36	2.07 (0.84), [0.96, 3.69]	36	1.88 (0.78), [1.03, 3.81]
eGFR (ml/min per 1.73 m^2)	72	35 (12), [15, 59]	36	34 (12), [15, 59]	36	35 (11), [16, 56]
Platelet count (×10-9/l)	71	236 (62), [117, 370]	35	240 (66), [127, 370]	36	232 (59), [117, 339]
Sodium (mmol/l)	72	139.8 (2.3), [135.0, 147.0]	36	140.0 (2.6), [135.0, 147.0]	36	139.6 (2.1), [136.0, 145.0]
Potassium (mmol/l)	72	4.6 (0.6), [3.0, 6.0]	36	4.5 (0.5), [3.0, 5.0]	36	4.7 (0.6), [4.0, 6.0]
ALT (IU/l)	69	20 (10), [5, 65]	34	20 (9), [6, 43]	35	20 (11), [5, 65]
AST (IU/l)	47	22.2 (6.9), [10.0, 48.0]	22	22.0 (6.5), [10.0, 41.0]	25	22.4 (7.4), [11.0, 48.0]
ALP (IU/l)	71	86 (31), [12, 175]	35	86 (33), [12, 175]	36	87 (30), [44, 170]
Albumin (g/l)	73	42.9 (2.9), [34.0, 48.0]	36	42.7 (3.0), [37.0, 48.0]	37	43.0 (2.7), [34.0, 48.0]
CRP (mg/l)	68	4.4 (4.3), [1.0, 23.0]	33	4.9 (4.3), [1.0, 23.0]	35	3.9 (4.2), [1.0, 20.0]
Phosphate mmol/l)	67	1.15 (0.20), [0.80, 1.70]	33	1.16 (0.21), [0.80, 1.70]	34	1.14 (0.20), [0.90, 1.70]
Total bilirubin (µmol/l)	70	7.3 (3.8), [1.0, 20.0]	35	7.4 (4.4), [3.0, 20.0]	35	7.2 (3.2) [1.0, 15.0]
6MWT (meters)	71	427 (174), [8, 738]	35	384 (195), [8, 660]	36	469 (142), [20, 738]
KDQOL-36						
SF-12 Physical Health Composite	72	40 (12), [16, 62]	37	40 (13), [17, 62]	35	40 (12), [16, 60]
SF-12 Mental Health Composite	72	43 (12), [20, 62]	37	44 (13), [20, 62]	35	42 (10), [20, 61]
Burden of kidney disease	73	65 (29), [0, 100]	37	68 (26), [12, 100]	36	62 (32), [0, 100]
Symptoms/problems	73	72 (21), [2, 100]	37	70 (19), [23, 100]	36	74 (23), [2, 100]
Effects of kidney disease	72	78 (22), [0, 100]	36	78 (18), [22, 100]	36	78 (25), [0, 100]
WSAS	73	15 (11) [0, 40]	37	15 (11) [0, 33]	36	15 (12) [0, 40]
Chalder Fatigue questionnaire	73	17.2 (5.7), [9.0, 32.0]	37	16.8 (5.2), [9.0, 30.0]	36	17.7 (6.2), [10.0, 32.0]
STS60	70	24 (8), [4, 49]	35	23 (8) [4, 39]	35	25 (9) [10, 49]
VO_2 peak (l/min)	45	1.36 (0.48), [0.66, 2.93]	19	1.39 (0.54), [0.66, 2.93]	26	1.34 (0.44), [0.71, 2.25]
VO_2 peak (ml/kg/min)	45	16.6 (5.6), [8.0, 33.0]	19	17.2 (5.8), [9.0, 33.0]	26	16.2 (5.5), [8.0, 33.0]
Peak heart rate (bpm)	54	128 (24), [71, 171]	22	128 (27), [71, 171]	32	128 (23), [85, 171]
Peak systolic blood pressure (mm Hg)	54	167 (26), [112, 216]	23	171 (28) [113, 210]	31	164 (24) [112, 216]
Peak diastolic blood pressure (mm Hg)	55	95 (22), [61, 165]	24	96 (23), [64, 161]	31	95 (22), [61, 165]
VO_2 peak test total duration achieved (min)	55	8.76 (2.80), [3.00, 15.00]	23	8.62 (3.12), [3.00, 15.00]	32	8.87 (2.60), [4.00, 15.00]
VO_2 peak test total duration achieved (sec)	54	23 (14), [0, 53]	23	20 (15), [0, 49]	31	24 (13), [2, 53]
VO_2 peak test peak power output (watts)	55	110 (41), [0, 210]	23	107 (44), [0, 210]	32	113 (38), [45, 210]
Maximal rating of perceived exertion on CR100 scale	55	87 (19), [35, 100]	23	85 (21), [35, 100]	32	88 (17), [40, 100]
VE/VCO_2 slope (ml/kg/min)	49	33.5 (5.5), [25.8, 48.7]	21	34.0 (6.5), [26.7, 48.7]	28	33.1 (4.8), [25.8, 47.0]
Systolic blood pressure (mm Hg)	72	134 (16), [105, 175]	36	133 (16) [105, 167]	36	135 (16), [108, 175]
Diastolic blood pressure (mm Hg)	72	78 (10), [54, 98]	36	79 (9), [62, 98]	36	78 (10), [54, 98]

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Table 1. (Continued) Baseline demographic data; total number of available data (N_d), mean (SD) and ranges [Min, Max], number (n) or percentage (%) for all patients and for the 2 randomized groups

Variable	n	Overall $N = 75$	n	IV iron $n = 38$	n	Placebo $n = 37$
Heart rate (bpm)	72	76 (13), [49, 115]	36	77 (14), [49, 115]	36	75 (12), [55, 101]
Comorbidities	74		37		37	
Myocardial infarction		2 (2.7%)		2 (5.4%)		0 (0%)
Ischemic heart disease		5 (6.8%)		3 (8.1%)		2 (5.4%)
Stroke/TIA		1 (1.4%)		1 (2.7%)		0 (0%)
Heart failure		0 (0%)		0 (0%)		0 (0%)
Peripheral vascular disease		2 (2.7%)		1 (2.7%)		1 (2.7%)
Atrial fibrillation		0 (0%)		0 (0%)		0 (0%)
Hypertension		50 (68%)		24 (65%)		26 (70%)
Diabetes						
Type I		0 (0%)		0 (0%)		0 (0%)
Type II		22 (30%)		12 (32%)		10 (27%)
No		52 (70%)		25 (68%)		27 (73%)
Cancer (excluding skin cancers)		4 (5.4%)		2 (5.4%)		2 (5.4%)
Hyperlipidemia		26 (35%)		13 (35%)		13 (35%)

ALT, alanine transaminase; ALP, alkaline phosphatase; ASP, aspartate aminotransferase; BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; KDQOL36 SF1.3, Kidney Disease Quality of Life 36 questionnaire; SBP, systolic blood pressure; SF, serum ferritin; STS60, sit-to-stand 60; TSAT, transferrin saturation; VO_2peak, volume of oxygen consumption; WSAS, Work and Social Adjustment scale; 6MWT, 6-minute walk test.

Our results revealed no significant change in the primary end point, 6MWT distance at 4 weeks, when compared with baseline, between participants treated with IV iron therapy and placebo. There were also no significant between-group differences in measures of muscle strength, physical function, aerobic capacity, fatigue, work and social adjustment, or health-related quality of life.

Our findings are comparable with those reported in the Iron and Heart Trial,[18] which did not reveal any significant change in 6MWT distance at 4 weeks post iron infusion in patients with CKD, and only a modest but nonsignificant improvement in summary component score in Quality of Life Short Form 36 scores when compared with placebo. Our findings contrast with findings from studies of patients with heart failure,[8-10] which demonstrated improvements in exercise capacity after iron therapy when compared with placebo. Like the Iron and Heart Trial,[18] our trial had a small sample size, a short follow-up period, and there was a relatively well-preserved 6MWT distance at baseline in both groups. Higher baseline values may have limited the margin for improvement that was achieved in studies of patients with heart failure where the baseline values were more than 100 meters less. Comorbidities may have impacted the walk distance at baseline, and subsequently impacted the follow-up result. In addition, it is plausible that the dose of iron, and the frequency at which it was administered, may have been insufficient to improve cellular energetics.

Our results revealed a numerical (42 m), although nonsignificant, mean improvement in 6MWT distance between 4 and 12 weeks in patients who received IV

Table 2. Summary of 6 MWT at baseline, 4 weeks, 12 weeks, change in 6 MWT from baseline to 4 weeks, from baseline to 12 weeks and change from 4 weeks to 12 weeks

			IV iron			Placebo	
Variable	n[a]	Mean (SD)	Median (IQR)	n[a]	Mean (SD)	Median (IQR)	*P*-value
From baseline to 4 wks							
Baseline	31	385 (202)	475 (304, 528)	31	454 (140)	480 (365, 542)	
4 wks	31	381 (220)	426 (265, 541)	31	468 (146)	480 (388, 572)	
Change	31	−4 (71)	3 (−32, 26)	31	14 (37)	10 (−4, 25)	0.261
From baseline to 12 wks							
Baseline	22	388 (207)	498 (293, 532)	20	438 (149)	461 (360, 545)	
12 wks	22	432 (226)	468 (338, 596)	20	458 (167)	458 (375, 586)	
Change	22	44 (103)	18 (2, 62)	20	20 (45)	10 (−6, 41)	0.338
From 4 wks–12 wks							
4 wks	23	396 (223)	428 (295, 565)	20	458 (157)	479 (392, 571)	
12 wks	23	438 (223)	477 (339, 590)	20	458 (167)	458 (375, 586)	
Change	23	42 (107)	17 (−10, 50)	20	0 (42)	−2 (−11, 17)	0.165

ANCOVA, analysis of covariance; IQR, interquartile range; IV, intravenous.
[a]Number of patients with complete data at baseline and at a time point (4 weeks or 12 weeks) or with complete data at 4 weeks and 12 weeks ± *P*-value for the treatment effect using ANCOVA analysis where the baseline and the binary stratification variable ferritin (defined as whether baseline ferritin is over 50 μg/l) are used as covariates.

Table 3. Summary of iron status measurements assessed by serum ferritin and transferrin saturation, hemoglobin, of renal function as assessed by urea (mmol/l), serum creatinine (μmol/l) and eGFR (ml/min per 1.73 m^2)

		IV iron		Placebo		
Variable		Mean (SD)	n[a]	Mean (SD)	n[a]	*P*-value[b]
Serum ferritin (μg/l)	Baseline	57 (54)	35	62 (33)	36	
	4 wks	372 (213)	31	60 (27)	31	<0.0001
	12 wks	256 (153)	23	78 (53)	20	<0.0001
TSAT (%)	Baseline	23 (12)	35	21 (6)	35	
	4 wks	34 (12)	29	22 (8)	31	<0.0001
	12 wks	32 (12)	24	22 (8)	17	0.019
Hb (g/dl)	Baseline	122.4 (92)	35	127.1 (132)	36	
	4 wks	122.9 (160)	30	128.0 (135)	31	0.667
	12 wks	130.5 (94)	23	125.4 (148)	21	0.009
Urea (mmol/l)	Baseline	12.4 (6.3)	34	10.7 (4.0)	32	
	4 wks	11.5 (5.7)	26	11.3 (5.6)	28	0.639
	12 wks	10.8 (4.4)	23	10.4 (4.6)	17	0.823
Serum creatinine (mg/dl)	Baseline	2.07(0.84)	36	1.88 (0.78)	36	
	4 wks	2.22 (0.92)	30	1.99 (0.84)	32	0.597
	12 wks	2.06 (0.85)	24	2.07 (0.96)	21	0.011
eGFR (ml/min per 1.73 m^2)	Baseline	34 (12)	36	35 (11)	36	
	4 wks	32 (13)	30	33 (11)	32	0.300
	12 wks	36 (14)	24	33 (12)	21	0.085

ANCOVA, analysis of covariance; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; IV, intravenous; TSAT, transferrin saturation.
[a]Number of patients with complete data at each time point; baseline, 1 month and 3 months.
[b]*P*-value for the treatment effect using ANCOVA analysis where the baseline and the binary stratification variable ferritin (defined as whether baseline ferritin is over 50 μg/l) are used as covariates.

iron therapy in addition to an exercise program. Indeed, despite the inclusion of prescribed exercise training between 4 and 12 weeks, which was achieved by a similar number of participants in both groups ($n = 16$), there was a small decline in the numerical mean 6MWT distance achieved in the placebo group. The numerical improvement in mean 6MWT distance reported in patients who received IV iron, accompanied by a mean numerical nonsignificant improvement in sit-to stand physical function score, could be due to a combination of the iron therapy and additional exercise training that was introduced to all study participants at 4 weeks. Exploratory analyses revealed a larger proportion (50%) of participants who were exposed to iron therapy plus exercise training per protocol exceeding the clinically relevant improvement of 25 m distance in the 6MWT distance, versus the placebo group plus exercise training per protocol (25%). Combining exercise training with iron therapy may target the disease-related derangements in the oxygen transport chain and result in more pronounced physiological adaptations to exercise in those participants exposed to the combined intervention.[20] The study was however not designed to investigate this mechanism of action. The sample size is too small, and it is acknowledged that the exploratory analysis no longer benefits from randomization and may therefore be subject to substantial confounding. It is difficult to rule out the phenomenon of regression to the mean, given the substantial difference in baseline 6 minute walked distance between the placebo and iron treated groups. The differences may be attributable to the impact of exercise comparing one population with a greater degree of mobility impairment to another. This potential complementary intervention to promote physical function and exercise capacity is nonetheless interesting and hypothesis generating for future studies.

Our study did not reveal between-group differences in fatigue or WSAS, with both groups improving the mean scores of these patients' reported outcomes. The impact on emotional wellbeing from being a part of research studies, regardless of treatment allocation, has been reported in other studies.[27] The impact of iron therapy on these important patient-reported outcomes may be explored further in larger studies with longer participant follow-up.

The Kidney Disease Improving Global Outcomes clinical practice guidelines recommends the use of iron therapy in patients with CKD with an SF of <500 μg/l or a TSAT ≤30% if it is desired to increase Hb or to reduce erythropoiesis stimulating agent therapy.[28] In our trial, there were significant differences in Hb concentrations between arms at 12 weeks, with patients receiving IV iron therapy demonstrating a significant mean improvement. There are few safety data available regarding effects of increasing Hb concentrations in patients with CKD who are nonanemic but iron-deficient, with clinicians often displaying

Table 4. Summary of VO_2 peak test (in a subset of participants), STS60, KDQOL-36 questionnaire, the WSAS questionnaire, and the Chalder Fatigue questionnaire scores at baseline, 4 and 12 weeks

		IV Iron		Placebo		
Variable		Mean (SD)	n[a]	Mean (SD)	n[a]	*P*-value[b]
VO_2 peak test (l/min)	Baseline	1.39 (0.54)	19	1.34 (0.44)	26	
	4 wks	1.15 (0.46)	16	1.36 (0.47)	21	0.049
	12 wks	1.27 (0.51)	16	1.38 (0.52)	15	0.507
VO_2 peak (ml/kg/min)	Baseline	17.2 (5.8)	19	16.2 (5.5)	26	
	4 wks	14.4 (6.5)	16	16.8 (5.5)	21	0.058
	12 wks	16.3 (7.3)	16	15.9 (4.7)	15	0.340
Chalder Fatigue scale	Baseline	16.8 (5.2)	37	17.7 (6.2)	36	
	4 wks	13 (5)	33	14 (7)	34	0.790
	12 wks	13 (6)	28	14 (6)	28	0.774
Work and Social Adjustment scale	Baseline	15 (11)	37	15 (12)	36	
	4 wks	12 (10)	33	12 (11)	34	0.878
	12 wks	10 (10)	28	11 (12)	28	0.210
Sit-to-stand 60 test (reps)	Baseline	23 (8)	35	25 (9)	35	
	4 wks	24 (7)	31	27 (10)	28	0.209
	12 wks	25 (7)	24	25 (9)	20	0.990
KDQOL-36 SF1.3						
Physical health	Baseline	40 (13)	37	40 (12)	35	
	4 wks	42 (12)	31	41 (12)	34	0.520
	12 wks	41 (13)	27	40 (13)	27	0.820
Mental health	Baseline	44 (13)	37	42 (10)	35	
	4 wks	47 (10)	31	47 (9)	34	0.474
	12 wks	45 (10)	27	48 (11)	27	0.055
Burden kidney disease	Baseline	68 (26)	37	62 (32)	36	
	4 wks	75 (19)	33	63 (29)	34	0.617
	12 wks	73 (23)	28	64 (32)	28	0.866
Symptoms/problems	Baseline	70 (19)	37	74 (23)	36	
	4 wks	78 (18)	33	76 (22)	34	0.632
	12 wks	77 (16)	28	76 (22)	28	0.871
Effects kidney disease	Baseline	78 (18)	36	78 (25)	36	
	4 wks	81 (17)	33	78 (24)	34	0.663
	12 wks	81 (19)	28	79 (25)	28	0.601

ANCOVA, analysis of covariance; KDQOL, Kidney Disease Quality of Life; VO_2, volume of oxygen consumption; WSAS, Work and Social Adjustment scale.
[a]Number of patients with complete data at each time point; baseline, 1 month and 3 months.
[b]*P*-value for the treatment effect using ANCOVA analysis where the baseline and the binary stratification variable ferritin (defined as whether baseline ferritin is over 50 μg/l) are used as covariates.

concern about treating patients with symptoms of iron deficiency if Hb is within the normal range. In our trial, in keeping with the Iron and Heart Trial,[18] patients assigned to treatment with IV iron were no more likely to experience an adverse event than those receiving placebo treatment. This trial was not designed to examine safety events; however, it does provide early data about safe clinical use of iron therapy in patients with CKD with iron deficiency without anemia.

The strengths of the Iron and Muscle Trial include the representative patient sample from all ethnicities, when compared with previous studies,[29] the double-blinded nature of the trial, and the novel inclusion of exercise training as a potential complementary intervention to iron therapy.

The limitations include the small sample size, which is likely to have contributed to the baseline imbalance of the 6MWT; and short follow-up period. The single dose of 1000 mg of ferric carboxymaltose iron therapy may require further investigation because recent studies, such as the NIMO study,[30] suggest it may not be a sufficient dose to achieve complete iron repletion and thus alter cellular energetics.

Conclusions

This randomized controlled trial showed that, among nonanemic patients with CKD, iron-deficiency, and a relatively well preserved 6MWT distance at baseline, IV iron therapy did not impact on exercise and functional capacity, quality of life, or patient-reported outcomes. Higher baseline physical performance scores in the control arm might have impacted these outcomes. Adequately powered studies, with sufficient participant follow-up, are warranted to investigate functional improvement in nonanemic patients with iron-deficiency and CKD who are treated with IV iron.

DISCLOSURE

SB is a Trustee for Kidney Research UK. All other authors have declared no conflicting interests.

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Data Availability

Findings from the study will be disseminated at national and international conferences. All baseline data generated or analyzed during this study are included in this published article.

Ethics Approval and Consent to Participate

The protocol and related documents were approved by Brent Research Ethics Committee, UK (REC) 19/LO/0128, the Health Research Authority and the UK Medicines and Healthcare products Regulatory Agency (MHRA). The study was prospectively registered on 28/01/2019 (EudraCT 2018-000144-25). All methods were carried out in accordance with relevant guidelines and regulations. Informed consent was obtained from all subjects and/or their legal guardian(s).

AUTHOR CONTRIBUTIONS

Authorship followed ICMJE guidelines. SG, DO, NB, FR, EW, TW, AS, and ICM were responsible for the inception and design of the project and prepared the manuscript. SG, NB, EA, JC, KM, DO, AM, SB, JB, ICM, PK, CR, PS, DB, DW, CL, LB, BO, KB, FR, SA, TM, AM, AG contributed to the design of the study, provided methodological input, and wrote the manuscript text and prepared tables. All authors reviewed the manuscript.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Trial consort diagram.

Table S1. Summary of adverse events.

Table S2. Summary of Isokinetic dynamometry (muscle strength, for both left and right leg) at baseline, 1 month, and 3 months.

Table S3. Baseline characteristics, mean (SD), number (n) or percentage (%) for patients who choose to exercise by treatment arm.

CONSORT 2010 checklist of information to include when reporting a randomized trial.

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