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ORGINAL RESEARCH ARTICLE

Effect of creatine monohydrate on motor function in children with facioscapulohumeral muscular dystrophy: A multicenter, randomized, double-blind placebo-controlled crossover trial

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Abstract

Background: Facioscapulohumeral muscular dystrophy (FSHD) is a rare, progressive muscle disease with no available disease-modifying therapy. Creatine monohydrate (CrM) has been shown to improve muscle strength in individuals with muscular dystrophies but has not been tested in young people with FSHD. This study aimed to explore the efficacy of CrM on motor function in children with FSHD.

Methods: In a randomized placebo-controlled double-blind crossover trial, powdered CrM at a dose of 100 mg/kg/day (maximum 10 g daily) was compared with placebo in two 12-week treatment periods with a 6-week washout between crossover arms. The primary outcome measure was the Motor Function Measure for Neuromuscular Disease (MFM-32) with secondary outcomes assessing safety, endurance, strength, patient-reported outcome measures, and muscle morphology measurements as assessed by whole-body magnetic resonance imaging (MRI).

Results: Thirteen children were enrolled (mean (standard deviation, SD) 12.2 (2.67) years of age) and 11 patients completed both trial treatment periods. In an intention-to-treat analysis, no clinically meaningful difference was seen between treatment groups as measured by the mean difference in MFM-32 (0.19, 95% confidence interval (CI) −0.71 to 1.08). However, there was an improvement in 6-minute walk distance of 27.74 m (95% CI −1.41 to 56.88) and trends to improvement in the FSHD-Composite Outcome Measure for Pediatrics (FSHD-COM Peds), 10 meter walk/run, and in MRI measures. There were no serious adverse events. Serum creatinine increased by a mean 12.63 µmol/L (95% CI 1.14 to 24.12) post-CrM treatment, though this was presumed to reflect increased creatinine production. No participants discontinued CrM due to adverse events.

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Conclusion: CrM is safe and well tolerated in children with FSHD. Although CrM had no effect on motor function as measured by the MFM-32 compared with placebo, there were trends toward improvement in the 6-minute walk distance and other secondary outcome measures. This study confirms the feasibility of conducting clinical trials in children with FSHD. Further assessment of the efficacy of CrM in pediatric FSHD is warranted in a larger randomized controlled clinical trial. Future studies may benefit from stratifying population cohorts according to functional ability or by MRI fat infiltration measurements.

KEYWORDS
creatine monohydrate, FSHD, neuromuscular, pediatrics

1 | INTRODUCTION

Facioscapulohumeral muscular dystrophy (FSHD) is an autosomal dominant progressive muscle disease with a prevalence of up to 1 in 8000 people.[1] The published literature reports a prevalence of 1 in 140,000 in young people[2] but this is likely an underestimate as up to 55% of individuals with FSHD have symptoms onset prior to 18 years of age, with a mean delay from symptom onset to diagnosis of 13 years.[3] Muscle involvement in FSHD generally progresses in a cephalocaudal pattern with the classic symptom of facial weakness, particularly affecting eye closure, smile, and facial pout as the earliest sign in many.[4] Individuals with pediatric onset FSHD have an increased likelihood of requiring a wheeled mobility aid (44% compared to 22% of classical onset FSHD) and a high incidence of restrictive lung disease.[5] There is currently no disease-modifying therapy available for FSHD. Pediatric onset FSHD is internationally recognized as a research area of unmet need and further potential therapeutic agents need to be discovered and trialed.[6,7]

Creatine (α-methylguanidinoacetic acid) is an endogenously produced guanidino compound synthesized in the liver and kidneys and involved in adenosine triphosphate (ATP) formation and thus cellular energy production.[8–11] Synthetically produced compounds creatine monophosphate and creatine monohydrate have been studied as potential therapeutic agents in neuromuscular disease for almost three decades.[12] Although the exact mechanism is unknown, it is postulated that creatine monohydrate (CrM) supplementation might improve muscle function in patients with neuromuscular disorders, either through direct effects on muscle force, by the effect on energy metabolism, or by a reduction in apoptosis through intracellular calcium effects, or by preventing oxidative stress.[13] In healthy controls, creatine monohydrate supplementation increases muscle force output by appr~10%.[14] When compared to control participants, people with neuromuscular disorders have lower skeletal muscle total creatine and phosphorylcreatine concentrations.[15] Supplementation with creatine can increase the levels of phosphorylcreatine and, in so doing, increase ATP synthesis.[16] This suggests that patients with neuromuscular disease may benefit more than healthy individuals from creatine supplementation. There is preclinical mouse data to support the use of creatine in the FSHD population.[17] Creatine supplementation given in conjunction with exercise increased quadriceps weight, mitochondrial content, and improved grip strength in FRG1-transgenic mice, a mouse model with similar muscular dysfunction to that seen in patients with FSHD.[17] A systematic review of randomized controlled trials demonstrated that CrM is well tolerated and can improve strength and functional performance in young people with muscular dystrophy.[15] However, CrM supplementation is not routinely recommended as part of standard of care practice in most regions. This study aimed to explore the efficacy of creatine monohydrate on motor function in children with FSHD.

2 | METHODS

2.1 | Trial design

This was a randomized double-blind placebo-controlled crossover trial. Two 12-week treatment periods were separated by a 6-week washout, with participants crossing over to receive the alternative treatment after completion of the first period. The serum half-life of creatine monohydrate is 20–172 min in humans, but the rate of clearance from the muscle by conversion to creatinine is not known. Extrapolation of murine data estimates creatine clearance in human muscle to be ~0.24 L/h/kg.[8] As such, a 6-week washout was considered adequate to ensure exogenous creatine was fully cleared from both serum and skeletal muscle stores.[18]

2.2 | Participants

Children with FSHD were recruited from Australian and New Zealand neuromuscular clinic databases. The trial was performed at two Australian children's hospitals: the Royal Children's Hospital, Melbourne, Victoria, and Queensland Children's Hospital, Brisbane, Queensland. Participants were recruited between December 2017 and January 2020, with the final participant trial visit in May 2021

(with a delay due to a prolonged washout phase related to the COVID-19 pandemic travel restrictions).

Individuals aged between 5 and 18 years inclusive with a confirmed genetic diagnosis of FSHD type 1 or 2 or those with clinical signs in keeping with FSHD (facial or upper limb weakness or scapular winging) and a genetically diagnosed first-degree relative were eligible for inclusion. Potential participants were excluded from the trial if at screening they had a plasma creatinine level above the upper limit of normal of the local laboratory reference range for age and sex, unexplained persistent hypertension, a prior diagnosis of acute or chronic renal failure, had a known hypersensitivity to creatine monohydrate or maltodextrin placebo, were already taking any medications to increase muscle bulk or strength including the use of regular sodium valproate, corticosteroids, or beta agonists such as salbutamol, or those with dairy intolerance or allergy precluding the ability to take the creatine supplement as described in the protocol.

2.3 | Study protocol

Eligible participants who consented were randomized to a treatment group and then dispensed CrM or placebo by the unblinded study dietitian using the statistician-derived random assignment protocol. Participants assigned to treatment group 1 received CrM for 12 weeks and then placebo, and participants assigned to treatment group 2 received placebo and then CrM. Enrolled participants underwent trial assessments, including safety bloodwork and functional assessments at screening and baseline visits, performed at least 1 week apart. Safety and efficacy outcome measures were recorded by the study investigators and clinical evaluators pre and post each 3-month treatment period. The lead trial clinical evaluator, blinded to treatment assignment, was a senior research physiotherapist at the Royal Children's Hospital, Melbourne.

2.4 | Randomization and investigational product dispensing

A randomization schedule was created by the Murdoch Children's Research Institute Clinical Epidemiology and Biostatistics Unit (CEBU) using a random number generator. The group allocation was provided by CEBU via a locked data file to the unblinded sub-investigator at Monash University, Department of Nutrition, Dietetics and Food, who dispensed the treatment according to the random assignment to the participant. The randomization list was only available to the independent statistician and dietitian who had no contact with participants.

2.5 | Treatment intervention

For each treatment period, participants were dispensed 90 sachets of either CrM or maltodextrin placebo. The prescribed dose for participants was stratified into weight bands based on a daily dose of around 100 mg/kg/day (participants weighing 15–25 kg received 2.5 g daily, 26–45 kg received 5 g daily, 46–75 kg received 7.5 g daily, and >76 kg received 10 g daily). Each sachet also contained 5 g of Splenda sucrose-based sweetener to mask any discrepancy in the flavors. The sachets were made up and dispensed by an unblinded dietitian based off-site in a commercial kitchen (Monash University, Melbourne). Apart from the unblinded sub-investigator and independent statistician, all other investigators and participants were blinded to treatment allocation. The participants were instructed to dissolve the powder in 250 mL of skimmed milk. Milk was selected as the preferred vehicle over water or juice as a drink typically accepted by children with additional benefits of protein and calcium. The resulting drink was ingested every morning for the duration of the trial period. There was no dose modification for the duration of the trial. Adherence to study intervention was estimated by counting returned unused sachets. No advice was provided to participants to alter their dietary intake or their daily level of activity.

2.6 | Outcome measures

2.6.1 | Primary outcome measure

The primary outcome measure was the change in Motor Function Measure for Neuromuscular Disease (MFM-32) score from baseline to 12 weeks in each treatment phase. The MFM-32 is a standardized assessment tool validated in neuromuscular disease, including in FSHD.[19] It contains 32 items scored on a 4-point scale assessing functional ability in axial, proximal, and distal muscles. A higher score in the MFM-32 is indicative of better function.[20–22]

2.6.2 | Secondary outcome measures

The FSHD-Composite Outcome Measure for Pediatrics (FSHD-COM Peds) is a newly developed FSHD-composite measure recently validated in children which includes 18 items scored on a 5- to 7-point scale (depending on the item) assessing the function of the upper limb, lower limb, trunk, and hand and functional balance. A higher score on the FSHD-COM Peds represents increasing disease severity.[23,24]

The FSHD-Health Index (FSH-HI) is a patient-reported outcome measure developed for adults with FSHD[25] and modified to suit a pediatric cohort for this trial (FSHD-HI Peds). It has not yet been validated for use in children with FSHD, but in the absence of any other disease-specific pediatric patient-reported outcome measure, it was included as a secondary outcome measure[26]

Other secondary outcome measures included Performance of the Upper Limb (PUL2.0),[27] 6-Minute Walk Test (6MWT),[28] 10 Meter Walk/Run (10 mW/R),[29] FSHD Clinical Severity Scale (FSHD-CSS),[30] FSHD Clinical Score (FSHD-CS),[31] and patient-reported outcomes: PedsQL Neuromuscular Module[32] and ACTIVLIM.[33]

2.6.3 | Magnetic Resonance Imaging (MRI)

Muscle MRI is a potential biomarker for disease staging in FSHD, and it may help in stratifying subgroups for detailed analysis and participant selection for clinical trials.[34] Previous research has indicated that certain muscles are more frequently involved than others, allowing for focused MRI analysis of specific muscles.[35,36] The muscles selected for analysis in this trial were the serratus anterior, trapezius, and pectoralis major in the upper body and the adductors, gluteus maximus, and semimembranosus in the lower body.[37]

Participants underwent whole-body MRI at 3T (Siemens Tim Trio/Prisma Fit; Siemens, Erlangen, Germany) using a flexible body matrix coil (16-channel coil). The MRI data were reviewed by a pediatric radiologist with expertise in musculoskeletal MRI (NV) and analyzed using the semi-quantitative visual modified Mercuri score for fat replacement on T1 Dixon[36,38,39] and using the scoring suggested by Borsato and modified by Kim for muscle edema as assessed on STIR MRI images.[40] The baseline data and MRI protocol have been previously published.[41]

2.7 | Safety monitoring

All participants underwent a clinical history and physical examinations at each research visit to assess for adverse events. Participants also had safety blood tests taken to check full blood count, renal, and liver function. Renal function or injury was additionally monitored by estimated glomerular filtration rate (eGFR) and urine protein: creatinine ratio. The GFR was estimated using the modified Schwartz formula (36.5 × height in centimeters)/serum creatinine level.

2.8 | Statistical analysis

2.8.1 | Sample size calculation

The primary outcome measure (MFM-32) does not have a widely accepted published and verified minimal clinically important difference (MCID) or standard deviation to allow an accurate power calculation. However, a single study of a heterogeneous group of patients with different types of neuromuscular disease found the annual mean change in MFM-32 score in 17 patients with FSHD to be 1.5 with a standard deviation of 3.4.[21] An estimation is that 20 participants would provide 80% power for an effect size of 0.9 of a standard deviation, which would be a change in the MFM-32 score of 3 or more with the planned intervention.

2.8.2 | Data analysis of the primary and secondary outcomes

It was necessary to make the dual assumptions that there was no period effect and no treatment-period interaction. The prolonged washout phase in the protocol ensures no carryover effect from the previous treatment group. Comparisons between the treatment groups were made using mixed-effects models applied to the change in the MFM-32 score from baseline during the two periods, with a fixed effect for treatment and period and using a random effect to allow for the multiple observations within an individual to take the crossover design into account.[42] This allowed for an intention-to-treat analysis to include data from all participants even if they did not complete both crossover treatment periods.

The full Statistical Analysis Plan (SAP) is included as Appendix S1.

2.9 | Ethics Committee approval

National Ethics Committee approval was obtained from the Royal Children's Hospital Human Research Ethics Committee (HREC 36298). The trial was carried out following Good Clinical Practice (GCP) guidelines and monitored by the Royal Children's Hospital Research Governance Office.

2.10 | Clinical trial registration

The trial was registered on clinicaltrials.gov (NCT02948244) prior to recruiting any participants (first submission date 26 October 2016).

3 | RESULTS

Eighteen children with FSHD aged 6–17 years were approached to participate in the trial. One participant failed screening due to the presence of elevated urinary protein: creatinine ratio but was able to be re-screened following nephrology review with confirmation of normal urine protein excretion. Thirteen participants were randomized (Figure 1). Baseline demographics are shown in Table 1. Twelve participants were ambulant at the baseline assessment, defined as being able to walk more than 100 m on the 6MWT, and one participant was wheelchair-dependent. Two participants completed treatment period 1 but then withdrew from the trial prior to starting treatment period 2 due to concerns about the infection risk of coming to the hospital during the COVID-19 global pandemic. One participant sustained an injury from a fall during the washout period and was subsequently non-ambulant for the second period of the trial. One participant from New Zealand was unable to return to the site in Melbourne, Australia for assessments during treatment period 2 due to pandemic-associated travel restrictions. These assessments were performed locally by a trained physiotherapist and observed online by the lead clinical evaluator.

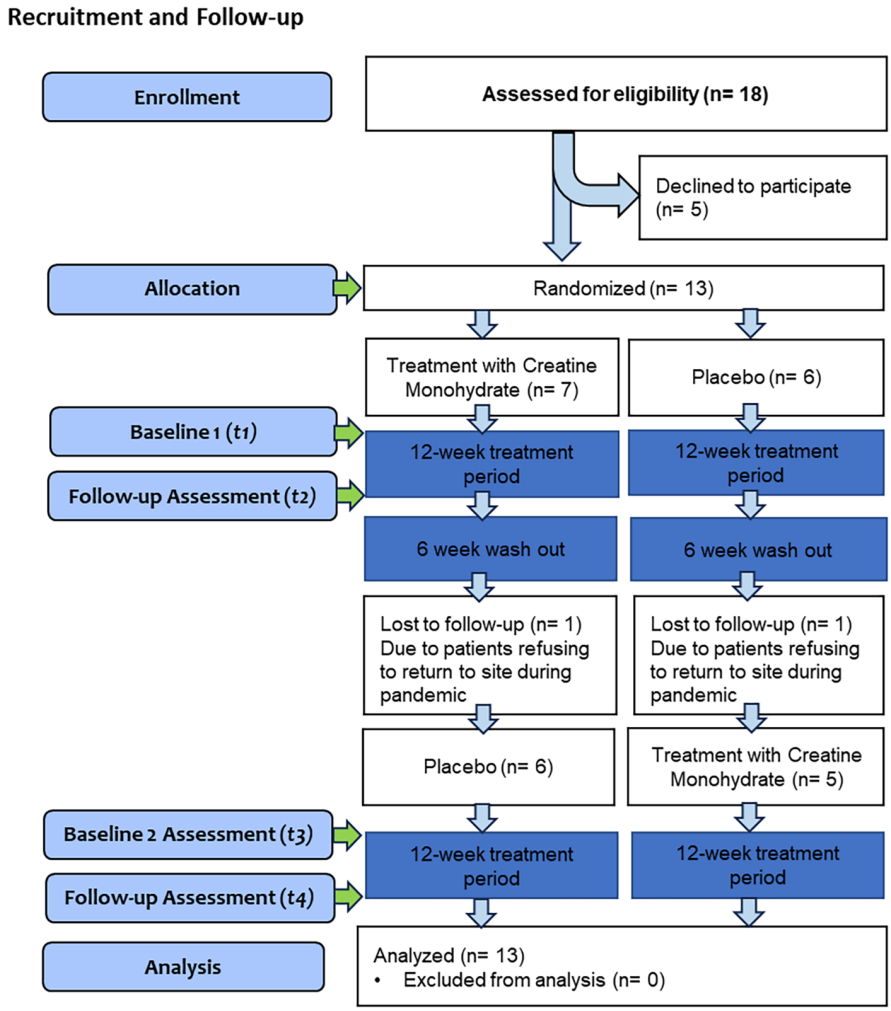

FIGURE 1 Creatine monohydrate in FSHD clinical trial CONSORT trial schema.

3.1 | Primary outcome measure analysis

The mean difference in the Motor Function Measure for Neuromuscular Disease (MFM-32) between baseline and week 12 was 0.25 points (95% CI −0.14 to 0.64) on creatine and 0.06 points (95% CI −1.24 to 1.24) on placebo. The mean difference between the treatments was 0.19 points (95% CI −0.71 to 1.08) (Table 2).

3.2 | Secondary outcome measure analysis

The mean difference in the FSHD-Composite Outcome Measure for Pediatrics (FSHD-COM Peds) between treatment and placebo at week 12 compared to baseline was an improvement in the score of −2.06 points (95% CI −4.82 to 0.71). Participants on creatine walked a mean additional 27.74 m on the 6MWT (95% CI −1.41 to 56.88). Similarly, the mean difference in the time taken to walk or run 10 m when on creatine supplementation decreased by 0.21 s (95% CI −0.45 to 0.02). Other secondary outcome measures are summarized in Table 2 and in Figures 2 and 3.

3.3 | MRI analysis

Analysis of the three domain scores found no change in mean difference between creatine and placebo (Table 2). Mean difference for fat replacement was −0.25 (95% CI −2.24 to 1.73), muscle atrophy −1.81 (95% CI −4.87 to 1.26), and edema −0.32 (95% CI −4.29 to 3.64).

3.4 | Safety analysis

There were no reported serious adverse events (SAEs) assessed by investigators to be related to CRM, but one participant became functionally non-ambulant during the trial period. This participant suffered a traumatic ankle soft tissue sprain following a fall during the washout phase and was unable to participate in the walking assessments for the second treatment period, including the final assessment 12 weeks later. The only reported adverse events (AEs) were alterations in serum creatinine level, leading to changes in the calculated 'eGFR', though these were consistent with changes in endogenous creatinine production, and all blood

TABLE 1 Participant baseline demographics.

Demographic	Cohort receiving CrM followed by placebo [mean, (range) or *n* (%)]	Cohort receiving placebo followed by CrM [mean, (range) or *n* (%)]	Total [mean, (range) or *n* (%)]
Number of participants	7	6	13
Age at screening (years)	12.7 (8–15)	11.5 (7–15)	12.2 (7–15)
Female Sex	3 (43%)	3 (50%)	6 (46%)
Genetic Diagnosis at screening[a]	6 (86%)	4 (67%)	10 (77%)
D4Z4 Contraction (size kb)[a]	13 (10–19)	19 (13–23)	16 (10–23)
D4Z4 Repeats (number)[a]	2 (2–4)	4 (2–5)	3 (2–5)
Independently Ambulant (Over 50 m)	6 (86%)	6 (100%)	12 (92%)
Wheelchair dependent	1 (14%)	0	1 (8%)
Positive Beevor sign	5 (71%)	3 (50%)	8 (62%)
Functional outcomes baseline data			
MFM-32	82 (51–96)	94 (90–96)	87 (51–96)
PUL2.0	31 (21–42)	39 (31–42)	35 (21–42)
PUL (Shoulder Module)	4 (0–12)	10 (6–12)	7 (0–12)
FSHD-CSS (age corrected)	379 (154–600)	202 (143–286)	297 (143–600)
FSHD-CS	6.7 (2–13)	2.8 (2–4)	5 (2–13)
FSHD-COM Peds	38.3 (13–72)	17.8 (5–26)	29 (5–72)
6MWT, m ($n=12$)[b]	($n=6$) 432 (264–697)	581 (422–787)	543 (264–787)
10 m Walk/Run, s ($n=12$)[b]	4.04 (2.93–10.83)	2.96 (2.40–3.25)	3.83 (2.40–10.83)
ACTIVLIM	46 (26–56)	52 (48–54)	49 (26–56)
PedsQL – Parent	69 (40–93)	80 (64–90)	74 (40–93)
PedsQL – Participant	65 (46–90)	75 (38–91)	69 (38–91)
FSHD-Health Index (FSHD-HI Peds)	19.1 (0.2–49.3)	6.2 (0.8–12.3)	13 (0.2–49.3)
MRI	***n*=6**	***n*=5**	***n*=11**
Fat Replacement score[c]	42 (22–78)	27 (24–44)	42 (22–78)
Atrophy score[c]	42 (22–80)	27 (22–44)	42 (22–80)
Oedema score[c]	25 (23–39)	26 (24–40)	30 (23–40)

Abbreviations: MFM, Motor Function Measure for Neuromuscular Disease; FSHD-COM Peds, FSHD-Composite Outcome Measure for Pediatrics; FSHD-CS, FSHD Clinical Score; FSHD-CSS, FSHD Clinical Severity Scale; PUL, Performance of the Upper Limb; 6MWT, Six-Minute Walk Test; PedsQL, Pediatric Quality of Life Measure.

[a]Those without a genetic diagnosis had a first-degree relative with a genetic diagnosis and clinical features consistent with a diagnosis of FSHD in the opinion of the investigators.

[b]One participant was wheelchair-dependent.

[c]Two participants seen in Queensland were not able to have MRI scans due to no availability of scanner at the site.

chemistry parameters returned to normal after ceasing creatine. Specifically, there was an increase in serum creatinine (mean difference 12.63 µmol/L, 95% CI 1.14 to 24.12) and decrease in eGFR (−25.79 mL/min/1.73 m^2, 95% CI −44.3 to −7.25) in individuals on creatine supplementation compared to placebo. The mean increase in serum creatinine after supplementation with CrM was 18 µmol/L (range −1 to 55) with mean decrease in calculated eGFR after supplementation of 33.9 mL/min/1.73 m^2. Two participants did not have blood testing while on creatine (one protocol deviation and one was lost to follow-up). No participants discontinued treatment due to AEs.

4 | DISCUSSION

This randomized crossover placebo-controlled trial of creatine monohydrate in children with FSHD did not show a difference in functional ability between treatment groups as measured by the primary outcome measure, the MFM-32. This trial finished under-recruited and thus under-powered, limiting the ability to detect a definitive treatment effect of creatine. CrM was found to be safe and well tolerated. Our study was too small to draw definitive conclusions regarding the secondary outcome measures; the FSHD-COM Peds and 10 MW/R suggested a possible functional

TABLE 2 Results of efficacy outcome measures.

	Mean change – treatment	Mean change – placebo		
Outcome	**Change in score (95% CI)**	**Change in score (95% CI)**	**Mean difference**	**95% Confidence interval**
MFM-32	0.25 (−0.14 to 0.64)	0.06 (−1.24 to 1.24)	0.19	−0.71 to 1.08
FSHD-COM Peds	−0.67 (−1.89 to 0.55)	1.42 (−1.35 to 4.19)	−2.06	−4.82 to 0.71
FSHD-CS	−0.5 (−1.14 to 0.14)	−0.42 (−0.99 to 0.16)	−0.04	−0.76 to 0.69
FSHD-CSS	0.13 (−0.21 to 0.46)	0 (−0.14 to 0.14)	0.10	−0.21 to 0.41
FSHD-CSS (Age-adjusted)	32.5 (−52.3 to 117.3)	−8.0 (−30.0 to 13.9)	35.9	−38.1 to 109.9
PUL	−0.33 (−0.83 to 0.16)	−0.25 (−0.80 to 0.30)	−0.03	−0.41 to 0.36
6MWT (meters)	12.5 (−7.9 to 32.9)	−15.4 (−40.7 to 9.9)	27.7	−1.4 to 56.9
10 m Walk/Run (seconds)	−0.09 (−0.27 to 0.10)	0.12 (−0.09 to 0.32)	−0.21	−0.45 to 0.02
Global Rating of Change	−0.33 (−1.12 to 0.45)	−0.36 (−1.12 to 0.39)	0.10	−0.88 to 1.07
MRI Fat Replacement	0.45 (−1.50 to 2.41)	0.8 (−0.58 to 2.18)	−0.25	−2.24 to 1.73
MRI Atrophy	1.36 (−0.68 to 3.41)	3.2 (0.38 to 6.02)	−1.81	−4.87 to 1.26
MRI Edema	−0.45 (−3.08 to 2.17)	−0.1 (−3.79 to 3.59)	−0.32	−4.29 to 3.64
ACTIVLIM	−4.67 (−14.72 to 5.39)	1.58 (−9.71 to 12.88)	−5.62	−19.01 to 7.83
FSHD-Health Index (FSHD-HI Peds)	−0.51 (−4.84 to 3.81)	−1.83 (−11.5 to 7.80)	1.28	−8.37 to 10.93
PedsQL Parent	−2 (−8 to 4)	−2 (−6 to 2)	−2	−5 to 0
PedsQL Participant	1 (−6 to 8)	−2 (−8 to 4)	3	−5 to 11

Abbreviations: 6MWT, Six-Minute Walk Test; FSHD-COM Peds, FSHD-Composite Outcome Measure for Pediatrics; FSHD-CS, FSHD Clinical Score; FSHD-CSS, FSHD Clinical Severity Scale; MFM, Motor Function Measure for Neuromuscular Disease; PedsQL, Pediatric Quality of Life Measure; PUL, Performance of the Upper Limb.

benefit with creatine supplementation, albeit with a large confidence interval in a small sample. Additionally, participants on creatine walked a mean 27.74 m further on the 6MWT (95% CI −1.41 to 56.88) suggesting a beneficial impact on functional mobility and endurance. For boys with Duchenne muscular dystrophy (DMD), the MCID in the 6MWT ranged from 14 to 30.5 m.[43,44] There is no published MCID for the 6MWT in FSHD, although the minimal detectable change within the 95% CI (MDC95) for adults with FSHD was 34.5 m.[28] Although recognizing the difference in these populations to the one studied in this trial, the 6MWT results are considered potentially important. A trial with a larger, more homogenous sample is required to determine if there is a true positive effect of creatine in FSHD.

Similar favorable trends with creatine supplementation have been seen in children with DMD as well as in adults with muscular dystrophy and other myopathies.[15,45,46] The largest of those trials in DMD included 50 boys randomized into three arms to receive creatine, glutamine, or placebo and reported "strong, consistent, non-statistically significant trends" with creatine supplementation.[47] Another study of 12 adults with FSHD among a mixed group of 32 participants with a myopathy, showed a 3% increase in strength as measured by Muscle Research Council (MRC) grades on creatine compared to a slight decline in strength on placebo.[46,48] In our study, the choice of primary outcome measure likely influenced the inconclusive trial results. A 2.06-point change in the FSHD-COM Peds compared with the 0.19-point change in the MFM-32 suggests that the MFM-32 as the primary outcome measure lacked sensitivity. At the time of trial design, the MFM-32 was chosen as the primary outcome measure as other pediatric FSHD measures were yet to be validated. The MFM-32 demonstrated a ceiling effect and lack of sensitivity to detect change in mildly affected participants in this study, in line with natural history data from our center.[49] The FSHD-COM Peds, an emerging outcome measure[24] currently being refined in large international natural history studies, may be a more appropriate primary outcome measure in future pediatric FSHD clinical trials. In this study, it showed sensitivity to change, even in those mildly affected, and was also used to evaluate function in non-ambulant individuals, although its validity in the latter population has not been determined. The 6MWT and 10 mW/R measure mobility, endurance, and lower limb function, and both were included as secondary outcomes.

MRI remains a potential biomarker in FSHD. A previous study showed that semi-quantitative changes as measured by the Mercuri scale of fat replacement on MRI correlate with disease-specific clinical staging scales and outcome measures[41] There is also growing evidence that MRI measures are responsive to change over time in FSHD,[50–52] and these studies are ongoing. MRI has been used as a secondary outcome measure in the phase 2b ReDUX4 trial (NCT04003974) of losmapimod and the phase 1/2 FORTITUDE trial (NCT05747924) in adults with FSHD.

Creatine monohydrate appears to be safe when taken in a dose up to 100 mg/kg/day in children with FSHD. There were no SAEs and

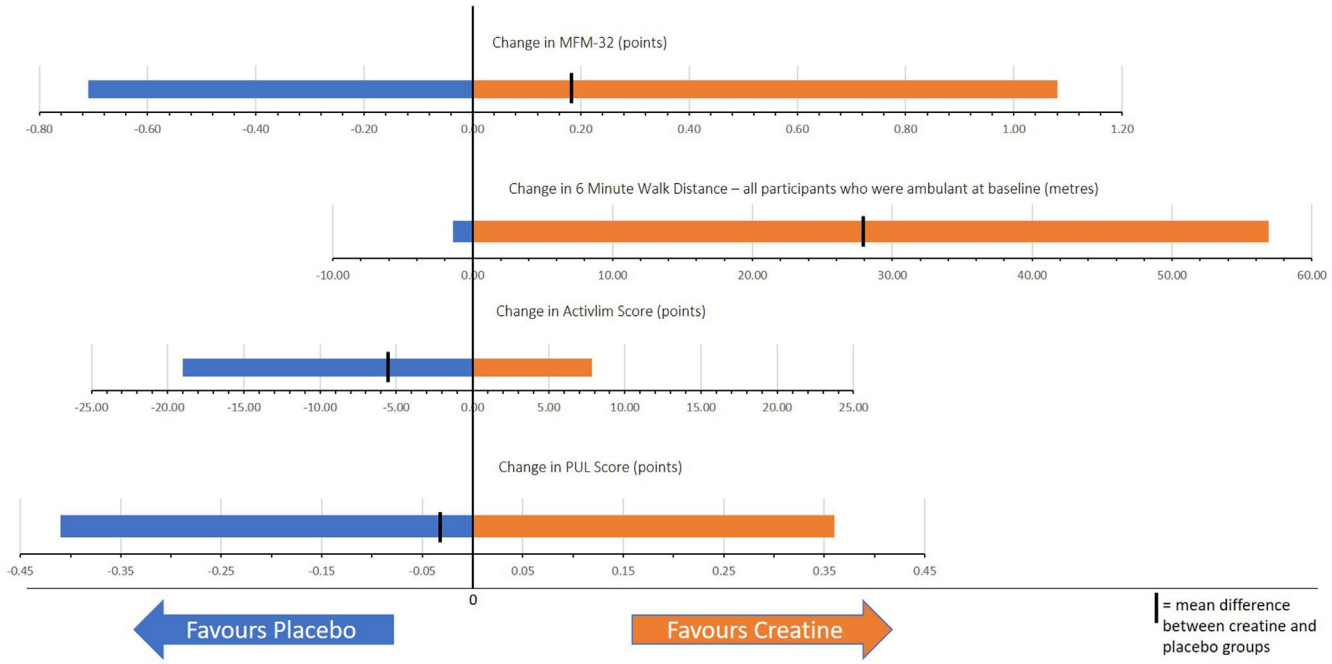

FIGURE 2 95% Confidence intervals of mean difference of creatine monohydrate versus placebo in outcome measures where an increase in score equates to less disease severity. 6MWT, Six-Minute Walk Test; MFM, Motor Function Measure for Neuromuscular Disease; PUL, Performance of the Upper Limb.

no study discontinuations due to AEs. One participant was injured in a fall during their trial washout period and, although they were subsequently non-ambulant for the second period of the trial, they remained in the study, completing all non-ambulation-related assessments. An increase in serum creatinine was seen, as has previously been reported in the setting of creatine supplementation.[45,53] However, this would be due to increased creatinine production rather than decreased clearance, leading to a reduction in the calculated value of "estimated GFR" though not in reality reflecting a change in glomerular filtration rate or kidney function.[9,54,55] Of note, serum creatinine is used as a surrogate for kidney function purely based on its disposition properties, with a (typically) stable production rate followed by renal excretion through glomerular filtration. At the same time, creatinine is a chemical waste product of creatine phosphate metabolism that has been shown to increase with creatine supplementation. This 'false-positive' elevation would be magnified in our population given the pathologically low muscle mass with a resulting low creatinine production rate in children with FSHD – not accounted for in the Schwartz formula – leading to a quantitatively greater impact on the calculated eGFR with any change in serum creatinine.[53] Therefore, if nephrotoxicity needs to be assessed in an individual using supplementary creatine, a serum biomarker unaffected by increased production of creatinine such as cystatin C would be a superior method to monitor renal function.[56–60] This was a limitation in our study design that should be corrected for in future clinical trials of individuals with myopathies or other conditions where creatinine is likely to be an unreliable biomarker of renal function.

There are several limitations to this trial, including the small sample size and lack of well validated sensitive outcome measures. FSHD is a heterogeneous disease with large variability in age at presentation, disease symptoms, severity, and rate of progression. The trial was designed to be as inclusive as possible (including both ambulant and non-ambulant participants along with participants with marked variability in muscle weakness), resulting in the two groups not being well matched at baseline. Recruitment was more challenging than expected, partly due to the lack of a national patient registry at the time affecting patient ascertainment, and a quarter of potential participants declining to take part in the clinical trial. The COVID-19 pandemic affected participant retention, with interstate and international participants unable to travel to and fearful of attending trial sites for assessments. Unfortunately, pharmacokinetic studies and creatine excretion studies were not performed during this clinical trial. This is a flaw that would have helped the understanding of creatine metabolism and clearance in this population and would have clarified if the washout period was long enough to prevent a carryover effect.

This is the first randomized controlled trial evaluating CrM in children with FSHD, and findings from this study can be used to inform future trial design. Given the heterogeneity of individuals with FSHD, as represented in this trial, a crossover trial was an appropriate design to allow each participant to be their own control.[61] However, attention to participant selection, stratifying population cohorts according to functional ability or disease stage based on clinical or MRI measures, and use of validated, sensitive disease outcome measures are important. The rarity of the disease means that multicenter collaborations and the use of patient registries to maximize participant ascertainment are essential to reach adequately powered sample sizes. Currently, there are no reliable

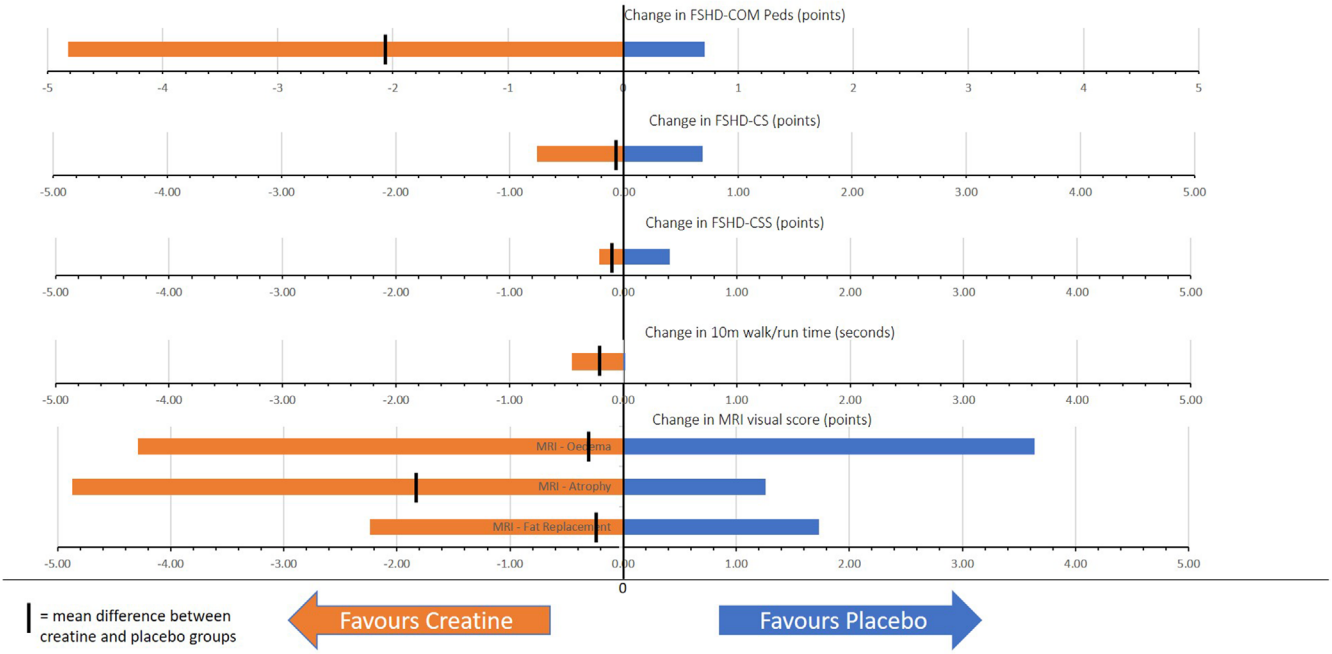

FIGURE 3 95% Confidence intervals of mean difference of creatine monohydrate versus placebo in outcome measures where a decrease in score equates to less disease severity. FSHD-COM Peds, FSHD-Composite Outcome Measure for Pediatrics; FSHD-CS, FSHD Clinical Score; FSHD-CSS, FSHD Clinical Severity Scale.

predictors of disease progression or loss of ambulation, and no biomarkers of disease stage or severity for FSHD. Further natural history studies in pediatric FSHD may be able to answer some of these questions.

Although the benefits of CrM supplementation remain unproven in children with FSHD, exercise with creatine supplementation increased quadriceps weight, mitochondrial content, and improved grip strength in a mouse model with similar muscular dysfunction to that seen in patients with FSHD.[17] This synergistic effect of creatine with exercise training has also been shown to improve functional and lean tissue mass in individuals at risk of functional disability.[62] Future trials assessing the efficacy of CrM in FSHD should evaluate exercise with creatine to establish if this provides additional benefit.

5 | CONCLUSION

This placebo-controlled crossover trial of CrM supplementation in children with FSHD shows that creatine is a generally safe and well tolerated treatment that may improve functional ability in ambulant young people with FSHD. Although there was no effect of CrM on motor function as measured by the MFM-32 compared to placebo, this study demonstrates the safety and feasibility of conducting a clinical trial evaluating CrM in children with FSHD. Considerations for future studies include careful selection of outcome measures, stratification of cohorts according to functional ability or disease stage, ensuring adequate sample size and power, and including targeted exercise programs in comparator arms. The findings from this study justify a larger randomized controlled clinical trial assessing creatine supplementation in children with FSHD.

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CONFLICT OF INTEREST STATEMENT

Dr. Woodcock has received honoraria for work performed, including educational activities and attendance at advisory board meetings from pharmaceutical companies Avidity, Biogen, Novartis, Roche, and Solid Biosciences. Dr. Woodcock has received grants for research work from FSHD Global Research Foundation, FSHD Society, Fulcrum Therapeutics, and the NIH. Dr. Woodcock has been the principal investigator on a number of industry-sponsored clinical trials, including Biogen, Catabasis, Dyne Therapeutics, EryDel, Novartis, Percheron Therapeutics, Pfizer, PTC, Roche, and Sarepta. None of these disclosures affected the work Dr. Woodcock performed on this clinical trial. Dr. Ryan has since left the above affiliations to take up public office. Dr. Davidson has received research grant funding from Pfizer. Dr. Yiu has received advisory board honoraria from Biogen and Roche, and has received research support from Biogen, Roche, Pfizer, and PTC therapeutics unrelated to the content of this manuscript. Dr. Yiu has been

the principal investigator on a number of industry-sponsored clinical trials. None of these disclosures affected the work Dr. Yiu performed on this clinical trial. Prof. Delatycki has received grant awards from NHMRC and is the principal investigator in industry-sponsored clinical trials including trials sponsored by Rearta and PTC. All other authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

All relevant data are included in the article or its Appendices S1 and S2 files.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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