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SYSTEMATIC REVIEW

Neuromuscular Electrical Stimulation in Chronic Kidney Failure: A Systematic Review and Meta-analysis

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Abstract

Objective: To systematically review the effects of neuromuscular electrical stimulation (NMES) in patients with chronic kidney failure (CKF) on hemodialysis (HD) on lower and upper limb muscle strength, functional capacity, and quality of life.

Data Sources: Data were obtained from MEDLINE (via PubMed), Embase, Scielo, Cochrane Central Register of Controlled Trials, and Physiotherapy Evidence Database. There were no mandatory language or publication date restrictions.

Study Selection: Clinical trials that assessed the chronic effect of NMES (alone or associated with other physical therapy) on lower limb muscle strength or functional capacity of CKF patients on HD compared with control, placebo, or another intervention were selected.

Data Extraction: Two independent reviewers extracted data using a predesigned data extraction form. Risk of bias was assessed with RoB 2.0 and ROBINS-I, and quality of evidence was assessed with Grading of Recommendations Assessment, Development, and Evaluation.

Data Synthesis: Ten studies were included, totaling 242 patients. Randomized clinical trials showed some concerns or high risk of bias, and the nonrandomized ones showed moderate or critical risk of bias. Random-effects meta-analysis showed that NMES increases quadriceps muscle strength (standardized mean difference=1.46; 95% confidence interval [CI], 0.86-2.07; P<.0001 moderate quality of evidence), upper limb strength (mean difference [MD]=10.02kgF; 95% CI, 0.78-19.27; P=.03 low quality of evidence), and functional capacity (MD=30.11m; 95% CI, 15.57-44.65; P<.0001 moderate quality of evidence). It was impossible to quantitatively analyze quality of life data; however, NMES associated or not with exercise appears to have positive effects on them.

Conclusions: NMES improves quadriceps muscle strength and the functional capacity of patients with CFK on HD. The effects on upper limb muscle strength and quality of life seem to be positive; however, the quality of evidence is very limited for these outcomes.

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Chronic kidney disease (CKD) consists of renal damage and progressive and irreversible loss of kidney function (glomerular, tubular, endocrine).[1] This is a worldwide problem, with an estimated prevalence of 8%-16%, which incurs high costs for the health system.[2,3] It is believed that these numbers will increase disproportionately in the coming years, especially in developing countries.[3]

Renal replacement therapy is indispensable in the more advanced stages of the disease as in chronic kidney failure (CKF), but even on dialysis, this patient presents high levels of uremic toxins.[4] This, over time and associated with loss of renal endocrine function causes systemic damage in different organs and tissues.[5,6]

There is a significant reduction of physical activities among patients with CKF, and this is associated with high morbidity and mortality, impairment of quality of life, depression, and reduction of physical capacity and muscle strength.[7] To the detriment of physical capacity, therapeutic resources such as conventional exercise,[7,8] inspiratory muscle training,[9] and neuromuscular electrical stimulation (NMES)[10] can mitigate the losses and improve the functionality of these patients.

The NMES involves the application of a series of intermittent and superficial stimuli to skeletal muscles to generate visible contractions by activating nerve branches,[11] and it has positive effects mainly on the muscle architecture and strength and on

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the functional capacity of patients with weaknesses and incapacities.[12] Therefore, NMES may be an alternative for patients who do not fit into conventional exercise-based rehabilitation programs or for those who are not motivated to perform the voluntary exercise. There is extensive evidence of the benefits of NMES in different populations[13-15]; however, few studies have used this therapy in patients with CKF,[10,16] and these trials differ in some points.

Dobsak et al[16] evaluated the effect of NMES in patients with CKF and showed an improvement in functional capacity. On the other hand, Schardong et al,[10] after the application of this therapy in the same population, observed an increase in the muscle strength of the lower limbs but no gains for the functional capacity. Thus, the efficacy of NMES has not been clearly demonstrated for these patients.

Considering that there is uncertainty regarding NMES efficacy in some outcomes and in the best intervention parameters and protocols, our objective was to systematically review the effects of this therapy in patients with CKF on hemodialysis (HD). A systematic review of current evidence may provide additional information and increase the accuracy of effect estimates to help health care professionals customize the treatment of patients with CFK.

Therefore, the research question for this systematic review was does NMES improve muscle strength, functional capacity, and quality of life of CKF patients?

Methods

This systematic review was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions[17] and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis.[18] It was registered in the Prospective Register of Systematic Reviews under number CRD42017076958.

Study selection

We included randomized clinical trials (RCTs), nonrandomized controlled clinical trials, and before-and-after studies that assessed the effects of NEMS (alone or in combination with another therapy) on lower limb muscle strength or functional capacity of patients with CKF on HD (for at least 3 mo). Secondary outcomes were upper limb muscle strength and quality of life. The strength of lower limb muscles should have been assessed by dynamometry, maximal repetition test, or sit-and-stand test (SST). Functional capacity could have been assessed by the 6-minute walk test (6MWT) or ergospirometry. Muscle strength of the upper limb was assessed by manual dynamometry and quality of life using the Kidney Disease Quality of Life—Short Form or EuroQol questionnaires. Regarding the comparison group for the case of randomized and nonrandomized clinical trials, this could be the control group, placebo group, or another physical therapy when there was no control group.

We excluded studies performed with children or animals, trials in which the muscles stimulated did not belong to the lower limb, those who used another electrical current than NMES, or those in which the treatment time was <1 month.

All identified citations were entered into a software for reference management, and duplicates were excluded. The titles and abstracts of all articles identified by the search strategy were evaluated by 2 researchers (J.S. and C.S.) separately and independently. Studies that did not meet eligibility criteria according to titles or abstracts were excluded. All abstracts that did not provide sufficient information concerning the inclusion and exclusion criteria were selected for evaluation of the full text. Disagreements regarding study eligibility were discussed between the 2 reviewers, and if there was no consensus a third reviewer was requested (R.P.).

List of Abbreviations:

CKD	**chronic kidney disease**
CKF	**chronic kidney failure**
HD	**hemodialysis**
MD	**mean difference**
NMES	**neuromuscular electrical stimulation**
RCT	**randomized clinical trial**
6MWT	**6-minute walk test**
SST	**sit-and-stand test**

Data sources and searches

We searched MEDLINE (via PubMed), Embase, Scielo, Cochrane Central Register of Controlled Trials, and Physiotherapy Evidence Database to retrieve potentially relevant articles from inception to January 27, 2019. In addition, the references included in the published articles identified were used as an additional source to identify other studies. Search terms included "renal insufficiency, chronic," "kidney failure, chronic," "electric stimulation," and "electric stimulation therapy." Keywords related to outcomes of interest and type of publication were not included to enhance the sensitivity of the search. No language or publication date restrictions were imposed. The tailored search terms and the complete search strategies are available in supplemental table S1 (available online only at http://www.archives-pmr.org/).

Data extraction and quality assessment

After reading and selecting the full texts, the same reviewers (JS and CS) independently extracted data from included studies using a predesigned data extraction form. Data extracted included study characteristics and outcomes of interest.

Regarding methodological quality, again, 2 reviewers (JS and CS) independently assessed the risk of bias of the included studies. The tool of Cochrane Group RoB 2.0[19] for RCTs and the ROBINS-I tool[20] to evaluate nonrandomized clinical trials were used. If there were disagreements a third reviewer (RP) was requested. The overall quality of evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation system.[21]

Data synthesis and analysis

Wherever possible, data were pooled using a meta-analytic approach. After data extraction, pooled-effect estimates were obtained by comparing the change from baseline to study end for each group. A random-effects model, with DerSimonian and Laird's variance estimator was used, and the results were presented as mean difference and standard mean difference, with 95% confidence intervals. A P value $\leq .05$ was considered significant. Statistical heterogeneity among studies was assessed using I^2 statistic. To reduce the statistical heterogeneity, a sensitivity analysis was performed considering the type of evaluation. All meta-analyses were performed using the R statistical software version 3.5, with meta package version 4.8-1. Studies not included in the meta-analysis were described.

Results

Description of studies

The electronic search strategy identified a total of 967 studies. Four additional studies were found through other sources. A total of 10 studies met the inclusion criteria for this systematic review, gathering data from 242 patients. Eight studies were included at meta-analysis because 2 studies did not have a comparison group (before-and-after studies). Unlike the muscle strength of lower limbs and upper limbs and functional capacity, it was not possible to perform meta-analysis for quality of life outcome because the 4 studies that evaluate this variable used different questionnaires, and 1 study was the before and after type. Figure 1 shows a flow diagram of study selection.

In 7 studies[10,16,22-26] the stimulation frequencies with NMES ranged from 5-80 Hz. Two studies[27,28] used fixed protocols in which the frequency varied from 2-90 Hz. One study[29] did not describe the stimulation characteristics. The pulse duration ranged from 200-400 μs, and only 1 study[23] used a higher pulse width (760-875μs). The intensity of stimulation was adjusted according to patient tolerance. The time of session ranged from 20-60 minutes, with a weekly frequency of 2-3 times/wk and total intervention time of 5-20 weeks. Two studies associated physical exercise with NMES.[22,29] All the protocols occurred in an outpatient environment (during HD). Table 1 summarizes characteristics of included studies, and table 2 demonstrates the variability of the parameters and protocols of electrical stimulation adopted by the studies included in this review based on the training volume.

Risk of bias and quality of evidence

The 6 RCTs included in this review were evaluated by the RoB 2.0 tool, and all showed low risk of bias for categories "deviations from intended intervention" and "missing outcome data." Regarding the randomization process, 4 of the studies[16,23,24,26] have some concerns for this topic. Regarding the bias of selective reporting, only 2 studies[10,23] present low risk of bias for this item, and 4 studies[16,24-26] show some concerns. The most

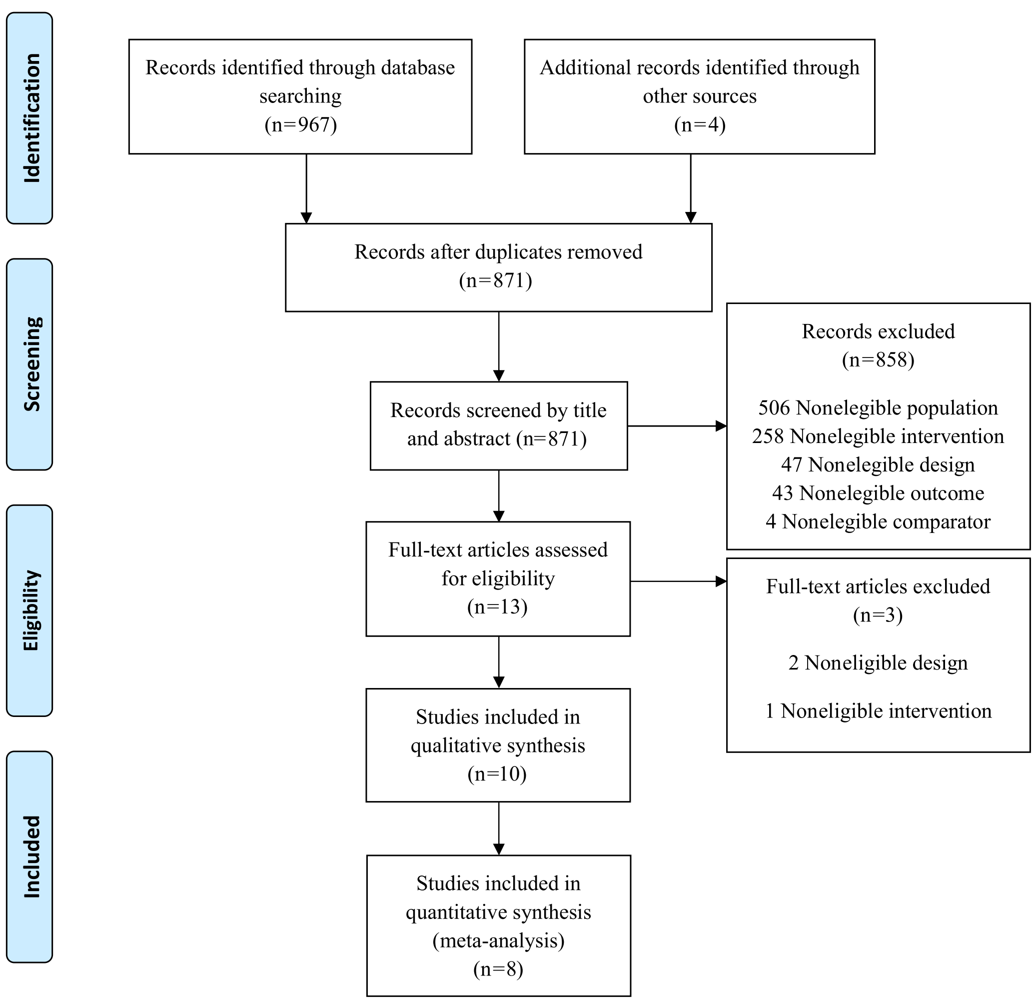

Fig 1 Flow diagram of study selection.

Table 1 Characteristics of included studies

Author	Design	Participants	Intervention	Comparison	Sex F/M (%)	Age (y), Mean ± SD	Protocol	Outcome Measures of Interest and Instruments
Dobsak et al[16]	Randomized clinical trial	21 patients with CKF on HD IG: 11 CG: 10	NMES	Control group	IG: 54.5/45.5 CG: 40/60	IG: 64.5±8.1 CG: 60.1±8.2	IG: 10 Hz; 200 μs pulse width; 20 s TON; 20s TOFF; 1 s rise and fall time; 60 min/session; maximum 60 mA; 3 times/wk for 20 wk; applied on quadriceps and gastrocnemius muscles. CG: no physiotherapeutic intervention.	- Functional capacity by 6MWT - Quadriceps muscle strength by isokinetic dynamometer - Quality of life by SF-36
Esteve et al[27]	Controlled clinical trial	20 patients with CKF on HD IG: 13 CG: 7	NMES	Control group	IG: 30.8/69.2 CG: 58.3/41.7	IG: 65.7±12.8 CG: 71.6±12.1	IG: 2-90 Hz; 1.5-2 s TON; 1.5-0.75 s TOFF; 25-38 min/session; maximum intensity tolerated; 3 times/wk for 12 wk; applied on quadriceps muscle. CG: No physiotherapeutic intervention. Only routine care.	- Functional capacity by 6MWT - Quadriceps muscle strength by traction dynamometer (load cell) - Lower limb strength by sit to stand to sit 10 test - Upper limb strength by hand grip dynamometer
Jiménez et al[29]	Clinical trial (Before and after study)	11 CKF patients on HD	NMES and exercise program	Not applicable	55/45	67.6 ± 16.7	NMES: Parameters of NMES not reported; maximum intensity tolerated by the patient; 2 times/week for 12 weeks; applied on quadriceps muscle. Exercise Program: exercises with balls, weights, elastics and cycle ergometers by 45-50min.	- Functional capacity by 6MWT - Quadriceps muscle strength by traction dynamometer (load cell) - Lower limb strength by sit to stand to sit 10 test - Upper limb strength by hand grip dynamometer

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Table 1 (*continued*)

Author	Design	Participants	Intervention	Comparison	Sex F/M (%)	Age (y), Mean ± SD	Protocol	Outcome Measures of Interest and Instruments
Martos et al[22]	Clinical trial (before and after study)	10 patients with CKF on HD	NMES and exercise program	Not applicable	Not reported	66.6±11.5	NMES: 50 Hz; 250 μs pulse width; 3 s TON; 6 s TOFF; maximum intensity tolerated by the patient; 3 times/wk for 5 wk; applied on quadriceps muscle. Exercise program: resistive exercises for lower limbs with weights and elastics (3 series-15 repetitions).	- Functional capacity by 6MWT - Quadriceps muscle strength by Daniels scale - Lower limb strength by sit to stand to sit 10 test - Quality of life (by KDQOL-SF
McGregor et al[23]	Randomized clinical trial	35 patients with CKF on HD IG: 17 CG: 18	NMES	Control group	IG: 18/82 CG: 39/61	IG: 51.5±19.3 CG: 54.3±17.9	IG: 5 Hz; 760-857 μs pulse width; 60 min/session; maximum intensity tolerated by the patient; 3 times/wk for 10 wk; applied on quadriceps and hamstrings. CG: no physiotherapeutic intervention.	- Functional capacity by ergospirometry - Quadriceps muscle strength by hand-held dynamometer
Miura et al[24]	Randomized clinical trial	20 patients with CKF on HD IG: 10 CG: 10	NMES	Control group	IG: 30/70 CG: 20/80	IG: 68.6±4.4 CG: 69.9±2.9	IG: 10 Hz; 20 s TON; 20 s TOFF; 60 min/session; 2 times/wk for 12 wk; applied on quadriceps and hamstrings muscles. CG: no physiotherapeutic intervention.	- Quadriceps muscle strength by hand-held dynamometer - Upper limb strength by hand grip dynamometer

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Table 1 (*continued*)

Author	Design	Participants	Intervention	Comparison	Sex F/M (%)	Age (y), Mean ± SD	Protocol	Outcome Measures of Interest and Instruments
Roxo et al[25]	Randomized clinical trial	40 patients with CKF on HD IG: 20 CG: 20	NMES	Control group	IG: 52.9/47.1 CG: 47.1/52.9	IG: 46.40±15.4 CG: 54.7±19.9	IG: 50 Hz; 350 μs pulse width; 2 s TON; 10 s TOFF; 30 min/session; maximum intensity tolerated by the patient; 3 times/wk for 8 wk; applied on quadriceps muscle. CG: no physiotherapeutic intervention.	- Functional capacity by 6MWT - Quadriceps muscle strength by 1RM test
Schardong et al[10]	Randomized clinical trial	21 patients with CKF on HD IG: 11 CG: 10	NMES	Control group	IG: 18.2/81.8 CG: 20/80	IG: 59.0±20.0 CG: 64.5±7.6	IG: 80 Hz; 400 μs pulse width; 10 s TON; 50-20 s TOFF; 20-34 min/session; maximum intensity tolerated; 3 times/wk for 8 wk; applied on quadriceps muscle. CG: no physiotherapeutic intervention.	- Functional capacity by 6MWT - Quadriceps muscle strength by traction dynamometer (load cell) - Lower limb strength SST
Simó et al[28]	Controlled clinical trial	38 patients with CKF on HD IG: 23 CG: 15	NMES	Control group	IG: 41.8/58.2 CG: 49.3/50.7	IG: 67.9±17.5 CG: 72.5±10.1	IG: 2-90 Hz; 4 s-25 min TON; 1.5-2 s rise and 1.5-0.75 s fall time; 30-45 min/session; maximum intensity tolerated by the patient; 12 wk; applied on quadriceps muscle. CG: no physiotherapeutic intervention.	- Functional capacity by 6MWT - Quadriceps muscle strength by traction dynamometer (load cell) - Lower limb strength by sit to stand to sit 10 test - Upper limb strength by hand grip dynamometer - Quality of life by EuroQol

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Table 1 (*continued*)

Author	Design	Participants	Intervention	Comparison	Sex F/M (%)	Age (y), Mean ± SD	Protocol	Outcome Measures of Interest and Instruments
Suzuki et al[26]	Randomized clinical trial	26 patients with CKF on HD IG: 13 CG: 13	NMES	Control group	IG: 7.7/92.3 CG: 7.7/92.3	IG: 66.2±12.8 CG: 65.1±8.1	IG: 20 Hz; 250 µs pulse width; 5 s TON; 2 s TOFF; 20 min/session; maximum intensity tolerated (range 30.6-104 mA); 3 times/wk for 8 wk; applied on gluteus and thigh and leg muscles. CG: no physiotherapeutic intervention.	- Quadriceps muscle strength by hand-held dynamometer - Quality of life (by SF-8)

Abbreviations: CG, control group; F, female; IG, intervention group; KDQOL-SF, Kidney Disease and Quality of Life—Short Form; M, male; 1RM, single repetition maximum lift; SF-8, Short Form—8 Health Survey; SF-36, Medical Outcomes Study 36-Item Short Form Health Survey; TOFF, time off; TON, time on.

problematic item was the "measurement of outcome" because 3 studies present a high risk of bias to the blinding of the outcome assessors, and these are highly influential. The overall score of RCTs ranged from "some concerns" (3 studies)[23,24,30] to "high risk of bias" (3 studies).[10,16,25]

The 4 nonrandomized clinical trials were evaluated by ROBINS-I tool and also have major limitations. All studies present confounders to a greater or lesser extent but low risk of bias for item "To departure from intended intervention." Three studies[22,27,29] present a serious risk of bias in "selection of participants," and 1 study[28] presents a moderate risk of bias. In the category "Measurement of intervention" 3 articles[22,27,28] presented a low risk of bias, and 1 study[29] presented a serious risk. As for loss of data, 3 studies[22,27,29] presented a low risk of bias, and 1 study[28] presented a moderate risk for this item. Regarding the measurement of the outcomes, none of the studies reported whether the evaluators were blinded, so it was not possible to assess the risk of bias for this category. Likewise, it is not possible to identify a selective reporting bias because none of the studies presented a registration of the research protocol in electronic platforms, and it was not possible to evaluate publication bias. Thus, the overall score of nonrandomized clinical trials ranged from moderate to critical risk of bias, 1 study being considered as moderate risk of bias,[28] another considered as serious risk of bias,[27] and 2 studies considered as critical risk.[22,29] The evaluation of methodological quality for all studies and their outcomes is available in detail in supplemental tables S2 and S3.

The quality of evidence, assessed through the Grading of Recommendations Assessment, Development, and Evaluation System, suggests moderate confidence in the functional capacity and quadriceps muscle strength outcomes and low confidence in lower limb muscle strength (assessed by SST) and upper limb muscle strength as well as in quality of life. The evidence profile is available in supplemental table S4.

Effects of intervention

Lower limb muscle strength

Quadriceps muscle strength was assessed by all studies included in the review. Eight studies evaluated muscle strength through dynamometry,[10,16,23,24,26-29] 1 study evaluated it by a maximal repetition test,[25] and another evaluated it by the Daniels scale.[22] Eight studies[10,16,23-28] totalizing 221 patients were included in the meta-analysis for this outcome. NMES increased the quadriceps muscle strength by 1.46 standard deviations when compared with the control group (standardized mean difference=1.46; 95% CI, 0.86-2.07; I^2:73%; P<.0001), and according to Cohen classification, this is considered a very large effect[31] (fig 2). Despite the large effect size for this outcome, the heterogeneity was high. Therefore, a sensitivity analysis was performed. The article by Roxo et al[25] was excluded from the analysis because this study was the only RCT that did not evaluate muscle strength by dynamometry (evaluated dynamic strength, not isometric strength). Therefore, the meta-analysis with 7 studies[10,16,23,24,26-28] and 181 patients showed that NMES increased the isometric quadriceps muscle strength by 1.19 standard deviations when compared with the control group presenting low heterogeneity (standardized mean difference=1.19; 95% CI, 0.85-1.53; I^2:8%; P<.0001) (fig 3). Two others studies (before-and-after studies)[22,29] were not included in

Table 2 Estimated treatment volume

Study	Intensity	Duty Cycle (ON-OFF) (s)	Total Treatment Time (min)	No. of Contractions
Dobsak et al[16]	MI	20-20	3.600	5.400
Esteve et al[27]	MI	1,75-1,00	1.134	1.701
Jiménez et al[29]	MI	NR	NR	___
Martos et al[22]	MI	3-6	NR	___
McGregor et al et al[23]	MI	NR	1.800	2.700
Miura et al[24]	MI	20-20	1.440	2.160
Roxo et al[25]	MI	2-10	720	1.080
Schardong et al[10]	MI	10-30	648	972
Simó et al[28]	MI	4-NR	1350	2.025
Suzuki et al[26]	67,3 mA	5-2	480	720

Abbreviations: MI, maximum intensity tolerated by the patient; NR, not reported.

the meta-analysis because they did not have a comparison group and combined NMES with exercise. However, these studies also demonstrate that the patients presented improvement for such an outcome (Jiménez et al: 13.7±8.1kgF vs 16.2±10.9kgF, $P=.043$; Martos et al: right leg 4.1±0.5kgF vs 4.7±0.3kgF, $P=.014$; left leg: 4.2±0.6kgF vs 4.9±0.3kgF, $P=.014$).

The lower limb muscle strength assessed by the SST was measured by 5 studies.[10,22,27-29] However, 4 of them used sit to stand to sit 10 test,[22,27-29] and 1 used conventional SST.[10] Of the studies that used sit to stand to sit 10 test, 2 were before-and-after studies[22,29]; therefore, only studies by Esteve et al[27] and Simó et al[28] were included in the meta-analysis. The quantitative analysis totaled 61 patients, and it did not show significant improvement for the NMES group in relation to the control group for this outcome (MD=−3.41s; 95%CI, −11.96 to 5.14; I^2:0%; $P=.43$) (fig 4).

Among the studies that were not included in the meta-analysis for the measurement of the muscle strength of lower limbs evaluated by SST, the study by Jiménez et al[29] did not show significant improvement to reduce the time needed to perform the 10 repetitions of the sit to stand to sit 10 test (24.6±13.4s vs 20.1±10.1s, $P=.054$). On the other hand, Martos et al[22] found positive results for the same outcome after combined use of NMES and physical exercise (35.3±20.3s vs 26.4±6.43s, $P=.005$). Similarly, Schardong et al[10] found an increase in the number of repetitions performed in the conventional SST, thus evidencing improvement of the muscle strength of the lower limb after the use of NMES compared with the control group (intervention group: 16.10±6.51 repetitions vs control group: 12.50±4.72 repetitions, $P=.029$).

Upper limb muscle strength

Upper limb muscle strength evaluated by manual dynamometer was verified by 4 studies.[24,27-29] The meta-analysis conducted with 3 studies,[24,27,28] totaling 81 patients, identified an increase of this outcome after NMES (MD=10.02kgF; 95% CI, 0.78-19.27; I^2:97%; $P=.03$] (fig 5). Jiménez et al[29] also observed a significant improvement in the hand grip strength of patients with CKF after an NMES-associated exercise program (23.8±15.9kgF vs 25.1±15.9kgF, $P=.007$).

Functional capacity

Seven studies included in this review evaluated functional capacity through the 6MWT. The meta-analysis of 5 studies[10,16,25,27,28] and 143 patients showed an increase in the distance covered in the 6MWT after NMES (MD=30.11m; 95% CI, 15.57-44.65; I^2:0%; $P<.0001$) (fig 6). Likewise, Jiménez et al[29] and Martos et al[22] combined NMES with physical exercise, and they also found significant improvement for this outcome (Jiménez et al: 332.6 vs 402.7m, $P=.014$; Martos et al.:r 428±106m vs 492±100m, $P=.005$).

One RCT[23] assessed functional capacity through ergospirometry, and it demonstrated that the group that received

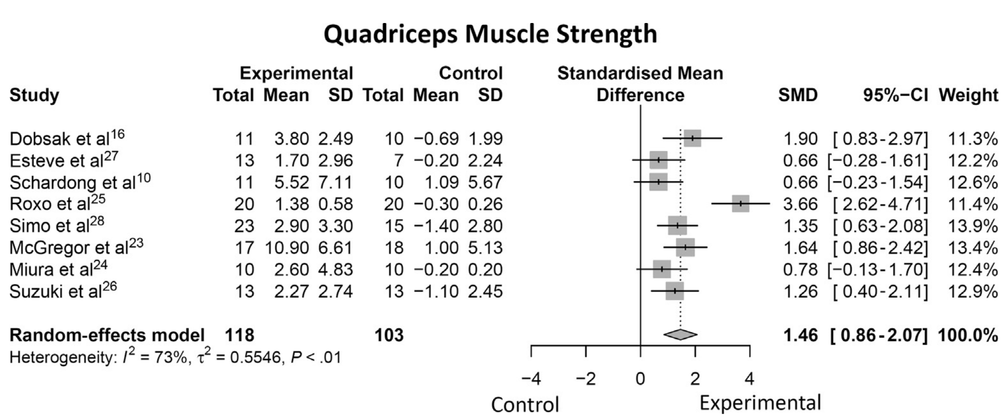

Fig 2 SMD and 95% CI on quadriceps muscle strength for NMES vs control group.; Abbreviations: CI, confidence interval; SMD, standardized mean difference.

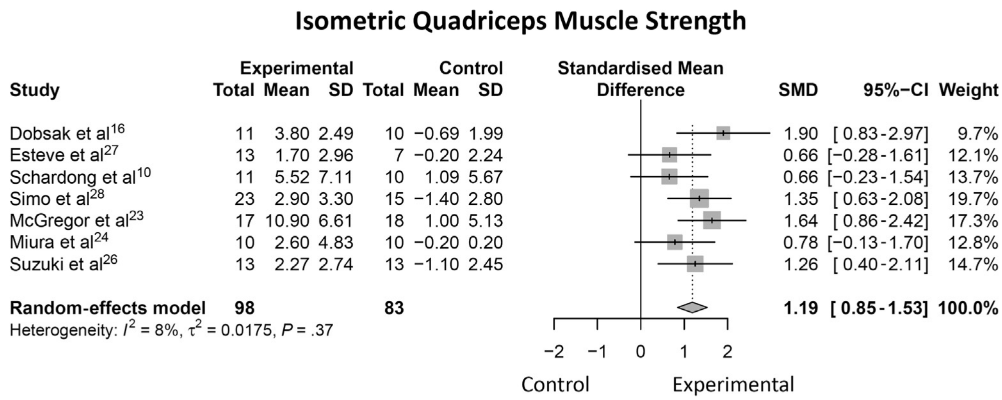

Fig 3 SMD and 95% CI on isometric quadriceps muscle strength evaluated by dynamometry for NMES vs control group. Abbreviations: CI, confidence interval; SMD, standardized mean difference.

NMES had peak oxygen uptake higher than the control group at the end of treatment (control group: 16.3±2.53 vs 15.9±5.56 mL•kg^{-1}•min^{-1} and GI: 19.6±7.1 vs 21±7.57mL•kg^{-1}•min^{-1}; P = .02), indicating the improvement of this outcome.

Quality of life

Four studies (n = 95 patients)[16,22,26,28] evaluated the effect of NMES associated or not with exercise on the quality of life of patients with CFK. Dobsak et al[16] used the Short Form−36 Health Survey questionnaire and found positive effects on aspects of mental health (vitality: 48.5±12.6 vs 54.3±7.9, P = .019; emotional aspects: 54±10.7 vs 63.1±9.1, P = .002; mental health: 62.4±12.4 vs 71.3±8.4, P = .009; and mental component: 57.3±6.4 vs 64.5±5.3, P < .001) but not on physical aspects. As opposed to the intervention group, no effect was observed in the control group for this outcome.

Martos et al,[22] on the other hand, through the Kidney Disease and Quality of Life−Short Form questionnaire observed significant effects on only the physical aspects (38.4±12.9 vs 45.3±13.1, P = .022) of quality of life after the combined use of NMES and exercise.

Simó et al[28] used the EuroQol-5D questionnaire to assess the quality of life and found a significant improvement in the "usual activities performance" dimension in the NMES group (1.7±0.9 vs 1.2±0.5, P = .010) and in the "general health" evaluation (52.7±16.3 vs 65.5±13.4, P = .001). The same results were not observed for the control group.

Suzuki et al[26] used the Short Form−8 Health Survey questionnaire to evaluate the quality of life and found no changes for this outcome for either group in any dimension.

Discussion

This is the first systematic review with meta-analysis to demonstrate that when NMES is applied chronically in patients with CFK during HD it improves functional capacity and muscle strength of lower and upper limbs. Some aspects of quality of life also presented positive results; however, because of the heterogeneity of the scales used to evaluate this outcome and diversity of study designs, the results were presented qualitatively.

Muscle strength of the quadriceps and of the lower limb can be assessed by different methods. Dynamometry, considered the gold standard method,[32,33] and the maximal repetition test are often used to measure this outcome. The SST in its different variations is an indirect evaluation of muscle strength and endurance for lower limbs, but because of its good applicability, it is widely used in clinical practice, also reflecting the patient's functionality.[34]

The NMES was effective in increasing quadriceps muscle strength in patients with CKD when evaluated by dynamometry or maximal repetition test, and the quality of evidence was considered moderate. This can be explained by the high risk of bias of some studies and different assessment tools used because when sensitivity analysis is performed the heterogeneity is practically nil for this outcome. On the other hand, when lower limb muscle strength was assessed by SST, the results were not positive. It was impossible to perform a more robust meta-analysis because different instruments were used for measuring, and only 2 studies included in the quantitative analysis were not enough to show positive results. Thus, the quality of evidence for this outcome was considered low because sample size is small, confidence intervals are large, and therefore there is significant lack of precision. In

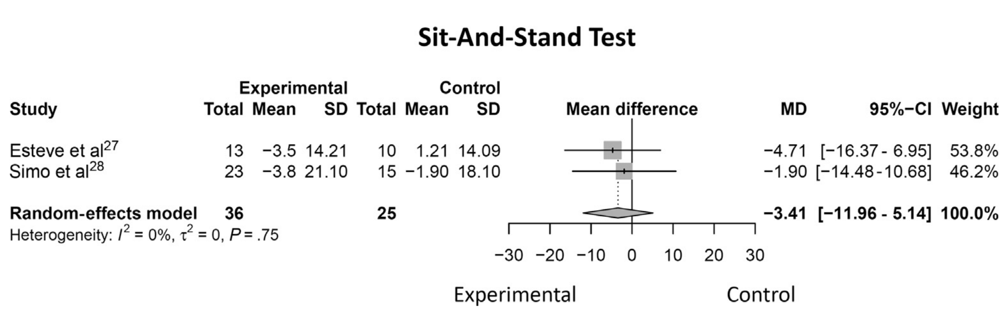

Fig 4 MD and 95% CI on lower limb muscle strength evaluated by SST for NMES vs control group. Abbreviations: CI, confidence interval; NMES, neuromuscular electrical stimulation; SST, sit-and-stand test.

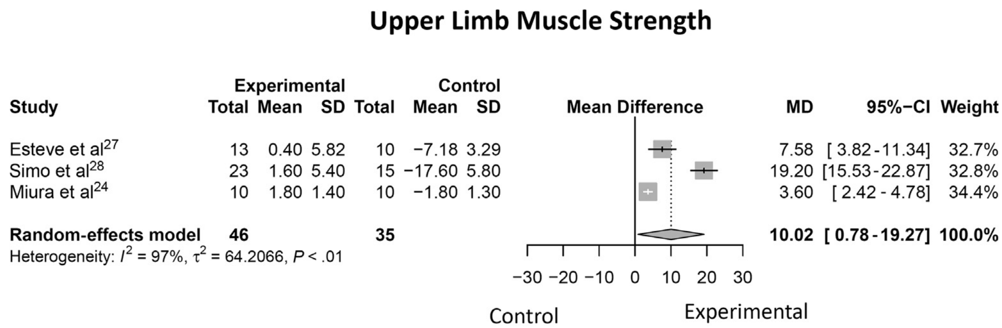

Fig 5 MD and 95% CI on upper limb muscle strength for NMES vs control group. Abbreviations: CI, confidence interval; NMES, neuromuscular electrical stimulation.

addition, the risk of bias was also considered serious for SST. It is believed that the small number of controlled clinical trials that evaluated the effect of NMES on patients with CKF for lower limb muscle strength was responsible for the results found.

Corroborating our findings, Medeiros et al[9], in their systematic review that assessed the effect of inspiratory muscle training on respiratory muscle strength in patients with CKD, encountered similar difficulties. The authors found few publications in the databases for this population, and the included studies presented a great heterogeneity of training protocols, which ultimately limited the quality of the evidence.

According to a meta-analysis conducted in this study, NMES increases upper limb muscle strength even when applied to leg muscles. Thomas[35] and Hooker[36] and colleagues suggest that cardiac output is frequently increased during NMES interventions because it is regulated by the volumetric overload imposed by increased venous return in leg muscles and not by neural regulation of heart rate. Based on this information, despite being considered a local therapy, it is believed that NMES has systemic effects because it promotes vasodilation, increased muscle blood flow, and increased cardiac output. This may partly explain the increased muscle strength of the upper limb. However, the quality of evidence for this outcome was considered low. Contrary to studies evaluating quadriceps strength, those that assessed upper limb strength used the same method of evaluation, and yet the heterogeneity presented in the meta-analysis was high ($I^2=97\%$). It is believed that the small number of studies included in the quantitative analysis (only 3), the broad confidence intervals, and the biases presented by the studies justify our findings.

All studies that evaluated functional capacity used the 6MWT (except the study of McGregor et al[23] that used ergospirometry) and observed that it had an increment in patients with CKF after the use of NMES alone or in combination with exercise. Meta-analysis did not show heterogeneity ($I^2=0\%$), and for this reason we are convinced that the standardization of evaluation methods increases confidence in the results found. Still, this is a relevant clinical finding because the increase in distance walked in the 6MWT is considered a predictor of survival for patients with CKF on HD.[37]

There is evidence of positive effects of NMES on outcomes such as functional capacity and muscle strength for the most diverse populations,[12] which demonstrates that this intervention is an effective strategy for patients who do not adapt to exercise-based conventional physical exercise programs[38] because they are very debilitated or because they do not feel motivated to perform the voluntary exercise.

Patients with CKD present sarcopenia even in the early stages of the disease,[39] and this is due to several complex systemic alterations that affect muscle homeostasis such as increased proteolysis, impaired muscle repair, and suppressed protein synthesis.[40] The muscle fibers of patients with CKD present many abnormalities, possibly because of the adaptation of these cells because of an altered internal environment. These abnormalities include changes in capillaries, enzymes, and contractile proteins.[41]

CKD-induced muscle atrophy is highly prevalent and, in association with common CKD comorbidities (such as cardiac arrhythmias, peripheral vascular disease, orthopedic disorder), is responsible for the reduction of physical capacity, reduction of

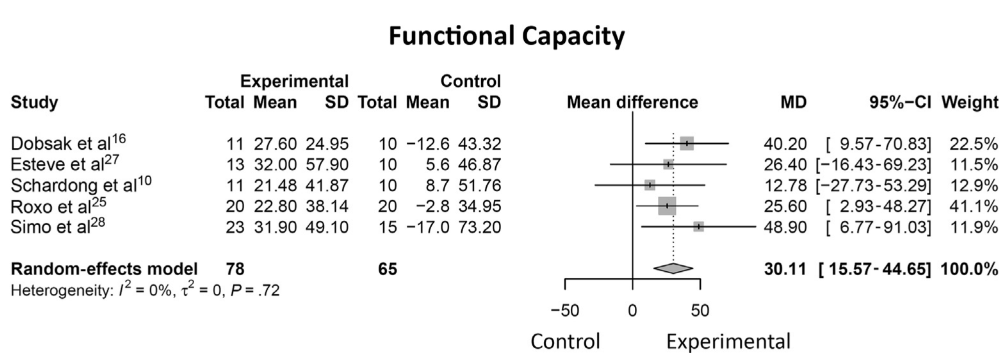

Fig 6 MD and 95% CI on functional capacity for NMES vs control group. Abbreviations: CI, confidence interval; NMES, neuromuscular electrical stimulation.

functional independence, and increase in mortality rates.[40] In addition to impaired physical capacity, patients with CKF have high levels of depression, which makes adherence to exercise-based rehabilitation programs difficult, although combined exercise and resistance aerobic exercise are strongly recommended for this population.[42,43] In this sense, other strategies should be considered that aim at the rehabilitation of these patients, and NMES can be one of them because it mimics voluntary muscle contraction and generates similar muscle adaptations to conventional exercise.

Although there is a large variability of parameters for the application of NMES in the literature, our systematic review has shown that for patients with CKD on HD the most commonly used parameters are frequency 5-80 Hz, pulse width between 200-400 μs, session time of 20-60 minutes, intensity adjusted according to patient tolerance, weekly frequency of 2-3 times/wk, and protocols between 5-20 weeks. These parameters are similar to those used in other populations such as patients who have suffered a stroke[44] or who have heart failure.[45]

Our study also demonstrated that the muscles stimulated in the lower limb are usually quadriceps or quadriceps and gastrocnemius. There is no consensus among the studies on knee angulation for the application of electrical stimulation, but those that describe the positioning of the lower limbs indicate that the patients were in a supine position, with the knees between 15°[27,28] or 60°.[10] However, the knee angulation that generates the highest torque peak in the quadriceps muscle is 60°.[46] Only Schardong et al[10] used this joint angle for training with NMES and obtained greater gains in quadriceps muscle strength compared with the other studies.

Only 4 studies[16,22,26,28] evaluated quality of life, and they had different designs and also used different tools for measurement. Although these questions make quantitative analysis unfeasible, the results found point to some positive effects of NMES on quality of life of patients with CKF in 3 of 4 studies.

Our systematic review with meta-analysis has several strong points. The research covered several databases and a search in gray literature, and there was no language restriction, thus making it unlikely that any relevant study was forgotten. In addition, we use current tools for bias risk assessment such as Robin-I and RoB 2.0 to make the results even more transparent.

Study limitations

Among the limitations of this review we can cite the small number of RCTs included. In addition, they present an important risk of bias in some dimensions. It can be said that methodological quality is impaired mainly by the absence of patient blinding in all studies because a control group is used as a comparison. Furthermore, it is not known whether the outcomes assessors were blinded in most studies, and the outcomes in question are highly influential if the evaluator or the patient is aware of the intervention received. Finally, the inability to assess the bias of selective reporting intrigues us if negative results regarding the use of NMES in CKF have not occurred or only have not been reported. These issues generally limit the quality of evidence.

Despite the limitations of the data, the estimates presented here show that NMES seems to be an effective therapy for patients with CKF on HD for improvement of physical function. Our findings may be helpful in supporting the decision making of physiotherapists, especially in situations where the patient does not fit into conventional rehabilitation programs (exercise-based). Thus, NMES may be an initial strategy within rehabilitation programs for physical conditioning, especially for those who are more debilitated or do not feel motivated to perform the voluntary exercise because it does not require effort on the part of the patient.

Conclusions

In conclusion, NMES when applied in a chronic form in patients with CKF during HD improves the quadriceps muscle strength and functional capacity with moderate certainty of the evidence. The effects of this therapy on upper limb muscle strength and quality of life seem to be positive; however, the quality of evidence is very limited. Thus, further RCTs are needed to investigate the real benefits of NMES in these outcomes in patients in the terminal stage of CKD. In addition, it is suggested that future research with high methodological rigor investigate the effect of NMES associated with other interventions such as exercise and drug treatment.

Keywords

Electric stimulation; Kidney failure; chronic; Rehabilitation; Renal dialysis

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