Effects of strength training to patients undergoing dialysis: a systematic review

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ABSTRACT

INTRODUCTION: Chronic kidney disease is associated with several negative factors that may counteract the potential effects of strength training. The purpose of this systematic review was to explore the effects of strength training on muscle mass, muscle strength, physical function and quality of life in patients undergoing dialysis.

METHODS: A literature search was conducted in The Cochrane Library, MEDLINE, Embase, CINAHL and PEDro. Eight randomised, controlled trials of patients undergoing haemodialysis (n = 290) were included.

RESULTS: There were inconsistencies in the results on the effects of strength training on muscle mass. Muscle strength was improved in six of eight tests. Objectively tested physical function remained unchanged. Pooled data for self-rated physical health and physical function from Short Form 36 were improved with strength training (mean (95% confidence interval) 10.05 (2.95-17.14), p = 0.006, and 9.38 (0.79-17.97), p = 0.03, respectively).

CONCLUSIONS: The results suggest that it may be difficult to increase muscle mass with strength training in patients who are undergoing haemodialysis. Muscle growth may be impaired as a result of several catabolic conditions. Strength training was associated with important clinical outcomes including increased muscle strength and improved self-rated physical health and function.

Protein energy waste is a common complication in patients undergoing dialysis, and it results from loss of proteins and a disturbed balance between protein breakdown and protein synthesis [1, 2]. First of all, there is an inappropriate removal of proteins during dialysis, and haemodialysis (HD) has been proposed to be catabolic per se [3]. The underlying reasons for the disturbance between protein breakdown and synthesis also include insulin resistance [4-6], reduced levels of and resistance to anabolic hormones [7, 8], acidosis [9, 10], chronic inflammation [11], physical inactivity [12] and insufficient total energy and protein ingestion [13]. Thus, protein energy waste in patients undergoing dialysis is a result of several factors and associated with an elevated risk of mortality [14]. Muscle atrophy prevention in patients undergoing dialysis is therefore an important target in clinical practice [15].

Strength training with high loads is recognised as the training modality with the most pronounced effect on muscle growth [16, 17]. Strength training involves an increase in protein synthesis but also an increase in protein breakdown. However, in general, the protein synthesis exceeds the protein breakdown, leading to a net hypertrophic effect in the muscle. The question remains if protein energy waste counteracts the potential protein accretion leading to muscle hypertrophy with strength training in patients undergoing dialysis.

Recent reviews have evaluated effects of general exercise training in patients undergoing dialysis in studies with different training modalities, intensities and research designs [18-22]. The objective of this systematic review was to investigate the effects of strength training on muscle mass, muscle strength, physical function and quality of life (QoL) in patients undergoing dialysis. Only randomised controlled trials (RCTs) with a strength training intervention were included.

METHODS

This study was conducted in accordance with the PRISMA statement and the protocol was registered with PROSPERO (no. CRD42016053338).

Published RCTs assessing the effects of an intervention with strength training versus a control group without exercise training were included. Trials with more than one intervention and thereby more than two study arms were included if it was possible to compare a strength training group with a control group. The participants had to be ≥ 18 years of age and be undergoing chronic dialysis (HD or peritoneal dialysis) ≥ 1 month. Exercise training programmes with or without a supplementary nutritional or pharmaceutical treatment to enhance the muscle mass or size were included. The training programme needed to be structured, described in a manner that made it re-producible and include strength training as defined by the authors.

The search for RCTs was performed with the assistance of a trained librarian. We searched The Cochrane Library (CENTRAL), MEDLINE (PubMed), Embase, CINAHL and PEDro. Manuscript languages were restricted to English, Danish, Swedish and Norwegian. An example of a search in MEDLINE: (Dialysis OR Hemodialysis OR Haemodialysis OR Peritoneal dialy-

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Dan Med J 2019;66(1):5526

sis) AND (Exercise OR Training). Reference lists were hand searched for other potentially relevant RCTs. Two authors independently screened the titles and abstracts to identify potential RCTs to be included, reviewed the full-text publications of the potentially included RCTs and extracted and collected data. Disagreements in the assessments were resolved through discussions between all authors.

The primary outcomes were tests of muscle mass or size including whole muscle mass (e.g. assessed using dual-energy X-ray absorptiometry (DXA), CT or magnetic resonance imaging (MRI) methods), muscle cross sectional area or single muscle fibre cross sectional area (e.g. by computer image analysis). The secondary outcomes were tests of muscle strength (e.g. using dynamometers or one repetition maximum (RM) tests), objectively tested physical function (e.g. the chair-stand test), QoL (e.g. Short Form 36 (SF36) questionnaire) and adverse effects.

Risk of bias in the included RCTs was assessed using

TABLE 1

The characteristics of the included studies. All participants were undergoing haemodialysis.

Reference	Participants: included/ follow-up, n	Participants: age, yrs, mean ± SD gender, m/f, n	Intervention	Outcome	Comment
Inter HD					
Dong et al, 2011, US [41]	32/22	Int: 46.5 ± 12.1, con: 40.2 ± 13.5[a] Int: 9/6, con: 12/5	Leg press 3 × 12 reps, up to 82% of 1RM, 3 × weekly for 6 mo.s	LBM: DXA Muscle strength: 1RM	Exercise prior to HD sessions
Kopple et al, 2007, US [34]	40[b]/29	Int: 46.0 ± 2.7, con: 41.3 ± 3.3[a] Int: 9/6, con: 9/5	Leg press, leg extension, leg curl, calf extension up to 3 × 6-8 reps, 80% of 5RM, 3 × weekly for 18 wks	Muscle area: formula FFM: DXA, bio impedance	Exercise prior to HD sessions
Song & Sohng, 2012, Korea [35]	44/40	Int: 52.1 ± 12.4, con: 54.6 ± 10.1 Int: 8/12, con: 12/8	6 upper + 6 lower body exercises 3 × 10-15 reps, BORG 11-15, 3 × weekly for 12 wks	Muscle mass, arm muscle circumference: bio impedance Muscle strength: dynamometer QoL: questionnaire	Exercise prior to HD sessions
DePaul et al, 2002, Canada [36]	38/29	Int: 55 ± 16, con: 54 ± 14 Int: 10/10, con: 13/4[c]	Knee flexion + knee extension up to 3 × 10 reps, 125% of baseline 5RM, 3 × weekly for 12 wks	Muscle strength: 5RM Physical function: 6MW QoL: questionnaire	Exercise prior to or after HD sessions
Intra HD					
Johansen et al, 2006, US [37]	40[b]/36	Int: 54.4 ± 13.6, con: 56.8 ± 13.8 Int: 12/8, con: 14/6	5 lower body exercises 3 × 10 reps, 60% of 3RM, 3 × weekly for 12 wks	LBM: DXA Muscle area: MRI Muscle strength: dynamometer + 3RM Physical function: stair climb, sit to stand, gait speed QoL: questionnaire	The control group received a placebo product
Chen et al, 2010, US [38]	50/44	Int: 71.1 ± 12.6, con: 66.9 ± 13.4 Int: 12/10, con: 11/11	5 lower body exercises 2 × 8 reps, 60% of 1RM, 3 × weekly for 24 wks	LBM: DXA Muscle strength: dynamometer Physical function: battery QoL: questionnaire	Pilot study, control group performed stretching
Cheema et al, 2007, Australia [39]	49/44	Int: 60.0 ± 15.3, con: 65.0 ± 12.9 Int: 17/7, con: 17/8	10 upper + lower body exercises 2 × 8 reps, BORG 15-17, 3 × weekly for 12 wks	Muscle area: CT scan Muscle size: circumference Muscle strength: dynamometer Physical function: 6MW QoL: questionnaire	
Kirkman et al, 2014, UK [40]	23/19	Int: 48 ± 18, con: 58 ± 15 Int: 7/2, con: 6/4	Leg press 3 × 8-10 reps, 80% of 1RM, 3 × weekly for 12 wks	Muscle area: MRI Muscle strength: dynamometer Physical function: 6MW, sit to stand QoL: questionnaire	Control group performed stretching

6MW = Six-min. Walk Test; BORG = rating of perceived exertion; con = control; DXA = dual-energy X-ray absorptiometry; f = female; FFM = fat free mass; HD = haemodialysis; int = intervention; LBM = lean body mass; m = male; QoL = quality of life; reps = repetitions; RM = repetition maximum; SD = standard deviation.
a) Mean ± standard error of the mean.
b) From the 2-treatment arms strength training and control.
c) Gender reported for 17 participants.

The Cochrane Collaboration's tool for assessment of risk of bias: Random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other bias.

Meta-analyses had to be performed, if possible according to the methods of the Cochrane Handbook [23] if there were comparable effect measures from more than one study and where measures of heterogeneity indicated that pooling of results was appropriate. The I^2 statistics were used to describe heterogeneity among the included trials [24]. Data are presented as summary of findings, and the principles in the GRADE system [25] were used to assess the quality in the body of evidence associated with specific outcomes. The GRADE approach is based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality considers: within-study risk of bias (methodological quality); the directness of the evidence; heterogeneity of the data; precision of effect estimates; and risk of publication bias.

RESULTS

Through the electronic search (updated 31 October 2017), a total of 6,927 hits were found. Once the search was limited to RCTs and supplied with results from hand searches, 214 references remained. After excluding duplicate reports, abstracts were screened, and 15 references were obtained for full text assessment. Seven trials were excluded due to an insufficient exercise programme description, insufficient results reporting or an inadequate amount of strength training in the interventions [26-32]. Eight RCTs met the inclusion criteria [33-40]. In total, 290 participants undergoing HD were included (178 men and 112 women) and their mean ± standard deviation age ranged from 40.2 ± 13.5 to 71.1 ± 12.6 years (**Table 1**). The intervention periods ranged from 12 weeks to six months. In one trial, the intervention and the control groups were supplied with an intradialytic oral high-protein nutrition supplement [41]. In three trials, the control group performed range of motion exercises [36] or stretching [38, 40], interventions that the authors of this review found not to have the potential to significantly increase the tested parameters.

Whole muscle size was assessed using a formula [34], MRI [37, 40] or CT [39]. Five trials assessed muscle mass using DXA [34, 37, 38, 41] or bio impedance techniques [34, 35]. Muscle strength was measured using 1-5RM tests [36, 37, 41], dynamometers [37-40] and an undefined equipment to measure leg press maximum strength [35]. Physical function was measured using the Six-minute Walk Test [36, 39, 40] or other tests [37, 38, 40]. QoL was measured using the SF36 questionnaire [35-40] and the Kidney Disease Questionnaire [36]. None of the eight trials were judged as having a low risk of bias in all domains (see the assessments in **Table 2**).

Effects of interventions

See the main results in **Table 3**. Given the substantial differences in tests of the selected outcomes between the included studies, data syntheses were performed only in cases with reasonably clinical homogeneity. The overall results were described from the individual studies.

Muscle size or mass

Muscle mass was measured in seven trials and in-

TABLE 2

Risk of bias assessment of the included studies.

Reference	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Inter HD						
Dong et al, 2011, US [41]	Low	Unclear	High	High	Low	Low
Kopple et al, 2007, US [34]	Low	Unclear	High	High	Low	Low
Song & Sohng, 2012, Korea [35]	Unclear	Unclear	High	High[a]	Low	Low
DePaul et al, 2002, Canada [36]	Low	Low	High	Low	Low	Low
Intra HD						
Johansen et al, 2006, US [37]	Low	Low	High	High	Low	Low
Chen et al, 2010, US [38]	Unclear	Unclear	High	High	Low	Low
Cheema et al, 2007, Australia [39]	Low	Low	High	Low[b]	Low	Low
Kirkman et al, 2014, UK [40]	Low	Low	High	Low	Low	Low

HD = haemodialysis.
a) The muscle strength tester was blinded.
b) The muscle size (primary outcome) tester was blinded.

TABLE 3

Results of strength training on muscle mass, muscle strength, physical function and quality of life in the four included studies. Data are mean ± standard deviation (n) [p-value]. The all over quality of evidence was downgraded to very low by serious risk of bias, serious inconsistence between studies and serious imprecision.

Reference	Muscle size	DXA scanning: LBM or FFM	Bio impedance: FFM, muscle mass or muscle circumference	Muscle strength and PF	QoL	Authors' conclusion
Inter HD						
Dong et al, 2011, US [41]	–	LBM leg, kg Int: 14.7 ± 7.0-14.6 ± 7.0 (10) Con: 17.4 ± 11.1-18. 2 ± 12.8 (12) [0.33]	–	Leg press, lb Int: 459 ± 370-582 ± 465 (10) Con: 475 ± 606-527 ± 482 (12) [0.12]	–	No effect on muscle protein accretion
Kopple et al, 2007, US [34][a]	Proximal thigh, cm^2 Int: 182.2 ± 44.5-179.7 ± 49.6 (15) Con: 183.1 ± 32.9-182.5 ± 37.0 (14) [> 0.05] *Mid-thigh, cm^2* Int: 144.0 ± 41.1-148.7 ± 56.2 (15) Con: 143.1 ± 28.1-144.5 ± 30.3 (14) [> 0.05]	*FFM leg, kg* Int: 14.03 ± 3.2-14.2 5 ± 3.2 (13) Con: 14.5 5 ± 3.4-14.72 ± 3.4 (14) [> 0.05]	*FFM body, kg* Int: 53.0 ± 12.8-53.1 ± 13.6 (15) Con: 51.1 ± 12.0-51.7 ± 12.0 (14) [> 0.05]			No changes in body composition
Song & Sohng, 2012, Korea [35]	–	–	Muscle mass, kg Int: 21.4 ± 3.6-22.2 ± 3.7 (20) Con: 22.8 ± 5.3-22.5 ± 5.2 (20) [0.002] *Arm circumference, cm* Int: 23.4 ± 1.4-23.5 ± 1.4 (20) Con: 23.7 ± 2.7-23.8 ± 2.6 (20) [0.747]	*Leg muscle strength, kg* Int: 33.0 ± 15.3-37.3 ± 19.0 (20); con: 34.8 ± 20.3-33.4 ± 19.5 (20) [0.027]	*PCS, pts* Int: 64.5 ± 13.0-72.5 ± 9.8 (20) Con: 66.3 ± 1 2.5-64.2 ± 12.2 (20) [0.002] *MCS, pts* Int: 62.9 ± 15.9-69.4 ± 13.7 (20) Con: 62.7 ± 11.8-60.8 ± 12.4 (20) [0.014]	The strength training increased muscle mass, leg muscle strength, and QoL
DePaul et al, 2002, Canada [36]	–	–	–	*Leg muscle strength, lb*[b] Int: 166 ± 94-228 ± 129 (15) Con: 171 ± 50-173 ± 46 (14) [0.02] *6MW, m* Int: 460 ± 136-464 ± 94 (15) Con: 426 ± 131-430 ± 80 (14) [0.52]	*SF36, pts* Int: 100 ± 23-100 ± 21 (15) Con: 100 ± 18-96 ± 16 (14) [0.55] *KDQ, pts* Int: 49 ± 10-50 ± 14 (15) Con: 52 ± 7-55 ± 7 (14) [0.39]	Int resulted in an increased muscle strength, whereas PF and QoL remained unchanged
Intra HD						
Johansen et al, 2006, US [37]	*Quadriceps, cm^2* Int: 47.9 ± 13.9-49.1 ± 13.5 (19) Con: 51.1 ± 10.9-47.6 ± 11.0 (17) [0.02]	*LBM body, kg* Int: 47.5 ± 12.3-47.1 ± 11.2 (19) Con: 48.4 ± 8.2-48.2 ± 8.8 (17) [0.66]		*Isometric knee extension 90°/s, Nm*[c] Int: 39.2 ± 25.1-46.8 ± 28.9 (19); con: 41.7 ± 19.4-43.3 ± 22.8 (17) [0.77] *Knee extension 3RM, kg*[d] Int: 14.0 ± 8.4-22.6 ± 11.6 (19); con: 19.2 ± 8.7-20.0 ± 9.1 (17) [< 0.0001] *Sit-to-stand, s*[e] Int: 18.0 ± 11.4-15.1 ± 7.4 (19); con: 15.2 ± 3.8-15.1 ± 5.1 (17) [0.30]	*PF, pts* Int: 46 ± 12-54 ± 12 (22) Con: 52 ± 11-50 ± 11 (22) [0.02]	Resistance exercise training increased muscle size

CONTINUES »

TABLE 3 CONTINUED

Reference	Muscle size	DXA scanning: LBM or FFM	Bio impedance: FFM, muscle mass or muscle circumference	Muscle strength and PF	QoL	Authors' conclusion
Intra HD						
Chen et al, 2010, US [38]	–	*LBM leg, kg* Int: 6.9 ± 1.7-7.2 ± 2.0 (21) Con: 7.2 ± 1.8-6.9 ± 1.7 (21) [0.0001] *LBM body, kg* Int: 45.8 ± 8.9-47.9 ± 9.9 (21) Con: 47.8 ± 9.0-46.3 ± 8.7 (21) [0.0001]	–	*Physical performance, battery*[f] Int: 5.0 (5.2)-7.0 (7.2) (22) Con: 6.0 (7.0)-6.5 (4.5) (22) [0.03] *Knee extension, kg* Int: 11.4 ± 5.0-15.8 ± 5.0 (21) Con: 14.8 ± 6.0-12.1 ± 6.1 (21) [0.0001]	*PCS, pts* Int: 64.5 ± 13.0-72.5 ± 9.8 (20) Con: 66.3 ± 12. -64.2 ± 12.2 (20) [0.002] *MCS, pts* Int: 37 ± 11-37 ± 9 (22) Con: 39 ± 11-38 ± 9 (22) [0.6]	Strength training improved physical performance
Cheema et al, 2007, Australia [39]	*Mid-thigh, cm²* Int: 104.2 ± 25.6-104.2 ± 25.6 (24) Con: 98.9 ± 21.5-97.4 ± 21.9 (25) [0.4]	–	*Mid-thigh circumference, cm*[g] Int: 47.5 ± 6.0-47.6 ± 5.8 (24) Con: 47.8 ± 5.9-48.2 ± 3.8 (25) [0.04]	*Muscle strength, kg*[b] Int: 98.1 ± 36.6-109.5 ± 35.1 (24) Con: 86.0 ± 33.8-85.2 ± 34.3 (25) [0.002] *6MW, m* Int: 497 ± 133-515 ± 155 (24) Con: 406 ± 123-414 ± 127 (25) [0.16]	*PF, pts* Int: 74 ± 26-81 ± 22 (24) Con: 64 ± 22-64 ± 25 (25) [0.02] *VT, pts* Int: 58 ± 22-61 ± 22 (24) Con: 56 ± 24-49 ± 28 (25) [0.02]	Progressive resistance training resulted in improved body composition
Kirkman et al, 2014, -UK [40]	*Thigh, cm²* Int: 2,822 ± 438-2,906 ± 489 (9) Con: 2,490 ± 601-2,380 ± 643 (10) [0.007]	–	–	*Knee extension, N* Int: 179 ± 109-287 ± 86 (9) Con: 151 ± 79-201 ± 77 (10) [0.012] *6MW, m* Int: 532 ± 95-571 ± 101 (9) Con: 460 ± 162-520 ± 160 (10) [0.4] *Sit-to-stand, s*[h] Int: 11 ± 2-13 ± 3 (9) Con: 10 ± 4-11 ± 5 (10) [0.2]	*SF36, pts* Data not shown, not significant	Progressive resistance training was safe and increased muscle volume and strength

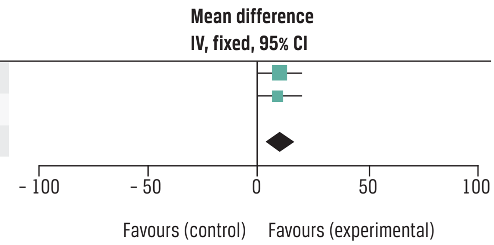
6MW = Six-min. Walk Test; con = control; FFM = fat free mass; HD = haemodialysis; int = intervention; KDQ = Kidney Disease Questionnaire; LBM = lean body mass; MCS = Mental Component Scale; PCS = Physical Component Scale; PF = physical function; QoL = quality of life; RM = repetition maximum; SF36 = Short Form 36; VT = vitality.
a) Data are concerted from mean ± standard error of the mean to mean ± standard deviation.
b) Combined measure of more tests.
c) Similar results in the 120°/s tests.
d) Similar results in hip abduction and hip flexion tests.
e) Similar results in gait speed and stairs tests.
f) Median (interquartile range).
g) Similar results in the mid-arm circumference tests.
h) Similar results in 8-feet up and go test.

creased in three trails using different outcome measures [35, 38, 40]. The same parameters remained unchanged in different tests in two other trails [33, 34]. In each of the remaining two trials, two methods to investigate the effects on muscle mass were used and the trials found positive as well as negative effects [37, 39]. The data for two trails' tests of the mid-thigh muscle area were pooled and showed no effect in favour of

FIGURE 1

Forest plot comparing the Physical Component Scale from the Short Form 36 questionnaire.

	Experimental			control				Mean difference
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, fixed (95% CI)
Chen et al, 2010 [38]	8	17	22	–2	15.6	22	54.2%	10.00 (0.36-19.64)
Song & Sohng, 2012 [35]	8	16.3	20	–2.1	17.5	22	45.8%	10.10 (–0.38-20.58)
Total (95% CI)			42			42	100.0%	10.05 (2.95-17.14)



Heterogeneity: chi^2 = 0.00, df = 1 (p = 0.99); I^2 = 0%
Test for overall effect: Z = 2.77 (p = 0.0006)
CI = confidence interval; IV = inverse variance.

strength training [34, 39] (mean difference (95% confidence interval) 1.81 (–15.33-18.95), p = 0.84, I^2 = 0). Two studies' data for leg lean body mass [33, 38] and two studies for lean body mass [37, 38] were also pooled without yielding any significant difference between groups (0.57 (–0.96-2.10), p = 0.46, I^2 = 0, and 2.05 (–3.96-8.05), p = 0.50, I^2 = 0), respectively). As presented in Table 3 there were more studies reporting on the primary outcome. However, because of incomparable methods and clinical heterogeneity, these trials could not be included in the meta-analysis. The results of the remaining trials did not show significant differences between the intervention and control groups.

Muscle strength

Muscle strength was measured in eight tests in seven studies. In five trials, muscle strength increased [35, 36, 38-40], and in one trial it remained unchanged [41]. In the sixth trail, muscle strength was increased when it was assessed using a 3RM test, whereas it remained unchanged when it was assessed using a dynamometer [37].

Objectively tested physical function

Physical function increased in a study that used a test battery [38], and it remained unchanged in three studies using the Six-minute Walk Test [36, 39, 40], and in two studies using the 30-Second Sit-to-Stand Test [37, 40]. This was also true when the data were pooled for the Six-minute Walk Test (7 (–52-67), p = 0.81, I^2 = 0) and the 30-Second Sit-to-Stand Test (–0.2 (–4.0-3.6), p = 0.92, I^2 = 0) [37, 40].

Quality of life

The SF36 scales Physical Component Scale [35, 38], Physical Function [37, 39] and Vitality [39] increased after strength training in four studies. In two studies, the Mental Component Scale [35, 38] and overall QoL scores [36] remained unchanged. Pooled data for the Physical Component Scale [35, 38] showed positive effects (**Figure 1**), and this was also true for pooled data for Physical Function [37, 39] (9.38 (0.79-18.0), p = 0.03, I^2 = 0). Pooled data for the Mental Component Scale showed no effects of strength training [35, 38] (3.47 (–3.39-17.97)). Finally, one study did not report data for the unchanged SF36 scale scores [40].

Adverse effects

In the trial by DePaul [36], five patients from the strength training group dropped out of the study due to reasons that could be results of the strength training intervention (fatiguing, sore legs, hypotension, a wound, and muscle pain). In the trial by Kirkman [40], no patients dropped out due to adverse effects associated with strength training, even though cramps, delayed onset muscle soreness, hypotension and a wound on the back were reported by participants in the strength training group.

Due to the small number and heterogeneous studies, it was not possible to undertake any of the planned subgroup or sensitivity analyses described in the protocol, including measuring differences between effects of inter- and intradialytic interventions. The GRADE Working Group grades of evidence [24] were categorised as being of "Very low quality" for all evaluated outcomes. The quality of evidence was downgraded because of imprecision (few studies, few participants); heterogeneity and a high or uncertain risk of bias. However, there was only a moderate to small degree of indirectness (limited use of surrogate outcomes/quality measurements) in the included trials.

DISCUSSION

The main finding of this study was inconsistent results of strength training on muscle mass in patients undergoing HD. While the results of the trials indicated positive effects on muscle strength, there were effects of strength training on self-reported physical function and physical health.

As only half of the tests of muscle mass found effects of strength training, it may be difficult to achieve muscle hypertrophy with strength training in patients undergoing HD. However, the variation between the trials in terms of age and gender distribution, tests used, and interventions made makes it difficult to draw any final conclusions. The inconsistent results of the interventions on muscle mass may also be related to relatively low training intensities. Furthermore, regarding tests of muscle mass and size, the analyses of muscle fibre sizes in cross sectional cuts of muscle biopsies has been recognised as more adequate methods for assessing muscle hypertrophy [16]. However, none of the included studies obtained muscle biopsies to investigate the muscle size before and after training, and the methods used may not be adequate for the detection muscle hypertrophy. An excluded trial investigated the effect of interdialytic strength training on muscle fibre cross sectional area analysed in cross sectional cuts of muscle biopsies [42]. After five months of progressive strength training thrice weekly, only a modest increase in type 2X fibres was found [43].

If muscle hypertrophy is difficult to achieve in patients undergoing HD, the question remains which compromising factors have the most significant counteracting effect on muscle growth. The anticipated hypertrophy related to strength training may have been suppressed by the disturbance of the patients' protein balance, as mentioned in the Introduction. In general, dialysis populations are relatively old, and in the attempt to increase muscle mass with strength training, increasing age is a limiting factor due to an age-related reduced protein synthesis rate [44]. However, in most of the trials, the patient samples in the studies included in this review had younger mean ages than in general dialysis populations, and age may therefore not be the primary limiting factor. Regarding the lack of evidence-based muscle hypertrophy in this review, it should be noted that all the included interventions used exercise sessions performed prior to or during HD sessions. If the exercises were performed in a fasting state and patients were not followed by an ingestion of proteins during the HD treatment, an additive protein breakdown may have occurred as a result of the strength training and the following catabolism related to HD. In the study by Dong et al, strength training was combined with an oral energy/protein supplement [41]. The strength training was, however, not associated with any additive positive effects on lean body mass. On the other hand, unchanged muscle mass could be a result of a relatively low training dose with only three sets of one exercise and only moderate progression during the intervention period.

Muscle strength increased in six of eight tests in the included trials, and this indicates an effect of strength training on muscle strength in patients undergoing HD [35-40]. It is, however, important to note that the tests used could have varying validity. In the trail by Johansen et al [37], muscle strength was measured using a dynamometer and a 3RM test. It may be easier to increase the results of RM tests, as the participants in such trials are tested with the equipment that they use in the exercises and with which they thereby become very familiarised. Indeed, in the trial with the two mentioned tests, there was an effect on muscle strength when it was measured using the 3RM test, but not with the dynamometer test.

An increase in muscle strength after a period of strength training may be the result of muscle hypertrophy and/or an improved neuromuscular function. Indeed, in the studies by Song & Sohng [35], Chen et al [38] and Kirkman et al [40] there were positive effects on muscle strength and muscle mass in parallel, suggesting an association. Likewise, in the trial by Dong et al there were no effects on either muscle strength or muscle mass [33]. However, positive effects of strength training on muscle strength may also occur as a result of improved neuromuscular functions [45]. In a study on patients undergoing HD that was not included in this review, increased muscle strength was, indeed, associated with a positive effect on the neuromuscular function assessed using surface electromyography [46]. In addition, only a modest muscle hypertrophy was achieved in the mentioned study, suggesting that an improved neuromuscular function is the primary driver in generating the effects of strength training in patients with several catabolic factors undergoing HD, as described above.

The most pronounced effects of strength training were reported on self-reported physical function and the Physical Component Scale from the SF36. The positive effects on QoL parameters have been presented in a previous study [47]. Whereas objectively tested muscle mass and muscle strength are important physiological outcomes, patient-reported outcomes may be of great importance in relation to motivation and adherence to exercise training interventions.

In this review inter- and intradialytic interventions were included. It may be hypothesised that exercise training during the HD treatment was an unfavourable situation for exercise with higher loads, and thereby associated with a reduced effect on muscle growth [16]. It was, however, not possible to discern any difference in the effects of the intra- and interdialytic strength training, and the two exercise regimes may thus have the same potential effects.

An important aspect of this review was that the investigated seriously ill patient population was able to conduct relatively rigorous strength training. Only one study found that adverse effects were related to the intervention [36]. However, only one drop-out was related to a wound, which may be a critical and concerning point. The risk of developing a wound emphasises the need for a careful approach when patients undergoing dialysis perform strength training, especially patients with diabetes and its complications. In addition, other training modalities should also be considered. Hence, previous studies have reported positive effects on other outcomes, among them aerobic capacity [18].

Based on the results of this review, strength training should be recommended as one of more training modalities to patients undergoing dialysis. The intervention can be used during or not concurrently with HD. Leg exercises should be prioritised as strong legs may have most significant effect on physical function. Furthermore, the legs hold the largest muscles and exercising them may therefore have the most pronounced metabolic effect. Good results should be possible to achieve with 30 min training thrice weekly. The effects may be achieved with different intensities, but the RM should not exceed 15 in order to define the intervention as strength training.

A future multicentre RCT would be welcome to further investigate these issues. The effects could be tested on hard end-points, among them death, after an intervention in the very early phase after HD is initialised. Another additional aim may be to compare effects of strength training performed during and not concurrently with HD. Whilst exercises that are not performed concurrently with HD may be possible to perform with higher loads than during HD, the later may be associated with a counteracting effect on the HD-induced protein catabolism.

The methods used in the individual trials were of various quality. However, because of a limited use of surrogate outcomes, we conclude that there was a medium-to-low degree of indirectness. None of the included trials were categorised as having a low risk of bias in all domains, as it was inherent in the study design that it was not possible to blind the patients undergoing strength training or those who were not. Furthermore, five of the trials did not blind the outcome assessment, and all over more types of potential bias were judged as “unknown”. Thus, the quality of evidence was downgraded as a result of a serious risks of bias. The number of trials and also the number of participants were relatively low, which resulted in a high degree of imprecision in the assessment. In conclusion, the overall quality of the body of evidence for all the outcomes was judged as being very low.

CONCLUSIONS

The data did not demonstrate evidence that strength training is an effective intervention to increase the amount of protein stored as muscle mass in patients undergoing HD. The effect of strength training on muscle strength was positive. The most positive effects of the interventions were found on self-reported physical function and the Physical Component Scale from the SF36 questionnaire. Few adverse effects were reported and patients undergoing dialysis should not be advised against strength training.

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ACCEPTED: 22 November 2018

CONFLICTS OF INTEREST: none. Disclosure forms provided by the authors are available with the full text of this article at Ugeskriftet.dk/dmj

ACKNOWLEDGEMENTS: We take this opportunity to thank *Jette Meelby* (librarian at Nordsjællands Hospital, Hillerød, Denmark) for her valuable assistance with phrasing of the search strategies.

LITERATURE

1. Bonanni A, Mannucci I, Verzola D, et al. Protein-energy wasting and mortality in chronic kidney disease. Int J Environ Res Public Health 2011;8:1631-54.
2. Fahal IH. Uraemic sarcopenia: aetiology and implications. Nephrol Dial Transplant 2014;29:1655-65.
3. Lim VS, Ikizler TA, Raj DS et al. Does hemodialysis increase protein breakdown? Dissociation between whole-body amino acid turnover and regional muscle kinetics. J Am Soc Nephrol 2005;16:862-8.
4. Pupim LB, Flakoll PJ, Majchrzak KM et al. Increased muscle protein breakdown in chronic hemodialysis patients with type 2 diabetes mellitus. Kidney Int 2005;68:1857-65.
5. Lee SW, Park GH, Lee SW et al. Insulin resistance and muscle wasting in non-diabetic end-stage renal disease patients. Nephrol Dial Transplant 2007;22:2554-62.
6. Siew ED, Pupim LB, Majchrzak KM et al. Insulin resistance is associated with skeletal muscle protein breakdown in non-diabetic chronic hemodialysis patients. Kidney Int 2007;71:146-52.
7. Kopple JD, Wang H, Fournier M et al. Transcriptional levels of growth factors in skeletal muscle of maintenance hemodialysis patients. J Ren Nutr 2006;16:212-5.
8. Carrero JJ, Qureshi AR, Nakashima A et al. Prevalence and clinical implications of testosterone deficiency in men with end-stage renal disease. Nephrol Dial Transplant 2011;26:184-90.
9. May RC, Kelly RA, Mitch WE. Metabolic acidosis stimulates protein degradation in rat muscle by a glucocorticoid-dependent mechanism. J Clin Invest 1986;77:614-21.
10. Clapp EL, Bevington A. Exercise-induced biochemical modifications in muscle in chronic kidney disease: occult acidosis as a potential factor limiting the anabolic effect of exercise. J Ren Nutr 2011;21:57-60.
11. Zhang L, Du J, Hu Z et al. IL-6 and serum amyloid A synergy mediates angiotensin II-induced muscle wasting. J Am Soc Nephrol 2009;20:604-12.
12. Garibotto G. Muscle amino acid metabolism and the control of muscle protein turnover in patients with chronic renal failure. Nutrition 1999;15:145-55.
13. Knudsen Sde P, Eidemak I, Molsted S. Health related quality of life in 2002 and 2015 in patients undergoing hemodialysis: a single center study. Ren Fail 2016;38:1234-9.
14. Gracia-Iguacel C, Gonzalez-Parra E, Barril-Cuadrado G et al. Defining protein-energy wasting syndrome in chronic kidney disease: prevalence and clinical implications. Nefrologia 2014;34:507-19.
15. Price SR, Gooch JL, Donaldson SK et al. Muscle atrophy in chronic kidney disease results from abnormalities in insulin signaling. J Ren Nutr 2010;20:S24-8.
16. Fry AC. The role of resistance exercise intensity on muscle fibre adaptations. Sports Med 2004;34:663-79.
17. Andersen JL, Aagaard P. Effects of strength training on muscle fiber types and size; consequences for athletes training for high-intensity sport. Scand J Med Sci Sports 2010;20 Suppl 2:32-8.
18. Cheema BS, Singh MA. Exercise training in patients receiving maintenance hemodialysis: a systematic review of clinical trials. Am J Nephrol 2005;25:352-64.
19. Sheng K, Zhang P, Chen L et al. Intradialytic exercise in hemodialysis patients: a systematic review and meta-analysis. Am J Nephrol 2014;40:478-90.
20. Chan D, Cheema BS. Progressive resistance training in end-stage renal disease: systematic review. Am J Nephrol 2016;44:32-45.
21. Smart N, Steele M. Exercise training in haemodialysis patients: a systematic review and meta-analysis. Nephrology (Carlton) 2011;16:626-32.
22. Bessa B, de Oliveira Leal V, Moraes C et al. Resistance training in hemodialysis patients: a review. Rehabil Nurs 2015;40:111-26.
23. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions 5.1.0. London: The Cochrane Collaboration, 2011.
24. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539-58.
25. Guyatt GH, Oxman AD, Santesso N et al. GRADE guidelines: 12. Prepar-

ing summary of findings tables-binary outcomes. J Clin Epidemiol 2013;66:158-72.
26. Konstantinidou E, Koukouvou G, Kouidi E et al. Exercise training in patients with end-stage renal disease on hemodialysis: comparison of three rehabilitation programs. J Rehabil Med 2002;34:40-5.
27. Molsted S, Eidemak I, Sorensen HT et al. Five months of physical exercise in hemodialysis patients: effects on aerobic capacity, physical function and self-rated health. Nephron Clin Pract 2004;96:c76-81.
28. van Vilsteren MC, de Greef MH, Huisman RM. The effects of a low-to-moderate intensity pre-conditioning exercise programme linked with exercise counselling for sedentary haemodialysis patients in The Netherlands: results of a randomized clinical trial. Nephrol Dial Transplant 2005;20:141-6.
29. Olvera-Soto MG, Valdez-Ortiz R, Lopez Alvarenga JC et al. Effect of resistance exercises on the indicators of muscle reserves and handgrip strength in adult patients on hemodialysis. J Ren Nutr 2016;26:53-60.
30. Matsufuji S, Shoji T, Yano Y et al. Effect of chair stand exercise on activity of daily living: a randomized controlled trial in hemodialysis patients. J Ren Nutr 2015;25:17-24.
31. de Lima MC, Cicotoste Cde L, Cardoso Kda S et al. Effect of exercise performed during hemodialysis: strength versus aerobic. Ren Fail 2013;35:697-704.
32. Bennett PN, Fraser S, Barnard R et al. Effects of an intradialytic resistance training programme on physical function: a prospective stepped-wedge randomized controlled trial. Nephrol Dial Transplant 2016;31:1302-9.
33. Dong J, Sundell MB, Pupim LB et al. The effect of resistance exercise to augment long-term benefits of intradialytic oral nutritional supplementation in chronic hemodialysis patients. J Ren Nutr 2011;21:149-59.
34. Kopple JD, Wang H, Casaburi R et al. Exercise in maintenance hemodialysis patients induces transcriptional changes in genes favoring anabolic muscle. J Am Soc Nephrol 2007;18:2975-86.
35. Song WJ, Sohng KY. Effects of progressive resistance training on body composition, physical fitness and quality of life of patients on hemodialysis. J Korean Acad Nurs 2012;42:947-56.
36. DePaul V, Moreland J, Eager T et al. The effectiveness of aerobic and muscle strength training in patients receiving hemodialysis and EPO: a randomized controlled trial. Am J Kidney Dis 2002;40:1219-29.
37. Johansen KL, Painter PL, Sakkas GK et al. Effects of resistance exercise training and nandrolone decanoate on body composition and muscle function among patients who receive hemodialysis: A randomized, controlled trial. J Am Soc Nephrol 2006;17:2307-14.
38. Chen JL, Godfrey S, Ng TT et al. Effect of intra-dialytic, low-intensity strength training on functional capacity in adult haemodialysis patients: a randomized pilot trial. Nephrol Dial Transplant 2010;25:1936-43.
39. Cheema B, Abas H, Smith B et al. Progressive exercise for anabolism in kidney disease (PEAK): a randomized, controlled trial of resistance training during hemodialysis. J Am Soc Nephrol 2007;18:1594-601.
40. Kirkman DL, Mullins P, Junglee NA et al.- Anabolic exercise in haemodialysis patients: a randomised controlled pilot study. J Cachexia Sarcopenia Muscle 2014;5:199-207.
41. Dong J, Sundell MB, Pupim LB et al. The effect of resistance exercise to augment long-term benefits of intradialytic oral nutritional supplementation in chronic hemodialysis patients. J Ren Nutr 2011;21:149-59.
42. Molsted S, Harrison AP, Eidemak I et al. The effects of high-load strength training with protein- or nonprotein-containing nutritional supplementation in patients undergoing dialysis. J Ren Nutr 2012;23:132-40.
43. Andersen JL, Aagaard P. Myosin heavy chain IIX overshoot in human skeletal muscle. Muscle Nerve 2000;23:1095-104.
44. Kumar V, Atherton P, Smith K et al. Human muscle protein synthesis and breakdown during and after exercise. J Appl Physiol 2009;106:2026-39.
45. Aagaard P. Training-induced changes in neural function. Exerc Sport Sci Rev 2003;31:61-7.
46. Molsted S, Andersen JL, Eidemak I et al. Increased rate of force development and neuromuscular activity after high load resistance training in patients undergoing dialysis. Nephrology (Carlton) 2013;18:770-6.
47. Molsted S, Harrison AP, Eidemak I et al. The effects of high-load strength training with protein- or nonprotein-containing nutritional supplementation in patients undergoing dialysis. J Ren Nutr 2013;23:132-40.