Patient-Oriented, Translational Research: Review Article

American Journal of Nephrology

Am J Nephrol 2019;50:240–254
DOI: 10.1159/000502447

Received: June 10, 2019
Accepted: July 21, 2019
Published online: August 27, 2019

Exercise Training and Outcomes in Hemodialysis Patients: Systematic Review and Meta-Analysis

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Keywords
End-stage renal disease · Exercising training · Dialysis efficacy · Physical function · Meta-analysis

Abstract
Background: Inadequate dialysis, renal hypertension, and impaired exercise capacity are factors that affect the quality of life (QoL) and mortality of adults with end-stage renal disease (ESRD) undergoing hemodialysis (HD). This systematic review provided valid evidence about the effect of exercise training on single-pool Kt/V (sp Kt/V), blood pressure, and peak uptake oxygen (VO_2 peak). ***Method:*** A systematic review and meta-analysis of published randomized controlled trials (RCTs) that evaluated the effects of no <8 weeks' exercise training on the physical fitness outcomes for adults with ESRD undergoing HD were accepted in this study. ***Results:*** Included 20 trials (677 participants) indicated that various exercise types improved aerobic capacity, walking capacity, and health-related QoL totally. Of note, aerobic exercise and combined exercise were the predominant exercise types. ***Conclusion:*** Based on our evidence, aerobic exercise or combined exercise at least for 8 weeks to 12 months, 3 times weekly, will be beneficial to physical conditions of the patients with ESRD undergoing HD. The clinical staff can treat patients with the evidence above. Future studies need to provide more information basis for the construction of patient exercise system by adding various exercise combinations.

Introduction

End-stage renal disease (ESRD), the final stage of chronic kidney disease (CKD) that exists in 8–16% population worldwide [1], is characterized as irreversible kidney function and the prevalence is increasing annually [2, 3]. Hemodialysis (HD) is an important and commonly used renal replacement therapy (RRT) for ESRD patients [4]. According to International Society of Nephrology, 2.62 million people received RRT to treat ESRD worldwide. Most of them were treated with HD.

Even as the HD treatment improves, the complications, such as renal hypertension [5] and reduced aerobic capacity and walking capacity, which were both severely impaired in patients with ESRD undergoing HD compared to the same stage patients [6, 7], resulting from

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ESRD or HD still exist. The complications degraded quality of life (QoL) and elevated the mortality of patients with ESRD [8, 9]. Recent studies reported that exercise can lower blood pressure (BP) and elevate aerobic capacity, walking capacity, and QoL in patients with ESRD receiving HD [10–14], while some did not [15, 16]. Hence, it is meaningful to synthesize eligible trials and analyze whether exercise had an effect on physical fitness of adults with ESRD. Besides, for patients receiving HD, inadequate dialysis indicates that excess water and toxins produced in the dialysis interval would persist in the body and rise up the rate of cardiovascular complications eventually. Exercise also could reduce morbidity and mortality by improving the dialysis adequacy [2].

Although the National Kidney Function recommends that exercise training should be a cornerstone for patients receiving HD to control complications and modality [17], the concise exercise training parameters, including exercise type, duration, intensity, and frequency, were not mentioned and still unclear. But recently, most systematic reviews had detailed part of exercise training parameters for CKD patients receiving HD [18–20]. Meanwhile, a few systematic reviews focus on patients with ESRD [21, 22]. And it is controversial whether the exercise evidence for patients with CKD could be used as evidence for patients with the most severe stage of CKD, ESRD. Besides, in these reviews, the exercise was limited during dialysis with 3 exercise types including aerobic exercise, resistance exercise, and combined exercise. But it is important to observe the effects of all types of exercise, such as home, intradialytic, and non-intradialytic, conducted at different exercise time. In addition, the number of randomized controlled trials (RCTs) is increasing, resulting in outcomes such as BP, exercise capacity, and dialysis efficacy. But the effect of exercise on these outcomes for patients with ESRD undergoing HD is vague.

This study aims to synthesize all the eligible RCTs and systematically analyze the effects of exercise training on dialysis efficacy, BP, exercise capacity, and QoL in adults with ESRD undergoing HD. Besides, this study can update the evidence base for the recommendation of exercise interventions.

Method

This review followed the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analyses. This systematic review is registered with the International Prospective Register of Systematic Reviews, and the registration number is CRD42019118294.

Data Sources and Searches

We searched the electronic bibliographic databases, including MEDLINE (from 1950 to November 2018), EMBASE (from 1974 to November 2018), the Cochrane Library (the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials; from the start to November 2018), CINAHL (from 1981 to November 2018), Web of Science (from 1900 to November 2018), PubMed (from 1950 to November 2018), 万方/Wan Fang data (from 1900 to November 2018), and 中国生物医学文献数据库/SinoMed (from 1860 to November 2018). The following terms were used to perform the search: intradialytic, hemodialysis, haemodialysis, renal dialysis, exercise, physical fitness, physical training, exercise therapy, randomized controlled trial, random, and controlled clinical trial. The detailed search strategy is shown in the PDF document (http://www.crd.york.ac.uk/PROSPEROFILES/118294_STRATEGY_20181218.pdf). For language restrictions, only studies in English and Chinese were accepted.

Selection Criteria for Studies

Only published RCTs that evaluated the effects of no <8 weeks' exercise training on any one of the outcomes were accepted in this study. Participants older than 18 years with a diagnosis of ESRD requiring maintenance HD and have been on HD >3 months were included. Patients undergoing any other RRT and affected by acute kidney failure were excluded. Exercise training consisting of aerobic training, resistance training, and combined training for a minimum of 8 weeks, either on intradialytic or on nondialysis days, were accepted in the intervention group. Usual HD care or low-intensity (sham) activity such as stretching was regarded as the control group. The main outcomes of this review are dialysis efficacy single-pool Kt/V (sp Kt/V), BP (systolic BP [SBP], diastolic BP [DBP]), and peak oxygen consumption (VO_2 peak). The secondary outcomes are physical function (6-min walk distance) and health-related QoL (physical and mental component dimensions [PCS, MCS] of the short-form 36 health questionnaire [SF-36]).

Data Extraction and Quality Assessment

The search results (titles and abstracts) were screened by 2 reviewers (M.H. and N.X.) independently until potential studies are identified. Then 2 reviewers assessed the full texts of these papers to determine whether they met the inclusion criteria. Data were extracted from the studies selected for inclusion by 2 reviewers to ensure consistency and accuracy. The data extracted from the RCTs included the study characteristics, interventions, and outcome measures.

The quality of each of the included studies was assessed for judging risk of bias, as recommended by the Cochrane Handbook for Systematic Reviews of Interventions, which considers 7 aspects (random generation, allocation concealment, blinding of participants and outcome assessment, incomplete outcome data, selective reporting, other bias). A third reviewer would adjudicate the disagreement related to data extraction and quality assessment (G.M.).

Data Synthesis and Analysis

A quantitative synthesis for the intervention effects of each study was summarized by calculating standardized mean differences because there are no dichotomous outcomes in the study. Data were analyzed using standard meta-analytic techniques.

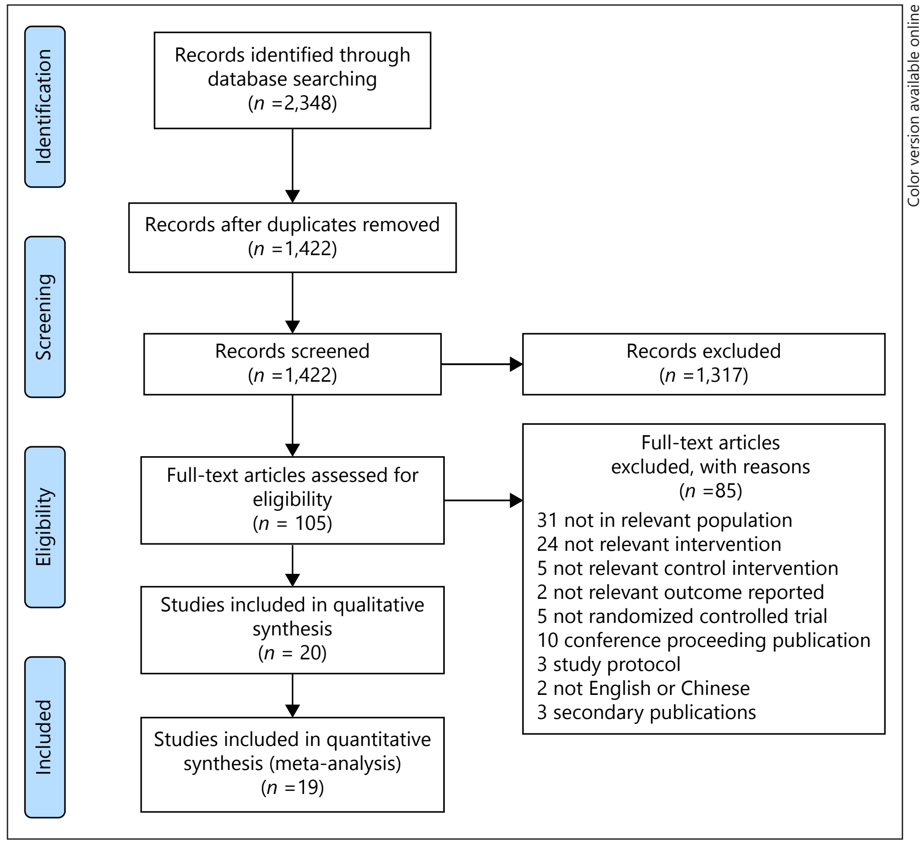

Fig. 1. PRISMA flow diagram for the systematic review and meta-analysis.

Assessment for heterogeneity was performed using the I^2 statistic, with values >25 and >50% being considered to be indicators of moderate and substantial heterogeneity, respectively. If significant heterogeneity was detected, subgroup analysis was conducted to identify the cause of exercise types such as aerobic exercise, resistance exercise, and combined exercise. Otherwise, the random-effects model was used as the default method of analysis. Alternatively, we would give up data synthesis instead of providing descriptions only.

Publication bias will be assessed by plotting the inverse of the SEs of the effect estimates using Egger's regression. When the number of outcomes was >10, funnel plots were used to explore symmetry, which will be assessed visually. Sensitivity analyses were used to test the reliability and stability of the results.

Analyses were conducted on Review Manager Software (RevMan 5.3). In addition, publication bias and sensitivity analyses were conducted by STATA.

Results

A total of 2,348 publications were screened first, and 926 duplicates were excluded (Fig. 1). Subsequently, 1,317 publications were rejected due to wrong population and wrong interventions after 2 reviewers read titles and abstracts. Then in the full-text reviewing stage, potentially 105 references were reviewed and checked whether they accord with the criteria. Finally, 20 references involving 677 participants were identified and included in the study.

Included trials were distributed in the United States, Australia, New Zealand, Sweden, Brazil, and Canada and occurred between 1986 and 2018. The minimum sample size was 13 and the maximum was 96. The mean age of participants ranged from 30 to 70 years old.

One trial may include 2 or 3 interventions. For example, there were 2 intervention groups, aerobic exercise and resistance exercise, in Afshar's trial [23]. Konstantinidou conducted a trial with 3 intervention groups including aerobic exercise at home and combination exercise at outpatient and during intradialytic days [24]. The most common exercise type was aerobic exercise, and there are 14 out of 25 comparisons [10, 13, 14, 16, 23–31]. The combined exercise [24, 31–35] and resistance exercise [15, 23, 36, 37] were followed. Eighteen trials took place during HD [13, 14, 16, 23–26, 28, 10]; others took place at home [16, 24, 30, 31] or during predialysis [37]. The total intervention duration ranged from 8 weeks [23, 31] to 12 months [25, 27]. Three months [13, 26, 28, 29, 32, 35–37] and 6 months [16, 24, 30] were chosen by most trials. When it comes to exercise frequency, 3 times per week [13–16, 23–34, 36, 37] was the most popular, followed by 2 [34] to 5 [24, 30] times per week. And one trial [27] did not report the frequency. In the included reports, the intensity of exercise often was moderate (55–60% of the peak power) [13, 14, 23, 24, 27, 30, 35, 37]. Moreover, single exercise duration ranged from 15 min [16, 31] to 90 min [25, 30, 33, 34]. The detailed characteristics of included reports are shown in Table 1.

Assessment of Risks of Bias and Publication Bias

The risks of bias were frequently high or uncertain because of the incomplete methodology description (Fig. 2, 3). Although every study reported that they used randomization, only 4 (20%) studies reported the way random sequence was generated and the participants in the 4 studies were allocated in a proper concealing way. The computer was used to automatically generate the numbers, and the numbers were separately put in sealed and opaque envelopes. Considering that exercise intervention was a trial that was not blind to both participants and investigators, the performance bias was high for all the trials included. In 4 studies, outcome measurement was blinded. Most trials (90%) reported the attrition, whereas only one study conducted the intent-to-treat analysis. Sixteen trials showed complete data. In 17 trials, an additional information revealed that potential low risk of bias existed in studies.

For publication bias, sp Kt/V, SBP, DBP, VO_2 peak, PCS, and MCS ($p = 0.91, 0.51, 0.30, 0.99, 0.74, 0.59 > 0.05$) showed no significant publications bias in the Egger's test. Funnel plot was symmetrical for VO_2 peak in 10 studies. Combined with the Egger's test of VO_2 peak, there was no publication bias of VO_2 peak.

Meta-Analysis

Dialysis Efficacy (sp Kt/V)

Sp Kt/V was measured in 8 trials involving 133 participants in the intervention group and 124 participants in the control group totally (Fig. 4) [14, 15, 23, 26, 31, 35, 36]. There was a low degree of heterogeneity across studies for sp Kt/V ($I^2 = 0\%$, $p = 0.79$). Data showed that exercise training did not significantly improve sp Kt/V in ESRD patients undergoing HD (SMD 0.19, 95% CI −0.06 to 0.43, $p = 0.14$). Sensitivity analysis was conducted and showed that the result did not change, which indicated that the result was stable and reliable.

Blood Pressure

BP was measured in 7 trials involving 137 participants in the intervention group and 123 participants in the control group (Fig. 5, 6) [16, 28, 30, 34, 35]. There were low and high degrees of heterogeneity across studies for SBP and DBP ($I^2 = 8\%$, $p = 0.37$, and $I^2 = 68\%$, $p = 0.005$, respectively). The meta-analysis of all patients in the 7 studies showed that exercise training did not decrease the patients' SBP at rest (SMD −0.17, 95% CI −0.41 to 0.08, $p = 0.18$). An exercise training-type subgroup analysis was conducted due to the high degree of heterogeneity existed in DBP. Data showed that both aerobic exercise and combined exercise could not decrease the patients' DBP at rest (SMD 0.07, 95% CI −0.32 to 0.46, $p = 0.73$; SMD −0.62, 95% CI −1.60 to 0.37, $p = 0.22$), and the low and high degree of heterogeneity existed across the aerobic exercise and combined exercise ($I^2 = 0\%$ and $I^2 = 86\%$, respectively). No trial had used resistance training only. Sensitivity analyses were conducted and showed that the results did not change, which indicated that the results of SBP and DBP were stable and reliable.

VO_2 peak

VO_2 peak was measured in 10 trials involving 196 participants in the intervention group and 175 participants in the control group (Fig. 7, 8) [13, 24, 25, 27, 29, 30, 33–35]. Totally, the meta-analysis of all patients showed that exercise training increased the VO_2 peak of ESRD patients (SMD 0.73, 95% CI 0.52–0.95, $p < 0.00001$). Because a high degree of heterogeneity existed in VO_2 peak, a subgroup analysis was conducted. Data showed that both aerobic exercise and combined exercise improved VO_2 peak significantly (SMD 0.64, 95% CI 0.28–1.01, $p = 0.0006$, and SMD 0.78, 95% CI 0.51–1.05, $p < 0.00001$, respectively). Sensitivity analysis was conducted and showed that the result did not change, which indicated that the result was stable and reliable. The effect of resistance exercise on VO_2 peak had not been studied.

Six-Minute Walk Test

Six-minute walk test (6MWT) was measured in 7 trials involving 100 participants in the intervention group and 105 participants in the control group (Fig. 9) [14–16, 29, 32, 36]. Totally, the meta-analysis of all patients showed that exercise training increased the 6MWT of ESRD patients (SMD 1.01, 95% CI 0.26–1.76, $p = 0.008$). Because a high degree of heterogeneity existed in 6MWT, a subgroup analysis was conducted to analyze the effect size of 6MWT for ESRD undergoing HD. The distances show a significant increase in 6 min in the aerobic exercise group

Table 1. Characteristics of included studies

Author, year	Country	Sample size (male), *n* (%)		Age, years, mean ± SD		Years of dialysis, months, mean ± SD		Time	Type	Duration	Frequency	Intervention	Outcomes
		intervention	control	intervention	control	intervention	control						
Goldberg et al. [27], 1986	America	13 (8)	12 (7)	40±14	36±10	23±18	40±31	Unclear	AE	12 months	Unclear	70–80% of VO_2max endurance training for 45 min (cycling using bicycle ergometer and walking-jogging)	VO_2 peak
Cheema et al. [37], 2007	New Zealand	24 (17)	25 (17)	60±15.3	65.0±12.9	26.4		Intradialytic	RE	12 weeks	3 times/week	Borg scale 15–17 two sets of 8 repetitions of 10 exercises using free-weight dumbbells, weighted ankle cuffs and thera-band tubing	6MWT, sp Kt/V
Toussaint et al. [28], 2008	Australia	9 (4)	10 (6)	67	70	35±31	72±56	Intradialytic	AE	3 months	3 times/week	At an intensity determined by patients' own perceived level of exertion using bicycle ergometers for minimum 30 min	SBP, DBP
Afshar et al. [23], 2010	Iran	7 (7)	7 (7)	50.7±21.06	53±19.4	25.71±7.61	24.86±15.44	Intradialytic	AE	8 weeks	3 times/week	At borg RPE of 12–16 5-min warm up, 10–30 min stationary cycling at an intensity of 12–16,5-min cool down	sp Kt/V
Afshar et al. [23] 2010	Iran	7 (7)	7 (7)	51±16.4	53±19.4	24.86±18.69	24.86±15.44	Intradialytic	RE	8 weeks	3 times/week	At an intensity of 15–17 10–30 min using ankle weights for knee extension, hip abduction and flexions	sp Kt/V
Koh et al. [16], 2010	Australia	15 (11)	16 (8)	52.3±10.9	51.3±14.4	30.5±26.6	30.5±26.6	Intradialytic	AE	6 months	3 times/week	At the first 2 h at borg RPE of 12–13 (low) trained on cycle ergometers of dialysis at least 15 min per exercise session in the first 2 weeks and progress to 30 min per exercise session by week 12 and 45 min by week 24	6MWT, PCS, MCS, SBP, DBP
Koh et al. [16], 2010	Australia	15 (10)	16 (8)	52.1±13.6	51.3±14.4	30.5±26.6	30.5±26.6	Home	AE	6 months	3 times/week	At borg RPE of 12–13 (low) start at 15 min/session and progress to 45 min by week 24	6MWT, PCS, MCS, SBP, DBP
Kouidi et al. [25], 2010	Greece	24	20	46.3 ±11.2	45.8±10.8	73.2±55.2	75.6±58.8	Intradialytic	AE	12 months	3 times/week	During the first 2 h of the HD treatment 11–13 between 60 and 90 min: 5-min warm-up, a 30–60 min active cycling, a 20-min strengthening program, and a 5-min cool-down period	VO_2 peak
Reboredo et al. [26], 2010	Brazil	11 (4)	11 (4)	49.6±10.6	43.5±12.8	41.9±42.4	60.1±54.4	Intradialytic	AE	12 weeks	3 times/week	During the first 2 h of hemodialysis between four and 6 warm up comprised stretching the lower limbs for approximately 10 min, conditioning consisted of aerobic exercise training for up to 35 min	sp Kt/V
Reboredo et al. [13], 2011	Brazil	12 (7)	12 (7)	50.7±10.7	42.2±13	39.6±40.8	57.6±52.8	Intradialytic	AE	12 weeks	3 times/week	During the first 2 h of HD between 4 and 6 a 10-point borg scale warmed-up for 10 min, 35 min of aerobic exercise	VO_2 peak

Table 1. (continued)

Author, year	Country	Sample size (male), *n* (%)		Age, years, mean ± SD		Years of dialysis, months, mean ± SD		Time	Type	Duration	Frequency	Intervention	Outcomes
		intervention	control	intervention	control	intervention	control						
Dobsak et al. [14], 2012	Czech Republic	11 (4)	10 (4)	58.2±7.2	60.1±8.2	49.2±25.2	49.2±27.6	Intradialytic	AE	20 weeks	3 times/week	Performed between the 2nd and the 3rd h of HD at the level of 60% of the individual peak 5 min of warm-up period, bicycle ergometer 2 * 20 min after the first 5 weeks which included 20 min bicycling	PCS, MCS, sp Kt/V , 6MWT
Song et al. [38], 2012	Korea	20 (8)	20 (12)	52.1±12.4	54.6±10.1	38.9±26.1	45.9±56.2	Predialysis	RE	12 weeks	3 times/week	In 11–15 Predialysis 5 min warm up and 5 min cool down, 20 min PRT to strengthen the participants' upper and lower body muscles, using elastic bands and sand bags	PCS, MCS
Pellizzaro et al. [15], 2013	Brazil	14 (7)	14 (8)	48.9±10.1	51.9±11.6	54	54	Intradialytic	RE	10 weeks	3 times/week	In the first 2 h of HD 50% of 1RM 3 sets of 15 knee extension repetitions	6MWT, sp Kt/V
Cooke et al. [10], 2018	Canada	10 (7)	10 (7)	58.2±17.2	52.5±15.4	Unclear		Intradialytic	AE	4 months	3 times/week	For safety, no patient exercised past the halfway mark of their dialysis session. 12–16 out of 20 points pedaling	SBP, DBP
Deligiannis et al. [31], 1999	Greece	16 (11)	12 (4)	46.4±13.9	50.2±7.9	78±62	79±86	Non-intradialytic	CE	6 months	3 times/week	60–70% of the HRmax 90 min each time, including 10-min warm up on a cycle-ergometer or treadmill, a 50-min intermittent aerobic exercise program, and a 10-min cool down 10-min stretching and low-weight resistance program after first 2 months after the first 3 months the younger patients were playing basketball and football once a week, whereas the older patients were swimming	VO_2 peak, SBP, DBP
Deligiannis et al. [31], 1999	Greece	10 (8)	12 (4)	51.4±12.5	50.2±7.9	62±37	79±86	Home	AE	6 months	5 times/week	Heart rate of SO to 60% cycle 30 min each time, performed simple flexibility and muscular extension exercises	VO_2 peak, SBP, DBP
DePaul et al. [33], 2002	Canada	20 (10)	18 (13)	55±16	54±14	50.4±57.6	55.2± 54	Intradialytic	CE	12 weeks	3 times/week	Borg scale 13 ("somewhat strong") 20 min of aerobic training progressive strength training: 1 set of 10 repetitions; number of sets: 1–3	6MWT, SF-36
Konstantinidou et al. [24], 2002	Greece	16 (11)	12 (4)	46.4±13.9	50.2±7.9	78±62	79±86	Outpatient	CE	6 months	3 times/week	60–70% of the HRmax 10-min warm up, a 30 min intermittent aerobic exercise program, a 10-min stretching and low-weight resistance program 10-min cool down	VO_2 peak
Konstantinidou et al. [24], 2002	Greece	10 (8)	12 (4)	48.3±12.1	50.2±7.9	72±66	79±86	Intradialytic	CE	6 months	3 times/week	First 2 h of their HD sessions. 70% of Hrmax aerobic and strength training for 60 min program 3 times per week (30 min with a bed bicycle ergometer and 30 min for strength and flexibility)	VO_2 peak

Table 1. (continued)

Author, year	Country	Sample size (male), *n* (%)		Age, years, mean ± SD		Years of dialysis, months, mean ± SD		Time	Type	Duration	Frequency	Intervention	Outcomes
		intervention	control	intervention	control	intervention	control						
Konstantinidou et al. [24], 2002	Greece	10 (8)	12 (4)	51.4±12.5	50.2±7.9	62±37	79±86	Home	AE	6 months	At least 5 times/week	Heart rate of 50–60% of the maximal heart rate cycling 30 min each time	VO_2 peak
Parsons et al. [32], 2004	Canada	6 (3)	7 (4)	60±17	49.0±25.0	35±25	49±26	Home	AE	8 weeks	3 times/week	First 3 h of their HD sessions. 40–50% maximal work capacity cycle ergometry exercise for 15 min	sp Kt/V, PCS, MCS
van Vilsteren et al. [36], 2005	Netherlands	53 (33)	43 (30)	52±15	58±16	38.6±49	46.8±52.9	Intradialytic	CE	12 weeks	2–3 times/ week	Borg scale 12–16 (<60% maximal capacity) A 5- to 10-min warm-up and cool-down; a 20-min exercise program including calisthenics, steps, flexibility, and low weight resistance training Cycling 20–30 min 2–3 times per week The techniques based on the transtheoretical model, motivational interviewing, and health counseling	VO_2 peak, SBP, DBP, PCS, MCS, sp Kt/V
Kouidi et al. [34], 2009	America	30 (18)	29 (16)	54.6±8.9	53.2±6.1	75.6±44.4	74.4±46.8	Intradialytic	CE	10 months	3 times/week	During the first 2 h of HD sessions. 13 (somewhat hard) on the borg 90 min (10 min warm-up, active cycling 40 min. progressive muscle strengthening 3 sets of 15 repetitions using thera-band tubinga and weights to the limbs and 10 min cool-down	VO_2 peak
Ouzouni et al. [35], 2009	Greece	19 (14)	14 (13)	47.4±15.7	50.5±11.7	92.4±84	103.2±72	Intradialytic	CE	10 months	3 times/week	The first 2 h of their hemodialysis at 13–14 (somewhat hard) of the borg 60–90 min (cycling: 30 min, strengthening: 30 min, flexibility exercise: 30 min)	VO_2 peak, SBP, DBP, PCS, MCS
Groussard et al. [30], 2015	France	8 (5)	10 (7)	66.5±4.6	68.4±3.7	36.6±8.2	41.2±8.1	Intradialytic	AE	3 months	3 days/week	The first 2 h of dialysis. at 55–60% of the peak power AE exercise consisting of 30 min cycling (5-min warm-up, 15–30 min at a tolerable pace and 5-min cool-down)	VO_2 peak, 6MWT

VO_2 peak, peak uptake oxygen; AE, AE exercise; RE, resistance exercise; CE, combined exercsie; 6MWT, 6-minute walk test; sp Kt/V, single-pool Kt/V; SBP, systolic blood pressure; DBP, diatolic blood pressure; PCS, phycisal compenont score; MCS, mental component dimensions ; HD, hemodialysis.

(SMD 0.79, 95% CI 0.01–1.56, $p = 0.05$), whereas the distances did not show a significant increase in 6 min in the resistance exercise group (SMD 2.12, 95% CI −1.02 to 5.26, $p = 0.19$). Meanwhile, there was only one trial that studied the effect of combined exercise on 6MWT and showed that there was no difference between the combined exercise and control groups. Sensitivity analysis was conducted and showed that the result did not change, which indicated that the result was stable and reliable. Though the Egger's test showed significant publication bias ($p = 0.02 < 0.05$), there was no indication of publication with the Duval's trim and fill method (no new studies added). Hence, the result for 6MWT was stable.

Health-Related QoL (SF-36)

SF-36 was measured in 7 trials involving 139 participants in the intervention group and 124 participants in the control group totally (Fig. 10, 11) [14, 16, 31, 34, 35, 37], and the moderate and low degree of heterogeneity existed in PCS and MCS ($I^2 = 27\%$, $I^2 = 0\%$). Data showed that exercise training improved PCS and MCS in the SF-36 significantly in ESRD patients undergoing HD (SMD 0.34, 95% CI 0.09–0.59, $p = 0.007$, and SMD 0.27, 95% CI: 0.02–0.51, $p = 0.03$, respectively). Sensitivity analyses were conducted and showed that the results did not change, which indicated that the results were stable and reliable.

Discussion

Dialysis replaced part of kidney's function in order to prolong the ESRD patients' survival time and the adequacy of dialysis reflected by dialysis efficacy. Sp Kt/V was measured to quantize the dialysis adequacy, and the target minimum dose was 1.2 recommended by K/DOQI [17]. Inadequate dialysis indicated that excess water and toxins produced in the dialysis interval would still remain in the body, resulting in uremic neuropathies and cardiovascular complications [38]. Intradialytic exercise was reported to improve the dialysis efficacy by increasing blood flow and perfusion of muscle tissue and enlarging surface area, which would diffuse greater flux in circulating toxins and urea from the muscle into circulation and removed by dialysis [2, 20]. Though the included exercise trainings were performed during dialysis, the result of this meta-analysis did not provide strong evidence for mechanism above. Even the effect size of increased sp Kt/V in the intervention group was more than the control group, there was no statistical significance. Of note, all the

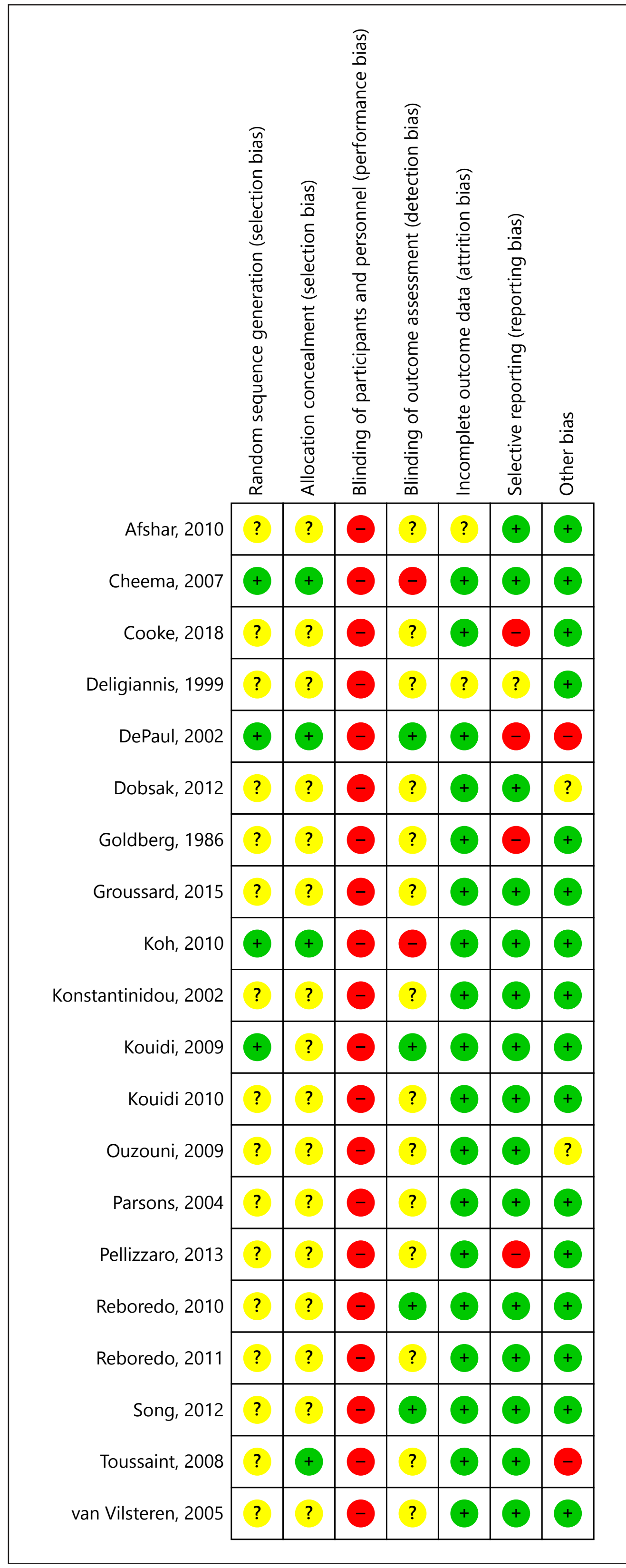

Fig. 2. Risk of bias summary.

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Am J Nephrol 2019;50:240–254
DOI: 10.1159/000502447

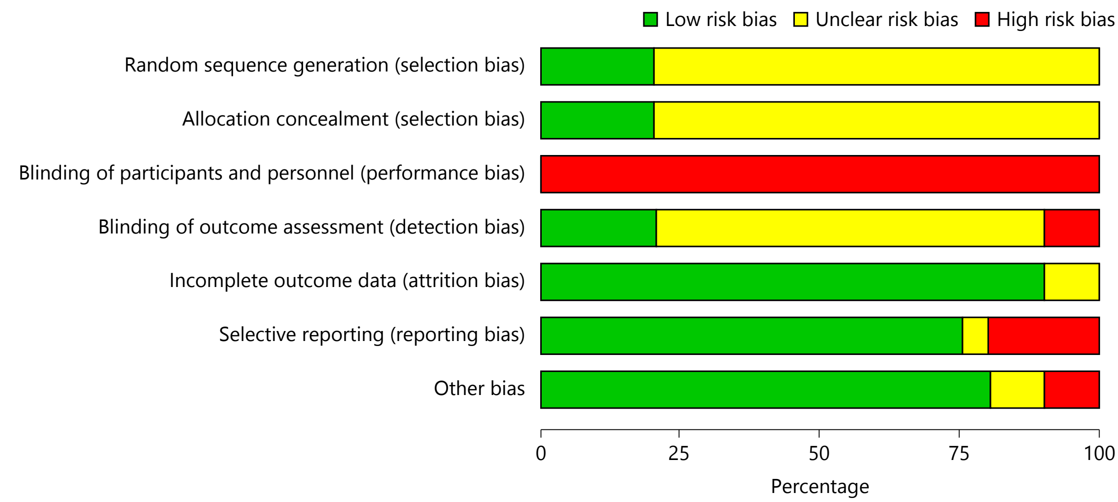

Fig. 3. Risk of bias graph.

Study of subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. mean differnce IV, fixed, 95% CI
Afshar, 2010	0	0.3	7	0.01	0.3	7	5.5%	–0.03 [–1.08, 1.02]
Afshar, 2010	0.01	0.3	7	0.01	0.3	7	5.6%	0.00 [–1.05, 1.05]
Cheema, 2007	0.1	0.5	24	0.1	0.4	25	19.4%	0.00 [–0.56, 0.56]
Dobsak, 2012	0.21	0.3	11	–0.08	0.4	10	7.6%	0.79 [–0.10, 1.69]
Parsons, 2004	0	0.3	6	–0.08	0.2	7	5.0%	0.30 [–0.80, 1.40]
Pellizzaro, 2013	0.08	0.1	14	0.1	0.1	14	11.0%	–0.19 [–0.94, 0.55]
Reboredo, 2010	0.4	0.7	11	0.2	0.6	11	8.6%	0.30 [–0.55, 1.14]
van Vilsteren, 2005	0.06	0.2	53	0	0.2	43	37.2%	0.30 [–0.11, 0.70]
Total (95% CI)			133			124	100.0%	0.19 [–0.06, 0.43]

Heterogeneity: Chi² = 3.87, df = 7 (p = 0.79); I^2 = 0%
Test for overall effect Z = 1.49 (p = 0.14)

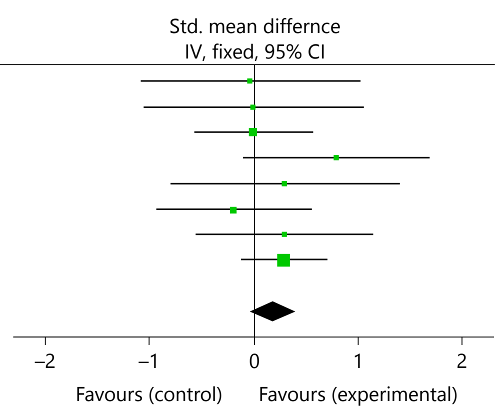

Fig. 4. Effects of exercise training on Sp Kt/V.

Study of subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. mean differnce IV, fixed, 95% CI
Deligiannis, 1999	–9	15.7	16	1	8.9	12	10.1%	–0.73 [–1.51, 0.04]
Deligiannis, 1999	–2	17.5	10	1	8.9	12	8.6%	–0.21 [–1.06, 0.63]
Koh, 2010	–2	30.6	15	–9	25.4	16	12.2%	0.24 [–0.46, 0.95]
Koh, 2010	–9	22	15	–9	25.4	16	12.3%	0.00 [–0.70, 0.70]
Ouzouni, 2009	–7.6	13.4	19	1.1	8.1	14	11.9%	–0.74 [–1.46, –0.02]
Toussaint, 2008	–3.1	14.1	9	–2.6	22	10	7.5%	–0.03 [–0.93, 0.88]
van Vilsteren, 2005	–5	25	53	–4	24.1	43	37.6%	–0.04 [–0.44, 0.36]
Total (95% CI)			137			123	100.0%	–0.17 [–0.41, 0.08]

Heterogeneity: Chi² = 6.49, df = 6 (p = 0.37); I^2 = 8%
Test for overall effect Z = 1.33 (p = 0.18)

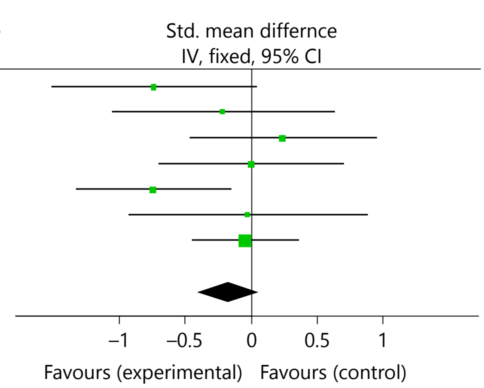

Fig. 5. Effects of exercise training on systolic BP.

Study of subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. mean differnce IV, random, 95% CI
2.4.1 aerobic exercise								
Dobsak, 2012	–4	11.4	10	0	4.4	12	12.7%	–0.46 [–1.32, 0.39]
Koh, 2010	–6	10	15	–5	13.1	16	14.6%	–0.08 [–0.79, 0.62]
Koh, 2010	1	16	15	–5	13.1	16	14.5%	0.40 [–0.31, 1.11]
Toussaint, 2008	1.9	10	9	–2.1	10.1	10	12.0%	0.38 [–0.53, 1.29]
Subtotal (95% CI)			49			54	53.8%	0.07 [–0.32, 0.46]
Heterogeneity: Tau^2 = 0.00; Chi^2 = 2.96, df = 3 (p = 0.40); I^2 = 0%								
Test for overall effect: Z = 0.34 (p = 0.73)								
2.4.2 resistance exercise								
Subtotal (95% CI)			0			0		Not estimable
Heterogeneity: not applicable								
Test for overall effect: not applicable								
2.4.3 combined exercise								
Deligiannis, 1999	–8	8	16	0	4.4	12	13.1%	–1.16 [–1.97, –0.34]
Ouzouni, 2009	–7.6	7.8	19	–0.5	4.6	14	14.2%	–1.04 [–1.78, –0.30]
van Vilsteren, 2005	–1	14.6	53	–4	13.7	43	18.9%	0.21 [–0.19, 0.61]
Subtotal (95% CI)			88			69	46.2%	–0.62 [–1.60, 0.37]
Heterogeneity: Tau^2 = 0.64; Chi^2 = 14.11, df = 2 (p = 0.0009); I^2 = 86%								
Test for overall effect: Z = 1.22 (p = 0.22)								
Total (95% CI)			137			123	100.0%	–0.23 [–0.69, 0.24]
Heterogeneity: Tau^2 = 0.26; Chi^2 = 18.55, df = 6 (p = 0.005); I^2 = 68%								
Test for overall effect: Z = 0.95 (p = 0.34)								
Test for subgroup differences: Chi^2 = 1.60, df = 1 (p = 0.21); I^2 = 37.3%								

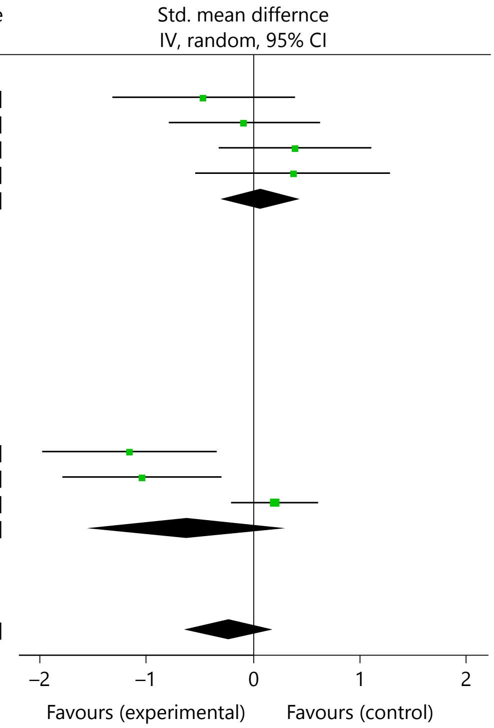

Fig. 6. Effects of exercise training on diastolic BP.

included resistance exercise interventions showed no effect on urea clearance. The result was also consistent with Scapini's network meta-analysis result, which presented that resistance exercise did not have an effect on dialysis efficacy either [39]. According to the mechanism above, it may be because that resistance exercise could not reach "muscle morphologic threshold" for increasing enough muscle blood with the transfer of toxins to intravascular compartment [15]. In other words, resistance exercise may not be appropriate to improve dialysis efficacy for patients with ESRD undergoing HD.

Besides, according to the mechanism above, sp Kt/V could be improved in a single exercise session and had been demonstrated in previous trials [2, 40]. And many experiments observed the effect of long-term exercise training on sp Kt/V. That is to say, sp Kt/V might be not only affected by exercise each time but also influenced by the duration. But most of these trials measured sp Kt/V only twice. One was measured at the beginning of the experiment; the other was at the end of the experiment. Only rare studies provided sp Kt/V dose at several points in time throughout the course of the experiments. Parsons et al. [31] traced the changes of sp Kt/V dose every 4 weeks from 4 to 20 weeks and compared the doses with each other. The results set out that sp Kt/V increased 11% by the end of 4 weeks and remained increasing at weeks 16 (19%) and 20 (18%) of the exercise intervention with statistical significance ($p < 0.05$). This showed that if the duration was longer, the dialysis might be more adequate. But the interaction time between exercise and sp Kt/V was not noticed. Furthermore, the measurement interval of sp Kt/V could be accurate to at least 1 week, so as to observe the detailed intention of time on sp Kt/V.

Hypertension was the most common symptom for patients with ESRD undergoing HD and its prevalence approaching 70–90% [5, 41]. Uncontrolled BP, which was also one of the most important risk factors of cardiovascular disease by increasing left ventricular workload and hypertrophy, strongly associated with cardiac mortality [42]. Though receiving antihypertensive medicine therapy, 35% of patients could not control hypertension adequately. Although exercise was deemed as a vital nonpharmacologic strategy to control BP by regulating sodium retention and water homeostasis [43], the effect size in SBP is –0.18 mm Hg (95% CI –0.42 to 0.07) with no statistical significance and the subgroup analysis

Am J Nephrol 2019;50:240–254
DOI: 10.1159/000502447

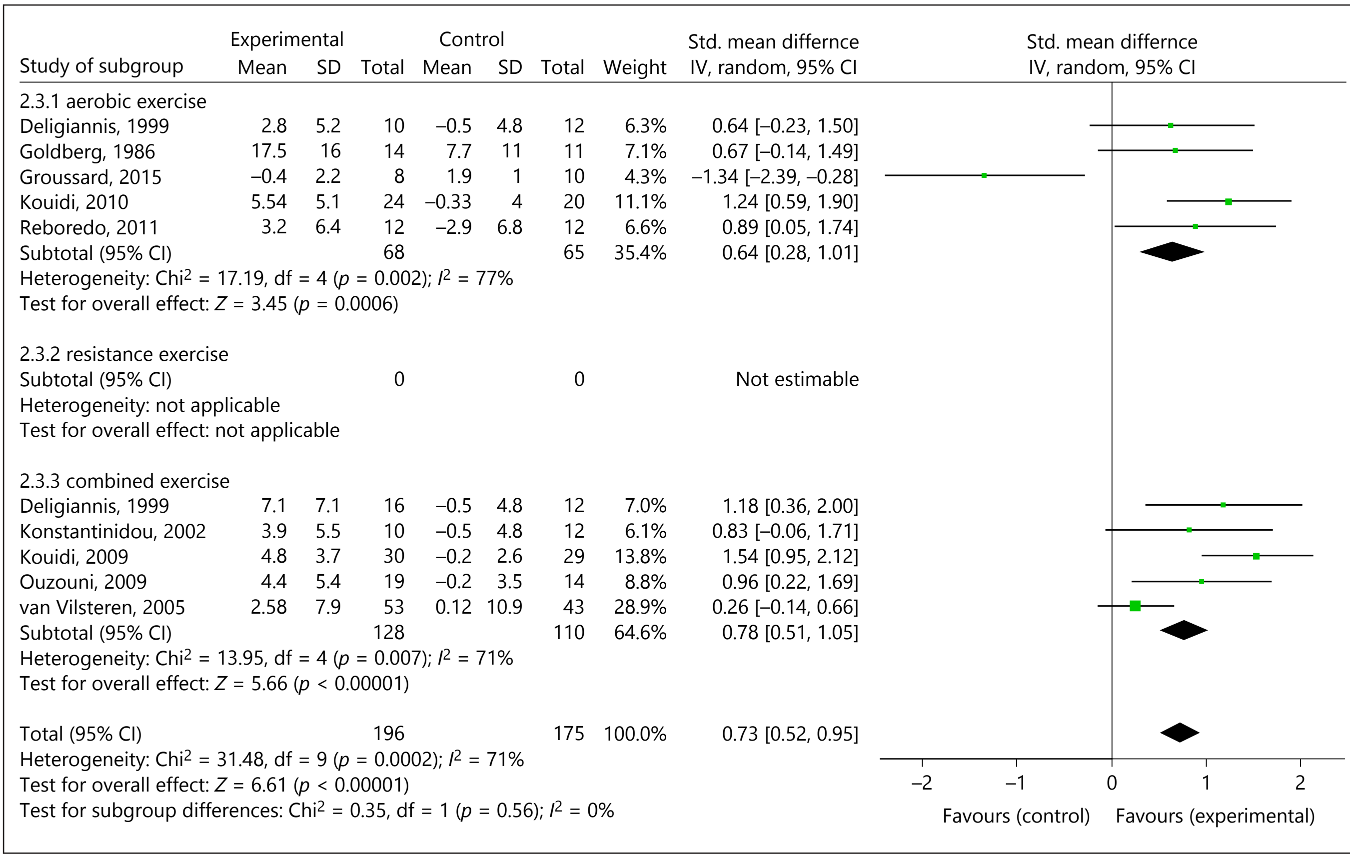

Fig. 7. Effects of exercise training on VO_2 peak.

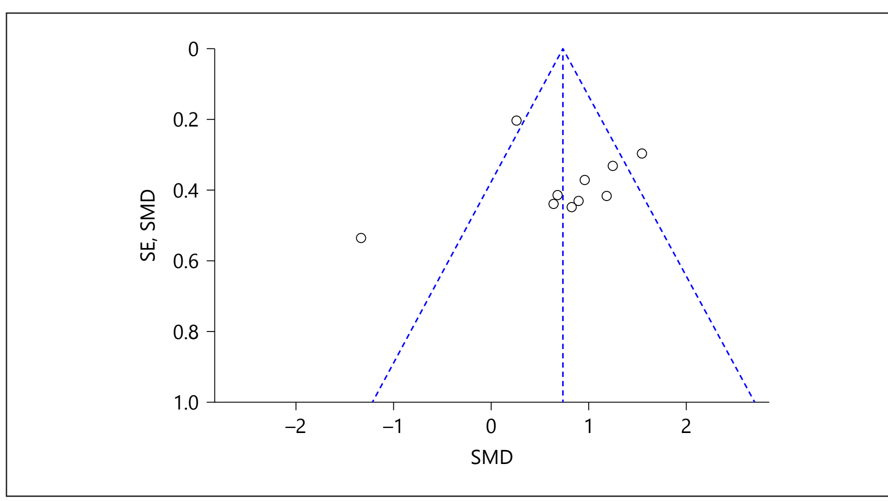

Fig. 8. Funnel of VO_2 peak.

showed that aerobic exercise and combined exercise could not decrease DBP either. This could be explained by neurohumoral mechanisms rather than structural adaptation changes (i.e., vascular remodeling or angiogenesis) driven by exercise training to a large extent [44]. And there is a "lag phenomenon" in structural adaptation changes in peripheral vascular resistances that might need to increase the intensity properly and extend exercise duration on the basis of exercising 3 times weekly [45]. For structural adaptation changes, it might

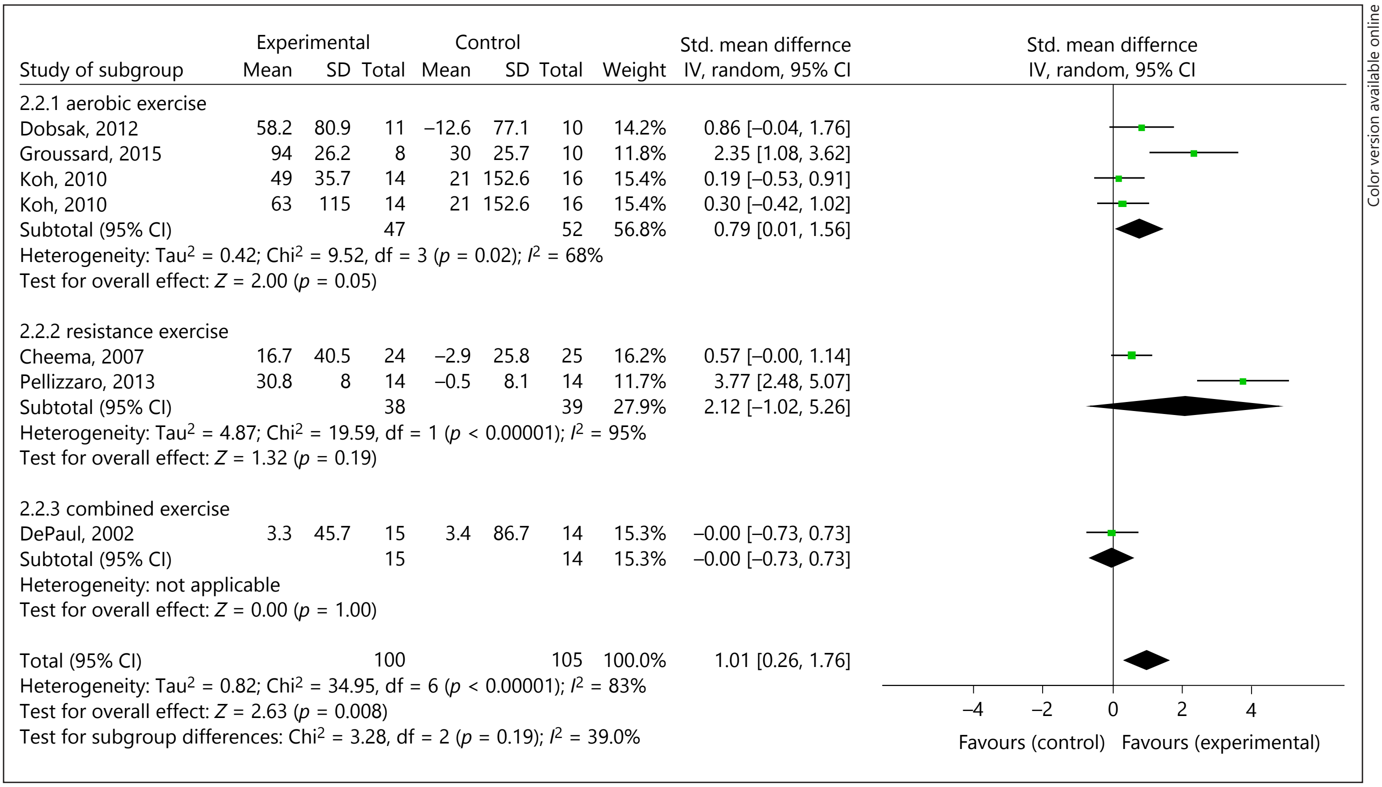

Fig. 9. Effects of exercise training on 6MWT.

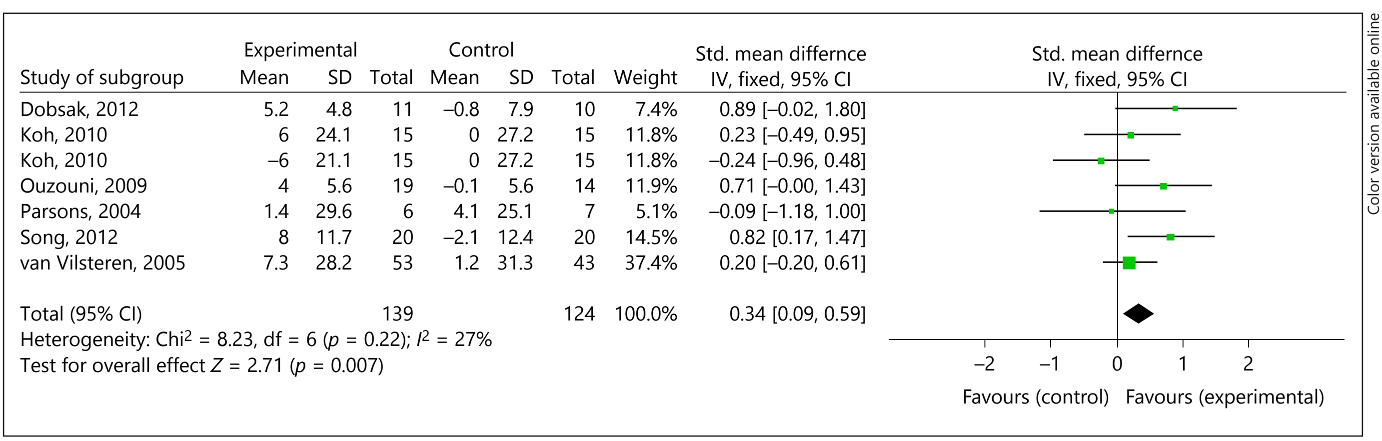

Fig. 10. Effects of exercise training on PCS of SF-36.

require the combination of intensity and duration. In the included trials, though Koh et al. [16] conducted 6-month exercise in 2 intervention groups with different exercise types, the intensity was low. And the results showed that both SBP and DBP were not different from the control group at the end of the trial. In Toussaint's and van Vilsteren's trials, SBP and DBP did not decrease either. It was probably because the training lasted only 3 months, though the intensity was moderate [28, 35]. Notably, there was no eligible literature about resistance exercise to pool in the meta-analysis. Future resistance exercise interventions could regard BP as an outcome and provide more reliable evidence for exercise training system.

Study of subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. mean differnce IV, fixed, 95% CI
Dobsak, 2012	4.7	4.8	11	1	7.6	10	7.8%	0.57 [–0.31, 1.44]
Koh, 2010	–2	21.1	15	–2	25.5	15	11.7%	0.00 [–0.72, 0.72]
Koh, 2010	6	22	15	–2	2.5.5	15	11.5%	0.33 [–0.39, 1.05]
Ouzouni, 2009	0	10.1	19	–0.2	6.9	14	12.6%	0.02 [–0.67, 0.71]
Parsons, 2004	–1.8	31.4	6	5.3	22.4	7	5.0%	–0.25 [–1.34, 0.85]
Song, 2012	6.5	14.9	20	–1.9	12.1	20	14.8%	0.61 [–0.03, 1.24]
van Vilsteren, 2005	7.9	23.5	53	0.9	25.5	43	36.6%	0.28 [–0.12, 0.69]
Total (95% CI)			139			124	100.0%	0.27 [0.02, 0.51]

Heterogeneity: $Chi^2 = 3.43$, df = 6 ($p = 0.75$); $I^2 = 0\%$
Test for overall effect $Z = 2.13$ ($p = 0.03$)

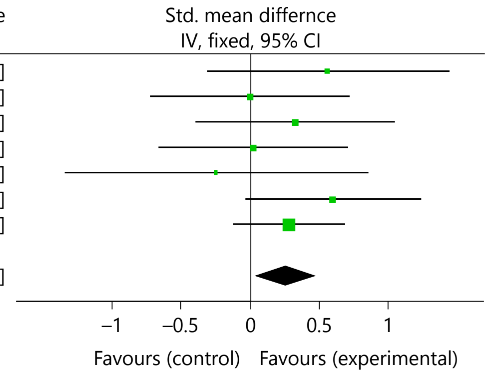

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Fig. 11. Effects of exercise training on MCS of SF-36.

Exercise capacity was impaired severely in ESRD patients with HD compared to the same stage of ESRD patients without HD because of the disease, side effects associated with HD, and worsening complications [7]. VO_2 peak was wildly used as an indirect measure of aerobic capacity, the peripheral muscle oxidative capacity, and indicated survival time of ESRD patients strongly [46, 47]. The subgroup analysis showed that the VO_2 peak increased effectively when patients did aerobic exercise or combined exercise, regardless of exercise duration, intensity, and frequency. This result was inconsistent with the results exhibited in previous meta-analysis, which estimated that regular exercise was good for aerobic capacity [18]. When VO_2 peak was enhanced by exercising, it indicated that aerobic capacity increases. Then, patients with ESRD undergoing HD could increase exercise time because of decline in their fatigue, break up in sedentary lifestyle, and decrease in mortality eventually [48, 49].

The 6MWT as an inexpensive instrument was more easy and safe to operate and could replace VO_2 peak to reflect exercise capacity, preferred to walking ability [30, 50]. When the 6-min walking distances significantly increased in the exercise group compared with the control group, VO_2 peak would also improve significantly in patients with ESRD because VO_2 peak was more sensitive than 6MWT. In this meta-analysis, the result of 6MWT was in step with VO_2 peak, which showed an increase in the subgroup of aerobic exercise. In contrast, 2 trials included in the subgroup of resistance exercise showed no effect on 6MWT. Maybe resistance exercise played an important role in muscle strength, but did not work on exercise capacity.

Based on this meta-analysis, exercise can improve aerobic capacity, walking capacity, and elevated QoL on the whole. Exercise training often consists of different kinds of types, duration, and intensity. And it is a tough question to combine the type, duration, and intensity into a reasonable exercise training plan for patients with ESRD undergoing HD, who are at the severe stage of CKD. For the type, we prefer aerobic exercise and combined exercise as exercise type according to the subgroup analysis results. And may be resistance exercise was not an appropriate way which could have an effect on these indexes according to the subgroup analyses of VO_2 peak and 6MWT. In addition, Pilate and yoga are popular worldwide and more interesting than traditional cycling and resistance exercise. However, these types should be taught by professionals and cannot proceed during the HD, which would take up the patients' extra leisure time.

The duration of included researches ranged from 8 weeks to 12 months. Three month was the most popular, followed by 6 months. But unfortunately, this meta-analysis did not conduct subgroup analyses of duration to distinguish which was the best duration and effected physical outcomes most. On the one hand, it was a tough question to divide the time period into long term or short term and there was no standard for this. On the other hand, to our knowledge, the longer duration might have a better effect of exercise, especially for structures restoration, such as BP. VO_2 peak could increase more when exercise lasted >6 months in Sheng's meta-analysis. But it may be difficult to carry out long-term exercise intervention in clinical, such as 12 months, because the dropout rate of participants would become higher with the prolongation of time. However, no matter how long the exercise lasted, the important thing for regular exercise was change in sedentary lifestyle for adults with ESRD undergoing HD. So patients can exercise continuously and evaluate their physical activity even after the intervention ended.

There are some limitations in this systematic review and meta-analysis. First, the methodology of included studies was rated B class according to Cochrane Handbook, which affected the credibility of the results directly. Randomization of participants, concealments, and dropout rate were unreported in included trials. Hence, future RCTs should complete and describe the randomization and concealment as clearly as possible to provide high-quality evidence. Second, most eligible trials about exercise of patients with ESRD undergoing HD were removed in the screened stage on account of that they did not fit the type of RCT. This suggested that trials could be designed as RCTs that can conduct high-quality comparisons to reveal the effects of exercise. Third, lack of eligible trials that regard resistance exercise and combined exercise as interventions and take sp Kt/V, BP, and exercise capacity as outcomes. Additionally for sp Kt/V, measuring continuously may shed more light on the impacts of exercise on it.

In conclusion, clinical staff can conduct aerobic exercise or combined exercise for adults with ESRD undergoing HD for at least 8 weeks to 12 months, 3 times weekly based on our evidence that proved to be beneficial for cardiovascular function reflected on exercise capacity and walking capacity and QoL. For the construction of patient exercise system, future studies still need to focus on high-quality evidence and increase the multiple plans for different conditions of the patients. Furthermore, studies evaluating possible adverse effects of exercise among HD patients are also suggested to provide more comprehensive evidence for developing relevant exercise program. The comparisons of exercise at home and during HD with resistance exercise and combined exercise also needed.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study received no specific funding.

Author Contributions

A.L., M.H., J.W., and Z.Z.: research idea and study design; M.H., N.X., G.M., Z.Z., B.Z., and J.G.: data acquisition; A.L., M.H., J.W., N.X., G.M., and Z.Z.: data analysis/interpretation; M.H., J.W., N.X., G.M., and Z.Z.: statistical analysis; A.L., J.W., Z.Z., J.G., and C.N.: supervision or mentorship. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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