In-Depth Topic Review

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Exercise Training in Patients Receiving Maintenance Hemodialysis: A Systematic Review of Clinical Trials

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Key Words
Aerobic training · Resistance training · End-stage renal disease · Quality of life · Health

Abstract
Background: Exercise is not routinely advocated in patients with end-stage renal disease (ESRD) receiving maintenance hemodialysis (HD), compared to best practice in other chronically diseased cohorts. Lack of widespread awareness of the exercise in HD literature may be contributing to these shortcomings of clinical practice. Therefore, our objectives are: (1) to systematically review trials of exercise training involving adult HD patients; (2) to provide empirical evidence that exercise can elicit health-related adaptations in this cohort, and (3) to provide recommendations for future investigations. ***Method:*** A systematic review of the literature using computerized databases was performed. ***Results:*** According to the 29 trials reviewed, HD patients can safely derive a myriad of health-related adaptations from engaging in appropriately structured exercise regimens involving aerobic and/or resistance training. However, methodological limitations within this body of literature may be partially responsible for minimal advocacy for exercise in this cohort. ***Conclusions:*** Robustly designed RCTs with thorough, standardized reporting are required if clinical practice and quality of life of this cohort is to be enhanced through the integration of exercise training and mainstream medical practice. Future trials should demonstrate the clinical importance, and long-term feasibility and applicability of exercise training for this vulnerable patient population.

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Introduction

According to the United States Renal Data System (USRDS), the incidence of end-stage renal disease (ESRD) continues to increase each year [1]. Over 100,000 new cases were reported in the USRDS 2004 report [1] and over 430,000 individuals in the United States currently live with ESRD [1]. Rising incidence and prevalence trends are being reported in many other countries maintaining renal registries [2].

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Approximately 91.9% of patients diagnosed with ESRD receive maintenance hemodialysis (HD) treatment as renal replacement therapy [1]. This intervention is typically prescribed 3 times per week, 4–6 h per session, and remains ongoing for the lifetime of the patient or until successful kidney transplantation. Although advances in HD treatment have extended the lifespan of patients with ESRD, this treatment alone does not ensure preservation of quality of life (QOL). Hemodialysis patients typically suffer from significant impairments of QOL as compared to their healthy counterparts, or those with successful kidney transplants.

Planned exercise, involving aerobic and resistance training modalities, has become well-recognized as a therapeutic intervention that can ameliorate the marked physiological, functional, and psychological deterioration which commonly accrues as a consequence of biological aging, catabolic illness, and a sedentary lifestyle, factors that may all contribute to the progressive decline of vitality and QOL commonly observed in HD patients. As such, many trials of exercise training have been conducted with HD patients over the past 3 decades. Findings from virtually all of these trials have demonstrated that prolonged exercise is safe and beneficial for this patient population. However, recent evidence has clearly suggested that exercise is still not routinely advocated or prescribed in this cohort [3, 4], compared to best practice in other diseased populations, such as those with cardiac and pulmonary disease. The lack of widespread awareness of the exercise in the HD literature may potentially be contributing to the shortcomings of clinical practice with regard to prescribing exercise.

Therefore our objectives are:

(1) To systematically review trials of exercise training involving adult hemodialysis patients.

(2) To provide empirical evidence that exercise can counteract the marked physiological, functional, and psychological wasting associated with ESRD.

(3) To provide recommendations for future investigations which may potentially lead to the integration of exercise prescription within the mainstream of medical practice for this patient population.

Method

A systematic, critical review rather than a meta-analytic approach has been taken as the heterogeneity of exercise modalities and dosages utilized and outcomes assessed do not lend themselves to meta-analytic methods. There are also clinically important results to discuss in some of the uncontrolled trials.

Criteria for Considering Studies

Study Designs

Randomized controlled trials (RCTs), controlled trials and uncontrolled trials were included. Abstracts and case reports were not considered.

Subjects

Subjects were adult (≥ 18 years) men and women receiving HD treatment for the management of ESRD. Studies involving young (<18 years) HD patients, continuous ambulatory peritoneal dialysis patients and/or pre-dialysis patients were not considered.

Interventions

Trials prescribing aerobic and/or resistance training modalities ≥ 5 weeks in duration were included. Studies investigating the effects of single, acute bouts of exercise, or studies applying interventions <5 weeks were excluded. Studies involving multimodal interventions (e.g. exercise combined with nutritional supplementation) were also excluded.

Outcome Measures

Outcome measures potentially responsive to exercise training, based on evidence of exercise training in other diseased and non-diseased cohorts, were considered. These outcomes included a broad spectrum of physiological, psychological, and functional measures.

Search Method

We conducted a literature review in November 2004 from the years 1966 to 2004, limited to the English language, using computerized databases, including Medline, CINAHL, SportDiscus, Embase, and Web of Science. The search combined key words related to HD treatment (i.e. hemodialysis, haemodialysis, dialysis, renal replacement therapy), ESRD (i.e. nephrology, nephron, kidney, renal disease, renal failure) and exercise (i.e. exercise, training, physical activity, rehabilitation, resistance training, aerobic training, strength training, muscle, endurance, VO_{2peak}). Articles retrieved were examined for further relevant references.

Results of Search

Study Designs and Research Quality

The search resulted in 34 articles presenting the findings of 29 trials, including 9 uncontrolled trials (9/29, 31%) [5–15], 7 controlled trials (7/29, 24%) [16–23], and 13 RCTs (13/29, 45%) [24–38].

All 9 uncontrolled trials [5–15] involved time series investigation of a single treatment group evaluated with repeated measures collected before and after training (table 1). One uncontrolled trial utilized the noncompliant subjects as a comparison group for statistical analyses [7]; however, the study was originally intended as a single treatment group design. None of the 9 uncontrolled trials mentioned the involvement of blinded outcomes assessors.

Table 1. Uncontrolled trials of exercise training in hemodialysis

Authors (year) country	n	Study groups	Exercise intervention				Outcomes		
			delivery	modality	prescription	duration	variable	% change	p
Goldberg et al. [5] (1979) Goldberg et al. [6] (1980) USA	7	exercise (n = 7)	NDT	AER	cycle erg., walking, jogging, calisthenics 65–75% HR_{max} to tolerance	8–9 months	plasma triglyceride	+39.2%	< 0.02
							VLDL triglygeride	–44.3%	< 0.02
							HDL cholesterol	+23.0%	< 0.05
							fasting plasma glucose	–6.3%	< 0.01
							glucose disappearance rate	+22.5%	< 0.01
							fasting plasma insulin	–40.1%	< 0.01
							hematocrit	+24.8%	< 0.01
							hemoglobin	+29.0%	< 0.04
							VO_{2peak}	+17.8%	< 0.10
							GXT duration	+41%	< 0.02
Shalom et al. [7] (1984) USA	14	exercise (n = 14)	NDT	AER	cycle erg., calisthenics, walking jogging up to 75–80% HR_{max} 45 min, 5×/week	12 weeks	GXT workload	increase	0.007
							VO_{2peak}	increase	0.001
							oxygen pulse	increase	0.026
Moore et al. [8] (1993) USA	23	exercise (n = 23)	ID	AER	cycle erg. training, RPE 6/10 ≤60 min, 3×/week	12 weeks	maximal workload	increase	≤0.05
							submaximal heart rate	decrease	≤0.05
							phosphofructokinase activity	increase	≤0.05
							type I muscle fibre area	no Δ	–
							type II muscle fiber area	no Δ	–
							capillary to muscle fibre ratio	no Δ	–
Kouidi et al. [9] (1998) Greece	7	exercise (n = 7)	NDT	COMBO	aerobic and strength training, 90 min, 3×/week	6 months	GXT duration	increase	≤0.05
							VO_{2peak}	increase	≤0.05
							peak blood lactate	decrease	≤0.05
							nerve conduction velocity	increase	≤0.05
							isometric strength (LB)	increase	≤0.05
							type 1 muscle fibre area	increase	≤0.05
							type II muscle fibre area	increase	≤0.05
							percentage of type II fibres	+23.0%	≤0.05
							mean muscle fibre area	increase	≤0.05
Ridley et al. [10] (1999) Canada	8	exercise (n = 8)	ID	COMBO	cycle ergometer, ≤30 min, to tolerance and 6 strength exercises up to 30 reps, 2×/week	12 weeks	6-minute walk distance	increase	≤0.006
							resistance training load	increase	≤0.013
							Piper Fatigue Scale:		
							affective fatigue	decrease	≤0.05
							sensory scale fatigue	decrease	≤0.03
Zaluska et al. [11] (2002) Poland	10	exercise (n = 10)	ID	AER	cycle ergometer 30 min, 3×/week	6 months	albumin	increase	≤0.024
							C-reactive protein	decrease	≤0.046
							protein catabolic rate	increase	≤0.001
							Kt/V	increase	≤0.026
Oh-Park et al. [12] (2002) USA	22	exercise (n = 22)	ID	COMBO	cycle ergometer up to 30 min to tolerance & knee extensions 3 sets × 15 reps, 50% 1RM, 2–3×/week	3 months	knee extension strength	increase	≤0.0001
							SF-36 – physical functioning	increase	≤0.003
							SF-36 – mental health	increase	≤0.0004
Headley et al. [13] (2002) Nindl et al. [14] (2004) USA	10	exercise (n = 10)	NDT& HB	PRT	machine weight exercises (8–9), 1–2 sets × 15 reps 2×/week and at week 7: 9 home-based PRT exercises using Theraband™ 1×/week	12 weeks	peak isometric force at 90°	increase	≤0.05
							6-minute walk distance	increase	≤0.05
							maximal walking speed	increase	≤0.05
							sit-to-stand time x 10 reps	increase	≤0.05
							percentage body fat	increase	≤0.05
							C-reactive protein	decrease	NR
							total IGF-1	decrease	≤0.039
							IGF-1:IGFBP-3 (×10) ratio	decrease	≤0.003
Mustata et al. [15] (2004) Canada	11	exercise (n = 11)	NDT	AER	treadmill walking or cycle ergometer 40–50 min, 2×/week	3 months	arterial stiffness	decrease	0.01
							pulse pressure (mm Hg)	decrease	< 0.05
							SBP	decrease	< 0.05
							insulin resistance	no Δ	

NDT = Nondialysis time; ID = intradialytic; HB = home based; AER = aerobic training; COMBO = aerobic plus lower-intensity strength training; PRT = progressive resistance training; GXT = graded exercise test; RPE = rating of perceived exertion; HR_{max} = maximal heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; NR = not reported.

All p values calculated by comparing within group change over time (i.e. pretest – posttest).

Seven controlled trials [16–23] involved a treatment (i.e. exercise) and a control (i.e. nonexercise) group, consisting of HD patients but without random assignment of subjects into these two groups (table 2). Statistical analyses performed in 4/7 trials (57%) involved repeated measures comparisons within groups only, while 3/7 trials (43%) [20–22, 27] performed statistical comparisons between groups. None of the 7 controlled trials mentioned the involvement of blinded outcomes assessors.

Thirteen trials involved randomization of subjects (table 3) [24–38]. Nine RCTs (9/13, 69%) assigned subjects to a treatment or nontreatment control group [24–26, 28–32, 35, 37, 38]. Three additional RCTs (3/13, 23%) randomized subjects to: (a) intradialytic vs. non-dialysis exercise interventions [36]; (b) exercise vs. sham exercise (i.e. placebo) [33], or (c) exercise vs. a social support group [27]. One study (1/13, 8%) compared the effects of exercise training plus the normalization of blood hematocrit within a 4-group RCT [34]. Eleven RCTs (11/13, 85%) performed between group comparisons on repeated measures [27, 29–38], while 2 trials (2/13, 15%) [24–26, 28] reported change over time within groups only. Six RCTs (6/13, 46%) [24–26, 29, 31, 35–37] reported that randomization of subjects occurred following baseline testing. Only two RCTs (2/13, 15%) reported that partial or complete collection of outcome measures were performed by blinded assessors [29, 33]. To date, only two RCTs (2/13, 15%) involved intention-to-treat strategy of analysis [33, 34].

Overview of the Subjects

Sample Sizes

Nine hundred and fifty-nine (n = 959) patients have been enrolled in the 29 trials reviewed. Sample size ranged from 7 to 286 enrolled patients. Thirteen trials (13/29, 45%) have enrolled <20 patients, 15 trials (15/29, 52%) have enrolled 20–75 patients, and only one trial (3/29, 3%) has enrolled >75 patients (n = 286) (tables 1–3) [20, 21].

Gender

Excluding two trials that did not provide a gender breakdown (where combined n = 20) [11, 16], 479 men and 460 women (51:49) have been enrolled in the trials reviewed. Except for one trial involving 12 men only [17], all trials included men and women.

Age

Age of the sample was expressed as mean ± SD in 10 trials (10/29, 34%) [18–23, 27, 28, 33, 34, 38] in which mean age ranged from 36 ± 3 to 60 ± 17 [27, 38]. In 18 trials (18/29, 62%) that presented an age range [5–10, 12–17, 24–26, 29–32, 35–37], the youngest and eldest patients enrolled were 19 years [24–26] and 84 years [12], respectively. A broad age range was generally reported. One trial (1/29, 3%) did not describe the age of their sample [11].

Duration of Hemodialysis

Entry criteria typically precluded patients receiving HD treatment <3 months. Length of HD treatment ranged from 0.25 to 17.4 years [13, 14] in trials providing these data. Three trials (3/29, 10%) did not delimit an entry criterion, or describe their sample with respect to this factor [10–12].

Etiology of Renal Failure

Sixteen trials (16/29, 55%) detailed the etiology of renal failure in their sample [5–9, 12–15, 20–22, 24–28, 33, 34, 37, 38]. Common causes of ESRD in these trials included glomerulonephritis (32%), hypertension (18.5%), and diabetes (12%). Diabetes was a prevalent predisposing factor despite the fact that 5/16 trials (31%) that described ESRD etiology excluded diabetics [7, 9, 24–27, 37].

Comorbidities

Eleven trials provided information regarding common comorbidities in their sample [5–8, 10, 17, 22, 31, 32, 35, 36, 38]. The average prevalence of common comorbidities among these trials included hypertension (71%), cardiovascular disease (34%), and diabetes (21%). Diabetes was prevalent in 4/29 trials (14%) providing these data [17, 22, 33, 38]. However, at least 11/29 trials to date (34%), including 9/13 RCTs (69%), have excluded patients with diabetes [7, 9, 26–29, 31–34, 37, 40, 41]. Other trials have excluded patients with ischemic heart disease [8, 33, 34], and congestive heart failure [10, 24–27, 36].

Overview of the Exercise Interventions

Duration

Duration ranged from 6 weeks [30] to 4 years [36]. The majority of interventions extended for 3–6 months [8–16, 18–22, 27–29, 31–35, 37], with 3 trials of shorter duration [23, 30, 38] and 4 trials of longer duration [5, 6, 17, 24–26, 36]. Kouidi et al. [36] have conducted the longest trial to date (4 years).

Table 2. Nonrandomized controlled trials of exercise training in hemodialysis

Authors (year) country	n	Study groups	Exercise intervention				Outcomes		
			delivery	modality	prescription	duration	variable	% change	p value
Zabetakis et al.	10	exercise (n = 5)	NDT	AER	treadmill walking/	10 weeks	after 5 weeks of training:		
[16] (1982)					jogging at AT,		VO_{2peak}	+21%	≤0.025[b]
USA		control (n = 5)			25–45 min, 3×/week		O_2 pulse	increase	≤0.025[b]
							GXT duration	increase	≤0.025[b]
							aerobic economy	increase	≤0.001[b]
							after 10 weeks of training:		
							anaerobic threshold	increase	≤0.05[b]
Hagberg et al.	12	exercise (n = 6)	NDT	AER	calisthenics, cycle	14 ± 5	VO_{2peak}	+17%	≤0.05[b]
[17] (1983)					erg., walking	months	GXT duration	+44%	≤0.01[b]
USA		control (n = 6)			≤30 min		hemoglobin concentration	increase	≤0.01[b]
					50–85%VO_{2peak}		hematocrit concentration	increase	≤0.01[b]
					3–5×/week		SBP	decrease	≤0.01[b]
							DBP in (n = 3) patients		
							with diastolic HT	decrease	≤0.05[b]
Carney et al.	8	exercise (n = 4)	NDT	AER	cycle ergometer,	6 months	VO_{2peak}	no Δ	–
[18] (1983)					walking, jogging		GXT duration	+28%	< 0.06[b]
USA		control (n = 4)			50–60% VO_{2peak},		depression/anxiety/hostility	decrease	< 0.06[b]
					3×/week		frequency and enjoyment of		
							pleasant activities	Increase	< 0.06[b]
Painter et al.	20	exercise (n = 14)	ID	AER	cycle ergometer	6 months	after 3 months of training:		
[19] (1986)					65–85% of VO_{2peak},		VO_{2peak}	+17%	≤0.05[b]
USA		control (n = 6)			30–45 min, 3×/week		after 6 months of training:		
							VO_{2peak}	+23%	≤0.05[b]
							vertical work capacity	+40%	≤0.05[b]
Painter et al.	286	exercise	HB&ID	COMBO	HB: walking/cycle	16 weeks	habitual gait speed	increase	≤0.021[a]
[20] (2000)					ergometer to tolerance		fastest gait speed	increase	≤0.001[a]
Painter et al.		control			and strength training		sit-to-stand speed	increase	≤0.05[a]
[21] (2000)					5–6×/weeks, 8 weeks		6-min walk distance	increase	≤0.05[a]
USA					ID (8 weeks):		SF-36 – physical functioning	increase	≤0.004[a]
					cycle erg to tolerance		SF-36 – role physical	increase	≤0.001[a]
					≤30 min, 3×/week,		SF-36 – general health	increase	≤0.05[a]
					8 weeks		SF-36 – bodily pain	increase	≤0.003[a]
							SF-36 – physical component	increase	≤0.001[a]
Miller et al.	75	exercise (n = 40)	ID	AER	cycle ergometer	6 months	blood pressure	no Δ	–
[22] (2002)					to tolerance		n antihypertensive		
USA		control (n = 35)			≤30 min, 3×/week		medications	–36%	0.018[a]
							expenditure on anti-HT		
							medications	decrease	0.005[a]
Moug et al.	17	exercise (n = 10)	ID	AER	cycle ergometer	6 weeks	leg extension strength	no Δ	–
[23] (2004)					60–85% VO_{2peak}		depression	no Δ	–
Scotland		control (n = 7)			45–60 min, 2×/week		anxiety	decrease	< 0.05[b]

NDT = Nondialysis time; ID = intradialytic; HB = home based; AER = aerobic training; COMBO = aerobic plus lower-intensity strength training; AT = anerobic threshold; GXT = graded exercise test; SBP = systolic blood pressure; DBP = diastolic blood pressure.

[a] Significant over time vs. control group.

[b] Significant vs. baseline value.

Modality

Nineteen trials (19/29, 66%) involved aerobic training as the sole exercise modality [5–8, 11, 15–19, 22–30, 34, 37, 38]. Cycle ergometer training, walking/jogging, aerobics, calisthenics, swimming, and ball games were reported among these trials. Nine trials (9/29, 31%) combined aerobic training with some form of strength training [9, 10, 12, 20, 21, 31–33, 35, 36]. Strength training interventions in these trials were generally not adequately described [9, 31, 32, 36], were of low intensity [9, 10, 12, 20, 21, 31–33, 35, 36], and/or involved lower extremity training only [12, 33, 35]. Only one trial to date [15,

Table 3. Randomized controlled trials of exercise training in hemodialysis

Authors (year) country	n	Study groups (n)	Exercise intervention				Outcomes		
			delivery	modality	prescription	duration	variable	% change	p value
Goldberg et al. [24] (1983) Goldberg et al. [25] (1986) Harter et al. [26] (1985) USA	25	exercise (n = 14) control (n = 11)	NDT	AER	walking, cycle erg. 50–80% VO_{2peak} 45–60 min, 3×/week	12 months	VO_{2peak} GXT duration plasma triglyceride VLDL triglyceride VLDL cholesterol HDL glucose disappearance rate insulin affinity hematocrit RBC mass hemoglobin basal insulin levels RBC survival Beck depression inventory	+17–21% +26% –29–33% –30–38% –16% +16–20% +35–42% +25–70% +27% +27% +16–20% –21% +46% –42%	≤0.01[b] ≤0.01[b] ≤0.01[b] ≤0.05[b] ≤0.02[b] ≤0.05[b] ≤0.02[b] ≤0.01[b] ≤0.02[b] ≤0.01[b] ≤0.01[b] ≤0.05[b] ≤0.02[b] ≤0.01[b]
Carney et al. [27] (1987) USA	21	exercise (n = 11) social support (n = 10)	NDT& HB	AER	calisthenics, cycle erg., walking 60–80% VO_{2peak} 45–60 min, 3×/week	6 months	Beck depression inventory prevalence of clin. depression VO_{2peak}	decrease decrease +20%	≤0.05[a] ≤0.05[a] NR
Akiba et al. [28] (1995) Japan	20	exercise (n = 10) control (n = 10)	NDT	AER	cycle ergometer, RPE ≥12 10–20 min, 3×/week	12 weeks	exercise group: VO_{2peak} VO_{2AT} lactate at VO_{2peak} control group: VO_{2max} VO_{2AT}	 no Δ no Δ increase decrease decrease	 – – < 0.001[b] < 0.05[b] < 0.05[b]
Kouidi et al. [29] (1997) Greece	31	exercise (n = 20) control (n = 11)	NDT	AER	cycle ergometer, walking/JOG, calisthenics, aerobics, swimming or ball games 50–70% VO_{2peak}, 90 min, 3–4×/week	6 months	VO_{2peak} GXT duration Beck depression inventory QLI – patient activity QLI – daily living QLI – health QLI – support QLI – outlook	increase increase increase increase increase increase increase increase	≤0.05[b] ≤0.05[b] ≤0.05[a] ≤0.05[a] ≤0.05[a] ≤0.05[a] ≤0.05[a] ≤0.05[a]
Frey et al. [30] (1999) USA	11	exercise (n = 5) control (n = 6)	ID	AER	cycle ergometer ≤45 min 60–80% HR_{max} 3×/week	7 weeks	Kt/V kilocalorie intake protein intake prealbumin transferrin	no Δ no Δ no Δ no Δ no Δ	– – – – –
Deligiannis et al. [31] (1999) Greece	60	exercise (n = 30) control (n = 30)	NDT	COMBO	calisthenics, aerobics, swimming or ball games, and strength exercise 50–70% VO_{2peak}, 90 min, 3–4×/week	6 months	VO_{2peak} GXT duration HRV index SD of R-R interval R–R interval length n patients. with HRV index <25 n patients with arrhythmias (Lown class >II)	+41% +33% +31% +18% +18% –40% –33%	< 0.05[b] < 0.05[b] < 0.05[b] < 0.05[b] < 0.05[b] < 0.05[a] < 0.05[a]
Deligiannis et al. [32] (1999) Greece	38	exercise 1 (n = 16)	NDT	COMBO	calisthenics, steps, up to 70 min, and strength exercise, 3×/week	6 months	exercise 1 left ventricle mass index ejection fraction stroke volume index cardiac output index	 +11% +12% +23% +20%	 ≤0.05[a] ≤0.01[a] ≤0.05[a] ≤0.05[a]
		exercise 2 (n = 10) control (n = 12)	HB	AER	cycle ergometer 30 min at 50–60% HR_{max}, >5×/week		exercise 2 no significant adaptations vs. control group		
DePaul et al. [33] (2002) Canada	37	exercise (n = 20) placebo (n=17)	ID	COMBO	cycle erg Borg RPE = 13/20 <80 HR_{max}, 20 min, & knee extensions (pre-dialysis) 3 sets × 10 reps at 50% of 5RM, 3×/week	12 weeks	submaximal ex. capacity knee extension strength	increase increase	< 0.02[a] < 0.02[a]

Table 3 (continued)

Authors (year) country	n	Study groups (n)	Exercise intervention				Outcomes		
			delivery	modality	prescription	duration	variable	% change	p value
Painter et al. [34] (2002) USA	48	exercise+EPO (n = 12)	ID	AER	cycle ergometer RPE 12-14 30 min, 3×/week	5 months	in post-HOC analysis exercise groups:		
							VO_{2peak}	increase	≤0.028[a]
		exercise only (n = 10)	ID	AER	cycle ergometer RPE 12-14 30 min, 3×/week		SF-36-physical functioning	increase	≤0.015[a]
		EPO only (n = 12)							
		control (n = 14)							
Konstantinidou [35] (2002) Greece	48	exercise 1 (n = 16)	ND	COMBO	aerobic training 50–70% VO_{2peak}, 60 min and strength exercise, 3×/week	6 months	exercise group 1		
							VO_{2peak}	+43%	≤0.05[a]
							GXT duration	+33%	≤0.05[a]
							VE_{peak}	+41%	≤0.05[a]
							VO_{2AT}	+37%	≤0.05[a]
		exercise 2 (n = 10)	ID	COMBO	cycle ergometer Borg RPE=13 60–90 min, and lower body strength exercise 3×/week		exercise group 2		
							VO_{2peak}	+24%	≤0.05[c]
							GXT duration	+22%	≤0.05[c]
							VE_{peak}	+12%	≤0.05[c]
							VO_{2AT}	+18%	≤0.05[c]
		exercise 3 (n = 10)	HB	AER	cycle erg., 50–60% HR_{max}, 30 min, 5×/week		exercise group 3		
							VO_{2peak}	+17%	≤0.05[c]
		control (n = 12)					GXT duration	+14%	≤0.05[c]
							VE_{peak}	increase	≤0.05[c]
							VO_{2AT}	+8%	≤0.05
Kouidi et al. [36] (2004) Greece	34	exercise 1 (n = 16)	ND	COMBO	aerobic training 50–70% VO_{2peak}, 60 min, and strength training, 3×/week	4 years	after 1 year exercise 1/exercise 2		
							VO_{2peak}	+47%/+34%	≤0.05[d]
							GXT duration	+38%/+26%	≤0.05[d]
							VE_{peak}	+24%/+13%	≤0.05[d]
							VO_{2AT}	+39%/+29%	≤0.05[d]
							HR_{peak}	increase	≤0.05
		exercise 2 (n = 18)	ID	COMBO	cycle ergometer Borg RPE = 13 60–90 min, and lower body strength exercise 3×/week		after 4 years exercise 1/exercise 2		
							VO_{2peak}	+70%/+50%	≤0.05[d]
							GXT duration	+53%/+43%	≤0.05[d]
							VE_{peak}	+43%/+26%	≤0.05[d]
							VO_{2AT}	+52%/+42%	≤0.05[d]
							HR_{peak}	increase	≤0.05
Molsted et al. [37] (2004) Denmark	33	exercise (n = 22)	NDT	AER	step exercises, cycling, aerobics, RPE 14-17 60 min, 2×/week	5 months	VO_{2peak}	increase	≤0.012[a]
		control (n = 11)					SF-36 – physical functioning	increase	≤0.01[a]
							SF-36 – bodily pain	improved	≤0.03[a]
							SF-36 – physical component	increase	≤0.004[a]
Parsons et al. [38] (2004) Canada	13	exercise (n = 6)	ID	AER	cycle ergometer 40–50% maximum 45 min, 3×/week	8 weeks	exercise group		
							maximal work capacity	no Δ	–
		control (n = 7)					blood urea clearance	no Δ	–
							dialysate urea clearance	increase	≤0.05[b]
							QOL	no Δ	–

NDT = Nondialysis time; ID = intradialytic; HB = home based; AER = aerobic training; COMBO = aerobic plus lower-intensity strength training; PRT = progressive resistance training; QLI = Quality of Life Index; HRV = heart rate variability; VE_{peak} = peak ventilation; HR_{peak} = peak heart rate; GXT = graded exercise test.

[a] Significant change over time versus comparison group(s).
[b] Significant vs. baseline values within group.
[c] Significant vs. control group only.
[d] Significant change over time between exercise group 1 and exercise group 2.

16] has prescribed a progressive resistance training (PRT) intervention targeting the upper and lower extremities performed at a relatively high intensity (10–15 RM) as currently recommended for improving the musculoskeletal fitness of healthy adults and the elderly [43].

Delivery

Exercise training has been prescribed:

- In non-dialysis time at a training center in 12/29 trials (41%) [5–7, 9, 15–18, 24–26, 28, 29, 31, 37].
- During HD treatment in 11/29 trials (38%) [8, 10, 11, 12, 19, 22, 23, 30, 33, 34, 38].
- In nondialysis time at a training center + at home in 2/29 trials (7%) [13, 14, 27].
- During HD treatment + at home in 1/32 trial (3%) [20, 21].

Additionally, 3 RCTs (3/29, 10%) assigned patients into treatment groups that trained in separate locations, including in non-dialysis time in a training center [32, 35, 36], at home [32, 35] and/or during HD [32, 35, 38].

Frequency

Exercise training was typically prescribed for 3–4 sessions/week (tables 1–3) [8, 9, 11, 16, 18, 19, 22, 24–36, 38]. In two RCTs (2/29, 7%), subjects randomized to home-based training were prescribed ≥5 training sessions/week [32, 35]. Painter et al. [20, 21] prescribed home-based exercise 5–6 sessions/week for 8 weeks followed by intradialytic training 3 sessions/week for 8 weeks. One trial (1/29, 3%) did not report on the frequency of exercise training [5, 6].

Intensity

Aerobic training interventions were generally of moderate intensity and progressed according to tolerance as the conditioning of the patient improved (tables 1–3). Two trials, however, prescribed and maintained aerobic training at a relatively low intensity (≤60% of maximal effort) [18, 38]. Additionally, several trials did not mention how aerobic training intensity was gauged [9, 10, 11, 22].

Strength training interventions were generally prescribed at a low to moderate intensity [9, 10, 12, 20, 21, 31–33, 35, 36], with 1 trial (1/29, 3%) prescribing higher-intensity PRT [15, 16] (tables 1–3).

Duration of Aerobic Training Sessions

In general, the duration of aerobic training sessions ranged from 30 to 60 min/session, with a few trials exceeding this duration with the inclusion of warm-up and cool-down periods [32, 35, 36]. Two trials (2/29, 7%) maintained aerobic training sessions to ≤20 min/session [28, 33]. One trial (1/29, 3%) did not define the duration of aerobic training per session [5, 6].

Supervision

Eighteen trials (18/29, 62%) reported that qualified health professionals including study personnel supervised exercise training sessions [5–10, 12–16, 24–26, 29, 31–37]. Nine trials did not provide details regarding supervision [11, 17, 18, 22, 23, 27, 28, 30, 38]. In one trial by Painter et al. [20, 21], which combined home-based and intradialytic training, subjects trained independently in both locations. In another trial by Painter et al. [19], the first half (3 months) of an intradialytic cycling program was directly supervised, while the latter half was not. Home-based interventions were never directly monitored however regular contact with study personnel was reported as being provided [13, 14, 20, 21, 27, 32, 35].

Compliance

Nine trials (9/29, 31%) provided information regarding compliance to exercise training (e.g. sessions attended). In these trials [7, 8, 13–15, 19, 22, 23, 29, 37], compliance ranged from fair (43%) [7] to excellent (99%) [23]. However, no trial to date has provided an a priori definition of 'compliance' within their methods section.

Adverse Events

Thirteen trials (13/29, 45%) have reported that no serious complications have resulted from participation in the prescribed exercise intervention [7, 9, 10, 12–14, 22, 23, 29, 32, 34–36]. Trials have noted that hypotension has been induced by exercise training [33, 38] though not always presenting with regularity [13–15]. One trial reported an acute gastrointestinal hemorrhage in an exercising subject [16]. DePaul et al. [33] reported more adverse events in exercising versus nonexercising patients, citing complaints such as fatigue (n = 1), soreness (n = 1), hypotension (n = 1), foot ulcer (n = 1) and foot pain (n = 1). No other serious adverse events have been reported in the 29 trials presented in this review. However, to date, no trial has provided an a priori definition of 'adverse event' within their methods section.

Adaptations to Exercise Training in Hemodialysis

Documented adaptations to exercise training in the 29 trials reviewed are presented in tables 1–3. A synopsis of these findings highlights some important physiological, functional, and psychological benefits of exercise training in this cohort.

Physiological Adaptations to Exercise Training

The Cardiorespiratory System and Aerobic Capacity

Several trials have reported that HD patients can significantly increase peak oxygen consumption (VO_{2peak}) 17–23% by performing aerobic training during nondialysis time [16, 17, 24–27, 29], during dialysis [19], and at home [35]. By contrast, a few trials have reported no significant improvement of VO_{2peak} with aerobic training, which may perhaps be due to prescribing low intensity (<60% VO_{2peak}) [24] and/or short duration (10–20 min/session) training [28]. Moreover, it has been well documented that oxygen consumption in this cohort is limited at the peripheral level (i.e. at the skeletal muscle) [40], which is not optimally enhanced with aerobic exercise training alone [8]. In support of this, the magnitude of improvement in VO_{2peak} secondary to combined (aerobic and strength) training (41–48%) [9, 31, 32, 35, 36] is notably superior to studies prescribing aerobic training only (17–23%). No studies have directly compared aerobic and strength training evaluating this outcome, or assessed VO_{2peak} after isolated strength training. Central, intermediary and peripheral cardiorespiratory system adaptations to exercise training documented in the literature are presented in tables 1–3.

Cardiac Functioning

Deligiannis et al. [32] in a RCT demonstrated that 6 months of combined training on nondialysis days improved left ventricle mass index, ejection fraction, cardiac output index, and stroke volume index. Another RCT by the same authors [31] revealed that 6 months of combined training could significantly increase heart rate variability index and the standard deviation of the R-R interval, while reducing the prevalence of arrhythmias (Lown class >II).

Muscle Architecture and Neuromuscular Control

Kouidi et al. [9] reported in an uncontrolled trial of 7 patients that cross-sectional area of type I and II muscle fibers obtained from the vastus lateralis significantly increased, 2,831 ± 846 to 3,565 ± 764 μm^2 and 2,683 ± 763 to 3,319 ± 1,049 μm^2, respectively, with 6 months of combined aerobic and strength training. Further, the ratio of type I to type II fibers improved from 54.6:45.4 to 31.6:68.4, which is reported to be near normal (1:2) for this biopsy site. Ultrastructural analysis revealed that the muscle appeared more normal, including positive adaptations of the capillaries and mitochondria. The authors also noted activation of satellite cells and an increased number of leukocytes and natural killer cells. Motor conduction of the peroneal nerve also significantly improved ($p < 0.05$). By contrast, Moore et al. [8] observed no hypertrophy secondary to 6 months of intradialytic aerobic training, which is not unexpected given that aerobic training is not the preferred exercise modality for eliciting myogenic adaptation.

Components of Metabolic Syndrome

Miller et al. [22] demonstrated that hypertensive patients could significantly reduce predialysis and postdialysis systolic blood pressure after 3 months of intradialytic cycling. The reduction in blood pressure was accompanied by a reduction in antihypertensive medications (–36%, $p < 0.018$) resulting in a cost savings of USD 885 per patient annually. Additional trials have observed reduced resting blood pressure [15, 17, 32], and blood pressure during maximal exercise [32] with >3 months of aerobic, or combined training. Other studies have expressed such findings anecdotally [5, 6, 19, 24].

Goldberg and colleagues [5, 6, 24–26] demonstrated that nondiabetic HD patients could significantly reduce fasting plasma glucose and insulin concentrations, while significantly increasing insulin-binding affinity and glucose disappearance rate with 8–12 months of aerobic training. The authors [5, 6, 24–26] also reported increased fasting plasma high-density lipoprotein (HDL) cholesterol, reduced very-low-density lipoprotein (VLDL), reduced VLDL triglyceride, and reduced total plasma triglyceride secondary to aerobic exercise training.

To date there have been no studies investigating the effects of exercise training on visceral obesity in this cohort, or studies of insulin sensitivity and glucose control in diabetic patients receiving maintenance HD.

Dialysis Adequacy

One uncontrolled trial has demonstrated an improvement in dialysis adequacy (Kt/V) with 6 months of intradialytic aerobic training using cycle ergometers [11]. By contrast, two trials implementing shorter training durations (7 and 8 weeks) have not observed an improvement in Kt/V [30, 38]. Evidence suggests that a single, acute bout of intradialytic cycling can significantly enhance the removal of urea, creatinine and potassium during HD by significantly reducing post-dialysis rebound of these damaging solutes [41]. Intradialytic exercise training could enhance dialysis adequacy chronically via this same mechanism [3]. However, this hypothesis has not yet been rigorously investigated within a longitudinal RCT [3].

Functional Adaptations to Exercise Training

Muscular Strength

Headley et al. [13] and Nindl et al. [14] prescribed high-intensity PRT to elicit improvements in muscular strength in HD patients. Four additional trials [9, 10, 12, 33] reported improved muscular strength with regimens involving lower-intensity strength training. By contrast, Moug et al. [23] reported no significant improvement of lower body strength secondary to 6 weeks of intradialytic cycling. This finding is not unexpected given that aerobic training is not the preferred modality for improving muscular strength, unlike resistance training [42].

Functional Performance

Hemodialysis patients can significantly improve exercise capacity (i.e. 6-min walk distance) secondary to PRT [13] or combined training [10, 21]. Other functional performance outcomes reported include increased maximal walking speed [13, 20, 21], habitual walking speed [20, 21], and sit-to-stand movement speed [13, 20, 21].

Disability

Independence in activities of daily living has not specifically been measured after exercise in this cohort. However, in the longest trial of exercise training conducted with HD patients, Kouidi et al. [36] demonstrated that combined training on non-dialysis days significantly improved the likelihood of returning to work after 1 and 4 years of training.

Psychological Adaptations to Exercise Training

Depression

Carney et al. [27], in a RCT, showed that aerobic training alleviated depression to a greater extent than participation in a social support group in this cohort, as evaluated by the Beck Depression Inventory (BDI) [43] ($p < 0.05$). Significantly reduced BDI scores following 3–12 months of aerobic exercise training have been observed in other trials [24, 25, 29]. Kouidi et al. [29] suggested that the most severely depressed patients benefited to the greatest extent.

Quality of Life

Several trials of exercise training in HD patients have evaluated Medical Outcomes Trust Short-Form 36 (SF-36) [44] scores as health-related QOL outcome measures. Improved perceptions of 'physical functioning' have been observed secondary to 3–5 months of aerobic [34, 37] and combined training [12, 20, 21]. Painter et al [20, 21] reported improvements in other SF-36 QOL domains including: 'role physical' [20, 21], 'bodily pain' [20, 21], 'general health' [20, 21], 'vitality' [20], and the 'physical component scale' [20, 21], especially in patients with low baseline perceptions of physical functioning. Oh-Park et al. [12] showed improved 'mental health' scores with combined training performed during HD. One trial did not yield improvements in any SF-36 scores [33]. The authors [33] speculated that the lack of significance could be due to the fact that their samples had high functional status at baseline and/or their study was inadequately powered. Improved measures of QOL have been ascertained in this cohort using other scales [31], including the Spitzer QOL Index (QLI) [45].

Discussion

Overall, the evidence gathered in this critical review suggests that appropriately prescribed exercise involving aerobic and/or resistance training modalities, is safe and beneficial for HD patients. Planned exercise can induce a myriad of positive health and clinical adaptations in this cohort, which may be associated with enhanced quality and quantity of life. However, current limitations within this body of the literature may be partially responsible for the fact that exercise training is not routinely recommended or prescribed in this cohort by practitioners [3, 4]. Despite nearly 3 decades of research demonstrating the benefits of exercise in ESRD, advocacy for exercise has been notably absent from official position stands and policy documents until the publication of a brief supportive statement in the recent Kidney Disease Outcomes Quality Initiative (KDOQI) in April 2005 [46].

Thirteen trails (13/29, 45%) reviewed were RCTs. Several of these RCTs were methodologically limited according to current standards of reporting [47]. Limitations were evident with respect to: statistical analyses where only 2 studies mentioned utilization of intention-to-treat strategy; the limited involvement of blinded outcomes assessors; and the inadequate reporting of subject characteristics, interventions, and outcome measures, including safety and compliance. Further, the external validity of 9/13 (69%) RCTs reviewed is compromised by the fact that these trials excluded diabetics. Diabetes has become the leading cause of ESRD in the United States affecting approximately 45% of newly diagnosed patients [1]. Currently, over 35% of patients with ESRD in the US are diagnosed diabetics [1].

Thorough and standardized reporting [47] is required of future clinical trials of exercise training in HD patients. Subject characteristics should be clearly described, including the etiology of renal failure and comorbidities. Interventions should be thoroughly defined with respect to frequency, intensity, modality, session duration, delivery, and supervision. This is essential for determining the exercise prescription required to positively affect specific outcomes. Clearly, the fact that some trials we reviewed observed no effect of exercise training on certain outcomes [8, 15, 23, 28, 30, 38] does not imply that exercise, in general, is ineffective in this cohort, but rather suggests that the exercise dose and/or modality prescribed was insufficient to positively affect the desired measure. Compliance to training should be defined a priori to determine the feasibility and generalizability of prescribing exercise training in this patient population. Thorough reporting of adverse events, including a priori definitions, is necessary to determine the risk to benefit ratio of exercise training in this cohort, which is suggested to be favorable among other chronically diseased populations [42].

The documented adaptations to exercise training in the 29 trials reviewed represent important areas of benefit to the HD population. The physiological, functional, and psychological adaptations induced by exercise may be associated with reduced cardiovascular risk profile, improved QOL, and extended lifespan. At present, however, robustly designed studies are required to further evaluate many of these, and other health-related and clinical outcomes, including skeletal muscle wasting, osteoporosis, the malnutrition-inflammatory complex, dialysis adequacy, metabolic syndrome, endothelial dysfunction, disability, depression, self-efficacy and QOL. Future investigations should also be conducted explicitly with targeted subpopulations within this cohort, including those suffering from clinical depression, obesity, hypertension, and insulin resistance/diabetes. For example, there are currently no trials evaluating insulin resistance/glucose homeostasis in diabetics on HD, nor are there trials of exercise in patients with clinically diagnosed depressive illness. Additionally, few studies have specifically targeted patients >65 years, an increasingly large cohort with a greater burden of complex comorbidities which may impact on both feasibility and benefit of exercise training interventions.

Trials prescribing aerobic and resistance training modalities, independently and in combination, should be conducted. It could be hypothesized that combined interventions elicit superior adaptations of VO_{2peak} (central and peripheral) and other health-related outcomes than either intervention on its own; however, studies isolating each modality will be useful for determining which beneficial adaptations can be assigned to each modality specifically. At present, there is only one report involving PRT in this cohort [13, 14]. This is a significant gap in the literature given the risk and critically important outcomes associated with skeletal muscle wasting in patients with chronic uremia [48]. PRT may also be a more feasible exercise modality in this cohort as patients with congestive and ischemic heart disease, who cannot engage in vigorous aerobic training, may be able to perform robust PRT safely. PRT is currently widely advocated and prescribed for health benefits in various healthy, and chronically diseased cohorts [42], though not in HD patients as yet.

Various methods of exercise delivery should continue to be investigated, compared and contrasted, as recently performed by Kouidi, Konstantinidou et al. [35, 36]. It should be noted, however, that training volume in these trials was not equated. Thus, the greater cardiorespiratory benefits achieved by patients training on nondialysis days could primarily be attributed to the fact that they received a greater volume of training. Future trials should therefore equate the volume of training to determine which method of training is more feasible, and beneficial. Novel exercise equipment customized to the HD setting will likely have to be developed to investigate such hypotheses.

Long-term behavioral change is the challenge to exercise prescription in most clinical cohorts, and patients receiving maintenance HD for the management of ESRD are no exception. Only 4 trials were identified which were >6 months in duration [5, 6, 17, 24–26, 36], compliance was often not reported, and virtually no information was presented on psychological, demographic, or clinical predictors of adoption and adherence in the patients studied. Future studies can contribute to the successful dissemination of their research findings and overcome barriers to behavioral change if such analyses are conducted and compliance, as well as reasons for noncompliance, is carefully documented.

The available literature supports the clinical utility of exercise participation for HD patients. Although methodological shortcomings exist, and gaps in knowledge are clearly evident in some specific areas, there is sufficient empirical published evidence to support the addition of exercise recommendations to clinical guidelines, as recently published by the KDOQI [46]. Further research is required to advance these guidelines toward the development of position stands on exercise prescription. There is no other available medical treatment with the capacity to induce beneficial adaptations across as wide a range of physiological, functional, psychological, and clinical domains as appears possible with sufficient doses of aerobic and resistance training. In addition, it appears possible to creatively modify the sedentary, often negative, and depressing ambiance of the typical HD unit by bringing the exercise treatment directly into this medical setting. Such complete integration of exercise and medicine is critical for its acceptance by practitioners as part of mainstream medical care, for enhancing compliance and safety, and perhaps for the actual improvement of dialysis adequacy itself.

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