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CKJ REVIEW

Effects of exercise in the whole spectrum of chronic kidney disease: a systematic review

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Abstract

Chronic kidney disease (CKD) is a public health problem. Although physical activity is essential for the prevention and treatment of most chronic diseases, exercise is rarely prescribed for CKD patients. The objective of the study was to search for and appraise evidence on the effectiveness of exercise interventions on health endpoints in CKD patients. A systematic review was performed of randomized clinical trials (RCTs) designed to compare exercise with usual care regarding effects on the health of CKD patients. MEDLINE, EMBASE, Cochrane Central, Clinical Trials registry, and proceedings of major nephrology conference databases were searched, using terms defined according to the PICO (Patient, Intervention, Comparison and Outcome) methodology. RCTs were independently evaluated by two reviewers. A total of 5489 studies were assessed for eligibility, of which 59 fulfilled inclusion criteria. Most of them included small samples, lasted from 8 to 24 weeks and applied aerobic exercises. Three studies included only kidney transplant patients, and nine included pre-dialysis patients. The remaining RCTs allocated hemodialysis patients. The outcome measures included quality of life, physical fitness, muscular strength, heart rate variability, inflammatory and nutritional markers and progression of CKD. Most of the trials had high risk of bias. The strongest evidence is for the effects of aerobic exercise on improving physical fitness, muscular strength and quality of life in dialysis patients. The benefits of exercise in dialysis patients are well established, supporting the prescription of physical activity in their regular treatment. RCTs including patients in earlier stages of CKD and after kidney transplantation are urgently required, as well as studies assessing long-term outcomes. The best exercise protocol for CKD patients also remains to be established.

Key words: chronic kidney disease, dialysis, exercise, physical activity

Introduction

Chronic kidney disease (CKD) is a current public health problem associated with progression to end-stage renal disease (ESRD), cardiovascular disease and increased mortality rates. The disease has a progressive course, and it is estimated that for every patient on renal replacement therapy (RRT) there are 20–25 patients with milder kidney damage [1].

The risk of cardiovascular events increases proportionally with the decline of glomerular filtration, reaching rates 10–20 times higher than in the general population among ESRD patients [1]. The mortality rate of CKD patients is 15–30 times higher than that of healthy individuals. The disease is also associated with greater health expenditures [2] and lower health-related quality of life (HRQOL) [3].

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Physical activity is one of the key elements for the prevention of chronic diseases. Among the general population, physical activity reduces the risk of complex chronic diseases, particularly ischemic heart disease, contributes to blood pressure and glucose control and improves the HRQOL [3].

The prescription of exercise for CKD patients is less usual than for other chronic diseases. This is noteworthy, considering that physical activity levels among CKD patients are significantly lower than among healthy individuals [4]. Moreover, low aerobic capacity, a physical fitness marker that can be improved by exercise, has been pointed to as the strongest predictor of mortality among ESRD patients [5]. Assuming that the benefits of exercise could also apply to CKD patients, physical activity deserves to be considered as a major component of treatment in all stages of the disease [4].

In order to critically appraise the evidence currently available on the issue, we conducted a systematic literature review on the effectiveness of exercise interventions among CKD patients.

Methods

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement for the conduct of meta-analyses of intervention studies was followed [6].

Eligibility criteria were randomized controlled trials (RCT) evaluating any type of exercise intervention, including advising for physical activity practice, in CKD patients, regardless of their disease stage. The studies based on the same sample, but with different outcomes were included. Only studies with adults (≥18 years) were selected.

Studies on the acute effects of exercise (intervention lasting <8 weeks) and/or quasi-experimental studies were excluded.

Literature search

A search for articles up to and including June 2015 was made from MEDLINE (accessed via PubMed) and EMBASE; we combined these search results with searches of the Cochrane Central Register, and clinical trials registry databases. Conference proceedings abstracts also were hand searched (American Society of Nephrology from 2003 to 2014, European Renal Association–European Dialysis and Transplant Association from 2002 to 2014 and World Congress of Nephrology from 2001 to 2012).

The initial search included terms such as 'exercise', 'physical activity', 'chronic renal disease' and related entry terms associated with a high-sensitivity strategy search. Most of the eligible studies were found on the PubMed database. By the specific search strategy used for the PubMed database, we used the following terms:

((((((((((exertion, physical[MeSH Terms]) OR exercise[MeSH Terms]) OR 'exercise therapy') OR physical activity[MeSH Terms]) OR physical fitness[MeSH Terms]) OR resistance training[MeSH Terms]) OR aerobic exercise[MeSH Terms]) OR exercise[MeSH Terms])) OR ((((((((((((((((exercise) OR 'exercise training') OR 'physical activity') OR 'aerobic exercise') OR 'aerobic training') OR 'resistance program') OR 'resistance exercise') OR 'resistance training') OR 'aerobic program') OR 'endurance exercise') OR 'endurance training') OR 'endurance program') OR 'physical activity') OR 'physical activities') OR 'exercise therapy') OR 'exercise test') OR 'physical rehabilitation'))).

(((((((((((((renal dialysis[MeSH Terms]) OR uremia[MeSH Terms]) OR renal replacement therapy[MeSH Terms]) OR hemodialysis[MeSH Terms]) OR hemodialyses[MeSH Terms]) OR dialysis [MeSH Terms]) OR chronic kidney failure[MeSH Terms]) OR renal insufficiency[MeSH Terms]) OR kidney failure[MeSH Terms]) OR kidney transplantation[MeSH Terms]) OR dialyses[MeSH Terms])) OR ((((((((((((uremia) OR 'renal replacement therapy') OR hemodialysis) OR hemodialyses) OR dialysis) OR dialyses) OR 'chronic kidney failure') OR 'chronic kidney disease') OR 'renal insufficiency') OR 'kidney failure') OR 'renal disease') OR 'kidney transplantation')).

Data extraction

The articles identified in the literature search were screened by two independent extractors (F.C.B and M.B) who were blinded to authorship. The initial screening was based on only titles and abstracts. After that, the full text of potentially eligible articles was evaluated. Data extraction of selected RCTs was performed by two independent reviewers (F.C.B and M.B). Discrepancies between the two extractors were discussed until consensus was reached.

Outcome measures

This review focused on clinically relevant outcomes, measured using physiological and psychological variables associated with progression and complications of CKD.

Primary outcomes:

1. Physical fitness: aerobic capacity, muscular strength;
2. Health-related quality of life (measured through well-established, reliable and validated instruments);
3. Cardiovascular dimensions: heart rate variability (HRV) index, mean RR, mean standard deviation of normal-to-normal intervals (SDNN), pulse wave velocity (PWV) and arterial stiffness;
4. Nutritional measures: body composition (visceral fat, waist circumference and leg lean mass), body mass index, waist circumference);
5. Depression;
6. Systemic inflammation: interleukin 6, C-reactive protein.

Secondary outcomes:

1. Blood lipids: total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides;
2. Progression of CKD: determined as glomerular filtration from serum creatinine and/or cystatin C and/or radioisotope tracing.

Assessment of risk of bias

Reviewers (F.C.B and M.B) independently assessed the risk of bias of included studies using the Cochrane Collaboration's tool [7]. The quality of RCTs was judged by selection bias (method of recruitment, proper method of randomization at baseline, concealment of treatment allocation, similarity of groups at baseline and provision of eligibility criteria), detection bias (use of masked outcome assessment, blinded administrator and blinded patients) and attrition bias (level of adherence to the intervention, completeness of follow-up and use of intention-to-treat analysis). Any disagreement concerning data extraction and/or quality was resolved in a consensus meeting.

Each item was rated by assigning a judgment of high, low or unclear risk of material bias. We define material bias as bias of sufficient magnitude to have a notable effect on the results or conclusions of the trial, recognizing the subjectivity of any such judgment.

Results

Literature search

We retrieved 5489 articles in searches from inception through June 2015 from MEDLINE, EMBASE, PubMed, Cochrane Central, clinical trials registries, and nephrology conference proceedings. Initially 486 duplicated articles were excluded. Of the 5003 articles examined for eligibility, 4861 were excluded based on the title or abstract. The full texts of 142 potentially eligible studies were evaluated. Of these, 59 fulfilled inclusion criteria and were included in the review (Figure 1).

Selected trials

Table 1 describes the studies in terms of sample size, type and duration of intervention, CKD stage, main outcome measures and results. Fifty-nine studies, randomizing 2858 participants, were identified and selected for this review. The number of participants was usually small, ranging from 11 [23] to 297 [42] subjects, the last being a multicenter study. In 38 studies (67%), the sample size was <50 participants [8–10, 12–19, 21–26, 28–30, 35, 37–41, 45–47, 49, 50, 52, 53, 55–58, 60]. Only three studies used a healthy control group [61, 51, 62] in addition to a CKD control group. Most interventions lasted from 8 to 24 weeks; six trials lasted ≥1 year [26, 31–33, 43, 63]. Only one study compared exercise advice and rehabilitation counseling for pre-dialysis and dialysis patients [22].

Twenty-eight of the 59 studies were published after 2009 (Table 1). Despite the fact that diabetes and hypertension are the main comorbidities associated to CKD, only one study was restricted to diabetic CKD [39] and one to obese pre-dialysis patients [10].

Assessment of the quality of studies

Results of the risk of bias assessment are presented in Figure 2. Risks of bias due to blinding and incomplete outcome data were assessed across all outcomes within each included study.

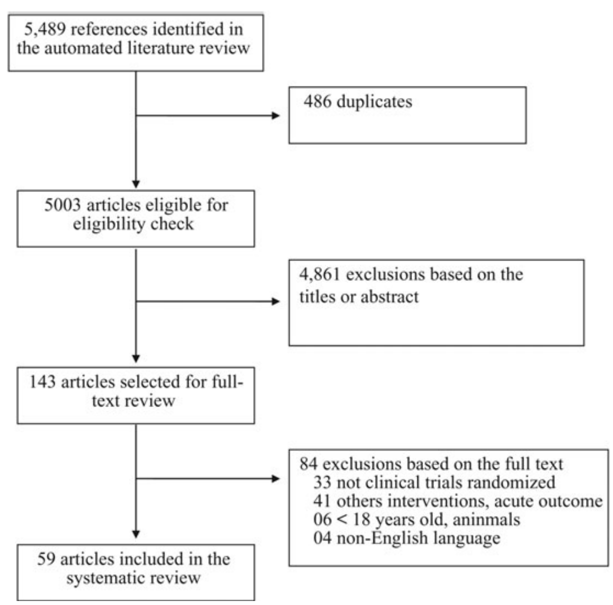

Fig. 1. Exercise interventions in chronic renal disease patients: literature search results.

Selection bias

Allocation: The most frequently detected shortcomings were related to randomization and generation of the allocation sequence. Only 23 studies had adequate randomization [13, 15, 17, 18, 24, 25, 31–33, 35–37, 39, 44, 45, 48, 50, 54, 55, 64–67] and concealment of the allocation sequence was described in only 14 RCTs [11, 15, 17, 18, 25, 31–33, 35–37, 45, 55, 65].

Detection bias

Blinding: The blinding process of participants, care providers and assessors was described in six studies [18, 32, 33, 45, 55, 59]. Only three studies used blinding of the outcomes [18, 44, 60].

Attrition bias

Dropout rates: Forty-one of 59 studies reported dropout rates. Thirty-two had a dropout rate between 0 and 30% [10, 11, 13, 14, 16–18, 20–25, 29, 32, 33, 36, 39, 43, 47, 49, 55, 57, 58, 61–66, 68]. One study [12] had a dropout rate >70%.

Intention-to-treat analysis: The analysis was conducted according to the intention-to-treat principle in only 10 studies [10, 13, 16, 18, 21, 24, 32, 33, 54, 67].

Adherence to interventions: Only nine RCTs reported on compliance, which was computed as the number of sessions attended out of the total possible sessions, expressed as a percentage [11, 15, 31, 38, 56, 64, 65, 67, 69]. The compliance ranged from 70 [31] to 89% [11, 65].

Other quality indicators

Sample size calculations were not consistently presented in the articles, making it difficult to interpret whether non-significant findings were due to insufficient study power in eight studies [16, 18, 21, 24, 32, 33, 48, 67].

Types and durations of interventions

The intervention was based on aerobic exercise in 44 studies [9–12, 16, 17, 21–24, 26, 29, 30, 32, 33, 35–37, 39, 42–46, 48–51, 53, 56–58, 60–63, 65, 66], lasting from 30 to 90 min per session, with intensities ranging from 60 to 80% of maximal oxygen consumption (VO_2 max). Resistance exercises were used in nine studies [8, 13–15, 20, 55, 56, 64], two were associated with nutrition [13, 20] and nine combined aerobic and resistance exercises [18, 31, 34, 36, 38, 47, 50, 54, 59]. One study applied as intervention intradialytic electromyostimulation of leg extensors [19]. Two RCTs [25, 64] compared drug treatment with exercise, with one of them including only CKD patients with restless legs [25]. Gordon *et al.* [27] and Yurtkuran *et al.* [17] used yoga-based exercise. Most studies used intradialytic exercise two to three times a week. Supervised exercise interventions were used in the most studies; one study used physical activity advice alone [22].

Outcomes measures

Health-related quality of life (HRQOL): HRQOL was analyzed in 21 studies [18, 19, 22, 32, 40, 43, 45–50, 55, 59, 64, 67, 70]. Five studies found improvements in only the Physical Component Score [32, 45, 47, 48, 64], with ∼10% higher scores in the exercise groups. The 36-item Short Form Health Survey (SF-36) [12, 15, 18, 23, 32, 40, 43, 67] was the instrument most frequently used. Only two studies used a disease-specific instrument, the Kidney Disease Quality of Life (KDQOL) [40, 50]. The Quality of Life Index [47], Scale of Life Satisfaction [63] and Sleep Quality [24] were each used once.

Physical fitness: Measures of physical fitness, such as oxygen peak consumption (VO_2 peak) were assessed in 20 aerobic interventions [9, 12, 16, 21, 29–32, 35–37, 39, 47, 48, 51, 53, 58, 61–63]. On

Table 1. Description of the studies on exercise interventions in CKD patients

Author, year	Groups (*n*)	Intervention	Time (weeks)	CKD stage	Outcome variables	Main results (refers to I group compared with C group)
Afshar *et al.* (2010) [8]	Ia = 7 Ir = 7 C = 7	Ia: aerobic training Ir: resistance training C: usual care	8	HD	Blood chemistry (urea, creatinine, lipids, CRP), Kt/V and anthropometric measure	CRP and creatinine reduction in aerobic exercise (P = 0.005) and resistance (P = 0.036), no effect on weight, urea, lipids or Kt/V
Akiba *et al.* (1995) [9]	I = 10 C = 10	I: exercise training C: usual care	12	HD	Aerobic capacity (VO_2 max, VO_2AT)	VO_2 max (P < 0.05) and VO_2AT (P < 0.05) were decreased in C group and unchanged in I group
Baria *et al.* (2014) [10]	Ic = 10 Ih = 8 C = 9	Ic: center aerobic Ih: home aerobic C: usual care	12	Obese PH	Body composition, abdominal distribution of fat	Visceral fat and waist circumference decreased 6.4 ± 6.4 mm (P < 0.01) and 2.0 ± 2.3 cm (P = 0.03) and leg lean mass increased 0.5 ± 0.4 kg (P < 0.01)
Bohm *et al.* (2014) [11]	Ic = 30 Ip = 30	Ic: cycle ergometer Ip: home-based walking	24	HD	Capacity aerobic, strength lower, flexibility, accelerometer and HRQL	No significant differences in any outcomes were identified between interventions groups
Carmack *et al.* (1995) [12]	I = 23 I = 25	I: aerobic training C: attention wait-list	10	HD	VO_2 peak, depression	Significant improvement in aerobic capacity. There were no significant changes between groups on measures of depression
Castaneda *et al.* (2001) [13]	I = 14 C = 12	I: low protein diet + resistance training C: low protein diet only	12	P-HD	TBP, muscle fibers type I and II, GFR	TBP, I and II fibers increased 4 ± 8%, 24 ± 31%, 22%; strength: I: 32 ± 14%; C: −13 ± 20% (P < 0.001); ΔGFR I: 1.18; C: −1.62 (P = 0.048)
Castaneda *et al.* (2004) [14]	I = 14 C = 12	I: low protein diet + resistance training C: low protein diet only	12	P-HD	CRP, IL-6, CSA of muscle fibers, muscle strength	CRP (−1.7 mg/L; P = 0.01), IL-6 (−4.2 pg/mL; P = 0.01) decreased, type I (24 ± 31%), type II (22 ± 41%) and strength (28 ± 14%; P = 0.001) increased
Cheema *et al.* (2007) [15]	I = 24 C = 25	I: intense resistance training C: usual care	12	HD	Muscle CSA, lipid content and strength, CRP and quality of life	Muscle strength (RR = 0.59; P = 0.04), body weight (RR = 0.62; P = 0.06) and CRP (RR = −0.63; 95% CI −0.54–0.00) improved; no change in muscle CSA
Chen (2010) [11]	I = 25 C = 25	I: intradialytic low-intensity strength training C: stretching	24	HD	SPPB, lower body strength, body composition and quality of life	SPPB improved 21.1% (43.1%) in I versus 0.2% (38.4%) in C (P = 0.03); sensitivity analysis: SPPB correlated to knee extensor strength (*r* = 0.33)
Deligiannis *et al.* (1999) [16]	I_{Hd} = 30 C_{Hd} = 30 C_S = 30	I_{Hd}: supervised training 3×/w non-dialysis C_{Hd} and C_s: usual care	28	HD	HRV, SDNN, VO_2 max	HRV increased from 22 ± 7 to 28 ± 9 (P < 0.05), SDNN from 0.11 ± 0.03 to 0.13 ± 0.04 (P < 0.05), VO_2 max by 41% and exercise testing duration by 33%
Deligiannis (1999) [17]	I_a = 16 I_b = 10 C_{hd} = 12 C_s = 15	I_a: aerobic HD I_b: aerobic at home C_{hd}: HD controls C_s: healthy controls	28	HD	Spiroergometric echocardiographic HRpeak, VO max, pulmonary ventilation	I_a and I_b: increased exercise time 33%/17% and VO_2 max 43%/14%; I_a: increase in FE 5% and SVI 14%; unchanged in C_{hd}
DePaul *et al.* (2002) [18]	I = 20 C = 18	I: resistance and aerobic C: range-of-motion exercises	12	HD	Submaximal workload, muscle strength, 6MWT, QOL, symptoms scores	Increased on the submaximal exercise test and muscle strength, but not in 6MWT, symptoms questionnaire or quality of life
Dobsak *et al.* (2012) [19]	Iet = 11 Iems = 11 C = 10	Iet: aerobic training Iems: electrostimulation C: usual care	20	HD	Wpeak, 6MWT, muscle power (Fmax), urea clearance and HRQOL	Significant improvement of Wpeak, Fmax and 6MWT in ET and EMS. No difference between ET and EMS groups
Dong *et al.* (2011) [20]	I = 33 C = 33	I: Resistance training plus nutrition C: nutrition alone	24	HD	Body composition, muscle strength, biochemical parameters, recall dietary	No difference in lean body mass. Weight and strength increased in I group
Eidemak *et al.* (1997) [21]	I = 15 C = 15	I: aerobic training C: usual care	24	P-HD	VO_2 max, BP, HR, serum lipids, GFR	Maximal work capacity increased in the exercise group. No difference in ΔGFR

Table 1. Continued

Author, year	Groups (*n*)	Intervention	Time (weeks)	CKD stage	Outcome variables	Main results (refers to I group compared with C group)
Fitts (1999) [22]	PR = 9 PC = 9 DR = 9 DC = 9	R: exercise coaching C: usual lifestyle P: pre-dialysis D: hemodialysis.	24	P-HD and HD	6MWT, HRQL, resting HR	PR walked more. Hematocrit increased in R. Quality of life was stable or improved in PR, but declined in PC. PR benefited more than DR
Frey (1999) [23]	I = 6 C = 5	I: cycle 60–80% of maximal heart rate C: usual care	12	HD	Dietary recalls, prealbumin, transferrin and pre-dialysis and post-dialysis albumin	No increased visceral proteins
Giannaki *et al.* (2013) [24]	I = 12 C = 12	I: aerobic training C: usual care	26	HD (RSL)	Severity of RLS, functional capacity, sleep quality, depression levels	RLS severity decreased ($P = 0.017$), depression score ($P = 0.002$) and daily sleepiness ($P = 0.05$) improved
Giannaki *et al.* (2013) [25]	$I_E = 16$ $I_{da} = 8$ C = 8	$I_{E:}$ aerobic training $I_{da:}$ dopamine agonist C: usual care	26	HD (RSL)	Severity of RLS, functional capacity, muscle quality, depression, sleep quality	RLS improved in groups exercise and dopamine agonist ($P = 0.03$) and only agonist group improved sleep score ($P = 0.016$)
Goldberg *et al.* (1983) [26]	I = 14 C = 11	I: aerobic training 3 to 5 times weekly C: usual care	52 ± 4	HD	Aerobic capacity, BP, lipids, Ht, weight, fasting plasma insulin	Increased aerobic capacity 21%, exercise stress test 19%, decrease in BP, plasma insulin 20%, TG 33%. Increase in HDL, Ht
Gordon *et al.* (2012) [27]	I = 33 C = 33	I: Hatha yoga exercise C: usual care	16	HD	Serum total cholesterol, LDL, HDL and TG	Decrease in TG, LDL and total cholesterol/HDL ratio
Gregory *et al.* (2011) [28]	I = 14 C = 11	I: supervised exercise and dietary counseling C: usual care.	48	P-HD	Treadmill testing, IGF-I, IGF-II, IGFBP-1	No difference in the IGF system. Interaction between group and time for VO_2 and total treadmill time
Headley *et al.* (2012) [29]	I = 14 C = 11	I: personal training and dietary counseling C: usual care	48	P-HD	VO_2 peak, eGFR, resting and ambulatory HR, lipids, CRP and IL-6	Increase in VO_2 peak from 18.1 ± 7.8 to 20.1 ± 7.3, reductions of HR, increases in LDL and TG, no effect in eGFR
Headley *et al.* (2014) [30]	I = 25 C = 21	I: aerobic training C: usual care	16	P-HD	Arterial stiffness, aerobic capacity, endothelin1, nitrate/nitrite, CRP, HRQL	No change in arterial stiffness (PWV). 8.2% increase in VO_2 peak, physical function, vitality, bodily pain
Howden *et al.* (2013) [31]	I = 41 C = 42	I: lifestyle and aerobic and resistance training C: usual care	52	P-HD	Peak VO_2, left ventricular function, arterial stiffness, anthropometric measures	Improved peak VO_2 ($P = 0.004$), weight loss ($P = 0.02$), diastolic function ($P = 0.001$), arterial elastance ($P = 0.01$). No change in BP
Johansen, (2006) [32]	$I_{ex} = 20$ $I_{ex/nd} = 20$ $I_{nd} = 19$ P = 20	I_{ex}: resistance training $I_{ex/nd}$: exercisee + nd I_{nd}: nandrolone P: placebo	12	HD	Body composition (LBM), muscle size and strength, physical performance and activity	LBM: nandrolone increased ($P < 0.0001$), ex no effect. Quadriceps CSA increased in ex ($P = 0.01$) and nd ($P < 0.0001$). Ex increased physical functioning ($P = 0.04$)
Koh (2010) [33]	$I_{Hd} = 27$ $I_{Ho} = 21$ C = 22	I_{Hd}: intradialytic cycle I_{Ho}: home-based walking C: usual care	24	HD	6MWT, PWV, augmentation index, physical activity, physical functioning.	No differences between Δ6MWT (intra Hd +14%, home +11%, usual care +5%), PWV, or any secondary outcome measure
Konstantinou (2002) [10]	$I_{Ohd} = 21$ $I_{Hd} = 12$ $I_{Ho} = 12$ $C_{Hd} = 13$ Cs = 15	I_{Ohd}: outpatient training I_{Hd}: during HD training I_{Ho}: non-supervised home C_{Hd}: HD controls Cs: healthy controls	24	HD	VO_2 peak, VO_2AT, exercise time, dropout rate	I_{Ohd}: higher dropout; VO_2 peak increased 43%, VO_2 AT 37%, exercise time 33% I_{Hd}: 24, 18 and 22%; I_{Ho}: 17, 8, 14%; respectively. Intense exercise outpatient is the most effective training

Table continues

Table 1. Continued

Author, year	Groups (*n*)	Intervention	Time (weeks)	CKD stage	Outcome variables	Main results (refers to I group compared with C group)
Kopple *et al.* (2007) [34]	Icve = 10 Ires = 15 Imix = 12 C = 14	Icve: aerobic training Ires: resistance training Imix: combined training C: usual care	20	HD	Mean body and fat mass, mid-thigh CSA, BMI, mRNA levels of growth factors genes in muscle	mRNA increased for IGF-IEa, IGF-IEc, IGF-IR, IGF-II, IGFBP-2, and IGFBP-3. No change in CRP, TNF, and IL-6 concentrations
Koufaki (2002) [35]	I = 18 C = 15	I: aerobic cycle C: usual care	12	HD/CAPD	Functional capacity, 6MWT, VO_2 peak, VO_2 at ventilatory threshold	Significantly improved peak exercise capacity 21.2 ± 7.2 to 26.9 ± 6.2 and C = 23.7 ± 6.8 to 24.1 ± 7.2
Kouidi (2009) [36]	I = 30 C = 29	I: combined training C: usual care	42	HD	VO_2 peak, FE, HR variability	VO_2 peak from 16.4 ± 5.4 to 21.4 ± 6.8 mL/kg/min and HRV increased 12.6 ± 16.3 ($P < 0.001$)
Kouidi *et al.* (2010) [37]	I = 25 C = 25	I: HD cycling C: usual care	52	HD	VO_2 peak, VCO_2/VO_2, depression (BDI and HADS), HRV (SDNN, LF/HF)	VO_2 peak increased 24%, exercise time 61.4%, LH/HF 17% and SDNN 59%. Decreased BDI 34.5% and HADS 23.5%
Kouidi *et al.* (2013) [38]	I = 12 C = 12	I: aerobic training C: usual care	24	TX	HRV, arterial baroreflex sensitivity	VO_2 peak increased by 15.8% ($P < 0.05$) and all depressed HRV and BRS indices were improved after training
Leehey *et al.* (2009) [39]	I = 7 C = 6	I: aerobic 6 weeks + 18 weeks home supervised C: usual care	24	P-HD + DM2	VO_2 max, exercise duration, GFR, Hb, HbA1, lipids, CRP and 24-h proteinuria	Increase in exercise duration. No difference in GFR, Hb, HbA1, lipids, CRP or 24-h proteinuria
de Lima *et al.* (2013) [40]	Ia = 10 Is = 11 C = 11	Ia: aerobic, bicycle Is: training load ankle C: usual care	8	HD	Respiratory strength, lung function, functional capacity, biochemistry, HRQOL	Improvement ($P < 0.05$) in the maximal inspiratory pressure, number of steps achieved, and quality of life
Makhlough *et al.* (2012) [41]	I = 25 C = 23	I: aerobic training C: usual care	8	HD	Calcium, phosphate, potassium, Hb	Decrease in serum phosphate (by 1.84 mg/dL) and potassium (0.69 mg/dL)
Mallamaci *et al.* (2014) [42]	I = 151 C = 146	I: home exercise program C: usual care	24	HD	6MWT and Sit-to-Stand test	Increased 6MWT, 369 ± 113 to 324 ± 116 ($P < 0.001$) and sit-to-stand 18.3 ± 19.7 ± 6.7 s between groups
Matsumoto *et al.* (2007) [43]	I = 22 C = 33	I: exercise training C: usual care	52	HD	Albumin, HRQOL, creatinine generation (CGR)	Serum albumin, CGR and HRQOL increased in the I group
Mohseni *et al.* (2013) [44]	I = 25 C = 25	I: aerobic training C: usual care	8	HD	Dialysis efficacy (Kt/v and URR)	Increased intragroup URR ($P = 0.003$) and Kt/v ($P = 0.001$), between groups not stated
Molsted *et al.* (2004) [45]	I = 22 C = 21	I: aerobic training 2× week C: usual care	20	HD	Aerobic capacity, 2-min stair climbing, squat test, SF-36, BP and lipids	Increase in aerobic capacity and Physical Summary Score (SF36)
Mortazavi *et al.* (2013) [46]	I = 13 C = 13	I: aerobic training 3× week C: usual care	16	HD RLS	Severity of RLS, HRQL (SF-63)	Decreased scores of RLS and HRQL no difference between groups
Orcy *et al.* (2012) [38]	I = 13 C = 13	I: resistance and aerobic C: resistance only	10	HD	Functional performance (6MWT)	6MWT changed 39.7 ± 61.4 m in I group and −19.2 ± 53.9 m in C group ($P = 0.02$)
Ouzouni *et al.* (2009) [47]	I = 20 C = 15	I: resistance and aerobic C: usual care	40	HD	VO_2 peak, HRQOL, personality parameters	Increased VO_2 peak (21.1%) and physical HRQOL, decreased depression
Painter *et al.* (2002a) [48]	$I_{HtU} = 10$ $I_{HtN} = 12$ $C_{HtU} = 14$ $C_{HtN} = 12$	I: aerobic training C: usual care HtU: Ht 30–33% HtN: Ht 40–42%	20	HD	Treadmill, VO_2 peak HRQL (SF-36)	I: increased VO_2 peak ($P = 0.03$), physical functioning ($P = 0.01$); HtN: increased general health ($P = 0.03$)
Painter *et al.* (2002b) [32]	I = 54 C = 43	I: exercise at home C: usual care	52	Tx	Symptom-limited exercise, VO_2 peak, isokinetic testing, body composition, SF-36	Increased VO_2 (24.0 ± 7.5 to 30.1 ± 10.3 mL/kg/min) and muscle strength. No differences in body composition or HRQL

Table 1. Continued

Author, year	Groups (*n*)	Intervention	Time (weeks)	CKD stage	Outcome variables	Main results (refers to I group compared with C group)
Painter (2003) [33]	I = 51 C = 45	I: aerobic training C: usual care	52	Tx	Maximal exercise testing, risk factors, Framingham equations	Increase in total cholesterol, HDL-C, and body mass index over time. No differences between groups
Parsons (2004) [49]	I = 6 C = 7	I: aerobic cycle C: usual care	08	HD	SF-36, KtV, 2-h DUC, BP, and maximal work capacity	Only DUC in the first 2-h was higher in I group
Pellizzaro *et al.* (2013) [50]	RMT = 11 PMT = 14 C = 14	RMT: inspiratory muscles PMT: knee extensor muscle C: usual care	10	HD	Respiratory strength, functional capacity, HRQOL, inflammatory state	ΔPI and ΔPE increased in RMT; Δ6MWT increased in RMT and PMT, CRP reduced and HRQOL increased in RMT and PMT
Petraki *et al.* (2008) [51]	I = 22 C_{HD} = 21 C_S = 20	I: aerobic during HD C_{HD}: HD controls C_s: healthy controls	28	HD	Arterial baroreflex sensitivity, spiroergometric study	Improvement in VO_2 peak, exercise time and arterial baroreflex sensitivity
Reboredo *et al.* (2010) [52]	I = 11 C = 11	I: aerobic during HD C: usual care	12	HD	HRV and LVF by Holter and echocardiography	No differences in HRV or LVF between the groups
Reboredo (2011) [53]	I = 14 C = 14	I: aerobic during HD C: usual care	12	HD	VO_2 peak and time to exercise intolerance (Tlim)	Training improved 50 to 200% in Tlim and VO_2 peak in 15–20%
Rossi *et al.* (2014) [54]	I = 59 C-48	I: treadmill cardiovascular and weight training+usual C: usual care	12	P-HD	6 MWT, sit-to-stand test	Intervention significant: 6-MWT 19% improvement ($P < 0.001$), sit-to-stand test 29% improvement ($P < 0.001$)
Segura-Ortí (2009) [55]	I_{RT} = 19 I_{LA} = 8	I_{RT}: resistance during HD. I_{LA}: aerobic	24	HD	Aerobic capacity, muscle strength, HRQOL	I_{RT} improved right knee extensor muscles strength. No difference in physical tests
Song and Sohng (2012) [56]	I = 20 C = 20	I: resistance training C: usual care	12	HD	Body composition, physical fitness, HRQOL, lipid profile	Muscle strength and HRQOL increased, cholesterol and triglyceride decreased
Toussaint (2008) [57]	I = 9 C = 10	I: aerobic cycle (cross-over) C = usual care	12	HD	PWV, measurements of BNP	PWPV improved, BNP decreased
Tsuyuki *et al.* (2003) [58]	I = 17 C = 12	I: aerobic exercise HD C: usual care	20	HD	VO_2 peak, BP, oxygen uptake efficiency slope (OUES)	OUES increased in physical training group, no change in control group
van Vilsteren (2005) [59]	I = 60 C = 43	I: resistance before and aerobic during HD C: usual care	12	HD	Kt/V, Ht, cholesterol, BP, weight, physical fitness, SF-36, behavior	Improvement in behavior, reaction time, lower extremity muscle strength, KtV and quality of life
Wilund *et al.* (2010) [60]	I = 8 C = 9	I: aerobic training C: usual care	16	HD	Walk test, cholesterol, OS, CRP, IL-6, K, P, Ca, ALP, urea, albumin, heart function	Walk increased 17%, OS and epicardial fat reduced. No change in CRP, IL-6 or other variables
Yurtkuran (2007) [17]	I = 19 C = 18	I: yoga-based exercises C: usual care	12	HD	Visual analogue scale (pain, fatigue, sleep), grip strength, biochemical variables	Improvement in pain −37%, fatigue −55%, sleep disturbance −25%, strength +15%, Ht +13%, creatinine −14%, cholesterol −15%

I, intervention group; C, control group; P-HD, pre-HD; HD, hemodialysis; Tx, renal transplantation; HRV, heart rate variability; SDNN, standard deviation of normal-to-normal intervals; HF, marker of vagal activity; LF, parameter that includes both sympathetic and vagal influences; ratio LF/HF, marker of sympathovagal balance; RPE, rating of perceived exertion; CRP, C-reactive protein; 6MWT, 6-minute walk test; CSA, cross-sectional area; VO_2AT, anerobic threshold; VO_2 max, maximal oxygen consumption; eGFR, estimated glomerular filtration rate; TBP, total body potassium; SPPB, Short Physical Performance Battery; RLS, restless leg syndrome; LBM, lean body mass; PWV, pulse wave velocity; RMT, respiratory muscle training; PMT, peripheral muscle training; PI(max), maximal inspiratory pressure; PE(max), maximal expiratory pressure; FVC, forced vital capacity; URR, urea reduction ratio; STS, sit-to-stand; Wpeak, peak workload; DUC, dialysate urea clearance; OS, oxidative stress; IL-6, interleukin 6; K, potassium; P, phosphorus; Ca, calcium; ALP, alkaline phosphatase.

Authors	Random sequence generation	Allocation concealment	Blinding participants/ personnel	Blinding outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Afshar	?	?	–	?	?		–
Akiba	?	?	–	?	?	?	–
Baria	?	–	–	–	+	+	+
Bohn	?	?	–	–	–	+	–
Carmack	?	?	–	?	–	?	–
Castaneda	+	?	–	?	?	+	?
Cheema	+	+	–	?	–	+	–
Chen	?	+	+	?	+	+	+
Deligianis	?	?	–	?	?	–	?
Deligiannis	?	?	–	–	+	–	+
DePaul	+	+	+	+	+	+	+
Dolbsak	?	?	–	?	–	+	?
Dong	?	?	–	–	–	–	–
Eidemak	?	?	–	–	+	–	+
Fitts	?	?	–	–	–	–	–
Frey	–	–	–	–	–	–	–
Giannaki	+	?	–	?	+	+	+
Giannaki	+	+	–	?	–	+	–
Gordon	?	?	–	–	–	–	?
Gregory	?	–	–	–	?	–	?
Headley	?	?	–	–	–	?	–
Headley	+	?	–	–	–	–	–
Howden	+	+	–	?	–	+	–
Johansen	+	+	–	–	–	+	–
Koh	+	+	–	–	–	+	–
Konstantinidou	?	?	–	–	–	+	–
Kopple	?	?	–	?	–	+	–
Koufaki	+	+	–	–	–	+	–
Koudi	+	?	–	–	–	+	–
Kouidi E	?	?	–	–	–	+	–
Kouidi	+	+	–	?	–	+	–
Leehey	+	?	–	–	–	–	–
Lima	?	?	–	–	–	–	–
Makhlough	+	?	–	+	?	–	?
Matsumoto	?	?	–	?	–	–	–
Mohseni	+	?	+	?	–	–	–
Molsted	+	+	–	?	–	–	–
Mortazavi	?	–	–	?	–	–	–
Orcy	?	?	–	–	–	?	–
Ouzouni	?	?	–	–	–	–	–
Painter (a)	+	?	–	–	+	+	+
Painter (b)	+	+	–	?	+	+	+
Painter	+	+	–	?	+	?	+
Parsons	?	?	–	–	–	–	–
Pellizzaro	+	?	–	?	–	+	–
Petraki	?	?	–	–	–	+	–
Reboredo	?	?	–	–	–	–	?
Reboredo	?	?	–	–	–	–	–
Rossi	+	?	–	–	+	–	+
Segura-Orti	+	+	+	–	–	–	–
Song	?	?	–	–	–	–	–
Toussant	?	?	–	?	?	+	–
Tsuyuki	?	?	–	?	?	–	–
Wilund	?	?	–	+	–	–	–
Van Vilsteren	?	?	–	–	–	–	–
Yurtkuran	+	+	–	–	–	+	–

Key
- + Low risk of bias
- – High risk of bias
- ? Unclear risk of bias

Fig. 2. Risk of bias assessments of RCTs on the effectiveness of exercise interventions among CKD patients.

average, aerobic exercise lasting from 8 weeks to 6 months improved VO_2 peak ~20%, from 8.2% [30] to 43% [61, 62].

Heart rate variability (HRV): Seven studies evaluated the effect of exercise on HRV [16, 29, 36, 37, 51, 52, 63]: five in hemodialysis, one in kidney transplant patients [37] and one pre-dialysis [29]. Only the study by Reboredo *et al.* [52] found no difference in HRV. When HRV was assessed in the time domain, the outcome measures were SDNN and HRV index.

Lipid profile: Most studies including lipid profiles [8, 15, 17, 20, 21, 26, 29, 39, 45, 56, 59, 60] as an outcome measure found no effect of the exercise intervention on LDL cholesterol, HDL cholesterol or triglycerides, with the exception of one study that used yoga as the intervention, which reported a 15% decrease in lipids after a 12-week follow-up [17].

Inflammatory markers: Inflammatory biomarkers such as C-reactive protein (CRP) and interleukins were evaluated in 10 studies [8, 13–15, 29, 30, 34, 39, 50, 60]; in general, a positive effect of exercise interventions was detected for such outcomes. Compared with the control group, a significant reduction of CRP ($P = 0.005$ and $P = 0.036$) was demonstrated in aerobic and resistance training groups in the Afshar *et al.* study [8]. In another study [15], high-intensity resistance training decreased CRP, with a risk reduction (RR) of −0.63 (95% CI −0.54–0.00). Castaneda *et al.* [14] also applied resistance training, which decreased CRP 1.7 mg/L ($P = 0.01$), with no change in the control group. Kopple *et al.* [34] compared the effect of different forms of exercise training (endurance, strength or combination), and found no change in serum CRP with exercise training or in the control group.

Muscular strength: Nine RCTs whose intervention was resistance training [8, 13–15, 20, 32, 55, 56, 67] or aerobic and resistance training [8, 54, 59] measured muscular strength as one of their outcome measures, two in pre-dialysis patients [11, 14], another in kidney transplant patients [32] and the remaining in hemodialysis patients. One study using aerobic and muscle electrostimulation [19] and an other with yoga [17] also measured the effects on muscular strength. All of these found an increase in strength after intervention. Mallamaci *et al.* [42] assessed lower limb strength in patients on hemodialysis, and scores on the sit-to-stand test increased from 18.3 ± 5.1 to 19.7 ± 6.7 ($P = 0.009$) in the intervention group compared with the control group. In pre-dialysis patients [11, 14, 54], the intervention group improved ~28% ($P < 0.001$) for muscular strength, as in kidney transplant patients [32]. Dobsak *et al.* [19] applied aerobic exercise (AT) or muscle electrostimulation (EMS) and muscle power increased with EMS to 222.2 ± 36.6 ($P = 0.046$) and with AT to 230.3 ± 31.1 ($P = 0.033$), while the control group remained at 187.8 ± 29.7. The yoga-based study found an improvement of 15% in muscular strength [17].

Body composition: Six studies analyzed the effects of resistance exercise on body composition. Four studied hemodialysis patients [15, 20, 64, 67] and one analyzed kidney transplant patients [32]. Resistance exercise did not change body composition. One RCT analyzed the effect of exercise in obese pre-dialysis patients [10] and found a visceral fat and waist circumference decrease of 6.4 ± 6.4 mm ($P < 0.01$) and 2.0 ± 2.3 cm ($P = 0.03$) and leg lean mass increased 0.5 ± 0.4 kg ($P < 0.01$).

CKD progression: The effect of aerobic [21, 29–31, 39] or resistance [13, 31] training on CKD progression was measured in four RCTs. A slower decline in the rate of change in glomerular filtration was found in one study in patients randomized to a low protein diet and resistance training [13].

PWV and arterial stiffness: Two studies measured PWV in pre-dialysis [30, 31] patients and found no effect of exercise. Toussant *et al.* [57] studied hemodialysis patients and found a positive effect of aerobic exercise (9.04±0.59 versus 10.16±0.74, $P = 0.008$), but Koh *et al.* [65] did not find a difference between intradialytic exercise or usual care.

Depression: Depression was analyzed in four RCTs, three of them using aerobic exercise [12, 24, 63] and one aerobic plus resistance exercise [47]. Exercise decreased depression scores. The Beck Depression Index decreased 34.5% in the Kouidi *et al.* trial [63] and 39.4% in Ozouni *et al.* trial [47], as occurred in the study by Ginakki *et al.* [24] ($P = 0.002$). Only Carmack *et al.* [12] was unable to find a benefit of exercise on depression.

CKD stage and type of treatment: Forty-five [8, 9, 11, 12, 15–20, 23–27, 34–38, 40, 41, 43–53, 55–62, 64, 67, 70] of 59 studies were carried out in ESRD patients on hemodialysis. Only one study included both hemodialysis and peritoneal dialysis patients [35]. Five of these studies had CRP as an outcome measure; in three of them CRP was inversely correlated with physical activity [8, 15, 50] and another found no change [34, 39, 60]. Fourteen studies assessed VO_2 peak and all of them found a significant increase with aerobic exercise [29–31, 36, 37, 47, 48, 51, 53, 62, 63]. Strength was measured in nine resistance studies [15, 18, 20, 32, 55, 56, 59, 67], all of them with a positive finding. HRQOL was assessed in 18 studies [15, 18, 19, 22, 40, 43, 45, 47–50, 55, 56, 59, 64, 67, 70]; 11 of them found increases in HRQOL in the exercise groups, both in aerobic and resistance training [22, 40, 43, 45, 47, 48, 50, 56, 59, 64]. However, four of these studies found improvements only in the physical component of the HRQOL [45, 47, 48, 64].

Pre-dialysis: Eleven studies [10, 13, 14, 21, 22, 28–31, 39, 54] included pre-dialysis patients; one study enrolled patients on dialysis and pre-dialysis [39]. The studies that included pre-dialysis patients actually reported findings from eight different interventions, because one study generated two different publications [13, 14]. Three studies used CRP as an outcome measure [14, 30, 39], of which only one found a positive association between exercise and decreased CRP [14]. Six studies [13, 21, 29–31,39] evaluated the progression of CKD, and only Castaneda *et al.* [13] found a significant positive effect of the exercise intervention on this outcome. Physical capacity was assessed through VO_2 peak in five studies [21, 28–31], all of them with positive results. Three publications [13, 14, 31] used resistance training, two of them using the same study [13, 14], and in another [30] the training was associated with lifestyle interventions. HRQOL was measured in two studies [22, 30], one of them [22] included pre-dialysis and dialysis patients, and both found improved HRQOL after exercise.

Kidney transplantation: Three RCTs [32, 33, 37] assessing exercise in kidney transplant patients were found, all of them using aerobic training interventions. The outcome measures were VO_2 peak, analyzed in two studies [32, 37], which increased 16–20%. HRV was analyzed in Koudi *et al.* [37], with positive findings as well. One of them found no difference in HRQOL with exercise [32] and another found increases in HDL cholesterol in the exercise group [33].

Discussion

This systematic review gathered consistent evidence of the positive effects of aerobic exercise on physical fitness, muscular strength and quality of life in ESRD patients. The evidence regarding exercise effects on other health outcomes and/or in earlier stages of CKD are weaker and heterogeneous.

The improvement in fitness through exercise in ESRD patients is a noteworthy finding. Functional capacity is usually impaired in CKD patients, reaching ~60–65% of the age-predicted value [71]. This low level of fitness is worrisome considering its association with poorer HRQOL [32, 48] and higher mortality in CKD patients [72].

Exercise requires the integrated function of multiple vital organs. Low exercise capacity is also an independent predictor of mortality in other chronic disease populations. Since physical training can improve functional capacity, maybe it can also increase survival. Although there is no RCT up to now confirming this hypothesis, the Dialysis Morbidity and Mortality Study, a cohort study, found that dialysis patients engaged in more frequent exercise presented a significantly reduced mortality rate versus less active peers [73].

Patients on dialysis are also weaker when compared with healthy sedentary subjects, and weakness may contribute to their poor physical functioning. Muscular strength has been described as a significant predictor of gait speed [73] and VO_2 peak [73] in dialysis patients.

The findings of our systematic review are in accordance with those of Heiwe and Jacobsen, whose meta-analysis for the Cochrane Collaboration was published in 2011 [74] and updated in 2014 [75]. They found significant beneficial effects of various exercise interventions in CKD patients on physical fitness, muscular functioning, walking capacity, cardiovascular function and HRQOL, with stronger evidence for dialysis patients and aerobic exercise programs.

Our finding about HRV is also interesting. Although there are few RCTs on the issue, six of the seven studies assessing HRV included in this review found significant improvement in this variable after exercise [16, 29, 36, 37, 51, 63]. The association between CKD and low HRV is consistent across multiple stages of the disease, including micro- and macro-albuminuria, decreased estimated glomerular filtration rate (eGFR) and ESRD [76]. In addition to CKD, other risk factors for low HRV include older age, obesity, diabetes, sedentary lifestyle, low HDL cholesterol, high insulin levels, elevated CRP and high systolic blood pressure [76]. Some studies [76] have shown that elevated resting heart rate and low HRV are associated with an increased risk of ESRD, CKD-related hospitalization and arrhythmias.

The Cochrane meta-analysis also found that the HRV index significantly improved after 6 months of mixed aerobic and resistance training in hemodialysis patients [74, 75]. The United Kingdom Heart Failure Evaluation and Assessment of Risk Trial (UK-Heart) [77] recently found that the SDNN, an HRV index, <100 ms was associated with increased mortality. The impact of HRV on mortality might be explained by the sympathetic/parasympathetic balance, with sympathetic nervous system overactivation in patients with lower HRV, which led to an increased susceptibility to malignant arrhythmia [78].

Considering that exercise improves HRV in hemodialysis patients, and that arrhythmia is one of the major causes of CV mortality in this subset of patients [79], we might expect a positive effect of exercise on mortality in hemodialysis patients. However, to date, only one study analyzed the effect of high-intensity mixed aerobic and resistance training in hemodialysis patients on arrhythmias and found no difference between the intervention and control groups [36].

Despite the auspicious findings, this systematic review has some limitations. The RCTs included present moderate to low quality and high risk of bias. Assessment of the quality of trial randomization, the avoidance of exclusions after trial entry and blinding have been proposed as the most important methodological components of controlled trials [80].

First, during the preparation of this review, a large number of exercise trials were excluded because no randomization of participants had been done. Allocation concealment also seems to be a significant issue. Inadequate concealment can lead to bias in many ways, sometimes as the result of deliberate subversions (usually well intentioned), or as the result of subconscious actions. Trials that reported either inadequate or unclear concealment methods yielded estimates of odds ratios that were exaggerated by an average of 41 or 30%, respectively, compared with estimates of odds ratios derived from trials that apparently had taken adequate steps to conceal treatment allocation [81]. Only 14 studies included in this review reported allocation concealment [11, 15, 17, 18, 25, 31–33, 35–37, 45, 55, 65]. Furthermore, most of them did not analyze data according to the intention-to-treat principle, thus increasing the risk of selection bias. Not using intention-to-treat analysis might have inflated the apparent results. Moreover, there were deficiencies in the reporting of methodological information and findings, such as method of randomization, dropout rate, adherence to the intervention and controls. Readers of the present study should be aware that it is possible that a trial could have been classified as having lower quality than it truly had because data and/or information were missing. Despite the availability of guidelines aimed at standardizing the reporting of clinical trials, publications often omit essential methodological details.

In addition to methodological and reporting problems with the current literature about the effects of exercise on health of ESRD, we detected the scarcity of trials including patients in earlier stages of CKD.

From a public health standpoint, the fact that most studies included only hemodialysis patients represents a point of concern, because patients as well as health systems would most benefit from primary prevention or from interventions that increase survival and/or delay the need for RRT in earlier stages of CKD, whose population is ~20 times greater than the ESRD population. The need for RCTs in pre-dialysis patients is amplified by positive findings from observational studies in CKD stages II–IV showing the association of higher physical activity with slower rates of glomerular filtration decline [82] and higher survival rates [72]. If could be confirmed that exercise interventions are effective in delaying CKD progression and/or decrease mortality, the potential impact of such interventions for public health would be enormous.

Despite the lack of RCT-based evidence about the effect of exercise on mortality, the already documented effects of exercise on physical function, strength, quality of life and cardiovascular index, such as HRV, are enough to support the recommendation of moderate-intensity physical activity for CKD patients. Exercise interventions need to be progressively included in the regimens of hemodialysis centers, aiming for inclusion in all dialysis centers, even though the best exercise protocol for dialysis patients remains to be established.

Conflict of interest statement

All the authors declared no competing interests. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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