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 kidney failure[MeSH Terms]) OR kidney transplantation[MeSH Terms]) OR dialysis[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 rate (GFR)<50 ml/min/1.73m², and as the doubling of serum creatinine; or renal replacement therapy.

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 administrators 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. All other studies 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.

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].

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 (VO2 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 electrolymoystimulation 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 most of the 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 (VO2 peak) were assessed in 20 aerobic interventions [9, 12, 16, 21, 29–32, 35–37, 39, 47, 48, 51, 53, 58, 61–63]. On
| 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 | Ia: aerobic training | 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 |
| | Ia = 7 | Ir: resistance training | 12 | HD | Aerobic capacity (VO₂ max, VO₂AT) | VO₂ max (P < 0.05) and VO₂AT (P < 0.05) were decreased in group C and unchanged in I group |
| | C = 7 | C: usual care | | | | |
| Akiba et al. (1995) [9] | I = 10 | I: exercise training | 10 | HD | Body composition, abdominal distribution of fat | Visceral fat and waist circumference decreased 6.4 ± 4.6 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) |
| | C = 10 | C: usual care | | | | |
| Baria et al. (2014) [10] | Ic = 10 | Ic: center aerobic | 12 | Obese PH | Body composition, abdominal distribution of fat | No significant differences in any outcomes were identified between interventions groups |
| | Ih = 8 | Ih: home aerobic | | | | |
| | C = 9 | C: usual care | | | | |
| Bohm et al. (2014) [11] | Ic = 30 | Ic: cycle ergometer | 24 | HD | Capacity aerobic, strength lower, flexibility, accelerometer and HRQL | No significant differences in any outcomes were identified between interventions groups |
| | Ip = 30 | Ip: home-based walking | | | | |
| | | | | | | |
| Carmack et al. (2019) [12] | I = 23 | I: aerobic training | 10 | HD | VO₂ peak, depression | Significant improvement in aerobic capacity. There were no significant changes between groups on measures of depression |
| | I = 25 | C: attention wait-list | | | | |
| Castaneda et al. (2001) [13] | I = 14 | I: low protein diet + resistance training | 12 | P-HD | TB, 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) |
| | C = 12 | C: low protein diet only | | | | |
| Castaneda et al. (2004) [14] | I = 14 | I: low protein diet + resistance training | 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 |
| | C = 12 | C: low protein diet only | | | | |
| Cheema et al. (2007) [15] | I = 24 | I: intense resistance training | 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 |
| | C = 25 | C: usual care | | | | |
| Chen (2010) [11] | I = 25 | I: intradialytic low-intensity strength training | 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) |
| | C = 25 | C: stretching | | | | |
| Deligiannis et al. (1999) [16] | Ihd = 30 | Ihd: supervised training 3×/w non-dialysis | 28 | HD | HRV, SDNN, VO₂ 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), VO₂ max by 41% and exercise testing duration by 33% |
| | Chd = 30 | C: usual care | | | | |
| Deligiannis (1999) [17] | Ia = 16 | Ia: aerobic HD | 28 | HD | Spiroergometric echocardiographic analysis | Ia and Ib: increased exercise time 33%/17% and VO₂ max 43%/14%; Ib: increase in FE 5% and SVI 14%; unchanged in Chd |
| | Ib = 10 | Ib: aerobic at home | | | | |
| | Chd = 12 | C: HD controls | | | | |
| | Cs = 15 | Cs: healthy controls | | | | |
| DePaul et al. (2002) [18] | I = 20 | I: exercise 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 |
| | C = 18 | | | | | |
| Dobsak et al. (2012) [19] | Iet = 11 | Iet: aerobic training | 20 | HD | Wpeak, 6MWT, muscle power (Fmax), urea clearance and HRQOL | Significant improvement of Wpeak, Fmax and 6MWT in ET and EMS groups. No difference between ET and EMS groups |
| | Iems = 11 | Iems: electrostimulation | | | | |
| | C = 10 | C: usual care | | | | |
| Dong et al. (2011) [20] | I = 33 | I: Resistance training plus nutrition | 24 | HD | Body composition, muscle strength, biochemical parameters, recall dietary questionnaire | No difference in lean body mass. Weight and strength increased in I group |
| | C = 33 | C: nutrition alone | | | | |
| Eidemak et al. (1997) [21] | I = 15 | I: aerobic training | 24 | P-HD | VO₂ max, BP, HR, serum lipids, GFR | Maximal work capacity increased in the exercise group. No difference in ΔGFR |
| 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 (RLS) | 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 in groups exercise and dopamine agonist (P = 0.03) and only agonist group improved sleep score (P = 0.016) |
| Giannaki et al. (2013) [25] | I = 16, Ida = 8, C = 8 | I: aerobic training, Ida: dopamine agonist, C: usual care | 26 | HD (RLS) | 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 | 48 | P-HD | Treadmill testing, IGF-I, IGF-II, IGFBP-1 | No difference in the IGF system. Interaction between group and time for VO2 and total treadmill time |
| Gregory et al. (2011) [28] | I = 14, C = 11 | I: supervised exercise and dietary counseling, C: usual care. | 48 | P-HD | VO2 peak, eGFR, resting and ambulatory HR, lipids, CRP and IL-6 | Increase in VO2 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. (2012) [29] | I = 14, C = 11 | I: personal training and dietary counseling, C: usual care. | 16 | HD | Arterial stiffness, aerobic capacity, endothelin1, nitrate/nitrite, CRP, HRQL | No change in arterial stiffness (PWV). 8.2% increase in VO2 peak, physical function, vitality, bodily pain |
| Headley et al. (2014) [30] | I = 25, C = 21 | I: aerobic training, C: usual care | 16 | P-HD | Peak VO2, left ventricular function, arterial stiffness, anthropometric measures | Improved peak VO2 (P = 0.004), weight loss (P = 0.02), diastolic function (P = 0.001), arterial elastance (P = 0.01). No change in BP |
| Howden et al. (2013) [31] | I = 41, C = 21 | I: lifestyle and aerobic and resistance training, C: usual care | 52 | P-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) |
| Johansen, (2006) [32] | Iex = 20, Iex/nd = 20, Iex = 19, Iex/nd = 20 | Iex: resistance training, Iex/nd: exercise + nd, Iex: nandrolone, P: placebo | 12 | HD | Body composition (LBM), muscle size and strength, physical performance and activity | No differences between Δ6MWT (intra Hd +14%, home +11%, usual care +5%), PWV, or any secondary outcome measure | LB: higher dropout; VO2 peak increased 43%, VO2 AT 37%, exercise time 33% |
| Koh (2010) [33] | I = 27, C = 22 | I: intradialytic cycle, 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 = 21, C = 13, Cs = 15 | I: outpatient training, C: during HD training, C: non-supervised home, Cs: HD controls | 24 | HD | VO2 peak, VO2AT, exercise time, dropout rate | 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 | Icve: aerobic training | 20 | HD | Mean body and fat mass, mid-thigh CSA, BMI, mRNA levels of growth factors genes in muscle | mRNA increased for IGF-1Ea, IGF-1Ec, IGF-1R, IGF-2, IGFBP-2, and IGFBP-3. No change in CRP, TNF, and IL-6 concentrations |
| de Lima et al. (2013) [40] | Ia = 10 | Ia: aerobic, bicycle | 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 |
| Mortazavi et al. (2013) [46] | I = 13 | I: aerobic training 3x week | 16 | HD | Severity of RLS, HRQOL (SF-63) | Decreased scores of RLS and HRQOL no difference between groups |
| Ouzouni et al. (2009) [47] | I = 20 | I: resistance and aerobic | 40 | HD | Functional performance (6MWT), VO2 peak, HRQOL, personality parameters | Increased VO2 peak (21.1%) and physical HRQOL, decreased depression |
| Painter et al. (2002a) [48] | I_{HtU} = 10 | I: aerobic training | 20 | HD | Treadmill, VO2 peak, HRQOL (SF-36) | i: increased VO2 peak (P = 0.03), physical functioning (P = 0.01); HtN: increased general health (P = 0.03) |
| Painter et al. (2002b) [32] | I = 54 | I: exercise at home | 52 | Tx | Symptom-limited exercise, VO2 peak, isokinetic testing, body composition, SF-36 | Increased VO2 (24.0 ± 7.5 to 30.1 ± 10.3 mL/kg/min) and muscle strength. No differences in body composition or HRQOL |
Table 1. Continued

| Author, year [Ref] | Groups (n) | Intervention | Time (weeks) | CKD stage | Outcome variables | Main results (refers to I group compared with C group) |
|--------------------|------------|--------------|--------------|------------|-------------------|------------------------------------------------------|
| Painter (2003) [33] | I = 51     | I: aerobic training | 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 Only DUC in the first 2 h was higher in I group |
|                    | C = 45     | C: usual care                          |              |            |                   |                                                     |
| Parsons (2004) [49] | I = 6      | I: aerobic cycle                       | 08           | HD         | SF-36, Kt/V, 2-h DUC, BP, and maximal work capacity |                                                     |
|                    | C = 7      | C: usual care                          |              |            |                   |                                                     |
| Pellizzaro et al. (2013) [50] | I = 11     | RMT: inspiratory muscles               | 10           | HD         | Respiratory strength, functional capacity, HRQOL, inflammatory state | ΔPI and ΔPE increased in RMT; 6MWT increased in RMT and PMT, CRP reduced and HRQOL increased in RMT and PMT |
|                    | C = 14     | PMT: knee extensor muscle              |              |            |                   |                                                     |
| Petraki et al. (2008) [51] | I = 22     | I: aerobic during HD                   | 28           | HD         | Arterial baroreflex sensitivity, spirometric study | Improvement in VO2 peak, exercise time and arterial baroreflex sensitivity |
|                    | C = 4     | C: usual care                          |              |            |                   |                                                     |
| Pellizzaro et al. (2013) [50] | I = 11     | C_HD = 21 HD: HD controls              | 12           | HD         | HRV and LVF by Holter and echocardiography | No differences in HRV or LVF between the groups |
|                    | C = 20    | C = healthy controls                   |              |            |                   |                                                     |
| Pelizzaro et al. (2013) [50] | I = 11     | I: aerobic during HD                   | 12           | HD         | VO2 peak and time to exercise intolerance (Tlim) | Training improved 50 to 200% in Tlim and VO2 peak in 15–20% |
|                    | C = 11     | C: usual care                          |              |            |                   |                                                     |
| Pellizzaro et al. (2013) [50] | I = 11     | I: aerobic during HD                   | 12           | HD         | 6MWT, sit-to-stand test | Intervention significant: 6MWT 19% improvement (P < 0.001), sit-to-stand test 29% improvement (P < 0.001) |
|                    | C = 11     | C: usual care                          |              |            |                   |                                                     |
| Pellizzaro et al. (2013) [50] | I = 11     | C = healthy controls                   | 12           | P-HD       | VO2 max, BP, oxygen uptake efficiency slope (OUES) | VO2 increased in physical training group, no change in control group |
|                    | C = 11     | C: usual care                          |              |            |                   |                                                     |
| Pellizzaro et al. (2013) [50] | I = 11     | I: aerobic exercise HD                 | 20           | HD         | Kt/V, Ht, cholesterol, BP, weight, physical fitness, SF-36, behavior | Improvement in behavior, reaction time, lower extremity muscle strength, Kt/V and quality of life |
|                    | C = 12     | C: usual care                          |              |            |                   |                                                     |
| Pellizzaro et al. (2013) [50] | I = 17     | I: resistance before and aerobic during HD | 12           | 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 |
|                    | C = 43     | C: usual care                          |              |            |                   |                                                     |
| Pellizzaro et al. (2013) [50] | I = 11     | I: aerobic training                    | 16           | 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% |
|                    | C = 9      | C: usual care                          |              |            |                   |                                                     |
| Wilund et al. (2010) [60] | I = 8      | I: aerobic training                    | 12           | HD         | Maximal oxygen consumption (VO2max) |                                                     |
|                    | C = 9      | C: usual care                          |              |            |                   |                                                     |
| Wilund et al. (2010) [60] | I = 19     | I: yoga-based exercises                | 12           | HD         | Maximal oxygen consumption (VO2max) |                                                     |
|                    | C = 18     | C: usual care                          |              |            |                   |                                                     |

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; VO2AT, anaerobic threshold; VO2 max, maximal oxygen consumption; eGFR, estimated glomerular filtration rate; TBP, total body potassium; SPPR, Short Physical Performance Battery; RLS, restless leg syndrome; LBM, lean body mass; PVW, 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.
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 VO2 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 Rebrodo 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 or triglycerides, with the exception of one study that used yoga as the intervention, which reported a 15% decrease in lipids or triglycerides, with the exception of one study that used yoga as the intervention, which reported a 15% decrease in lipids or triglycerides, with the exception of one study that used yoga as the intervention, which reported a 15% decrease in lipids or triglycerides, with the exception of one study that used yoga as the intervention, which reported a 15% decrease in lipids or triglycerides, with the exception of one study that used yoga as the intervention, which reported a 15% decrease in lipids or triglycerides, with the exception of one study that used yoga as the intervention, which reported a 15% decrease in lipids or triglycerides, with the exception of one study that used yoga as the intervention, which reported a 15% decrease in lipids or triglycerides.

C-reactive protein (CRP) and interleukins were evaluated in 10 RCTs. A slower decline in the rate of change in glomerular filtration rate (GFR) and estimated glomerular filtration rate (eGFR) was observed in patients with CKD stages 3a and 3b, with a decrease in CRP 1.7 mg/L (P = 0.01), with no change in the control group. Koppel 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 another 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]. Dobrak 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 Koudi et al. trial [63] and 39.4% in Ozoumi 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, 34–40, 41, 43–53, 55–63, 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 VO2 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 VO2 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 VO2 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 VO2 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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