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Comparative efficacy of different modes of exercise on inflammatory markers in patients with chronic kidney disease: a systematic review with pairwise and network meta-analyses

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This systematic review with pairwise and network meta-analyses aimed to evalute the effects of different modes of exercise on improving inflammation in patients with chronic kidney disease (CKD). A comprehensive search was conducted in the PubMed, Scopus, Web of Science, and Embase from inception to February 2025. Randomized trials investigating the effects of different exercise modes on interleukin-6 (IL-6), interleukin-10 (IL-10), tumor necrosis factor (TNF-α), or C-reactive protein (CRP) in patients with CKD were included. A total of 37 randomized trials, including 1,930 participants were included. All exercise modes reduced IL-6, TNF-α, and CRP, and increased IL-10 significantly more than control (CON). As compared with the CON, resistance training resulted in larger reductions in IL-6, TNF-α, and CRP, and larger increases in IL-10. Aerobic training led to larger reductions in IL-6 and TNF-α, but no significant effects were observed on IL-10 and CRP. Combined training did not significantly affect any inflammatory markers. A range of exercise modes is effective for improving markers of inflammation in patients with CKD, and resistance training may be more beneficial as compared with aerobic and combined training for anti-inflammatory effect. However, further high-quality randomized trials are needed to fully elucidate the anti-inflammatory potential of exercise.

Keywords Aerobic training, Resistance training, Combined training, High-intensity interval training, Inflammation, Cytokine, Chronic kidney disease

Chronic kidney disease (CKD) is a gradual, progressive loss of kidney function, and since the kidney regulates electrolyte balance, filters waste, controls blood pressure, and produces hormones, CKD leads to serious health complications[1]. As of 2021, an estimated 673.7 million people worldwide were living with CKD, representing 8.54% of the global population, and this number reflects a 92% increase compared with 1990[2]. As with most chronic non-communicable diseases, CKD is closely associated with inflammation, with persistent low-grade inflammation now recognized as a main cause of disease progression and related complications[3]. There are five stages of CKD based on two criteria: the glomerular filtration rate (GFR), and the presence of kidney damage[4]. End-stage renal disease (ESRD) is the final stage for patients suffering from CKD and is becoming increasingly prevalent. Renal replacement therapy is the sole treatment once this stage is reached[5].

Most individuals with ESRD require multiple medications to manage comorbidities such as type 2 diabetes, dyslipidemia, hypertension, and coronary heart disease[6], leading to further health deterioration given the

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compromised kidney function in these patients[7]. Patients with CKD often have a sedentary lifestyle, resulting in diminished physical functionality and performance, due in part to uremic myopathy and neuropathy[8,9]. Current evidence indicates that the beneficial effects of structured exercise in individuals with ESRD are comparable to those observed in apparently healthy people[10–12], with exercise training being an effective intervention for patients with ESRD undergoing dialysis[13]. Current exercise prescription guidelines for individuals with CKD recommend moderate-intensity aerobic activity on most days of the week, aiming for about 150 min per week, adjusted to the patient's functional capacity[12,14,15]. Resistance training is also deemed safe for this population, especially when undertaken at moderate intensity and low volume[12,14,15]. Together, these types of exercise result in substantial health and fitness gains amongst individuals with CKD[12,14,15]. Extensive evidence demonstrates a robust correlation between CKD and chronic low-grade inflammation, underscoring the potential anti-inflammatory efficacy of exercise training[16–20]. Nonetheless, evidence on the comparative effects of these interventions on chronic low-grade inflammation remains inconclusive[11,21]. Furthermore, the efficacy of alternative exercise modalities, including high-intensity interval training[22,23], and flexibility training[24], for mitigating inflammatory markers in this population has not been thoroughly investigated.

Numerous systematic reviews have highlighted the beneficial effects of regular aerobic, resistance, and combined aerobic and resistance exercise for reducing various pro-inflammatory markers, including interleukin-6 (IL-6), tumor necrosis factor (TNF-α), and C-reactive protein (CRP) and increasing anti-inflammatory marker, including interleukin-10 (IL-10) in this population[14,17,25–29]. However, the comparative effects of different exercise modalities on markers of inflammation are unknown in patients with CKD. Taking this into account, the principal methodological innovation of the present network meta-analysis is its ability to combine direct and indirect evidence to compare and rank multiple exercise interventions simultaneously within a single, coherent statistical model. The present systematic review therefore employed both pair-wise and network meta-analyses in order to ascertain these comparative effects.

Methods

This systematic review and pairwise and network meta-analyses were performed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and the Cochrane Handbook for Systematic Reviews of Interventions[30,31]. The systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO; ID: CRD420251135984).

Search strategy

A systematic search was performed in the three primary electronic databases (PubMed, Scopus, Web of Science) from inception to February 2025 to identify relevant randomized controlled trials. Only English-language publications were considered for inclusion. Three main groups of keywords, including "Inflammation" OR "inflammatory" OR "cytokine" OR "adipokine" OR "adipocytokine" OR "interleukin" OR "interleukin-6" OR "interleukin 6" OR "IL-6" OR "IL6" OR "interleukin-10" OR "interleukin 10" OR "IL-10" OR "IL 10" OR "tumor necrosis factor alpha" OR "TNF-α" OR "TNF α" OR "TNF" OR "C-Reactive protein" OR "Reactive protein" OR "hsCRP" OR "CRP" OR "leptin" OR "adiponectin" AND "exercise" OR "exercise training" OR "physical activity" OR "aerobic training" OR "aerobic exercise" OR "endurance training" OR "endurance exercise" OR "resistance training" OR "resistance exercise" or "strength training" or "strength exercise" or "combined training" or "combined exercise" OR "concurrent training" OR "concurrent exercise" OR "interval training" OR "interval exercise" OR "sprint training" OR "sprint exercise" AND "end-stage kidney" OR "end-stage renal" OR "endstage kidney" OR "endstage renal" OR "chronic kidney disease" OR "chronic renal disease" OR "chronic kidney failure" OR "chronic renal failure" OR "chronic kidney disorder" OR "chronic kidney insufficiency" OR "chronic nephropathy" OR "chronic renal insufficiency" OR "kidney chronic failure" OR "kidney disease, chronic" OR "kidney failure, chronic" OR "kidney function, chronic disease" OR "renal insufficiency, chronic" OR "renal transplantation" OR "kidney grafting" OR "kidney transplantation" OR "hemodialysis" OR "haemodialysis" OR "hemodiafiltration" OR "ESRD" OR "ESRF" OR "ESKD" OR "ESKF" were adopted for the search strategy. The full search strategy is summarized in the Supplementary Table 1. In addition, the reference lists of included studies, articles that cited the studies (snowballing), and previously published reviews, were manually searched for any additional studies that may have been missed. A search was also conducted in Google Scholar, and up to 300 articles were screened. The search was conducted by one author (M Kh).

Selection process

All retrieved studies were imported into EndNote version 21, where duplicate records were removed. The screening process was carried out in two phases against predefined inclusion and exclusion criteria. In the first phase, the titles and abstracts were screened for relevance, and in the second phase, the full texts were assessed to determine eligibility. The study selection process was conducted independently by two authors (M A, E M), and any disagreements were resolved by discussion with other authors (M Kh and S F).

Eligibility criteria

Studies published in the English language and in peer-reviewed journals were included if they met the following criteria according to the PICOS framework: Population: studies involving human participants aged ≥ 18 years who were clinically diagnosed with CKD, irrespective of dialysis status; Intervention: studies involving any mode of exercise training such as aerobic training, resistance training, combined training, or high-intensity interval training, with intervention durations ≥ 2 weeks, regardless of their intensity and number of weekly sessions; Comparator: studies including a non-exercise control group or those comparing an exercise intervention against an alternative form of exercise; Outcomes: studies that assessed and reported data on inflammatory biomarkers including IL-6, IL-10, TNF-α, and CRP; Study Design: randomized controlled or clinical trials with parallel-group

designs. In addition, studies comparing exercise training plus a dietary intervention to a dietary intervention alone were included, only when the dietary intervention was the same between groups. Non-original studies, non-randomized trials, studies using combined interventions such as exercise plus supplementation, and studies including patients who had undergone kidney transplants, were excluded from the current systematic review.

Data extraction and synthesis

Two independent authors (M A and E M) extracted information from each eligible study, and disagreements were resolved through discussions with other authors (M Kh and S F). Extracted information included study characteristics, including first author name, year of publication, and study design; participant characteristics, including biological sex, age, body mass index (BMI), and health status; intervention characteristics, including exercise mode, intensity, duration of intervention, and protocol; and outcomes of interest. In addition, the following data were extracted in order to perform meta-analyses: means, standard deviations (SDs), and sample sizes, derived either from change score values or, when unavailable, calculated from pre- and post-intervention values. We used the recommended formulas provided in the Cochrane Handbook for Systematic Reviews of Interventions to calculate mean changes and standard deviations (SDs) from pre- and post-intervention values, whenever change score data were not directly reported. When required, means and SDs were calculated from other relevant data, including medians, IQRs, 95% confidence intervals, and standard errors[32–34]. GetData software was used to extract data from figures. In addition, data presented as the geometric means or logarithmic values were converted to arithmetic means using the recommended formulas[35]. For studies with missing data, we contacted the corresponding author through email to obtain the necessary information.

Quality assessment

The methodological quality of the included studies was evaluated using the Physiotherapy Evidence Database (PEDro) scale, a valid and reliable instrument for assessing the quality of randomized trials[36]. The reliability of the total PEDro score, based on consensus judgments, is well recognized. The scale is sufficiently reliable for use in systematic reviews of physical therapy RCTs[37]. Study quality was determined by two independent authors (S F and E M), resolving any disagreements via discussion with a third author (M Kh). In this assessment, two items, including blinding of participants and personnel to exercise intervention, were excluded, as blinding was not feasible in the exercise trials. Supplementary Table 2 shows the remaining scale items that were used to evaluate the methodological quality of studies.

Meta-analyses

To investigate the effects of exercise training versus non-exercise controls (CON) on each outcome, pairwise meta-analysis was conducted using Comprehensive Meta-Analysis version 3 (CMA3, Biostat, Inc., NJ, USA). To calculate effect sizes, standardized mean differences (SMD) with 95% confidence intervals (CIs) were calculated using random effects models. We chose SMDs for effect sizes because outcomes were reported in different measurement units, and random effects models were chosen due to the assumption of heterogeneity among the included clinical trials[38]. To assess heterogeneity among the included studies, we used I^2 statistics, interpreted as low (0 – 25%), moderate (26 – 50%), substantial (51 – 75%), and considerable (> 75%) heterogeneity; and Q statistics, with p-values < 0.05 considered statistically significant[39]. To assess publication bias, visual interpretation of funnel plots was conducted. Additionally, Egger's tests were used to statistically evaluate publication bias, with p-values < 0.05 considered indicative of significant publication bias[40]. The trim and fill method was applied to evaluate and account for potential publication bias when such bias was suggested through visual inspection of the funnel plot[41]. Several subgroup analyses were performed as follows: ages of participants (younger adults: < 50 years, older adults: ≥ 50 years), disease status (with and without dialysis), and intervention duration (medium-term: <16 weeks, long-term ≥ 16 weeks).

In order to investigate the effects of the exercise modes on each outcome, network meta-analysis was conducted using the Netmeta package in the statistical software R (V.4.4.1) with a frequentist framework[42,43]. The SMDs and 95% CIs were calculated using random effects models to pool the results from both direct and indirect comparisons. The choices of SMDs and random effects models were consistent across pairwise and network meta-analyses. To show effect sizes and 95% CIs, forest plots and league tables were generated. In addition, to rank each exercise mode, P-score values were calculated[44]. To assess heterogeneity among included studies, I^2 statistics, tau (τ), tau-squared (τ^2), and Q statistics were calculated[45]. To assess the assumption of consistency, both global and local methods were applied[45–47]. Global consistency was evaluated using Q statistics under the assumption of a full design-by-treatment interaction random effects model, and local consistency was assessed using node-splitting models, respectively. To assess publication bias, Egger's tests were used with p-values < 0.05 considered indicative of significant publication bias[40].

Results

Study characteristics

As shown in Fig. 1, initial database searches yielded 1,934 records. No additional records were identified from other sources ($n = 0$). After removing duplicates, the number of remaining records was 1,504. Next, the titles and abstracts of the remaining records were screened, and 1,355 records were removed at this stage; thus, 149 articles remained for full-text review. These articles were screened for eligibility, and 110 articles were excluded for the following reasons: intervention not relevant (54 cases), lack of relevant Outcome variables (26 cases), non-randomized study (20 cases), duplicate study (6 cases), cross-over study (2 cases), and unavailability of full text (2 cases). Ultimately, 39 studies were eligible for meta-analysis, but 2 studies were excluded because they did not provide sufficient information to perform meta-analysis, leaving 37 studies for inclusion in the meta-analyses[48–84].

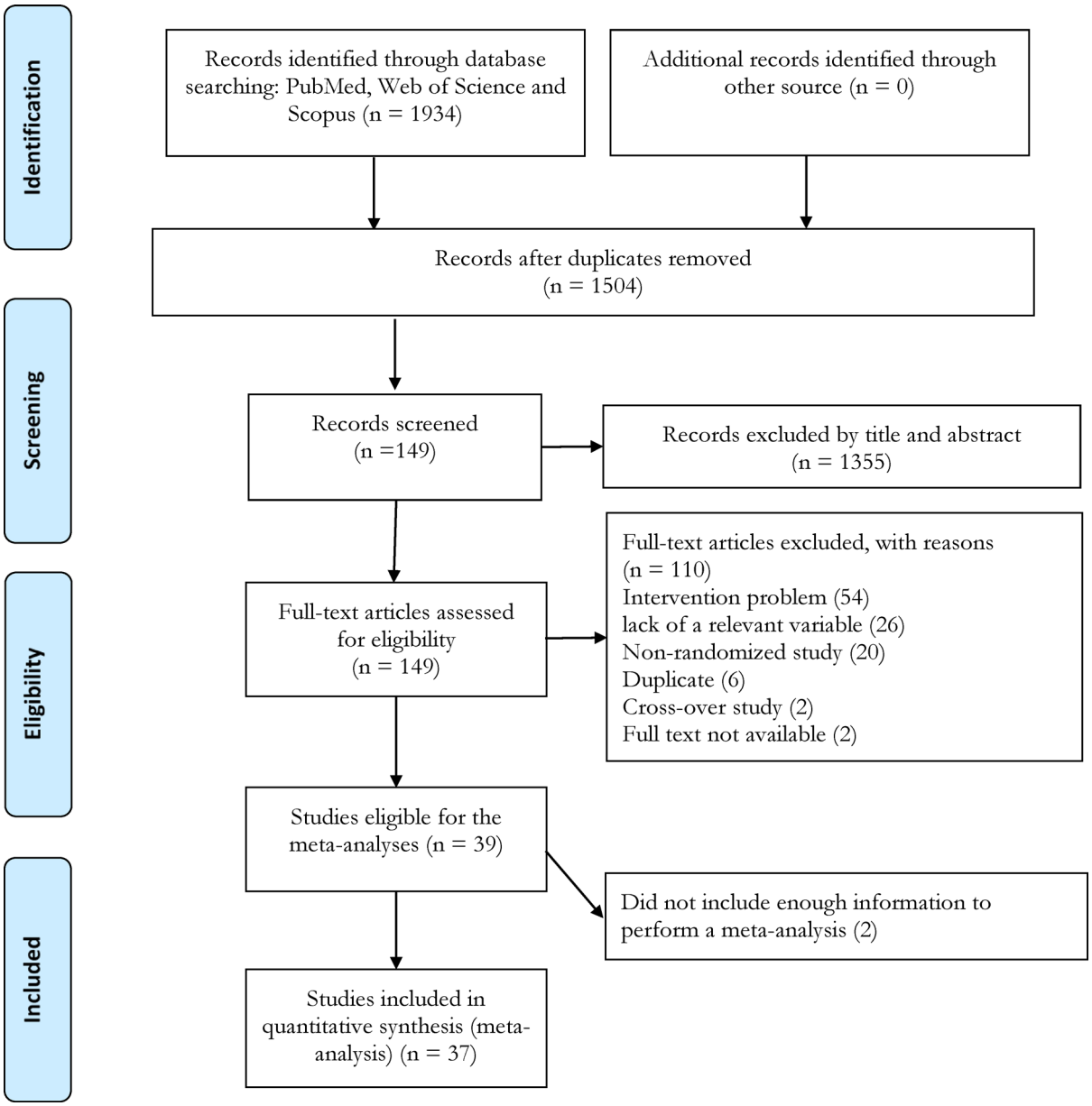

Fig. 1. Flow diagram of systematic literature search.

A total of 1,930 participants with CKD, both undergoing dialysis and not on dialysis, aged 40–79 years old, and with BMIs ranging from 19 to 38 kg/m^2, were included. The different exercise modes included aerobic training, resistance training, and combined (aerobic and resistance) training, with intervention durations ranging from 8 to 96 weeks. Detailed study characteristics, patient demographics, and intervention specifics are provided in Table 1. The overall methodological quality of the included studies is summarized in Supplementary Table 2, with total quality scores ranging from 5 to 9.

Pairwise meta-analysis

IL-6

As shown in Supplementary Fig. 1, compared with CON, exercise training led to significantly larger reductions in IL-6 [SMD: −0.50; 95% CI: −0.68, −0.32; $P = 0.001$; $I^2 = 38.53$, $P = 0.04$; 20 trials]. Visual interpretation of the funnel plot suggested publication bias, which was not confirmed by the Egger's test ($P = 0.76$). After accounting for missing studies with the trim and fill method, the overall effect size increased to [SMD: −0.55; 95% CI: −0.73, −0.36]. Subgroup analyses demonstrated that exercise training reduced IL-6 significantly more than CON in both younger (SMD: −0.44, $P = 0.001$) and older adults (SMD: −0.62, $P = 0.001$), patients undergoing dialysis (SMD: −0.46, $P = 0.001$) as well as those not on dialysis (SMD: −0.64, $P = 0.002$), and those who participated in a long-term intervention (SMD: −1.00, $P = 0.02$).

First author, year	Sample size (biological sex)	Participant characteristics	Age (years)	BMI (kg/m²)	Exercise training characteristics				Inflammatory markers
					Exercise protocol	Exercise mode	Exercise vs. comparison group	Durations (freq d/w)	
Abreu et al., 2017[52]	44 (F&M)	HD	RET:45.70 ± 15.20 CON:42.50 ± 13.50	RET:23.90 ± 4.70 CON:24.40 ± 4.80	RET: 3 × 10 reps, 60% 1RM	RET	RET CON	12 weeks (3) Supervised	hs-CRP
Afshar et al., 2010[55]	21 (M)	HD	AET:50.7 ± 21.06 RET:51.00 ± 16.40 CON:53.00 ± 19.40	AET:22.71 ± 2.98 RET:21.96 ± 1.41 CON:22.3 ± 2.18	AET: RPE 12–16, 65–85% maximal capacity, stationary cycling, 10–30 min. RET: 3 × 8 reps, RPE 15–17, 60% 3RM, knee extension, hip abduction and flexions, 10–30 min	AET RET	AET RET CON	8 weeks (5) Supervised	hs-CRP
Assawasaksakul et al., 2021[58]	12 (M)	OL-HDF	CET:52.50 ± 12.09 CON:53.07 ± 17.20	CET:24.80 ± 5.10 CON:23.40 ± 6.20	CET: AET: RPE 12, 80–100 RPMs & 10 m and then + 5 min/ week, 30 min, resistance increased each week until up to 10 W + RET: RPE 13, 10 W, + 5 W/week	CET	CET CON	24 weeks (2) Supervised	hs-CRP
Barcellos et al., 2018[63]	150 (F&M)	HTN and CKD	CET:65.0 ± 10.46 CON:65.10 ± 11.18	CET:29.70 ± 6.10 CON:30.1 ± 5.16	AET: 60%–80% VO_{2peak}, 60 min + RET: full-body resistance exercises, low-intensity plyometric training, horizontal jumps, weeks 1–14, vertical jumps during weeks 15–16	CET	CET CON	16 weeks (3) Supervised	hs-CRP
Bogataj et al., 2020[65]	34 (M)	HD	CET:65.02 ± 12.10 CON:61.90 ± 13.00	NR	CET: AET: RPE 4–5, up to 60 min, cycling + RET: full-body resistance exercises, RPE 7–8, 30 min/session	CET	CET CON	16 weeks (3) Mix	hs-CRP
Castaneda et al., 2004[80]	26 (F&M)	CKD	RET+Diet:65 + 9 Diet:64 + 12	RET+Diet:29.3 + 6.6 Diet:26.8 + 2.7	RET: full-body resistance exercises, 3 × 8 reps each, 2 s concentric + pause + 4 s eccentric, 1–2 min rest between sets, 80% 1RM, 35 min/session + Diet. Diet: low-protein diet, 0.6 g/kg/d	RET	RET CON	12 weeks (3) Supervised	CRP, IL-6
Cheema et al., 2007[78]	49 (F&M)	HD	RET:60.00 ± 15.30 CON:65.00 ± 12.90	RET:27.00 ± 6.00 CON:28.00 ± 5.70	RET: full-body resistance exercises, 2 × 8 reps, RPE 15–17	RET	RET CON	12 weeks (3) Supervised	hs-CRP
Cheng et al., 2020[54]	67 (F&M)	HD	RET:54.64 ± 12.55 CON:55.83 ± 11.98	RET:23.09 ± 3.79 CON:23.45 ± 4.15	RET: Arm curl, arm raise, leg raise, 10 reps/ set + 2 min arm raise with hand grip + 2 min leg raise, RPE 11–12, 20 min/ session	RET	RET CON	96 weeks Supervised	hs-CRP
Correa et al., 2022[76]	25 (F&M)	HD	68.28 ± 1.06	RET:28.48 ± 1.26 CON:27.94 ± 0.89	RET: full-body resistance exercises, 3 × 8–12 reps, OMNI RPE 5–8, 60 min, 2 min rest between sets and exercises	RET	RET CON	24 weeks (3) Supervised	TNF-α, IL-6, IL-10
Correa et al., 2020[79]	55 (M)	HD	RET:66.00 ± 4.00 CON:65.70 ± 3.80	RET:24.70 ± 1.70 CON:25.20 ± 2.10	RET: full-body resistance exercises, 3 × 8–12 reps, OMNI 6–8, 2 min rest between sets, 50 min, variable resistance (Thera-band, dumbbells, 2–15 kg fixed weights)	RET	RET CON	12 weeks (3) Supervised	TNF-α, IL-10
Correa et al., 2021[50]	70 (F&M)	CKD	RET:58.00 ± 6.00 CON:58.00 ± 5.00	RET:33.60 ± 2.00 CON:33.20 ± 1.60	RET: full-body resistance exercises,1–3 sets, 50–70% 1-RM, 8–12 reps, 2 min rest between sets	RET	RET CON	24 weeks (3) Supervised	IL-6, IL-10, TNF-α
Cruz et al., 2018[71]	30 (F&M)	HD	AET:43.5 ± 14.4 CON:39.9 ± 13.5	AET:24.6 ± 3.7 CON:23.6 ± 3.4	AET: cycle ergometer, Borg 6–7, 30 min/session	AET	AET CON	12 weeks (3) Supervised	IL-6, IL-10, and TNF-α
de Araujo et al., 2023[57]	31 (F&M)	CKD	RET:57.94 ± 2.74 CON:58.07 ± 5.22	RET:26.64 ± 3.47 CON:26.84 ± 1.95	RET: home-based, 5 cycles, elastic bands and bodyweight, 1–3 × 4–14 reps, OMNI-RES scale; cycles 1–2: 3 d/week: alternating upper/lower-body in same session, cycle 3: 4 d/week: Mon/ Thu upper, Tue/Fri lower), 2 s concentric, 2 s eccentric	RET	RET CON	22 weeks (3–4)	TNF-α, IL-6, IL-10, CRP

Continued

First author, year	Sample size (biological sex)	Participant characteristics	Age (years)	BMI (kg/m^2)	Exercise training characteristics				Inflammatory markers
					Exercise protocol	Exercise mode	Exercise vs. comparison group	Durations (freq d/w)	
de Castro et al., 2023[67]	78 (F&M)	HD	RET:57.27 ± 3.89 RET-CS:57.23 ± 3.11 CON:58.15 ± 5.02	RET:26.75 ± 3.43 RET-CS:26.91 ± 3.41 CON:26.51 ± 1.92	RET: full-body resistance exercises, 3 × 8–12 reps, RPE 5–8, 80 min, 2 min rest between sets. RET-CS: Same protocol as RET, with a pause after every 4 reps, 120 min/session	RET	RET CON	24 weeks (3) Supervised	IL-6, IL-10, and TNF-α
Dong et al., 2019[59]	41 (F&M)	HD	RET:52.66 ± 27.30 CON:61 ± 15.55	RET:18.96 ± 3.08 CON:20.49 ± 3.41	RET: lower-body training, ankle weight 0–5 kg, training board angle 150°–90°, upper-body elastic ball, 10 × 10 cycles, 3–5 s hold, 1–2 h	RET	RET CON	12 weeks (3) Supervised	TNF-α, IL-6, IL-10, CRP
Frih et al., 2017[53]	41 (M)	HD	CET:64.20 ± 3.40 CON:65.20 ± 3.10	CET:25.40 ± 2.80 CON:24.30 ± 3.20	CET: RET: 50% 1RM, 12–15 reps, + 5% 1-RM/ month for 20 min + AET: aerobic exercise equipment, 20 min at Borg 5–6, 60 min/session	CET	CET CON	16 weeks (4) Supervised	hs-CRP
Gadelha et al., 2021[60]	107 (F&M)	HD	sRET:65.00 ± 3.60 non-sRET:68.10 ± 3.30 sCON:63.80 ± 4.10 non-sCON:65.60 ± 2.90	sRET:23.10 ± 2.20 non-sRET:29.70 ± 3.50 sCON:25.10 ± 3.00 non-sCON:27.30 ± 2.00	RET: full-body resistance, 3 × 8 reps at RPE 5–8, exercises, 40 min, 2 min rest between sets	RET	RET CON	24 weeks (3) Supervised	TNFα, IL-6, IL-10
Headley et al., 2012[64]	21 (NR)	CKD	AET:57.50 ± 11.50 CON:52.50 ± 10.60	AET:32.70 ± 7.20 CON:34.20 ± 5.70	AET: 50–60% VO_{2peak}, aerobic exercise equipment, 55 min/session	AET	AET CON	24 weeks (3) Supervised	hs-CRP, IL-6
Headley et al., 2014[81]	46 (F&M)	CKD, DM, and/or HTN	AET:58.00 ± 8.00 CON:57.10 ± 9.00	AET:34.90 ± 8.00 CON:36.50 ± 8.90	AET: 50–60% VO_{2peak}, aerobic exercise equipment, 55 min/session	AET	AET CON	16 weeks (3) Supervised	hs-CRP
Highton et al., 2022[73]	40 (F&M)	HD	AET:51.40 ± 18.10 CON:56.80 ± 14.00	AET:28.12 ± 6.44 CON: 28.67 ± 7.53	AET: 60–70 rpm, RPE 12–14, 30 min/session	AET	AET CON	24 weeks (3) Supervised	TNF-a, IL-6, IL-10
Kopple et al., 2007[62]	51 (F&M)	HD	AET:45.90 ± 12.95 RET:46.00 ± 10.44 CET:42.70 ± 13.14 CON:41.30 ± 12.34	AET:26.90 ± 6.00 RET:28.70 ± 9.67 CET:26.20 ± 5.19 CON:24.90 ± 4.11	AET: aerobic exercise equipment, 50% VO_{2peak}- increased intensity as tolerated, 20 to ≥ 40 min, 4:1 work/rest. RET: lower-body resistance exercises, 1–3 × 12–15 reps, 70–80% 5RM. CET: Half duration AET + half duration RET, same intensity and progression as respective programs	AET RET CET	AET RET CET CON	18 weeks (3)	TNF-a, IL-6, CRP
Leehey et al., 2009[48]	20 (M)	Obese, DM, CKD	66.00	> 30 kg/m^2	AET: 25–84% VO_{2peak}, 6–22 min/session, weeks 1–6, supervised + home-based walking + 10% weekly step count, 30–40 min/session	AET	AET CON	24 weeks (5) Mix	hs-CRP
Leehey et al., 2016[82]	32 (M)	Obese, DM, CKD	CET:65.40 ± 8.70 CON:66.60 ± 7.50	CET:36.20 ± 4.80 CON:37.40 ± 4.20	CET: AET: aerobic exercise equipment, 25–84% VO_{2peak} + RET: lower-body, bands/ weights, 60–90 min, weeks 1–12, supervised + home-based aerobic training, walking or equivalent, 3×week for 60 min or 6×week for 30 min, weeks 13–52. Diet: Energy-restricted renal diet, −200-250 kcal/day	AET	CET CON	52 weeks (3–6)	hs-CRP
Liao et al., 2016[70]	40 (F&M)	HD	AET:62.00 ± 8.00 CON:62.00 ± 9.00	AET:22.87 ± 3.30 CON:23.67 ± 4.16	AET: 20 min, cycling, Borg 12–15, 30 min/ session	AET	AET CON	12 weeks (3) Supervised	hs-CRP, IL-6
Lopes et al., 2019[75]	50 (F&M)	HD	RET_1:48.10 ± 10.80 RET_2:56.20 ± 12.50 CON:56.90 ± 12.40	RET_1:24.50 ± 4.70 RET_2:25.50 ± 5.10 CON:26.30 ± 3.70	RET: lower-body resistance training, HLG: 8–10 reps, MLG: 16–18 reps, 20–40 min, volitional fatigue, 1 min rest between sets and exercises	RET	RET CON	12 weeks (3) Supervised	TNF-a, IL-6, IL-10
March et al., 2021[51]	92 (F&M)	HD	AET:53.00 ± 15.00 CON:61.00 ± 14.00	AET:27.06 ± 5.71 CON:27.47 ± 6.15	AET: cycling, RPE 12–14, 30 min/session	AET	AET CON	24 weeks (3) Supervised	TNF-a, hs-CRP, IL-6, IL-10

Continued

First author, year	Sample size (biological sex)	Participant characteristics	Age (years)	BMI (kg/m²)	Exercise training characteristics				Inflammatory markers
					Exercise protocol	Exercise mode	Exercise vs. comparison group	Durations (freq d/w)	
Marinho et al., 2016[68]	13 (F&M)	HD	RET:72.40 ± 27.36 CON:72.66 ± 22.04	RET: 28.46 ± 14.01 CON:28.13 ± 13.22	RET: 60%–70% 3RM, elastic bands, 1 min rest between sets and 3 min between exercises	RET	RET CON	8 weeks (3) Supervised	hs-CRP
Marzougui et al., 2024[83]	21 (F&M)	HD	CET:49.00 ± 12.51 CON:41.00 ± 9.68	CET: 23.25 ± 3.99 CON: 24.54 ± 3.99	CET: RET: knee extension, hip abduction and flexion, 2–3 × 10 reps, 60% 3-RM, 1 min rest between sets, 3 min between exercises + AET: cycle ergometer, 50–60% HR_{max}, 15–60 min/session	CET	CET CON	12 weeks (3) Supervised	hs-CRP
Moura et al., 2020[61]	17 (F&M)	HD	RET:67.30 ± 3.20 CON:66.30 ± 3.90	RET:27.30 ± 3.70 CON:26.80 ± 2.90	RET: full-body resistance exercises, 3 × 8–12 reps, OMNI RPE 5–8, 2 min rest between sets	RET	RET CON	24 weeks (3) Supervised	TNF-a, IL-6, IL-10
Otobe et al., 2021[77]	60 (F&M)	CKD	CET:78.40 ± 6.40 CON:78.10 ± 7.40	CET:23.80 ± 4.10 CON:24.10 ± 3.70	CET: center-based: AET: cycling ergometer, Borg 11–13, 20 min + RET: full-body resistance exercises, 1 × 20 reps + balance: 5 min, tandem and one-leg, 60 min/week + home phase: RET + walking ≥ 2/week	CET	CET CON	24 weeks (3) Supervised	hs-CRP
Rosa et al., 2021[56]	197 (F&M)	HD	RET:53.00 ± 13.00 IRET:54.00 ± 10.00 CON:52.00 ± 17.00	NR	Dynamic RET: Full-body resistance exercises, 3 × 8–12 reps, OMNI-RES 5–8. Isometric RET: Same exercises and load, fixed joint angles, matched time under tension	RET	RET CON	24 weeks (3) Supervised	CRP
Silva et al., 2019[49]	30 (F&M)	HD	AET:50.00 ± 17.20 CON:58.00 ± 15.00	AET:25.70 ± 3.58 CON:26.70 ± 4.60	AET: 65–75% HR_{max}, Borg 13, 30 min/session	AET	AET CON	12 weeks (3) Supervised	hs-CRP
Sovatzidis et al., 2020[72]	20 (F&M)	HD	AET:52.80 ± 17.10 CON:53.00 ± 7.60	AET:24.60 ± 3.54 CON:25.50 ± 1.84	AET: cycling, RPE 11–13, 10–24 min, 0–61 W	AET	AET CON	24 weeks (3) Supervised	hs-CRP
Uchiyama et al., 2021[66]	46 (F&M)	CKD	CET:73.33 ± 7.90 CON:74.33 ± 7.11	CET:24.70 ± 22.06 CON:23.00 ± 20.62	CET: home-based, AET: 40–60% HR_{peak}, Borg 11–13 + RET: 10–15 reps, 70% 1RM, TheraBand, major muscle groups	CET	CET CON	24 weeks (5) unsupervised	hs-CRP, IL-6
Watson et al., 2022[69]	41 (F&M)	CKD	AET:65.00 ± 8.00 CET:59.00 ± 18.00	NR	AET: aerobic exercise equipment, 70–80%HR_{max}, 30 min. CET: AET (same) + leg extension and leg press: 3 × 12–15, 70% 1RM	AET CET	AET CET	12 weeks (5) Supervised	IL-6, IL-10, TNF-a
Wilund et al., 2010[74]	17 (F&M)	HD	AET:60.80 ± 9.02 CON:59.00 ± 14.70	AET:30.10 ± 6.76 CON:29.00 ± 6.00	AET: cycle ergometers, Borg 12–14, 5–45 min/session	AET	AET CON	16 weeks (3) unsupervised	hs-CRP, IL-6
Zhou et al., 2020[84]	112 (F&M)	CKD	AET:66.00 ± 13.00 CET:67.00 ± 14.00	AET:27.00 ± 4.70 CET:28.00 ± 5.20	AET: 60 min/week, 2 sessions, RPE 13–15, walking, jogging, or cycling + Balance training: 90 min/week, 3 sessions, RPE 13–17, 4–6 exercises (e.g., standing with feet together, one-leg stance, balance board, planking), 2–3 × 10. CET: RET: full-body resistance exercises, 90 min/week (3 sessions), RPE 13–17, 2–3 × 10 + AET: same	AET CET	AET CET	48 weeks (2–3) unsupervised	hs-CRP, IL-6

Table 1. Characteristics of participants and interventions. *RET* Resistance exercise training, *AET* Aerobic exercise training, *CET* Combined exercise training, *IRET* Isometric resistance exercise training, *sRET* Sarcopenic resistance exercise training, *RET-CS* Resistance exercise training – cluster set, *CON* Control group, *sCON* Sarcopenic control, *non-sRET* Non-sarcopenic resistance exercise training, *non-sCON* Non-sarcopenic control, *HLG* High load group, *MLG* Moderate load group, *HD* Hemodialysis, *CKD* Chronic kidney disease, *OL-HDF* Online hemodiafiltration, *VO_2peak* Peak oxygen consumption, *HRpeak* Peak heart rate, *RPE* Rating of perceived exertion, *RM* Repetition maximum, *OMNI-RES* OMNI Resistance Exercise Scale, *1-RM* One repetition maximum, *5-RM* Five repetition maximum, *CRP* C-reactive protein, *hs-CRP* High-sensitivity C-reactive protein, *TNF-α* Tumor necrosis factor alpha, IL-6 Interleukin 6, *IL-10* Interleukin 10, *DM* Diabetes mellitus, *HTN* Hypertension, *HRmax* Maximum heart rate, *HRR* Heart rate reserve, *F* Female, *M* Male, *min* minute, *reps* repetitions, *NR* Not reported, *wk* week, *d/w* days per week, *kg* kilogram, *h* hour, *s* seconds, *W* watt.

IL-10

As shown in Supplementary Fig. 2, exercise training increased IL-10 [SMD: 1.11; 95% CI: 0.50, 1.71; $P=0.001$; $I^2=92.94$, $P=0.001$; 12 trials] significantly more than CON. Visual interpretation of the funnel plot suggested publication bias, which was not confirmed by the Egger's test ($P=0.08$). After accounting for missing studies with the trim and fill method, the overall effect size increased to [SMD: 1.60; 95% CI: 0.84, 2.35]. Subgroup analyses demonstrated that exercise training increased IL-10 signicantly more than CON in both younger (SMD: 1.21, $P=0.01$) and older adults(SMD: 0.97, $P=0.001$), patients undergoing dialysis (SMD: 0.63, $P=0.001$) as well as those not on dialysis (SMD: 3.76, $P=0.001$), and those who participated in both short-term (SMD:0.83, $P=0.02$) and long-term (SMD: 1.26, $P=0.003$) interventions.

TNF-α

Supplementary Fig. 3 shows that exercise training reduced TNF-α [SMD: −0.73; 95% CI: −1.08, − 0.39; $P=0.001$; $I^2=77.57$, $P=0.001$; 14 trials] significantly more than CON. Visual interpretation of the funnel plot suggested publication bias, which was not confirmed by the Egger's test ($P=0.35$). After accounting for missing studies with the trim and fill method, the overall effect size increased to [SMD: −0.79; 95% CI: −1.13, − 0.45]. Subgroup analyses demonstrated that exercise training reduced TNF-α in both younger (SMD: −0.56, $P=0.001$) and older adults (SMD: −1.33, $P=0.001$), patients undergoing dialysis (SMD: −0.67, $P=0.001$), as well as those not on dialysis (SMD: −1.06, $P=0.001$), and those who participated in long-term interventions (SMD: −0.83, $P=0.001$).

CRP

As shown in Supplementary Fig. 4, exercise training decreased CRP significantly more than CON [SMD: −0.38; 95% CI: −0.66, −0.10; $P=0.007$; $I^2=78.16$, $P=0.001$; 28 trials]. The visual interpretation of the funnel plot suggested publication bias, which was not confirmed by the Egger's test ($P=0.63$). After accounting for missing studies with the trim and fill method, the overall effect size increased to [SMD: −64; 95% CI: −0.91, −0.37]. Subgroup analyses demonstrated that exercise training reduced CRP in younger adults (SMD: −0.39, $P=0.005$), patients undergoing dialysis (SMD: −0.50, $P=0.007$), and those who participated in short-term interventions (SMD: −1.00, $P=0.02$).

Network meta-analysis

IL-6

Supplementary Fig. 5 shows that eighteen studies involving 23 pairwise comparisons, 4 treatment arms, and 5 study designs were included in the network meta-analysis. Resistance training [SMD: −0.62; 95% CI: −0.84, −0.40; $P=0.001$] and aerobic training [SMD: −0.34; 95% CI: −0.60, −0.08; $P=0.01$] reduced IL-6 significantly more than CON, but combined training [SMD: −0.33; 95% CI: −0.70, 0.03; $P=0.07$] did not have a significantly larger effect (Fig. 2). In addition, as shown in Supplementary Table 3, there were no significant differences among the various exercise modes. Based on the P-score rankings, resistance training was ranked as likely to be the most effective modality ($P=0.95$), followed by aerobic training ($P=0.52$), and combined training ($P=0.51$). The heterogeneity tests indicated low to moderate heterogeneity ($tau^2=0.0400$; $tau=0.2000$; $I^2=32.9\%$ [0.0%; 62.0%]). The global inconsistency test indicated no significant inconsistency ($Q=4.51$, $df=4$, and $p=0.34$) (Supplementary Table 4). As shown in Supplementary Table 5, node-splitting analyses also demonstrated no significant inconsistency between direct and indirect evidence. Supplementary Fig. 6 shows that Egger's test results indicated no evidence of publication bias ($P=0.90$).

IL-10

Supplementary Fig. 7 shows that Thirteen studies involving 13 pairwise comparisons, 4 treatment arms, and 3 study designs were included in the network meta-analysis. Resistance training [SMD: 1.39; 95% CI: 0.79, 2.06; $P=0.001$] increased IL-10 significantly more than CON, but aerobic training [SMD: 0.34; 95% CI: −0.90, 1.39; $P=0.67$] and combined training [SMD: 0.56; 95% CI: −1.72, 2.86; $P=0.62$] did not have a significantly larger effects (Fig. 3). In addition, there were no significant differences among the various exercise modes (Supplementary Table 6). Based on the P-score rankings, resistance training was ranked as likely to be the most effective modality ($P=0.90$), followed by combined training ($P=0.52$), and aerobic training ($P=0.36$). The heterogeneity tests indicated high heterogeneity ($tau^2=0.9282$; $tau=0.9634$; $I^2=91.9\%$ [87.5%; 94.8%]). As shown in Supplementary Table 4, the global inconsistency test could not be calculated ($Q=-0.0$, $df=0$),

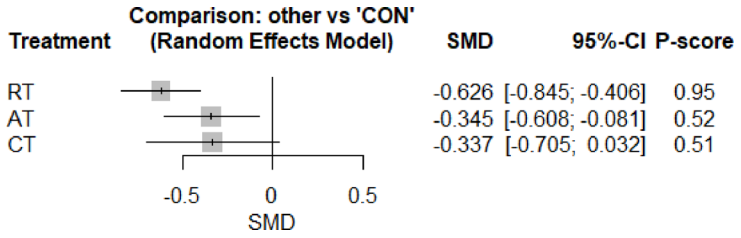

Fig. 2. Forest plot of the network meta-analyses of the effects of exercise training on IL-6.

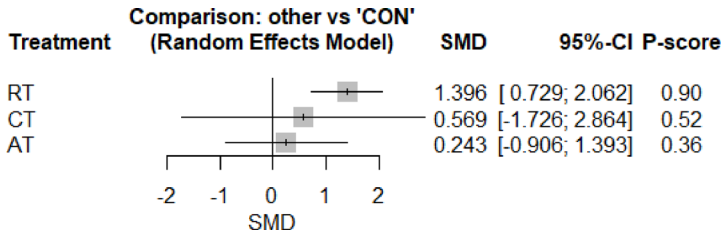

Fig. 3. Forest plot of the network meta-analyses of the effects of exercise training on IL-10.

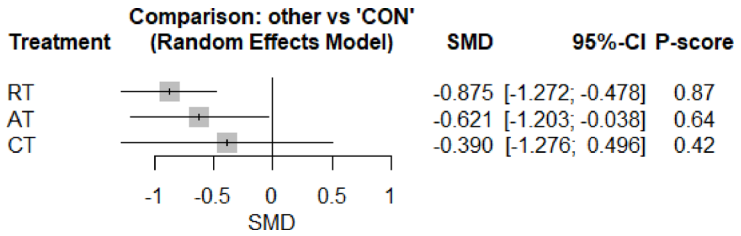

Fig. 4. Forest plot of the network meta-analyses of the effects of exercise training on TNF-α.

indicating that there was no variability in study design within the network. Also, Supplementary Fig. 8 shows that Egger's test results indicated evidence of publication bias ($P=0.02$).

TNF-α

As shown in Supplementary Fig. 9, thirteen studies involving 18 pairwise comparisons, 4 treatment arms, and 4 study designs were included in the network meta-analysis. Resistance training [SMD: −0.87; 95% CI: −1.27, −0.47; $P=0.001$] and aerobic training [SMD: −0.62; 95% CI: −1.20, 0.03; $P=0.03$] reduced TNF-α significantly more than CON, but combined training [SMD: −0.38; 95% CI: −1.27, 0.49; $P=0.38$] did not have a significantly larger effect (Fig. 4). In addition, Supplementary Table 7 shows that there were no significant differences among the various exercise modes. Based on the P-score rankings, resistance training was ranked as likely to be the most effective modality ($P=0.87$), followed by aerobic training ($P=0.64$), and combined training ($P=0.42$). The heterogeneity results indicated high heterogeneity ($tau^2=0.2850$; $tau=0.5338$; $I^2=76.9\%$ [60.7%; 86.4%]). Supplementary Table 4 shows that the global inconsistency test indicated no significant inconsistency ($Q=3.96$, $df=3$, and $p=0.26$). As shown in Supplementary Table 8, node-splitting analyses also demonstrated no significant inconsistency between direct and indirect evidence. Supplementary Fig. 10 shows that Egger's test results indicated no evidence of publication bias ($P=0.61$).

CRP

As shown in Supplementary Fig. 11, thirteen studies involving 13 pairwise comparisons, 4 treatment arms, and 3 study designs were included in the network meta-analysis. Resistance training [SMD: −0.81; 95% CI: −1.25, −0.38; $P=0.001$] decreased CRP significantly more than CON, but aerobic training [SMD: −0.32; 95% CI: −0.70, 0.06; $P=0.10$] and combined training [SMD: −0.12; 95% CI: −0.53, 0.28; $P=0.55$] did not have a significantly larger effects (Fig. 5). Supplementary Table 9 shows that in addition, compared with combined training, resistance training [SMD: −0.69; 95% CI: −1.27, −0.11; $P=0.01$] yielded significantly larger reductions in CRP. Based on the P-score rankings, resistance training was ranked as likely to be the most effective modality ($P=0.98$), followed by aerobic training ($P=0.59$), and combined training ($P=0.32$). The heterogeneity results indicated moderate to high heterogeneity ($tau^2=0.3273$; $tau=0.5721$; $I^2=75.6\%$ [64.8%; 83.0%]). As shown in Supplementary Table 4, the global inconsistency test indicated no significant inconsistency ($Q=6.06$, $df=6$, $P=0.41$). Supplementary Table 10 shows that node-splitting analyses also demonstrated no significant inconsistency between direct and

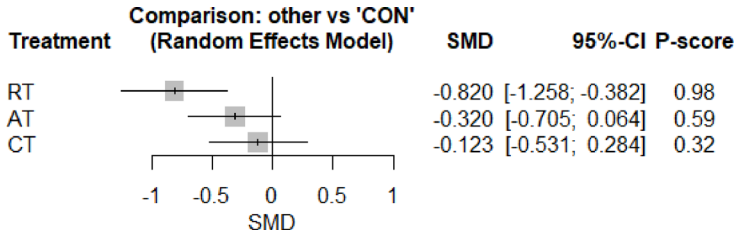

Fig. 5. Forest plot of the network meta-analyses of the effects of exercise training on CRPh.

indirect evidence. Supplementary Fig. 12 shows that Egger's test results indicated no evidence of publication bias ($P = 0.44$).

Discussion

Summary of findings

The present systematic review and network meta-analysis of randomized controlled trials investigated the effects of different exercise modalities on inflammatory markers in patients with CKD, indicating substantial improvements in IL-6, IL-10, TNF-α, and CRP status. Specifically, resistance training, and then aerobic training, were ranked as the most likely to be effective modalities for reducing chronic low-grade inflammation. These findings underscore the potential of cardiorespiratory and muscle-strengthening activities as lifestyle interventions for reducing inflammation associated with CKD. Notably, our findings were unaltered by the presence of dialysis, the participant ages, or the duration of intervention.

IL-6

IL-6, a pro-inflammatory cytokine that is elevated in CKD, has been linked to renal damage and is a promising biomarker for predicting disease progression of CKD[85,86]. Regular exercise training is an effective lifestyle strategy for reducing IL-6 in individuals with CKD, and shifts IL-6 signaling toward anti-inflammatory pathways[18]. Exercise results in a reduction of visceral and ectopic fat, lower oxidative stress, removal of uremic toxins implicated in IL-6 production, and modulation of immune function, thereby improving inflammatory balance in CKD[87]. Our study corroborates findings of other reviews that exercise interventions may be effective for reducing IL-6 in patients with CKD[18]. However, resistance or aerobic training alone are more efficacious in reducing IL-6 in CKD compared with combined training[17,18,88,89]. The present meta-analysis indicates that resistance training may be the most effective exercise mode, while aerobic training seems to be the second best option. These comparative findings are consistent with results found in sedentary, apparently healthy individuals[90], those with obesity[91], and those with diabetes[92]. Overall, it appears that muscle-strengthening is a critical component of exercise training for patients with CKD, resulting in favorable changes in IL-6, and should be considered when revising the existing exercise prescription guidelines for this population[12,14,15].

IL-10

IL-10, an anti-inflammatory cytokine that can be mediated by exercise training[88] and has the capacity to counteract kidney injury[93]. Individuals with CKD may benefit from increases in IL-10, which may lead to improvements in inflammatory responses, immune regulation, and tissue fibrosis[94]. These improvements occur through the modulation of immune cell activity, the mitigation of oxidative stress and uremic toxin effects, and the initiation of myokine signaling from skeletal muscle. The shift towards an anti-inflammatory environment will combat the persistent low-grade inflammation that exacerbates CKD progression and its associated complications[18]. The present review confirms that different modes of exercise significantly increase IL-10 in patients with CKD[17,20,89,95,96], with resistance training being likely the most effective mode of exercise[18]. Aerobic exercise may also have potential benefits, although with much smaller and non-significant effects[18]. The effect of combined training on IL-10 in this population has not yet been adequately investigated and requires further research[18]. The present study shows that resistance training may be the best form of exercise for increasing anti-inflammatory IL-10, which aligns with those reported in other reviews on exercise interventions in general[97] and other clinical populations characterized by metabolic derangements[98,99].

TNF-α

TNF-α is a pivotal pro-inflammatory mediator in the progression and complications of CKD, contributing to renal decline, cardiovascular risk, and systemic inflammation when elevated[100,101]. A substantial body of research has demonstrated that exercise, particularly resistance training, decreases TNF-α[18,20,102] and emphasises the potential of exercise as a therapeutic lifestyle intervention for individuals with CKD[18]. Exercise induces an anti-inflammatory cytokine cascade, exemplified by the release of IL-6 from muscle tissue, followed by the upregulation of IL-10, a response that suppresses TNF-α production from immune cells[103,104]. Findings from our systematic review confirm that various exercise modes may reduce TNF-α in CKD patients[18,20,102]. Current data suggest that resistance training may be most effective for lowering TNF-α[18], whereas aerobic training also provides significant benefits, with a combined exercise training showing no significant benefit as compared to CON[23]. The effects of resistance training on reducing TNF-α are multifactorial, primarily involving myokine-driven anti-inflammatory signaling, reduced uremic toxin burden, improved muscle mass, and mitigation of

sarcopenia-related inflammation[18,105,106]. Taken together, the current literature may underscore the importance of incorporating resistance training as a core element of exercise prescriptions for CKD patients.

CRP

From a clinical perspective, elevated CRP is a risk factor for CKD patients and may play a pathogenic role in the progression of CKD, leading to renal inflammation and fibrosis[107]. Exercise has potential anti-inflammatory effects, thereby reducing CRP[19,103,108–110]. Current evidence based on systematic reviews and meta-analyses shows that various exercise modes lower CRP, with resistance training being more effective than aerobic or combined training[18], in agreement with the current results in CKD patients, thereby substantiating its anti-inflammatory properties[16]. These findings underline the significance of integrating exercise, particularly resistance training, into the management of CKD to curtail systemic inflammation and enhance patient anti-inflammatory outcomes. Nevertheless, a recent randomized controlled trial revealed no difference in CRP between patients who underwent resistance or aerobic training[111]. Resistance exercise in CKD patients reduces CRP through multiple mechanisms, including myokine-mediated anti-inflammatory signaling, decreased adiposity, increased muscle mass, mitigation of sarcopenia-related inflammation, reduced oxidative stress, and modulation of immune function. These interconnected effects make resistance training particularly effective for alleviating systemic inflammation in CKD patients[16–19], but require further investigation.

Resistance training: the primary driver of anti-inflammatory effects

The potential anti-inflammatory effects of resistance training in CKD may be attributable to its direct impacts on skeletal muscle mass and anabolic signaling[18]. CKD is characterized by chronic inflammation and sarcopenia, with persistent activation of catabolic pathways such as nuclear factor kappa-light-chain-enhancer of activated B cells and forkhead box class O[112]. Resistance training activates integrin–Focal Adhesion Kinase and Insulin-like Growth Factor-1/Protein Kinase B/Mechanistic/Mammalian Target of Rapamycin signaling, promoting protein synthesis while suppressing proteolysis and inflammatory transcription[80]. Contracting muscle also releases anti-inflammatory myokines, including exercise-induced IL-6; increases IL-10, and inhibits TNF-α, shifting the cytokine profile toward an anti-inflammatory state[113]. Gains in muscle mass further improve insulin sensitivity and reduce adiposity and oxidative stress, key contributors to inflammation in CKD. Finally, actin-mediated mechanotransduction may additionally modulate intracellular inflammatory pathways within this broader anabolic–anti-inflammatory network[114].

Limitations

It is important to acknowledge the limitations of the present systematic review. First, the investigation was unable to assess any effects of flexibility training and HIIT in patients with CKD, and these are a critical component of the current health-related fitness guidelines, that influences the risk of musculoskeletal injury[12]. Secondly, the absence of additional cardiometabolic health-related outcomes limits the current findings, thereby precluding a more comprehensive contextualization of the results. Finally, some heterogeneity and potential publication bias were observed in certain analyses, which may limit the certainty of the pooled estimates and the generalizability of the findings. Accordingly, the results should be interpreted with caution, and further high-quality, well-powered randomized trials are warranted to confirm these findings.

Conclusion

The findings of this systematic review and network meta-analysis suggest that different exercise modes induce significant anti-inflammatory effects among patients with CKD, particularly resistance training, which had significant beneficial effects on all of the included inflammatory markers. Additionally, aerobic training and combined aerobic and resistance training were associated with reduced expression of pro-inflammatory markers (IL-6, TNF-α, and CRP) and an increase in the anti-inflammatory cytokine IL-10 in this population, regardless of whether or not they underwent dialysis. The findings of this study suggest the importance of a multifaceted exercise programming strategy for this cohort, incorporating both cardiorespiratory and muscle-strengthening activities regularly. Further high-quality studies are necessary to evaluate the long-term safety, effectiveness, and outcomes following other exercise modes, particularly flexibility training and HIIT, in patients with CKD, with particular attention to additional cardiometabolic health indicators.

Data availability

All data generated or analyzed for this study are contained within this published article.

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Author contributions

M.Kh., E.M.F., M.E.S. S.K.R., S.F and A.B. conceptualized and designed the protocol. M.Kh., S.F., M.A., and E.M.F. carried out the screenings and reviews, and the analysis of the articles. M.Kh., and A.B. drafted the manuscript, and M.E.S. and S.K.R. revised the manuscript. All authors read and approved the final manuscript.

Declarations

Competing interests

The authors declare no competing interests.

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