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SYSTEMATIC REVIEW

Effect of Progressive Resistance Training on Measures of Skeletal Muscle Hypertrophy, Muscular Strength and Health-Related Quality of Life in Patients with Chronic Kidney Disease: A Systematic Review and Meta-Analysis

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Abstract

Background and Objective Skeletal muscle wasting resulting in reduced muscular strength and health-related quality of life (HR-QOL) is common in chronic kidney disease (CKD) and may be reversed with progressive resistance training (PRT). Therefore, we systematically assessed the effect of PRT on measures of skeletal muscle hypertrophy, muscular strength and HR-QOL in this cohort to inform clinical practice and guidelines.

Design We performed a systematic review and meta-analysis.

Inclusion Criteria We included randomised controlled trials (RCTs) that investigated the independent effect of PRT (>6 weeks) on measures of skeletal muscle hypertrophy [muscle mass or cross-sectional area (CSA)], muscular strength and/or HR-QOL in adults with CKD.

Data Extraction and Analysis The standardised mean difference (SMD) from each study was pooled to produce an overall estimate of effect and associated 95 % confidence interval (95 % CI) between treatment and control groups on primary outcomes.

Results Seven RCTs in 271 patients with Stage 3–5 CKD yielded seven studies on muscular strength ($N = 249$), six studies on total body muscle mass ($N = 200$) and six studies on HR-QOL ($N = 223$). PRT significantly improved standardised muscular strength [SMD 1.15 (95 % CI 0.80–1.49)] and HR-QOL [SMD 0.83 (95 % CI 0.51–1.16)], but not total body muscle mass [SMD 0.29 (95 % CI −0.27 to 0.86)] in our primary analysis. However, secondary analysis of six studies showed that PRT induced significant muscle hypertrophy of the lower extremities (leg mass, or mid-thigh or quadriceps CSA) [SMD 0.43 (95 % CI 0.11–0.76)], a pertinent analysis given that most studies implemented lower-body PRT only.

Conclusions Robust evidence from RCTs indicates that PRT can induce skeletal muscle hypertrophy and increase muscular strength and HR-QOL outcomes in men and women with CKD. Therefore, clinical practice guidelines should be updated to inform clinicians on the benefits of PRT in this cohort.

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1 Introduction

According to the United States Renal Data System, more than 15 % of the adult population in the USA has chronic

kidney disease (CKD) [1], while global estimates reveal a burgeoning epidemic (8–16 % prevalence) [2]. These trends are being driven largely by escalating rates of obesity and type 2 diabetes mellitus [3]. The prevention and treatment of CKD will present a major challenge for healthcare systems in the coming decades [3]. A major part of this challenge will involve providing quality care to patients with advanced CKD, including those with pre-dialysis (Stage 3–4 CKD) and end-stage renal disease (ESRD) [3].

Skeletal muscle wasting is common in advanced CKD [4–6] due to factors such as sedentary behaviour [7], acidosis [8], co-morbid illnesses, corticosteroid usage, aging, oxidative stress, dialysis treatment [9], insulin resistance, chronic inflammation and protein-restricted diet. This wasting contributes to reductions in muscular strength and associated functional impairment [10–12]. Functional impairment, in turn, contributes to impaired health-related quality of life (HR-QOL), particularly the physical dimension of HR-QOL [13]. Many investigations have shown that muscle wasting [14], loss of functional activities [15] and/or low HR-QOL contribute to greater hospitalization and all-cause mortality in patients with CKD [16–18].

Progressive resistance training (PRT) has been shown to induce skeletal muscle hypertrophy and improve functioning and HR-QOL in older adults and those with advanced chronic diseases [19]. Since there is an association of muscle wasting in CKD with high morbidity and mortality, it has been hypothesized that PRT may be important in terms of clinical outcomes in this patient population as well [20–24]. In fact, Exercise and Sport Science Australia has recently recommended PRT as a central component of the exercise prescription for patients with CKD [25]. Since 2001, a number of randomised controlled trials (RCTs) have investigated the independent effect of PRT on measures of skeletal muscle hypertrophy and related health outcomes in patients with CKD [26–32]. However, there is currently no consensus regarding the effectiveness of PRT for counteracting catabolic disease outcomes in this cohort [25]. Accordingly, PRT is not routinely prescribed [33] and recommendations for undertaking this form of exercise remain absent from CKD clinical practice guidelines [34].

Our initial analysis of the published literature indicated an absence of high-quality reviews specifically elucidating the effect of PRT in patients with CKD. We therefore conducted a systematic review of the literature to assess the independent effect of PRT on measures of skeletal muscle hypertrophy, muscular strength and HR-QOL in patients with CKD to inform clinical practice and guidelines.

2 Methods

2.1 Search Strategy

A systematic review of all published literature using the following electronic databases was conducted in June 2013: MEDLINE (OvidSP, Wolters Kluwer), PubMed (NCBI, U.S. National Library of Medicine), ScienceDirect (SciVerse, Elsevier), SPORTDiscus (EBSCOhost, EBSCO), Scopus (SciVerse, Elsevier), Web of Science (Web of Knowledge, Thomson Reuters), the Cochrane Library (John Wiley & Sons), EMBASE (OvidSP, Wolters Kluwer), CINAHL, and Google Scholar. Search syntaxes were developed in consultation with an experienced university librarian, taking into account a broad range of terms and phrases used in definitions related to CKD (e.g. chronic kidney disease, haemodialysis, end-stage renal disease, etc.) and resistance training (e.g. resistance training, resistance exercise, weight training, weight lifting, strength training, etc.). Sample search strategies (PubMed and Scopus) are presented in the Electronic Supplementary Material, Appendix S1. Reference lists of retrieved full-text articles and recent reviews were examined to identify additional articles not found by our search.

2.2 Study Selection

Electronic references were compiled in an Endnote X6© (Thomson Reuters) file and duplicates were identified and deleted. Two authors (BSC and DC) independently reviewed the titles and abstracts of each reference for potential inclusion. Each reviewer then performed a second screening on the full-text version of these articles, and disagreements were resolved by discussion. RCTs that investigated the independent effect of PRT intervention on measures of skeletal muscle hypertrophy [muscle mass or cross-sectional area (CSA)], muscular strength and/or HR-QOL in adults with CKD (Stage 1–5) were eligible. PRT interventions may have included, but were not restricted to, any form of resistive type exercise using body weight (calisthenics), equipment (machine weights, free weights) or apparatus (elastic bands), and had to have been at least 6 weeks in duration. There were no language restrictions for articles.

2.3 Primary Outcomes

The primary outcomes were the mean difference in measures of skeletal muscle hypertrophy (muscle mass or CSA), muscular strength and HR-QOL after intervention (post-treatment) between the treatment and control (e.g.

non-treatment, placebo-treatment) group. Where multiple muscular strength outcomes were reported, we prioritised lower-body over upper-body measures, and knee extension over other lower-body measures. Where multiple measures of muscle mass or CSA were reported, we prioritised measures of muscle mass over CSA, and whole-body over regional measures. Where multiple HR-QOL outcomes were reported, we first prioritised subscales then summary measures of the physical component of HR-QOL.

2.4 Data Extraction

Data extraction and quality assessment of included studies were performed and/or verified independently by three reviewers (BSC, DC and PF). Discrepancies were resolved through discussion. Authors of relevant studies were contacted, where possible, for data that could not be extracted from the published articles.

2.5 Quality Assessment

The following data were extracted from included studies using a standard proforma checklist: study design, study population characteristics, PRT intervention [e.g. specific exercises, number of sets per exercise, number of repetitions per set, intensity (load), frequency and duration of training, and loading progression]. Our quality checklist was designed based on established criteria for the assessment of RCTs [35]. Quality items for RCT studies reviewed were (each worth 1.0 numerical point) as follows: (1) evidence of randomisation and concealment of treatment allocation; (2) statistical similarity of groups at baseline; (3) specification of eligibility criteria; (4) blinding of outcomes assessors; (5) reporting of compliance; (6) supervision of exercise sessions; (7) reporting of dropouts; (8) presenting data for primary and secondary outcomes; (9) use of intention-to-treat analysis; and (10) reporting of adverse events. Summed scores ranged from 0 to 10 points with higher scores reflecting better quality.

2.6 Data Synthesis

Three reviewers (DC, BSC and EA) independently collated and/or verified extracted data to present a descriptive synthesis of important study characteristics and a quantitative synthesis of effect estimates.

2.7 Secondary Outcomes

The secondary outcomes were data about adverse events for a descriptive synthesis.

2.8 Statistical Methods

We pooled and weighted studies first using random–effects meta-analysis models, and second using fixed–effects models for verification [36]. The effect was measured as the difference between groups in the improvement in outcome over the treatment period. Where papers did not present the mean and standard deviation of the improvement in outcome, we estimated these from the pre- and post-treatment standard deviations [37]. This estimation requires an estimate of the pre–post correlation, which we obtained from papers which provided pre-, post- and change means and standard deviations [37]. As the estimated correlations were quite consistent across studies (Electronic Supplementary Material, Table S1) we used the average correlation in our calculations.

In examining the effects of PRT on skeletal muscle hypertrophy, muscular strength and HR-QOL outcomes, the standardised mean difference (SMD) from each study was pooled to produce an overall estimate of effect and associated 95 % confidence interval (95 % CI) between treatment and control groups. For each meta-analysis model, the degree of heterogeneity in SMDs was assessed by visual inspection, the I^2 statistic (moderate being <50 %) [38] and the chi-squared (χ^2) test of goodness of fit [39]. Where evidence of heterogeneity was observed, we checked data extracted from individual outlier studies, qualitatively investigated reasons for their different results, and explored the effects of study exclusion in sensitivity analyses.

The subset of studies examining the impact of PRT on lean body mass (in kg) as measured by dual-energy X-ray absorptiometry (DEXA) were pooled to estimate the inverse variance weighted mean difference (WMD), including the DerSimonian and Laird [36] 95 % CI, between cases and controls. This preserved the original measurement units. We also used sensitivity analysis to investigate the robustness of the meta-analyses models. We variously excluded studies that combined PRT with other therapies (including haemodialysis), studies in older patients (>60 years), studies conducted outside the USA, longer duration trials (≥12 weeks), and studies of lower quality (score <6.0). Publication bias, which reflects the tendency for smaller studies to be published in the literature only when findings are positive, was assessed visually using funnel plots [40]. All calculations were performed in Stata® version 12 (StataCorp, College Station, TX, USA) using the 'metan' and 'metafunnel' commands. A two-tailed P value <0.05 was considered statistically significant throughout the analyses.

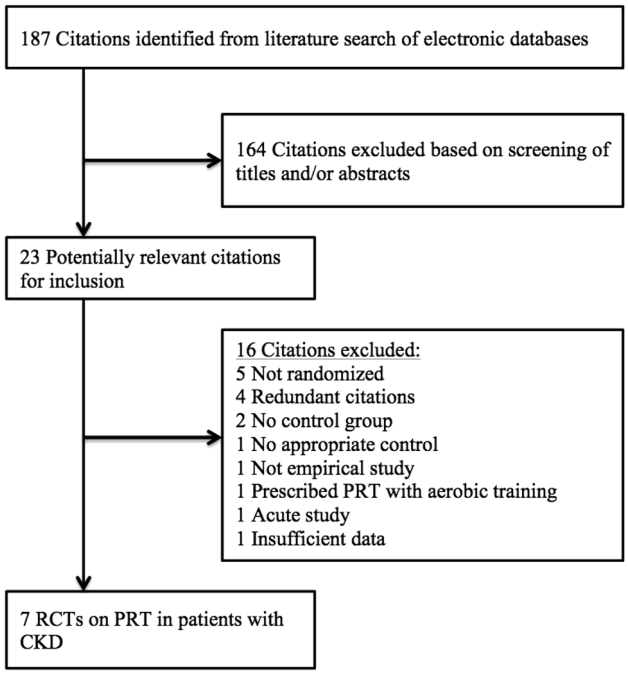

Fig. 1 Flowchart summarising identification of studies for review. *CKD* chronic kidney disease, *PRT* progressive resistance training, *RCT* randomised controlled trial

3 Results

Figure 1 presents a flowchart summarising identification of potentially relevant studies, and those included. Our search strategy identified 187 citations after duplicates were removed. Of these, 164 citations were excluded after the first screening of titles and/or abstracts for inclusion and exclusion criteria. After further assessment of the remaining 23 citations, 16 were excluded (Electronic Supplementary Material, Appendix S2) for reasons listed in Fig. 1, leaving seven for inclusion in the review. Most citations were excluded due to no randomisation or to being redundant citations of the same study.

3.1 Descriptive Data Synthesis

Table 1 presents study characteristics of the seven RCTs included for review, which were published between 2001 and 2013. Four of seven studies were conducted in the USA [26, 28, 30, 31], with others conducted in Australia [27], Brazil [29] and South Korea [32]. The major inclusion criterion was pre-dialysis (Stage 3–4) CKD [30] or ESRD [26–29, 31, 32]. All studies in ESRD involved maintenance haemodialysis patients. In most of these studies it was noted that the patients were adequately dialyzed [haemodialysis treatment adequacy (Kt/V) > 1.2] and receiving dialysis treatment for more than 3 months. Major exclusion criteria primarily emphasised uncontrolled cardiovascular diseases and other conditions that would contraindicate PRT. Analysed sample sizes ranged from 22 to 68, resulting in a total of 271 participants across studies. Mean age of the samples ranged from 43 to 69 years. All studies enrolled both men and women. PRT interventions were prescribed two to three times per week during haemodialysis treatment in four studies with all employing weighted ankle cuffs [26–29]. Only three studies targeted both the upper and lower body musculature with PRT exercises [27, 30, 32], while four targeted the lower body musculature only [26, 28, 29, 31]. Two studies prescribed PRT just prior to each haemodialysis treatment session (3 sessions/week) using machine weights [31] or elastic bands and sandbags [32]. Only one study was conducted in patients not receiving haemodialysis and prescribed PRT using standard machine weights three sessions per week [30]. Three studies compared PRT intervention to usual care (no exercise) [27, 29, 32], one study compared PRT to stretching exercise using light-resistance bands [28], one study compared PRT plus nutritional supplementation with nutritional supplementation only [31], and one study compared PRT plus a protein restricted diet to protein-restricted diet only. Further, a study by Johansen et al. [26] compared PRT + anabolic steroid (i.e. nandrolone decanoate) with anabolic steroid only and PRT + placebo with placebo only. Hence, this study was included as two separate comparisons in relevant meta-analyses. Trial durations ranged from 8 to 24 weeks.

Primary outcomes were muscular strength measures evaluated by knee extension [26–28, 30] and leg press [31, 32], total body muscle mass measures evaluated by total body potassium [30], DEXA [26, 28, 31] and bioelectrical impedance analysis (BIA) [32], mid-thigh muscle CSA evaluated by computed tomography (CT) [27, 30], quadriceps muscle CSA evaluated by magnetic resonance imaging (MRI) [26], lean leg mass evaluated by DEXA [28, 31], and the physical dimension of HR-QOL evaluated by the Medical Outcomes Trust Short Form-36 (SF-36) physical functioning domain [26, 27, 29] and physical component summary scale [28, 32]. Mean quality scores ranged from 5.5 to 9.5, and five studies received a score of 8.0 or higher (Electronic Supplementary Material, Table S2).

3.2 Quantitative Data Synthesis

Figure 2 presents the SMD for muscular strength outcomes after PRT between the treatment and control groups. PRT significantly improved standardised muscular strength outcomes compared with control conditions [SMD 1.15 (95 % CI 0.80–1.49)], and there was only slight evidence of statistical heterogeneity between studies ($I^2 = 35.0$ %, $P = 0.161$). The sensitivity analyses presented in Table 2

Table 1 Characteristics of randomised controlled trials reviewed

Study; country	Sample (*n*)	Population		Mean age (years)	Treatments	Control conditions	Trial duration (weeks)	Outcomes (assessments; units)	Quality score (/10)
		Inclusion criteria	Exclusion criteria						
Castaneda et al. [30]; USA	26	Serum creatinine 1.5–5.0 mmol/L; physician approval to follow low-protein diet; confirmed CKD diagnosis by nephrologist (via renal biopsy and clinical records)	Myocardial infarction within previous 6 months; any unstable chronic condition, dementia, alcoholism, dialysis or previous renal transplant; current resistance training; recent involuntary weight change; albumin <30 g/L, proteinuria >10 g/L; abnormal exercise stress test results	65	Standard PRT using machine weights (knee extension, knee flexion, lat pulldown, chest press, leg press) 3 sets × 8 reps at 80 % 1RM, 3 sessions/week, 1RM tested each month to adjust loading, plus protein-restricted diet (0.6 g/kg/day)	Protein-restricted diet (0.6 g/kg/day)	12	Muscle [total body potassium (kg), mid-thigh muscle CSA via CT (cm^2), type I and II muscle fibre CSA (μm^2)]; dynamic 1RM upper body strength (chest press, lat pulldown; kg), dynamic 1RM lower body strength (leg press, knee extension, knee flexion; kg)	8.5
Johansen et al. [26]; USA	68	Adequate dialysis (Kt/V ≥ 1.2) and compliant with haemodialysis treatment (i.e. missing <2 treatment sessions over previous month)	Haemodialysis <3 months; catabolic state (e.g. HIV with opportunistic infection, malignancy or infection requiring intravenous antibiotics over prior 2 months); unable to provide informed consent; active intravenous drug use; thigh graft; contraindications to PRT	56	(a) PRT during dialysis using weighted ankle cuffs (knee extension, hip abduction and flexion, ankle dorsiflexion and plantarflexion), 2–3 sets × 10 reps at 60 % 3RM, 3 sessions/week, weights increased when patient could perform 3 sets × 10 reps, plus placebo injection weekly (b) Intervention (a) + nandrolone decanoate injection weekly (men = 200 mg/dose; women = 100 mg/dose)	(a) Placebo injection weekly (b) Nandrolone decanoate injection administered weekly (men = 200 mg/dose; women = 100 mg/dose)	12	Muscle [lean body mass via DEXA (kg), quadriceps muscle CSA via MRI (cm^2), serum creatinine (mg/dL)]; dynamic lower-body strength (knee extension, hip abduction, hip flexion; lb); isokinetic lower-body strength (knee extension at 90 and 120 deg/s; Nm); HR-QOL (SF-36 physical functioning)	8

Table 1 continued

Study; country	Sample (*n*)	Population		Mean age (years)	Treatments	Control conditions	Trial duration (weeks)	Outcomes (assessments; units)	Quality score (/10)
		Inclusion criteria	Exclusion criteria						
Cheema et al. [27]; Australia	49	Adult (≥18 years); haemodialysis >3 months; independent ambulation with or without assistive device; adequately dialyzed (Kt/V ≥ 1.2); stable during dialysis; ability to provide written informed consent; willingness to be randomly assigned and undergo protocols	Acute or chronic medical conditions that would preclude PRT or collection of outcome measures	63	PRT during dialysis using weighted dumbbells (shoulder press, side shoulder raise, triceps extension, biceps curl, external rotation), weighted ankle cuffs (seated knee extension, supine hip flexion, supine hip abduction, supine straight-legged raise), elastic tubing (seated hamstring curl) and body weight (bilateral leg raises—seated or supine), 2 sets × 10 reps at RPE 15–17, 3 sessions/week	Usual care (no exercise)	12	Muscle (mid-thigh muscle CSA via CT; cm^2); total body isometric muscular strength (knee extensor + hip abductor + tricep, kg); isometric knee extensor strength[a] (kg); HR-QOL (SF-36 physical functioning)	9.5
Chen et al. [28]; USA	44	Age ≥30 years; serum albumin <4.2 g/dL and haemodialysis thrice weekly for >3 months with ≥80 % compliance	Unstable cardiovascular disease; any uncontrolled chronic condition; cardiac surgery, retina laser therapy, myocardial infarction, joint replacement or lower extremity fracture in previous 6 months; severe cognitive impairment; lower extremity amputation; current strength training	69	PRT during first 2 h of haemodialysis using weighted ankle cuffs (knee extension, dorsi/plantar flexion, leg curl, inner leg raises, dorsi/plantar flexion with straight legs, seated pelvic tilt), first 8 sessions with no loading (RPE 2–4/10) progressed to 1–2 sets × 8 reps (RPE 6/10), 2 sessions/week	Stretching exercises using light resistance bands, 2 sets, 20–30 s/stretch	18	Muscle (lean whole-body mass and lean leg mass via DEXA; kg); muscle strength (knee extensor; kg), HR-QOL (SF-36 physical and mental component summary scales)	8

Table 1 continued

Study; country	Sample (*n*)	Population		Mean age (years)	Treatments	Control conditions	Trial duration (weeks)	Outcomes (assessments; units)	Quality score (/10)
		Inclusion criteria	Exclusion criteria						
Dong et al. [31]; USA	22	Age >18 years; thrice-weekly haemodialysis for >3 months; adequate dialysis (Kt/V > 1.2), using a biocompatible dialysis membrane	Active inflammatory or infectious disease; pregnancy, hospitalisation within previous 1 month; with cardiovascular disease and/or osteoarthritis and unable to exercise	43	PRT prior to each haemodialysis treatment using pneumatic resistance equipment (leg press only), 3 sets × 12 reps at 70 % 1RM. 1RM tested at month 3 for load adjustment, plus same nutritional supplement as control, 3 sessions/week	Nutritional supplement: 2 cans of lactose-free formula (Nephro®) containing 240 mL and 480 kcal (66.8 kcal from protein, 211.2 kcal from carbohydrates and 204.3 kcal from fat), taken 3 times/week during dialysis	24	Muscle (lean body and leg mass via DEXA; kg, %); muscle strength (leg press 1RM; lb)	6.5
Song et al. [32]; South Korea	40	Age >18 years; haemodialysis for >3 months; permission of nephrologist; ability to maintain a seated position; independent ambulation with or without an assistive device; adequate dialysis (Kt/V = 1.2); stable during dialysis; willingness to be randomly assigned and undergo study protocols	None specified	53	PRT prior to each haemodialysis treatment using elastic bands (6 upper body exercises) and sandbags (6 lower body exercises), 3 sets × 10–15 reps at RPE 11–15, 3 sessions/week	Usual care (no exercise)	12	Muscle (lean body mass via BIA; kg); muscle strength (grip and leg strength; kg); HR-QOL (SF-36 physical and mental component summary scales)	8

Table 1 continued

Study; country	Sample (*n*)	Population		Mean age (years)	Treatments	Control conditions	Trial duration (weeks)	Outcomes (assessments; units)	Quality score (/10)
		Inclusion criteria	Exclusion criteria						
de Lima et al. [29]; Brazil	22	Age 18–75 years; thrice-weekly haemodialysis; men and women; sedentary	Uncontrolled arterial hypertension; ischaemic cardiopathy; amputation; deep vein thrombosis; excessive pallor; severe dyspnoea; femoral fistula; arrhythmias; precordial pain; orthopaedic or neurological condition and cognitive alterations affecting participation	47	PRT during first 2 h of dialysis using weighted ankle cuff (knee flexion/knee extension, and hip and knee flexion with foot dorsiflexion), 3 sets × 15 reps at 40 % 1RM, 3 sessions/week. 1RM tested every 15 days for load adjustment	Usual care (no exercise)	8	HR-QOL[a] (SF-36 physical functioning)	5.5

BIA bioelectrical impedance analysis, *CKD* chronic kidney disease, *CSA* cross-sectional area, *CT* computed tomography, *DEXA* dual energy X-ray absorptiometry, *HR-QOL* health-related quality of life, *Kt/V* haemodialysis treatment adequacy, *lat* latissimus dorsi, *MRI* magnetic resonance imaging, *PRT* progressive resistance training, *reps* repetitions, *RM* repetition maximum, *SF-36* Medical Outcomes Short-Form 36 Quality of Life Questionnaire

[a] Data requested and received from authors (not available in publication)

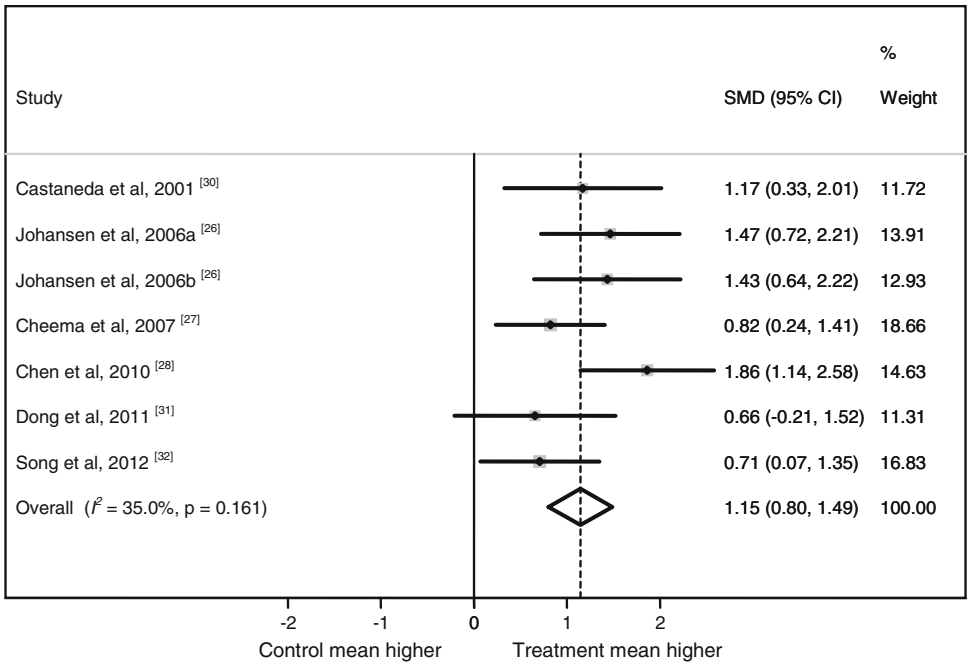

Fig. 2 Standardised mean difference in muscular strength outcomes between the treatment and control groups. *CI* confidence interval, *SMD* standardised mean difference

Table 2 Sensitivity analysis of randomised controlled trials investigating muscular strength outcomes

Sensitivity analysis	Studies (*n*)	Sample (*n*)	SMD	LCL	UCL	*P* value	I^2	*P* value
Fixed–effects model	7	249	1.13	0.86	1.4	<0.001	35	0.161
Exclusion of 1 study involving PRT + nandrolone decanoate	6	217	1.1	0.72	1.49	<0.001	41.8	0.126
Exclusion of 3 studies in cohorts >60 years	4	130	1.06	0.62	1.49	<0.001	24.7	0.263
Exclusion of 2 studies outside USA	5	160	1.36	0.98	1.74	<0.001	15.3	0.317
Exclusion of 1 study in non-dialysis CKD	6	223	1.15	0.75	1.54	<0.001	45.8	0.1
Exclusion of 2 studies on PRT + diet	5	201	1.22	0.79	1.66	<0.001	49.7	0.093
Exclusion of 2 studies of longer duration	5	183	1.05	0.74	1.37	<0.001	0	0.426
Exclusion of 4 studies prescribing PRT during dialysis time	3	110	0.82	0.38	1.26	<0.001	0	0.633

CKD chronic kidney disease, I^2 *I* squared statistic, *LCL* lower confidence interval, *PRT* progressive resistance training, *SMD* standardised mean difference, *UCL* upper confidence interval

shows that the pooled SMD was similarly large in the fixed–effect model and after each of the various studies was excluded (SMD 0.82–1.36). In addition, a funnel plot was produced and showed little evidence of publication bias, since the SMD in muscular strength outcomes was consistently medium to large in all studies (Electronic Supplementary Material, Figure S1).

Figure 3 presents the SMD for total body muscle mass outcomes after PRT between the treatment and control groups. Our primary analysis revealed that PRT failed to increase standardised total body muscle mass outcomes compared with control conditions [SMD 0.29 (95 % CI −0.27 to 0.86); $I^2 = 73.5$ %, $P = 0.002$]. A funnel plot showed no evidence of publication bias (Electronic Supplementary Material, Figure S2). The sensitivity analyses showed that this null effect was comparable after each of the various studies was excluded (Electronic Supplementary Material, Table S3). Conversely, PRT significantly improved total body muscle mass in the fixed–effect model [SMD 0.34 (95 % CI 0.05–0.63)] but the fixed–effect assumption was violated given the strong evidence of statistical heterogeneity between studies ($I^2 = 73.5$ %, $P = 0.002$).

Given that the majority of trials reviewed investigated the effect of lower-body PRT only (Table 1), we pooled studies to investigate the SMD in lower-body muscle mass and CSA outcomes in a secondary analysis (Fig. 4). This analysis of six studies showed that PRT induced significant muscle hypertrophy of the lower extremities (leg mass, or mid-thigh or quadriceps CSA) [SMD 0.43 (95 % CI 0.11–0.76); $I^2 = 26.8$ %, $P = 0.234$]. A funnel plot showed little evidence of publication bias (Electronic

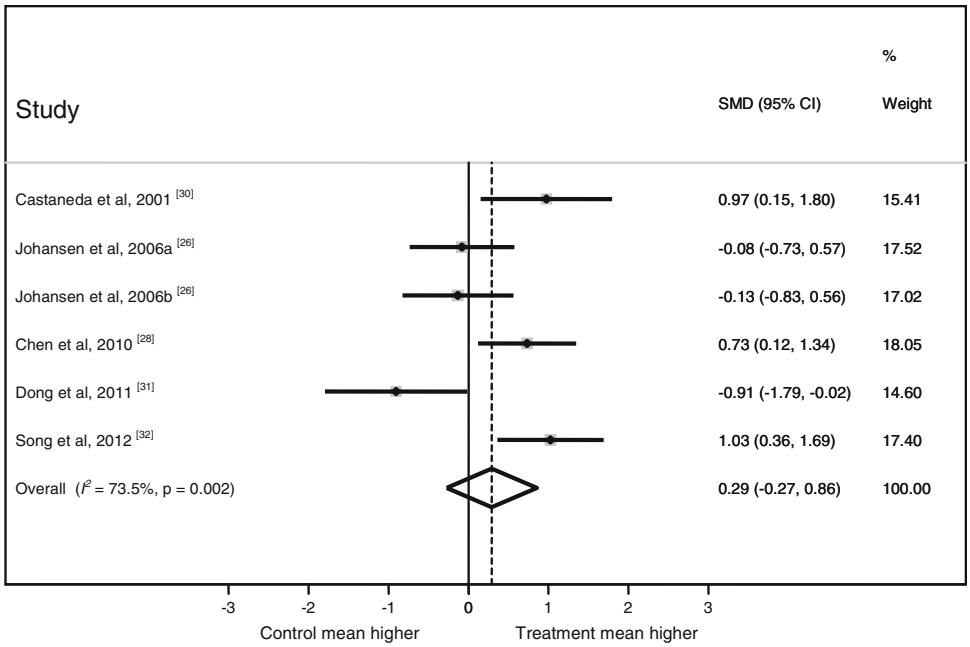

Fig. 3 Standardised mean difference in total body muscle mass outcomes between the treatment and control groups. *CI* confidence interval, *SMD* standardised mean difference

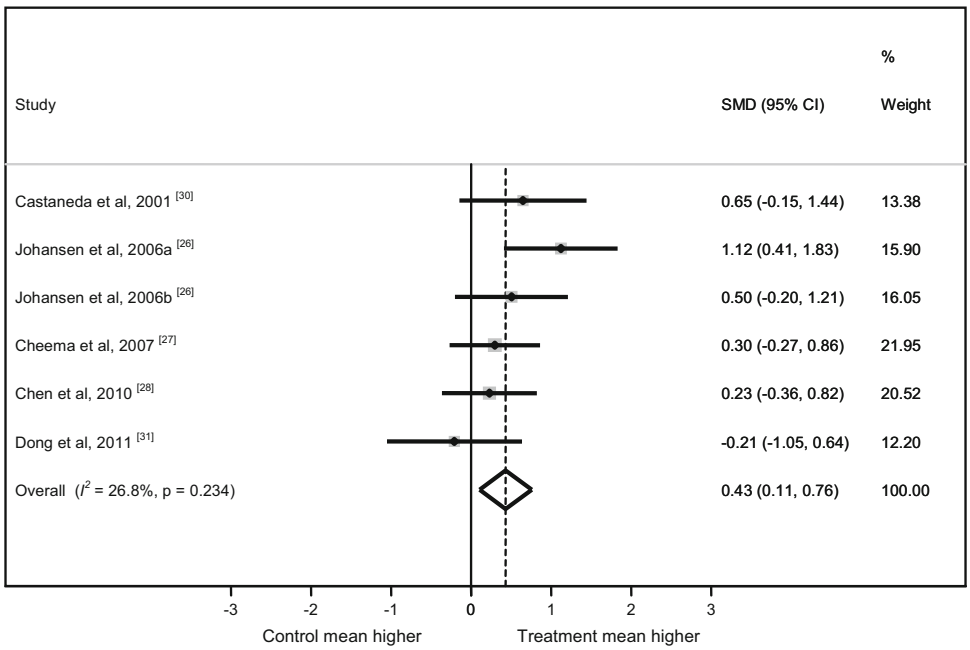

Fig. 4 Standardised mean difference in lower body muscle outcomes (i.e. leg mass, or mid-thigh or quadriceps cross-sectional area) between the treatment and control groups. *CI* confidence interval, *SMD* standardised mean difference

Supplementary Material, Figure S3). Additionally, we pooled studies to estimate the inverse variance WMD in muscle mass outcomes after PRT between the treatment and control groups. PRT significantly improved quadriceps muscle CSA measured by MRI [pooled WMD for two studies [26] was 3.83 cm^2 (95 % CI 1.73–5.94); $I^2 = 1.0$ %, $P = 0.315$], but not total body muscle mass measured by DEXA only [pooled WMD for four studies [26, 28, 31] was −0.06 kg (95 % CI −1.94 to 1.83)] or thigh muscle CSA measured by CT [pooled WMD for two studies [27, 30] was 3.03 cm^2 (95 % CI −0.15 to 6.21)].

Figure 5 presents the SMD for HR-QOL outcomes after PRT between the treatment and control groups. PRT significantly improved standardised HR-QOL outcomes compared with control conditions [SMD 0.83 (95 % CI 0.51–1.16)], and there was little evidence of statistical heterogeneity between studies ($I^2 = 27.8$ %, $P = 0.226$). The sensitivity analyses presented in Table 3 shows that the pooled SMD was similarly large in the fixed–effect model and after each of the various studies was excluded (SMD 0.70–0.94). In addition, a funnel plot was produced and showed little evidence of publication bias, since the

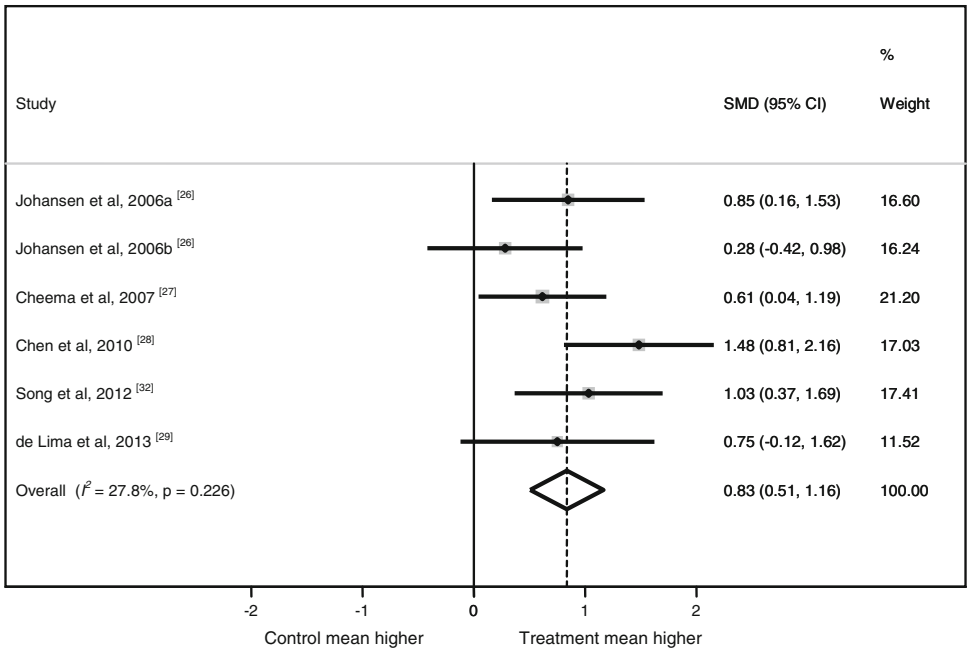

Fig. 5 Standardised mean difference in health-related quality-of-life outcomes between the treatment and control groups. *CI* confidence interval, *SMD* standardised mean difference

Table 3 Sensitivity analysis of randomised controlled trials investigating health-related quality of life outcomes

Sensitivity analysis	Studies (*n*)	Sample (*n*)	SMD	LCL	UCL	*P* value	I^2	*P* value
Fixed–effects model	6	223	0.83	0.56	1.11	<0.001	27.8	0.226
Exclusion of 1 lower-quality study (score <6.0)	5	201	0.85	0.46	1.23	<0.001	41.9	0.142
Exclusion of 2 studies in cohorts >60 years	4	130	0.73	0.38	1.09	<0.001	0	0.474
Exclusion of 1 study involving PRT + nandrolone decanoate	5	191	0.94	0.63	1.24	<0.001	1.2	0.399
Exclusion of 3 studies outside USA	3	112	0.87	0.19	1.56	0.012	66.3	0.052
Exclusion of 1 study of longer duration	5	179	0.7	0.4	1	<0.001	0	0.622

I^2 *I* squared statistic, *LCL* lower confidence interval, *PRT* progressive resistance training, *SMD* standardised mean difference, *UCL* upper confidence interval

SMD in HR-QOL outcomes was consistently medium to large in all studies (Electronic Supplementary Material, Figure S4).

3.3 Adverse Events

Four studies reported that no adverse events occurred as a consequence of PRT [27, 28, 30, 32]. One study that prescribed intradialytic PRT reported no statistically significant differences between the experimental and control group in the number of dialysis-related complaints (i.e. headache, hypotension, cramping and fistula cannulation difficulties), falls, acute illnesses and number of visits to healthcare professionals [27]. However, one adverse event was documented in this study: a 73-year-old woman in the PRT group sustained a partial tear of the right supraspinatus. The injury was documented [41] and managed conservatively; the patient resumed lower-body PRT for the remainder of the trial [27]. One study reported on adverse events related to anabolic steroid use, but not in relation to PRT [26]. Two studies did not report on adverse events [29, 31].

4 Discussion

4.1 Summary of the Evidence

Based on RCT evidence in patients with CKD, our results were consistent and indicate that PRT significantly improves measures of muscular strength [SMD 1.15 (95 % CI 0.80–1.49)] and HR-QOL [SMD = 0.83 (95 % CI 0.51–1.16)]. There was an absence of evidence showing that PRT significantly increases total body muscle mass [SMD 0.29 (95 % CI −0.27 to 0.86)]. However, secondary analysis of lower body muscle mass and CSA outcomes (i.e. leg mass, or mid-thigh or quadriceps CSA) revealed a significant effect for PRT versus control conditions [SMD

0.43 (95 % CI 0.11–0.76)], a pertinent analysis given that the majority of trials (4/7) were limited to lower-body training [26, 28, 29, 31]. Overall, this robust evidence from RCTs indicates that PRT can induce skeletal muscle hypertrophy and increase muscular strength and HR-QOL with no risk of serious adverse events in men and women with CKD.

The size of the effect of PRT on these key outcomes is moderate to large, and clinically relevant. For instance, studies have consistently shown that skeletal muscle wasting is a strong predictor of mortality in patients with ESRD [14, 42, 43], and a recent observational study noted that the loss of muscle is particularly rapid in pre-dialysis CKD [10]. Carrero et al. [43] have shown that incident and prevalent haemodialysis patients (dialysis vintage 8–78 months) with mild to moderate/severe muscle wasting (SMD 0.38–0.69) suffer a greater risk of systemic inflammation [odds ratio (OR) 2.81 (95 % CI 1.33–5.91)], cardiovascular disease [OR 3.08 (95 % CI 1.43–6.65)] and all-cause mortality (hazard ratio 1.29–3.04) than CKD patients with no evidence of muscle wasting. Similarly, studies have shown that the loss of muscular strength (SMD 0.66) is associated with significantly greater risk of renal endpoint (i.e. pre-dialysis mortality or reaching ESRD) in CKD [44] while impairments in the physical component of HR-QOL (SMD 0.60) have been shown to predict mortality [45]. Therefore, the results of our study suggest that the size of the effect of PRT on skeletal muscle hypertrophy [SMD 0.43 (95 % CI 0.11–0.76)], muscular strength [SMD 1.15 (95 % CI 0.80–1.49)] and HR-QOL [SMD 0.83 (95 % CI 0.51–1.16)], which could be expected in practice, could theoretically protect against disease-related complications and reduce the mortality burden in patients with CKD. Hence, our findings are clinically relevant.

Notably, the effect of PRT on muscle strength and HR-QOL outcomes remained robust in fixed–effect models and after exclusion of studies that combined PRT with other therapies (including haemodialysis), studies in older patients, studies conducted outside the US, longer duration trials, and studies of lower quality. In summary, our results indicate that PRT should be considered for inducing muscle hypertrophy and increasing muscular strength and HR-QOL outcomes in men and women with CKD.

4.2 Limitations

Several limitations require careful consideration. Since only a small number of studies were included, the findings of this review may not be relevant to other countries and key groups within the CKD population. In particular, most of the RCTs reviewed were conducted in patients with ESRD undergoing haemodialysis treatment, while only one trial enrolled patients with pre-dialysis CKD. We found no RCTs that tested the efficacy of PRT in patients undergoing peritoneal dialysis or kidney transplant and hence research on these unique CKD populations is required. Second, there was heterogeneity with respect to the exercise prescriptions (Table 1). Several studies did not prescribe full-body PRT, while others prescribed low-intensity [26, 29] or few exercises [26, 29, 31], factors that can potentially reduce the effectiveness of the training regimen. It has been shown that patients with CKD can safely tolerate higher-intensity and more comprehensive PRT regimens (i.e. involving a greater number of exercises) [27, 30]. Such programmes, involving longer training durations, are likely to be most effective in terms of adapting outcome measures. However, we did not investigate any dose–response effects in the present review and, accordingly, the optimal dosages of PRT to adapt the specific outcomes in this cohort remain unknown and require further research. Finally, combined across all studies, the total number of participants is relatively modest ($N = 200$–249).

5 Conclusions

We believe that our meta-analytic results are sufficiently reliable to recommend that clinicians consider prescribing PRT for inducing skeletal muscle hypertrophy and increasing muscular strength and HR-QOL outcomes in patients with CKD. Future high-quality research is needed to clarify the long-term clinical benefits and risks of PRT in this cohort.

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Conflict of interest None.

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