

REVIEW ARTICLE**Title: Effectiveness of resistance training on functional strength and quality of life in patients undergoing haemodialysis: A systemic review****Sanjaitha Jayaprakash¹, Deepak B. Anap²**¹M.P.T. student Department of Musculoskeletal Sciences, ²Ph. D. Professor & HOD. Department of Musculoskeletal Sciences

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ABSTRACT:

Abstract: ESRD patient population continues to grow, and hence more significant efforts must be directed toward improving morbidity, mortality and health-related quality of life (HRQoL) in these patients. There are studies which show that resistance exercises are beneficial for these patients when it is individually structured according to the patients exercise tolerance. Hence, the purpose of the present systemic review is to provide an overview of the recent literature on the role of resistance exercises in patients with ESRD. Articles published on an online electronic database were included. We included studies published in English from 2015 to 2019, which focused only on resistance exercises in the intervention. This systemic review included six articles which were. RCT, controlled trials, prospective study, and investigated the isolated effect of PRT in adults with ESRD. The review shows that resistance training can increase skeletal muscle quantity and quality, aspects of physical functioning (e.g. lower body strength) and dimensions of health-related quality of life. This systematic review has provided an overview of the recent literature on resistance exercises' role and their effect on various parameters in patients undergoing haemodialysis.

Key-words: End-stage renal disease, haemodialysis, physiotherapy, resistance exercises

Introduction:

End-stage renal disease (ESRD) has been increasing in recent decades; it affects 8 to 16% of the population worldwide. This increase is mainly due to the increased prevalence of risk factors, such as diabetes mellitus and hypertension, and as a result of the ageing of the population¹. As of 2017, there are over 1,30,000 patients receiving dialysis in India, and the number is increasing by about 232 per million population². As the ESRD patient population continues to grow, more significant efforts must be directed toward improving morbidity, mortality and health-related quality of life (HRQoL) in cohort³.

It is well documented that people with end-stage renal disease have reduced aerobic capacity, muscle strength and exercise tolerance, which are factors that contribute to higher levels of physical inactivity. Several trials have demonstrated that exercise training improves functional ability, arterial blood pressure, lipid profile, heart rate variability, and quality of life in people with end-stage renal disease¹. Therefore exercise interventions could be an interesting nonpharmacological strategy to improve overall health in this population.

Physiotherapy treatment in the form of exercises is advised to patients undergoing dialysis.

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Studies show that aerobic exercises, resistance exercises, endurance training, and balance-specific exercises are beneficial for these patients when individually structured according to the patients' exercise tolerance^{4,5}.

Resistance exercises involve challenging skeletal muscles with unaccustomed loads, usually in free or machine weights. Clinical trials have consistently shown that resistance exercises (>6 weeks) can counteract many impairments that accrue due to ageing and chronic diseases. Resistance exercises induce skeletal muscle hypertrophy and enhance bone mineral density. These adaptations often underlie physical functioning improvements (e.g. muscular strength), activities of daily living and health-related quality of life (HRQoL). The many potential benefits of resistance exercises might be particularly vital for ESRD patients who suffer from various physiological, functional and psychological impairments contributing to poor HRQoL, low physical activity and fitness. Since the first study conducted by Headley et al. in 2002, many trials have shown that resistance exercises prescribed within or outside of routine HD treatment is safe and can induce clinically significant adaptations in patients with ESRD³. However, these exercises are not routinely prescribed in clinical practise to enhance health outcomes or are combined with aerobic exercises in this cohort. This shortcoming of clinical practice may be due to a lack of widespread awareness of ESRD literature's resistance exercises. Therefore, the purpose of the present systemic review is to provide an overview of the recent literature on the role of resistance exercises in patients with ESRD.

Methodology:

Search Strategy:

Articles published on an online electronic database were included. A search of all published literature was conducted in April 2020 using

PubMed (NCBI), ScienceDirect (Elsevier), Google Scholar, PEDro, ResearchGate using the following as MeSH search terms and free words: "ESRD", "chronic renal disease", "haemodialysis", "renal replacement therapy", "physiotherapy", "resistance exercises", "progressive resistance training", "strength training", etc.

Study Selection:

A systemic review was undertaken. We included studies published in English from year 2015 to 2019, which focused only on resistance exercises in the intervention. RCT, controlled trials, prospective study, and investigating the isolated effect of PRT in adults with ESRD were included. The participants had to be ≥ 18 years of age and be undergoing haemodialysis (HD or peritoneal dialysis) ≥ 3 month. The intervention included exercises for the upper limb without the arteriovenous fistula: shoulder press, biceps curl and triceps curl using dumbbells. For the lower limbs, the exercises included are leg extension, hip flexion, leg curl and hip abduction using ankle weights or elastic band.

Data Extraction:

All steps in the selection and extraction processes were assessed independently by two reviewers. The titles and abstracts of the retrieved references were screened. Full texts of relevant publications were reviewed and were included if they met the inclusion criteria. The following data were extracted: study design, study population characteristics (inclusion/exclusion criteria), group(s) and sample size, resistance exercise intervention (e.g. specific exercises, number of sets per exercise, number of repetitions per set, intensity (load), frequency and duration of training), selected outcome measures, and key findings.

Table 1. :Summary of studies prescribing resistance training in patients with ESRD undergoing haemodialysis

Study	Inclusion criteria	Intervention	Selected Outcome Measure	Key Findings
Dong ZJ et al. 2019, China ⁶	older than 18 years, on hemodialysis for at least three months, residents of Mexico City, and those who provided informed consent signed	Lower leg extension, straight leg extension, seated marching. 500-g weight belts were attached to each ankle, and four series of 30 repetitions were performed for each of the four exercises. The exercise program included 24 sessions that were distributed over 12 weeks, which was at a frequency of twice a week. The sessions lasted an average of 50 minutes and were performed during the second hour of hemodialysis	BIA skeletal muscle mass index, handgrip strength, daily gait speed, international physical activity questionnaire, Kt/V, Cytokine, albumin, and high-sensitivity C-reactive protein measurements.	Statistically significant increase in maximal grip strength, daily stride rate, physical activity level, Kt/V and nutritional index, serum albumin between groups. No statistically significant difference in neutrophil ratio, haemoglobin, serum creatinine. No significant differences in body component related to nutritional indicators.
Marinho SM et.al., 2017, Brazil ⁷	were age >18 years and treatment by maintenance dialysis for at least six months.	During initial two hours of hemodialysis, resistance exercise was performed three times/week for approximately six months. The patients performed the exercises with elastic bands (Theraband® Akron-OH, U.S.A.), and the intensity varied depending on the colour. Ankle-cuffs were also used to perform exercises.	Biochemical data measured: serum OPG, OC, OPN and iPTH plasma levels were analyzed. Kt/V. Routine biochemical parameters, including albumin, creatinine, haemoglobin, hematocrit, calcium, phosphate and potassium. BMI, DXA	OPG levels significantly increased in the exercise group (EG). Serum OPG levels correlated considerably with serum iPTH levels only after the exercise training period and exclusively in EG.

Table 1. :Contd.

Study	Inclusion criteria	Intervention	Selected Outcome Measure	Key Findings
Olvera-Soto MG. et al. 2016, Mexico ⁸	18–80 years old, stable dialysis time = three months, no central system disease, can walk independently, no physical disability, muscle strength =III, dialysis patients with upper limb internal haemorrhoids, can communicate normally, and voluntarily participation	Control group underwent the usual haemodialysis protocol. The exercise group performed intradialytic resistance exercise with high or moderate intensity. 12 weeks; three times/week. Resistance exercise: for the one-leg raise-and-down exercise, and upper limb bouncing ball movement. 10×10 cycles repeatedly	Primary measures: Mid-arm circumference measurements; triceps skinfold measurements, Handgrip strength, Secondary measures: Body fat percentage measurements were performed with triceps, biceps, subscapular and suprailiac skinfolds.	Statistically significant changes anthropometric variables of exercise group: arm muscle circumference and the arm muscle area, handgrip strength increased in exercise group when compared to control group
Lourenço B.S. et.al.; 2018; Brazil ⁹	Both male and female patients, undergoing dialysis since three months by arterial-venous fistula	Shoulder press, biceps curl and triceps curl using dumbbells; leg extension, hip flexion, leg curl and hip abduction using ankle weights or elastic band. 12 weeks protocol; three times/week, one hour after the HD session start and lasting approximately 30 minutes. Exercises were performed between the 75 and 105 minutes of the HD session.	Catabolic and protein breakdown Mean blood pressure (MBP) and double product (DP), Kidney Disease and Quality-of-Life Short-Form (KDQOL-SFTM), Latin American Group of Development for Maturity (GDLAM) oxidative stress: Nitric oxide (NO), Thiobarbituric acid reactive substances (TBARS)	No significant differences in hemodynamic and oxidative stress parameters. Significant increase in six dimensions of KDQOL-SFTM questionnaire after resistance training. Significant reduction of the time necessary to perform the GDLAM protocol

Table 1. :Contd.

Study	Inclusion criteria	Intervention	Selected Outcome Measure	Key Findings
Filho N. J. B. A. et al.; 2018; Brazil ¹⁰	In end-stage of chronic kidney disease; over 18 years of age; and agree to sign the informed consent	Warm-up: using an ergometer (Treadmill or stationary cycle); squats; 45° leg press; extensor chair; flexor chair; hips adduction and abduction followed by stretching to calm down. Initially adjusted to a number of 15 to 20 reps. After the period of adaptation to resistance training, the load was modified by an increase in weight and intensity with a decrease in the number of reps divided into three series of 8 to 12 maximal reps with 2 to 3 min interval between series.	30-sec sit-to-stand test, handgrip strength test performed using the Camry digital hand dynamometer, Kidney Disease and Quality of Life - Short Form (KDQOL-SF), Body Mass Index, skinfold measurements,	A significant difference was seen in 30-sec sit-to-stand test; no significant differences in handgrip strength. Significant gains in the following dimensions of the questionnaire: the burden of kidney disease, sexual function, physical functioning, physical function pain, emotional wellbeing, social functioning
Rosa C.S. et.al.; 2018; Brazil ¹¹	Older than 18years, time since starting hemodialysis of more than three months, without acute or chronic medical conditions that would preclude the exercise or the collection of the outcome measure data,	Upper limb exercises were performed in the waiting room before the hemodialysis session, and the lower limb exercises were performed during the hemodialysis session, three times per week. The approximate total workout time in each session was 40–50minutes. 11 exercises were	Primary outcome: Body composition was assessed by dual-energy X-ray absorptiometry (DXA). Body composition variables: total mass, total fat mass, lean body mass and bone mass contend.	Total lean body mass and total fat mass did not change significantly between the groups. Leg lean mass differed significantly between the groups decreasing in the control group while increasing in the exercise group.

Table 1. :Contd.

Study	Inclusion criteria	Intervention	Selected Outcome Measure	Key Findings
Contd.	with the permission of the attending nephrologist, independent ambulation for >50m with or without an assistive device, cognition and willingness to be randomly assigned into groups and to undergo the study protocols	used for progressive resistance training. The control group received. Active mobilization of the arms and legs, circumduction of the cervical and scapular girdle, and a breathing exercise with no loads in two sets of three to five repetitions.	Secondary outcomes: 6-minute walking test, 19 30-seconds sit-to-stand test, 20 and handgrip strength, 21 and leg and back flexibility was measured by the sit and reach test using a Wells bench.	Bone mineral content improved to a statistically significant degree in the exercise group versus the control group. Statistically significant increase in the leg strength in 30-second sit-to-stand test repetitions and flexibility in the exercise group.

Table 1. :Contd.

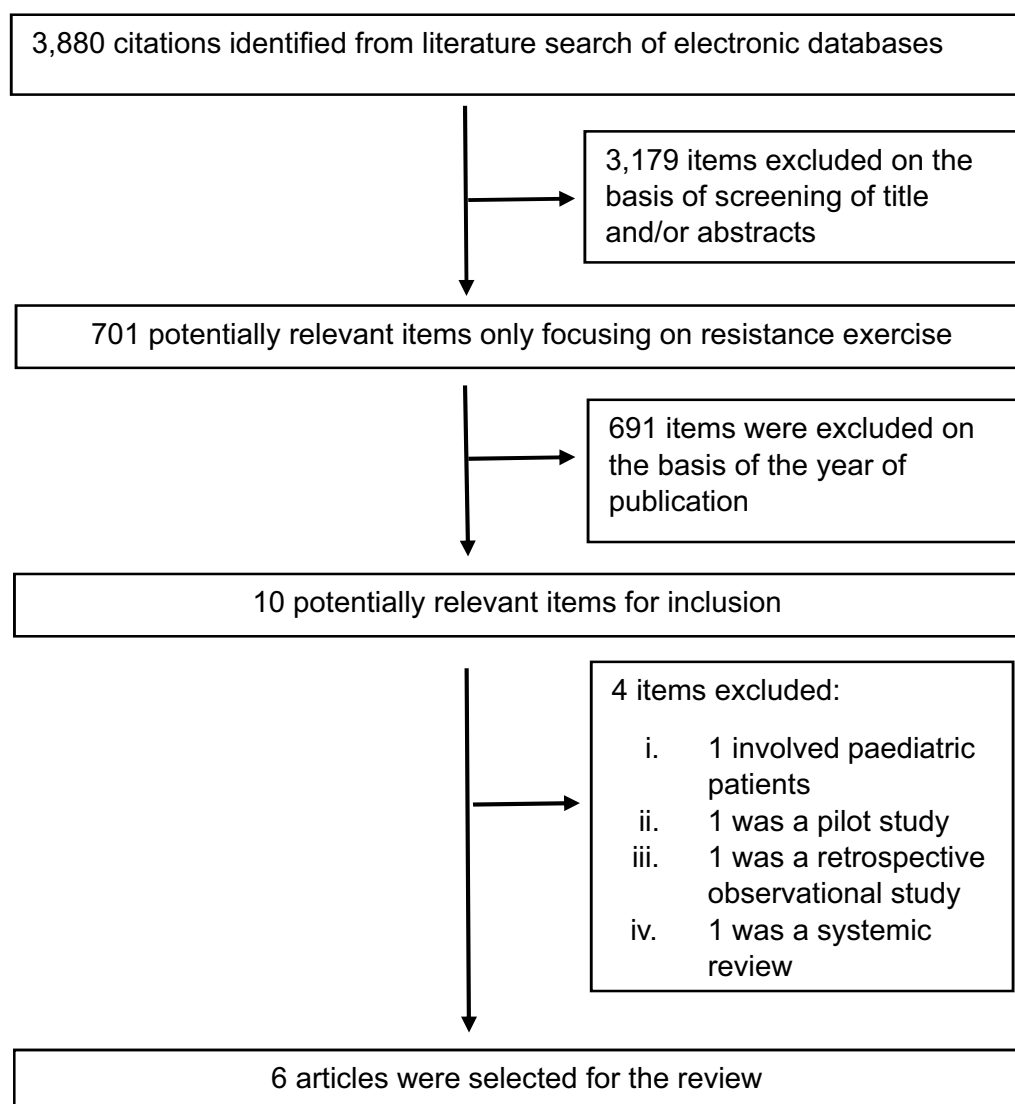
Results:

Fig. 1: Flowchart summarising the selection of the articles for the review

Fig. 1 represents the summary of the selection process of the articles. The literature search produced a total of 3,880 items from the year 2015 to 2020, from which when the search was limited to only resistance exercises, there were 701 items found. After excluding duplicate reports, abstracts were screened, and ten references were obtained for full-text assessment. Four articles were excluded as they involved paediatric patients, pilot study, retrospective observational study and systemic review. Six articles met the inclusion criteria. The studies were published between 2015 and 2019. The studies are summarized in table 1.

Outcome measures:

A study by Dong ZJ et al.⁶:

There were statistically significant differences in maximal grip strength, daily stride rate, and physical activity level between exercise and control groups ($P < 0.05$). A statistically significant difference was seen in the patient's Kt/V and nutritional index serum albumin. There was a statistically significant difference seen in CRP ($P < 0.05$) in the group analysis. IL-6 and IL-10, which represent the anti-inflammatory factors, were increased after the intervention, and the pro-inflammatory factor TNF- α decreased significantly after the intervention. There were no significant differences in body component related to nutritional indicators between exercise and control groups. BMI and FMI differences were statistically significant only in the comparison between groups.

Study by Marinho S.M. et.al.⁷ :

After resistance training, the OPG levels were significantly increased in the exercise group ($P < 0.05$). Serum OPG levels correlated considerably with serum iPTH levels only after the exercise training period and exclusively in the exercise group ($r = 0.60$; $P = 0.02$).

A study by Olvera-Soto MG. et al.⁸ :

The group receiving the resistance exercise intervention showed beneficial and statistically significant changes in the following anthropometric variables: arm muscle circumference increased from 233.6 (IQR 202-254) mm to 241.4 (IQR 203-264) mm ($P = 0.001$) and arm muscle area from 35.9 (26-41) cm² to 36.6 (IQR 26-46) cm² ($P = 0.002$). Handgrip strength in the exercise group increased from 19.6 (IQR 11-28) kg to 21.2 (IQR 13-32) kg; meanwhile, in the control group, handgrip strength diminished from 19.8 (IQR 14-26) kg to 17.8 (IQR 15-26) kg. On comparing the percentage of body fat changes, the resistance exercise group was shown to have a higher percentage of change than the control group, 5.44% versus 0.42%.

Study by Lourenço B.S. et.al.⁹ :

A significant increase was seen in the score, particularly of the six dimensions of SF-36 after the resistance training, i.e. functional capacity, physical aspects, vitality, social aspects, emotional aspects and mental health. There was a trend to improve the dimension related to pain. The eleven CKD specific dimensions did not show differences; however, there was a trend to improve the symptoms/problems dimension. A significant reduction was seen in the time needed to perform the GDLAM protocol tests after the exercise training. 1 RM showed a significant increase in the strength after RT in all exercises ($p < 0.01$). There were no significant differences seen in hemodynamic and oxidative stress parameters during the study, except heart rate, which showed differences after exercise at 1st, 6th and 12th week vs baseline (85.6 ± 15.4 , 87.6 ± 19.2 , 87.3 ± 17.2 , vs 80.3 ± 14.1 , $P < 0.05$).

A study by Filho N. J. B. A. et al.¹⁰ :

In the analysis of handgrip strength values, no significant differences were observed after 12 weeks of training. In sit-to-stand test, there were significant differences after the training program (15.0 ± 5.0 vs. 25.0 ± 4.0 ; $P < 0.01$). After 12 wks, there were significant gains in the following dimensions of the questionnaire: (a) burden of kidney disease ($P = 0.01$); (b) sexual function ($P = 0.01$); (c) physical functioning ($P = 0.001$); (d) pain ($P = 0.007$); (e) emotional wellbeing ($P = 0.034$); (f) social functioning ($P = 0.009$); (g) besides negative contributions on the effects of kidney disease ($P = 0.01$); and (h) dialysis' staff encouragement ($P < 0.001$). Positive and strong associations were also observed between: (a) variations in general health and sleep ($\rho = 0.737$; $P = 0.004$); (b) pain and physical functioning ($\rho = 0.723$; $P = 0.005$); (c) and general health and physical functioning ($\rho = 0.729$; $P = 0.005$). There were moderate associations observed: (a) between vitality and global health ($\rho = 0.627$; $P = 0.029$); and (b) a moderate negative association between work status and burden of chronic kidney disease ($\rho = -0.699$; $P = 0.008$).

A study by Rosa C.S. et.al.¹¹ :

Total lean body mass and total fat mass did not change significantly between the groups after the 12-week intervention; however, when lean body mass was analyzed by body region, lean leg mass differed significantly between the groups with a moderate effect size of 0.56 (95% confidence interval (CI) 0.0; 1.11), decreasing in the control group while increasing in the exercise group. Similarly, bone mineral content improved to a statistically significant degree in the exercise group versus the control group (effect size of 0.65 (95% CI 0.09; 1.21)). The control group exhibited a decrease in bone mass. A medium effect size of 0.66 (95% CI 0.10; 1.22) was found to increase the functional leg strength in 30-second sit-to-stand test repetitions, which was statistically significant between the groups. The exercise group also demonstrated statistically significantly improved flexibility.

Discussion:

This systematic review summarises the current literature on resistance training for patients undergoing haemodialysis for end-stage renal disease. There is consistent evidence that resistance training can increase skeletal muscle quantity and quality, aspects of physical functioning (e.g. lower body strength) and dimensions of health-related quality of life.

A study by Dong ZJ et al.⁶:

CRP represents acute phase inflammation in human tissues, while IL-6 as an anti-inflammatory cytokine and is resistant to the pro-inflammatory cytokine TNF- α . It is known that excess adipose tissue increases the production of the pro-inflammatory cytokine TNF- α . When the body is subjected to resistance training, the anti-inflammatory cytokine IL-6, by contracting skeletal muscle fibres, improves its production and release, stimulates other anti-inflammatory cytokines such as IL-10, and inhibits the production of the pro-inflammatory cytokine TNF- α . In this study, after the 12-week intervention period, the CRP level in the exercise group was significantly lower than that before the intervention, and there was a statistically significant difference between the two groups. It is indicated that the anti-resistance movement during dialysis can reduce CRP. Besides, TNF- α in the exercise group was higher than before intervention and IL-6, and IL-10 decreased significantly when compared with that before the intervention. After 12 weeks of intervention, the difference of Kt/V between the two groups was statistically significant and indicated that resistance to dialysis could improve dialysis adequacy. Kirkman et al. study report also support this finding¹². Exercise can increase the pace of blood flow in muscle tissue with high solute content such as uric acid, urea, and creatinine during the dialysis, thus increasing the transport speed of solute in cells and a large

amount of metabolic waste moves into the bloodstream, which helps promote haemodialysis. An international survey by Avesani C.M. et al. has shown that sedentary lifestyles in MHD patients result in generally lower levels of physical activity¹³. Grip strength and daily pace are simple, widely used indicators of muscle strength assessment, and their baseline values are related to regular physical activity. Isoyama et al. reported reduced muscle strength compared with simple muscle mass reduction, which increased the risk of death in maintenance haemodialysis patients. Regular resistance exercise is effective in improving the muscle strength of these patients¹⁴.

A Study by Marinho S.M. et al.⁷:

Serum OPG plasma levels increased significantly in the patients who underwent resistance training, which was not observed in the control group. This increase in plasma OPG levels after the exercise period may represent a protective factor that acts through increasing skeletal resistance in response to the adverse effects caused by the high levels of iPTH in HD patients. OPG inhibits osteoclast maturation and protects bone tissue from the resorptive action of osteoclasts. High levels of OPG might also offer protection against the adverse effects of iPTH, which lead to the stimulation of bone resorption. It is possible that resistance exercise can decrease plasma iPTH levels in CKD patients. The iPTH levels can vary after physical exercise depending on the activity's duration and intensity, suggesting that there is, likely, a stimulation threshold for exercise training. Resistance exercise probably contributed to the increase in bone alkaline phosphatase among HD patients, leading the authors to suggest that the osteogenic stimuli triggered by exercise may significantly impact bone formation in HD patients.

A study by Olvera-Soto MG. et al.⁸:

Physical inactivity has been related to biological, psychological, and social factors. Besides, a sedentary lifestyle has been recognized as a factor that favours fragility and limits physical functionality. Muscle strength evaluated by dynamometry showed a decrease from a baseline of 19.8 kg to 17.8 kg at the end ($p < 0.001$), which may explain a loss of reserves and functionality of muscle mass for patients who did not perform resistance exercise.

Study by Lourenço B.S. et al.⁹:

The study demonstrated that 12 weeks of intra-dialytic RT improves the quality of life, functional autonomy and strength, without altering hemodynamic parameters or oxidative stress. Patients undergoing HD have increased TBARS levels because of the inflammatory process resulting from HD treatment. A significant increase in six of eight dimensions of the questionnaire was observed, indicating that performing resistance training intra-dialysis could be useful in these patients for increasing quality of life. A study by Oh - Park et al. support the findings regarding improvement in the dimensions of functional capacity, physical aspects and mental health¹⁵. This study was the first to use the GDLAM method of assessment in CKD patients. The chronic disease might decrease functional capacity. Hence the GDLAM test of functional autonomy was used, which is typically applied in the elderly. The test was used because of the resemblances of comorbidities, the accuracy and ease of application. The specific characteristics of this test do not induce exhaustion in the patient. The study showed significant changes in the functional autonomy index scores, presenting improvement of daily activities such as walking without help, standing up from a chair, and going up and downstairs. Resistance training for CKD

patients can minimize muscle mass loss that is frequent in these patients, improving muscle strength. The resistance training increased strength in almost all the exercises assessed with the 1 RM test, which occurred possibly because of neuromuscular and organism adaptation.

A study by Filho N. J. B. A. et al.¹⁰:

CKD is a severe consequence of overweight and obesity, of which both are strongly associated with the accumulation of visceral adiposity, the development of hypertension, and the predisposition to diabetes. Another necessary consequence of CKD is reducing functional capacity that directly influences patients' independence and quality of life. The decrease in physical function is because patients on haemodialysis have multiple metabolic and nutritional alterations that favour developing a different type of malnutrition called "protein-energy wasting" characterized by abnormalities in skeletal muscle. The changes are due to the haemodialysis treatment, the chronic inflammatory process, metabolic acidosis, and insulin resistance. Each of these conditions activates molecular signalling pathways that promote protein degradation, muscle atrophy, and protein synthesis suppression. Resistance exercise promotes an anabolic environment that increases the subjects' muscle mass, muscle strength, muscle catabolism, inflammatory environment, and a reduction in protein-caloric loss.

A study by Rosa C.S. et al.¹¹:

Even though upper body exercises were prescribed in this study, no statistically significant changes were observed in upper body composition and handgrip strength. This may be due to low training volume because only three small muscle groups were exercised in the upper body (biceps, back and shoulder) and low adherence to upper limb training.

The use of exercises for the upper limbs in this population is a major challenge as arteriovenous fistulas in the upper limbs accomplish vascular access in most patients, which does not allow patients to exercise both arms during haemodialysis. This study showed an increase in the number of repetitions in the sit to stand test, which could be related to the rise in the strength gains of the lower limbs, as resistance exercise has proven to be effective among this population. While improving leg strength, resistance training adaptations do not involve the cardiorespiratory pathways.

Conclusion:

This systematic review has provided an overview of the recent literature on resistance exercises' role and their effect on various parameters in patients undergoing haemodialysis. The studies show that resistance exercises help improve the handgrip, functional leg strength and the physical functional components of the kidney disease quality of life questionnaire. Future studies are required to design a structured protocol of the resistance exercises for haemodialysis patients, which can be either done within the first 2 hours of the haemodialysis session or after the haemodialysis session completed.

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