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Meta-Analysis

Effects of Physical Exercise on Inflammatory Biomarkers in Patients with Chronic Kidney Disease: A Meta-Analysis

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ABSTRACT

Chronic Kidney Disease (CKD) is found to be associated with systemic inflammation with increased levels of inflammatory biomarkers which increases the risk of cardiovascular events in these patients. This systematic review and meta-analysis was done to assess the effects of exercise on inflammatory biomarkers in patients with CKD. PubMed, Google Scholar, Scopus and PEDro databases were systematically searched. All published articles till March 2023 were included in this review. Of the articles retrieved 15 were included in qualitative analysis and among them 9 were quantitatively analysed. Included studies were of fair and good quality on PEDro rating scale. Cochrane Collaboration tool of risk of bias was used to assess the risk of bias. Results of the analysis suggested that exercise is effective in lowering the level of inflammatory C-reactive protein (CRP) level. The result was statistically significant (mean difference = -1.51, 95% CI: -2.23 to -0.79, I^2= 71%, p-value 0.004). For tumour necrosis factor (TNF- α) the differences were found statistically significant (mean difference = -0.67, 95 % CI: -1.31 to -0.03, I^2= 81%, p-value <0.001). For Interleukins (IL) -6 the result was statistically significant (mean difference = -0.68, 95% CI: -1.74 to 0.37, I^2= 61%, p-value <0.001). For IL-10 the result was statistically significant (mean difference = 1.80, 95% CI: 0.18, 3.42, I^2= 95%, p-value <0.001). It is concluded that various exercises like aerobic training, resistance training and inspiratory muscle training balance training have a significant effect on reducing the inflammation in patients with CKD and thereby helps in reducing the cardiac events among these subjects.

Keywords: Aerobic Exercise, Biomarkers, Chronic Renal Insufficiency, Exercise, Inflammation, Resistance Training.

INTRODUCTION

Globally, Chronic Kidney Disease (CKD) is an emerging public health problem nowadays because of its association with high morbidity and mortality. It poses a significant burden on individuals, families and societies as a whole.[1] CKD is caused by a variety of diverse disease processes that, over the course of months or years, irreversibly affect the structure and function of the kidney. The presence of structural kidney damage and a persistent decline in renal function is necessary for the diagnosis of CKD. Glomerular filtration rate (GFR), which measures the total volume of fluid that is passed through all of the working nephrons in a given amount of time, is the best indicator currently known of kidney function as a whole. The definition and classification of CKD have changed over time, but according to the most recent international recommendations, it is defined as having a GFR of less than 60 mL/min per 1.7 m^2 or indicators of kidney damage, or both, for at least three months.[2] The condition is characterized by impaired capacity of the kidneys to remove waste from the blood. Patients with CKD may consequently develop bodily inflammation, which can result in a number of complications. Inflammatory biomarkers can be used to track inflammation in people with CKD. Patients with CKD frequently have elevated levels of circulating inflammatory indicators including C-reactive protein

(CRP), Interleukins: IL-1, IL-6, IL-10, and tumour necrosis factor (TNF- α).[3] Chronic, low-grade inflammation has been identified as a key factor in the pathophysiology of CKD, playing a special role in mortality from cardiovascular and other causes as well as the progression of protein-energy wasting. Intestinal dysbiosis, oxidative stress, chronic and recurrent infections, altered metabolism of adipose tissue, and increased production and decreased clearance of pro-inflammatory cytokines are just a few of the factors that contribute to chronic inflammatory status in CKD.[4,5] Therefore, early and effective management of inflammation is crucial for reducing CKD-related morbidity. Moreover, a significant correlation between healthcare expenses and the severity of CKD has been reported. For these reasons, effective CKD management is crucial to preventing renal failure, extending healthy life expectancy, and lowering medical expenses.

Many therapies, such as pharmaceutical medications, lifestyle changes, and dialysis optimization, have been suggested to target inflammation in CKD. Regardless of the kind of treatment used, low levels of physical activity and poor physical functioning are substantially linked to mortality and subpar therapeutic results in adult patients with CKD.[6]

Physical exercise plays a major role in the treatment of CKD patients. It has been observed that physically active CKD patients have a lower risk of death as compared to sedentary patients. Exercise increases functional ability and lowers inflammatory markers and cardiovascular risk in CKD patients.[7] An inverse relationship has been observed between inflammatory marker concentration and regular physical activity.[8] Regular moderate-intensity exercise has been shown to improve numerous aspects of immune function and have anti-inflammatory benefits because it is associated with low levels of pro-inflammatory cytokines and high levels of anti-inflammatory cytokines.[9] A study reported intradialytic aerobic cycling exercise for three months to be effective in lowering IL-6 and CRP levels.[10] Regular exercise has confirmed the potential systemic anti-inflammatory effects by decreasing the plasma IL-6 and increasing IL-10 concentration. IL-10 is an important antiinflammatory immune cytokine that lowers the risk of cardiovascular events in patients with CKD.[11]

Various systematic reviews reported the effects of different types of exercises on physical function, physical fitness, functional capacity and health-related quality of life in CKD.[12-14] However, the effect of physical exercise on inflammatory biomarkers has not been explored much. The investigation of the effect of physical exercise on inflammatory biomarkers is clinically very important as raised inflammatory biomarkers may increase the risk of cardiovascular events and mortality. Therefore, this systematic review and meta-analysis aimed to evaluate the effects of physical exercise on inflammatory biomarkers among patients with CKD.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed for conducting this systematic review and meta-analysis.[15] This review was registered under the International Prospective Register of Systematic Reviews (PROSPERO) with Registration number CRD42023404711.

Eligibility Criteria:

Studies were considered if they fulfilled the following eligibility criteria:

Type of Studies:

(a) All full-text original manuscripts written in the English language and published in peer-reviewed journals.
(b) Study designs as Randomized control trials and case-control studies
(c) All exercise intervention studies carried out with CKD patients of either gender with concurrent control groups and at least two groups examining the impacts of physical activity performed for at least four weeks (including aerobic training, resistance training, respiratory muscle training, or physical activities exercise) on inflammatory markers (CRP, IL-6, IL-10, and TNF-a).
(d) Reviews, editorials, animal experiments, and comments were excluded.

Type of Participants:

Studies that enrolled adults with CKD (age >18 years) who had never participated in an exercise program before entering the trial. This review did not include participants from researches published in conferences, abstracts, and study protocols.

Search Sources:

We searched four databases: PubMed, Google Scholar, Scopus and PEDro for articles related to effect of physical exercise training on inflammatory biomarkers in CKD patients from inception till February 2023.

Search Strategy:

A combination of Mesh and free-text terms related to the keywords was used in the searches.

(((("CKD"[All Fields] OR "Chronic Kidney Disease"[All Fields] OR "Chronic Renal Disease"[All Fields] OR "Renal Disease"[All Fields] OR "Kidney disease"[All Fields] OR "hemodialysis"[All Fields] OR "renal dialysis"[All Fields] OR "Kidney dialysis"[All Fields]) AND "exercise"[MeSH Terms]) OR "exercise"[All Fields] OR "exercises"[All Fields] OR "exercise therapy"[MeSH Terms] OR ("exercise"[All Fields] AND "therapy"[All Fields]) OR "exercise therapy"[All Fields] OR "exercise s"[All Fields] OR "exercised"[All Fields] OR "exerciser"[All Fields] OR "exercisers"[All Fields] OR "exercising"[All Fields]) OR "Exercise training"[All Fields] OR "Exercise training"[All Fields] OR "Resistance training"[All Fields] OR "Aerobic training"[All Fields] OR "Inspiratory Muscle Training"[All Fields]) AND "Inflammatory biomarkers"[All Fields] OR ("biomarkers"[All Fields] OR "biomarkers"[MeSH Terms] OR "biomarkers"[All Fields] OR "biomarker"[All Fields] OR "TNF-alphalevel"[All Fields] OR ("interleukin 6"[MeSH Terms] OR "interleukin 6"[All Fields] OR "IL 6"[All Fields]) OR ("interleukin 10"[MeSH Terms] OR "interleukin 10"[All Fields] OR "IL10"[All Fields]))).

Data Extraction:

Based on keyword searches, Potentially relevant published articles in peer-reviewed journals were originally found. Following this, titles and abstracts of the articles were screened independently by two co-authors (SP and SK), Following the predetermined inclusion and exclusion criteria, and ultimately the pertinent articles that were closely related to the objective of the review were included and any discrepancies were resolved with consensus.

Author, publication year, country, demographic information about the participants (such as the number of cases and controls, gender, and mean age), exercise intervention characteristics and mean and standard deviation (SD) of continuous outcomes at baseline, post-intervention, and/or changes between baseline and post-intervention were obtained from all the studies and added into excel spreadsheets.

Quality and Risk of Bias Assessment:

Physiotherapy Evidence Database (PEDro) quality scale was used to assess the quality of the included studies.[16] The quality evaluation was carried out independently by two co-authors (PA and MS). This review included studies that had a PEDro score of 5 or more. Information was retrieved from the included studies regarding random allocation, allocation concealment, blinding of subjects, therapist and accessor, similar baseline, the incomplete outcome of data, selective reporting, and other sources of bias.

Data Analysis:

Review Manager 5.3 (RevMan 5.3), a Cochrane Collaboration's Software was used to perform meta-analysis. To determine the efficacy of therapy, the mean change from baseline to end of the study in the inflammatory biomarkers was compared between the experimental group and control group. Weight %, mean difference, 95% confidence interval (CI), and the overall effect were calculated by documenting the value of the mean, (SD) and total number of subjects in the experimental group and control group. Forest plots were generated for different inflammatory biomarkers. The heterogeneity of treatment effects between studies was assessed by the $\chi 2$ test and I2- statistic (degree of heterogeneity). The data analysis was performed by co-author RR.

RESULTS

Search Results:

The electronic databases search from PubMed, Google Scholar, Scopus and PEDro yielded 3274 articles. There were 3029 articles that remained after the removal of duplication. Of 3029 papers, 2875 were eliminated by reading the titles or abstracts since they did not meet the criteria for the current review. Thirty Six full-text articles were assessed for eligibility. Out of these twenty one more articles were excluded, and seven articles were excluded because of no comparison of exercise with the control group for any of the study variables. Furthermore, five articles were excluded because of the unavailability of data in terms of mean and SD. Nine articles were excluded because they studied only the acute effects of exercise. Figure 1 represents the flow chart for the study selection.

Study Characteristics:

Characteristics of the included studies are presented in Table 1. Out of 15 included studies 5 studies were conducted in Brazil,[7,19,20,23,28] four studies were conducted in England,[11,21,25,26] two in China, [8,22] and one each in Greece,[17] Taiwan,[10] and Japan.[27] Subjects in these included studies underwent aerobic training,[7,10,11,21,22,24-27] resistance training,[18,20,28] and respiratory muscle training.[23] From the included studies 368 subjects were in the exercise group and 341 subjects were in the control group.

Quality and Risk of Bias Assessment:

The PEDro rating scale was used to evaluate the quality of included studies as encapsulated in Table 2.[16] All the included studies had a score of 6 or more except one study scoring 5, which evidenced that the included studies were of fair (4-5), good (6-8) and excellent (9-10) quality. The cochrane risk of bias tool was used to assess the risk of bias assessment in the included studies and is represented in Figure 2 and 3.

Table 1: Characteristic of the included studies

S. No	Authors	Study Location	Design of Study	Sample Size	Age (years)	Treatmnt	Outcomes	Results
1	Sovatzidis A. et al. 2020 (17)	Greece	Experimental study design	20 C= 10 E= 10	35.7-69.9	C= Received only HD E= Performed bedside cycle ergometer intradialytic cardiovascular exercise training	VO_2 peak, functional capacity, quality of life and inflammation	Increased VO_2 peak by 15%, functional capacity and quality of life improved by 4-13% and hs-CRP reduced by 15 % in training group
2	Cruz L.G. et al. 2018 (7)	Brazil	Randomized clinical trial	30 C= 15 E= 15	18-65	C= Routine daily activities E= Intradialytic aerobic training at severe intensity (Borg 6-7)	BMI, inflammatory biomarkers and cardiorespiratory fitness	Significant reduction of serum levels of interleukin-1β, interleukin-6, interleukin-8, tumor necrosis factor and an increase in serum level of interleukin-10 and functional capacity in exercise group
3	Liao M.T. et al 2016 (10)	Taiwan	Randomized controlled trial	40 C= 20 E= 20	53-71	C= Routine haemodialysis E= Cyclic aerobic training at intensity of 12-15 Borg Scale of Perceived Exertion Scale	Inflammatory markers, biochemical markers, nutritional status and serum endothelial progenitor cells count, Bone mineral density and functional capacity	Significant improvement in biochemical markers, BMI, inflammatory cytokine levels, number of serum endothelial progenitor cells and functional capacity was observed in exercise group as compared to control group
4	Viana J. L. et al. 2014 (11)	England	Randomized controlled trial	24 C= 11 E= 13	40- 72	C= Subjects continued with usual physical activities E= Home based exercise program at an intensity of somewhat hard (RPE; 12-14)	Inflammatory biomarkers	Anti-inflammatory effects were observed after regular exercises
5	Dong Z. J. et al. 2019 (18)	China	Randomized controlled trial	41 C= 20 E= 21	18-80	C= Routine haemodialysis care E= Performed progressive moderate or high intensity intradialytic resistance training	Inflammatory biomarkers	Reduced micro inflammatory reactions were observed after intradialytic resistance exercise training
6	Silva V.R.O.et al. 2019 (19)	Brazil	Randomized clinical trial	30 C=15 E=15	32-73	C= Routine haemodialysis E= Aerobic training with a cycloergometer with intensity of 65-75 % and Borg scale score at 13	Physical activity, VO_2 max, heart rate reserve and inflammatory biomarkers	Significant reduction of serum aldosterone occur in exercise group and CRP was found to increase in control group
7	Correa H. L. et al. 2020 (20)	Brazil	Randomized controlled trial	55 C= 25 E= 30	50-70	C= Routine haemodialysis E= Periodized interdialytic resistance training of upper and lower limb at an intensity of 6-8 perceived exertion on OMNI-Res Scale	Redox profile, inflammatory biomarkers, endothelial functions	Resistance training significantly improved the sleep quality, redox profile and biomarkers of inflammation and endothelial function

8	Ikizler T. A. et al. 2018 (21)	England	Randomized clinical trial	53 C= 26 E= 27	48-64	C= Usual diet E= Aerobic training	Inflammatory biomarkers	Significant reduction in inflammatory biomarkers
9	Zaho C. et al. 2017 (22)	China	Randomized controlled trial	126 C= 63 E= 63	42-67	C= Routine medicine E= Aerobic training by bicycle riding	Inflammatory biomarkers, quality of life and depression severity	Serum IL -6, IL-8 and depression severity reduced significantly and quality of life improved in aerobic group than control group
10	Campos N. G. et al. 2017 (23)	Brazil	Randomized controlled trial	41 C=12 E=29	36-64	C= Routine haemodialysis E= Respiratory muscle training	Oxidative stress biomarkers, pulmonary functions	Respiratory muscle training yielded improvement in pulmonary functions and reduced the serum biomarkers
11	Elshinnawy H.A. et al. 2021 (24)	Egypt	Experimental Study Design	40 C= 20 E=20	20-70	C= Routine haemodialysis E= Intradialytic aerobic cycling training	Physical performance and inflammatory biomarkers	Significant increase in physical performance and reduction of serum CRP and IL-6 levels was observed in exercise group
12	March D.S. et al. 2021 (25)	England	Randomized controlled trial	92 C= 46 E= 46	38-75	C= Usual care E= Intradialytic aerobic cycling training with usual care	Circulating cytokine	No significant differences were observed in circulating cytokines between intradialytic cycling group and control group following 6 month of intradialytic cycling program
13	Highton P.J. et. al. 2022 (26)	England	Experimental Study Design	40 C= 20 E= 20	33-75	C= Routine haemodialysis E= Moderate intensity intradialytic aerobic cycling training	Circulating micro particles, cytokines and chemokines	No significant differences were observed in circulating micro particles, cytokines and chemokines following six months of moderate intensity IDC
14	Uchiyama K. et. al. 2021 (27)	Japan	Randomized controlled trial	46 C= 23 E=23	69-79	C= Usual care E= Home based aerobic training at 40-60% peak hear rate and resistance training at 70% RM twice weekly in addition to usual care	Aerobic capacity, heath related quality of life, renal functions and inflammation	Significant improvement was observed in aerobic capacity and health related quality of life in exercise group as compared to control group. There was significant reduction in CRP in exercise group as compared to control group
15	Araujo T.B. et al 2023 (28)	Brazil	Randomized controlled trial	31 C= 15 E= 16	52-65	C= Usual care E= Supervised home based progressive resistance training for 22 weeks	Functional capacity, bone mineral density, uremic profile, inflammation, glycemic homeostasis, and redox balance	Significant improvement in functional performance, bone density, glycaemic homeostasis, uremic profile and anti-inflammatory markers were seen after twenty two weeks of resistance training as compared to control group

C: Control Group, E: Exercise Group, HD: Haemodialysis, BMI: Body Mass Index, VO_2: Oxygen uptake, CRP: C reactive protein, RPE: Rate of perceived Exertion, Hs: high-sensitivity, IL: Interleukin, IDC: Intradialytic Cycling, RM: Repetition Maximum

Table 2: Assessment of quality of studies by PEDro scoring

Author, year	Ref	Eligibility Criteria	Random Allocation	Concealed Allocation	Similar Baseline	Subject Blinding	Therapist Blinding	Assessors Blinding	Key Measures Outcome from >85% cases	Intention to Treat Analysis of at Least One Key Outcome	Between Group Statistical Comparison of at Least One Key Outcome	Variability for at Least one Key Outcome	Total
Sovatzidis A. et al. 2020	17	Yes	Yes	No	Yes	No	No	No	No	No	Yes	Yes	5/11
Cruz L.G. et al. 2018	7	Yes	Yes	No	Yes	No	No	No	Yes	No	Yes	Yes	6/11
Liao M.T. et al 2016	10	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes	7/11
Viana J. L. et al. 2014	11	Yes	No	No	Yes	No	No	No	Yes	Yes	Yes	Yes	6/11
Dong Z. J. et al. 2019	18	Yes	Yes	No	Yes	No	No	No	Yes	No	Yes	Yes	6/11
Silva V.R.O. et al. 2019	19	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8/11
Correa H. L. et al. 2020	20	Yes	Yes	No	Yes	Yes	No	No	No	Yes	Yes	Yes	7/11
Ikizler T. A. et al. 2018	21	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes	7/11
Zaho C. et al. 2017	22	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes	7/11
Campos N. G. et al. 2017	23	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes	7/11
Elshinnawy H.A. et al. 2021	24	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes	7/11
March D.S. et al. 2021	25	Yes	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	8/11
Highton P.J. et. al. 2022	26	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	9/11
Uchiyama K. et. al. 2021	27	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	9/11
Araujo T.B. et al 2023	28	Yes	Yes	No	Yes	No	No	No	Yes	No	Yes	Yes	6/11

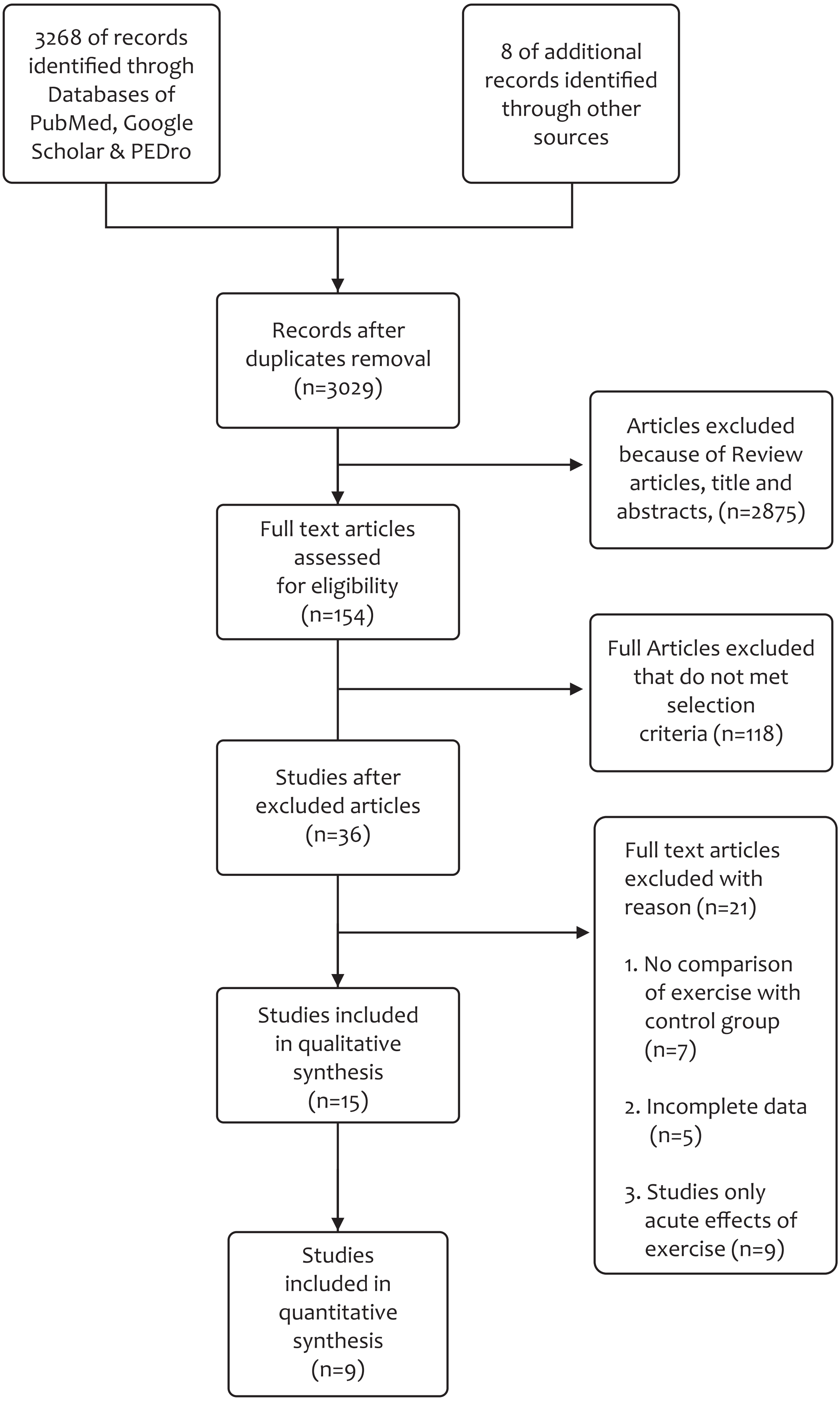

Figure 1: Flowchart for studies selection process according to PRISMA guidelines

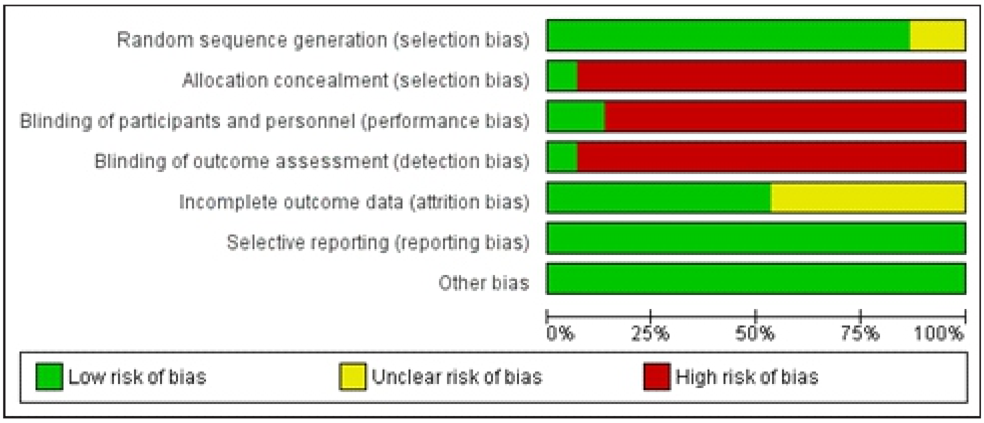

Figure 2: Risk of bias graph

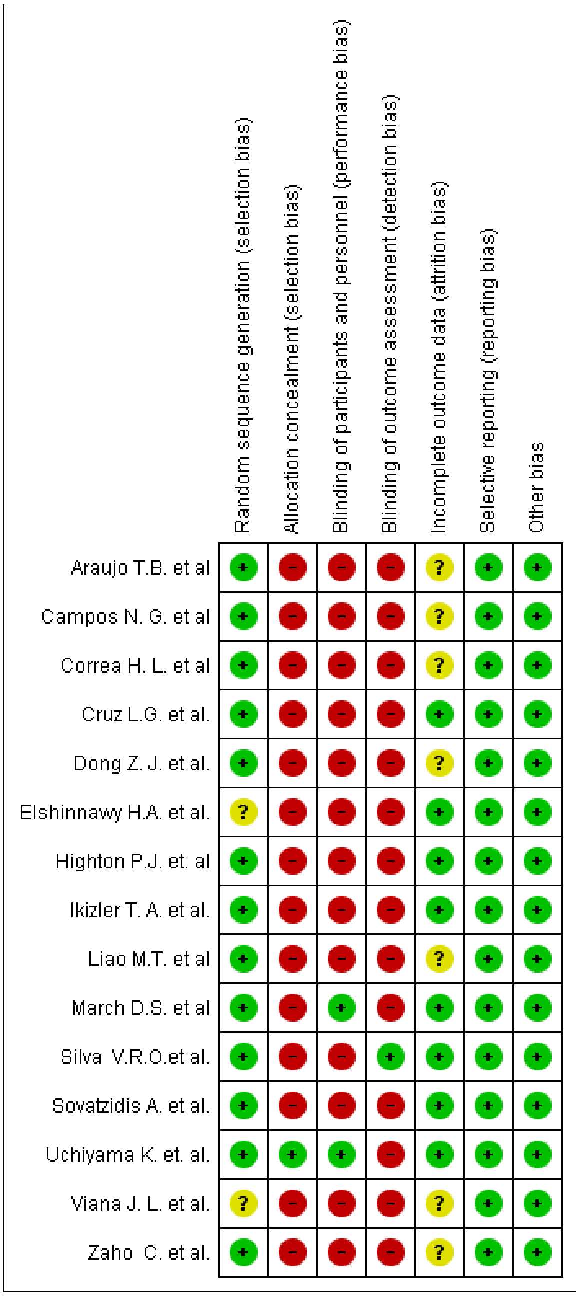

Figure 3: Risk of bias summary

Meta-analysis:

Six studies were included in the meta-analysis with outcome measure CRP level to compare the effectiveness of exercise in the Experimental Group and Control Group. Results of the analysis suggested that exercise is effective in lowering the level of inflammatory CRP level. The result was statistically significant at p-value < 0.05 (mean difference = -1.51, 95% CI: -2.23 to -0.79) with a substantial amount of heterogeneity (I2= 71%, p-value 0.004). (Figure 4)

	Experimental			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Araujo T.B. et al	5.84	1.6	16	8.28	1.61	15	16.8%	-2.44 [-3.57, -1.31]
Elshinnawy H. A. et al	5.3	1.31	20	7.7	1.11	20	21.8%	-2.40 [-3.15, -1.65]
March D.S. et al.	15.76	33.3	46	13.8	18.39	46	0.4%	1.96 [-9.03, 12.95]
Silvia VRO et al.	0.6	0.2	15	1.5	0.89	15	25.5%	-0.90 [-1.36, -0.44]
Uchiyama K. et. al.	-0.85	0.96	23	0.57	1.47	23	22.3%	-1.42 [-2.14, -0.70]
Viana J. L. et al.	2.6	2.5	13	2.9	0.89	11	13.2%	-0.30 [-1.76, 1.16]
Total (95% CI)			**133**			**130**	**100.0%**	**-1.51 [-2.23, -0.79]**

Heterogeneity: Tau² = 0.48; Chi² = 17.06, df = 5 (P = 0.004); I² = 71%
Test for overall effect: Z = 4.09 (P < 0.0001)

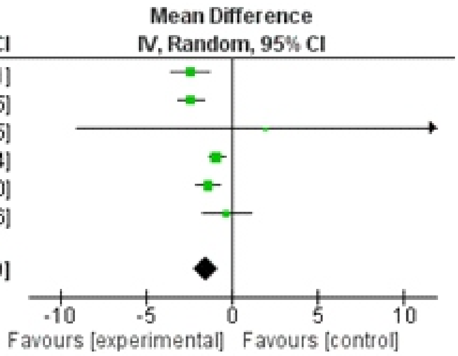

Figure 4: Comparison of CRP level between experimental and control group

Four Studies were included in meta-analysis with the TNF-α as an outcome measure to compare the effectiveness of exercise with the control group. The differences were found statistically significant (p-value <0.05) (mean difference = -0.67, 95 % CI: -1.31 to -0.03) but with a substantial amount of heterogeneity (I^2= 81%, p-value <0.001). (Figure 5)

	Experimental			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Araujo T.B. et al	19.3	4.92	16	23.99	4.29	15	3.9%	-4.69 [-7.93, -1.45]
Correa H.L. et al.	14.55	4.78	30	16.52	6.25	25	4.6%	-1.97 [-4.96, 1.02]
Cruz L.G. et al.	11.04	2.57	15	14.87	3.87	15	7.5%	-3.83 [-6.18, -1.48]
March D.S. et al.	6.11	1.37	46	6.24	2	46	84.0%	-0.13 [-0.83, 0.57]
Total (95% CI)			**107**			**101**	**100.0%**	**-0.67 [-1.31, -0.03]**

Heterogeneity: Chi² = 15.85, df = 3 (P = 0.001); I² = 81%
Test for overall effect: Z = 2.04 (P = 0.04)

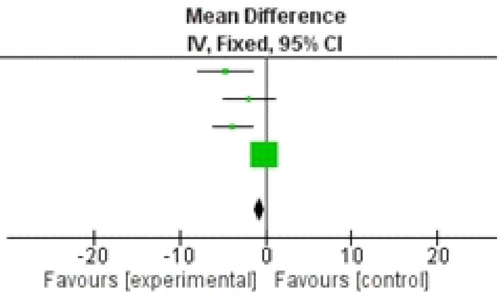

Figure 5: Comparison of TNF-α level between experimental and control group

Seven Studies were included in the meta-analysis of IL-6 as an outcome measure. The result was statistically significant at (p- value < 0.05) (mean difference = -0.68, 95% CI: -1.74 to 0.37) with a substantial amount of heterogeneity (I^2= 61%, p-value <0.001) (Figure 6).

	Experimental			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Araujo T.B. et al	13.14	3.53	16	15.99	3.23	15	12.1%	-2.85 [-5.23, -0.47]
Cruz L.G. et al.	5.45	3.4	15	4.8	5.55	15	7.7%	0.65 [-2.64, 3.94]
Elshinnawy H. A. et al	251	123.5	20	395	161.5	20	0.0%	-144.00 [-233.10, -54.90]
Liao MT et al.	3.48	2.95	20	4.4	2.15	20	18.3%	-0.92 [-2.52, 0.68]
March D.S. et al.	3.17	2.73	46	3.11	2.31	46	24.3%	0.06 [-0.97, 1.09]
Uchiyama K. et. al.	0.92	0.65	23	1.31	0.82	23	30.1%	-0.39 [-0.82, 0.04]
Viana J. L. et al.	8.1	4.3	13	9.4	4.1	11	7.5%	-1.30 [-4.67, 2.07]
Total (95% CI)			**153**			**150**	**100.0%**	**-0.68 [-1.74, 0.37]**

Heterogeneity: Tau² = 0.91; Chi² = 15.87, df = 6 (P = 0.01); I² = 62%
Test for overall effect: Z = 1.27 (P = 0.20)

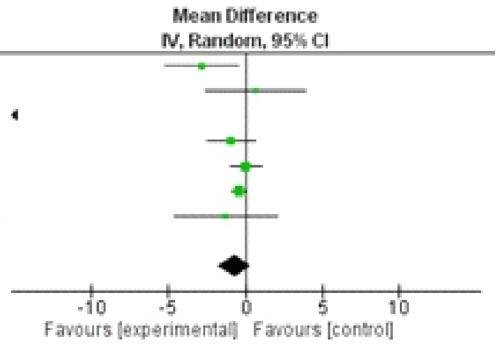

Figure 6: Comparison of IL-6 level between experimental and control group

Five Studies were included in the meta-analysis of IL-10 as an outcome measure. The result was statistically significant at (p-value < 0.05) (mean difference = 1.80, 95% CI: 0.18, 3.42) with a considerable amount of heterogeneity (I^2 = 95%, p-value <0.001) (Figure 7).

	Experimental			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Araujo T.B. et al	8.76	1.53	16	5.36	1.25	15	20.4%	3.40 [2.42, 4.38]
Correa H.L. et al.	8.54	2.7	30	6.15	2.58	25	19.0%	2.39 [0.99, 3.79]
Cruz L.G. et al.	2.72	1.58	15	0.93	0.58	15	20.8%	1.79 [0.94, 2.64]
March D.S. et al.	0.46	0.24	46	0.54	0.37	46	22.1%	-0.08 [-0.21, 0.05]
Viana J. L. et al.	5.6	2.7	13	3.9	1.5	11	17.7%	1.70 [-0.01, 3.41]
Total (95% CI)			**120**			**112**	**100.0%**	**1.80 [0.18, 3.42]**

Heterogeneity: Tau² = 3.09; Chi² = 79.14, df = 4 (P < 0.00001); I² = 95%
Test for overall effect: Z = 2.18 (P = 0.03)

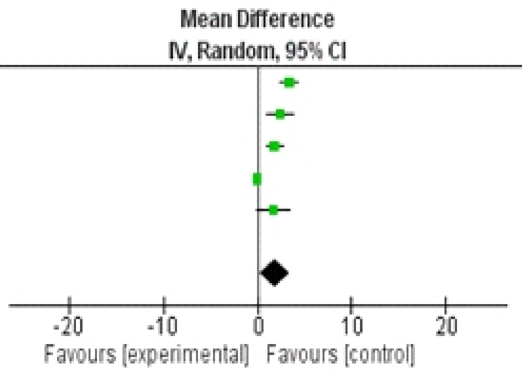

Figure 7: Comparison of IL-10 level between experimental and control group

DISCUSSION

CKD is a progressive condition that can lead to End Stage Renal Disease (ESRD) if left untreated. Due to increased cardiovascular disease (CVD) risk factors brought on by elevated levels of inflammatory biomarkers and cytokines, patients with CKD are more likely to suffer morbidity and mortality. Cytokines are proven to be the chief controllers of subject response to infection and inflammation and play a significant role in the development of arterial disease and mortality in CKD patients.[29] This systematic review and meta-analysis evaluated the effectiveness of different exercises on inflammatory biomarkers in CKD patients. Results of the meta-analysis showed that physical activity and exercises can have positive effects on inflammatory biomarkers i.e. CRP, TNF-αlevel, IL-6 and IL-10 as outcome measures. Fifteen studies incorporating different types of exercises for CKD patients were included in this review.

The immune system is severely compromised in people with CKD, which results in immunological depression, increased susceptibility to infections, chronic inflammation, and oxidative stress. Chronic infection and high levels of oxidative stress are key factors for increasing the risk of cardiovascular events and the progression of CKD.[30] It is observed that an increased level of CRP in CKD patients enhances the risk of cardiovascular events and decreases renal function. [31] The inflammation assessed by CRP levels is found to be related to endothelial dysfunction and atherosclerotic changes in subjects with CKD.[32] Regular exercise reduces the CRP level by a reduction in body fat mass and adipose tissue inflammation, thereby reducing the risk of cardiovascular events in CKD patients. In this review, aerobic training has been found to reduce the CRP level.[11,19]

In CKD patients IL-6 is found to increase an association with reduced muscle strength. Exercise increases muscle strength and maintains the balance between inflammation and CK levels.[33] In the present review, three studies showed that aerobic training helped to reduce the level of IL-6.[3,5,6] It has been suggested that aerobic training leads to an increase number of circulating regulatory T cells and reduced the levels of pro-inflammatory circulating markers and increased an anti-inflammatory cytokine.[7]

It is observed that IL-6 exerts anti-inflammatory effects mainly when this marker is synthesized and released from myocytes during skeletal muscle contraction. IL-6 exerts anti-inflammatory effects by inhibiting the production of pro-inflammatory markers such as TNF-αand IL-8.[34] Aerobic and resistance training have been found to reduce the level of pro-inflammatory biomarkers as measured by TNF-α (3, 14). IL-10 plays a significant role in normal kidney function with anti-inflammatory and immunomodulatory function and helps to control inflammation and instruct adaptive immune system and protect the subjects from bacterial, viral, and other pathogens.[35] Increased levels of IL-10 in the exercise group indicate the anti-inflammatory effects of exercise (IL-10) is a cytokine with potent anti-inflammatory properties that plays a central role in limiting host immune response to pathogens, thereby preventing damage to the host and maintaining normal tissue homeostasis.[36] A study conducted by Adhr and Kader in 2022 showed similar results and suggested that exercise training promotes the modulation of inflammatory cytokines and reduces the systemic inflammation.[37] Hence, the present systematic review and meta-analysis strengthens the existing literature of evidence which states that regular exercise alleviates inflammation in patients with CKD. Results of the present study recommend that regular physical exercises should be incorporated in the form of resistance, aerobic, respiratory muscle training, and physical activity like walking to reduce inflammation and the risk of cardiovascular events, and improve renal functions. Due to the limitation of incomplete outcome reporting in the included studies, all the outcomes assessed were not included in the meta-analysis.

CONCLUSION

Based on the findings of the present meta-analysis, it can be concluded that exercise yields a significant reduction in inflammatory biomarkers in patients with CKD.

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REFERENCES

1. Van der Velde M, Matsushita K, Coresh J, Astor BC, Woodward M, Levey A, et al Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. Kidney Int 2011; 79:1341-52. doi:10.1038/ki.2010.536
2. Webster AC, Nagler EV, Morton RL, Masson P. Chronic Kidney Disease. Lancet 2017; 389 :1238-52. doi:10.1016/S0140-6736(16)32064-5
3. Peres A, Perotto DL, Dorneles GP, Fuhro MI, Monteiro MB. Effects of intradialytic exercise on systemic cytokine in patients with chronic kidney disease. Ren Fail 2015; 37:1430-4. doi:10.3109/0886022X.2015.1074473
4. Mihai S, Codrici E, Popescu ID, Enciu AM, Albulescu L, Necula LG, et al. Inflammation-related mechanisms in chronic kidney disease prediction, progression, and outcome. J Immunol Res 2018; 2018:2180373. doi:10.1155/2018/2180373
5. Akchurin OM, Kaskel F. Update on inflammation in chronic kidney disease. Blood Purif 2015; 39:84-92. doi:10.1159/000368940
6. Painter P, Roshanravan B. The association of physical activity and physical function with clinical outcomes in adults with chronic kidney disease. Curr Opin Nephrol Hypertens 2013; 22:615-23. doi:10.1097/MNH.0b013e328365b43a
7. da Cruz LG, Zanetti HR, Andaki AC, Mota GR, Neto OB, Mendes EL. Interdialytic aerobic training improves inflammatory markers in patients with chronic kidney disease. A randomized clinical trial. Motriz Rio Claro 2018; 24:1-5. doi:10.1590/s1980-657420180003e017517
8. Kasapis C, Thompson PD. The effects of physical activi-ty on serum C-reactive protein and inflammatory markers: a systematic review. J Am Coll Cardiol 2005; 45:1563-9. doi:10.1016/j.jacc.2004.12.077
9. Gleeson M, Bishop NC, Stensel DJ, Lindey MR, Mastana SS, Nimmo MA. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. Nat Rev Immunol 2011; 11:607-15. doi:10.1038/nri3041
10. Liao MT, Liu WC, Lin FH, Huang CF, Chen SY, Liu CC, et al. Intradialytic aerobic cycling exercise alleviates inflammation and improves endothelial progenitor cell count and bone density in hemodialysis patients. Medicine (Baltimore) 2016 ; 95:e4134. doi:10.1097/MD.0000000000004134
11. Viana JL, Kosmadakis G C, Watson E L, Bevington A, Feehally J, Bishop NC, et al. Evidence for anti-inflammatory effects of exercise in CKD. J Am Soc Nephrol 2014 ; 25:2121-30. doi:10.1681/ASN.2013070702
12. Heiwe S, Jacobson SH. Exercise training for adults with chronic kidney disease. Cochrane Database Syst Rev 2011; 2011:CD003236. doi:10.1002/14651858.CD003236
13. Heiwe S, Jacobson SH. Exercise training in adults with CKD: a systematic review and meta-analysis. Am J Kidney Dis 2014; 64:383-93. doi:10.1053/j.ajkd.2014.03.020
14. Pei G, Tang Y, Tan L, Tan J, GeL, Qin W. Aerobic exercise in adults with chronic kidney disease (CKD): a meta-analysis. Int Urol Nephrol 2019; 51:1787-795. doi:10.1007/s11255-019-02234-x
15. Arya S, Kaji AH, Boermeester MA. PRISMA Reporting Guidelines for Meta-analyses and Systematic Reviews. JAMA Surg 2021; 156:789-90. doi:10.1001/jamasurg.2021.0546
16. PEDro Physiotherapy Evidence. [Internet] 2023. Available from https://www. scholar.google.com.pk/scholar?q=16.+PEDro+Physiotherapy+Evidence.+PEDro+Physiotherapy+evidence
17. Sovatzidis A, Chatzinikolaou A, Fatouros IG, Panagoutsos S, Draganidis D, Nikolaidou E, et al. Intradialytic cardiovascular exercise training alters redox status,

reduces inflammation and improves physical performance in patients with chronic kidney disease. Antioxidants (Basel) 2020; 9:868. doi:10.3390/antiox9090868

18. Dong ZJ, Zhang HL, Yin LX. Effects of intradialytic resistance exercise on systemic inflammation in maintenance hemodialysis patients with sarcopenia: a randomized controlled trial. Int Urol Nephrol 2019; 51:1415-24. doi:10.1007/s11255-019-02200-7
19. Oliveira E Silva VR, Stringueta -Belik F, Hueb JC, de Souza -Gonçalves R, Costa Teixeira Caramori J, Perez Vogt B, et al. Aerobic exercise training and nontraditional cardiovascular risk factors in hemodialysis patients: results from a prospective randomized trial. Cardiorenal Med 2019; 9:391-9. doi:10.1159/000501589
20. Correa HL, Moura SR, Neves RV, Tzanno-Martins C, Souza MK, Haro AS, et al. Resistance training improves sleep quality, redox balance and inflammatory profile in maintenance hemodialysis patients: a randomized controlled trial. Sci Rep 2020; 10:11708. doi:10.1038/s41598-020-68602-1
21. Ikizler TA, Robinson-Cohen C, Ellis C, Headley SA, Tuttle K, Wood R, et al. Metabolic Effects of Diet and Exercise in Patients with Moderate to Severe CKD: A Randomized Clinical Trial. J Am Soc Nephrol 2018; 29:250-9. doi:10.1681/ASN.2017010020
22. Zhao C, Ma H, Yang L, Xiao Y. Long-term bicycle riding ameliorates the depression of the patients undergoing hemodialysis by affecting the levels of interleukin-6 and interleukin-18. Neuropsychiatr Dis Treat 2016; 13:91-100. doi:10.2147/NDT.S124630
23. Campos NG, Marizeiro DF, Florencio AC, Silva IC, Meneses GC, Bezerra GF, et al. Effects of respiratory muscle training on endothelium and oxidative stress biomarkers in hemodialysis patients: A randomized clinical trial. Respir Med 2018;134:103-9. doi:10.1016/j.rmed.2017.12.005
24. Elshinnawy HA, Fayez MM, Farrag DA, AbdElgawad MA. The effect of intradialytic exercise on inflammatory markers in hemodialysis patients. Egypt Rheumatol Rehabil 2021; 48:1-6. doi:10.1186/s43166-021-00084-z
25. March DS, Lai KB, Neal T, Graham - Brown MP, Highton PJ, Churchward DR, et al. Circulating endotoxin and inflammation: associations with fitness, physical activity and the effect of a 6-month programme of cycling exercise during haemodialysis. Nephrol Dial Transplant 2022; 37:366-74. doi:10.1093/ndt/gfab178
26. Highton PJ, March DS, Churchward DR, Grantham CE, Young HML, Graham-Brown MPM, et al. Intradialytic cycling does not exacerbate microparticles or circulating markers of systemic inflammation in haemodialysis patients. Eur J Appl Physiol 2022; 122:599-609. doi:10.1007/s00421-021-04846-7
27. Uchiyama K, Adachi K, Muraoka K, Nakayama T, Oshida T, Yasuda M, Home-based aerobic exercise and resistance training for severe chronic kidney disease: a randomized controlled trial. J Cachexia Sarcopenia Muscle 2021; 12:1789-1802. doi:10.1002/jcsm.12775
28. de Araujo TB, de Luca Corrêa H, de Deus LA, Neves RV, Reis AL, Honorato FS et al, The effects of home-based progressive resistance training in chronic kidney disease patients. Exp Gerontol 2023; 171:112030. doi:10.1016/j.exger.2022.112030
29. Abdel-Messeih PL, Alkady MM, Nosseir NM, Tawfik MS. Inflammatory markers in end-stage renal disease patients on haemodialysis. J Med Biochem 2020; 39:481-7. doi:10.5937/jombo-25120
30. Cervantes-Gracia K, Raja K, Llanas-Cornejo D, Cobley JN, Megson IL, Chahwan R, Husi H. Oxidative stress and inflammation in the development of cardiovascular disease and contrast induced nephropathy. Vessel Plus 2020; 4:27. doi:10.20517/2574-1209.2020.22
31. Stuveling EM, Hillege HL, Bakker SJ, Gans RO, De Jong PE, De Zeeuw D. C-reactive protein is associated with renal function abnormalities in a non-diabetic population. Kidney Int 2003; 63:654-61. doi:10.1046/j.1523-1755.2003.00762.x
32. Muslimovic A, Rasic S, Tulumovic D, Hasnspahic S, Rebic D. Inflammatory markers and procoagulants in chronic renal disease stages 1-4. Med Arch 2015; 69:307-10. doi:10.5455/medarh.2015.69.307-310
33. Souza MK, Neves RVP, Rosa TS, Cenedeze MA, Arias SC-A, Fujihara CK, et al. Resistance training attenuates inflammation and the progression of renal fibrosis in chronic renal disease. Life Sci 2018; 206:93-7. doi:10.1016/j.lfs.2018.05.034
34. Cheema BS, Abas H, Smith BC, O'Sullivan AJ, Chan M, Patwardhan A, et al. Effect of resistance training during hemodialysis on circulating cytokines: a randomized controlled trial. Eur J Appl Physiol 2011; 111:1437-45. doi:10.1007/s00421-010-1763-5
35. Sinuani I, Beberashvili I, Averbukh Z, Sandbank J. Role of IL-10 in the progression of kidney disease. World J Transplant 2013; 3:91-8. doi:10.5500/wjt.v3.i4.91
36. Iyer SS, Cheng G. Role of interleukin 10 transcriptional regulation in inflammation and autoimmune disease. Crit Rev Immunol 2012; 32:23-63. doi:10.1615/critrevimmunol.v32.i1.30
37. Aldahr MH, Abd El-Kader SM. Impact of exercise on renal function, oxidative stress, and systemic inflammation among patients with type 2 diabetic nephropathy. Afr Health Sci 2022; 22:286-95. doi:10.4314/ahs.v22i3.30