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PHYSICAL EXERCISE AND PATIENTS WITH CHRONIC RENAL FAILURE A META-ANALYSIS

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Abstract

Chronic renal failure is a severe clinical problem which has some significant socioeconomic impact worldwide and hemodialysis is an important way to maintain patients' health state, but it seems difficult to get better in short time. Considering these, the aim in our research is to update and evaluate the effects of exercise on the health of patients with chronic renal failure. The databases were used to search for the relevant studies in English or Chinese. And the association between physical exercise and health state of patients with chronic renal failure has been investigated. Random-effect model was used to compare the physical function and capacity in exercise and control groups. Exercise is helpful in ameliorating the situation of blood pressure in patients with renal failure and significantly reduces VO2 in patients with renal failure. The results of subgroup analyses show that, in the age >50, physical activity can significantly reduce blood pressure in patients with renal failure. The activity program containing warm-up, strength, and aerobic exercises has benefits in blood pressure among sick people and improves their maximal oxygen consumption level. These can help patients in physical function and aerobic capacity and may give them further benefits.

Key words: Renal failure, Hemodialysis, Exercise, Activity & Control.

1. INTRODUCTION

Renal failure is characterized with the loss of its function and results in the accumulation of metabolites in blood [1]. As a result, the balance of fluids and electrolytes in the body gets disturbed, thereby causing serious health problems [2]. A gradual loss of kidney function over a period of several years is termed as chronic kidney disease (CKD) or chronic kidney failure [3]. Symptoms are usually very mild and could go unnoticed for a long time[3]. More often

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than not, the symptoms are noticed when it is too late, and in a majority of cases very little can be done to reverse the situation [4]. In the general people, the physical activity is related to improved physical capacity and further helping in the control of chronic diseases, including chronic kidney disease [5]. It is reported that physical fitness level of hemodialysis patients tends to improve their function levels; physical activity is an important nursing intervention for patients with hemodialysis in improving their physical performances [6].

Several kinds of exercise interventions containing strength training and aerobic exercise were studied [7]. The exercise program is usually implemented twice or three times per week, and for the participation time it is about 1 hour [8]. The period ranges from 3 months to 1 year.

Several published randomized controlled trials (RCT) studies about the effect of exercise on patients with renal failure have shown inconsistent results [8]. As far as we know, the previous reviews suggested physical activity can improve the health situation in renal failure patients [9].

However, there still exist some reports that physical exercise is a risk factor for patients with renal failure [10]. Therefore, an updated meta-analysis to assess the effects of exercise on patients with renal failure is imperative.

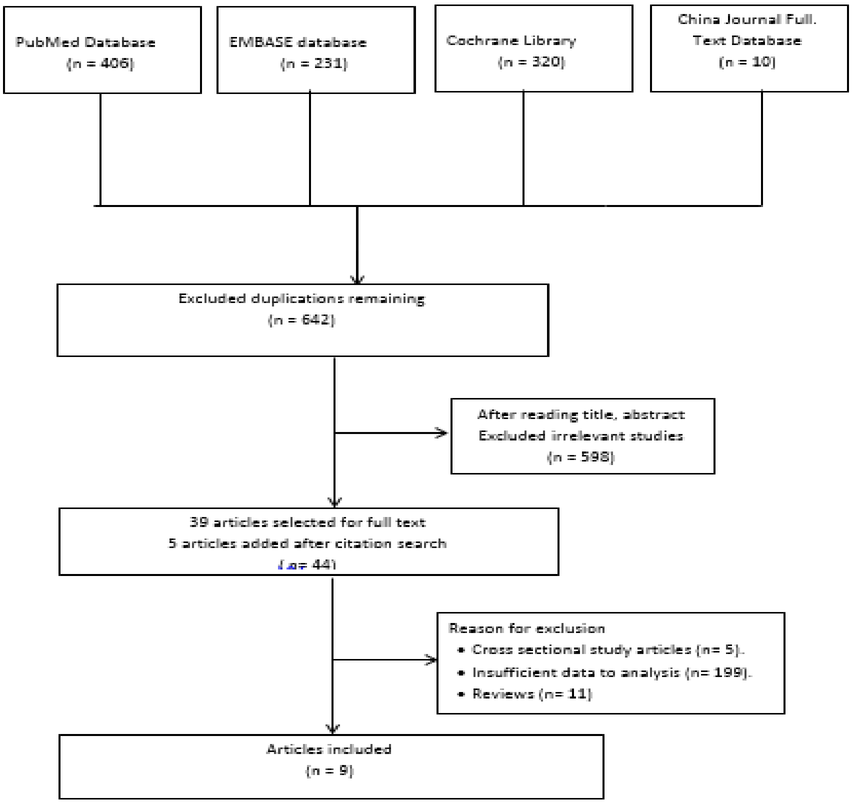

Figure 1: Flow Diagram of the Study Selection

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2. MATERIALS AND METHODS

2.1. Search Strategy and Study Selection. The literature search was conducted in July 2021 among multiple databases including PubMed, EMBASE, Cochrane Library, and China Journal Full-Text Database, from January 1995 to January 2021 (Figure 1).

The following search terms were used: (1) "renal failure" OR "kidney failure"OR"acute renal failure" OR "chronic renal failure" OR "ARF" OR "CRF" and (2) "exercise" OR "sports" OR "activity" OR "movement".

These search keywords were assembled to seek for the articles using the Boolean operator "and" without restriction. Besides, the references cited in these papers were used to complete the search. To be qualified for inclusion in this article, researches used the following inclusion criteria: (1) the study was RCT study; (2) it investigated the correlation between exercise and renal failure; (3) these studies must be conducted on adults; (4) the population in researches should be in dialysis; (5) full text is available. Studies were excluded if they were the following: animal studies, abstracts, review articles, case reports, letters, editorials, comments, and conference proceedings. The number of studies excluded was 633, in which there were 251 animal studies, 37 abstracts, 28 review articles, 116 case reports, 36 letters, 42 editorials, 53 comments, and 70 conference proceedings. Finally, there were 9 articles selected in this meta-analysis [19–28].

2.2. Data Abstraction and Quality Assessment.

The reviewers independently read the full text of the manuscripts and extracted the following data from each eligible research: first author's name, country of origin, publication year, sampling size, study period, method of ascertainment of exercise and drinking, and method of ascertainment of adult renal failure.

Table 1: Characteristics of RCT studies included in the Meta-Analysis

Study	Year	Country	Groups	Sample size	Age	Renal failure confirmation	Matching
Molsted et al.	2004	Denmark	Exercise Control	11 9	59 48	Medical records	Age , Sex
Henrique et al.	2019	Brazil	Exercise Control	7 7	47.6 42.5	Pathologically confirmed	Age
Greenwood et al.	2015	UK	Exercise Control	8 10	53.8 53.3	Medical records	Age , Sex
Svarstad et al.	2020	Norway	Exercise Control	7 8	50 31	Medical records	Age
Messonnier et al.	2021	France	Exercise Control	11 11	26.4 25.3	Pathologically confirmed	Age , Sex
McMahon et al.	1999	Australia	Exercise Control	5 9	58 34	Pathologically confirmed	Age, income
Cupisti et al.	2010	Italy	Exercise Control	28 28	46 43	Medical records	Age , Sex
Cho & Sohng.	2017	Korea	Exercise Control	23 23	60.8 57.7	Pathologically confirmed	Age , Sex
Li et al.	2012	China	Exercise Control	25 25	24.24 22.12	Medical records	Age

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2.3. Statistical Analysis. Review Manager (Version 5.0, The Cochrane Collaboration, 2011) was used to estimate the effects of the outcomes among selected reports. Continuous variables are represented by mean and standard deviation, with heterogeneity across studies using *I* 2 statistic (a quantitative measure of inconsistency across studies). Studies with an *I* 2 of 25% to 50% were considered low heterogeneity, *I* 2 of 50% to 75% was considered moderate heterogeneity, and

I 2 > 75% was considered high heterogeneity. If *I* 2 > 50%, potential sources of heterogeneity were tested by sensitivity analysis conducted by eliding one study in each turn and investigating the influence of a single study on the combined estimate. A subgroup analysis was implemented based on different age ranges. Furthermore, when heterogeneity was observed, a random-effect model was adopted, and while it was absent, the fixed-effect model was utilized. Funnel plots were used to examine the potential publication bias. In addition, sensitivity analysis was conducted to test the robustness. We examine whether the quality of reports could influence the results of this analysis. After that, subgroup analysis was carried out according to different criteria such as geographical region and source of control and risk factor.

3. RESULTS

3.1. Search Results. The initial search found 957 related publications, in which 315 were excluded for duplication. After the screening based on the titles and abstracts, 44 articles remained. Then, 35 researches were excluded because of type of article and insufficient data. In the end, 9 RCT studies were selected for this meta-analysis, in which 8 were published in English and 1 was published in Chinese.

3.2. Study Characteristics. The main characteristics of the selected researches are shown in (Table 1). These articles were published between 1999 and 2014. All the studies were performed in different countries. Sampling size ranged from 15 to 56. The mean age was between 22.12 and 60.8. Casesin all selected studies were confirmed based on medical records or pathological findings. The data about matching were extracted from all of the included studies.

3.3. Meta-Analysis of Outcome Measures

3.3.1. Patients' Blood Pressure. All the studies reported that physical activity is associated with the state of health. The aggregated results suggested that exercise is helpful in improving the situation of blood pressure in patients with renal failure (MD = −4.46, 95% CI [−9.11, −0.01], *P* = 0.06, *P* for heterogeneity < 0.0001, and *I* 2 = 77%) (Table 2).

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Table 2: A Forest Plot for Blood Pressure of Patients with Chronic Renal Failure

Study or subgroup	Exercise			Control			Weight	Mean difference IV, random, 95% CI
	Mean	SD	Total	Mean	SD	Tot al		
Cho & Sohng. 2017	135.4	9	23	132.6	11	23	13.3%	2.80
Cupisti et al. 2010	132	8	28	138	9	28	14.5%	– 6.00
Greenwood et al. 2015	131.13	10.9	8	132.3	23..2	10	5.5%	–1.00
Henrique et al. 2019	143	10.5	7	150	18.4	7	5.8%	– 7.00
Li et al. 2012	140	8	25	142	13	25	13.1%	– 2.00
McMahon et al. 1999	117	9	5	147	10	9	9.3%	– 30.00
Messonnier et al. 2021	140	5	11	141	3	11	15.4%	– 1.00
Molsted et al. 2004	141	8	11	144.5	15	9	8.7%	– 3.50
Svarstad et al. 2020	123	5	7	123	4	8	14.4%	0.00
Total (95% CI)			125			130	100%	– 4.46
Heterogeneity: $r^2 = 33.59$, $x^2 = 35.48$, df = 8 (P = 0.0001) ; I^2= 77% Test for overall effect Z = 1.88 (P = 0.06)								

Table 3: A Forest Plot for Maximal Oxygen Consumption of Patients with Chronic Renal Failure

Study or subgroup	Exercise			Control			Weight	Mean difference IV, random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Cho & Sohng. 2017	20.1	5.1	23	20.9	5.7	23	5.1%	– 0.80
Cupisti et al. 2010	20.1	2.8	28	21.7	3.8	28	16.2%	– 1.60
Greenwood et al. 2015	20.1	5.8	8	16.1	4	10	2.2%	4.00
Henrique et al. 2019	20.7	2.91	7	21.3	10.13	7	0.6%	– 0.60
Li et al. 2012	21.5	2.7	25	23.2	1.8	25	30.6%	– 1.70
McMahon et al. 1999	18.9	2.5	5	22.1	4.2	9	4.0%	– 3.20
Messonnier et al. 2021	19.1	1.4	11	20.1	1.6	11	31.3%	– 1.00
Molsted et al. 2004	20.9	3.2	11	24	6.2	9	2.5%	– 3.10
Svarstad et al. 2020	17.3	2.7	7	18.7	2.3	8	7.6%	– 1.40
Total (95% CI)			125			130	100%	– 1.36
Heterogeneity: x2 = 7.40, df = 8 (P = 0.49) ; I^2= 0% Test for overall effect Z = 3.78 (P = 0.0002)								

3.3.2. Patients' Maximal Oxygen Consumption

Sports can influence maximal oxygen consumption (VO2) which was supported in the included studies. The combined results demonstrated that exercise is associated with improving the situation of VO2max in renal failure patients (MD = −1.36, 95%CI [−2.06, −0.65], *P* = 0.0002, *P* for heterogeneity = 0.49, and *I* 2 = 0%) (Table 3).

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3.4. Subgroup Analyses

3.4.1. Patients' Blood Pressure. Subgroup analyses were performed according to age: >50 yrs, 40–50 yrs, and 20–40 yrs. In the age >50, physical activity can significantly reduce blood pressure in patients with renal failure (MD = −5.23, 95% CI [−8.13, −2.33], *P* = 0.0004, *P* for heterogeneity < 0.0001, and *I* 2 = 86%); in the age between 40 and 50, exercise can also significantly reduce blood pressure in patients with renal failure (MD = −6.07, 95% CI [−10.37, −1.78], *P* = 0.006, *P* for heterogeneity = 0.90, and *I* 2 = 0%); in the age between 20 and 40, the effects of sports on blood pressure among kidney failure patients is insignificant (MD = −1.25, 95% CI [−4.24, 1.74], *P* = 0.41, *P* for heterogeneity = 0.78, and *I* 2 = 0%) (Table 4).

3.4.2. Patients' Maximal Oxygen Consumption. In the age >50, the effect of sports onVO2 among kidney failure patients is insignificant (MD = −1.23, 95% CI [−2.75, 0.29], *P* = 0.11, *P* for heterogeneity = 0.15, and *I* 2 = 40%); in the age between 40 and 50, exercise can also significantly reduce VO2 in patients with renal failure (MD = −1.56, 95% CI [−10.37, −1.78], *P* = 0.07, *P* for heterogeneity = 0.83, and *I* 2 = 0%); in the age between 20 and 40, physical activity can significantly reduce VO2 in patients with renal failure (MD = −1.35, 95% CI [−2.24, −0.45], *P* = 0.003, *P* for heterogeneity = 0.44, and *I* 2 = 0%) (Table 5).

Table 4: A forest plot for the subgroup analyses of blood pressure in patients with chronic renal failure based on their age

Study or subgroup	Exercise			Control			Weight	Mean difference IV, random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
1.3.1 age > 50								
Cho & Sohng. 2017	132	8	28	138	9	28	14.7%	– 6.00
Greenwood et al. 2015	131.3	10.9	8	132.3	23.2	10	5.0%	– 1.00
McMahon et al. 1999	117	9	5	147	10	9	8.8%	– 30.00
Molsted et al. 2004	141	8	11	144.5	15	9	8.3%	– 3.50
Svarstad et al. 2020	123	5	7	123	4	8	12.5%	0.00
Subtotal (95%CI)			59			64	51.3%	– 8.01
Heterogeneity: $r^2 = 79.98$. $x^2 = 27.85$, df = 4 (P = 0.0001) ; $I^2 = 86\%$ Test for overall effect Z = 1.76 (P = 0.08)								
1.3.2 40 < age > 50								
Cupisti et al. 2010	132	8	28	138	9	28	14.7%	– 6.00
Henrique et al. 2019	143	10.5	7	150	18.4	7	5.3%	– 7.00
Subtotal (95%CI)			35			35	20%	– 6.07
Heterogeneity: $r^2 = 0.00$. $x^2 = 0.01$, df = 1 (P = 0.90) ; $I^2 = 0\%$ Test for overall effect Z = 2.78 (P = 0.006)								
1.3.3 20 < age < 40								
Li et al. 2012	140	8	25	142	13	25	13.1%	– 2.00
Messonnier et al. 2021	140	5	11	141	3	11	15.7%	– 1.00
Subtotal (95%CI)			36			36	28.7%	– 1.25

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Heterogeneity: $r^2 = 0.00$. $x^2 = 0.08$, df = 1 (P = 0.78) ; $I^2 = 0\%$ Test for overall effect Z = 0.82 (P = 0.41)								
Total (95% CI)			130			135	100%	– 5.53
Heterogeneity: $r^2 = 27.83$. $x^2 = 32.76$, df = 8 (P = 0.0001) ; $I^2 = 76\%$ Test for overall effect Z = 2.51 (P = 0.01) Test for subgroup differences: $X^2 = 4.49$, df = 2 (P = 0.11), $I^2 = 55.4\%$.								

Table 5: A forest plot for the subgroup analyses of maximal oxygen consumption in patients with chronic renal failure based on their age

Study or subgroup	Exercise			Control			Weight	Mean difference IV, random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
1.4.1 age > 50 Cho & Sohng. 2017	20.1	5.1	23	20.9	5.7	23	5.1%	– 0.80
Greenwood et al. 2015	20.1	5.8	8	16.1	4	10	2.2%	4.00
McMahon et al. 1999	18.9	2.5	5	22.1	4.2	9	4.0%	– 3.20
Molsted et al. 2004	20.9	3.2	11	24	6.2	9	2.5%	– 3.10
Svarstad et al. 2020	17.3	2.7	7	18.7	2.3	8	7.6%	– 1.40
Subtotal (95%CI)			54			59	21.3%	– 1.23
Heterogeneity: $x^2 = 6.68$, df = 4 (P = 0.15) ; $I^2 = 40\%$ Test for overall effect Z = 1.59 (P = 0.11)								
1.4.2 40 < age > 50 Cupisti et al. 2010	2.1	2.8	28	21.7	3.8	28	16.2%	– 1.60
Henrique et al. 2019	20.7	6.91	7	21.3	10.13	7	0.6%	– 0.60
Subtotal (95%CI)			35			35	16.8%	– 1.56
Heterogeneity: $x^2 = 0.04$, df = 1 (P = 0.44) ; $I^2 = 0\%$ Test for overall effect Z = 2.95 (P = 0.003)								
1. 4.3 20 < age < 40 Li et al. 2012	21.5	2.7	25	23.2	1.8	25	30.6%	– 1.70
Messonnier et al. 2021	19.1	1.4	11	20.1	1.6	11	31.3%	– 1.00
Subtotal (95%CI)			36			36	61.9%	– 1.35
Heterogeneity:. $x^2 = 0.59$, df = 1 (P = 0.44) ; $I^2 = 0\%$ Test for overall effect Z = 0.95 (P = 0.003)								
Total (95% CI)			125			130	100%	– 1.36
Heterogeneity: $x^2 = 7.40$, df = 8 (P = 0.49) ; $I^2 = 0\%$ Test for overall effect Z = 3.78 (P = 0.0002) Test for subgroup differences: $X^2 = 0.08$, df = 2 (P = 0.96), $I^2 = 0\%$.								

3.5. Sensitivity Analyses. To examine the stability of the outcome in blood pressure, a sensitivity analysis is needed. A relative outlier was excluded, and the result demonstrates that, in heterogeneity part, *I* 2 changed from 77 to 2%. It indicates that the heterogeneity is mainly due to McMahon's report in 1999 (table 6).

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Table 6: A forest plot for the subgroup analyses of blood pressure in patients with chronic renal failure for sensitivity test

Study or subgroup	Exercise			Control			Weight	Mean difference IV, random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Cho & Sohng. 2017	135.4	9	23	132.6	11	23	11.6%	2.80
Cupisti et al. 2010	132	8	28	138	9	28	19.7%	– 6.00
Greenwood et al. 2015	131.3	10.9	8	132.3	23.2	10	1.5%	– 1.00
Henrique et al. 2019	143	10.5	7	150	18.4	7	1.6%	– 7.00
Li et al. 2012	140	8	25	142	13	25	10.9%	– 2.00
Messonnier et al. 2021	140	5	11	141	3	11	33.0%	– 1.00
Molsted et al. 2004	141	8	11	144.5	15	9	3.3%	– 3.50
Svarstad et al. 2020	123	5	7	123	4	8	18.3%	0.00
Total (95% CI)			120			121	100%	– 1.65
Heterogeneity: $x^2 = 7.11$, df = 7 (P = 0.42) ; $I^2= 2\%$ Test for overall effect Z = 1.63 (P = 0.10)								

3.6. Bias Analyses. A funnel plot for blood pressure and maximal oxygen consumption was performed. All the studies were included in the plot. To some extent, the result indicated that there existed some publication bias (Figure 2). The changes in the outcomes from baseline for blood pressure and VO2max were 11.6% and 88.4, respectively.

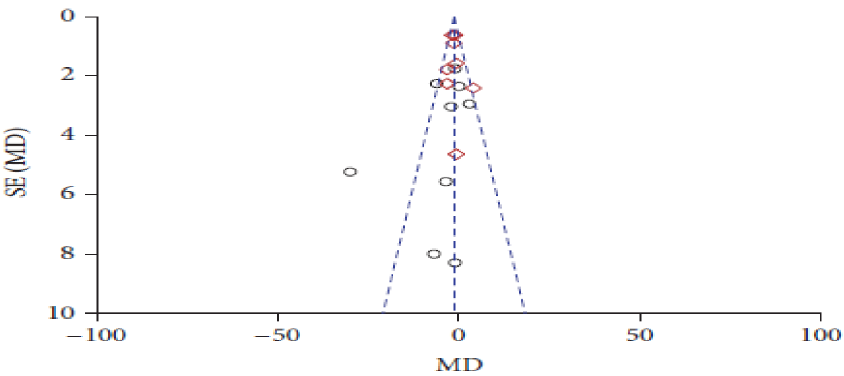

Figure 2: A funnel plot for blood pressure and maximal oxygen consumption in patients with chronic renal failure

4. DISCUSSION

Chronic renal failure is a severe clinical problem which has some significant socioeconomic impact worldwide [11]. Despite advances in renal replacement therapies and organ transplantation, there exist abundant concerns like poor quality of life for dialysis patients and long transplantation waiting lists [12]. Besides the treatment to cure patients, the ways to improve the quality of patients' life are important [13]. It is reported that the number of chronic kidney failures treated by hemodialysis is continuously increasing and most patients have

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reduced physical exercise and have a high risk of cardiac and vascular disease [14].

Physical activity program is suggested to help in making patients' life quality better. The activity is usually conducted mainly twice or three times per week, and the participation time is about 1 hour [15]. The period ranges from 3 months to 1 year. The items of the exercise contain warm-up and strength and aerobic exercises. The studies about the necessity of physical activity showed that renal failure patients have seriously reduced physical capacity and they have a high risk of cardiac and vascular diseases. Therefore, physical exercise should be considered as both prevention and rehabilitation. This meta-analysis aims to update and evaluate the effects of exercise on the health state in renal failure patients. The results in this study show that physical activity have benefits in blood pressure among sick people and improve their maximal oxygen consumption. These can help patients in physical function and aerobic capacity and may give them further benefits. These findings are in accord with the conclusion reported by Adams and Vaziri, which noted that exercise restores some level of physical performance and quality of life, which can be beneficial in patients with renal failure [16] .

Our study also finds that the effects of exercise showed difference in various age groups. In the subgroup analyses of blood pressure, the elderly (age > 40) have significant improvement in controlling blood pressure, while young people' results (20 < age < 40) are insignificant. These may be because the condition of blood pressure in old people is worse compared to young man, and the change of blood pressure in old men is relatively easier to achieve. In the maximal oxygen consumption part, people in all the age ranges make their ability better after performing the exercise program. Jiang reported that diet and proper exercise were helpful in the elderly with chronic renal failure [17].

This meta-analysis includes the studies which are all from randomized trials. According to the GRADE quality assessment scale, the quality of the individual studies in this meta-analysis was confirmed. To control selection bias, a sensitivity analysis was applied and found that McMahon's results were outliers and should be dropped. The result in this research is a suggestion both in scientific viewpoint and in clinical practice. However, there were some limitations in this article: the number of included researches was not abundant, and long-term effects of exercise on people with renal failure cannot be inferred in this study. Besides, methodological differences and confounding factors of selected studies were unavoidable.

5. CONCLUSION

Exercise program is associated with health state of people with kidney failure. Physical activity will improve body function and physical capacity, which will benefit patients with hemodialysis and help them in their blood pressure and maximal oxygen consumption. In spite of these benefits, the other potential effectiveness of exercise is needed. The results in the included randomized controlled trials could be more comprehensive. Besides, more randomized controlled trials are required to determine the influence of physical activity on a larger sampling size.

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