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ORIGINAL ARTICLE

The efficacy of exercise training in kidney transplant recipients: a meta-analysis and systematic review

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Abstract

Background The effectiveness of exercise in kidney transplant recipients is not well established. We, therefore, performed a systematic review of the effects of exercise training in kidney transplantation recipients.

Methods We searched two electronic databases for articles up to April 2017. Inclusion criteria were as follows: randomized controlled trial and kidney transplant recipients aged 18 years or older. The main outcomes were allograft function (estimated glomerular filtration rate, eGFR), exercise tolerance (VO_2 peak), and quality of life (QOL).

Results After screening of 1303 references in PubMed and Ichushi, six randomized control trials were analyzed. For kidney transplant recipients, supervised exercise training was shown to significantly improve VO_2 peak [mean difference 2.42; 95% confidence interval (95%CI) 0.22–4.63] and QOL (mean difference 7.23; 95%CI 0.94–13.52). However, exercise training did not improve allograft kidney function (mean difference 6.22; 95%CI − 13.00 to 25.44). No reporting bias was observed in any of the outcomes. There were no reports including patient survival rates and the harm associated with exercise training.

Conclusions Exercise training for kidney transplant recipients significantly improved exercise tolerability and QOL, but a significant improvement was not obtained with respect to allograft kidney function. Evaluation of patient survival rates and the harm associated with exercise training has not been reported, therefore, future studies are needed to resolve these issues.

Keywords Exercise training · Kidney transplantation · Peak VO_2 · Allograft function · QOL

Introduction

Kidney transplantation is the preferred therapy for end stage renal disease in terms of survival rates [1], quality of life (QOL) [2], and exercise tolerance [3] compared with dialysis.

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However, metabolic syndrome is a very large and prevalent problem both before and after renal transplantation [4, 5]. Kidney transplant recipients receive maintenance immunosuppressants including calcineurin inhibitors, antimetabolite agents, and corticosteroids, and tend to develop metabolic syndrome induced by these immunosuppressants and the improvement of uremic state [6]. Moreover, corticosteroids are reported to be a risk factor for muscle loss [7] and osteoporosis or bone fracture [8]. Because post-transplant metabolic syndrome is a risk factor for allograft dysfunction and cardiovascular disease [9], dietetic therapy and exercise therapy should also be initiated to improve or to prevent metabolic syndrome. However, recommendations for exercise training for kidney transplant recipients were not described in the KDIGO Clinical Practice Guidelines for the Care of Kidney Transplant Recipients 2009 [10].

The objective of exercise training for kidney transplant recipients is to prevent cardiovascular diseases through the maintenance of exercise tolerability, improvement of QOL, long-term preservation of transplanted kidney function, and prevention of lifestyle diseases via prevention of increased frailty and sarcopenia after kidney transplantation. For kidney transplant recipients, it is important whether they can achieve sufficient long-term allograft function, QOL, and exercise tolerance equivalent to patients without chronic kidney disease (CKD). In recent years, the ages of kidney transplant recipients have been much higher, especially in Japan. Therefore, low physical activity and sarcopenia have been major problems for kidney transplant recipients. Because kidney transplant recipients traditionally tended to be young, have higher physical activity levels and not suffer from time constraints compared with patients under hemodialysis, it has also been reported that kidney transplant recipients increase their physical activity after transplantation [11]. Notably, in recent studies, exercise training was reported to improve both exercise tolerance (VO_2 peak) [12] and QOL [13] for kidney transplant recipients.

A recent review summarized studies of exercise training for solid organ transplants including heart, kidney, lung and liver; however, this review did not perform a meta-analysis [14]. To date, there has been no meta-analysis study on the effect of exercise intervention for kidney transplant recipients. Therefore, the efficacy of exercise training for renal transplant recipients is not well established. In this study, we performed a systematic review of the effects of exercise training in kidney transplantation recipients to evaluate the efficacy of exercise training on exercise tolerance, QOL, allograft kidney function, and the prognosis of the kidney transplant recipients.

Materials and methods

This systematic review was conducted in accordance with guidelines from Minds Handbook for Clinical Practice Guideline Development 2014 [15]. The protocol used for the systematic review and meta-analysis was registered in the UMIN Clinical Trials Registry (UMIN000032086). Ethical approval was not required because this study did not include confidential personal data and did not involve patient intervention.

Study selection and data management

An electronic database search was performed in PubMed and Ichushi, a Japanese medical bibliography [16]. The study search was conducted in April 2017. The full search strategy is described in Supplementary Appendix S1. Two different reviewers (HO and MT) screened all titles and abstracts for the first screening, then the full texts for the second screening. To identify any articles missed by the initial search, we also evaluated the reference lists of previously reported systematic reviews.

Inclusion and exclusion criteria

We include only randomized control trials (RCTs) investigating exercise training in the setting of kidney transplant recipients. Supervised exercise training included resistance training (RT), aerobic exercise training (AT), or exercise training combined with RT and AT. Only RCTs that included kidney transplant recipients at least 18 years of age were included in this meta-analysis. The initial main outcomes of this study were patient's survival, allograft function (estimated glomerular filtration rate, eGFR), exercise tolerance (VO_2 peak), QOL, and the harm of exercise training.

Risk of bias

The methodological quality of trials was evaluated independently using the Minds Handbook for Clinical Practice Guideline Development 2014 [15] for the assessment of risk of bias by two reviewers (HO and MT). Studies were graded as having a "low risk", "high risk", or "moderate risk" of bias across the following seven specified domains: randomization, concealment, blinding (performance bias), blinding (detection bias), incomplete outcome data, selective outcome report, and other biases.

Data analysis and statistical methods

Quantitative evaluation (meta-analysis) by Inverse-variance method using Review Manager Software (RevMan version 5.3; Cochrane Collaboration, Oxford, UK) was carried out for items that can be quantitatively evaluated. In the meta-analysis, according to the Cochrane handbook 5-1 (http://handbook-5-1.cochrane.org/chapter_9/9_4_5_2_meta_analysis_of_change_scores.htm), the difference of the average before and after exercise training in each study was adopted as the mean value in Forest plots, and the standard deviation (SD) after the exercise training in each studies was adopted as the SD value in Forest plots. In each study, when several time points of the outcome were measured, we selected the data closer in time between the studies. We chose the model of random effects in RevMan owing to expected clinical heterogeneity among the studies. A P value < 0.05 was considered statistically significant.

Results

Of the total of 1303 references that were extracted from the PubMed ($n = 1214$) and Ichushi ($n = 89$) databases by the first screening, 1270 references were rejected based on the titles and abstracts. We analyzed 33 references (all records from PubMed) that were identified for potential inclusion and full-text review, and six RCTs were entered into the quantitative analysis (Fig. 1). A summary of studies is shown in Table 1. The exercise training intervention ranged from 12 weeks to 12 months in duration. Of the six RCTs, weight/resistance training (RT) alone was performed in two trials, assignment to aerobic exercise training (AT) or RT was performed in one trial, AT alone was performed in one trial, and combined intervention with AT and RT was performed in two trials. We aimed to determine the outcomes of allograft kidney function, exercise tolerance, QOL, survival rates and the harm of exercise; however, there were no reports evaluating patient survival rates and the harm associated with exercise training. Therefore, we performed quantitative analysis for the remaining three outcomes; allograft kidney function, exercise tolerance, and QOL (Table 2).

Outcome of meta-analysis and evaluation of risk of bias for allograft function

To evaluate allograft function (eGFR) of the kidney transplant recipients, two references [12, 18] were included with a total of 22 subjects in the intervention group and 22 control subjects. Blinded assignment of kidney transplant recipients to treatment groups could not be performed for the six RCTs due to the intervention characteristics of exercise therapy, therefore, the blinding (performance bias) was high. The exercise regimens consisted of 12 months of RT monotherapy [18], or assignment to AT or RT for 12 weeks [12], thus differences were present in both the intervention period and intervention method. Evaluation of the eGFR confirmed the difference between the evaluation period and the evaluation method, as one study evaluated renal function by the CKD-EPI formula at 12 weeks [12], while the other study evaluated renal function by the MDRD formula at 12 months [18]. Thus, moderate indirectness existed for both intervention and outcome when assessing indirectness. Two other studies

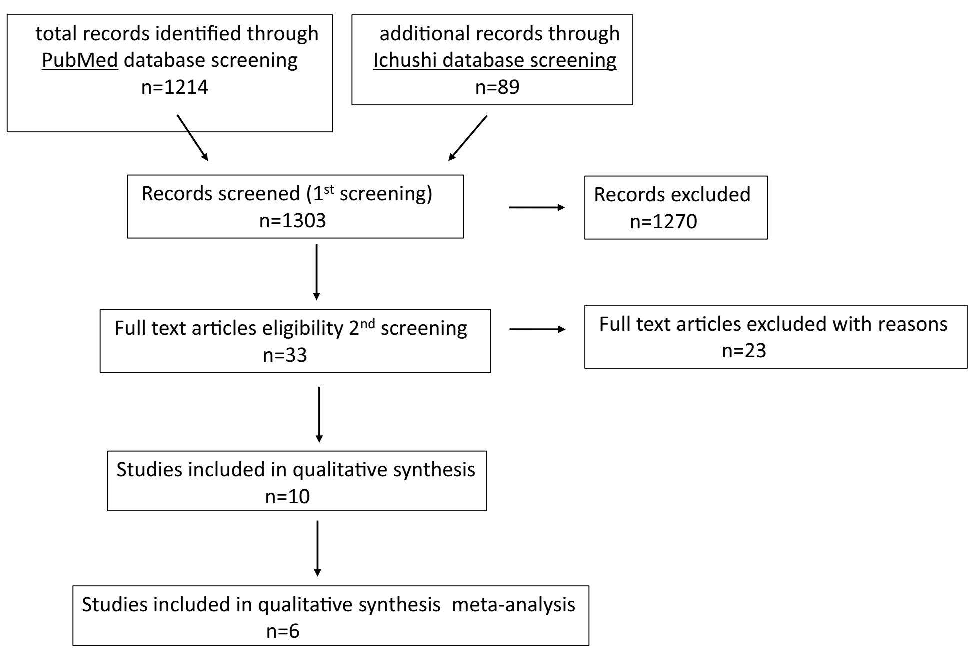

Fig. 1 Diagram of study selection, systematic review and meta-analysis according to Minds guideline handbook 2014

Table 1 Characteristics of included studies

References	Country	Type of study	Mean age (SD), years	Mean duration after kidney transplantation (SD)	Number of recipients, *n*	Duration of intervention	Intervention	Intensity of intervention	Control	Outcome
Painter et al. [17]	United States	Randomized controlled trial	Ex : 39.7 (12.6) Con : 43.7 (10.7)	No data	Ex : 54 Con : 43	12 months	Walking or cycling for at least 30 min 4 times a week	Initially 60–65% of maximal heart rate, gradually increased to 75–80% every 2 week	Usual care	Exercise tolerance (VO_2 peak) QOL Quadriceps muscle strength
Tzetanov et al. [18]	United States	Randomized controlled trial	Ex : 46 (6.9) Con : 45 (19)	No data	Ex : 9 Con : 8	12 months	Low-impact, low-repetition, resistance-based weight training with two 1-h session a week	No data	Usual care	eGFR QOL Weight lifting capacity
Riess et al. [19]	Canada	Randomized controlled trial	Ex : 56.9 (12.2) Con : 52.4 (14.3)	Ex : 6.4 (4.1) years Con : 9.1 (8.8) years	Ex : 16 Con : 15	12 weeks	Endurance training (3 days/week) and strength training (2 days/week) for 30–60 min/session	Borg scale 11–13	Usual care	Exercise tolerance (VO_2 peak) QOL Lower extremity muscle strength
Karelis et al. [13]	Canada	Randomized controlled trial	Ex : 45.3 (14) Con : 39.4 (8)	No data	Ex : 10 Con : 10	16 weeks	Resistance training program for 45–60 min 3 times a week	Approximately 80% of the 1-repetition maximum	Usual care	Exercise tolerance (VO_2 peak) QOL Lower- and upper-body muscle strength

Table 1 (continued)

References	Country	Type of study	Mean age (SD), years	Mean duration after kidney transplantation (SD)	Number of recipients, n	Duration of intervention	Intervention	Intensity of intervention	Control	Outcome
Greenwood et al. [12]	United Kingdom	Randomized controlled trial	Ex : aerobic training 53.9 (10.7), resistance training 54.6 (10.6) Con : 49.5 (10.6) weeks	Ex : aerobic training 26.5 (21) weeks, resistance training 30.0 (20) weeks Con : 29.6 (19) weeks	Ex : aerobic training 13, resistance training 13 Con : 20	12 weeks	Aerobic training : stationary exercise cycles, a treadmill, and elliptical trainer for 60 min 3 times a week Resistance training : upper and lower body muscle training for within a 60 min 3 times a week	RPE scale 13–15	Usual care	eGFR Exercise tolerance (VO_2 peak) Isometoric quadriceps muscle force QOL Sit-to-Stand 60
Kouidi et al. [21]	Greece	Randomized controlled trial	Ex : 52.1 (5.6) Con : 52.6 (5.4)	Ex : 22.0 (4.6) months Con : 22.1 (4.0) months	Ex : 11 Con : 12	6 months	30–40 min aerobic exercise programme followed by 10–30 min of strengthening exercise for upper and lower extremity and abdominal muscles	50–75% VO_2 peak or 65–85% maximal heart rate	Usual care	Exercise tolerance (VO_2 peak)

The Borg rating of perceived exertion (RPE) scale was applied to obtain an estimation of exercise intensity [22]

Table 2 Risk of bias assement

References	Selection bias Randomization	Selection bias Concealment	Blinding (performance bias)	Blinding (detection bias)	Incomplete outcome data	Selective outcome report	Other biases
eGFR							
Greenwood et al. [12]	Low	Low	High	Low	Moderate	Low	Moderate
Tzetanov et al. [18]	Low	Low	High	High	Moderate	Low	Moderate
QOL							
Riess et al. [19]	Low	Low	High	High	Low	Low	Moderate
Karelis et al. [13]	Low	High	High	High	Low	Low	Moderate
Greenwood et al. [12]	Low	Low	High	Low	Moderate	Low	Moderate
Painter et al. [17]	Low	Low	High	High	Moderate	Low	Moderate
VO_2 peak							
Greenwood et al. [12]	Low	Low	High	Low	Moderate	Low	Moderate
Riess et al. [19]	Low	Low	High	High	Low	Low	Moderate
Painter et al. [17]	Low	Low	High	High	Moderate	Low	Moderate
Kouidi et al. [21]	Low	Low	High	High	Low	Low	Moderate

eGFR estimated glomerular filtration rate, *QOL* quality of life

reported allograft kidney function as serum creatinine levels [17, 23], however, we could not obtain individual values for eGFRs from the data in these two RCTs. Despite the indirectness, we decided that quantitative evaluation of the two reports was possible. Quantitative evaluation of the 44 kidney transplant recipients revealed that exercise intervention did not consistently improve eGFR [mean difference 6.22; 95% confidence interval (CI) − 13.00 to 25.44; $P = 0.53$] (Fig. 2). As there were few references for outcome, we determined that there was no reporting bias.

Exercise tolerance as determined by the VO_2 peak

To evaluate exercise tolerability (VO_2 peak) of the kidney transplant recipients, five RCTs [12, 17, 19, 21, 24] were analyzed. Because the trial by O'Connor et al. [24] used the same cohort as Greenwood et al. [12], we excluded it and performed the meta-analysis using four RCTs with a total of 92 subjects in the intervention group and 90 control subjects. Blinded assignment could not be performed, therefore, blinding (performance bias) was high. The exercise regimens consisted of 12 months AT [17], 6 months RT and AT combination therapy [21], 12 weeks RT and AT combination therapy [19], and 12 weeks of AT or RT [12]. Therefore, there were differences observed in both the intervention period and intervention method. There was no difference in the evaluation index, however, there was a difference in the evaluation period (12 weeks [12, 19] versus 6 and 12 months [17, 21]). In one RCT [21], because only the SD before exercise therapy was described, we used the SD as before exercise therapy as SD values.

Quantitative evaluation of the 182 kidney transplant recipients revealed that exercise intervention significantly increased VO_2 peak, with a mean difference of 2.42 (95% CI 0.22–4.63, $P = 0.03$), and reporting bias was not indicated because of the small number of studies. As there were few articles for outcome, we determined that there was no publication bias (Fig. 3).

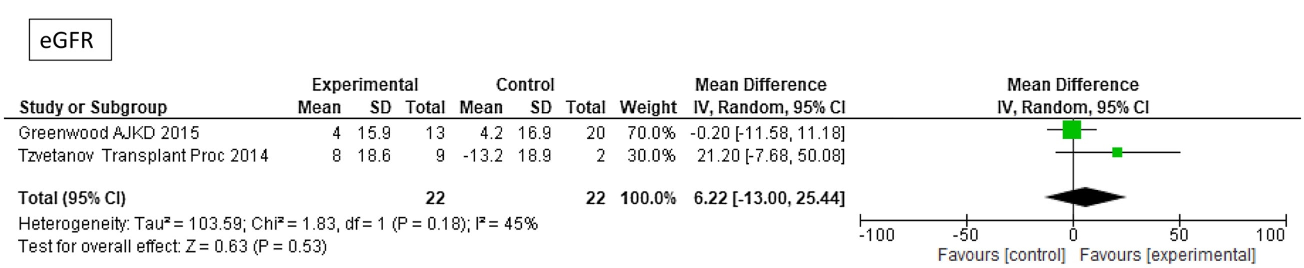

Fig. 2 Forest plot of the effects of exercise intervention compared with usual care on changes in eGFR for transplant recipients

VO2 peak

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Greenwood AJKD 2015	2.7	3.9	13	1	3	20	43.4%	1.70 [-0.79, 4.19]
Kouidi Nephrol Dial Transplant 2013	5.4	4.8	11	-0.1	4.5	12	25.0%	5.50 [1.69, 9.31]
Painter Transplantation 2002	3.8	11	52	3.6	9.2	43	22.7%	0.20 [-3.86, 4.26]
Riess Appl Physiol Nutr Metab 2014	3	10	16	0	10	15	8.9%	3.00 [-4.04, 10.04]
Total (95% CI)			**92**			**90**	**100.0%**	**2.42 [0.22, 4.63]**

Heterogeneity: Tau² = 1.30; Chi² = 3.99, df = 3 (P = 0.26); I² = 25%
Test for overall effect: Z = 2.15 (P = 0.03)

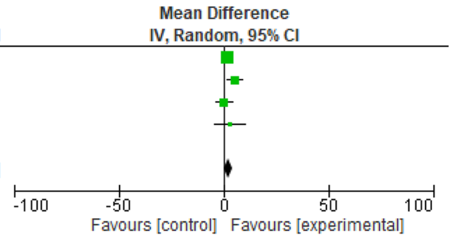

Fig. 3 Forest plot of the effects of exercise intervention compared with usual care on changes in VO_2 peak for transplant recipients

Quality of life

For the quantitative evaluation of QOL, five references [12, 13, 17–19] were examined. The article by Tzvetanov [18] described only the mean value of QOL as evaluated by the Short Form (SF)-36 after intervention, and it was not used for quantitative evaluation as it was only a comparison in a few cases. Blinded assignment could not be performed, therefore, blinding (performance bias) was high. The exercise regimens consisted of 12 weeks RT and AT combination therapy [19], 12 months RT monotherapy [18], and 16 weeks RT therapy [13], thus differences were present in both the intervention period and intervention method. Evaluation of QOL also showed a difference in the evaluation period and evaluation method, as it was evaluated by the SF-36 at 12 weeks [12, 19], 12 months [17] in three RCTs, and by the WHO-5 well-being score at week 16 in another RCT [13]. In the three RCTs evaluating QOL by the SF-36, the article by Riess et al. [19] reported over all QOL scores, mental composite score and social functioning, the article by Painter et al. [17] reported physical functioning scale, role physical score and physical composite score, and the article by Greenwood et al. [12] reported physical composite score and mental composite score. We adopted overall QOL scores in the article of Riess et al. [19], and physical composite scores in the articles by Greenwood et al. [12] and Painter et al. [17] as the data for the Forest plot. Thus, moderate indirectness existed for both intervention and outcome when assessing indirectness. In one RCT, because only the changes before and after exercise therapy were described for the overall QOL score, we adopted this value as the QOL score [19]. Despite the indirectness, we decided that quantitative evaluation of the four RCTs was possible.

We examined the background of transplant recipients in the exercise and usual care groups in four RCTs [12, 13, 17, 19] ($n = 93$ in the exercise group, $n = 88$ in the usual care group) used for a meta-analysis on QOL outcome. Socio-economic factors were not described in the background sections of these four RCTs, and racial factors were described in only two RCTs [12, 17] ($n = 67$ in the exercise group, $n = 63$ in the usual care group). The supplementary table shows the distribution of race in the exercise and usual care groups of the two combined RCTs. Importantly, no significant differences were observed in race between the exercise group and usual care group.

Quantitative evaluation of the 179 kidney transplant recipients revealed that exercise intervention significantly increased QOL, with a mean difference of 7.23 (95%CI 0.94–13.52, $P = 0.02$), and reporting bias was not indicated because of the small number of studies. As there were only a few articles for outcome, we determined that there was no publication bias (Fig. 4).

QOL

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Greenwood AJKD 2015	1	19.9	13	0.5	8.3	20	17.9%	0.50 [-10.91, 11.91]
Karelis Can J Diabetes 2016	8.4	8.5	10	-5.2	10.2	10	24.9%	13.60 [5.37, 21.83]
Painter Transplantation 2002	6.9	11.3	52	4	12.9	43	34.2%	2.90 [-2.03, 7.83]
Riess Appl Physiol Nutr Metab 2014	8.6	13.4	16	-3.4	12.1	15	23.0%	12.00 [3.02, 20.98]
Total (95% CI)			**91**			**88**	**100.0%**	**7.23 [0.94, 13.52]**

Heterogeneity: Tau² = 23.78; Chi² = 7.39, df = 3 (P = 0.06); I² = 59%
Test for overall effect: Z = 2.25 (P = 0.02)

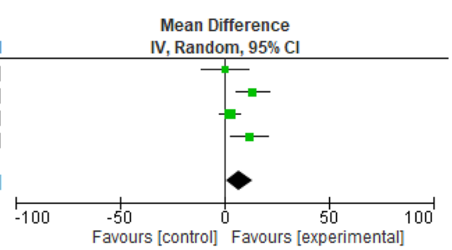

Fig. 4 Forest plot of the effects of exercise intervention compared with usual care on changes in quality of life for transplant recipients

Discussion

This is the first quantitative meta-analysis of the efficacy of exercise training intervention for kidney transplant recipients. From the results of the meta-analysis of six RCTs, exercise training significantly improves exercise tolerability (VO_2 peak) and QOL for kidney transplant recipients, however, we concluded that there was no significant improvement in kidney allograft function (eGFR). We also evaluated the search outcome of a previously reported systematic review. A systematic review published in 2016 analyzed nine RCTs [14], all of which were found using the search parameters of the current study.

Six RCTs included in this meta-analysis had moderate indirectness in terms of intervention method and period, the measurement of outcome, and the period of measurement. Notably, the type of exercise intervention varied between AT, RT, or combined (AT and RT) training. Because most of the trials used RT as exercise intervention, we determined RT was the standard intervention. Therefore, in this study, we mainly analyzed the data of RT where possible. RCTs which used AT alone thus had indirectness of intervention method.

The most relevant outcome of allograft function is allograft survival rate. However, we could not determine the effect of exercise intervention on allograft survival rate because of the short-term observation period of the included RCTs. Therefore, we determined allograft kidney function (eGFR) as a surrogate marker for allograft survival rate. Our quantitative evaluation revealed that exercise intervention did not improve eGFR in kidney transplant recipients. Because we combined eGFRs evaluated by two different formulas, it is debatable if any coherent result could be obtained analyzing only these results. In the setting of pre-dialysis CKD patients, a previous report indicated that a significant improvement in eGFR was observed in the physical rehabilitation group compared with the usual care group, however, there was no significant difference between the groups in terms of absolute eGFR after 12 months of rehabilitation, and this study concluded that the effect of 1-year of exercise is inconclusive [20]. This study also stated that improvement of eGFR could be explained by reductions in waist circumference and is probably related to central adiposity [20]. In contrast, a previous report for kidney transplant recipients showed that exercise intervention did not improve the waist circumference [12]. To consider the relationship between exercise intervention and allograft function, we are also aware that exercise intervention may increase the muscle mass which is related to serum creatinine level.

VO_2 peak is an established methodology to determine cardiorespiratory function [12]. It is reported that physical activity levels are lower overall in kidney transplant recipients compared with the general population, although somewhat higher compared with the dialysis population [3]. Another previous report also described that the changes in VO_2 peak following transplant are due to increases in central mechanisms, and the improved oxygen delivery is the result of an increase in peak cardiac output that is due to an increase in peak heart rates rather than changes in peak stroke volume [25]. Thus, this report concluded that a kidney transplantation appears to exert its beneficial effects on cardiorespiratory fitness through mitigation of the limitation of peak heart rate observed in hemodialysis patients [25]. However, the additional beneficial effects of exercise-based rehabilitation on exercise tolerability are not well established for kidney transplant recipients. Our quantitative analysis confirmed that exercise intervention significantly increased exercise tolerability (VO_2 peak) in kidney transplant recipients. The included references had a low degree of methodological differences in terms of the type of exercise intervention, and evaluation period of VO_2 peak.

The Short Form-36 (SF-36) is the most frequently used tool for the quantitative analysis of QOL [26]. A previous trial showed that kidney transplant recipients had a higher QOL compared with patients receiving peritoneal dialysis or hemodialysis [2]. However, the additional beneficial effects of exercise-based rehabilitation on QOL is not well established for kidney transplant recipients. Our quantitative evaluation confirmed that exercise intervention significantly increased QOL in kidney transplant recipients. However, the included references had a moderate degree of methodological differences in terms of the type of exercise intervention, evaluation period, and the method of evaluating QOL.

In the Dialysis Outcomes and Practice Patterns Study (DOPPS) of patients receiving hemodialysis racial and socio-economic factors were described in the report background using the SF-36 [27]. We examined the background information of four RCTs [12, 13, 17, 19] used for a meta-analysis of QOL outcome. Notably, no significant differences were observed in race when the two RCTs were combined [12, 17] (Supplementary Table), although we did not obtain data on race from the other two RCTs [13, 19]. There were no socio-economic data available from the four RCTs.

Our study thus has several limitations. First, we could not evaluate the effect of exercise intervention on long-term survival and allograft prognosis or harm of exercise intervention for the kidney transplant recipients as we found no reports focused on these outcomes in the kidney transplant recipients. Therefore, we could not evaluate these outcomes although they are very important issues for the recommendation of exercise therapy for kidney transplant recipients. Second, it is impossible to conduct blinded RCTs using exercise intervention due to the characteristics of the intervention. Overall, the characteristics of the six included RCTs were a small number of patients with relatively short intervention period. Moreover, we could not determine the most preferred modality and period of exercise intervention for kidney transplant recipients or whether the effects of exercise intervention for kidney transplant recipients is different between recipients with or without metabolic syndrome. Therefore, further research including examining the effect of long-term exercise intervention is required.

In conclusion, our systematic review showed that exercise intervention for kidney transplant recipients significantly improves exercise tolerability and QOL, but we could not confirm a significant improvement in allograft kidney function. However, it is important to note that there were no reports of patient survival rates and the risk associated with exercise training, therefore, future studies are needed to resolve these issues.

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Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

Human and animal rights This article does not contain any studies with human participants performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study by each investigator.

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