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META-ANALYSIS

Cardiorespiratory fitness in kidney transplant recipients compared to patients with kidney failure: a systematic review and meta-analysis

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SUMMARY

Patients with kidney failure often present with reduced cardiovascular functional reserve and exercise tolerance. Previous studies on cardiorespiratory fitness examined with cardiopulmonary exercise testing (CPET) in kidney transplant recipients (KTR) had variable results. This is a systematic review and meta-analysis of studies examining cardiovascular functional reserve with CPET in KTR in comparison with patients with kidney failure (CKD-Stage-5 before dialysis, hemodialysis or peritoneal dialysis), as well as before and after kidney transplantation. Literature search involved PubMed, Web-of-Science and Scopus databases, manual search of article references and grey literature. From a total of 4,944 identified records, eight studies (with 461 participants) were included in quantitative analysis for the primary question. Across these studies, KTR had significantly higher oxygen consumption at peak/max exercise (VO_2peak/VO_2max) compared to patients with kidney failure (SMD = 0.70, 95% CI [0.31, 1.10], I^2 = 70%, P = 0.002). In subgroup analyses, similar differences were evident among seven studies comparing KTR and hemodialysis patients (SMD = 0.64, 95% CI [0.16, 1.12], I^2 = 65%, P = 0.009) and two studies comparing KTR with peritoneal dialysis subjects (SMD = 1.14, 95% CI [0.19, 2.09], I^2 = 50%, P = 0.16). Across four studies with relevant data, oxygen consumption during peak/max exercise showed significant improvement after kidney transplantation compared to pretransplantation values (WMD = 2.43, 95% CI [0.01, 4.85], I^2 = 68%, P = 0.02). In conclusion, KTR exhibit significantly higher cardiovascular functional reserve during CPET compared to patients with kidney failure. Cardiovascular reserve is significantly improved after kidney transplantation in relation to presurgery levels.

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Introduction

Chronic kidney disease (CKD) has a major effect on public health, both as a direct cause of morbidity and mortality and as a major source of disability and reduced quality of life (QOL) [1]. Several factors have been suggested to affect the complex associations between CKD and associated QOL decrease, including significant changes in physical and mental functioning that lead to a vicious cycle of inactivity, deconditioning, social isolation, and depression [2]. Exercise intolerance appears as an important feature of CKD that is present even in patients with early CKD stages and rises exponentially with the progression to advanced stages and end-stage kidney disease [3]. Exercise intolerance was previously shown to be closely correlated with reduced QOL [3] and to be independently associated with cardiovascular events and death in this population [4–6].

Cardiopulmonary exercise testing (CPET) is the gold-standard method for assessment and differential diagnosis of reduced cardiovascular functional reserve and exercise intolerance, as it can evaluate in parallel the complex cardiovascular, respiratory and metabolic responses during exercise and provide valuable insight into potential underlying mechanisms of exercise capacity, including gas exchange, ventilator efficacy, and cardiovascular function [7]. Among other applications, CPET is also successfully used in preoperative assessment of patients undergoing different surgery procedures [8], as well for risk stratification in different populations, such as patients with lung diseases and heart failure [9,10]. Among the numerous parameters measured during a maximum CPET, peak oxygen consumption (VO_2peak) is probably the most important, as it reflects the ability of a person to take in, transport, and use oxygen, and defines that person's cardiorespiratory reserve and functional aerobic capacity. According to Fick equation, VO_2 equals cardiac output times the arterial-mixed venous oxygen content difference [11]. Thus, any factor that may impair one or more of the Fick principals, that is cardiovascular, respiratory, and peripheral muscle disorders or decreased oxygen-carrying capacity of the blood, may result to abnormal peak oxygen uptake. Since several of these abnormalities are commonly present among patients with CKD, assessment of VO_2 peak can be of great clinical value [12].

Over the past few years, a number of studies had evaluated cardiovascular reserve with CPET methodology in patients with CKD, including those with kidney failure under renal replacement therapy. Hemodialysis patients appear to have lower levels of VO_2peak compared with essential hypertensives [13,14], but higher compared to heart failure patients [15]. In hemodialysis, pulse wave velocity and left ventricular (LV) filling pressure were independent predictors of reduced cardiovascular reserve [14], while VO_2 peak and not vascular or echocardiographic characteristics was associated with QOL [13]. Similar associations have been observed for patients undergoing peritoneal dialysis [13].

In addition to the above, previous studies have examined the cardiopulmonary reserve with CPET before and after kidney transplantation, as well as in kidney transplant recipients versus dialysis patients; these works had variable results, a fact that could be related to differences in study power, study design, and baseline comorbidity status of the studied populations. Early case-control and cross-sectional studies showed that there were no significant differences in cardiovascular functional reserve between hemodialysis patients and kidney transplant recipients [16–18], as well as between examinations performed before and after kidney transplantation [19,20]. In contrast, a recent study suggested that cardiovascular reserve significantly improved in 81 kidney transplant recipients one year after transplantation, and as a result the cardiovascular functional reserve of transplant recipients was better than that of patients with kidney failure [21]. In light of the above, we conducted the first systematic review and meta-analysis of studies examining cardiovascular functional reserve with CPET in kidney transplant recipients in comparison with patients with kidney failure. As a secondary analysis, we performed a meta-analysis of studies examining cardiovascular functional reserve with CPET in patients before and after kidney transplantation.

Materials and methods

This systematic review and meta-analysis followed the Preferred-Reporting-Items-for-Systematic Reviews-and-Meta-Analyses (PRISMA) and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines. The relevant protocol was submitted in PROSPERO database (CRD42021234487).

Search strategy and eligibility criteria

Two authors (MT and EP) performed independently systematic literature search in three major databases (PubMed/MEDLINE, Scopus, and Web of Science) from database inception up to December 2020. Keywords and an example of the search strategy used are

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presented in the Table S1. Reference lists of retrieved articles and reports, including relevant reviews and meta-analyses, were scrutinized for additional potentially relevant records. Grey literature sources were also searched, including abstract books of relevant international meetings. We considered as eligible observational studies and randomized trials (if a control group was included at baseline and relevant baseline comparisons were available) that used CPET to assess cardiorespiratory fitness in kidney transplant recipients versus patients with kidney failure (either Stage 5 CKD patients before initiation of renal replacement therapy or patients receiving chronic hemodialysis or peritoneal dialysis treatment [22]) or studies that have examined CPET parameters before and after kidney transplantation. Preclinical studies, studies in non-adult patients, and studies including CKD stage 1–4 were excluded. The search strategy was developed with English language restriction.

Study selection

Originally retrieved records were imported into a reference management software for duplicate removal. Two authors (MT, EP) examined thoroughly titles and abstracts of records retrieved to identify potentially eligible studies. Subsequently, these authors performed full-text assessment to select the studies that would be finally included in the systematic review. Disagreement between the two reviewers on study selection was solved by a third author (MA).

Data extraction and quality assessment

The following data were collected according to the Cochrane checklist of Items: author, year of publication, study design, demographics, outcome measurements, and details relevant to quality assessment. In case of missing data, study authors were contacted by e-mail to try to retrieve original data. Finally, in case we identified multiple publications about an original study, the one that provided more adequate data was included in the meta-analysis. Again, discrepancies between the two authors on data extraction were solved by consensus and a third author (MA).

The quality of the retrieved studies was examined by two reviewers (MT, EP) using the Newcastle–Ottawa scale (NOS) for case-control and cohort studies and the modified NOS for cross-sectional studies [23]. With NOS, all studies are judged on the basis of eight items, grouped into three main categories (participant selection, group comparability and ascertainment of exposure/outcome); scores range from 0 to 9, with scores ≥7 indicating high-quality studies. Modified NOS evaluates seven methodological items and their reporting (scores 0–10), with scores≥7 consistent with high-quality studies. Any disagreements were resolved through consensus.

Outcome measures

The primary outcome measure was the oxygen consumption, expressed either as peak oxygen uptake (VO_2peak) during CPET (ml/min/kg or l/min) or as maximum oxygen uptake (VO_2max) (ml/min/kg). Secondary outcomes included: (i) separate evaluation of VO_2peak; (ii) separate evaluation of VO_2max; and (iii) oxygen consumption at anaerobic threshold (VO_2AT) (ml/min/kg or l/min). In a secondary analysis, we also examined the changes in the above outcomes in studies evaluating patients before and after kidney transplantation.

Data synthesis and analysis

Data analysis was performed using Review Manager (RevMan) version 5.3. For continuous data, the weighted mean between-group difference (WMD) was calculated with pertinent 95% confidence intervals (95% CI) when data were expressed in the same measurement scale. To pool studies that reported data on VO_2peak/VO_2max in different measurement scales (i.e., ml/min/kg or l/min), we calculated the respective standardized mean difference (SMD, with 95% CI). In case of multiple comparator groups (i.e. hemodialysis and peritoneal dialysis), we combined all relevant groups into a single group, to perform a single pair-wise comparison, according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [24]. Similarly, for subgroup analysis with a shared group (i.e., kidney transplant recipients) and different comparator groups (i.e., hemodialysis and peritoneal dialysis), the shared group was divided out approximately evenly among subgroup comparisons [24]. Study weights were estimated using the inverse variance method.

For the evaluation of statistical heterogeneity across studies, we used the Cochran's Q-test ($P < 0.1$ indicating existence of heterogeneity) along with the I^2 statistic (with a result >50% suggesting significant heterogeneity). Because of high clinical between-study heterogeneity, the random-effects meta-analytic model was applied to combine our data. To explore the robustness of our findings, we also employed a sensitivity analysis including only studies judged as of high quality (NOS score ≥7). For the total of the studies, subgroup analysis was performed based on (i) presence and type of renal replacement modality and (ii) time from transplantation surgery (dividing studies in those with strictly defined time from transplantation ≤12 months and in those with time from transplantation >12 months or without time selection criterion). Presence of publication bias was assessed by visual inspection of the corresponding funnel plot.

Results

Search results

The study selection process is presented in Fig. S1. Our initial search yielded 4918 records from the database searching and 26 from other sources. A total of 4683 studies were screened at a title/abstract level; following assessment of 130 records at full text, we excluded 118 studies. Overall, 12 studies met inclusion/exclusion criteria and were included in this systematic review [16–21,25–30]. From those, eight studies (with 461 participants) were included in the quantitative analysis for the primary question [16–18,21,25–27,29], since one study [28] had the same population sample with another included study in this review [16] and three studies included only patients before and after kidney transplantation [19,20,30]. Similarly, four studies with 144 participants were included in the quantitative analysis for the secondary question [19–21,30]. Corresponding authors of studies with inadequate data were contacted by e-mail requesting supplemental data, with none of them responding.

Study characteristics

The characteristics of the included studies are depicted in Table 1 and in Table S2. From studies eligible for the primary analysis, one study included comparisons between kidney transplant recipients and groups of patients with kidney failure before dialysis, hemodialysis and peritoneal dialysis patients [21]; two included comparisons between kidney transplant recipients and groups of hemodialysis and peritoneal dialysis patients [26,27]; six included comparisons between kidney transplant recipients and hemodialysis patients [16–18,25,28,29]. All included studies evaluated the primary outcome (either VO_2peak [16–18,27,28] or VO_2max [21,25,26,29]); three studies assessed also VO_2AT [21,25,27].

Quality assessment

The study quality assessment results for studies included in the primary analysis are presented in Table S3. According to the NOS score, six studies [17,18,21,25,27,28] were classified as high quality (NOS ≥ 7) and the remaining two studies as low quality [26,29].

Publication bias

Figure S2 depicts the funnel plot for assessment of publication bias. According to the figure, some publication bias may be present for the primary outcome, since some small studies expected in the bottom right quadrant are missing.

Oxygen consumption during CPET

When pooling all studies together, that is eight studies with 461 participants, kidney transplant recipients had significantly higher oxygen consumption at peak/max exercise compared to patients with kidney failure (SMD: 0.70, 95% CI 0.31–1.10), with high heterogeneity across studies (I^2 = 70%, P = 0.002; Fig. 1). In four studies with 171 participants that reported VO_2peak values, kidney transplant recipients showed borderline higher VO_2peak levels than patients with kidney failure (SMD: 0.31, 95%CI −0.04 to 0.66, I^2 = 11%, P = 0.34; Fig. 2a). In the four studies with 290 participants that report VO_2max values, kidney transplant recipients had higher VO_2max levels than patients with kidney failure (SMD: 1.07, 95% CI 0.57–1.57, I^2 = 66%, P = 0.03; Fig. 2b).

Oxygen consumption at anaerobic threshold

As depicted in Fig. S3, in two studies with n = 224 participants providing sufficient data about VO_2AT, kidney transplant recipients had significantly higher VO_2AT compared with patients with kidney failure (WMD 3.14, 95% CI 2.39–3.90, I^2 = 0%, P = 0.66).

Subgroup analysis

In subgroup analysis, we examined the differences in oxygen consumption of kidney transplant recipients with patients with kidney failure stratified by presence

Table 1. Studies included for primary analysis in this systematic review.

		Population		Age		Gender (male/female)	
Study	CPET parameters	KTR	Kidney failure patients	KTR	Kidney failure patients	KTR	Kidney failure patients
Lim *et al*. 2020 [21]	VO_2max, VO_2AT	81	85 (16 predialysis, 58 HD and 11 PD)	43.1 ± 14.2	49.7 ± 12.8	46/35	53/32
Painter *et al*. 1986 [26]	VO_2max, HRmax	20	30 (18 HD and 12 PD)	34 ± 9	HD: 45 ± 6 PD: 63 ± 10	13/7	17/13 (HD: 11/7 and PD: 6/6)
Painter *et al*. 2011 [17]	VO_2peak, Cardiac output (peak), Stroke volume (peak), HRpeak, a-VO_2diff, arterial O_2 content, mixed venous O_2 content	20	23 HD	43.5 ± 10.9	41.0 ± 11.3	17/3	20/3
Schneider *et al*. 2020 [27]	VO_2peak, HRpeak, VO_2AT, VEpeak, VE/VCO_2 slope, OUES	12	46 (20 HD and 26 PD)	53.3 ± 8.6	HD: 56.2 ± 11.3 PD: 61.2 ± 16.3	10/2	31/15 (HD: 14/6 and PD: 17/9)
Van den Ham 2007 [28]	VO_2peak, Workrate peak,	33	14 HD	52.1 ± 10.3	48.4 ± 11.9	18/15	9/5
Van den Ham *et al*. 2005 [16]	VO_2peak, VCO_2peak, HRpeak, HRRpeak, Workloadpeak	35	16 HD	49.0 ± 11.9	52.3 ± 10.4	18/17	10/6
Violan *et al*. 2002 [25]	VO_2max, HRpeak, VO_2AT,	12	9 HD	35.1 ± 12.9	27.1 ± 4.1	11/1	7/2
Petersen *et al*. 2012 [18]	VO_2peak, Workrate peak	9	10 HD	41.3 ± 10.6	39.2 ± 8.6	6/3	7/3
Kettner-Melsheimer *et al*. 1987 [29]	VO_2max, HRmax, Workload max	18	35 HD	36.0 ± 10.0	31.0 ± 11.0	14/4	28/7

AT, anaerobic threshold; CPET, cardiopulmonary exercise testing; HD, hemodialysis; HR, heart rate; KTR, kidney transplant recipients; OUES, Oxygen Uptake Efficiency Slope; PD, peritoneal dialysis; VE, ventilation; VO_2, oxygen uptake.

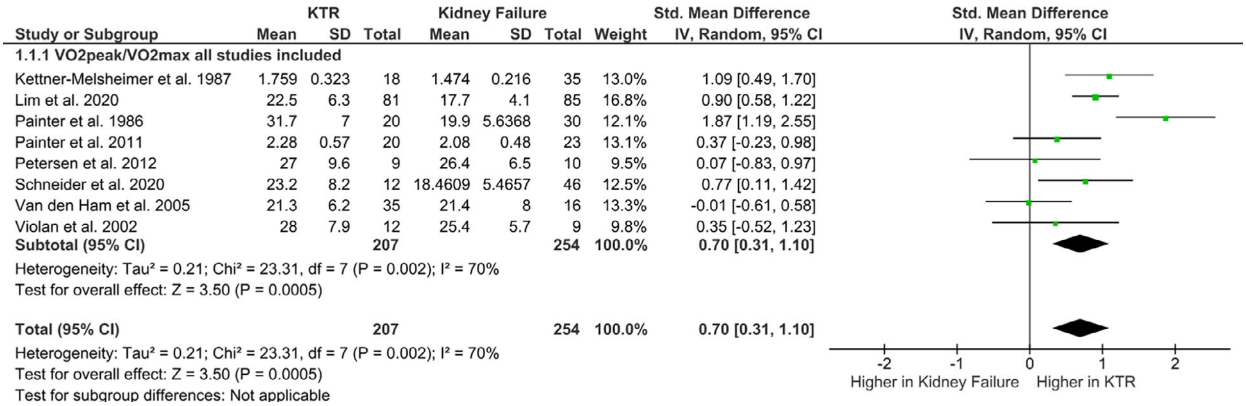

Figure 1 Difference in oxygen consumption at peak/max exercise (VO_2peak/VO_2max) during CPET between kidney transplant recipients (KTR) and patients with kidney failure.

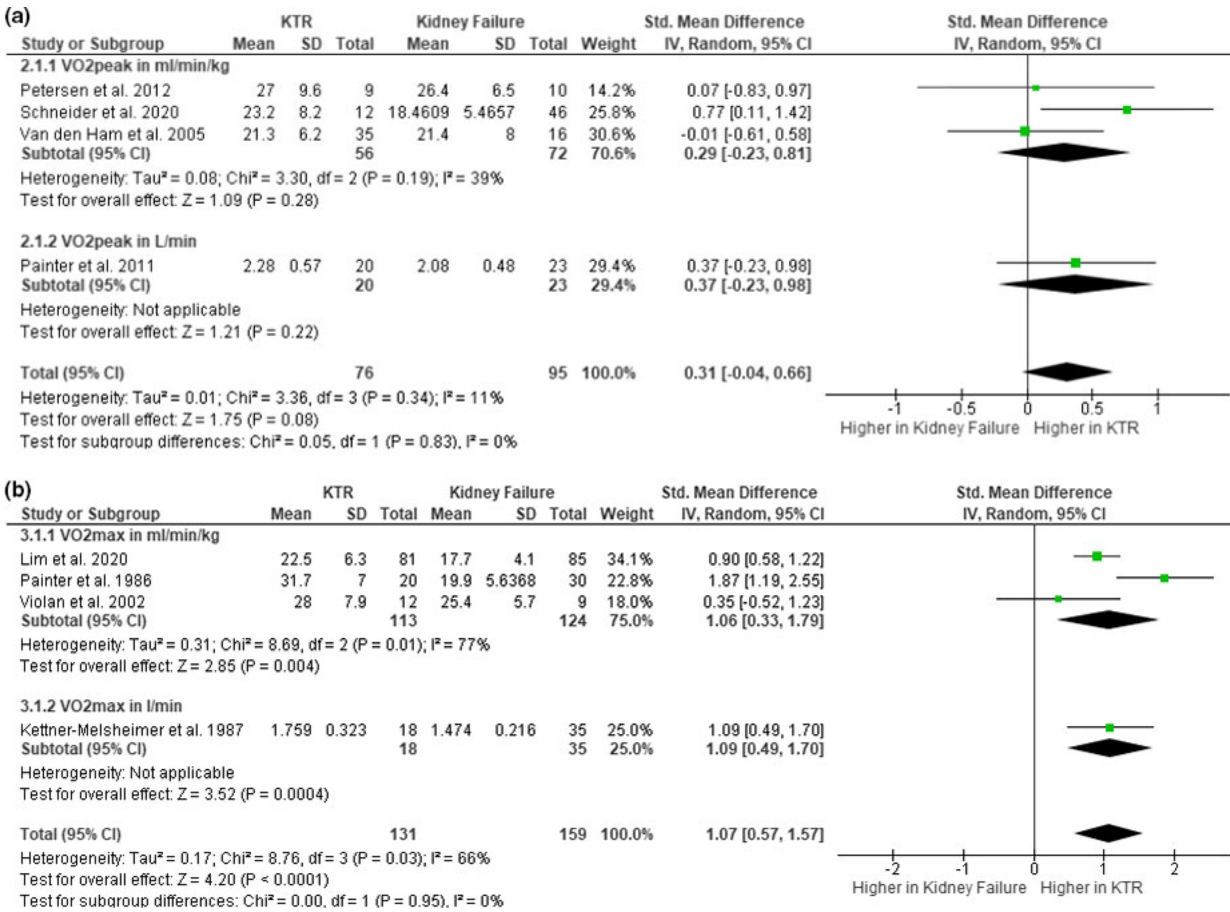

Figure 2 Difference in (a) peak oxygen uptake (VO_2peak) and (b) maximum oxygen uptake (VO_2max) during CPET between kidney transplant recipients and patients with kidney failure.

and type of renal replacement modality, as well as by time from transplantation surgery (≤12 months and >12 months). Only one study included patients with kidney failure before dialysis [21], which were grouped together with hemodialysis and peritoneal dialysis patients; this study was excluded from this subgroup analysis because of absence of data for individual subgroups. As presented in Fig. 3, among seven studies comparing oxygen consumption during CPET between kidney transplant recipients and hemodialysis patients,

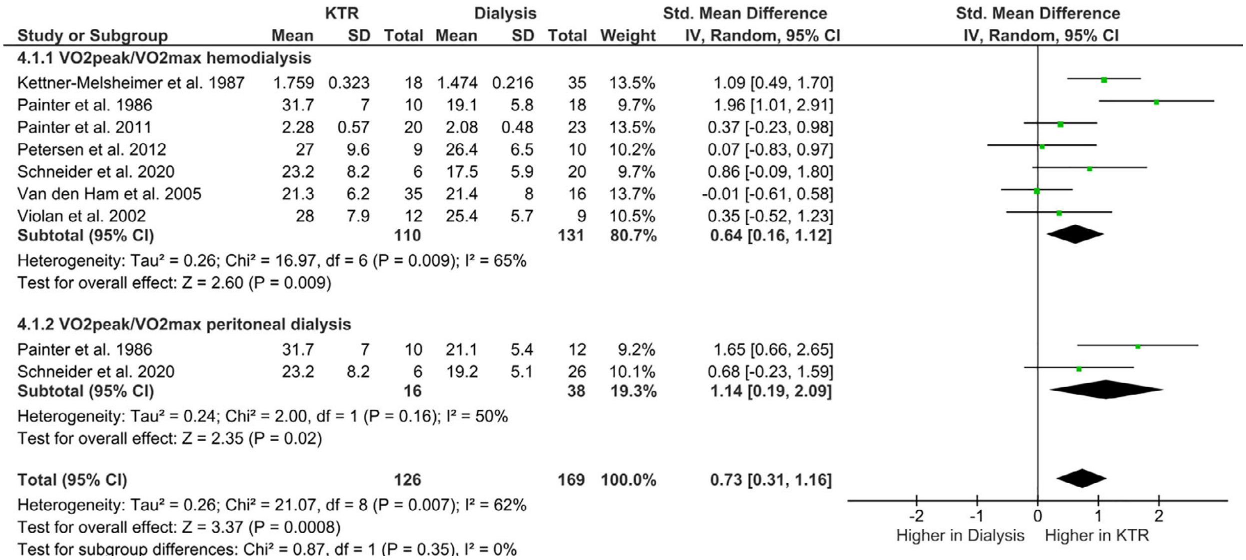

Figure 3 Difference in oxygen consumption at peak/max exercise (VO_2peak/VO_2max) during CPET between kidney transplant recipients (KTR) and patients with kidney failure under renal replacement therapy.

the former had significantly higher oxygen consumption at peak/max exercise (SMD: 0.64, 95% CI 0.16–1.12, I^2 = 65%, P = 0.009). In the two studies comparing kidney transplant recipients with patients on peritoneal dialysis subjects, the relevant difference was more pronounced (SMD: 1.14, 95% CI 0.19–2.09, I^2 = 50%, P = 0.16). Finally, as depicted in Fig. S4, in two studies with n = 76 participants providing sufficient data about oxygen consumption at peak/max exercise, no significant differences between peritoneal dialysis versus hemodialysis patients were observed (WMD 1.82, 95% CI −0.72 to 4.35, I^2 = 0%, P = 0.91).

As presented in Fig. S5, among two studies including patients with time from transplantation ≤12 months, kidney transplant recipients had higher oxygen consumption at peak/max exercise than patients with kidney failure (SMD: 0.70, 95% CI 0.20–1.21, I^2 = 56%, P = 0.13). Similarly, among five studies including kidney transplant recipients with time from transplantation >12 months, kidney transplant recipients had significantly higher oxygen consumption at peak/max exercise compared with patients with kidney failure (SMD: 0.88, 95% CI 0.29–1.46, I^2 = 69%, P = 0.01).

Sensitivity analysis

To explore the robustness of our findings, we repeated the main analysis by including only high quality studies (NOS score ≥7) identified in the quality assessment process. In six studies with high quality including 358 participants, kidney transplant recipients had again significantly higher oxygen consumption at peak/max exercise compared with patients with kidney failure (SMD: 0.48 95% CI 0.13–0.8; I^2 = 50%, P = 0.07; Fig. S6).

Oxygen consumption before and after kidney transplantation

Four studies evaluated cardiovascular reserve before and after kidney transplantation [19–21,30]. In all the above, the CPET examination before kidney transplant surgery

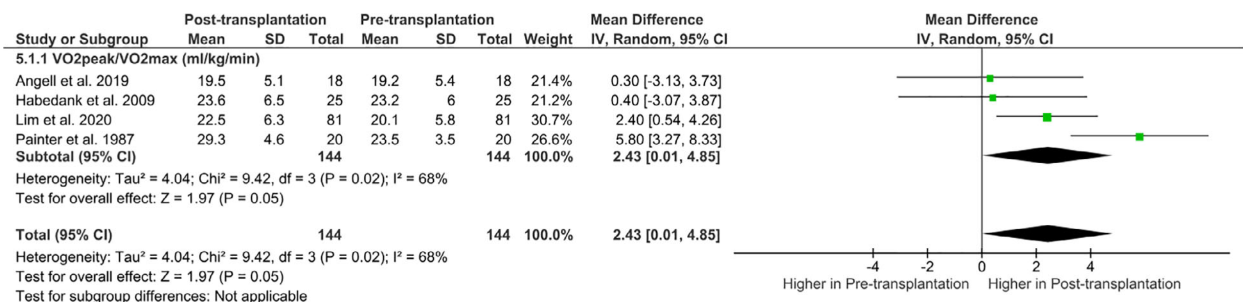

Figure 4 Differences in oxygen consumption at peak/max exercise (VO_2peak/VO_2max) during CPET before and after kidney transplantation.

was performed within 0–4 weeks prior to surgery. One study evaluated the recipients at 8 weeks [30], one at 14 weeks [19], and two at 12 months [20,21] after transplant surgery. In pooled analysis (Fig. 4), oxygen consumption during peak/max exercise was significantly improved after kidney transplantation compared to pretransplantation values (WMD: 2.43, 95% CI 0.01–4.85, $I^2 = 68\%$, $P = 0.02$). In two studies with 43 participants that reported VO_2peak values, no significant differences between post- and pretransplantation values were observed (WMD: 0.35, 95% CI −2.09 to 2.79, $I^2 = 0\%$, $P = 0.97$; Fig. S7a). In the two studies with 101 participants that report VO_2max values, VO_2max was significantly improved after kidney transplantation compared to pretransplantation values (WMD: 3.99, 95% CI 0.66–7.31, $I^2 = 78\%$, $P = 0.03$; Fig. S7b).

Discussion

This is the first systematic review and meta-analysis of studies utilizing CPET to assess the differences in cardiovascular functional reserve between kidney transplant recipients and patients with kidney failure. The main finding of the primary analysis is that kidney transplant recipients exhibit significantly better cardiovascular functional reserve during CPET compared with patients with kidney failure. These observations were independent of dialysis modality, since they were evident in subgroup analyses against either hemodialysis or peritoneal dialysis patients, and independent of time from transplantation surgery. Sensitivity analysis including only high-quality studies confirmed these results. With regard to the secondary question cardiovascular functional reserve was found to be significantly improved in kidney transplant recipients at 2–12 months after kidney transplantation in relation to presurgery levels.

Exercise tolerance is determined by a wide range of factors, including performance of cardiovascular system (cardiac and peripheral vascular function), mechanical constraints of respiratory system and pulmonary gas exchange, hemoglobin concentration, and skeletal muscle metabolism [11]. The diminished exercise tolerance of CKD patients is multifactorial; impaired cardiac function, vascular dysfunction, anemia, uremic myopathy, and neuropathy can impact the muscle oxygen utilization during activity and subsequently exercise capacity [31–33]. In addition to the above, deconditioning is part of a vicious cycle leading to exertional fatigue and further physical inactivity resulting in deterioration of exercise tolerance in the same population [34].

Cardiopulmonary exercise testing is a dynamic, noninvasive technique that is long considered to be the gold standard for evaluating the degree and differentiating the causes of exercise intolerance and reduced cardiovascular functional reserve [35,36]. Oxygen uptake (VO_2) is the volume of O_2 extracted from the air inhaled during pulmonary ventilation in a period of time. It is usually expressed in ml/min/kg or l/min. VO_2max reflects the maximal ability of a person to take in, transport, and use oxygen, and it is the basic measurement during CPET. VO_2max is historically defined by the VO_2 plateau demonstrated by analysis of a series of high intensity constant work-rate tests [37]. However, the flattening of the Vtype="InCombining_Diacritical_Marks">O_2-work rate relationship is often not seen during incremental exercise tests; thus, in practice the highest VO_2 achieved for a presumed maximal exercise effort (VO_2peak), which equals the VO_2max in normal subjects, is used interchangeably with VO_2max [11]. As both VO_2max and VO_2peak are not reported in all studies of interest in this meta-analysis, we have prespecified a primary outcome of either of the above metrics and also provided separate pooled estimates of either of two, for reasons of accuracy.

As mentioned above, previous studies showed that hemodialysis and peritoneal dialysis patients had significantly impaired cardiovascular functional reserve compared with essential hypertensives [13] and healthy controls [15,38]. However, when compared with patients with advanced predialysis CKD, no significant differences between hemodialysis and predialysis CKD patients in VO_2peak and other CPET-derived parameters were observed [39]. Several recent studies including mostly patients with CKD under dialysis investigated the effects of various interventions (mostly rehabilitation programs) on cardiovascular functional reserve and physical functioning. Recent meta-analyses of such studies showed that various types of exercise training can substantially improve cardiovascular functional reserve, physical functioning, and quality of life in this population [40–42].

Receiving a kidney transplant is the optimal treatment for patients with kidney failure as it is associated with reduced cardiovascular morbidity and overall mortality and improved quality of life [5]. As such, one could hypothesize that kidney transplantation would be also associated with improved cardiovascular functional reserve and physical functioning. However, the results of the few previous studies in this field were not all to the same direction, a fact that could be related to the power and design of the individual studies and the characteristics of the studied populations. In the studies from Petersen *et al.* [18] and van den Ham *et al.* [16], no significant differences in oxygen consumption indexes between hemodialysis and kidney transplanted patients were observed. In contrast, Schneider *et al.* [27], reported that kidney transplant recipients had significantly higher VO_2peak and VO_2AT compared with hemodialysis individuals, while Painter *et al.* [17] showed that they had significantly higher VO_2max than hemodialysis and peritoneal dialysis patients [26]. Moreover, in the recent CAPER study, kidney transplant recipients one year after transplantation had higher VO_2max than the patients with kidney failure, but the value did not reach the VO_2max of controls having essential hypertension [21]. Our findings help to clarify both the above issues, by showing significantly increased oxygen consumption during CPET in kidney transplant recipients compared to subjects with kidney failure, as well as after in relation to before transplant surgery. The underlying mechanisms of these associations have not been identified previously. Kidney transplant recipients are commonly have lower prevalence of anemia and are younger than dialysis individuals [43]. A hemoglobin decrease of 3 g/dl results in approximately 20% decrease in blood oxygen-carrying capacity and relevant VO_2peak decline, independently of the cardiac output [44]. In the same context, age is also known to have a significant influence on CPET parameters [45]. Even in those included studies with the best design, between group differences in age, hemoglobin, and other cardiovascular risk factors, including phosphorus, parathormone, albumin, and hs-CRP levels existed [46]. Hence, it is likely that improvement in all these factors following kidney transplantation significantly contributes to the increased cardiovascular functional reserve in the kidney transplant recipients; future proper-designed efforts are needed to examine these phenomena and shed light in the field.

To our knowledge, this is the first meta-analysis of studies examining differences in cardiovascular functional reserve using CPET between kidney transplant recipients and patients with kidney failure, as well as before and after kidney transplantation. We performed a careful literature search of major databases and followed a rigorous methodology, according to relevant recommendations [24]. Apart from the primary outcome of VO_2max or VO_2peak, we also searched for other CPET parameters (VO_2AT). We also included subgroup analyses according to dialysis modality and sensitivity analyses. However, the present study has some limitations. First, we observed high clinical heterogeneity across the included studies; we attempted to minimize its influence by using the random-effects model and performing subgroup analyses. Second, our search was restricted in English-language journals and studies published in non-English journals could have been missed. Most of the included studies did not report the prevalence of major comorbid conditions or excluded individuals with common diseases (such as diabetes and ischemic heart disease), and thus, we were not able to perform subgroup analyses on the basis of presence or absence of common co-morbidities. In addition, the majority of the included studies did not provide data on immunosuppressive medication in a form that would allow us to perform further analyses and investigate potential effect of immunosuppressive drugs on possible differences in CPET parameters examined. Most primary studies also did not report information about the presence of arteriovenous fistulas or grafts, and none included separate comparisons for patients with or without arteriovenous fistulas or grafts; thus, any effect of these types of vascular access on CPET parameters could not be assessed. Finally, although we tried to retrieve missing data for the primary and secondary outcomes by contacting corresponding authors of the primary studies, we could not use data from a few studies because of missing values.

In conclusion, this systematic review and meta-analysis suggests that kidney transplant recipients have significantly better cardiovascular functional reserve compared to patients with kidney failure. This should be a combined result of kidney transplantation as the pooled analyses of relevant studies suggest significantly improvement in cardiovascular functional reserve at evaluations after kidney transplantation in relation to presurgery levels. Thus, improvement in cardiovascular reserve and exercise tolerance assessed with CPET should be added in the list of benefits that kidney transplantation has to offer in comparison with dialysis modalities. Elegant future studies are warranted to delineate which factors contribute toward these improvements in kidney transplant recipients among the array of cardiac, vascular, respiratory, and neuromuscular and physical activity functions that affect cardiovascular functional reserve.

Authorship

PS and AB: research idea and study design. MT and AB: manuscript drafting; MT, EP, MA and DP: data acquisition. MT and MA: statistical analysis. PS, KD and EK: data interpretation. AP and PS: supervision.

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Conflicts of interest

The authors declare no conflicts of interest.

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None.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Keywords and search strategy used for this systematic review and meta-analysis.

Table S2. Information about time from transplantation and use of concomitant immunosuppressive medication in the kidney transplant recipients of the included studies.

Table S3. Quality evaluation of the included studies for the primary analysis according to Newcastle-Ottawa Scale (NOS).

Figure S1. Flow diagram of study selection process.

Figure S2. Funnel plot assessing publication bias for the primary outcome.

Figure S3. Difference in oxygen consumption at anaerobic threshold (VO_2AT) during CPET between kidney transplant recipients (KTR) and patients with kidney failure.

Figure S4. Difference in oxygen consumption at peak/max exercise (VO_2peak/VO_2max) during CPET between hemodialysis and peritoneal dialysis patients

Figure S5. Difference in oxygen consumption at peak/max exercise (VO_2peak/VO_2max) during CPET between kidney transplant recipients (KTR; with time from transplantation ≤12 months and >12 months, respectively) and patients with kidney failure.

Figure S6. Difference in oxygen consumption at peak/max exercise (VO_2peak/VO_2max) during CPET between kidney transplant recipients and patients with kidney failure [only high quality studies (NOS score ≥7)].

Figure S7. Differences in oxygen consumption at (a) peak oxygen uptake (VO_2peak) and (b) maximum oxygen uptake (VO_2max) during CPET before and after-kidney transplantation.

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