



CKJ REVIEW

Exercise training in patients after kidney transplantation

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ABSTRACT

Kidney transplantation is the treatment of choice for patients with end-stage renal disease. Next to the risk of allograft failure, major obstacles for disease-free survival after kidney transplantation include a higher incidence of cancer, infection and cardiovascular events. Risk factors for adverse clinical outcomes include pre-existent comorbidities, the introduction of an immunodeficient status and (lack of) lifestyle changes after transplantation. Indeed, physical inactivity and poor physical fitness are important targets to address in order to improve clinical outcomes after kidney transplantation. This review summarizes the current evidence on exercise training after kidney transplantation, derived from randomized controlled trials. As much as possible, results are discussed in the perspective of the Standardized Outcomes in Nephrology-Transplantation core outcomes, which were recently described as critically important outcome domains for trials in kidney transplant recipients.

Keywords: clinical trial, exercise, kidney transplantation, physical activity, systematic review

KIDNEY TRANSPLANTATION: A SPECIFIC ENTITY

Solid organ transplantation (SOT) has emerged from an experimental approach in the 20th century to now being an established treatment option for patients with end-stage organ dysfunction. Over the past decades, the field of SOT has seen considerable advances in surgical techniques and pharmacotherapy [1]. Remaining obstacles for long-term disease-free survival after SOT include allograft rejection, malignancy, infection and a tremendously high cardiovascular (CV) risk [2–4]. Risk factors for adverse outcomes, some of them modifiable, include pre-existing conditions, the introduction of an immunodeficient status and (lack of) lifestyle changes after transplantation. This holds true for all SOT recipients, but kidney transplant recipients

(KTRs) have some specific features in the light of which existing literature on SOT should be carefully interpreted.

First, about half of all incident patients with end-stage renal disease worldwide are >65 years of age [5, 6]. This results in a higher proportion of ‘older’ KTRs compared with other SOT recipients. In the Eurotransplant countries, about one in four kidney transplantations is performed in a recipient >65 years of age which is rather uncommon for heart, lung and pancreas transplantations. Next, advancements in dialysis techniques allow for a variable, sometimes very long, waiting time on dialysis. However, this is counterproductive, as the waiting time on dialysis negatively impacts post-transplant survival [7]. The majority of deceased-donor KTRs required a waiting time of 2–4 years, compared with 0–5 months for liver, heart and lung transplant recipients. This chronic disease burden has great

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impact on the progression of comorbid conditions and quality of life and translates to poor physical function, a summary measure of health and an independent predictor of mortality post-transplantation [8]. Apart from age and comorbidities, another specific challenge for KTRs is organ function after transplantation. Many KTRs have an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² 1 year after transplantation, placing them in chronic kidney disease (CKD) Stage 3 or worse [9]. As such, the pre-transplant uraemic state may continue to exist, but at a decreased severity. However, KTRs are different from CKD patients without transplantation as they require immunosuppressive therapy on a daily basis. Common side effects of immunosuppressive regimens comprise hypertension, hyperlipidaemia, diabetes mellitus, nephrotoxicity and anaemia. In the long run, this immunosuppressed state places the patients at a higher risk of cancer, CV disease and infection [10].

PHYSICAL INACTIVITY AND POOR PHYSICAL FITNESS AS MODIFIABLE RISK FACTORS FOR ADVERSE CLINICAL OUTCOMES

An overview of relevant terminology is given in Table 1. Low physical activity and poor physical fitness are integral features of SOT, with a debilitating impact on quality of life [11]. In KTRs, low physical activity is associated with higher CV and all-cause mortality [12, 13]. Pre-transplantation physical activity levels predict all-cause mortality in KTRs [14] and greater physical activity in *de novo* KTRs associates with improved graft function in the initial year post-transplant [15]. Although KTRs modestly improve their physical activity status compared with patients with advanced CKD, relatively few patients meet the minimum recommendations [16, 17]. The World Health Organization (WHO) recommends ≥ 150 min of moderate-intensity, ≥ 75 min of vigorous-intensity or an equivalent combination of moderate- and vigorous-intensity aerobic physical activity on a weekly basis [18]. Physical activity levels in KTRs are in fact lower than similar-aged patients with rheumatoid arthritis and osteoarthritis [13]. Different factors contribute to low physical activity levels in KTRs, both at the environmental and individual level, such as fear of harming the graft [16, 19]. Multiple comorbidities

and immunosuppressive drugs (corticosteroids in particular) impaired physical fitness are also at play [16, 20].

In line with physical activity, physical fitness does not fully normalize after transplantation [21, 22]. This definitely adds to the vicious circle of inactivity. Many KTRs are considered sarcopenic (low muscle strength, muscle mass and physical function/performance) [23, 24] and frail [25], which may or may not be in combination with obesity. After transplantation, an increase in cardiorespiratory fitness is seen, but peak oxygen uptake (VO_{2peak}) remains lower than that in age-matched healthy controls [21, 26]. VO_{2peak} is a potentially stronger predictor of mortality than smoking, hypertension, hypercholesterolaemia and type 2 diabetes [27]. In healthy adults, each 1 metabolic equivalent of task (MET; 3.5 mL/kg/min) improvement in VO_{2peak} is associated with a 15% reduction in CV events and a 13% reduction in all-cause mortality [28].

Given their relation with adverse clinical outcomes, physical inactivity and physical fitness represent important targets for intervention in KTRs [26, 29–32]. In the general population, the pleiotropic health benefits of physical activity and exercise include attenuation of CV and cancer risk, as well as beneficial effects on metabolic, muscular, bone, digestive, reproductive and mental health [33–37]. Regular exercise at moderate intensity is also associated with lower infection rates, but excessive strenuous exercise may induce immune dysfunction [38].

The current review critically revises the available evidence on the effects of exercise training programmes in KTRs from randomized controlled trials (RCTs). The search strategy is given in Table 2. Interventions addressing solely physical activity are beyond the scope of this review, but physical activity and exercise training interventions are clearly a continuum with a sustainable active lifestyle as the ultimate goal.

EFFECTS OF EXERCISE TRAINING: EVIDENCE FROM RCTS

Outcomes of interest

Seventeen RCTs (Table is provided in [supplementary file](#)) report on a wide variety of different outcomes and exercise interventions. Consensus-based identification of critically important

Table 1. Exercise terminology (adapted from references 39–43)

Physical activity	Any bodily movement produced by skeletal muscles that result in energy expenditure. Physical activity refers to all movement including during leisure time, for transport to get to and from places or as part of a person's work
Exercise and exercise training	A subset of physical activity that is planned, structured and repetitive and has as a final or an intermediate objective the improvement or maintenance of physical fitness
Physical fitness	A set of attributes that is either health- or skill-related or that has the ability to perform physical activity. Health-related physical fitness encompasses cardiorespiratory fitness, musculoskeletal fitness and motor fitness
Cardiorespiratory fitness Synonym: aerobic capacity	The capacity of the CV, respiratory and muscular system to supply and combust oxygen for execution of physical activity. Often expressed as VO_{2max} or VO_{2peak} . The latter is the peak oxygen consumption by the body achieved during maximal incremental exercise testing
Musculoskeletal fitness	The combination of muscular strength (force generation with a single maximal effort), muscular endurance (capacity to resist repeated contractions over time or a voluntary contraction for a prolonged period of time), muscular power (high-velocity maximal force production in as short a time as possible) and muscular flexibility (extensibility of muscle, tendon, fascia and joint structures enabling joint movement throughout a full range of motion)
Motor fitness	Physical traits related to speed (ability to perform a movement within a short period of time), agility (ability to rapidly change body position in space with speed and accuracy) and balance (ability to maintain equilibrium while stationary or moving)
Physical functioning	The ability to perform physical demands of daily life

Table 2. Search strategy

Sources	Electronic search on the database of PubMed; all eligible articles to 1 November 2020 Handsearching of references
Eligibility criteria	Population: adult (≥ 18 years) male and female KTRs, irrespective of the time after transplantation. No combined transplantations Intervention: all types of exercise training studied in RCTs Comparator: usual care or minimal intervention Outcomes: safety, feasibility, mortality, malignancy, hospital admissions, CV events, CV risk factors, graft function, quality of life, physical fitness (cardiorespiratory fitness, musculoskeletal fitness, motor fitness), physical function, body composition, bone health, fatigue, long-term physical activity, social connectedness, employment rate and implementation potential (amongst other including implementation cost, cost-effectiveness, feasibility, sustainability, penetration) Publication language: only English, French, Dutch and German reports
Data collection	Study authors (S.D.S. and A.V.C.) screened the literature and performed data extraction
Search query	Exercise training AND (kidney transplantation OR renal transplantation)

outcome domains for trials in KTRs was recently established by the Standardized Outcomes in Nephrology-Transplantation (SONG-Tx) initiative [44]. A large sample of patients, family members and healthcare professionals acknowledged graft health, CV disease, cancer, infection, life participation and mortality as core outcomes critically important for all stakeholder groups. Although a thorough selection process generated an initial list of 35 outcome domains to be graded on their importance, some outcome domains relevant to the field of physical rehabilitation may have been left out. From the perspective of the rehabilitation field, physical fitness and physical functioning are considered important outcomes. Both are closely related to mortality, CV disease and life participation after kidney transplantation [12, 13, 26, 29–32, 45]. Next, in the evaluation of an exercise intervention, reporting of exercise-induced injuries or any other adverse events is mandatory. Figure 1 gives a schematic overview of the effects of exercise training in KTRs.

Long-term (>12 months) effects of exercise training

The SONG-Tx outcomes are typically long-term outcomes, and none of them are addressed in the available studies. Only five records from four studies reported follow-up data at ~12 months after the start of the intervention [46–50]. Importantly, in three of four studies the intervention rather than the follow-up itself was long term. In the study by Painter *et al.* [46, 50], 167 KTRs were recruited within 1 month after transplantation to investigate the effects of 11 months of home-based aerobic exercise training *versus* usual care. The study was powered to detect changes in VO_{2peak} , which significantly improved in the intervention compared with the control group. Other outcomes comprised muscle strength (improved) [46], body composition (no change) [46], quality of life (improved) [46] and CV risk factors (no change) [50]. Exercise training did not affect mortality ($n = 1$ death in each group). Two patients allocated to usual care *versus* none of the patients in the training group dropped out due to graft rejection. One patient in usual care dropped out due to CV concerns, but no other CV events were reported. No significant effect of exercise training was seen on graft function as assessed with creatinine levels.

Another 12-month training study by Korabiewska *et al.* [47] recruited 67 recipients immediately after transplantation to investigate the effects of an exercise regimen composed of resistance, walking, breathing, coordination and relaxation exercises. In addition to a lot of methodological flaws, this study

did not report on mortality, CV events or any other adverse events that may have occurred. Although this study did not include clear statistical reports on graft function, reported data did not suggest any effect of exercise training on creatinine levels.

A pilot study by Tzvetanov *et al.* [48] in 17 *de novo* obese KTRs investigated the effects of 12 months of individually supervised, low-impact, low-repetition resistance training in conjunction with cognitive behaviour therapy and nutritional advice. eGFR in the exercise group tended to improve compared with usual care, although without significant group differences in serum creatinine. No deaths occurred throughout the study period. Interestingly, a significantly higher employment rate was observed in the intervention group.

O'Connor *et al.* [49] studied the long-term effects of 3 months of aerobic training *versus* resistance training *versus* usual care on arterial stiffness at 9 months follow-up (12 months after training initiation) in 60 *de novo* recipients. Exercise training, and resistance training in particular, appeared to induce a long-term beneficial effect on arterial stiffness. There were no deaths across the sample. A CV event occurred in both the aerobic and resistance training groups, but not in the usual care group. One myocardial infarction was deemed unrelated to the exercise intervention and occurred in a participant in the resistance training group who was non-compliant with all medications. The other CV event occurred in a participant in the aerobic training group who was non-compliant with the exercise intervention and was investigated for a pre-existing cardiac issue. There were 11 unplanned hospitalizations across the sample: 7 in usual care, 3 in the aerobic training group and 1 in the resistance training group. Six episodes of graft rejection occurred: 3 in usual care, 1 in the aerobic training group and 2 in the resistance training group. Graft function at 12 months post-transplant was not reported.

In conclusion, current available evidence falls short in the formal evaluation of the SONG-Tx core outcomes. Indirect evidence points to the absence of exercise-induced effects on mortality, graft health and major CV events in the first year after transplantation. Arterial stiffness, a surrogate marker of CV disease, improves after training. No data exist regarding the effect of exercise training on the incidence of malignancy and infections in KTRs. Only one study reports on the formal outcome of life participation (i.e. employment rate). Therefore, high-quality RCTs with long-term follow-up assessments of core outcomes are eagerly awaited.

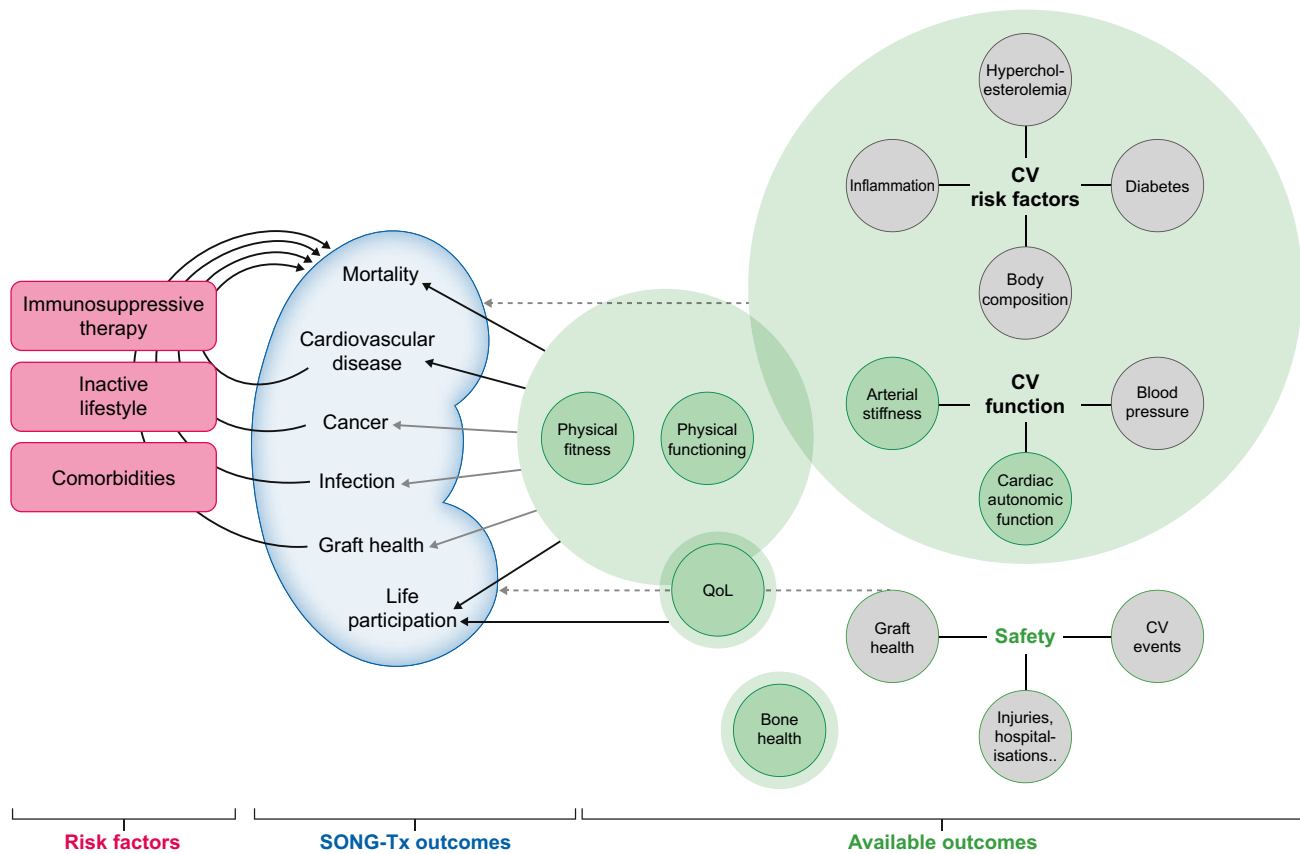


FIGURE 1: Schematic representation of the effects of exercise training on different outcome domains. The SONG-Tx outcomes have not been directly addressed in the RCTs. The available outcomes of the RCTs are somehow linked to the SONG-Tx outcomes (thickness of the line represents the strength of the association). Green circles represent clear evidence of exercise-induced improvement; grey circles represent no exercise-induced effects.

Short-term (<12 months) effects of exercise training

Health-related physical fitness and physical function. Aerobic exercise with [51–54] or without [46, 55] resistance training is effective in improving cardiorespiratory fitness in both *de novo* and stable KTRs. Although not a consistent finding [56], some data suggest resistance training on its own improves cardiorespiratory fitness in *de novo* [55] and stable [52] recipients. However, these training effects were reported to be less sustainable compared with those elicited by aerobic exercise [49]. Recent data in a small group of 12 KTRs suggest discarding whole-body vibration training as an efficient strategy to improve cardiorespiratory fitness [58].

Ample evidence also shows resistance training, with [47–49] or without [55, 57] aerobic training, improves muscle strength, irrespective of the time after transplantation. Eleven months [46], but not 3 months [55], of aerobic training were reported to improve muscle strength in *de novo* recipients. Resistance training in stable recipients improved lower body muscular endurance assessed by the 60-s sit-to-stand test (STS; physical function) test [57]. In *de novo* recipients, both aerobic and resistance training improved lower body muscular endurance over time [55]. However, only patients engaged in 3 months of resistance training showed greater STS repetitions compared with usual care [55]. A brief study investigating early physiotherapy during a 7-day hospitalization period after transplantation found no effects on upper or lower body muscle strength [59].

Several RCTs evaluated physical function assessed with the 6-min walk test (6MWT) [54, 57, 59], 60-s STS [55, 57] and the 8-foot timed up and go (TUG) test [57]. The 6MWT correlates well with cardiorespiratory fitness, the 60-s STS can be considered an estimate of lower body muscular endurance and the 8-foot TUG test requires a combination of speed, agility and dynamic postural stability. Compared with usual care, early physiotherapy after transplantation did not improve 6MWT results at hospital discharge (7 days post-transplant) [59]. However, 10–12 weeks of resistance training, with or without aerobic training, improved 6MWT results in stable KTRs [54, 57]. Resistance and aerobic training on their own also improved 60-s STS results [55, 57]. Finally, resistance training was shown to improve the 8-foot TUG test [57].

Not a single study reported exercise benefits on isolated postural balance. Although often neglected, the clinical value of exercise training to reduce falls and related complications is not to be underestimated [60, 61].

Graft health. The evaluation of graft function was included in several studies, but never as a primary outcome [54, 55, 59, 62]. Two studies investigated the impact of a short-term (7 days–5 weeks) exercise training programme initiated immediately after transplantation; no effects on creatinine levels were observed [59, 62]. In the study by Juskowa *et al.* [62], no formal between-group comparison was reported. One small study reported a beneficial effect of a 12-week combined resistance and aerobic training programme on renal function [54]. Indeed,

creatinine levels decreased and eGFR increased significantly in the intervention group ($n = 7$), whereas an increase in creatinine levels and worsening of eGFR was observed in the control group ($n = 5$). Although the authors describe a *post hoc* power of 0.9 to detect significant changes in renal function, the unexplained decrease in renal function in the control group remains somewhat puzzling. In a well-designed RCT evaluating 12-week home-based aerobic ($n = 13$) or resistance ($n = 13$) training in *de novo* recipients (~7 months after transplantation), no significant effects on creatinine levels or eGFR were observed in comparison with usual care ($n = 20$) [55].

CV function and risk factors. Short-term effects on surrogate markers of CV disease are readily addressed in existing RCTs. Blood pressure (BP; $n = 8/17$) and blood lipid profile ($n = 6/17$) appear to be the most often assessed outcomes. Other outcomes include arteriosclerosis (arterial stiffness; $n = 2/17$), cardiac autonomic function (heart rate variability and baroreceptor sensitivity; $n = 2/17$), obesity [body mass index (BMI); $n = 5/17$], body composition (fat and fat-free tissue analysis; $n = 5/17$), diabetes ($n = 6/17$) and chronic low-grade inflammation ($n = 2/17$).

CV function. BP, ARTERIAL STIFFNESS AND CARDIAC AUTONOMIC FUNCTION. BP was reported in eight studies (one aerobic training, two resistance training, four combined training, one whole-body vibration), but none showed exercise training to modulate 24-h ambulatory BP [52] or BP at rest [48–51, 55, 56, 58]. Peak exercise diastolic but not systolic BP, however, was shown to decrease with 6 months of combined training compared with usual care [51].

Despite a lack of effect on BP, in *de novo* KTRs both aerobic and resistance training improved arterial stiffness, assessed with carotid–femoral pulse wave analysis as the primary outcome, after 3 months of training [55]. Resistance training resulted in a more sustainable effect 12 months after training initiation [49]. Conversely, a combined 6-month training programme in stable KTRs did not have an impact on small and large arterial compliance assessed by computerized arterial pulse waveform analysis [52]. Whether these discrepant findings reflect a power issue (unlikely, since the sample size is comparable), characteristics of the study populations (*de novo* KTRs versus stable KTRs several years after transplantation), differences in assessment of arterial stiffness or a true effect of the exercise modality remains to be elucidated.

Lastly, 6 months of training considerably improved autonomic regulation of the heart [51]. Exercise training increased both vagal and sympathetic cardiac modulation while shifting the autonomic balance towards greater vagal control. Whole-body vibration training on the other hand was shown to be ineffective in improving autonomic cardiac activity [58].

CV risk factors. BLOOD LIPID PROFILE. Two studies reported aerobic and resistance exercise benefits on the total cholesterol (TC):high-density lipoprotein cholesterol (HDL-C) ratio [50, 62] and one study [63] reported that combined exercise improved TC, low-density lipoprotein cholesterol (LDL-C) and triglycerides. However, most training interventions failed to impact TC [48, 50, 52, 56, 62], HDL-C [48, 50, 52, 56, 62, 63], LDL-C [48, 56, 62] and/or triglycerides [48, 56, 62]. Of note, the blood lipid profile is frequently studied, but never as a primary outcome.

BODY WEIGHT AND BODY COMPOSITION. Body weight, BMI and the proportion of overweight or obese patients rapidly increased after transplantation [64–65]. Excessive weight gain in the initial

1–2 years post-transplant is a risk factor for death and graft failure, irrespective of pre-transplant BMI [64–66]. Furthermore, independent of other CV risk factors, obesity at 1-year post-transplant increases the risk for death and graft failure [64]. Many patients are sarcopenic pre-transplant [67]. Lean body mass further deteriorates in the early aftermath of transplantation [68], following which no or only modest improvements take place [46, 69, 70]. Low muscle mass is therefore a common condition in KTRs [71] that, together with excessive fat accretion, leads to a dual disturbance in body composition known as sarcopenic obesity [72].

Current evidence is not supportive of a beneficial effect of aerobic, resistance or combined exercise training on the evolution of body weight or BMI, irrespective of the length of training and follow-up [46, 48, 54–56]. However, BMI is a crude tool that does not provide any insights into body composition. Using dual-energy X-ray absorptiometry scans, the increase in lean mass, fat mass and percent body fat in *de novo* KTRs was found to increase to a similar extent in usual care and patients receiving aerobic [46] or resistance training [56]. Three months of combined training in stable recipients likewise failed to improve skinfold-based lean mass compared with usual care [52]. One could speculate that participants in the latter study did not train at sufficient intensity [50% 1 repetition maximum (RM)] to induce muscle hypertrophy. However, 10 weeks of resistance training at ~75% 1 RM also failed to increase muscle hypertrophy assessed by ultrasound [57]. The small ($n = 12$) study by Lima *et al.* [49] was the only one reporting that 3 months combined aerobic and resistance training reduces fat percentage and improves fat-free and lean body mass, compared with no significant within-group effects in the usual care group.

In conclusion, there is a lack of convincing effect of any studied type of training on body weight and composition. In healthy adults and frail elderly patients, a combination of resistance training with dietary protein supplementation appears to be effective in inducing a muscle hypertrophic response and improving lean mass [73, 74]. Whether a combination of exercise training and interventions regarding quality, distribution and total intake of dietary protein would also have a beneficial effect in KTRs remains to be established [75–77].

GLUCOSE HOMEOSTASIS AND DIABETES. In the study by Painter *et al.* [50], 11 months of home-based aerobic training did not change the percentage of patients pharmacologically treated for diabetes. Another home-based training study reported that new-onset diabetes after transplant (NODAT) developed in 10% ($n = 2$) of patients allocated to usual care versus 31% of patients allocated to home-based aerobic ($n = 4$) or resistance ($n = 4$) training [49]. Blood glucose in the fasting state or at the end of a 2-h oral glucose tolerance test, glycated haemoglobin (HbA1c) or the homeostatic model of assessment of insulin resistance (HOMA-IR) were not affected by training protocols aimed at increasing muscle strength either during [62] or after [48, 56] the post-transplant hospitalization period.

Despite overwhelming evidence on the beneficial effects of exercise on glycaemic control in patients with type 2 diabetes mellitus, current RCTs in KTRs fail to prove any significant effect on the prevalence and incidence of NODAT or on glycaemic control in general [78–80]. Current studies might be underpowered to detect a training effect or the type of exercise training might be particularly relevant. The training prescription may need to combine aerobic and resistance training, increase training volume, increase aerobic training intensity and/or implement aerobic training with low carbohydrate availability [81].

SYSTEMIC INFLAMMATION. Three months of aerobic or resistance training in *de novo* recipients had no significant effect over time on high-sensitivity C-reactive protein, tumour necrosis factor α (TNF- α), soluble TNF receptor 1 (sTNFR-1), sTNFR-2, fetuin A or interleukin 6 (IL-6) values when compared with usual care [55]. Exercise training during hospitalization immediately after transplantation did not change the levels of the pro-inflammatory cytokine IL-18 compared with usual care [62].

Bone health. KTRs are prone to osteoporosis and bone fractures [82]. Exercise training involving impact (i.e. vertical jumps, skipping, etc.) and resistance training should be considered as complementary therapy to a pharmacological treatment regimen for osteoporosis [83]. Bone mineral density in *de novo* transplant recipients was reported to remain stable in patients whether or not engaged in aerobic training [46]. Three months of combined resistance and aerobic training improved bone mineral density and bone mineral content compared with usual care in two small studies [54, 84].

Quality of life. Kidney transplantation modestly improves quality of life compared with dialysis [85]. With a few exceptions [55], the majority of RCTs indicate that exercise improves some indices of health-related quality of life in KTRs, irrespective of the type of training or the time after transplantation [46, 48, 52, 56, 57]. Fatigue is highly prevalent in KTRs and inversely correlated with quality of life [86]. A single trial in *de novo* KTRs showed graded exercise training compared with usual care improved levels of fatigue after 6 and 12 weeks of training [53].

Safety. Exercise training did not reduce the length of the hospital stay (Juskowa *et al.* [62]: usual care 31 ± 12 days, intervention 22 ± 6 days; Onofre *et al.* [59]: usual care 7.1 ± 3.5 days, intervention 6.7 ± 2.2 days). Greenwood *et al.* [50] reported that 3 months of home-based aerobic ($n=13$) or resistance ($n=13$) training in *de novo* recipients (~7 months after transplantation) did not induce adverse events, musculoskeletal injuries, hypoglycaemic episodes, CV events or hospitalizations [55]. Pilot studies investigating resistance training at a considerable intensity of ~75–80% of 1 RM initiated either 6–8 weeks [56] or several years [57] after transplantation likewise reported that training did not induce injuries or adverse events. Higher training volumes including five training sessions per week of both aerobic and resistance training in 14 stable recipients did not induce any adverse events [52]. The effect of exercise training interventions on cancer and infection incidence has not yet been formally studied.

In conclusion, aerobic and/or resistance training interventions can be considered safe, irrespective of the time after transplantation. Of note, patients participating in the present studies were frequently selected based on their stable graft function and absence of severe comorbidities.

IMPLEMENTATION POTENTIAL IN REAL-WORLD SETTINGS

Research efforts are in vain when evidence-based interventions fail to find uptake in a real-world setting. Implementation science is the methodology to support successful translation of evidence from trial settings to daily clinical practice [87]. Implementation science focuses not only on the evaluation of effectiveness outcomes, but also on the evaluation of the implementation pathway, including implementation outcomes such

as acceptability, appropriateness, adoption, feasibility, fidelity, implementation costs, reach and sustainability [88, 89]. Ideally, future studies should use hybrid designs allowing for such dual evaluation [90].

The studies included in this review would have benefited from an implementation science approach. However, a careful analysis of the recruitment, retention and attrition during the study (i.e. dropouts) and fidelity with the intervention provides some indications of the possible implementation issues. Pooling together 11 studies that reported on eligibility, 35% ($n=562/1621$) of potential participants were eligible and agreed to participate in the training study. Not surprisingly, exclusion criteria were relatively strict in KTRs, precluding the ‘reach’ of the intervention (extent to which the intended audience comes into contact with the intervention) as well as the generalizability of the study results. Twelve of 17 RCTs reported the number of dropouts. From these studies, the dropout rate in usual care [$n=70-76/300$ (25%)] was similar to that in the intervention groups [$n=89/339$ (26%)]. Karelis *et al.* [56] reported that their initial intervention, comprising three supervised resistance training sessions per week, needed to be revised to one supervised and two home-based training sessions on a weekly basis. Furthermore, they noted that their patients expressed concerns about the feasibility and safety of the exercise programme and hence needed to be reassured. Thus the ‘acceptability’ (the perception that the intervention is agreeable, palatable or satisfactory) and ‘appropriateness’ (the perceived fit, relevance and compatibility) of the intervention may not have been optimal for these patients at that time, presumably leading to low ‘fidelity’ to the training programme. Fidelity is described as the degree to which the intervention was implemented as it was intended, whereas ‘adherence’ is here regarded as the number of performed versus intended training sessions. Eight of the 17 RCTs assessed and transparently reported the exercise adherence rate. Except for one trial reporting that 67% of the intervention group regularly exercised compared with 36% in the control group [46, 50], exercise adherence equalled or surpassed 80% in the remaining studies [48, 52, 55–58].

In conclusion, current evidence indicates that in a selected group of eligible KTRs willing to participate in an exercise training intervention, adherence and fidelity are relatively high. Dropout rates appear to be comparable in the intervention and usual care groups (about one-fourth). Future RCTs should imply stakeholder involvement throughout the research cycle, a thorough contextual analysis, as well as the co-creation of interventions and a choice of implementation strategies, with a sustainable active lifestyle as the ultimate goal.

PRACTICAL CONSIDERATIONS—KEY MESSAGES FOR THE CLINICAL PRACTITIONER

1. Exercise interventions are feasible even early after transplantation [47, 53, 59, 62]: walking, aerobic, resistance and balance exercises may quickly progress according to the patients’ abilities and capabilities. Onofre *et al.* [59] showed that in living donor KTRs, it is feasible to implement breathing, ambulation and step exercises at postoperative Day 1, complement the programme with resistance exercises and stair climbing at postoperative Day 2 and progressively increase exercises from Day 3 onwards.
2. The optimal frequency, intensity, time and type of the training prescription remains to be determined for KTRs: aerobic,

resistance, combined, balance and flexibility exercises appear to be feasible and safe at moderate intensity. Several studies showed that a 3-month programme of aerobic and/or resistance training is effective in improving cardiorespiratory fitness [49, 52, 54, 55].

- Exercise-induced improvements in physical fitness allow patients to be physically active. It is essential that every training programme is succeeded by a physical activity intervention promoting a lifelong physically active lifestyle. Ideally the physically active lifestyle corresponds or progresses to the WHO recommendations [18]. The effects of physical activity are dose dependent, with health benefits already present from minor increases in physical activity [91]. The final goal would be the implementation of patient appropriate, acceptable and, hence, sustainable levels of physical activity in daily living. Therefore co-development of preference-based activity programmes is more likely to impact patients' health than instructing them to behave in a way that they cannot or will not adhere to on the long term. Behavioural change techniques such as motivational interviewing, goal setting, self-monitoring of physical activity behaviour and follow-up prompts may promote adoption of a sustainable active lifestyle [92].
- Both supervised and home-based training interventions have been shown to be effective in improving outcomes: whether one mode of delivery is superior to another has not yet been formally investigated in KTRs. Home-based remotely mediated exercise programmes may overcome patient-level barriers such as limited programme availability, inconvenience of attending classes several times a week, transport problems, infection risks and financial costs associated with facility-based rehabilitation programmes [93–95]. On the other hand, supervised centre-based rehabilitation may be postulated to be associated with superior execution of intended exercise intensity, volume and technique. Patients may feel safer and enjoy the social aspect of training in a group of peers. A hybrid form in which supervised centre-based rehabilitation is progressively replaced by home-based training and subsequent physical activity well-embedded into daily life may allow a smooth transition to a sustainable physically fit and active status.

CONCLUSIONS

Well-designed large RCTs in KTRs addressing endpoints important for all stakeholders (SONG-Tx outcomes) are scarce. However, clinical evidence on the beneficial effects clearly outweighs data on potential harm. Exercise training in KTRs has been shown to be effective in improving quality of life, physical function, physical fitness (surrogate markers of adverse clinical outcomes) and some selected markers of CV disease, such as cardiac autonomic function and arterial stiffness. Whether this effectively leads to an improvement in core outcomes needs to be addressed in future studies with long-term follow-up. Moreover, the stage has been set to test and formally establish from which type of exercise training and at what dose (intensity, frequency and duration) patients derive the greatest benefits, using well-designed RCTs with sufficient power. Implementation science methods should be included early in the projects to speed the translational process.

SUPPLEMENTARY DATA

Supplementary data are available at [ckj online](http://ckjonline.com).

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CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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