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**Outcomes in randomized controlled trials of exercise interventions in solid organ transplant**

**Running title: Outcomes in exercise intervention in transplantation**

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**Abstract.**

AIM: The objectives of this systematic review were to identify the outcome measures that have been used in randomized controlled trials (RCTs) of exercise training in solid organ transplant (SOT) recipients and to link these outcomes to the International Classification of Functioning, Disability and Health (ICF) framework.

METHODS: Electronic literature searches of Medline, EMBASE, CINAHL, Cochrane, Scopus, and Web of Science were performed. We sought RCTs that investigated the effect of exercise training in SOT recipients. Reference lists of all eligible publications were searched for other appropriate studies not identified by the electronic search. A complete list of outcome measures used in the RCTs was generated and each of these was linked to an ICF category.

RESULTS: Four hundred and thirteen articles were retrieved, of which 35 met our inclusion criteria. The studies included were designed to compare the effects of exercise training programs to usual care or to another exercise training program and reported on recipients of heart (n=21), kidney (n=9), lung (n=3) or liver (n=2) transplant. Of the 126 outcome measures identified, 62 were used as primary outcome measures. The most commonly occurring primary outcomes were aerobic capacity using the peak VO2 (n=13), quality of life using the SF-36 (n=8), and muscle strength (n=7). These outcome measures were linked to 113 ICF categories and the majority of outcomes fall into the body function domain (n=93).

CONCLUSION: There is little standardization in outcome measures used in RCTs of exercise interventions in SOT recipients. The ICF framework can be used to select a core set of outcomes that cross all domains of ICF and that would be appropriate to all SOT recipients.

**Key words:** Solid organ transplantation; systematic review; rehabilitation; exercise, outcome measures; International Classification of Functioning, Disability and Health; ICF

**CORE TIP**

Over 30 RCTs have been conducted to examine the effectiveness of exercise training on outcomes in SOT recipients. However, the synthesis of findings across studies has been limited by the lack of similar outcomes. We identified 126 unique outcomes used in RCTs of exercise training and categorized them according to the ICF framework. Most commonly, outcomes fell into the domains of body structure and body function, whereas there were a limited number of outcomes examining activities and participation. This review highlights the need for a core set of outcomes for RCTs in exercise training for this population.

INTRODUCTION

 As the acute morbidity and mortality associated with solid organ transplantation continues to improve, interventions that improve quality of life and long-term health outcomes are needed. Exercise training has several important health benefits for solid organ transplant (SOT) recipients, such as improving maximal aerobic capacity (VO2 peak), body composition and quality of life [1]. Exercise and physical activity also have potential effects for mitigating long-term complications post-transplant and side-effects of immunosuppressant medication such as reducing blood pressure, controlling blood glucose [2], managing weight gain [3], improving muscle [4] and bone strength [5], and reducing fatigue [6-8]. A limitation of the current literature on exercise for SOT is the inability to combine outcomes from studies due to the wide range of reported outcomes. In a systematic review of exercise training in SOT recipients conducted in 2012 by Didsbury and colleagues [1], the authors included 15 randomized controlled trials with 28 unique outcomes. The majority of outcomes were related to cardiovascular parameters (VO2 peak, blood pressure, cholesterol), with fewer studies examining body composition, frailty indicators or quality of life. The authors were therefore hampered in their ability to conduct meta-analyses, which limited the conclusions of their comprehensive review.

The inability to synthesize data from studies in the field of SOT is of particular concern, as this is a small population and studies on exercise training are often conducted at single transplant centres with relatively small sample sizes. In order to gain greater statistical power to draw conclusions, studies need to be combined using knowledge synthesis approaches, which require common outcomes. Inconsistencies in the reporting of outcomes can affect the conclusions of systematic reviews and may contribute to reporting bias [9]. Therefore, in order to facilitate standard reporting of key outcomes across studies, the development of core outcomes sets for clinical trials is gaining more attention [10, 11].

The International Classification of Functioning, Disability and Health (ICF) is an established framework developed by the World Health Organization and is commonly used in rehabilitation. The ICF is designed to describe health and health-related status from biological, personal and societal perspectives [12]. The framework classifies human function into four domains: body functions; body structures; activities and participation; and environmental factors [12]. These domains match well with the goals of exercise training and physical rehabilitation programs; specifically to identify, measure and treat physical impairments (body function and structure); to reverse or normalize activity limitations; and to enhance participation in all settings [13]. Using the ICF to map the outcomes of the current literature on exercise training in SOT recipients will assist in classifying the breadth of outcomes that have been used in the studies to date and also in identifying any domains that are understudied in this population. This information can provide a starting point for developing a core set of standard outcomes [10] for clinical trials of exercise and physical rehabilitation in SOT recipients.

The objectives of this systematic review were to identify the outcome measures that have been used in randomized controlled trials (RCTs) of exercise training in SOT recipients and to link these outcomes to the ICF framework.

## METHODS

### Data Sources and Search Strategy

This systematic review is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [14]. A librarian designed and performed electronic literature searches of Medline from inception until May 2016. The search was then adapted for EMBASE, CINAHL, Cochrane, Scopus, and Web of Science and run on these databases. Search terms included organ transplantation, transplant recipients, graft recipient, heart, lung, kidney, pancreas, liver, exercise, exercise therapy, rehab, rehabilitation, resistance training, physical education, training, physical activity, and physical exertion (Table 1). The searches were limited to randomized controlled trials (RCTs), published in English, and in humans. One investigator (S. K.) also conducted hand searches of the reference lists of all the studies that met the inclusion criteria to identify additional relevant articles.

**Table 1 – Electronic Search Strategy Used in Medline**

|  |  |
| --- | --- |
| *Search #* | *Keywords and Number of Records Identified* |
| Search #1 | Organ transplantation (110179) |
| Search #2 | Transplantation conditioning (7738) |
| Search #3 | Transplant recipients (195) |
| Search #4 | "transplant recipient$" (27594) |
| Search #5 | 1 or 2 or 3 or 4 (122169) |
| Search #6 | Exercise/ or Exercise Therapy/ or exercise$ (192344) |
| Search #7 | Rehab$/ or rehabilitation (151761) |
| Search #8 | Resistance training/ or "physical education and training"/ or training (181282) |
| Search #9 | "Physical activity” (47446) |
| Search #10 | Physical exertion (11451) |
| Search #11 | 6 or 7 or 8 or 9 or 10 (474657) |
| Search #12 | 5 and 11 (2399) |
| Search #13 | Heart or lung or kidney or pancreas or liver (1433618) |
| Search #14 | 12 and 13 (2200) |
| Search #15 | Limit 14 to humans (2156) |
| Search #16 | Limit 14 to animals (76) |
| Search #17 | 15 not 16 (2121) |
| Search #18 | Limit 17 to randomized controlled trial (60) |

### Criteria for Including Studies in the Review

We selected all RCTs that investigated the effect of exercise training in SOT recipients. We included trials that compared the effects of exercise training programs to standard care as well as trials that compared two or more different exercise training programs in SOT recipients. In the case of multiple publications of the same study, we considered all of them if the outcomes measures were different. We excluded studies that did not have an isolated exercise intervention group (i.e. those that examined the effect of a drug combined with exercise). We also excluded non-English articles and conference abstracts. One investigator (S. K.) reviewed the study titles and abstracts to determine potential study eligibility. When this investigator was uncertain, a second reviewer (T. J.-F.) was consulted. Two investigators independently reviewed the full texts of the articles to determine eligibility (S. K. and T. J.-F.).

### Data Extraction and Synthesis

Two reviewers (S. K. and C.B.) performed the data extraction and tabulation. A third reviewer (T. J-F.) double-checked the extracted data. Outcome measures were abstracted using a standard form and imported into a spreadsheet, sorted into primary and secondary outcomes and classified according to four domains of the ICF (body functions, body structures, activities and participation, and environmental factors). Information about the exercise interventions and patient populations were also retrieved. Considering the purpose of this review, study quality or risk of bias assessments of the included studies were not deemed to be necessary.

## RESULTS

### Literature Search

The electronic and hand searches led to the identification of 522 articles. After excluding 109 duplicates, there were 413 articles left for title and abstract screening. Following the study title and abstract screening, 366 were considered to be unrelated to the objectives of the review. Of the 47 articles that remained for full-text analysis, 12 were excluded. This left a total of 35 [2-5, 15-45] articles for inclusion in this review. The study flow and reasons for exclusion are shown in Figure 1.

**Figure 1 - PRISMA 2009 Flow Diagram**

Full-text articles excluded, with reasons
(n = 12)

-Not RCT (n = 6)

-Not related to exercise (n = 2)

-Did not have an isolated exercise group (e.g. exercise was combined with drugs) ( n = 3)

- only abstract (n =1)

Studies included in quantitative synthesis (meta-analysis)
Not applicable

Studies included in qualitative synthesis
(n = 35)

Full-text articles assessed for eligibility
(n = 47)

Records excluded
(n = 366)

Records screened
(n = 413)

Records after duplicates removed
(n = 413)

Additional records identified through other sources
(n = 5)

## Identification

## Eligibility

## Included

## Screening

Records identified through database searchs
(n = 517)

*From:*  Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

**For more information, visit** [**www.prisma-statement.org**](http://www.consort-statement.org/)**.**

Review of Studies and Outcome Domains Assessed

The studies included were designed to compare the effects of exercise training programs to usual care or to another exercise training program and reported on transplantation of heart (n=21), kidney (n=9), lung (n=3), and liver (n=2). A total of 1313 patients were randomized in the 35 studies. Description of the exercise programs and other details about the studies is presented in Table 2.

INCLUDE TABLE 2 HERE – Description of Studies

**Table 3 – List of Outcome Measures by Study**

| **Author** | **Year** | **Organ Group** | **Primary Outcome Measures** | **Secondary Outcome Measures** |
| --- | --- | --- | --- | --- |
| Braith | 1996 | Heart | Bone mineral density (body and regional: femur neck, lumbar vertebra)  | Bone mineral content |
|   |  |   | Total bone calcium |
|   |  |   | Acute rejection episodes |
| Braith | 1998 | Heart | Body mass | Percent body fat |
|   |  |   | Fat-free mass | Acute rejection episodes |
|   |  |   | Fat mass |  |
|   |  |   | Muscle strength (upper and lower body) |   |
| Kobashigawa | 1999 | Heart | Blood pressure (peak and resting) | Muscle strength (lower limb) |
|   |  |   | Heart rate (peak and resting) |  |
|   |  |   | Anaerobic threshold |  |
|   |  |   | Exercise duration (to exhaustion) |  |
|   |  |   | Peak ventilation |   |
|   |  |   | Peak VO2 |  |
|   |  |   | Peak workload |  |
|   |  |   | Ventilatory equivalent for carbon dioxide & oxygen |  |
| Painter | 2002 | Kidney | Body mass indexBody weightFat mass/ body fatLean tissue massPercent body fatBlood pressure (peak)Muscle strength (quadriceps)Peak ventilationPeak VO2SF-36\* | Self-reported activity level (frequency, type, length, and intensity of exercise) |
|   |  |   | Blood creatinine |
|   |  |   | Blood urea nitrogen levels |
|   |  |   | Hematocrit |
|   |  |   | Hemoglobin |
|   |  |   | Bone mineral density |
|   |  |   | Peak workload |
|   |  |   | Rating of perceived exertion (Borg) |
|   |  |   | Peak respiratory exchange ratio |
|   |  |   | Immunosuppression use (type, dose) |
| Mitchell | 2003 | Lung | Bone mineral density (lumbar spine) | Acute rejection episodes |
|   |  |   |   | Muscle strength (lumbar extensor) |
| Painter | 2003 | Kidney | Cholesterol (TC\*, HDL\*) | Blood lipids |
|   |  |   | Body mass index | Incidence of diabetes |
|   |  |   | Total CVD risk (Framingham) | Smoking status |
|   |  |   | Blood pressure  |  |
|   |  |   | Peak workload (Maximal metabolic units (METs)) |  |
| Braith | 205 | Heart | Muscle composition (fiber types) | Muscle strength (upper and lower body) |
|   |  |   | Muscle metabolic enzyme activity |  |
| Juskowa | 2006 | Kidney | Blood lipids | Blood calcium level |
|   |  |   | Cholesterol (TC\*, HDL\*, LDL\*) | Blood creatinine |
|   |  |   | Body mass index | Blood electrolytes |
|   |  |   |   | Blood glucose |
|   |  |   |   | Blood phosphorus |
|   |  |   |   | Blood protein levels (albumin, fibrinogen, total protein level) |
|   |  |   |   | Enzyme levels (alanine transferase, alkaline phosphatase, aspartate aminotransferase) |
|   |  |   |   | Folate concentrations |
|   |  |   |   | Hemoglobin |
|   |  |   |   | Interleukin-18 |
|   |  |   |   | Total-homocysteine |
|   |  |   |   | Vitamin B12 |
|   |  |   |   | Blood pressure |
|   |  |   |   | Muscle strength (upper limbs) |
|   |  |   |   | Peak expiratory flow |
| Krasnoff | 2006 | Liver | Body mass index | Rating of perceived exertion (Borg) |
|   |  |   | Body weight |  |
|   |  |   | Bone mineral content |  |
|   |  |   | Bone mineral density |  |
|   |  |   | Fat mass/ body fat |  |
|   |  |   | Lean tissue mass |  |
|   |  |   | Percent body fat |  |
|   |  |   | Muscle strength (quadriceps) |  |
|   |  |   | Peak VO2 |  |
|   |  |   | SF-36\* |  |
|   |  |   | Peak respiratory exchange ratio |  |
|   |  |   | Nutritional intake (Block-95 - calories/day; protein, carb and fat calories) |  |
| Bernardi | 2007 | Heart | Baroceptor control of blood pressure | Blood pressure; Heart rate |
|   |  |   | Baroceptor control of heart rate | Neck pressure |
|   |  |   |   | RR\* interval |
|   |  |   |   | Anaerobic threshold |
|   |  |   |   | CO2 production |
|   |  |   |   | Exercise duration (to exhaustion) |
|   |  |   |   | Peak ventilation |
|   |  |   |   | Peak VO2 ; Peak workload |
|   |  |   |   | Ventilatory equivalent for CO2 & oxygen |
| Karapolat | 2007 | Heart | Peak VO2 |  |
|   |  |   | Beck Depression Inventory |  |
|   |  |   | SF-36\* |  |
|   |  |   | State-Trait Anxiety Inventory |  |
| Braith | 2008 | Heart | Endothelial function (flow-mediated dilation)  | Blood glucose |
|   |  |   | Blood lipids |
|   |  |   | Cholesterol (TC\*, HDL\*, LDL\*) |
|   |  |   | Oxidative stress-induced lipid peroxidation |
|   |  |   | Plasma norepinephrine |
|   |  |   | Serum metabolic and hematologic indicators |
|   |  |   | Body mass |
|   |  |   | Acute rejection episodes |
|   |  |   | Blood pressure (resting and peak) |
|   |  |   | Brachial artery diameter |
|   |  |   | Exercise duration (to exhaustion) |
|   |  |   | Peak VO2 |
| Karapolat | 2008 | Heart | Chronotropic response index | Duke Treadmill Score |
|   |  |   | Heart rate recovery |  |
|   |  |   | Heart rate reserve |  |
|   |  |   | Peak VO2 |  |
| Pierce | 2008 | Heart | C-reactive protein | Blood glucose |
|   |  |   | Interleukin-6 | Cholesterol (TC\*, HDL\*, LDL\*) |
|   |  |   | Serum metabolic profile | Cytomegalovirus IgG status |
|   |  |   | Soluble cell adhesion molecules (sICAM-1) | White blood cell levels |
|   |  |   | Tumour necrosis factor-alpha | Acute rejection episodes |
|   |  |   | Muscle vasodilation (forearm and calf) | Blood pressure (resting) |
|   |  |   |   | Heart rate (peak and resting) |
|   |  |   |   | Exercise duration (to exhaustion) |
|   |  |   |   | Rating of perceived exertion (Borg) |
|   |  |   |   | Peak respiratory exchange ratio |
| Wu | 2008 | Heart | Muscle endurance (quadriceps) | Daily physical activity |
|   |  |   | Muscle strength (quadriceps) | Blood pressure |
|   |  |   | Peak VO2 | Heart rate (resting and peak) |
|   |  |   | World Health Organization Questionnaire on Quality of Life – BREF\* | Nutritional intake (caloric intake questionnaire) |
|   |  |   |  | Peak ventilation |
|   |  |   |   | Peak workload |
|   |  |   |   | Rating of perceived exertion (Borg) |
| Haykowsky   | 2009 | Heart   | Peak VO2        | Lean tissue mass (total and leg)Blood pressure (peak)Endothelial function (endothelial-dependent vasodilation, endothelial-independent vasodilation, reactive hyperemia index)Heart rate (peak)Left ventricular systolic functionMuscle strength (upper and lower body)Peak power outputPeak respiratory exchange ratio |
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| Mandel | 2009 | Liver | 6MWD\* |  |
|   |  |   | Muscle strength (lower body) |  |
|   |  |   | Chronic liver disease questionnaire (CLDQ) |  |
|   |  |   | SF-36\* (physical function/ limitations) |  |
| Hermann | 2011 | Heart | Peak VO2 | Blood creatinine |
|   |  |   |   | Blood glucose; Blood lipids |
|   |  |   |   | Blood protein levels (adiponectin, MR-proANP, NT-proBNP, provasopressin/ copeptin) |
|   |  |   |   | Cholesterol |
|   |  |   |   | Hemoglobin |
|   |  |   |   | High sensitive C-reactive protein |
|   |  |   |   | Interleukin-6 |
|   |  |   |   | Serum insulin |
|   |  |   |   | Tumour necrosis factor-alpha |
|   |  |   |   | Body mass index; Body weight |
|   |  |   |   | Hip-waist ratio |
|   |  |   |   | Blood pressure (resting) |
|   |  |   |   | Brachial artery diameter |
|   |  |   |   | Endothelial function (flow-mediated vasodilation, nitroglycerin-induced vasodilation) |
|   |  |   |   | Heart rate (resting) |
|   |  |   |   | Peak power output |
| Ihle | 2011 | Lung | 6MWD\* | Heart rate (peak and resting) |
|   |  |   | Peak VO2 | Anaerobic threshold |
|   |  |   | SF-36\* | Oxygen uptake at anaerobic threshold |
|   |  |   | St. George's Respiratory Questionnaire  | Peak workload |
|   |  |   |  | Peak respiratory exchange ratio |
|   |  |   |   | Ventilatory reserve and capacity |
| Christensen | 2012 | Heart | Hospital Anxiety and Depression Scale | Peak VO2 |
|   |  |   | SF-36\* |  |
| Langer | 2012 | Lung | Daily walking time (time spend in different postures: sedentary, standing, walking)  | Daily steps |
|   |  |   | Movement intensity |
|   |  |   | Time spent in moderate intense activities |
|   |  |   | Blood lipids |
|   |  |   | Body weight |
|   |  |   | Bone mineral density |
|   |  |   | Blood pressure |
|   |  |   | 6MWD\* |
|   |  |   | Muscle strength (quadriceps and handgrip) |
|   |  |   | Peak workload |
|   |  |   | Mood status |
|   |  |   | SF-36\* |
|   |  |   | Forced expiratory volume |
|   |  |   | Respiratory muscle force |
|   |  |   | Incidence of morbidity (diabetes, hyperlipidemia, hypertension, osteoporosis) |
| Nytrøen | 2012 | Heart | Peak VO2 | Blood lipids |
|   |  |   |   | Blood protein levels (NT-proBNP) |
|   |  |   |   | C-reactive protein |
|   |  |   |   | Interleukin-6, 8 & 10 levels  |
|   |  |   |   | Body mass index; Body weight; % body fat |
|   |  |   |   | Chronotropic response index |
|   |  |   |   | Glycemic control parameters |
|   |  |   |   | Blood pressure (peak and resting) |
|   |  |   |   | Heart rate (peak and resting) |
|   |  |   |   | Heart rate recovery & reserve |
|   |  |   |   | Stroke volume (O2 pulse; resting & peak) |
|   |  |   |   | Anaerobic threshold |
|   |  |   |   | Exercise duration (to exhaustion) |
|   |  |   |   | Muscle strength (quadriceps and hamstrings) |
|   |  |   |   | Peak ventilation |
|   |  |   |   | Rating of perceived exertion (Borg) |
|   |  |   |   | SF-36\* |
|   |  |   |   | Visual Analog Scale (subjective difference in HRQoL\*) |
|   |  |   |   | Peak respiratory exchange ratio |
| Rustad | 2012 | Heart | Echocardiographic parameters (rest and during exercise; systolic and diastolic parameters)Peak VO2 | Biochemical parameters |
|   |  |   | Blood pressure |
|   |  |   | Cardiac allograft vasculopathy (coronary angiography) |
|   |  |   | Cardiac output |
|   |  |   | Heart rate (resting and peak) |
|   |  |   | Stroke volume |
|   |  |   | Peak workload |
|   |  |   | Peak respiratory exchange ratio |
| Kawauchi  | 2013 | Heart  | 6MWD\*Forced vital capacityRespiratory muscle force/ strength | Muscle strength (upper and lower limbs)Maximum expiratory/ inspiratory pressure |
|  |  |  |
| Kouidi | 2013 | Kidney | Baroreflex sensitivityHeart rate variability parameters (SDNN\*, rMSSD\*, pNN50\*, LF\*, HF\*, LF\*/HF\*)  | Baroreflex effectiveness indexBlood pressure (peak and resting)Heart rate (peak and resting)Exercise duration (to exhaustion)Peak ventilationPeak VO2 |
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|   |  |   |
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| Nytrøen | 2013 | Heart | Cardiac allograft vasculopathy (intravascular ultrasound and virtual histology)  | Blood creatinineBlood glucoseBlood lipidsC-reactive proteinCholesterol (TC\*, HDL\*, LDL\*)HemoglobinInterleukin-6, 8 & 10 levelsBody mass indexBody water (total)Body weightBone massLean tissue massPercent body fatVisceral fat scaleBasal metabolic rateGlycemic control parametersMetabolic ageMuscle strength (quadriceps and hamstrings)Peak VO2 |
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| Dall         | 2014 | Heart         | Peak VO2  | Body weightBlood pressureHeart rate (peak and resting)Heart rate recoveryHeart rate reserveCO2 productionPeak ventilationPeak workloadPeak respiratory exchange ratio |
| Monk-Hansen | 2014 | Heart | Echocardiography parameters (systolic and diastolic function) | Body mass indexBlood pressureHeart rate (peak and resting)Peak VO2Peak workload |
|   |  |   |
|   |  |   |
|   |  |   |
|   |  |   |
| Pascoalino        | 2014 | Heart        | Arterial stiffness (carotid-femoral pulse wave velocity)Blood pressure (ambulatory; peak and resting)     | Plasma norepinephrineHeart rate (peak and resting)Anaerobic thresholdCO2 productionExercise duration (to exhaustion)Peak VO2Peak respiratory exchange ratioRespiratory compensation point |
| Pooranfar | 2014 | Kidney | Blood lipids |  |
|   |  |   | Cholesterol (TC\*, HDL\*, LDL\*) |  |
|   |  |   | Sleep quality and quantity questionnaire (self-report; Pittsburgh Sleep Quality Index) |  |
| Riess | 2014 | Kidney | Peak VO2 | Cholesterol (TC\*, HDL\*) |
|   |  |   |   | Lean tissue mass |
|   |  |   |   | Total CVD\* risk (Framingham) |
|   |  |   |   | Arterial pressure (mean) |
|   |  |   |   | Arterial stiffness (pulse wave velocity) |
|   |  |   |   | Arteriovenous oxygen difference (a-vO2) |
|   |  |   |   | Blood pressure (ambulatory; peak & resting) |
|   |  |   |   | Cardiac output |
|   |  |   |   | Heart rate (peak); Stroke volume |
|   |  |   |   | Systemic vascular endurance |
|   |  |   |   | Muscle strength (lower body) |
|   |  |   |  | Peak workload |
|   |  |   |   | SF-36\* |
|   |  |   |   | Peak respiratory exchange ratio |
| Tzvetanov | 2014 | Kidney | Glomerular filtration rate | Blood creatinine |
|   |  |   | SF-36\* | Blood glucose |
|   |  |   | Adherence to training and follow-up | Blood lipids |
|   |  |   | Employment status | Cholesterol (TC\*, HDL\*, LDL\*) |
|   |  |   |   | Hemoglobin |
|   |  |   |   | Body mass index |
|   |  |   |   | Body weight |
|   |  |   |   | Bone mineral content |
|   |  |   |   | Lean tissue mass |
|   |  |   |   | Percent body fat |
|   |  |   |   | Arterial stiffness (carotid-femoral pulse wave velocity |
|   |  |   |   | Blood pressure |
|   |  |   |   | Carotid intima-media thickness |
|   |  |   |   | Muscle strength |
| Dall | 2015 | Heart | Blood glucose | Body weightHomeostasis model assessmentHeart rate (peak)Peak VO2Peak respiratory exchange ratio |
|   |  |   | Blood protein levels (adiponectin, orosomucoid, YLK 40) |
|   |  |   | Interleukin-6 |
|   |  |   | Serum insulin |
|   |  |   | Tumour necrosis factor-alpha |
|   |  |   | Arterial stiffness (augmentation index) |   |
|   |  |   | Endothelial function (reactive hyperemia index) |   |
|   |  |   | Hospital Anxiety and Depression Scale |  |
|   |  |   | SF-36\* |  |
| Greenwood | 2015 | Kidney | Muscle strength (quadriceps) | Arterial stiffness (pulse wave velocity) |
|   |  |   |   | Blood pressure (peak and resting) |
|   |  |   |   | Heart rate (peak and resting) |
|   |  |   |   | STS-60\* |
|   |  |   |   | Peak VO2 |
|   |  |   |   | Body mass index; Body weight |
|   |  |   |   | Waist girth |
|   |  |   |   | Glomerular filtration rate |
|   |  |   |   | high-sensitivity C-reactive protein  |
|   |  |   |   | interleukin-6 |
|   |  |   |   | Fetuin A |
|   |  |   |   | Tumor necrosis factor-alpha |
|   |  |   |   | tumor necrosis factor receptors 1 & 2 |
|   |  |   |   | SF-36\* |
|   |  |   |   | Duke Activity Status Index |
| Karelis | 2015 | Kidney | World Health Organization-5 Well-Being IndexMuscle strength indexAdherence to training and follow-up (feasibility)         | Body weight |
|   |  |   | Body height |
|   |  |   | Body mass index |
|   |  |   | Waist girth |
|   |  |   | Hip girth |
|   |  |   | Fat mass/ body fat |
|   |  |   | Lean tissue mass |
|   |  |   | Cholesterol (TC\*, HDL\*, LDL\*) |
|   |  |   | Blood glucose |
|   |  |   | Blood pressure |
|   |   |   | Peak VO2 |

\*Abbreviations: SF-36=short-form 36; TC=total cholesterol; HDL= high-density lipoprotein fraction of cholesterol; LDL= low-density lipoprotein fraction of cholesterol; RR-interval= inter-beat interval (heart rate); BREF=a shorter version of the original; rMSSD=root-mean-square of successive NN interval differences; pNN50=percentage value of NN50 count; LF= low-frequency components; HF= high-frequency components; CVD=cardio-vascular disease; STS-60= sit-to-stand 60;

Table 3 outlines the outcome measures that were used in each study. In total, there were 126 outcome measures. Of the 126 outcome measures, 62 were used as primary outcome measures in at least one study. The most commonly occurring primary outcomes were peak VO2 (n=13), SF-36 (n=8), and muscle strength (n=7).

INCLUDE TABLE 4 HERE – ICF Outcome Classifications

Each outcome measure was linked to an ICF domain and the list is shown in Table 4. The majority of outcomes fell into the body function domain (n=93). Fourteen outcome measures were linked to the activities and participation, 5 to body structures, 2 to environmental factors and 2 described outcomes were unclassified in the ICF. Frailty indicators such as grip strength (n=1), fatigue (n=0) or gait speed (6-minute-walk) (n=3) were rarely used. Ten multi-dimensional questionnaires were used in the studies reviewed.

## DISCUSSION

Physical rehabilitation in SOT patients strives to minimize the impairments associated with prolonged chronic illness, allowing individuals to improve their ability to carry out daily tasks and activities and to participate in life roles. When selecting outcome measures to use in clinical trials of SOT recipients, it is important to capture changes across all domains that are relevant to the primary goals of the physical rehabilitation intervention. We have used the ICF categories to classify the outcome measures used in RCTs of exercise interventions after SOT. From this systematic review, we have learned that the outcome measures used in these RCTs vary widely. This finding is in line with the results of similar systematic reviews conducted in other populations (e.g. individuals with critical illness, post-surgery and stroke) [11] Some of the studies focused on multiple primary outcomes and others used just two or three. In total, 62 different primary outcomes were used with the most common being peak VO2 (n=13) and the SF-36 (n=8). Most of the outcomes used fell into the body functions domain (n=93) with very few in the activities and participation domain (n=14). Few studies included outcomes that are also considered frailty indicators. These are important outcomes as frailty is present in many SOT recipients and can have a negative impact on transplant outcomes [6-8].

As we did, Disdbury *et al*. found that the most commonly used outcome measure was VO2 peak. [1] However, this is an expensive test that requires complex equipment as well as expertise from a professional to interpret the results. Functional exercise capacity tests that are more relevant to patients’ activities and participation in daily life and less costly to administer should be considered.

Disdbury *et al*. were unable to merge data on health-related quality-of-life (HRQoL) measures since so many different questionnaires were used. [1] We found that 11 of the RCTs analyzed used multi-dimensional questionnaires as an outcome measure with several using more than one. These questionnaires each cover many different ICF categories. For instance, Cieza & Stucki have linked individual questions from the Short-Form-36 (SF-36) questionnaire to ICF domains and found that this questionnaire incorporates at least 21 ICF codes [46]. Linking individual items on HRQoL questionnaires could help researchers select a questionnaire that covers many ICF codes and that would be most suited to be part of the core set of outcome measures recommended, thus making it possible to meaningfully merge data from multiple studies.

A core set of outcome measures to be used in all of these populations would be helpful to minimize and standardize the number of outcomes used in this patient group. While it is important to conduct a comprehensive assessment, the use of a large number of outcome measures can be burdensome for both patients and evaluators. Ideally, the core set of variables should cover all four domains of the ICF, i.e., they need to cover all aspects of the health condition. Furthermore, the core set of variables needs to include outcomes that are common to all organ groups. Many of the issues that affect physical function and exercise capacity are common across the transplant types despite each SOT having its own unique characteristics and challenges [47]. Some of the pre-transplant issues that limit physical function are specific to the failing organ, but the physiological changes associated with severe chronic disease, deconditioning and nutritional depletion are common to all groups [48]. Post-transplant issues that limit physical function vary depending on the phase of recovery, but include things such as extended hospital and intensive care stay, prolonged sedentary time, immunosuppressant medications and episodes of organ rejection [48]. Outcome measures that relate to these commonalities and to increasing physical function would be suitable for inclusion in the core set of variables. However, there are some organ specific issues that may be important to address differently among the groups (e.g., the effects of exercise in the denervation of the heart after transplant or the effects of exercise on early onset of diabetes after kidney transplant) and researchers should be encouraged to include secondary outcomes to address them.

The selection of outcome measures should reflect the length of time since the transplant and whether the course of recovery has been complicated. For example, the main goal of physical rehabilitation for acute phase post-transplant is usually to improve basic mobility and activities of daily living while rehabilitation for long-term recipients is generally focused on improving their exercise capacity and levels of physical activity to prevent cardiovascular complications. When considering appropriate outcomes, is also important to take into account their psychometric properties. [49] Knowing the validity of the outcomes in the transplant population can help researchers with sample size calculations for interventional studies and justify the use of the selected primary outcomes.

None of the studies reviewed included an economic evaluation of the exercise programs and the potential cost savings if SOT recipients experience less long-term cardiovascular disease and fewer hospital readmission related to frailty and physical disability. Although robust economic studies can be challenging, they may be important to convince healthcare funders that exercise programs can be cost-effective and have a positive impact on transplant outcomes and survival. Exercise programs also need to be more readily available for transplant recipients as lack of availability of post-transplant exercise programs has been identified for example in Canada. [50]

#### Limitations

A limitation of this systematic review is the inclusion of only RCTs. There are other studies on exercise training in SOT recipients that use different research designs, especially observational studies using pre-post designs that were not included. We chose this strategy because RCTs are of the highest quality of study design. We assumed that investigators conducting RCTs have chosen their outcomes carefully and that this group of studies is representative of all rehabilitation trials in transplant recipients. We have also limited our search to studies published in English, which may have reduced our sample size.

## CONCLUSION

There is little standardization in outcome measures used in RCTs of exercise interventions in SOT recipients. Outcome measures for clinical trials should also be selected based on their psychometric properties, stage post transplantation and severity of impairments of the patient population. Further research is needed to develop consensus on a standardized core set of outcomes to measure the effectiveness of such interventions. The ICF framework can be used to select appropriate outcomes that cross all domains and that would be appropriate to all SOT recipients.

**COMMENTS**

**Background**

Over 30 RCTs have been conducted to examine the effectiveness of exercise training on outcomes in SOT recipients. However, the synthesis of findings across studies has been limited by the lack of similar outcomes across studies. The objectives of this systematic review were to identify the outcome measures that have been used in randomized controlled trials (RCTs) of exercise training in solid organ transplant (SOT) recipients and to link these outcomes to the International Classification of Functioning, Disability and Health (ICF) framework.

**Research Frontiers**

Between 1996 and 2015 more than 30 RCTs were published on the effects of exercise training in SOT recipients. Taken together, the results of these RCTs show that exercise training improves maximal aerobic capacity, muscle strength, body composition, cardiopulmonary variables and quality of life. There is little evidence for the effect of exercise in physical activity and participation in SOT recipients. In a systematic review of exercise training in SOT recipients conducted in 2012 by Didsbury and colleagues, the authors included 15 randomized controlled trials with 28 unique outcomes. The majority of outcomes were related to cardiovascular parameters (VO2 peak, blood pressure, cholesterol), with fewer studies examining body composition, frailty indicators or quality of life. The authors were therefore hampered in their ability to conduct meta-analyses, which limited the conclusions of their comprehensive review.

**Innovations and breakthroughs**

There are numerous studies examining the role of exercise training to improve outcomes following SOT. Exercise training has several important health benefits for SOT recipients, such as improving maximal aerobic capacity (VO2 peak), body composition and quality of life. A limitation of the current literature on exercise for SOT is the inability to combine outcomes from studies due to the wide range of reported outcomes.

**Applications**

This systematic review suggests that there is a need to develop consensus on a standardized core set of outcomes to measure the effectiveness of exercise interventions in SOT. A standardized core set of outcomes would facilitate standard reporting of key outcomes across studies.

**Terminology**

The International Classification of Functioning, Disability and Health (ICF) is an established framework developed by the World Health Organization and is commonly used in rehabilitation. The ICF is designed to describe health and health-related status from biological, personal and societal perspectives. The framework classifies human function into four domains: body functions; body structures; activities and participation; and environmental factors. These domains match well with the goals of exercise training and physical rehabilitation programs; specifically to identify, measure and treat physical impairments (body function and structure); to reverse or normalize activity limitations; and to enhance participation in all settings.

**REFERENCES**

1 Didsbury M, McGee RG, Tong A, Craig JC, Chapman JR, Chadban S, Wong G. Exercise training in solid organ transplant recipients: a systematic review and meta-analysis. *Transplantation* 2013; **95**(5): 679-687 [PMID: 23364480 DOI: 10.1097/TP.0b013e31827a3d3e]

2 Langer D, Burtin C, Schepers L, Ivanova A, Verleden G, Decramer M, Troosters T, Gosselink R. Exercise training after lung transplantation improves participation in daily activity: a randomized controlled trial. *American Journal of Transplantation* 2012; **12**(6): 1584-1592 [PMID: 22390625 DOI: 10.1111/j.1600-6143.2012.04000.x]

3 Krasnoff J, Vintro A, Ascher N, Bass N, Paul S, Dodd M, Painter P. A randomized trial of exercise and dietary counseling after liver transplantation. *American journal of transplantation* 2006; **6**(8): 1896-1905 [PMID: 16889545 DOI: 10.1111/j.1600-6143.2006.01391.x]

4 Braith RW, Welsch MA, Mills Jr RM, Keller JW, Pollock ML. Resistance exercise prevents glucocorticoid-induced myopathy in heart transplant recipients. *Medicine and science in sports and exercise* 1998; **30**(4): 483-489 [PMID: 9565927 DOI: 10.1097/00005768-199804000-00003]

5 Braith RW, Mills RM, Welsch MA, Keller JW, Pollock ML. Resistance exercise training restores bone mineral density in heart transplant recipients. *Journal of the American College of Cardiology* 1996; **28**(6): 1471-1477 [PMID: 8917260 DOI: 10.1016/S0735-1097(96)00347-6]

6 McAdams‐DeMarco M, Law A, King E, Orandi B, Salter M, Gupta N, Chow E, Alachkar N, Desai N, Varadhan R. Frailty and mortality in kidney transplant recipients. *American Journal of Transplantation* 2015; **15**(1): 149-154 [PMID: 25359393 DOI: 10.1111/ajt.12992]

7 McAdams‐DeMarco MA, Law A, Salter ML, Boyarsky B, Gimenez L, Jaar BG, Walston JD, Segev DL. Frailty as a novel predictor of mortality and hospitalization in individuals of all ages undergoing hemodialysis. *Journal of the American Geriatrics Society* 2013; **61**(6): 896-901 [PMID: 23711111 DOI: 10.1111/jgs.12266]

8 McAdams‐DeMarco MA, Law A, Salter ML, Chow E, Grams M, Walston J, Segev DL. Frailty and early hospital readmission after kidney transplantation. *American journal of transplantation* 2013; **13**(8): 2091-2095 [PMID: 23731461 DOI: 10.1111/ajt.12300]

9 Kirkham JJ, Dwan KM, Altman DG, Gamble C, Dodd S, Smyth R, Williamson PR. The impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews. *Bmj* 2010; **340**: c365 [PMID: 20156912 DOI: 10.1136/bmj.c365]

10 Williamson PR, Altman DG, Blazeby JM, Clarke M, Devane D, Gargon E, Tugwell P. Developing core outcome sets for clinical trials: issues to consider. *Trials* 2012; **13**(1): 132 [PMID: 22867278 DOI: 10.1186/1745-6215-13-132]

11 Core Outcome Measures in Effectiveness Trials Initiative (COMET). http://www.comet-initiative.org/

12 World\_Health\_Organization. Towards a common language for functioning, disability and health: ICF. World Health Organisation, 2002 http://www.who.int/classifications/icf/en/

13 Gilchrist LS, Galantino ML, Wampler M, Marchese VG, Morris GS, Ness KK. A framework for assessment in oncology rehabilitation. *Physical Therapy* 2009; **89**(3): 286-306 [PMID: 19147708 DOI: 10.2522/ptj.20070309]

14 Mother D, Liberati A, Tetzlaff J. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6**(6): e1000097 [PMID: 19621072 DOI: 10.1371/journal.pmed.1000097]

15 Kobashigawa JA, Leaf DA, Lee N, Gleeson MP, Liu H, Hamilton MA, Moriguchi JD, Kawata N, Einhorn K, Herlihy E. A controlled trial of exercise rehabilitation after heart transplantation. *New England Journal of Medicine* 1999; **340**(4): 272-277 [PMID: 9920951 DOI: 10.1056/NEJM199901283400404]

16 Painter PL, Hector L, Ray K, Lynes L, Dibble S, Paul SM, Tomlanovich SL, Ascher NL. A randomized trial of exercise training after renal transplantation. *Transplantation* 2002; **74**(1): 42-48 [PMID: 12134097 DOI: 10.1097/00007890-200207150-00008]

17 Mitchell MJ, Baz MA, Fulton MN, Lisor CF, Braith RW. Resistance training prevents vertebral osteoporosis in lung transplant recipients. *Transplantation* 2003; **76**(3): 557-562 [PMID: 12923444 DOI: 10.1097/01.TP.0000076471.25132.52]

18 Painter PL, Hector L, Ray K, Lynes L, Paul SM, Dodd M, Tomlanovich SL, Ascher NL. Effects of exercise training on coronary heart disease risk factors in renal transplant recipients. *American journal of kidney diseases* 2003; **42**(2): 362-369 [PMID: 12900820 DOI: 10.1016/S0272-6386(03)00673-5]

19 Braith RW, Magyari PM, Pierce GL, Edwards DG, Hill JA, White LJ, Aranda JM. Effect of resistance exercise on skeletal muscle myopathy in heart transplant recipients. *The American journal of cardiology* 2005; **95**(10): 1192-1198 [PMID: 15877992 DOI: 10.1016/j.amjcard.2005.01.048]

20 Juskowa J, Lewandowska M, Bartłomiejczyk I, Foroncewicz B, Korabiewska I, Niewczas M, Sierdziński J. Physical rehabilitation and risk of atherosclerosis after successful kidney transplantation. *Transplantation proceedings* 2006; **38**(1): 157-160 [PMID: 16504691 DOI: 10.1016/j.transproceed.2005.12.077]

21 Bernardi L, Radaelli A, Passino C, Falcone C, Auguadro C, Martinelli L, Rinaldi M, Viganò M, Finardi G. Effects of physical training on cardiovascular control after heart transplantation. *International journal of cardiology* 2007; **118**(3): 356-362 [PMID: 17050012 DOI: 10.1016/j.ijcard.2006.07.032]

22 Karapolat H, Eyigör S, Zoghi M, Yagdi T, Nalbangil S, Durmaz B. Comparison of hospital-supervised exercise versus home-based exercise in patients after orthotopic heart transplantation: effects on functional capacity, quality of life, and psychological symptoms. *Transplantation proceedings* 2007; **39**(5): 1586-1588 [PMID: 17580194 DOI: 10.1016/j.transproceed.2007.01.079]

23 Braith RW, Schofield RS, Hill JA, Casey DP, Pierce GL. Exercise training attenuates progressive decline in brachial artery reactivity in heart transplant recipients. *The Journal of Heart and Lung Transplantation* 2008; **27**(1): 52-59 [PMID: 18187087 DOI: 10.1016/j.healun.2007.09.032]

24 Karapolat H, Eyigor S, Zoghi M, Yagdi T, Nalbantgil S, Durmaz B, Ozbaran M. Effects of cardiac rehabilitation program on exercise capacity and chronotropic variables in patients with orthotopic heart transplant. *Clinical Research in Cardiology* 2008; **97**(7): 449-456 [PMID: 18317667 DOI: 10.1007/s00392-008-0648-7]

25 Pierce GL, Schofield RS, Casey DP, Hamlin SA, Hill JA, Braith RW. Effects of exercise training on forearm and calf vasodilation and proinflammatory markers in recent heart transplant recipients: a pilot study. *European Journal of Cardiovascular Prevention & Rehabilitation* 2008; **15**(1): 10-18 [PMID: 18277180 DOI: 10.1097/HJR.0b013e3282f0b63b]

26 Wu Y-T, Chien C-L, Chou N-K, Wang S-S, Lai J-S, Wu Y-W. Efficacy of a home-based exercise program for orthotopic heart transplant recipients. *Cardiology* 2008; **111**(2): 87-93 [PMID: 18376119 DOI: 10.1159/000119695]

27 Haykowsky M, Taylor D, Kim D, Tymchak W. Exercise training improves aerobic capacity and skeletal muscle function in heart transplant recipients. *American Journal of Transplantation* 2009; **9**(4): 734-739 [PMID: 19344465 DOI: 10.1111/j.1600-6143.2008.02531.x]

28 Mandel DW. Comparison of Targeted Lower Extremity Strengthening and Usual Care Progressive Ambulation in Subjects Post-Liver Transplant: A Randomized Controlled Trial. 2009

29 Hermann TS, Dall C, Christensen S, Goetze J, Prescott E, Gustafsson F. Effect of High Intensity Exercise on Peak Oxygen Uptake and Endothelial Function in Long‐Term Heart Transplant Recipients. *American Journal of Transplantation* 2011; **11**(3): 536-541 [PMID: 21219582 DOI: 10.1111/j.1600-6143.2010.03403.x]

30 Ihle F, Neurohr C, Huppmann P, Zimmermann G, Leuchte H, Baumgartner R, Kenn K, Sczepanski B, Hatz R, Czerner S. Effect of inpatient rehabilitation on quality of life and exercise capacity in long-term lung transplant survivors: a prospective, randomized study. *The Journal of Heart and Lung Transplantation* 2011; **30**(8): 912-919 [PMID: 21489819 DOI: 10.1016/j.healun.2011.02.006]

31 Christensen SB, Dall CH, Prescott E, Pedersen SS, Gustafsson F. A high-intensity exercise program improves exercise capacity, self-perceived health, anxiety and depression in heart transplant recipients: a randomized, controlled trial. *The Journal of Heart and Lung Transplantation* 2012; **31**(1): 106-107 [PMID: 22153554 DOI: 10.1016/j.healun.2011.10.014]

32 Nytrøen K, Rustad LA, Aukrust P, Ueland T, Hallén J, Holm I, Rolid K, Lekva T, Fiane AE, Amlie JP. High‐Intensity Interval Training Improves Peak Oxygen Uptake and Muscular Exercise Capacity in Heart Transplant Recipients. *American Journal of Transplantation* 2012; **12**(11): 3134-3142 [PMID: 22900793 DOI: 10.1111/j.1600-6143.2012.04221.x]

33 Rustad LA, Nytrøen K, Amundsen BH, Gullestad L, Aakhus S. One year of high-intensity interval training improves exercise capacity, but not left ventricular function in stable heart transplant recipients: A randomised controlled trial. *European journal of preventive cardiology* 2012; **21**(2): 181-191 [PMID: 23185084 DOI: 10.1177/2047487312469477]

34 Kawauchi TS, Almeida POd, Lucy KR, Bocchi EA, Feltrim MIZ, Nozawa E. Randomized and comparative study between two intra-hospital exercise programs for heart transplant patients. *Revista Brasileira de Cirurgia Cardiovascular* 2013; **28**(3): 338-346 [PMID: 24343683 DOI: 10.5935/1678-9741.20130053]

35 Kouidi E, Vergoulas G, Anifanti M, Deligiannis A. A randomized controlled trial of exercise training on cardiovascular and autonomic function among renal transplant recipients. *Nephrology Dialysis Transplantation* 2013; **28**(5): 1294-1305 [PMID: 23129823 DOI: 10.1093/ndt/gfs455]

36 Nytrøen K, Rustad LA, Erikstad I, Aukrust P, Ueland T, Lekva T, Gude E, Wilhelmsen N, Hervold A, Aakhus S. Effect of high-intensity interval training on progression of cardiac allograft vasculopathy. *The Journal of Heart and Lung Transplantation* 2013; **32**(11): 1073-1080 [PMID: 23906899 DOI: 10.1016/j.healun.2013.06.023]

37 Dall C, Snoer M, Christensen S, Monk‐Hansen T, Frederiksen M, Gustafsson F, Langberg H, Prescott E. Effect of High‐Intensity Training Versus Moderate Training on Peak Oxygen Uptake and Chronotropic Response in Heart Transplant Recipients: A Randomized Crossover Trial. *American Journal of Transplantation* 2014; **14**(10): 2391-2399 [PMID: 25135383 DOI: 10.1111/ajt.12873]

38 Monk-Hansen T, Dall CH, Christensen SB, Snoer M, Gustafsson F, Rasmusen H, Prescott E. Interval training does not modulate diastolic function in heart transplant recipients. *Scandinavian Cardiovascular Journal* 2014; **48**(2): 91-98 [PMID: 24320690 DOI: 10.3109/14017431.2013.871058]

39 Pascoalino LN, Ciolac EG, Tavares AC, Castro RE, Ayub-Ferreira SM, Bacal F, Issa VS, Bocchi EA, Guimarães GV. Exercise training improves ambulatory blood pressure but not arterial stiffness in heart transplant recipients. *The Journal of Heart and Lung Transplantation* 2015; **34**(5): 693-700 [PMID: 25662857 DOI: 10.1016/j.healun.2014.11.013]

40 Pooranfar S, Shakoor E, Shafahi M, Salesi M, Karimi M, Roozbeh J, Hasheminasab M. The effect of exercise training on quality and quantity of sleep and lipid profile in renal transplant patients: a randomized clinical trial. *International journal of organ transplantation medicine* 2013; **5**(4): 157-165 [PMID: 25426284]

41 Riess KJ, Haykowsky M, Lawrance R, Tomczak CR, Welsh R, Lewanczuk R, Tymchak W, Haennel RG, Gourishankar S. Exercise training improves aerobic capacity, muscle strength, and quality of life in renal transplant recipients. *Applied Physiology, Nutrition, and Metabolism* 2013; **39**(5): 566-571 [PMID: 24766239 DOI: 10.1139/apnm-2013-0449]

42 Tzvetanov I, West-Thielke P, D'Amico G, Johnsen M, Ladik A, Hachaj G, Grazman M, Heller R, Fernhall B, Daviglus M. A novel and personalized rehabilitation program for obese kidney transplant recipients. *Transplantation proceedings* 2014; **46**(10): 3431-3437 [PMID: 24766239 DOI: 10.1139/apnm-2013-0449]

43 Dall CH, Gustafsson F, Christensen SB, Dela F, Langberg H, Prescott E. Effect of moderate-versus high-intensity exercise on vascular function, biomarkers and quality of life in heart transplant recipients: a randomized, crossover trial. *The Journal of Heart and Lung Transplantation* 2015; **34**(8): 1033-1041 [PMID: 25840503 DOI: 10.1016/j.healun.2015.02.001]

44 Greenwood SA, Koufaki P, Mercer TH, Rush R, O’Connor E, Tuffnell R, Lindup H, Haggis L, Dew T, Abdulnassir L. Aerobic or resistance training and pulse wave velocity in kidney transplant recipients: a 12-week pilot randomized controlled trial (the Exercise in Renal Transplant [ExeRT] Trial). *American Journal of Kidney Diseases* 2015; **66**(4): 689-698 [PMID: 26209542 DOI: 10.1053/j.ajkd.2015.06.016]

45 Karelis AD, Hébert M-J, Rabasa-Lhoret R, Räkel A. Impact of Resistance Training on Factors Involved in the Development of New-Onset Diabetes After Transplantation in Renal Transplant Recipients: An Open Randomized Pilot Study. *Canadian journal of diabetes* 2015 [PMID: 26656280 DOI: 10.1016/j.jcjd.2015.08.014]

46 Cieza A, Stucki G. Content comparison of health-related quality of life (HRQOL) instruments based on the international classification of functioning, disability and health (ICF). *Quality of Life Research* 2005; **14**(5): 1225-1237 [PMID: 16047499 DOI: 10.1007/s11136-004-4773-0]

47 Williams TJ, McKenna MJ. Exercise limitation following transplantation. *Comprehensive Physiology* 2012 [PMID: 23723030 DOI: 10.1002/cphy.c110021]

48 Mathur S, Janaudis‐Ferreira T, Wickerson L, Singer LG, Patcai J, Rozenberg D, Blydt‐Hansen T, Hartmann EL, Haykowsky M, Helm D. Meeting report: consensus recommendations for a research agenda in exercise in solid organ transplantation. *American Journal of Transplantation* 2014; **14**(10): 2235-2245 [PMID: 25135579 DOI: 10.1111/ajt.12874]

49 Cleemput I, Dobbels F. Measuring patient-reported outcomes in solid organ transplant recipients. *Pharmacoeconomics* 2007; **25**(4): 269-286 [PMID: 17402802 DOI: 10.2165/00019053-200725040-00002]

50 Trojetto T, Elliott R, Rashid S, Wong S, Dlugosz K, Helm D, Wickerson L, Brooks D. Availability, characteristics, and barriers of rehabilitation programs in organ transplant populations across Canada. *Clinical transplantation* 2011; **25**(6): E571-E578 [PMID: 21955056 DOI: 10.1111/j.1399-0012.2011.01501.x]