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SYSTEMATIC REVIEWS

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

Tania Janaudis-Ferreira, Sunita Mathur, Stacey Konidis, Catherine M Tansey, Cecile Beaurepaire

Tania Janaudis-Ferreira, Sunita Mathur, Canadian National Transplant Research Program, Edmonton, AB T6G 2E1, Canada

Tania Janaudis-Ferreira, Catherine M Tansey, Cecile Beaurepaire, School of Physical and Occupational Therapy, McGill University, Montreal, QC H3G1Y5, Canada

Sunita Mathur, Stacey Konidis, Department of Physical Therapy, University of Toronto, ON M5G 1V7, Canada

Author contributions: Janaudis-Ferreira T designed the research question and protocol, screened titles and abstracts and drafted the manuscript; Mathur S assisted with the interpretation of the findings and provided critical feedback on the manuscript; Konidis S screened titles, abstracts and full-texts, assisted with extracting the data and drafting the manuscript; Tansey CM assisted with data extraction and tabulation and manuscript writing; Beaurepaire C assisted with data extraction and tabulation; all authors read and approved the final manuscript.

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Correspondence to: Tania Janaudis-Ferreira, PhD, School of Physical and Occupational Therapy, McGill University, 3630 Promenade Sir-William-Osler, Montreal, QC H3G1Y5, Canada. tania.janaudis-ferreira@mcgill.ca
Telephone: +1-514-3985326
Fax: +1-514-3988193

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Abstract

AIM

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 VO_2 (n = 13), quality of life using the short-form-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

Core tip: Over 30 randomized controlled trials (RCTs) have been conducted to examine the effectiveness of exercise training on outcomes in solid organ transplant 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 International Classification of Functioning, Disability and Health 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.

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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 (VO_2 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 *et al*[1], the authors included 15 randomized controlled trials (RCTs) with 28 unique outcomes. The majority of outcomes were related to cardiovascular parameters (VO_2 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 RCTs of exercise training in SOT recipients and to link these outcomes to the ICF framework.

MATERIALS AND 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.

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)

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 RCTs, published in English, and in humans. One investigator (Stacey Konidis) also conducted hand searches of the reference lists of all the studies that met the inclusion criteria to identify additional relevant articles.

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 (Stacey Konidis) reviewed the study titles and abstracts to determine potential study eligibility. When this investigator was uncertain, a second reviewer (Tania Janaudis-Ferreira) was consulted. Two investigators independently reviewed the full texts of the articles to determine eligibility (Stacey Konidis and Tania Janaudis-Ferreira).

Data extraction and synthesis

Two reviewers (Stacey Konidis and Cecile Beaurepaire) performed the data extraction and tabulation. A third reviewer (Tania Janaudis-Ferreira) 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.

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.

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 VO_2 (n = 13), SF-36 (n = 8), and muscle strength (n = 7).

Each outcome measure was linked to an ICF

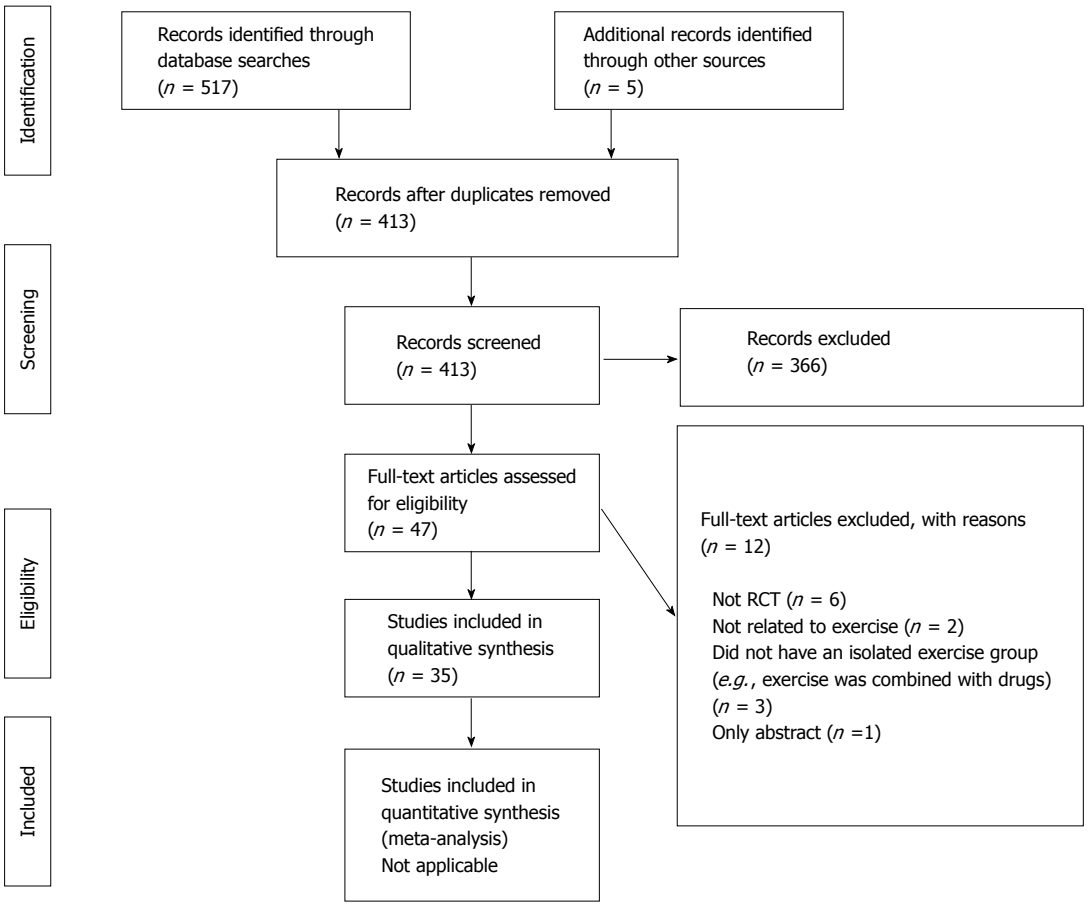

Figure 1 PRISMA 2009 flow diagram. From: Moher *et al*[14]. For more information, visit www.prisma-statement.org.

Table 2 Description of studies

Ref.	Country	Year	Organ	Time-post transplant (wk)	Treatment duration (wk)	Randomized patients[1]	Exercise intervention	Comparison
Braith *et al*[5]	United States	1996	Heart	> 8	24	16	Lumbar extension 1 d/wk; variable resistance exercises 2 d/wk	Usual care
Braith *et al*[4]	United States	1998	Heart	> 8	24	16[2]	Lumbar extension 1 d/wk; variable resistance exercises 2 d/wk	Usual care
Kobashigawa *et al*[15]	United States	1999	Heart	> 2	26	27	Individualized cardiac rehabilitation (strengthening, flexibility, and moderate aerobic exercises) 1-3 d/wk	Usual care (unstructured therapy at home)
Painter *et al*[16]	United States	2002	Kidney	4-8	48	167	Independent home-based exercise 4 d/wk	Usual care
Mitchell *et al*[17]	United States	2003	Lung	> 8	26	16	Lumbar extension resistance exercise 1 d/wk and walking program	Usual care (walking program)
Painter *et al*[18]	United States	2003	Kidney	> 4	48	96	Independent home-based exercise 4 d/wk	Usual care
Braith *et al*[19]	United States	2005	Heart	> 8	24	15	Variable resistance exercises 2 d/wk	Usual care
Juskowa *et al*[20]	Poland	2006	Kidney	> 0.5	4-5	69	Strength exercise training 7 d/wk	Usual care
Krasnoff *et al*[3]	United States	2006	Liver	> 8	40	151	Cardiovascular exercise training 3 d/wk	Usual care
Bernardi *et al*[21]	Italy	2007	Heart	> 24	24	26	Stationary bicycle; 30 min/5 d per week	Usual care
Karapolat *et al*[22]	Turkey	2007	Heart	Mean 14-17	8	38	Hospital-based exercise program (flexibility, stretching, aerobic, strengthening, breathing, relaxation) 3 d/wk	Home-based exercise program (flexibility, stretching, aerobic, strengthening, breathing, relaxation) 3 d/wk
Braith *et al*[23]	United States	2008	Heart	> 8	12	20	Aerobic treadmill exercise	Usual care

Karopola *et al*[24]	Turkey	2008	Heart	Mean 14-17	8	38[3]	Hospital-based exercise program (flexibility, stretching, aerobic, strengthening, breathing, relaxation) 3 d/wk	Home-based exercise program (flexibility, stretching, aerobic, strengthening, breathing, relaxation) 3 d/wk
Pierce *et al*[25]	United States	2008	Heart	> 8	12	20	Aerobic exercise training	Usual care
Wu *et al*[26]	Taiwan	2008	Heart	> 52	8	37	Resistance and aerobic training 3 d/wk	Usual care
Haykowsky *et al*[27]	Canada	2009	Heart	> 26	12	23	Aerobic 5 d/wk and strength training 2 d/wk	Usual care
Mandel *et al*[28]	United States	2009	Liver	6-12	12	50	Targeted lower body resistance strengthening exercise 3-4 d/wk	Usual care (walking program)
Hermann *et al*[29]	Denmark	2011	Heart	> 52	8	27	Aerobic interval training program 3 d/wk	Usual care
Ihle *et al*[30]	Germany	2011	Lung	> 52	4	60	Inpatient rehabilitation (exercise training 4 d/wk and aerobic session 5 d/wk)	Outpatient physiotherapy
Christensen *et al*[31]	Denmark	2012	Heart	Mean 84	8	[4]	High-intensity aerobic interval training 3 d/wk	Usual care
Langer *et al*[2]	Belgium	2012	Lung	1-6	12	40	Aerobic and resistance training 3 d/wk	Usual care
Nytrøen *et al*[32]	Norway	2012	Heart	52-416	52	52	High-intensity aerobic interval training 3 d/wk	Usual care
Rustad *et al*[33]	Norway	2012	Heart	52-416	12	52	High-intensity aerobic interval training 3 d/wk	Usual care
Kawauchi *et al*[34]	Brazil	2013	Heart	< 1	to hospital discharge	22	10-phase incremental exercise program (breathing, active resistance exercises, aerobic exercises, stretching)	Institution exercise routine (breathing, stretching walking) 5 d/wk
Kouidi *et al*[35]	Greece	2013	Kidney	> 52	26	24	Aerobic exercise and strength training 4 d/wk	Usual care
Nytrøen *et al*[36]	Norway	2013	Heart	52-416	52	52[5]	High-intensity aerobic interval training 3 d/wk	Usual care
Dall *et al*[37]	Denmark	2014	Heart	> 52	12 (5 mo washout)	17	High-intensity aerobic interval training 3 d/wk	Moderate biking exercise 3 d/wk
Monk-Hansen *et al*[38]	Denmark	2014	Heart	> 52	8	30	High intensity training 3 d/wk	Usual care
Pascoalino *et al*[39]	Brazil	2015	Heart	> 52	12	42	Endurance exercise training 3 d/wk	Usual care
Pooranfar *et al*[40]	Iran	2013	Kidney	104-156	10	44	Aerobic and resistance training 3 d/wk	Usual care
Riess *et al*[41]	Canada	2013	Kidney	> 26	12	31	Endurance and strength training 2 d/wk	Usual care
Tzvetanov *et al*[42]	United States	2014	Kidney	> 4	52	17	Resistance exercise training 2 d/wk (as well as behaviour and nutrition)	Usual care
Dall *et al*[43]	Denmark	2015	Heart	> 52	12 (5 mo washout)	17[6]	High-intensity aerobic interval training 3 d/wk	Moderate biking exercise 3 d/wk
Greenwood *et al*[44]	England	2015	Kidney	< 52	12	60	Home-based aerobic training and resistance training 3 d/wk	Usual care
Karelis *et al*[45]	Canada	2015	Kidney	6-8	16	24	Resistance training 3 d/wk (once a week in hospital and 2 × /week at home)	Usual care (no exercise)

[1]Does not add to 1313 since some patients included in more than one study; [2]Same patients as Braith 1996; [3]Same patients as Karolopat 2007; [4]Same patients as Hermann 2011; [5]Same patients as Nytrøen 2012; [6]Same patients as Dall 2014. BMD: Bone mineral density; HR: Heart rate; BP: Blood pressure; HRQOL: Health-related quality-of-life; CVD: Cardiovascular disease; BMI: Body mass index; METs: Metabolic unit of task; HRRe: Heart rate reserve; HRR1: Heart rate recovery; CRI: Chronotropic response index; CRP: C-reactive protein; IL-6: Interleukin-6; TNF-a: Tumor necrosis factor-alpha; sICAM-1: Intercellular adhesion molecule-1; 6MWD: 6 minute walk distance; FVC: Forced vital capacity; HRV: Heart rate variability; BRS: Baroreflex sensitivity.

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

Table 3 List of outcome measures by study

Ref.	Year	Organ group	Primary outcome measures	Secondary outcome measures
Braith *et al*[5]	1996	Heart	Bone mineral density (body and regional: Femur neck, lumbar vertebra)	Bone mineral content Total bone calcium Acute rejection episodes
Braith *et al*[4]	1998	Heart	Body mass Fat-free mass Fat mass Muscle strength (upper and lower body)	Percent body fat Acute rejection episodes
Kobashigawa *et al*[15]	1999	Heart	Blood pressure (peak and resting) Heart rate (peak and resting) Anaerobic threshold Exercise duration (to exhaustion) Peak ventilation Peak VO_2 Peak workload Ventilatory equivalent for carbon dioxide and oxygen	Muscle strength (lower limb)
Painter *et al*[16]	2002	Kidney	Body mass index Body weight Fat mass/body fat Lean tissue mass Percent body fat Blood pressure (peak) Muscle strength (quadriceps) Peak ventilation Peak VO_2 SF-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 *et al*[17]	2003	Lung	Bone mineral density (lumbar spine)	Acute rejection episodes Muscle strength (lumbar extensor)
Painter *et al*[18]	2003	Kidney	Cholesterol (TC, HDL) Body mass index Total CVD risk (Framingham) Blood pressure Peak workload (METs)	Blood lipids Incidence of diabetes Smoking status
Braith *et al*[19]	2005	Heart	Muscle composition (fiber types) Muscle metabolic enzyme activity	Muscle strength (upper and lower body)
Juskowa *et al*[20]	2006	Kidney	Blood lipids Cholesterol (TC, HDL, LDL) Body mass index	Blood calcium level Blood creatinine 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 *et al*[3]	2006	Liver	Body mass index Body weight Bone mineral content Bone mineral density Fat mass/body fat Lean tissue mass Percent body fat Muscle strength (quadriceps) Peak VO_2 SF-36 Peak respiratory exchange ratio Nutritional intake (Block-95 - calories/day; protein, carb and fat calories)	Rating of perceived exertion (Borg)

Bernardi *et al*[21]	2007	Heart	Baroceptor control of blood pressure Baroceptor control of heart rate	Blood pressure; Heart rate Neck pressure RR interval Anaerobic threshold CO_2 production Exercise duration (to exhaustion) Peak ventilation Peak VO_2; Peak workload Ventilatory equivalent for CO_2 and oxygen
Karapolat *et al*[22]	2007	Heart	Peak VO_2 Beck depression inventory SF-36 State-trait anxiety inventory	
Braith *et al*[23]	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 VO_2
Karapolat *et al*[24]	2008	Heart	Chronotropic response index Heart rate recovery Heart rate reserve Peak VO_2	Duke Treadmill Score
Pierce *et al*[25]	2008	Heart	C-reactive protein Interleukin-6 Serum metabolic profile Soluble cell adhesion molecules (sICAM-1) Tumour necrosis factor-alpha Muscle vasodilation (forearm and calf)	Blood glucose Cholesterol (TC, HDL, LDL) Cytomegalovirus IgG status White blood cell levels Acute rejection episodes Blood pressure (resting) Heart rate (peak and resting) Exercise duration (to exhaustion) Rating of perceived exertion (Borg) Peak respiratory exchange ratio
Wu *et al*[26]	2008	Heart	Muscle endurance (quadriceps) Muscle strength (quadriceps) Peak VO_2 World Health Organization Questionnaire on Quality of Life - BREF	Daily physical activity Blood pressure Heart rate (resting and peak) Nutritional intake (caloric intake questionnaire) Peak ventilation Peak workload Rating of perceived exertion (Borg)
Haykowsky *et al*[27]	2009	Heart	Peak VO_2	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 function Muscle strength (upper and lower body) Peak power output Peak respiratory exchange ratio
Mandel *et al*[28]	2009	Liver	6MWD Muscle strength (lower body) Chronic liver disease questionnaire (CLDQ) SF-36 (physical function/limitations)	
Hermann *et al*[29]	2011	Heart	Peak VO_2	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 *et al*[30]	2011	Lung	6MWD Peak VO_2 SF-36 St. George's Respiratory Questionnaire	Heart rate (peak and resting) Anaerobic threshold Oxygen uptake at anaerobic threshold Peak workload Peak respiratory exchange ratio Ventilatory reserve and capacity
Christensen *et al*[31]	2012	Heart	Hospital Anxiety and Depression Scale	Peak VO_2
Langer *et al*[2]	2012	Lung	SF-36 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 *et al*[32]	2012	Heart	Peak VO_2	Blood lipids Blood protein levels (NT-proBNP) C-reactive protein Interleukin-6, 8 and 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 and reserve Stroke volume (O_2 pulse; resting and 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 *et al*[33]	2012	Heart	Echocardiographic parameters (rest and during exercise; systolic and diastolic parameters) Peak VO_2	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 *et al*[34]	2013	Heart	6MWD Forced vital capacity Respiratory muscle force/strength	Muscle strength (upper and lower limbs) Maximum expiratory/inspiratory pressure
Kouidi *et al*[35]	2013	Kidney	Baroreflex sensitivity Heart rate variability parameters (SDNN, rMSSD, pNN50, LF, HF, LF/HF)	Baroreflex effectiveness index Blood pressure (peak and resting) Heart rate (peak and resting) Exercise duration (to exhaustion) Peak ventilation Peak VO_2
Nytrøen *et al*[36]	2013	Heart	Cardiac allograft vasculopathy (intravascular ultrasound and virtual histology)	Blood creatinine Blood glucose Blood lipids

				C-reactive protein Cholesterol (TC, HDL, LDL) Hemoglobin Interleukin-6, 8 and 10 levels Body mass index Body water (total) Body weight Bone mass Lean tissue mass Percent body fat Visceral fat scale Basal metabolic rate Glycemic control parameters Metabolic age Muscle strength (quadriceps and hamstrings)
Dall *et al*[37]	2014	Heart	Peak VO_2	Peak VO_2 Body weight Blood pressure Heart rate (peak and resting) Heart rate recovery Heart rate reserve CO_2 production Peak ventilation Peak workload Peak respiratory exchange ratio
Monk-Hansen *et al*[38]	2014	Heart	Echocardiography parameters (systolic and diastolic function)	Body mass index Blood pressure Heart rate (peak and resting) Peak VO_2 Peak workload
Pascoalino *et al*[39]	2015	Heart	Arterial stiffness (carotid-femoral pulse wave velocity) Blood pressure (ambulatory; peak and resting)	Plasma norepinephrine Heart rate (peak and resting) Anaerobic threshold CO_2 production Exercise duration (to exhaustion) Peak VO_2 Peak respiratory exchange ratio Respiratory compensation point
Pooranfar *et al*[40]	2013	Kidney	Blood lipids Cholesterol (TC, HDL, LDL) Sleep quality and quantity questionnaire (self-report; Pittsburgh Sleep Quality Index)	
Riess *et al*[41]	2013	Kidney	Peak VO_2	Cholesterol (TC, HDL) Lean tissue mass Total CVD risk (Framingham) Arterial pressure (mean) Arterial stiffness (pulse wave velocity) Arteriovenous oxygen difference (a-vO_2) Blood pressure (ambulatory; peak and resting) Cardiac output Heart rate (peak); Stroke volume Systemic vascular endurance Muscle strength (lower body) Peak workload SF-36 Peak respiratory exchange ratio
Tzvetanov *et al*[42]	2014	Kidney	Glomerular filtration rate SF-36 Adherence to training and follow-up Employment status	Blood creatinine; Blood glucose; Blood lipids 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 *et al*[43]	2015	Heart	Blood glucose 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	Body weight Homeostasis model assessment Heart rate (peak) Peak VO_2 Peak respiratory exchange ratio
Greenwood *et al*[44]	2015	Kidney	Muscle strength (quadriceps)	Arterial stiffness (pulse wave velocity) Blood pressure (peak and resting) Heart rate (peak and resting) STS-60 Peak VO_2 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 and 2 SF-36 Duke Activity Status Index
Karelis *et al*[45]	2015	Kidney	World Health Organization-5 Well-Being Index Muscle strength index Adherence 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 VO_2

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 4 International Classification of Functioning, Disability and Health outcome classifications

ICF component	Domain	Category	Outcome measures	Count primary[1]	Organ group
Body Function	Global mental functions	b134	Sleep quality and quantity	1	Kidney
		b152	Mood status	0	Lung
	Functions of the cardiovascular system (heart functions)	b410	Cardiac output	0	Heart, kidney
		b410	Carotid intima-media thickness	0	Kidney
		b410	Echocardiographic parameters	2	Heart
		b410	Endothelial function	2	Heart
		b410	Left ventricular systolic function	0	Heart
		b410	RR interval	0	Heart
		b410	Stroke volume	0	Heart, kidney
		b410	Systemic vascular endurance	0	Kidney
	Functions of the cardiovascular system (heart rate)	b4100	Heart rate	1	Heart, kidney, lung
		b4100	Heart rate recovery	1	Heart
		b4100	Heart rate reserve	1	Heart
		b4100	Heart rate variability	1	Kidney
	Functions of the cardiovascular system	b410-429	Baroceptor control of blood pressure	1	Heart
		b410-429	Baroceptor control of heart rate	1	Heart
		b410-429	Baroflex effectiveness index	0	Kidney
		b410-429	Baroflex sensitivity	1	Kidney
		b410-429	Chronotropic response index	1	Heart
		b410-429	Total CVD risk	1	Kidney
		b410-429	Cardiac allograft vasculopathy	1	Heart
	Functions of the cardiovascular system (blood vessel functions)	b415	Arterial stiffness	3	Heart, kidney
		b415	Brachial artery diameter	0	Heart
	Functions of the cardiovascular system (blood pressure functions)	b420	Arterial pressure	0	Kidney
		b420	Blood pressure	4	Heart, kidney, lung

	b420	Neck pressure	0	Heart
Functions of the cardiovascular system (oxygen-carrying functions of the blood)	b4301	Arteriovenous oxygen difference	0	Kidney
Functions of the hematological and immunological	b430-439	Biochemical parameters	0	Heart
systems	b430-439	Blood calcium level	0	Kidney
	b430-439	Blood creatinine	0	Heart, kidney
	b430-439	Blood electrolytes	0	Kidney
	b430-439	Blood glucose	1	Heart, kidney
	b430-439	Blood lipids	2	Heart, kidney, lung
	b430-439	Blood phosphorus	0	Kidney
	b430-439	Blood protein levels	1	Heart, kidney
	b430-439	Blood urea nitrogen levels	0	Kidney
	b430-439	C-reactive protein	1	Heart
	b430-439	Cholesterol	3	Heart, kidney
	b430-439	Folate concentrations	0	Kidney
	b430-439	Hematocrit	0	Kidney
	b430-439	Hemoglobin	0	Heart, kidney
	b430-439	High sensitive C-reactive protein	0	Heart
	b430-439	Interleukin levels	2	Heart, kidney
	b430-439	Plasma norepinephrine	0	Heart
	b430-439	Soluble cell adhesion molecules	1	Heart
	b430-439	Total-homocysteine	0	Kidney
	b430-439	Tumour necrosis factor-alpha	2	Heart
	B430-439	Tumor necrosis factor receptor	0	Kidney
	b435	Cytomegalovirus IgG status	0	Heart
	b435	White blood cell levels	0	Heart
	b435	Acute rejection episodes	0	Heart, lung
Functions of the respiratory system (respiration functions)	b440	Forced expiratory volume	0	Lung
functions)	b440	Forced vital capacity	1	Heart
	b440	Maximum expiratory/inspiratory pressure	0	Heart
	b440	Peak expiratory flow	0	Kidney
	b440	Peak respiratory exchange ratio	1	Heart, kidney, liver, lung
	b440	Respiratory compensation point	0	Heart
	b440	Ventilatory reserve and capacity	0	Lung
Functions of the respiratory system (respiration rate)	b4400	CO_2 production	0	Heart
	b4400	Oxygen uptake at anaerobic threshold	0	Lung
	b4400	Peak ventilation	2	Heart, kidney
	b4400	Peak VO_2	13	Heart, kidney, liver, lung
	b4400	Ventilatory equivalent for carbon dioxide and oxygen	1	Heart
Functions of the respiratory system (respiratory muscle functions)	b445	Respiratory muscle force/strength	1	Heart, lung
Functions of the cardiovascular system (general physical endurance)	b4550	Rating of perceived exertion	0	Heart, kidney, liver
Functions related to the digestive, metabolism and the endocrine system	b530	Body mass index	4	Heart, kidney, liver
endocrine system	b530	Body weight/mass	3	Heart, kidney, liver, lung
	b530	Fat mass/body fat	3	Heart, kidney, liver
	b530	Fat-free mass	1	Heart
	b530	Hip girth	0	Kidney
	b530	Hip-waist ratio	0	Heart
	b530	Lean tissue mass	2	Heart, kidney, liver
	b530	Percent body fat	2	Heart, kidney, liver
	b530	Visceral fat scale	0	Heart
	b530	Waist girth	0	Kidney
General metabolic functions, unspecified	b5400	Basal metabolic rate	0	Heart
	b5400	Metabolic age	0	Heart
General metabolic functions, other, specified	B5408	Maximal metabolic units	1	Kidney
Functions related to metabolism and the endocrine system	b540-559	Enzyme levels	0	Kidney
system	b540-559	Fetuin A	0	Kidney
	b540-559	Oxidative stress-induced lipid peroxidation	0	Heart
	b540-559	Serum insulin	1	Heart

		b540-559	Serum metabolic and/or hematologic profile	1	Heart
		b540-559	Vitamin B_{12}	0	Kidney
		b540-559	Glycemic control parameters	0	Heart, kidney
		b540-559	Muscle metabolic enzyme activity	1	Heart
		b545	Body water	0	Heart
		b545	Homeostasis model assessment	0	Heart
	Functions of the genitourinary and reproductive functions (urinary functions)	b610-639	Glomerular filtration rate	1	Kidney
	Neuromusculoskeletal and movement-related functions (muscle power functions)	b730	Peak workload/power output	1	Heart, kidney, lung
		b730	Muscle strength	7	Heart, kidney, liver, lung
		b730-b749	Muscle vasodilation	1	Heart
		b740	Muscle endurance	1	Heart
Body structure	Structures related to movement - additional musculoskeletal structures related to movement (bones)	s7700	Bone mass	0	Heart
		s7700	Bone mineral content	1	Heart, kidney, liver
		s7700	Bone mineral density	3	Heart, kidney, liver, lung
		s7700	Total bone calcium	0	Heart
		s7702	Muscle composition (fibre types)	1	Heart
Activities and participation	Mobility - walking and moving	d410	STS-60	0	Kidney
participation	Mobility - walking and moving (walking)	d450	Daily steps	0	Lung
		d450	Daily walking time	1	Lung
		d450	6 Minute Walk Distance	3	Heart, liver, lung
		d450	Anaerobic threshold	1	Heart, lung
	Mobility - walking and moving	d450-469	Daily physical activity	0	Heart
		d450-469	Movement intensity	0	Lung
		d450-469	Self-reported activity level	0	Kidney
		d450-469	Time spent in moderate intense activities	0	Lung
		d450-469	Duke Treadmill Score	0	Heart
		d450-469	Exercise duration	1	Heart, kidney
	Managing diet and fitness	d5701	Caloric intake	0	Heart
		d5701	Nutritional intake	1	Liver
	Major life areas (work and employment)	d840-859	Employment status	1	Kidney
Environmental factors	Products or substances for personal consumption, other specified	e1108	Smoking status	0	Kidney
	Drugs	e1101	Immunosuppression use	0	Kidney
Questionnaires			DASI	0	Kidney
			Quality of Life Profile for Chronic Diseases Questionnaire	1	Lung
			SF-36	8	Heart, kidney, liver, lung
			St. George's Respiratory Questionnaire	1	Lung
			State-Trait Anxiety Inventory	1	Heart
			Beck Depression Inventory	1	Heart
			Hospital Anxiety and Depression Scale	2	Heart
			Visual Analog Scale (change in HRQoL)	0	Heart
			WHOQOL-BREF	2	Heart, kidney
Not covered by ICF			Chronic Liver Disease Questionnaire	1	Liver
			Incidence of morbidity	0	Kidney, lung
			Adherence to training and follow-up	2	Kidney

[1]Count Primary: Count of studies that used this measure as a primary measure. RR-interval: Inter-beat interval (heart rate); CVD: Cardio-vascular disease; STS-60: Sit-to-stand 60; SF-36: Short-form 36; HRQoL: Health-related quality of life; WHOQOL-BREF: A shorter version of the original World Health Organization Quality of Life Questionnaire; DASI: Duke Activity Status Index.

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 VO_2 (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*[1] found that the most commonly used outcome measure was VO_2 peak. 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*[1] were unable to merge data on health-related quality-of-life (HRQoL) measures since so many different questionnaires were used. 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 and Stucki[46] 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. 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 relating 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.

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 randomized controlled trials (RCTs) have been conducted to examine

the effectiveness of exercise training on outcomes in solid organ transplant (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 RCTs of exercise training in 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 *et al*, the authors included 15 RCTs with 28 unique outcomes. The majority of outcomes were related to cardiovascular parameters (VO_2 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 (VO_2 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 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.

Peer-review

It is a well written review concerning several domains to assess the function outcome of patients with organ transplants subjected to exercise training. It is very helpful for the readers.

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