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

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

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 VO₂ (n = 13), quality of life using the short-form-36 (n = 8), and muscle strength (n = 7). These

Conflict-of-interest statement: All the authors declare that they have no competing interests.

Data sharing statement: The original tables are available from the corresponding author at tania.janaudis-ferreira@mcgill.ca.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited manuscript

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

Received: June 29, 2016
Peer-review started: July 1, 2016
First decision: September 5, 2016
Revised: September 29, 2016
Accepted: October 22, 2016
Article in press: October 24, 2016
Published online: December 24, 2016

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 VO₂ (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

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

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.

Janaudis-Ferreira T, Mathur S, Konidis S, Tansey CM, Beaurepaire C. Outcomes in randomized controlled trials of exercise interventions in solid organ transplant. World J Transplant 2016; 6(4): 774-789 Available from: URL: http://www.wjgnet.com/2220-3230/full/v6/i4/774.htm DOI: http://dx.doi.org/10.5500/wjt.v6.i4.774

**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 transplantation (SOT) recipients, such as improving maximal aerobic capacity ($\text{VO}_2$ 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$^6$. 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$^6$, the authors included 15 randomized controlled trials (RCTs) with 28 unique outcomes. The majority of outcomes were related to cardiovascular parameters ($\text{VO}_2$ 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.
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 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 VO2 (n = 13), SF-36 (n = 8), and muscle strength (n = 7).

Each outcome measure was linked to an ICF

| 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 recipients” (27594)          |
| Search #5 | 1 or 2 or 3 or 4 (122169)                |
| Search #6 | Exercise/or Exercise Therapy/or exercise5 (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) |
Records after duplicates removed (n = 413)

Records screened (n = 413)

Records excluded (n = 366)

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 qualitative synthesis (n = 35)

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

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 | 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                  | Lumbar extension 1 d/wk; variable resistance exercises 2 d/wk                        | Usual care                                                                |
| Kobashigawa et al[11] | 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[6] | United States | 2002 | Kidney | 4-8                       | 48                      | 167                 | Independent home-based exercise 4 d/wk                                               | Usual care                                                                |
| Mitchell et al[7] | United States | 2003 | Lung  | > 8                       | 26                      | 16                  | Lumbar extension resistance exercise 1 d/wk and walking program                      | Usual care (walking program)                                               |
| Painter et al[8] | United States | 2003 | Kidney | > 4                       | 48                      | 96                  | Independent home-based exercise 4 d/wk                                               | Usual care                                                                |
| Braith et al[9] | 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[10] | United States | 2006 | Liver | > 8                       | 40                      | 151                 | Cardiovascular exercise training 3 d/wk                                              | Usual care                                                                |
| Bernardi et al[11] | Italy         | 2007 | Heart | > 24                      | 24                      | 26                  | Stationary bicycle; 30 min/5 d per week                                               | Usual care                                                                |
| Karapolat et al[12] | 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 |
### Outcomes in exercise intervention in transplantation

| Study                  | Country          | Year | Study Group | Duration/MO | Study Details                                                                 |
|------------------------|------------------|------|-------------|-------------|-------------------------------------------------------------------------------|
| Pierce et al.          | United States    | 2008 | Heart       | > 8         | 12 | Aerobic exercise training                                                    |
| Wu et al.              | Taiwan           | 2008 | Heart       | > 52        | 8  | Resistance and aerobic training 3 d/wk                                      |
| Haykowsky et al.       | Canada           | 2009 | Heart       | > 26        | 12 | Aerobic 5 d/wk and strength training 2 d/wk                                  |
| Mandel et al.          | United States    | 2009 | Liver       | 12-12       | 12 | Targeted lower body resistance strengthening exercise 3-4 d/wk                |
| Hermann et al.         | Denmark          | 2011 | Heart       | > 52        | 8  | Aerobic interval training program 3 d/wk                                       |
| Ihle et al.            | Germany          | 2011 | Lung        | > 52        | 4  | Inpatient rehabilitation (exercise training 4 d/wk and aerobic session 5 d/wk) |
| Christensen et al.     | Denmark          | 2012 | Heart       | Mean 84     | 8  | High-intensity aerobic interval training 3 d/wk                               |
| Langer et al.          | Belgium          | 2012 | Lung        | 1-6         | 12 | Aerobic and resistance training 3 d/wk                                        |
| Nytryen et al.         | Norway           | 2012 | Heart       | 52-416      | 52 | High-intensity aerobic interval training 3 d/wk                               |
| Rustad et al.          | Norway           | 2012 | Heart       | 52-416      | 12 | High-intensity aerobic interval training 3 d/wk                               |
| Kawauchi et al.        | Brazil           | 2013 | Heart       | < 1         | to hospital discharge 22 | Institution exercise routine (breathing, stretching walking) 5 d/wk          |
| Kouidi et al.          | Greece           | 2013 | Kidney      | > 52        | 26 | Aerobic exercise and strength training 4 d/wk                                |
| Nytryen et al.         | Norway           | 2013 | Heart       | 52-416      | 52 | High-intensity aerobic interval training 3 d/wk                               |
| Dall et al.            | Denmark          | 2014 | Heart       | > 52        | 12 | High-intensity aerobic interval training 3 d/wk                               |
| Monk-Hansen et al.     | Denmark          | 2014 | Heart       | > 52        | 8  | High intensity training 3 d/wk                                                |
| Pascoalino et al.      | Brazil           | 2015 | Heart       | > 52        | 12 | Endurance exercise training 3 d/wk                                             |
| Pooranfar et al.       | Iran             | 2013 | Kidney      | 104-156     | 10 | Aerobic and resistance training 3 d/wk                                        |
| Riess et al.           | Canada           | 2013 | Kidney      | > 26        | 12 | Endurance and strength training 2 d/wk                                        |
| Tzvetanov et al.       | United States    | 2014 | Kidney      | > 4         | 52 | Resistance exercise training 2 d/wk (as well as behaviour and nutrition)     |
| Dall et al.            | Denmark          | 2015 | Heart       | > 52        | 12 | High-intensity aerobic interval training 3 d/wk                               |
| Greenwood et al.       | England          | 2015 | Kidney      | > 52        | 12 | Home-based aerobic training and resistance training 3 d/wk                    |
| Karelis et al.         | Canada           | 2015 | Kidney      | 6-8         | 16 | Resistance training 3 d/wk (once a week in hospital and 2 * 1/week at home)  |

### 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 reviewed.

1Does not add to 1313 since some patients included in more than one study; 2Same patients as Braith 1996; 3Same patients as Karolopat 2007; 4Same patients as Hermann 2011; 5Same patients as Nytryen 2012; 6Same patients as Dall 2014. BMI: Body mass index; METs: Metabolic unit of task; HRR: Heart rate reserve; HRR1: Heart rate recovery; CRE: 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.

When selecting outcome measures to use in clinical trials 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.
| 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 |
| | | | | Percent body fat |
| | | | | Acute rejection episodes |
| | | | | Muscle strength (upper and lower body) |
| | | | | Blood pressure (peak and resting) |
| | | | | Heart rate (peak and resting) |
| | | | | Anaerobic threshold |
| | | | | Exercise duration (to exhaustion) |
| | | | | Peak ventilation |
| | | | | Peak VO2 |
| | | | | Ventilatory equivalent for carbon dioxide and oxygen |
| | | | | 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) |
| Painter et al[8] | 2002 | Kidney | Body mass index | Muscle strength (lumbar extensor) |
| | | | Body weight | Acute rejection episodes |
| | | | Fat mass/body fat | Muscle strength (lumbar spine) |
| | | | Lean tissue mass | Body lipids |
| | | | Percent body fat | Incidence of diabetes |
| | | | Blood pressure (peak) | Smoking status |
| | | | Muscle strength (quadriceps) | |
| | | | Peak ventilation | |
| | | | Peak VO2 | |
| | | | SF-36 | |
| Mitchell et al[7] | 2003 | Lung | Bone mineral density (lumbar spine) | Muscle strength (upper and lower body) |
| | | | | Acute rejection episodes |
| Painter et al[8] | 2003 | Kidney | Cholesterol (TC, HDL) | Blood lipids |
| | | | Body mass index | Incidence of diabetes |
| | | | Total CVD risk (Framingham) | Smoking status |
| | | | Blood pressure | |
| | | | Peak workload (METs) | |
| | | | Muscle composition (fiber types) | |
| | | | Muscle metabolic enzyme activity | |
| | | | Blood lipids | |
| | | | Cholesterol (TC, HDL, LDL) | |
| | | | Body mass index | |
| Braith et al[9] | 2005 | Heart | Muscle composition (fiber types) | 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 |
| | | | | Rating of perceived exertion (Borg) |
| Juskowa et al[23] | 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 |
| | | | | Rating of perceived exertion (Borg) |
| Mitchell et al[7] | 2003 | Kidney | Bone mineral density (lumbar spine) | |
| | | | | |
| Painter et al[8] | 2003 | Kidney | Cholesterol (TC, HDL) | |
| | | | | |
| Mitchell et al[7] | 2003 | Kidney | Bone mineral density (lumbar spine) | |
| | | | | |
| Painter et al[8] | 2003 | Kidney | Cholesterol (TC, HDL) | |
| | | | | |
| Mitchell et al[7] | 2003 | Kidney | Bone mineral density (lumbar spine) | |
| | | | | |
| Painter et al[8] | 2003 | Kidney | Cholesterol (TC, HDL) | |
| | | | | |
| Mitchell et al[7] | 2003 | Kidney | Bone mineral density (lumbar spine) | |
| | | | | |
| Painter et al[8] | 2003 | Kidney | Cholesterol (TC, HDL) | |
| | | | | |
| Mitchell et al[7] | 2003 | Kidney | Bone mineral density (lumbar spine) | |
| | | | | |
| Painter et al[8] | 2003 | Kidney | Cholesterol (TC, HDL) | |
| | | | | |
| Mitchell et al[7] | 2003 | Kidney | Bone mineral density (lumbar spine) | |
| | | | | |
| Painter et al[8] | 2003 | Kidney | Cholesterol (TC, HDL) | |
| | | | | |
| Mitchell et al[7] | 2003 | Kidney | Bone mineral density (lumbar spine) | |
| | | | | |
| Painter et al[8] | 2003 | Kidney | Cholesterol (TC, HDL) | |
| | | | | |
| Mitchell et al[7] | 2003 | Kidney | Bone mineral density (lumbar spine) | |
| | | | | |
| Painter et al[8] | 2003 | Kidney | Cholesterol (TC, HDL) | |
| | | | | |
| Mitchell et al[7] | 2003 | Kidney | Bone mineral density (lumbar spine) | |
| | | | | |
| Painter et al[8] | 2003 | Kidney | Cholesterol (TC, HDL) | |
| | | | | |
| Mitchell et al[7] | 2003 | Kidney | Bone mineral density (lumbar spine) | |
| | | | | |
| Painter et al[8] | 2003 | Kidney | Cholesterol (TC, HDL) | |
| | | | | |
| Mitchell et al[7] | 2003 | Kidney | Bone mineral density (lumbar spine) | |
| | | | | |
| Painter et al[8] | 2003 | Kidney | Cholesterol (TC, HDL) | |
| | | | | |
| Mitchell et al[7] | 2003 | Kidney | Bone mineral density (lumbar spine) | |
| | | | | |
| Painter et al[8] | 2003 | Kidney | Cholesterol (TC, HDL) | |
| | | | | |
| Author(s)          | Year | Type   | Measures                                                                 | Notes                                                                 |
|-------------------|------|--------|---------------------------------------------------------------------------|----------------------------------------------------------------------|
| Bernardi et al.   | 2007 | Heart  | Baroreceptor control of blood pressure                                    | Blood pressure; Heart rate                                           |
|                   |      |        | Baroreceptor control of heart rate                                        | Neck pressure                                                        |
| Karapolat et al.  | 2007 | Heart  | Peak VO₂; Beck depression inventory                                      | Blood glucose                                                        |
|                   |      |        | SF-36                                                                      | Blood glucose                                                        |
| Braith et al.     | 2008 | Heart  | Endothelial function (flow-mediated dilation)                             | Blood glucose                                                        |
|                   |      |        | State-trait anxiety inventory                                             | Blood glucose                                                        |
| Karapolat et al.  | 2008 | Heart  | Chronotropic response index                                               | Blood glucose                                                        |
|                   |      |        | Heart rate recovery                                                       | Blood glucose                                                        |
|                   |      |        | Heart rate reserve                                                        | Blood glucose                                                        |
| Pierce et al.     | 2008 | Heart  | C-reactive protein                                                        | Blood glucose                                                        |
|                   |      |        | Interleukin-6                                                             | Blood glucose                                                        |
|                   |      |        | Serum metabolic profile                                                   | Blood glucose                                                        |
|                   |      |        | Soluble cell adhesion molecules (sICAM-1)                                 | Blood glucose                                                        |
|                   |      |        | Tumour necrosis factor-alpha                                               | Blood glucose                                                        |
|                   |      |        | Muscle vasodilation (forearm and calf)                                    | Blood glucose                                                        |
| Wu et al.         | 2008 | Heart  | Muscle endurance (quadriceps)                                             | Blood glucose                                                        |
|                   |      |        | Muscle strength (quadriceps)                                              | Blood glucose                                                        |
|                   |      |        | Peak VO₂                                                                  | Blood glucose                                                        |
|                   |      |        | World Health Organization Questionnaire on Quality of Life - BREF         | Blood glucose                                                        |
| Haykowsky et al.  | 2009 | Heart  | Peak VO₂                                                                  | Blood glucose                                                        |
|                   |      |        | Rating of perceived exertion (Borg)                                       | Blood glucose                                                        |
|                   |      |        | Lean tissue mass (total and leg)                                          | Blood glucose                                                        |
|                   |      |        | Blood pressure (peak)                                                     | Blood glucose                                                        |
|                   |      |        | Endothelial function (endothelial-dependent vasodilation, endothelial-independent vasodilation, reactive hyperemia index) | Blood glucose                                                        |
| Mandel et al.     | 2009 | Liver  | 6MWD                                                                       | Blood glucose                                                        |
|                   |      |        | Muscle strength (lower body)                                              | Blood glucose                                                        |
|                   |      |        | Chronic liver disease questionnaire (CLDQ)                               | Blood glucose                                                        |
| Hermann et al.    | 2011 | Heart  | Peak VO₂                                                                  | Blood glucose                                                        |
|                   |      |        | Blood creatinine                                                          | Blood glucose                                                        |
|                   |      |        | Blood protein levels (adiponectin, MR-proANP, NT-proBNP, provasopressin/copeptin) | Blood glucose                                                        |
|                   |      |        | Cholesterol                                                               | Blood glucose                                                        |
|                   |      |        | Hemoglobin                                                                | Blood glucose                                                        |
|                   |      |        | High sensitive C-reactive protein                                         | Blood glucose                                                        |
|                   |      |        | Interleukin-6                                                             | Blood glucose                                                        |
|                   |      |        | Serum insulin                                                              | Blood glucose                                                        |
|                   |      |        | Tumour necrosis factor-alpha                                               | Blood glucose                                                        |
|                   |      |        | Body mass index; Body weight                                              | Blood glucose                                                        |
| Study          | Year | Organ | Outcome Measures                                                                 |
|---------------|------|-------|-----------------------------------------------------------------------------------|
| Ihle et al.   | 2011 | Lung  | 6MWD, SF-36, St. George’s Respiratory Questionnaire                                 |
| Christensen et al. | 2012 | Heart | Hospital Anxiety and Depression Scale                                              |
| Langer et al. | 2012 | Lung  | SF-36, Daily walking time (time spend in different postures: sedentary, standing, walking) |
| Nytrøen et al. | 2012 | Heart | Peak VO₂                              |
| Rustad et al. | 2012 | Heart | Echocardiographic parameters (rest and during exercise; systolic and diastolic parameters) |
| Kawauchi et al. | 2013 | Heart | 6MWD, Forced vital capacity, Respiration muscle force/strength, Baroreflex sensitivity, Heart rate variability parameters (SDNN, rMSSD, pNN50, LF, HF, LF/HF) |
| Kouidi et al. | 2013 | Kidney| Respiration muscle force/strength, Baroreflex sensitivity, Heart rate variability parameters (SDNN, rMSSD, pNN50, LF, HF, LF/HF) |
| Nytrøen et al. | 2013 | Heart | Cardiac allograft vasculopathy (intravascular ultrasound and virtual histology)         |
| Authors          | Year | Organ | Measurements                                                                 |
|------------------|------|-------|------------------------------------------------------------------------------|
| Dall et al.      | 2014 | Heart | Peak VO₂, Blood pressure, Heart rate (peak and resting), Heart rate reserve, CO₂ production, Peak ventilation, Peak workload, Peak respiratory exchange ratio, Body mass index, Blood pressure, Heart rate (peak and resting), Peak VO₂, Peak workload, Respiratory compensation point |
| Monk-Hansen et al | 2014 | Heart | Echocardiography parameters (systolic and diastolic function), Plasma norepinephrine, Heart rate (peak and resting), Anaerobic threshold, CO₂ production, Exercise duration (to exhaustion), Peak VO₂, Peak respiratory exchange ratio, Respiratory compensation point |
| Pascoalino et al | 2015 | Heart | Arterial stiffness (carotid-femoral pulse wave velocity), Blood pressure (ambulatory; peak and resting), Blood pressure, Heart rate (peak and resting), Peak VO₂, Peak workload, Respiratory compensation point |
| Pooranfar et al  | 2013 | Kidney| Blood lipids, Cholesterol (TC, HDL, LDL), Sleep quality and quantity questionnaire (self-report; Pittsburgh Sleep Quality Index), 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, Respiratory compensation point |
| Riess et al.     | 2013 | Kidney| Peak VO₂, 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 |
| Tzvetanov et al  | 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 VO₂  
- 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 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 and 2  
- SF-36

Karelis et al. [45] 2015 Kidney  
- World Health Organization-5 Well-Being Index  
- Muscle strength index  
- Adherence to training and follow-up (feasibility)  
- Duke Activity Status Index  
- 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

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 | 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) | b410 | Heart rate | 1 | Heart, kidney, lung |
| | | b410 | Heart rate recovery | 1 | Heart |
| | | b410 | Heart rate reserve | 1 | Heart |
| | | b410 | Heart rate variability | 1 | Kidney |
| | Functions of the cardiovascular system | b410 | Baroreceptor control of blood pressure | 1 | Heart |
| | | b410 | Baroreceptor control of heart rate | 1 | Heart |
| | | b410 | Baroreflex effectiveness index | 0 | Kidney |
| | | b410 | Baroreflex sensitivity | 1 | Kidney |
| | | b410 | Chronotropic response index | 1 | Heart |
| | | b410 | Total CVD risk | 1 | Kidney |
| | | b410 | 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 |
| Code | Function Description | Location |
|------|----------------------|----------|
| b420 | Neck pressure         | Heart    |
| b4301| Arteriovenous oxygen difference | Kidney |
| b430-439| Biochemical parameters | Heart |
| b430-439| Blood calcium level | Kidney |
| b430-439| Blood creatinine | Heart, kidney |
| b430-439| Blood electrolytes | Kidney |
| b430-439| Blood glucose | Heart, kidney |
| b430-439| Blood lipids | Heart, kidney, lung |
| b430-439| Blood phosphorus | Kidney |
| b430-439| Blood protein levels | Heart, kidney |
| b430-439| Blood urea nitrogen levels | Kidney |
| b430-439| C-reactive protein | Heart |
| b430-439| Cholesterol | Heart, kidney |
| b430-439| Folate concentrations | Kidney |
| b430-439| Hematocrit | Kidney |
| b430-439| Hemoglobin | Heart, kidney |
| b430-439| High sensitive C-reactive protein | Heart |
| b430-439| Interleukin levels | Heart, kidney |
| b430-439| Plasma norepinephrine | Heart |
| b430-439| Soluble cell adhesion molecules | Heart |
| b430-439| Total-homocysteine | Kidney |
| b430-439| Tumour necrosis factor-alpha | Heart |
| b430-439| Tumor necrosis factor receptor | Kidney |
| b435 | Cytomegalovirus IgG status | Heart |
| b435 | White blood cell levels | Heart |
| b435 | Acute rejection episodes | Heart, lung |
| b440 | Forced expiratory volume | Lung |
| b440 | Forced vital capacity | Heart |
| b440 | Maximum expiratory/inspiratory pressure | Heart |
| b440 | Peak expiratory flow | Kidney |
| b440 | Peak respiratory exchange ratio | Heart, kidney, liver, lung |
| b440 | Respiratory compensation point | Heart |
| b440 | Ventilatory reserve and capacity | Lung |
| b440 | CO₂ production | Heart |
| b440-400 | Oxygen uptake at anaerobic threshold | Lung |
| b440-400 | Peak ventilation | Heart, kidney |
| b440-400 | Peak VO₂ | Heart, kidney, liver, lung |
| b440-400 | Ventilatory equivalent for carbon dioxide and oxygen | Heart |
| b445 | Respiratory muscle force/strength | Heart, lung |
| b4550 | Rating of perceived exertion | Heart, kidney, liver |
| b530 | Body mass index | Heart, kidney, liver |
| b530 | Body weight/mass | Heart, kidney, liver, lung |
| b530 | Fat mass/body fat | Heart, kidney, liver |
| b530 | Fat-free mass | Heart |
| b530 | Hip girth | Kidney |
| b530 | Hip-waist ratio | Heart |
| b530 | Lean tissue mass | Heart, kidney, liver |
| b530 | Percent body fat | Heart, kidney, liver |
| b530 | Visceral fat scale | Heart |
| b530 | Waist girth | Kidney |
| b540 | Basal metabolic rate | Heart |
| b540 | Metabolic age | Heart |
| b540-408 | Maximal metabolic units | Kidney |
| b540-459 | Enzyme levels | Kidney |
| b540-559 | Fetuin A | Kidney |
| b540-559 | Oxidative stress-induced lipid peroxidation | Heart |
| b540-559 | Serum insulin | Heart |
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\textsubscript{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

| Functions of the genitourinary and reproductive functions (urinary functions) | b540-559 | Serum metabolic and/or hematologic profile | 1 | Heart |
|-----------------------------|----------|------------------------------------------|----|-------|
|                              | b540-559 | Vitamin B\textsubscript{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 |

| 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, lung |
|                | s7700                                | Bone mineral density                 | 3   | Heart, kidney, liver, lung |
|                | s7700                                | Total bone calcium                   | 0   | Heart |
|                | s7702                                | Muscle composition (fibre types)     | 1   | Heart |

| Body structure | Structures related to movement - additional musculoskeletal structures related to movement (bones) | s7700 | Bone mineral content | 1 | Heart, kidney, liver, lung |
|----------------|-----------------------------------------------------------------------------------|------|---------------------|----|------------------------|
|                | s7700                                | Bone mineral density                 | 3   | Heart, kidney, liver, lung |
|                | s7700                                | Total bone calcium                   | 0   | Heart |

| Body structure | Structures related to movement - additional musculoskeletal structures related to movement (bones) | s7702 | Muscle composition (fibre types) | 1 | Heart |

| Activities and 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 |
|                              | 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 |
|                              | d5701                                 | Caloric intake                        | 0   | Heart |
|                              | d5701                                 | Nutritional intake                    | 1   | Liver |
|                              | d840-859                               | Employment status                     | 1   | Kidney |

| Activities and participation | Mobility - walking and moving | d410 | STS-60 | 0 | Kidney |

| Activities and participation | Mobility - walking and moving | d410 | STS-60 | 0 | Kidney |

| Environmental factors | Products or substances for personal consumption | e1108 | Smoking status | 0 | Kidney |

| Environmental factors | Products or substances for personal consumption | e1108 | Smoking status | 0 | Kidney |

| Questionnaires | Quality of Life Profile for Chronic Diseases Questionnaire | SF-36 | 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 |
|                | Chronic Liver Disease Questionnaire                      | 1    | Liver |
|                | Incidence of morbidity                                   | 0    | Kidney, lung |
|                | Adherence to training and follow-up                      | 2    | Kidney |

| Questionnaires | Quality of Life Profile for Chronic Diseases Questionnaire | SF-36 | 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 |
|                | Chronic Liver Disease Questionnaire                      | 1    | Liver |
|                | Incidence of morbidity                                   | 0    | Kidney, lung |
|                | Adherence to training and follow-up                      | 2    | Kidney |

1Count 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.
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, Disbury et al[1] found that the most commonly used outcome measure was VO2 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.

Disbury 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 Stuckl[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[49]. 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, it 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 (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 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.

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: 679-687 [PMID: 23364840 DOI: 10.1097/TP.0b013e31827da3be]
2. Langer D, Burtin C, Schepers L, Ivanova A, Verleden G, Decramer M, Troosters T, GoseliNik R. Exercise training after lung transplantation improves participation in daily activity: a randomized controlled trial. Am J Transplant 2012; 12: 1584-1592 [PMID: 22390625 DOI: 10.1111/j.1600-6143.2012.04000.x]
3. Krasnow JJ, Vintro AQ, Ascher NL, Bass NM, Paul SM, Dodd MJ, Painter PL. A randomized trial of exercise and dietary counseling after liver transplantation. Am J Transplant 2006; 6: 1896-1905 [PMID: 16889545 DOI: 10.1111/j.1600-6143.2006.01391.x]
4. Braith RW, Welsch MA, Mills RM, Keller JW, Pollock ML. Resistance exercise prevents glucocorticoid-induced myopathy in heart transplant recipients. Med Sci Sports Exerc 1998; 30: 483-489 [PMID: 9565927 DOI: 10.1097/00005768-199804000-00003]
5. Braith RW, Welsch MA, Mills RM, Welsch MA, Keller JW, Pollock ML. Resistance exercise training restores bone mineral density in heart transplant recipients. J Am Coll Cardiol 1996; 28: 1471-1477 [PMID: 8912760 DOI: 10.1016/S0735-1097(96)00347-6]
6. McAdams-DeMarco MA, Law A, King E, Orandi B, Salter M, Gupta N, Chow E, Alachkar N, Desai N, Varadhan R, Walston J, Segev DL. Frailty and mortality in kidney transplant recipients. Am J Transplant 2015; 15: 149-154 [PMID: 25359390 DOI: 10.1111/ajt.12920]
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. J Am Geriatr Soc 2013; 61: 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. Am J Transplant 2013; 13: 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: c363 [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: 132 [PMID: 22667278 DOI: 10.1186/1475-927X-13-132]
11. Core Outcome Measures in Effectiveness Trials Initiative (COMET). Available from: URL: http://www.comet-initiative.org/
12. World Health Organization. Towards a common language for functioning, disability and health: ICF. World Health Organisation, 2002 Available from: URL: 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. Phys Ther 2009; 89: 256-306 [PMID: 19147708 DOI: 10.2522/ ptj.200907309]
14. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; 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, Laks H. A controlled trial of exercise rehabilitation after heart transplantation. N Engl J Med 1999; 340: 277-277 [PMID: 9920951 DOI: 10.1056/NEJM199902283400404]
16. Painter PL, Hector L, Ray K, Lynes L, Dibb S, Paul SM, Tomlanovich SL, Ascher NL. A randomized trial of exercise training after renal transplantation. Transplantation 2002; 74: 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: 557-562 [PMID: 12932444 DOI: 10.1097/01.TP.000076471.25132.52]
18. Painter PL, Hector L, Ray K, Lynes L, Paul SM, Dodd MJ, Tomlanovich SL, Ascher NL. Effects of exercise training on coronary heart disease risk factors in renal transplant recipients. Am J Kidney Dis 2003; 42: 362-369 [PMID: 12900820 DOI: 10.1016/S0272-6386(03)07635-5]
19. Braith RW, Maggari PM, Pierce GL, Edwards DG, Hill JA, White LJ, Aranda JM. Effect of resistance exercise on skeletal muscle myopathy in heart transplant recipients. Am J Cardiol 2005; 95: 1192-1198 [PMID: 15877992 DOI: 10.1016/j.amjcard.2005.01.048]
20. Juskowska J, Lewandowska M, Bartłomiejczyk J, Foroczewicz B, Korabiewska I, Niewczas M, Sierdziński J. Physical rehabilitation and risk of atherosclerosis after successful kidney transplantation. Transplant Proc 2006; 38: 157-160 [PMID: 16504691 DOI: 10.1016/j.tram.2005.12.077]
21. Bernardi L, Radellì A, Passino C, Falcone C, Auguadro C, Martinelli
Outcomes in exercise intervention in transplantation

Janaudis-Ferreira T et al.

hospital exercise programs for heart transplant patients. Rev Bras Cir Cardiovasc 2013; 28: 338-346 [PMID: 24343683 DOI: 10.5955/1678-9741.20130053]

Kouidi E, Vergoulas G, Anifanti M, Deligiannis A. A randomized controlled trial of exercise training on cardiovascular and autonomic function among renal transplant recipients. Nephrol Dial Transplant 2013; 28: 1294-1305 [PMID: 23129823 DOI: 10.1093/ndt/gfs455]

Nytroen K, Rustad LA, Erikstad I, Aukrust P, Ueland T, Lekva T, Gade E, Wilhelmsen L, Hervold A, Aakhus S, Gullestad L, Arora S. Effect of high-intensity interval training on progression of cardiac allograft vasculopathy. J Heart Lung Transplant 2013; 32: 1073-1080 [PMID: 23906899 DOI: 10.1016/j.healun.2013.06.023]

Dall CH, Snor 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. Am J Transplant 2014; 14: 2391-2399 [PMID: 25513583 DOI: 10.1111/apt.12875]

Mønken Høst T, Dall CH, Christensen SB, Snor M, Gustafsson F, Rasmussen H, Prescott E. Interval training does not modulate diastolic function in heart transplant recipients. Scand Cardiovasc J 2014; 48: 91-98 [PMID: 23426090 DOI: 10.1016/j.scsctj.2013.07.058]

Pascoalino LN, Ciocac 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. J Heart Lung Transplant 2015; 34: 693-700 [PMID: 25662857 DOI: 10.1016/j.healun.2014.11.013]

Pooranfar S, Shahoor E, Shafahi M, Saleis M, Karimi M, Roozbah J, Hasheminassab M. The effect of exercise training on quality and quantity of sleep and lipid profile in renal transplant patients: a randomized clinical trial. Int J Organ Transplant Med 2014; 5: 157-165 [PMID: 25426284]

Riess JK, Haykowsky M, Lawrance R, Tomczak CR, Welsh R, Lewanczuk R, Tymchak W, Haenmel RG, Gourishankar S. Exercise training improves aerobic capacity, muscle strength, and quality of life in renal transplant recipients. Appl Physiol Nutr Metab 2014; 39: 566-571 [PMID: 24766239 DOI: 10.1139/apnm-2013-0449]

Tzetanov L, West-Thielke P, D’Amico G, Johnsen M, Ladik A, Hachaj G, Grazman M, Heller R, Fernhall B, Davivthis M. A novel and personalized rehabilitation program for obese kidney transplant recipients. Transplant Proc 2014; 46: 3431-3437

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. Int J Organ Transplant Med 2015; 34: 1033-1041 [PMID: 25840503 DOI: 10.1016/j.ijotm.2015.02.001]

Greenwood SA, Koufaki P, Mercer TH, Rush R, O’Connor E, Tuffnell R, Lindup H, Haggis L, Dew T, Abdulnassir L, Nugent E, Goldsmith D, Macdougall IC. Aerobic or Resistance Training and function, biomarkers and quality of life in renal transplant recipients. Am J Transplant 2014; 14: 1033-1041 [PMID: 25840503 DOI: 10.1016/j.ajkd.2015.06.016]

Karolis AD, Hebert MJ, Rabasa-Lloret 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. Can J Diabetes 2015; 40: 382-388 [PMID: 26656280 DOI: 10.1016/j.cjd.2015.02.001]

Ciezà A, Stucki G. Content comparison of health-related quality of life (HRQOL) instruments based on the international classification of functioning, disability and health (ICF). Qual Life Res 2005; 14: 1225-1237 [PMID: 16047499 DOI: 10.1007/s11136-004-4774-z]

Williams TJ, McKenna MJ. Exercise limitation following transplantation. Compr Physiol 2012; 2: 1937-1979 [PMID: 23723030 DOI: 10.1002/cphy.c110021]

Mathur S, Janaudis-Ferreira T, Wickerson L, Singer LG, Pataki J, Rozenberg D, Blydt-Hansen T, Hartmann EL, Haykowsky M, Helm D, High K, Howes N, Kamath BM, Lands L, Marzolini S, Sonneday C. Meeting report: consensus recommendations for a research agenda in exercise in solid organ transplantation. Am J Transplant 2014; 14: 3431-3437

L, Rinaldi M, Viganò M, Finardi G. Effects of physical training on quality of life in long-term heart transplant recipients. Eur J Cardiovasc Prev Rehabil 2011; 18: 91-98 [PMID: 21160334 DOI: 10.1007/s11350-010-0043-3]

Ibhe F, Neuhr C, Huppmann P, Zimmermann G, Luchte H, Baumgartner R, Kenn K, Sceps B, Hatz R, Czerner S, Frey L, Uebefuhr P, Bittmann I, Behr J. Effect of inpatient rehabilitation on quality of life and exercise capacity in long-term lung transplant survivors: a prospective, randomised study. J Heart Lung Transplant 2011; 30: 912-919 [PMID: 21489819 DOI: 10.1016/j.healun.2011.02.006]

Christensen SB, Dall CH, Christensen SB, Goette JP, Prescott E, Gustafsson F. Exercise training improves aerobic capacity and skeletal muscle function in heart transplant recipients. Am J Transplant 2011; 11: 536-541 [PMID: 21219582 DOI: 10.1111/j.1600-6143.2010.03403.x]

Christensen SB, Dall CH, 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. J Heart Lung Transplant 2012; 31: 106-107 [PMID: 22153554 DOI: 10.1016/j.healun.2011.10.014]

Nytroen K, Rustad LA, Aukrust P, Ueland T, Hallén J, Holm I, Rolid K, Lekva T, Fiane AE, Amlie JP, Aakhus S, Gullestad L. High-intensity interval training improves peak oxygen uptake and muscular exercise capacity in heart transplant recipients. Am J Transplant 2012; 12: 3134-3142 [PMID: 22900793 DOI: 10.1111/j.1600-6143.2012.04221.x]

Rustad LA, Nytroen 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. Eur J Prev Cardiol 2014; 21: 181-191 [PMID: 23445795 DOI: 10.1177/2047438313489477]

Kawauschi TS, Almeida PO, Lucy KR, Bocchi EA, Feltrim MI, Nozawa E. Randomized and comparative study between two intra-
Cleemput I, Dobbels F. Measuring patient-reported outcomes in solid organ transplant recipients: an overview of instruments developed to date. *Pharmacoeconomics* 2007; 25: 269-286 [PMID: 17402802 DOI: 10.2165/00019053-200725040-00002]

Trojetto T, Elliott RJ, 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. *Clin Transplant* 2011; 25: E571-E578 [PMID: 21955056 DOI: 10.1111/j.1399-0012.2011.01501.x]

P- Reviewer: Kelesidis T, Kin T, Pan SC, Shi YJ  S- Editor: Ji FF  L- Editor: A  E- Editor: Lu YJ
