Exercise-based pre-habilitation in individuals awaiting solid organ transplantation

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Abstract

Transplantation is a lifesaving procedure that gives patients a second chance at life and the opportunity for a better quality of life. The journey of getting an organ transplantation can be long and tiring depending on the transplant center; patients might wait years to receive an organ. Patients awaiting transplantation are living with the consequences of their chronic disease and experience a decline in their quality of life and physical function which can have a significant negative impact on their chances of receiving a transplant and on their health post-transplant. The benefits of exercise in transplant recipients are well described in the literature. However, the benefits of exercise for patients awaiting transplantation and the type of exercise training that should be offered are much less clear.

Within this context, the objectives of this thesis were to: 1) synthesize evidence on safety, acceptability, and effectiveness of exercise interventions in solid organ transplant candidates (SOT); 2) generate preliminary results on the feasibility of implementing a home-based exercise program to patients waiting for kidney transplantation (KT), and 3) provide recommendations to improve the field of exercise prescription in SOT.

This thesis consists of two studies presented as separate manuscripts. The first manuscript comprises a systematic review identifying the acceptance, safety, and effects of exercise interventions on exercise capacity and health-related quality of life in solid organ transplant candidates, as well as a summary of the exercise interventions available for these patients. The second manuscript is an original study assessing the feasibility, safety, and effectiveness of delivering a 12-week home-based pre-habilitation program to KT candidates.

The findings of both manuscripts indicate that exercise interventions in solid organ transplant candidates (including kidney transplant candidates) are feasible to be delivered, safe,

and acceptable to patients. There is some evidence that exercise interventions pre-transplant improves exercise capacity, HRQoL, lower-extremity function and frail status in transplant candidates.

Abrégé

La transplantation est une procédure qui sauve des vies, donne aux patients une seconde chance et la possibilité d'avoir une meilleure qualité de vie. Le trajet pour obtenir une transplantation d'organe peut être long et fatigant. Selon le centre de transplantation, les patients peuvent attendre des années avant de recevoir un organe, et durant ce temps doivent vivre avec les conséquences de leur maladie chronique ainsi qu'une baisse de leur qualité de vie et de leur fonction physique. Ceci peut avoir un impact négatif significatif sur leurs chances de recevoir une greffe et sur leur santé après la transplantation. Les avantages de l'exercice chez les receveurs de greffe sont bien décrits dans la littérature. Cependant, les avantages de l'exercice pour les patients en attente de transplantation et le type d'entraînement physique qui devrait leur être offert sont beaucoup moins clairs.

Dans ce contexte, les objectifs de cette thèse sont les suivants: 1) Synthétiser les données probantes sur la sécurité, l'acceptabilité et l'efficacité des interventions d'exercice chez les candidats à une greffe d'organe solide ; 2) Générer des résultats préliminaires sur la faisabilité de la mise en œuvre d'un programme d'exercices à domicile pour les patients en attente d'une transplantation rénale, et 3) Fournir des recommandations pour améliorer le domaine de la prescription d'exercices dans la greffe d'organe solide.

Cette thèse est composée de deux études, chacune présentée dans un manuscrit. Le premier manuscrit comprend une revue systématique identifiant l'acceptation, la sécurité et les effets des interventions d'exercice sur la capacité à l'exercice et la qualité de vie liée à la santé chez les candidats à une greffe d'organe solide, ainsi qu'un résumé des interventions d'exercice disponibles pour ces patients. Le deuxième manuscrit est une étude originale évaluant la faisabilité, la sécurité

et l'efficacité de la prescription d'un programme de pré-habilitation à domicile de 12 semaines aux candidats de transplantation rénale.

Les résultats des deux manuscrits indiquent que les interventions d'exercices chez les candidats à une greffe d'organe solide (y compris les candidats à une greffe de rein) sont réalisables, sûres et acceptables pour les patients. Il existe aussi des preuves que les interventions d'exercice avant la transplantation améliorent la capacité à l'exercice, la qualité de vie liée à la santé et la fonction des membres inférieurs chez les candidats à la transplantation, ainsi que diminue leur fragilité.

Acknowledgments

In this meaningful journey as a Master's student, I have been lucky to meet and work with many new colleagues and friends. I had the opportunity to talk about my projects with some of these people, and they assisted me in different ways. I give my sincerest thanks to all those who have supported me along the way.

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Preface

This thesis consists of two studies presented as separate manuscripts designed to answer specific research questions related to exercise interventions in patients awaiting solid organ transplantation.

The first study was a systematic review investigating the acceptability, safety, and effectiveness of exercise intervention in solid organ transplant candidates. The second study assessed the feasibility, safety, and effectiveness of a home-based exercise intervention in kidney transplant candidates. Both studies made recommendations for future interventions to improve evidence on the effects of exercise interventions in solid organ transplant candidates.

This is a manuscript-based thesis, organized according to the McGill School of Physical and Occupational Therapy's Research and Thesis Requirements for the fulfillment of a M.Sc. in Rehabilitation Science, and the regulations of McGill University's Faculty of Graduate and Postdoctoral Studies for a manuscript-based thesis.

Both manuscripts included detailed descriptions of the methodology utilized, the results obtained, and a discussion of the findings. As the first manuscript has been published in Clinical Transplantation prior to the submission of this thesis, word limits were enforced that required this manuscript to be written concisely.

A literature review precedes both manuscripts in order to provide greater context and background. The organization of the thesis is described below.

Thesis Organization and Overview

The introduction provides an overview of the rationale, objectives, and expected contribution of the thesis as a whole. Chapter 1 consists of a comprehensive literature review introducing solid organ transplantation, chronic kidney disease and the methodology used. Chapter 2 contains the first manuscript, “Exercise intervention in solid organ transplant candidates: a systematic review”. Chapter 3 contains the second manuscript, “Feasibility, safety, and effectiveness of a 12-week home-based pre-habilitation program implemented to individuals awaiting kidney transplantation”. Chapter 4 summarises and discusses the findings of both manuscripts and provides a conclusion for the overall thesis, along with suggestions for future research. References and Appendices follow chapter 4.

Statement of Originality

This thesis, including both manuscripts and all other chapters, constitutes my original work, informed by the valuable guidance and feedback of my thesis supervisor, my supervisory committee and all the collaborators. Only chapter 2 has been published.

The main contributions of this thesis are: 1) synthesizing the evidence on safety, acceptability, and effectiveness of exercise intervention in solid organ transplant candidates; and 2) generating preliminary results on the feasibility of implementing a home-based exercise program to patients waiting for kidney transplantation. This two-pronged approach enabled me to address the third objective that was to provide recommendations to improve the field of exercise prescription in solid organ transplant candidates.

This research was informed by my previous experience working with heart and lung transplant candidates and recipients, and by the best available research evidence. In addition, Dr. Tania Janaudis-Ferreira guided me through this process with her expertise and extensive knowledge in rehabilitation in solid organ transplantation and was invaluable as a source of inspiration for this research.

Contribution of Co-Authors

The Master's candidate, Fernanda Pesce de Souza, coordinated all elements of the work constituting this thesis under the supervision of her supervisor, Dr. Tania-Janaudis Ferreira, and her supervisory committee members, Drs. Judith Soicher and Julio Flavio Fiori.

For manuscript 1, "Exercise intervention in solid organ transplant candidates: a systematic review" (Fernanda P. de Souza, Daniela Massierer, Uma A. Raje, Catherine M. Tansey, Jill Boruff, Tania Janaudis-Ferreira), the Master's candidate contributed to the creation of the research question and search strategy, screened titles, abstracts and full-texts, created the data extraction forms, conducted data extraction, created tables and figures, interpreted the findings and wrote and revised the manuscript. Jill T. Boruff reviewed and provided feedback on the research question and systematic review protocol, created and conducted the search strategy and reviewed the final draft of the manuscript. Uma A. Raje assisted with the screening of abstracts and full texts and provided feedback on the draft of the manuscript. Daniela Massierer double-checked the extracted data and provided feedback on the draft of the manuscript. Tania Janaudis-Ferreira, the senior author, created the research question, provided feedback on the systematic review protocol and data extraction forms, reviewed the tables, provided critical feedback on the interpretation of the findings and final draft of the manuscript, and will be the guarantor of the publication.

For manuscript 2, the Master's candidate assisted with designing the study, wrote the protocol, applied to the research ethics board, created the data extraction forms, collected, extracted, analysed and interpreted the data, created the tables and figures, and wrote and revised the manuscript. Drs. Nancy Mayo, Jean Tchervenkov, Steve Paraskevas and Franco Carli provided critical feedback on the study protocol, particularly on the research question, study design and outcome measures and provided feedback on the manuscript. Daniela Massierer provided feedback

on the data extraction forms and assisted with the assessment of study quality and data collection. Catherine M. Tansey assisted with the assessment of the quality of the studies, with the translation of the files to French and provided feedback on the consent form and final manuscript. Tania Janaudis-Ferreira conceived and designed the study, interpreted the data, assisted with drafting the manuscript, provided critical revisions that were important for the intellectual content, approved the final version of the manuscript, and was the senior author and guarantor of the manuscript.

Chapter 1- Literature Review - Introduction

1.1 SOLID ORGAN TRANSPLANTATION (SOT)

Starting in the 20th century as an experimental procedure, SOT became a life-saving medical intervention in which an organ was removed from one body (donor) and placed in another (recipient), with the aim of replacing a damaged heart, lung, pancreas, kidney or liver due to an end-stage disease[1, 2].

Due to the advances in medicine, life is often prolonged. The subjects who would not have been considered for transplantation years ago (e.g. elderly or frail individuals) are now on the waiting list. This fact has significantly increased the number of people waiting for organ transplantation[3], and has led to shortage of donors in many countries[4]. Depending on the type of transplantation, the organ can be donated from a deceased or living donor.

In regard of organ donation in Canada (including Quebec), there has been a steady increase in the total number. Organ donation has increased by 56% since 2009[5]. The average deceased donor age has ranged from 27 (pancreas) to 44 (liver and kidney) years depending on the organ type, and with the majority (60%) of the donors being male[5]. Canada has one of the highest rates of living donation, which totalled 555 in 2018, and 63% of these donors were female [5].

The total number of patients (pediatric and adult) waiting for a single transplant in Canada was 4,351 in 2018, with 2,890 patients on the active waiting list and 1,461 patients on hold (patients that temporarily cannot receive a transplant for a medical or other reason)[6]. The waiting list time is hard to predict and varies by province, health center and organ type.

From the total of 139,024 transplants performed worldwide in 2017[7], the most common type was kidney transplantation (KT) at 90,306 of the cases, followed by liver at 32,348 cases[7].

The latest data about the number of SOT in Canada (Quebec included), shows that in total 2,782 transplants (including all organs type) were performed in 2018, showing an increase of 33% in comparison to 2009[5]. Kidney was again by far the most common organ transplanted, with 1706 single procedures performed in adults[5]. Diabetes and high blood pressure are the main causes of end-stage kidney disease[8], and KT is the preferred and most common treatment choice, both in terms of survival and improving quality of life (QoL)[9].

1.2 BENEFITS OF SOT TO THE INDIVIDUAL AND SOCIETY

Transplantation offers a positive impact on outcomes such as survival, reduction of comorbidity, and QoL[10]. Data from the United States (US) shows that among transplant recipients, the median survival time is 9.4 years in heart transplant and 12.4 years in KT; however, median survival ranges between 2.4 and 5.4 years for patients on the transplant waiting list[11]. In Canada, over a five year period, the survival rate of transplanted patients varied from 69.7% to 88.1% depending of the organ replaced, with the lowest rate in lung recipients and the highest rate in kidney recipients[5]. After being listed for transplantation, on average, patients gain a life expectancy of 3-15 years[12].

Improvements in QoL after transplantation can be perceived in the early stage after the surgery, in physical health dimensions and psychosocial functioning[13]. Among all organ transplant groups, heart recipients showed a more positive impact on life expectancy and general QoL after transplantation than others[13].

SOT is one of the most expensive treatments available in healthcare [14]. Regardless of the high cost, transplantation has some economically advantageous. For instance, in KT, after the second year, the healthcare system saves between $33,000 and $84,000 per transplant patient when compared to a year of dialysis treatment[15].

1.3 IMPAIRMENTS IN SOT CANDIDATES AND RECIPIENTS

Physical and psychological impairments are often present in SOT candidates and recipients. In heart and lung transplant candidates, physical impairments such as limited exercise capacity, and muscle weakness pretransplant, are due to primary organ failure[16], and in people suffering from chronic kidney or liver disease, it is commonly a secondary consequence of the main disease[17]. In patients with chronic kidney disease, the lower the kidney function, the worse the muscle impairments[18] and functional limitation[19]. Lower physical performance[20] and physical function[21, 22] are two main impairments that contribute to a higher prevalence of frailty[23] and mobility disability[24, 25] in this population.

Patients in the pre-transplant phase face the psychological impact of the waiting period until transplantation, which can be uncertain and is considered the most stressful part of the transplant experience[26]. Depression and anxiety are also common among transplant candidates[27, 28]. Other psychosocial stressors such as disability, and financial pressure are also present[26]. When compared with the general population, patients with chronic kidney disease have a higher prevalence of cognitive impairments, such as difficulty concentrating, poorer memory and planning abilities [29, 30]. The more severe the kidney disease, the greater the impairment[31].

Even with the significant health improvement promoted by organ replacement[32, 33], transplant recipients frequently face post-transplant complications, including graft rejection, infections and side-effects of immunosuppression medications[34], which may lead to impairments of physical functioning[35]. In a systematic review, Williams et al.[17], concluded that reduction in exercise capacity starts at the pre-transplant phase and persists following all solid organ transplants. The authors also observed that kidney and liver recipients show a lower degree of exercise impairment compared to the other organ groups[17]. Especially during the first-year post-

transplant, transplant organ recipients are likely to develop psychological disorders (up to 20% of kidney recipients, 30% of liver recipients and 63% of heart recipients)[36, 37]. The reasons can be related to the adjustment of their expectations (occupation, physical and social stands)[36]. The use of immunosuppression requires that patients be aware of the risk of infection and this can be a burden for many patients[36].

1.4 EXERCISE PRE-TRANSPLANTATION

Exercise based pre-habilitation has the objective of improving tolerance for the upcoming physiological stressor (e.g. major surgery), and enhancing patient functional capacity before the procedure[38]. Pre-habilitation has been used extensively in elective general surgery (e.g. abdominal surgery, and total knee replacement/arthroplasty), and has been shown to improve levels of physical activity and functional exercise capacity, as well as contribute to a reduction of postoperative recovery time and a quicker return to functional ability[39-47].

Evidence regarding the effectiveness of preoperative exercise-based interventions is still not clear for patients waiting for transplantation. Until 2019, only one systematic review[48] on the effects of exercise intervention in SOT candidates had been published. This study[48], from 2016, included eleven studies, totalizing 874 patients. The main limitation of the review is that it only analyzed studies involving lung and heart transplant candidates. The authors concluded that exercise training is feasible in patients awaiting heart or lung transplant, but more evidence on the effectiveness of the intervention is needed[48]. In 2019, a joint position statement was published on exercise for solid organ transplant candidates and recipients[49]. Similarly, the authors recommended that “exercise training should be offered in the pre- and posttransplant phase” and “exercise training pretransplant was safe, but there was insufficient evidence to provide specific guidelines on the training characteristics”[49]. The statement[49] recommended a combination of

aerobic exercise and resistance training, however, there was insufficient evidence for recommending the specific dose and duration of the exercise training.

The main goals of an exercise-based pre-habilitation intervention are to optimize fitness and quality of life prior to transplantation, and to decrease the hospital length of stay and increase functionality/independence at hospital discharge[49]. The evidence is stronger when the exercise-based intervention is focused only on patients with chronic disease (not those on the waiting list for transplantation yet). One example is the benefit of exercise in patients with chronic kidney disease. In many studies, regardless of the type of exercise performed[50-52], fitness, sarcopenia, physical performance, self-reported physical function and QoL were improved with exercise training in this population[50-52].

In conclusion, there is a need for more studies investigating and summarizing the results on effects of pre-habilitation in SOT.

1.5 METHODOLOGICAL APPROACHES UTILIZED

1.5.1 SYSTEMATIC REVIEW

A systematic review is "a type of study that has a clear formulated question that in a systematic and explicit way uses methods to identify, select, and critically appraise relevant research in the literature, and to collect and analyze data from the studies that are included in the review"[53]. Systematic reviews are often used as a starting point for developing clinical practice guidelines[53]. This type of study is also frequently used by clinicians as a form to keep them up to date with their speciality[54, 55]. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement is recommended to be followed and it consists of a checklist of 27-items, and a four-phase flow diagram that aim at improving the reporting of the study[53].

A systematic review was performed to answer the research questions of Manuscript 1. Due to the few reviews that explored the effects of exercise interventions in SOT candidates, there was no study that included data on all types of organ transplantation. With this literature gap in mind, Manuscript 1 addresses not only the effects of exercise intervention in this population, but also safety and patients' acceptance. The findings of this review will help to guide future studies and give an overview of the interventions described for SOT candidates.

A complete and detailed reporting of interventions is often lacking in the clinical research field. The understanding of the explicit and direct characteristics of an intervention is essential for the interpretation, translation, implementation and reproducibility of research findings into clinical practice[56]. The Consensus on Exercise Reporting Template (CERT) was developed by Slade et al, in 2016[57] to provide some additional direction for the reporting of exercise intervention. This tool is composed of 16 items listed under 7 sections/domains which are: what (materials); who (provider); how (delivery); where (location); when; how much (dosage); tailoring (what, how); and how well (compliance/planned and actual). The CERT checklist was used in our systematic review (Chapter 2 - Manuscript 1) to assess the quality of the description in studies that implemented an exercise intervention in the pre-transplant phase, and we also used this guide to describe in detail the exercise intervention in the feasibility study (Chapter 3 – Manuscript 2).

Table 1 – CERT Item description

Item	Description
1	Detailed description of the type of exercise equipment
2	Detailed description of the qualifications, expertise and/or training
3	Describe whether exercises are performed individually or in a group
4	Describe whether exercises are supervised or unsupervised; how they are delivered
5	Detailed description of how adherence to exercise is measured and reported
6	Detailed description of motivation strategies
7 a	Detailed description of the decision rule(s) for determining exercise progression
7 b	Detailed description of how the exercise program was progressed
8	Detailed description of each exercise to enable replication
9	Detailed description of any home programme component

10	Describe whether there are any non-exercise components
11	Describe the type and number of adverse events that occur during exercise
12	Describe the setting in which the exercises are performed
13	Detailed description of the exercise intervention
14 a	Describe whether the exercises are generic (one size fits all) or tailored
14 b	Detailed description of how exercises are tailored to the individual
15	Describe the decision rule for determining the starting level
16 a	Describe how adherence or fidelity is assessed/measured
16 b	Describe the extent to which the intervention was delivered as planned.

1.5.2 FEASIBILITY

A feasibility study is a type of study that focuses on the process of developing and implementing an intervention. This study gives the opportunity to examine some preliminary results of participants' responses to the intervention[58]. Because of their similarities, such as small sample size, the terms feasibility and pilot testing have been used interchangeably in the literature and are often misused. As presented in Figure 1, the main difference between these types of studies is the focus/objective of each method[59].

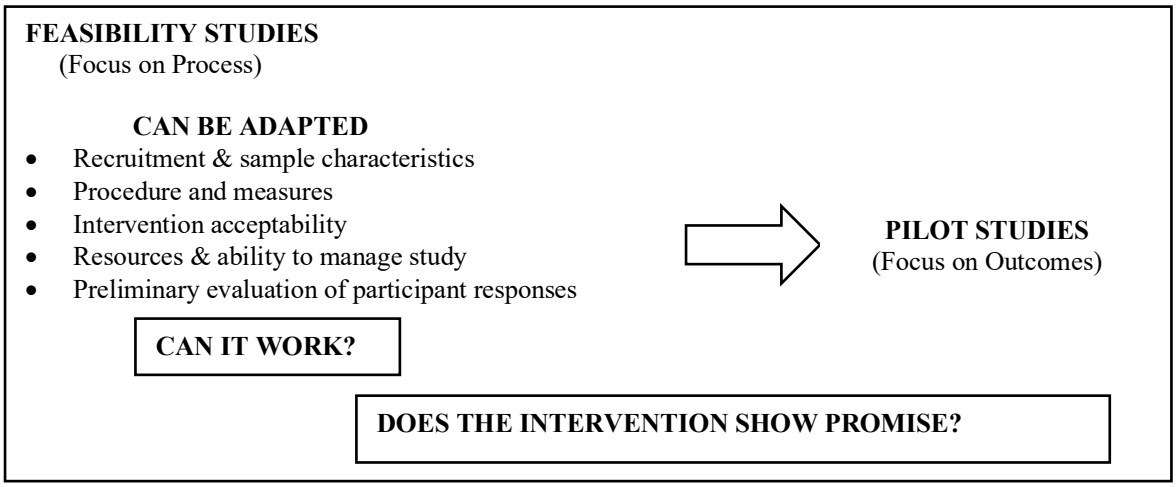

Figure 1 – Features of a feasibility study as described by Orsmond and Cohn, 2015[59]

According to the guideline published by Orsmond and Cohn, 2015[59], a feasibility study should focus on: a) evaluation of the capability and resulting sample characteristics, (b) evaluation and refinement of data collection procedures and outcome measures, (c) evaluation of the acceptability and suitability of the intervention and study procedures, (d) evaluation of the

resources and ability to manage and implement the study and intervention, and (e) preliminary evaluation of participant responses to the intervention[59].

Even though there is some evidence that exercise pre-transplant is feasible[48, 49], manuscript 2 was designed as a feasibility study to test the specific components associated with the implementation of a 12-week home-based exercise program delivered to KT candidates and to gather information for future research related to exercise interventions in this population.

1.6 SUMMARY

There is much that still needs to be discussed and investigated in regard to exercise interventions in SOT candidates, especially in organ groups that are not commonly explored by researchers, such as kidney, liver and pancreas transplant candidates.

Even with different disease mechanisms, physical and psychological impairments are present independent of the organ group in question. There is a strong need to develop exercise interventions that are tailored to patients with chronic disease who are waiting for a transplant. Exercise in the pre-transplant phase is a promising intervention that may bring important benefits to patients.

In Manuscript 1, we examined the evidence that currently exists in the literature with regards to exercise interventions in SOT candidates. We were able to identify some important gaps, leading to Manuscript 2, which focuses on preoperative exercise for KT candidates.

1.7 OBJECTIVES OF THE THESIS

This thesis sought to: 1) synthesize evidence on safety, acceptability, and effectiveness of exercise interventions in SOT candidates; 2) generate preliminary results on the feasibility of implementing a home-based exercise program to patients waiting for KT, and 3) provide recommendations to improve the field of exercise prescription in SOT.

Chapter 2 - MANUSCRIPT 1: Exercise interventions in solid organ transplant candidates: a systematic review

2.1 PREFACE TO MANUSCRIPT 1

Despite the research efforts to evaluate the effectiveness of exercise interventions in solid organ transplant candidates, there is still a big gap in the literature among the different types of organs and more studies are needed to observe the effectiveness of the interventions on different physical outcomes. In order to determine the acceptance, safety and effectiveness of exercise interventions in this specific population, a systematic review was conducted which is presented as Manuscript 1.

Manuscript 1 makes reference and compares our findings (when relevant) to a previous systematic review conducted by another research group that investigated similar outcomes in transplant candidates. The manuscript also adds new findings, especially in kidney and liver transplant candidates, which the previous study failed to do.

This systematic review is the first one to include the results from all solid organ transplant candidate groups, with the exception of the pancreas.

Manuscript 1 has been published in Clinical Transplantation.

2.2 TITLE PAGE

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Short title/running head: Exercise interventions in solid organ transplant candidates: a systematic review

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2.3 ABSTRACT

Introduction: Exercise training may be recommended to solid organ transplant (SOT) candidates to improve fitness and tolerance before surgery. We aimed to determine the acceptance, safety and effectiveness of exercise interventions in SOT candidates. **Methods:** Online databases were searched. Studies of any design were included. Outcomes of interest were acceptance, safety, exercise capacity and health-related quality of life. **Results:** Twenty-three articles were included. Acceptance ranged from 16% to 100%. In the fifteen studies that assessed adverse events, none mentioned any adverse events occurring during the study. Five out of seven studies reported an increase in maximal exercise capacity post-exercise in the intervention group (range of mean change: 0.45 to 2.9 mL/kg). Eight out of fourteen studies reported an increase in 6-minute walking distance in the intervention group after the training period (range of mean change: 40 to 105 meters). Two articles showed an improvement in the mental composite scores as well as in the physical composite scores post-exercise in the intervention group. **Conclusion:** There was a lack of significant finding among most randomized controlled trials. Exercise training is acceptable and safe for selective SOT candidates. The effects of exercise training on exercise capacity and HRQoL in SOT candidates are unclear.

Key words: Exercise, Pre-Habilitation, Solid Organ Transplantation

2.4 INTRODUCTION

Solid organ transplantation (SOT) saves the lives of patients suffering from end-stage liver, heart, kidney, pancreas and lung diseases[2, 60] and improves disease related symptoms as well as the quality of life in these individuals[61]. Recent statistics show that close to 100,800 SOT are performed every year worldwide[62].

Many SOT candidates suffer from their chronic disease for years before receiving a transplant and, depending on their health condition and which organ is involved, multiple systems may be compromised[17, 63]. Studies have shown that SOT candidates experience limitations in exercise capacity secondary to central and peripheral factors[17, 64-66] which may impact their levels of daily physical activity[67-70] and consequently on the psychosocial aspects of their lives[71]. In the general population, physical inactivity reduces normal functioning of major organ systems such as the cardiovascular, cardiopulmonary and musculoskeletal systems[72], and is associated with the development of chronic diseases[73] and early mortality[74]. Lower physical function in SOT candidates has been shown to be associated with higher rates of pre-transplant mortality[75, 76] and worse post-transplant outcomes, and hospitalization[77, 78].

Exercise training or regular physical activity is an evidence-based treatment that has been shown to promote many health benefits (e.g. improved exercise capacity, muscle strength, health-related quality of life and cardiovascular risk factors) in various chronic conditions[79-81] as well as in transplant recipients[16, 82]. Exercise training has also been shown to be an effective pre-surgery intervention to increase physiological reserve to minimize the risk of peri-operative complications[83], and to counteract physical function decline after surgery in many patient populations, such as in cardiac[84-86], total knee replacement/arthroplasty[87-89] and colorectal cancer patients[90-92]. However, the benefits of exercise training in candidates for SOT surgery are less

established. A systematic review[48] published in 2016 described the safety, adherence and efficacy of exercise training programs in SOT candidates. The authors concluded that "exercise training is feasible in patients awaiting heart or lung transplant; however, longer-term, adequately powered, randomized control trials are required to determine the safety and efficacy". A limitation of this review[93] is that it included only studies involving lung, and heart transplant candidates (even though the literature search had considered all organ groups). After their publication[93], new studies including liver, kidney, heart and lung transplant candidates were published. Our primary objectives were to determine the acceptance and safety of exercise interventions in SOT candidates as well as the effects of these interventions on exercise capacity and HRQoL in this population. Our second objective was to determine the effects of exercise interventions on muscle strength (respiratory, lower and upper limb), frailty, symptoms of fatigue and dyspnea, anxiety, depression, sleep quality and post-transplant outcomes in this population.

2.5 METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses **(**PRISMA) guidelines[94] (Figure 1). This review protocol was registered in the PROSPERO (International Prospective Register for Systematic Reviews) database (CRD number 42018114865).

2.5.1 SEARCH STRATEGY

A health sciences librarian (JB) developed the search strategy and performed the literature searches in MEDLINE (Ovid), EMBASE (Ovid), CINAHL, Cochrane Library, and Proquest Dissertations and Theses from database inception until February 5, 2019, with no limits or language restrictions. The MEDLINE strategy was developed with input from the project team.

After the initial MEDLINE strategy was finalized, it was adapted for use in the other databases. The search strategy (table 1) was designed to identify all relevant clinical literature on exercise in SOT candidates (heart, lung, kidney, liver, and pancreas). Manual searches of the reference list of all primarily included studies and pertinent review articles were conducted for additional references.

Table 1 – Example of search strategy using the Ovid MEDLINE

#	**Searches**
1	((organ or heart or kidney or pancreas or liver or lung) adj (transplant or transplantation or transplanted or transplants)).ti,ab,kf.
2	Physical activity.ti,ab,kf.
3	exercise.ti,ab,kf.
4	exp Exercise/ or exp Exercise Therapy/
5	Physical Fitness/
6	physical fitness.ti,ab,kf.
7	exp Organ Transplantation/
8	1 or 7
9	2 or 3 or 4 or 5 or 6
10	End Stage Liver Disease/
11	Kidney Failure, Chronic/
12	Waiting Lists/
13	(preoperative or pre-operative or candidate* or wait* list* or prehabilitation or pre-transplant* or pretransplant* or end stage).ti,ab,kf.
14	Preoperative Care/
15	Heart-Assist Devices/
16	(VAD or RVAD or LVAD or BIVAD or artificial heart* or ((ventricular or ventricle or heart) adj2 (device* or pump*))).tw,kw.
17	10 or 11 or 12 or 13 or 14 or 15 or 16
18	8 and 9 and 17

2.5.2 INCLUSION CRITERIA

We included original studies of any design that examined the effects of exercise training programs in SOT candidates. We considered studies that included adult (> 18 years) candidates of heart, lung, kidney, pancreas or liver transplant. To be included, the majority (80%) of the study

population should have been on a transplant waiting list or using a ventricular assist device (VADs) as a bridge to transplantation.

We included studies that offered an inpatient, outpatient or home-based exercise program and that included aerobic, resistance, or a combination thereof as well as any alternative type of exercise (e.g. yoga). Finally, we included studies that compared an exercise training program with a control group that received no exercise or a comparison of two types of exercises or compared exercise with other types of interventions (such as diet, relaxation therapies, and education). We also considered pre/post studies where no comparison group was included. Editorials, letters to the editor and conferences abstracts without published peer-reviewed manuscripts were excluded.

2.5.3 OUTCOMES OF INTEREST

Primary outcomes were acceptance, safety, and effectiveness (maximal or functional exercise capacity and HRQoL).

- Acceptance was defined as the proportion of patients who agreed to participate in the intervention in relation to the number of patients approached.

- Safety was defined as the number, type (e.g. serious or non-serious; expected or unexpected) and severity of adverse events (e.g. adverse symptoms, death) that occurred during the study.

- Effectiveness was defined as a positive change in maximal or functional exercise capacity and HRQoL. Maximal exercise capacity was defined as the peak aerobic capacity acquired during a laboratory incremental exercise test (treadmill or cycle ergometer). Functional exercise capacity was defined according to the results of walking field tests (e.g. six-minute walk test). Generic or disease-specific measures of HRQoL were considered.

Secondary outcomes were maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), lower and upper limb muscle strength, frailty, symptoms of fatigue and dyspnea, anxiety, depression, sleep quality and post-transplant outcomes such as hospital length of stay, intensive care unit length of stay, time on mechanical ventilation, allograft function and mortality (true observations of all-cause deaths).

2.5.4 SCREENING PROCESS OF STUDY ELIGIBILITY

Two investigators (FPS and UR) independently reviewed the titles and abstracts, followed by full texts of retrieved articles. Reasons for exclusion were recorded and reported in the PRISMA chart (Figure 1). Any discrepancies or disagreements were resolved by a third investigator (TJF). All these steps were performed using COVIDENCE online software.

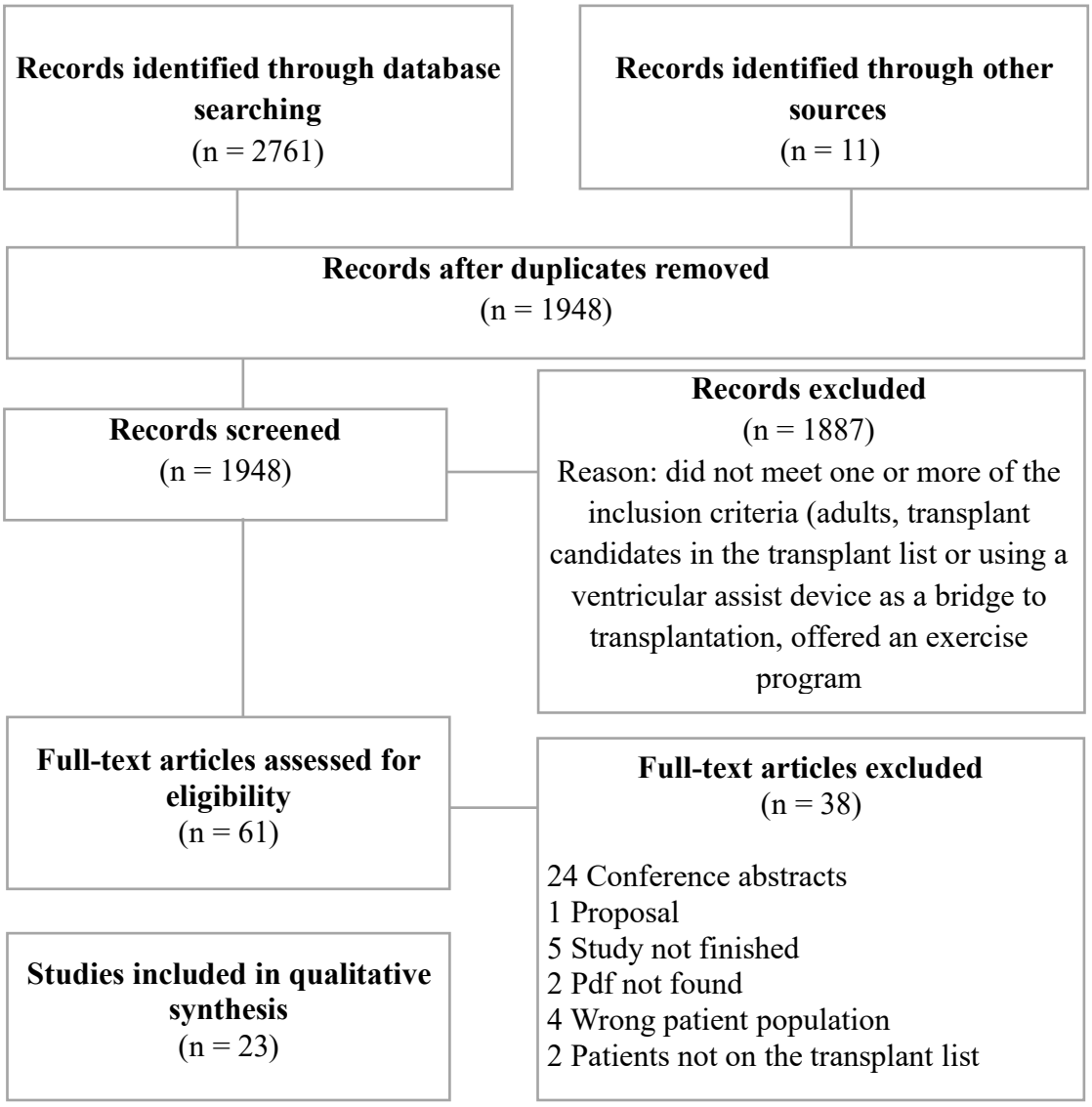


Figure 1 – PRISMA flow chart

2.5.5 DATA EXTRACTION STRATEGY

A standardized table was used for data extraction. One reviewer (FPS) extracted the data of interest from the included articles and a second reviewer (DM) double checked the extracted data. Information retrieved was authors' names, year of publication, country; study design, sample size, organ group, time on the waiting list, primary diagnosis, age and sex of the participant, characteristics of the intervention, outcomes of interest and significant findings.

2.5.6 QUALITY ASSESSMENT OF THE INCLUDED STUDIES

The methodological quality of randomized controlled trials (RCTs) was appraised using Cochrane's tool for assessing the risk of bias[95]. The tool contains seven sections with options for classifying each one as low risk, high risk or unclear. To assess the quality of non-randomized control trials (non-RCTs) we used the modified Downs and Black checklist[96] which contains 27 'yes' or 'no' questions across five sections. The tool provides an overall score for study quality, with a maximal score of 28. The questions that were not relevant to non-RCTs were categorized as 'not applicable'. Two reviewers independently extracted the data (FPS and CMT) related to the methodological quality of each included study. We also used the Consensus on Exercise Reporting Template (CERT)[57] checklist to evaluate the quality of exercise reporting. Two investigators (FPS and UR) independently applied the checklist on the included articles, extracted information and entered data into a standardized form. The CERT checklist consists of 16 items characterized into 7 sections: what (materials); who (provider); how (delivery); where (location); when, how much (dosage); tailoring (what, how); and how well (compliance/planned and actual). Items 7, 14 and 16 have one sub-item each, resulting in a total of 19 items. Each CERT item is rated 0 (no, not described or description unclear) or 1 (yes, well-described). A third assessor (TJF) resolved any outstanding divergences related to methodological quality assessment.

2.6 RESULTS

Twenty-three articles including a total of 2,006 participants met the inclusion criteria (a full description of the search results can be found in Figure 1). Eight of the 23 included articles were RCTs[97-104], five non-RCTs[105-109], and 10 pre-post studies[75, 110-118]. The majority of the articles included lung (n=10)[75, 97, 103, 104, 109, 110, 114-117] (Li et al[75] also included lung-heart transplant candidates) and heart transplant candidates[99, 100, 105-107, 111, 112] (n=7). Four articles

include liver[101, 102, 113, 118] and two included kidney transplant candidates[98, 108] (Gross et al[98] include kidney-pancreas transplant candidates in addition to kidney patients). No articles included pancrease alone transplant. The characteristics of the included studies are presented in table 2 (pre-post studies) and table 3 (RCTs and non-RCTs).

The exercise training programs included in the studies used a variety of exercise interventions, which are described in table 4. The majority of the programs offered a combination of aerobic training and another type of exercise (n=17)[75, 97, 99, 100, 102-110, 113-115, 117], for instance, upper and/or lower limb strength or inspiratory muscle exercises. Five programs offered only aerobic exercise training[97, 103, 105, 109, 115]. Upper and/or lower limb strength training was an embedded component in thirteen programs[75, 99, 101, 102, 104, 106-108, 110, 113, 114, 116, 117]. None of the programs included strength training exclusively. The frequency of the training sessions varied between two and seven days a week, and programs lasted from 3 to 26 weeks. The study settings varied from in-patient[75, 97, 107, 113, 114, 116] to out-patient[110] and home-based[101, 102, 118] programs. Eight studies[98-100, 104, 108, 109, 115, 117] had more than one setting(e.g. in-patient and home-based program or out-patient and home-based program or dialyze unit and home-based program). Five trials did not report the setting of their programs[103, 105, 106, 111, 112].

Table 2 – Characteristics of the pre-post studies

Author/ Year	Country	Design	Organ group	Population	Sample size	Demographics	Time on waiting list	Intervention	Included outcomes of interest	Significant findings	Acceptance	Adherence	Safety
Byrd et al. 2019[110]	USA	R	Lung	Lung disease: Restrictive (n= 83) Obstructive (n=34) Cystic Fibrosis (n=21) Pulmonary vascular (n=3)	141	**Age** 58.5±14.9 **Gender** Both (Men: n= 85, 60%)	NR	**Exercise training + education** - aerobic exercise - balance exercise - breathing exercise - strength exercise - flexibility exercise - therapeutic education	**Functional exercise capacity** - 6MWT **Dyspnea** - San Diego shortness of breath questionnaire (SOBQ) **Depression** - the center for epidemiological studies-depression scale (CESD)	↑ 6MWD (p<0.001) 386±96 m to 455±96 m ↑QLI (p<0.001) 18.8±3.7 to 19.8±3.4 ↓CESD (p<0.001) 10.7±7.6 to 8.9±6.2	**Recruited/ Enrolled** 153/149	**Enrolled/Completed ET** 149/141	NR
Cahalin et al. 1997[111]	USA	P	Heart	Chronic HF: Idiopathic dilated cardiomyopathy (n=7) Ischemic cardiomyopathy (n=6) Restrictive cardiomyopathy (n= 1)	8	**Age** 52± 8.5 years, range 32-64 **Gender** Both (Men: n= 12, Women: n=2)	NR	Inspiratory muscle training	**Respiratory Muscle Strength** - MIP - MEP	↑ MIP (p-value not reported) After 2 weeks 51±21 to 63±23 cm H_2O ↑24% + additional 8% after 6 weeks ↑ MEP (p-value not reported) (↑13%) 85±22 to 96±19 cm H_2O	**Recruited/ Enrolled** 14/14	63%±24% **Enrolled/Completed ET** 14/8 **Reasons drop-out** -transplantation - coronary artery bypass surgery - intra-aortic balloon pump placement - death	NR
Dean et al. 2011[112]	USA	P	Heart	Advanced (end-stage) HF	9	**Age** 44.11(SEM= 4.79, range= 24-58) years **Gender** Both (Men: n= 7, Women: n=2)	NR	Strength exercises	**Muscle Strength** - Maximal Voluntary Contraction: Handgrip dynamometry	No statistically significant difference in any outcomes	**Recruited/ Enrolled** 9/9	Reported that patients had no difficulties maintaining the program **Enrolled/Completed ET** 9/9	No AE observed
Debette-Gratien et al. 2015[113]	France	P	Liver	Liver disease	8	**Age** 51±12 years **Gender** Both (Men: n= 6, Women: n=7)	Median waiting time of 3.5 months	Aerobic exercise Strength exercises Therapeutic Education	**Maximal exercise capacity** - Peak oxygen consumption: VO2 peak **Functional exercise capacity** - 6MWT **Muscle strength** - Quadriceps (knee extensor) strength **Health-related Quality of life** - SF-36: physical and mental component summary	↑ VO2 peak (p<0.008) 21.5±5.9 to 23.2±5.9 mL/kg ↑ 6MWD (p=0.02) 481±69 to 521±64 m ↑ Muscular strength (p=0.008) 30±10 to 37±13 kg force	**Recruited/ Enrolled** 13/13	"Adherence to this program was good for all candidate" **Enrolled/Completed ET** 13/8 **Reasons drop-out** - deterioration of health condition	No AE observed

Florian et al. 2013[114]	Brazil	P	Lung	Idiopathic pulmonary fibrosis (n= 27) Pulmonary emphysema (n=13) Other types of advanced lung disease (n= 18)	58	**Age** 46±14 years Did not complete the intervention 51±11 **Gender** Both (Women: 52%)	NR	Aerobic exercise Strength exercises Breathing exercises Stretching	**Functional exercise capacity** - 6MWT **Health-related Quality of life** - SF-36: physical functioning, vitality, social functioning, mental component summary	↑ 6MWD (p=0.001) 367±136 to 439±114 m ↑ Physical functioning (p<0.001) 20(10-35) to 45(30-55)† ↑ Vitality (p<0.001) 57(38-75) to 65(53-81)† ↑ Social functioning (p=0.001) 50(25-75) to 64(50-87)† ↑ Mental component summary (p=0.001) 82(64-88) to 84(79-92)†	**Recruited/ Enrolled** 112/112	"Excellent adherence" **Enrolled/Completed ET** 112/58 **Reasons drop-out** - transplanted - died - gave up transplantation - hospitalized for a long time	NR
Jastrzebsk et al. 2013[115]	Poland	P	Lung	COPD (n= 7) Idiopathic pulmonary fibrosis (n= 3) Idiopathic interstitial pneumonia (n= 12)	22	**Age** 50.4 year **Gender** Men	NR	Aerobic exercise	**Functional exercise capacity** - 6MWT **Health-related Quality of life** - SF-36: social functioning and physical component summary	↑ 6MWD (p<0.05) After 6 weeks 310±130.2 to 361.9±131.5 m After 12 weeks 310±130.2 to 371.1±163.7 m ↑ Social functioning (p<0.05) After 6 weeks 35.0±30.5 to 45.3±30.4 After 12 weeks 35.0±30.5 to 40.0±26.4 ↑ Physical component summary (p<0.05) After 6 weeks 27.2±8.3 to 29.9±9.1 After 12 weeks 27.2±8.3 to 30.8±7.3	**Recruited/ Enrolled** 26/26	85% **Enrolled/Completed ET** 26/22 **Reasons drop-out:** - transplanted - general weakness	No AE observed
Kenn et al. 2015[116]	Germany	R	Lung	COPD (n= 360) Alpha-1 Antitrypsin Deficiency (n= 127) Interstitial lung disease (n= 195) Cystic Fibrosis (n= 69) Other (n= 60)	811	**Age** 47±9.67 COPD 54±7.6 years Alpha-1 Antitrypsin Deficiency 51±6.3 years Interstitial lung disease 54±8.7 years Cystic Fibrosis 31±7.4 years	NR	Strength exercise Breathing and controlled coughing exercises Educational sessions	**Functional exercise capacity** - 6MWT **Health-related Quality of life** - SF-36: physical and mental component summary	↑ 6MWD (p<0.001) Change of 55.9±58.3 m ↑ Physical component summary (p<0.001) Change of 1.9±8.5 ↑ Mental component summary (p<0.001) Change of 8.7±13.5	**Recruited/ Enrolled** 902/811	NR **Enrolled/Completed ET** 811/811	"no severe adverse events directly related to the PR program were registered"

						Other 45±12.9 years **Gender** Both							
Li et al. 2013[75]	Canada	R	Lung (Single, double) or heart–lung transplant	Pulmonary Fibrosis (n= 116) COPD (n= 106) Cystic Fibrosis (n= 70) Pulmonary Arterial Hypertension (n=17) Sarcoidosis (n=13) Bronchiectasis (n= 11) Other (n= 12)	345	**Age** 51±14 years **Gender** Both (Men: n=191, Women: n= 46)	Average of 185±217 days	Aerobic exercise Strength exercises Stretching	**Maximal exercise capacity** - Peak oxygen consumption: VO2 peak **Functional exercise capacity** - 6MWT **Health-related Quality of life** - SF-36: physical and mental component summary - EQ-5D **Post-transplant outcome** - discharge disposition - LOS in the ICU, hospital and time intubated (in days)	↑ VO2 peak (p< 0.0001) 7.0±1.6 to 7.6±2.0 mL/kg/min Change of +0.69±1.4 mL/kg/min ↓ Mental component summary (p<0.05) 47±11 to 45±12 Change of – 5.6±11.9 ↓ EQ-5D (p<0.05) 0.55±0.24 to 0.47±0.27 Change of -0.13±0.27 ↑ SGRQ (p<0.05) -Symptom 64±21 to 67±18 Change of +7.6±19.3 -Activity 84±14 to 88±9 Change of +4.4±11.1 - Impact 55±17 to 59±15 Change of +6.0±15.0 - Total 65±14 to 69±11 Change of +5.8±11.1 LOS (p=0.003) 95% CI 0.9 to 4.3 days Each 100m increase in pre-transplant in 6MWD was associated with a 2.6 day decrease in median length of stay	**Recruited/ Enrolled** 435/422	47±59 sessions attended **Enrolled/Completed ET** 422/345	NR
Singer et al. 2018[117]	USA	P	Lung	Pulmonary Fibrosis (n=10) COPD (n=5)	13	**Age** 62.9±5.7 **Gender** Both (Men: n= 66.7%)	NR	**Phase 1** (In-patient) explanation of exercise + nutrition - aerobic exercise - strength exercises - stretching - breathing technics - nutrition counseling **Phase 2** (Home-based) exercise + nutrition	**Frailty** - Short Physical Performance Battery (SPPB) - Fried Frailty Phenotype (FFP) **Functional exercise capacity** - 6MWT **Grip strength** - Handheld dynamometer **Safety**	No statistically significant difference in any outcomes	**Recruited/ Enrolled** 45/15	"moderate adherence, completing an average of 60% to the pre- scribed exercise regimen. The variation in adherence was large (range: 31%-94%)"	No AE observed

								- using a mobile device platform - same exercises	- SaO2 < 85% during exercise - Falls/injuries (Home oximetry monitoring / Weekly phone calls) **Adherence** - Percent of activities completed per day - Percent of days exercised per week			**Enrolled/Completed ET** 15/13 **Reason drop-out** - transplanted - others not mentioned	
Williams et al. 2019[118]	UK	P	Liver	Alcohol/non-alcoholic fatty liver disease - 5 (27.8%) Primary sclerosing cholangitis - 4 (22.2%) Primary biliary cirrhosis - 2 (11.1%) Variant disease- 7 (38.8%)	9	**Age** 55 (44-63) **Gender** Both (Men: 50%; Women: 50%)	414 (153-834)	Aerobic exercise Functional strength exercises	**Functional exercise capacity** - incremental shuttle walk test (ISWT) **Health-related Quality of Life** - EuroQol-5 Dimension-5 Levels (EQ-5D- 5L) (version 2.1) **Depression** -Hospital Anxiety and Depression (HAD) **Anxiety** -Hospital Anxiety and Depression (HAD)	↑ISWT After 6 weeks ($p<0.008$) From median score of 260m (IQR 70-1020) to 310m (IQR 180-800) median difference from baseline +50m Between 6 and 12 weeks ($p<0.008$) median increase of 470m (IQR 190-880) median difference of +210m	**Recruited/Enrolled** 46/18	Week 1-6: daily step program (82%) and functional resistance-exercises (90%) Week 7-12: daily step program (53%) and functional resistance-exercises (78%) **Enrolled/Completed ET** 18/9 **Reasons drop-out** - transplanted - palliative care - unable to attend - did not attend - fractured tibia	No AE observed

Mean±SD; †median (interquartile range); ††Difference[95%CI]; ††† median(min-max)

Legend: P- prospective, R-retrospective, NR- not reported; ET- exercise training; 6MWT- 6-minutes walking test; 6MWD- 6-minutes walking distance; m- meters; HF- heart failure; MIP- maximal inspiratory pressure; MEP- maximal expiratory pressure; AE- adverse events; $VO_{2\ peak}$- peak oxygen consumption; SF-36- Short Form-36 questionnaire; ml/kg- milliliter per kilogram; kg- kilogram; COPD - Chronic Obstructive Pulmonary Disease; min – minutes; SaO_2- Oxygen saturation.

Table 3 – Characteristics of the RCTs and non-RCTs

Author/ Year	Country	Design	Organ group	Population	Sample size	Demographics	Time on waiting list	Exercise intervention	Included outcomes of interest	Significant findings (between group analysis)	Acceptance	Adherence	Safety
Ben-Gall et al. 2000[105]	Israel	Non-RCT	Heart	End stage heart failure: Ischemic cardiomyopathy (coronary artery disease) (n=9) Non-ischemic cardiomyopathy (dilated cardiomyopathy) (n=3)	8	**Age** NR **Gender** NR	NR	**Intervention group** - aerobic exercise **Control group** (formed by patients that drop-out the intervention) - no exercise	**Maximal exercise capacity** - Peak oxygen consumption: VO2 peak **Functional exercise capacity** - 6MWT	Analysis between groups not performed **Within group analysis** **Intervention group** ↑ $VO2_{peak}$ (p=0.01) 11.5±1.6 to 14±2 mL/kg ↑ 6MWD (p= 0.006) 409±82 to 480±108 m **Control group** ↓ $VO2_{peak}$ (p=0.02) 13.7±1 to 11±2.2 mL/kg 6MWD (data not measured)	**Recruited/ Enrolled** 12/12	Excellent 92% **Intervention group** **Enrolled/Completed ET** 12/5 **Reasons drop-out** - did not tolerate the exercise training - geography inconvenient -transplantation **Control group** **Enrolled/Completed ET** 6/3 **Reasons drop-out** - transplantation - hospitalized	No AE observed
De Jonge et al. 2001[106] ** Data extracted just from group A**	Netherland	Non-RCT	Heart VAD as bridge to transplant	Dilated cardiomyopathy (n= 8) Ischemic heart disease (n= 7)	**Group A** -exercise test at 8 weeks (n=10) - exercise test at 12 weeks (n=15)	**Age** 37±12 years (both groups) **Gender** Men	NR (bridged to HTx after a mean duration of support of 181±125 days)	Aerobic exercise Strength exercises Coordination exercise	**Maximal exercise capacity** - Peak oxygen consumption: VO2 peak	**Data from one arm of the study that included patients after LVAD implantation (Group A)** Comparison between 8 weeks and 12 weeks after implantation ↑ VO2 peak (p=0.003) (95% CI 4.7 to 1.3) 21.3±3.8 to 24.2±4.8 mL/kg	**Recruited/ Enrolled** 15/15	**LVAD group** **Enrolled/Completed ET** 8 weeks: 15/10 (missing data of 5 participants) 12 weeks: 15/15	NR
Gloeckl et al. 2012[97]	Germany	RCT	Lung	COPD stage IV	60 **High-intensity interval training group** n= 30 **Moderate intense continuous training group** n= 30	**Age** 53±6 years (both groups) **High-intensity interval training group** 52± 6 years **Moderate intense continuous training group** 55 ±7 years **Gender** Both	NR	**High-intensity interval training group** - aerobic exercise **Moderate intense continuous training group** - aerobic exercise	**Functional exercise capacity** - 6MWT **Health-related quality of life** - SF-36: physical and mental component summary	No statistically significant difference in any outcomes	**Recruited/ Enrolled** 97/71	100% **High-intensity interval training group** **Enrolled/Completed ET** 35/30 **Reasons drop-out** - exacerbation - transplanted - other reasons not mentioned **Moderate intense continuous training group**	No AE observed

												Enrolled/Completed ET 36/30 **Reasons drop-out** - exacerbation - non comliance - other reasons not mentioned	
Gross et al. 2017[98]	USA	RCT	Kidney or kidney-pancreas	Kidney failure	55 **Intervention group (tMBSR)** n= 27 **Control group (tSupport)** n= 28	**Age** 54± 12 years (both groups) **Intervention group (tMBSR)** 52.6 ± 12.6 years **Control group (tSupport)** 54.6 ± 11.7 years **Gender** Both (Women: 56%)	**Range** 3 days to 5 years **Intervention group (tMBSR)** 442.6 ± 485.5 **Control group (tSupport)** 438.1 ± 370.5	**Intervention group (tMBSR)** - yoga - meditation - therapeutic education **Control group (tSupport)** - no exercise - support group	**Anxiety** - State-Trait Anxiety Inventory state version **Depression** - The Center for Epidemiologic Studies Depression Scale **Sleep quality** - The Pittsburgh Sleep Quality Index **Fatigue** PROMIS-Fatigue Short Form v1.0 **Health-related quality of life** - SF-12: Mental component summary (MCS) and Physical component summary (PCS)	↑ MCS follow-up (p= 0.01) (tMBSR group) +6.23 points [95%CI 1.66, 10.80] than control group	**Recruited/ Enrolled** 388/63	"Attendance was excellent, averaging 7 out of 8 sessions" **Intervention group (tMBSR)** **Enrolled/Completed ET** 31/27 **Reasons drop-out** - did not attend - refused **Control group (tSupport)** **Enrolled/Completed ET** 32/28 **Reasons drop-out** - too ill - refused - transplanted	No AE observed
Hayes et al. 2012[99]	Australia	RCT	Heart VAD as bridge to transplant	Idiopathic Dilated Cardiomyopathy (n=9) Ischemic Cardiomyopathy (n= 5)	14 **Intervention group** n=7 **Control group** n=7	**Age** 47.3±2.0 years (both groups) **Intervention group** 48.7±14.5 years **Control group** 45.9±14.6 years **Gender** Both	NR	**Intervention group** - aerobic exercise - strength exercise - mobilization **Control group** - aerobic exercise (mobilization protocol)	**Maximal exercise capacity** - Peak oxygen consumption: VO2 peak **Functional exercise capacity** - 6MWT **Health-related Quality of life** - SF-36: physical functioning, role physical, mental health, social functioning, bodily pain, vitality	No statistically significant difference in any outcomes	**Recruited/ Enrolled** 18/14	21.3±1.5 of 24 sessions **Intervention group** **Enrolled/Completed ET** 7/7 **Control group** **Enrolled/Completed ET** 7/7	No AE observed

Karapolat et al. 2013[107] ** Data extracted just from group LVAD**	Turkey	Non-RCT/ R	Heart VAD as bridge to transplant	Patients who were implanted an LVAD (no specific description)	11	**Age** 45.57±14.05 years (both groups) **Gender** Both (Men: 85.7%)	NR (Mean duration of the LVAD: 2.8 ±2.13 mo)	Aerobic exercise Strength exercise Flexibility exercise Breathing exercise Relaxation exercise	**Maximal exercise capacity** - Maximal oxygen consumption: VO2 maximal **Depression** - Beck Depression Inventory (BDI) **Anxiety** - State-Trait Anxiety Inventory (STAI) **Health-related Quality of life** - SF-36: physical functioning, role physical, role emotional, mental health, social functioning, bodily pain, general health, vitality	**Data from one arm of the study that include patients with LVAD** **Within group LVAD analysis** ↑ VO2 max ($p<0.05$) 14.68±3.63 to 15.13±3.42 mL/kg	**Recruited/ Enrolled** 11/11	**LVAD group** **Enrolled/Completed ET** 11/11	No AE observed
Laoutaris et al. 2011[100]	Greece	RCT	Heart VAD as bridge to transplant	Dilated Cardiomyopathy	15 **Intervention group** n= 10 **Control group** n= 5	**Age** 38.3±15.9 years (both groups) **Intervention group** 37.2±17.7 years **Control group** 41.8±14.6 years **Gender** Both (Men: n= 14, Women: n=1)	NR	**Intervention group** - aerobic exercise - inspiratory muscle training **Control group** - aerobic exercise	**Maximal exercise capacity:** - Peak oxygen consumption: VO2peak **Functional exercise capacity:** - 6MWT	No statistically significant difference in any outcomes	**Recruited/ Enrolled** 23/21	**Intervention group** **Enrolled/Completed ET** 14/10 **Reasons drop-out** - transplanted **Control group** **Enrolled/Completed ET** 7/5 **Reasons drop-out** - transplanted	NR
Limongi et al. 2014[101]	Brazil	RCT	Liver	Alcohol (n=4) Hepatitis C (n=6) Carolli syndrome (n=1) Autoimmune hepatitis (n=1) Hepatocellular carcinoma + Hepatitis C (n=2)	17 **Intervention group** n= 5 **Control group** n= 12	**Age** 55.48 ±8.67 years (both groups) **Intervention group** 56.2±3.96 years **Control group** 53.41±8.42 years	NR	**Intervention group** - breathing exercise - cough guidance - inspiratory muscle strength - strength exercise	**Respiratory Muscle Strength** - MIP - MEP **Health-related Quality of life** - SF-36: physical functioning, role physical, role emotional, mental	Analysis between groups not performed **Within group analysis** **Intervention group** ↑ MIP (p-value not reported) 86±35.8 to 122±62.6 Kg/m^2 ↑ MEP (p-value not reported)	**Recruited/ Enrolled** 42/17	**Intervention group** **Enrolled/Completed ET** 5/5 **Control group** **Enrolled/Completed ET** 12/12	NR

				Alcohol + Hepatitis C (n=1) Alcohol + Hepatitis B (n=1) Alcohol + Hepatitis C + Hepatocellular carcinoma (n=1)		**Gender** Both		- mobilization **Control group** - no exercise	health, social functioning, bodily pain, general health, vitality	88±26.8 to 130±44.7 Kg/m^2 **Control group** ↑ MIP (p-value not reported) 90±53.6 to 96.7±49.6 Kg/m^2 ↑ MEP (p-value not reported) 107.5±49.9 to 110±54.3 Kg/m^2			
Limongi et al. 2016[102]	Brazil	RCT	Liver	Hepatitis C (n=9) Hepatocellular carcinoma + Hepatitis C (n=4) Alcohol (n=6) Hepatocellular carcinoma (n=3) Alcohol + Hepatitis C (n=5) Alcohol + Hepatocellular carcinoma (n=1) Alcohol + Hepatitis C + Hepatocellular carcinoma (n=1) Autoimmune hepatitis (n=1) Polycystic liver disease (n=1) Cryptogenic cirrhosis (n=1) Sclerosing cholangitis (n=1) Hepatitis B + Hepatitis C (n=1)	37 **Intervention group** n= 14 **Control group** n= 23	**Age** 55.6 years (both groups) **Intervention group** 55.8±5.4 years **Control group** 55.4±9.9 years **Gender** Both	NR	**Intervention group** - breathing exercise - cough guidance - inspiratory muscle strength - strength exercise **Control group** - no exercise	**Respiratory Muscle Strength** - MIP - MEP **Health-related Quality of life** - SF-36: physical functioning, mental health, general health	No statistically significant difference in any outcomes	**Recruited/ Enrolled** 49/49	**Intervention group** **Enrolled/Completed ET** 22/14 **Reasons drop-out** - transplanted - died - declined **Control group** **Enrolled/Completed ET** 27/23 **Reasons drop-out** - transplanted - died	NR
Manzetti et al. 1994[103]	USA	RCT	Lung	Emphysema (n=1) Bronchiectasis (n=2) Cystic fibrosis (n=2) Pulmonary fibrosis (n=2) Sarcoidosis (n=2)	9 **Intervention group** n= 5	**Age** 40±10 years (both groups) **Gender** Both	NR	**Intervention group** **Education classes + exercise** - aerobic exercise - strength exercise	**Functional exercise capacity** - 6MWT	No statistically significant difference in any outcomes	Recruited/ Enrolled: 36/21	**Intervention group** **Enrolled/Completed ET** 21/5 **Control group**	"Patients can safely participate in pulmonary

					Control group n= 4	(Men: n=2, Women: n=7)		- education classes **Control group** **Education classes** - education classes (no exercise)				**Enrolled/Completed ET** 21/4	rehabilitation"
McAdam-De Marco et al. 2019[108]	USA	Non-RCT	Kidney	End-stage renal disease caused by: Glomerular (33.3%) Diabetes (16.7%) Hypertension (33.3%) Other (16.7%)	43 **Intervention group** n= 18 **Control group** n= 25	**Age** 52±12.9 years (both groups) **Gender** Both (Men: 61%)	Mean time of 3.1 years (prior to starting pre-habilitation)	**Intervention group** - breathing exercise - stretching exercise - balance, motor skill, coordination exercise - strength exercise - aerobic exercise **Control group:** (historical) - standard care	**Post-transplant outcome:** -Length of stay (LOS) **Safety** - medical monitor	↓ LOS (p = 0.02) (intervention group) RR= 0.69; 95%CI: 0.50-0.94	**Recruited/ Enrolled** 136/49	8 participants (44%) attended less than 4 sessions **Intervention group** **Enrolled/Completed ET** 24/18 **Reasons drop-out** - transportation issues - schedule conflict - health/medical issues - too much commitment **Control group** **Enrolled/Completed ET** 25/25	No AE observed
Ochman et al. 2018[109]	Poland	Non- RCT / R	Lung	**Intervention group** COPD (n= 7) Idiopathic Fibrosis (n= 7) Allergic Alveolitis (n= 2) Sarcoidosis (n= 1) Histiocytosis (n= 1) Silicosis (n= 1) Bronchiectasis (n= 2) Nonspecific interstitial pneumonia (n= 1) **Control group** COPD (n= 4) Allergic Alveolitis (n= 2) Sarcoidosis (n= 1)	40 **Intervention group** n= 22) **Control group** n=18	**Age** 52±2.26 years (both groups) **Intervention group** 50.4±7.84 years **Control group** 53.6±8.79 years **Gender** Both (Men: n=38, Women: n=2)	NR	**Intervention group** - aerobic exercise **Control group** - no exercise	**Functional exercise capacity** - 6MWT **Dyspnea** - Medical Research Council (MRC) dyspnea scale - Baseline Dyspnea Index (BDI) **Health-related Quality of life** - SF-36: physical and mental component summary	↑ 6MWD (p= 0.034) (Intervention group) After 12 weeks - 373m in intervention group vs 268m in control group (numerical data not reported) ↓ MRC (p= 0.002) (control group) (numerical data not reported) ↑ BDI (p=0.002) (Intervention group) (numerical data not reported) ↑ Physical Component Summary (p= 0.039) (Intervention group)	**Recruited/ Enrolled** 40/40	**Intervention group** **Enrolled/Completed ET** 22/22 **Control group** **Enrolled/Completed ET** 18/18	No AE observed

				Histiocytosis (n= 1) Silicosis (n= 1) Systemic Lupus Erythematosus (n= 1)						After 12 weeks (numerical data not reported)			
Pehlivan et al. 2018[104]	Turkey	RCT	Lung	Bronchiectasis (n=12) Cystic fibrosis (n=5) COPD (n=6) Interstitial lung disease (n= 3) Silicosis (n=3) Sarcoidosis (n=2) Kartagener syndrome (n=1) Rheumatoid arthritis lung disease (n=1) Alveolar proteinosis (n=1)	34 **PR + IMT group** n=17 **PR group** n=17	**Age** 37±14 years(both groups) **PR + IMT group** 39.05±12.44 years **PR group** 36.05±15.86 years **Gender** Both (Men: 61%)	NR	**PR + IMT group** - aerobic exercise - strength exercise - inspiratory muscle training **PR group** - aerobic exercise - strength exercise	**Functional exercise capacity** - 6MWT **Respiratory Muscle Strength** - MIP - MEP **Dyspnea:** - Modified Medical Research Council (mMRC) dyspnea scale	↑ 6MWD (p=0.03) (PR + IMT group) 100m (0 - 308) ↑ MIP (p=0.001) (PR + IMT group) 26cmH_2O (-10 - 67) median(min-max)	**Recruited/ Enrolled** 38/34	**PR + IMT group** **Enrolled/Completed ET** 17/17 **PR group** **Enrolled/Completed ET** 17/17	"None of the patients experienced any complications or harmful clinical problems"
Mean±SD **Legend** Non-RCT- Non-randomized controlled trial; RCT- randomized controlled trial; NR- not reported; AE- adverse event; ET- exercise training; $VO_{2\ peak}$- peak oxygen consumption; 6MWT- six-minutes walking test; ml/kg- millilitre per kilogram; 6MWD- six-minutes walking distance; m- meters; VAD- ventricular assist device; HTx- heart transplant; LVAD- left ventricular assist device; COPD- chronic pulmonary disease; SF-36- short form-36 questionnaire; tMBSR- telephone-adapted Mindfulness-based Stress Reduction; tSupport- telephone-based support ; SF-12- Short Form-12v2; PR- pulmonary rehabilitation; IMT- inspiratory muscle training; MIP- maximal inspiratory pressure; MEP- maximal expiratory pressure.												

Table 4 – Description of the exercise interventions

Author/ Year	Exercise Intervention	Setting	Frequency	Duration of the program	Supervision	Group or Individually	Initial intensity	Rule for Progression
Ben-Gall et al.[105]	**Intervention group** Aerobic - cycle ergometer training: interval method with work phases of 30 seconds and recovery phases of 60 seconds during which patients pedaled at 10 to 20 W for a total of 15 min/session - walking training: using a treadmill, alternating 60 seconds of slow walking and 60 seconds of fast walking **Control group** - no exercise	NR	Twice a week	Mean of 6.5 months	Supervised by physician	NR	Aerobic exercise - cycle ergometer training: 50% of the maximal work rate achieved - walking training: NR	NR
Byrd et al. 2019[110]	**Individual training** Aerobic exercise - ambulation indoor - stationary cycling Strength exercise alternating days of upper body and lower body exercises - lower extremities: leg press, leg extension, leg curl, hip abduction, hip extension - upper extremities: triceps pushdowns, upright row, bicep curls, horizontal shoulder, abduction, shoulder external rotation - sit to stands, ascend/descend stairs, squats, heel raises, toe raises Balance exercise - semi-tandem Stance, tandem stance, single leg stance Flexibility exercise - lower body: hamstrings, calf, piriformis/gluteal - upper body: chest, shoulder, back **Group training** (30 min) Sitting - head turns, shoulder circles, scapular retraction and depression, shoulder abduction, bicep curls, overhead press Supine lower body - pelvic tilts, bridging, marching, single leg lowering from 90/90 position, ankle plantarflexion, ankle circles, single leg bicycling motion Supine upper body	Out-patient (Duke Cardiopulmonary Rehabilitation)	Exercise: 5 times/week Educational lectures: 4 to 5 times/week Group class: 7 times/week Maintenance program: 5 times/week	23 sessions	Supervised by therapist with experience in treating patients with lung disease	Individually + Group class (30 min)	Aerobic exercise - NR Endurance training - initial weight was set to elicit muscle fatigue at 15 to 20 repetitions Balance exercise - NR	Aerobic exercise -ambulation: duration gradually increased to a goal of 20 continuous min, 3 days per week, and 30 continuous min, 2 days per week -cycling (stationary): once the participant could cycle 20 min continuously, the pedal resistance was gradually increased to maintain a moderately intense workload, which equated to a rating of 4 to 6 on a 0 to 10 rate of perceived exertion visual analog scale Endurance exercise - once the patient performed one set of 20 or more repetitions for 2 consecutive visits, the weight was increased by 5 pounds on weight machines and 1 pound for free weights Balance exercise - eyes closed, head turns, standing on foam, standing on half-balance ball or balance disc

	- chin tucks, chest press, shoulder flexion and abduction, triceps extension, diaphragmatic breathing Side-lying - hip abduction, hip adduction, hip abduction and external rotation with hips and knees bent							
Cahalin et al. 1997[111]	Inspiratory muscle exercise - for a total of 5 to 15 min/session	NR	3 times/day	8 weeks	Supervised during the initial IMT session	NR	IMT - 20% of MIP and duration of *5 to 15* min	IMT - when subjects were free of overt anxiety, dyspnea, fatigue, and respiratory muscle discomfort, the duration was progressed by 2 to *5* min until 15 min was achieved - training prescriptions were progressed based on weekly measurements of MIP to maintain IMT at 20% of MIP
Dean et al. 2011[112]	Upper-body endurance exercises -handgrip dynamometry exercise. Repetition 1 set of 6 to 10 - free-weight exercises (biceps brachii and the triceps muscle groups). Repetitions not reported	NR	3 times/week with 1 day of rest between each training day	4 weeks	Supervised by cardiac rehabilitation nurse or an exercise physiologist	NR	Handgrip dynamometry - 60% of their MVC (first 2 days of exercise) Free-weight exercises - not reported	Handgrip dynamometry - progressively worked up to 6 sets of 6 to 10 repetitions at 70% to 80% of the MVC Free-weight exercises - same progression except that the amount of weight used was based on tolerance, which was determined by the weight that the patient could lift comfortably without producing a rating of perceived exertion greater than 13 on the 6- to 20-point scale of rating of perceived exertion
Debette-Gratien et al. 2015[113]	Aerobic exercise - with cycle ergometer for 20 min Strength exercise - on a weight bench for 20 min The program included two sessions of therapeutic education on the benefits of physical activity	In-patient (Physiological Functional Exploration Unit)	Twice a week (approximately 2 hours/session)	12 weeks	Nurse assisted patients each session and supervised by the trained physician	The sessions were conducted in pairs	Aerobic exercise - begun at ventilatory threshold power Strength exercise - It depended on the measurement of the knee extensor force. The maximal charge that a patient could lift was then defined by a maximal repetition	Aerobic exercise - incrementation of the load in case of decrease of the cardiac frequency Strength exercise - 70% to 80% of the maximal repetition
De-Jonge et al. 2001[106]	Aerobic exercise - bicycle, treadmill, and rowing machine Strength exercise* Coordination exercise - games such as badminton, tennis and volleyball	NR	3 - 5 times/ week	12 weeks	Supervised by a physical therapist	NR	2 to 6 min of low-level activities, alternated with 1 to 2 min of rest	Intensity increases based on Borg RPE Duration of exercise gradually increased to 20-40 min/day

	* Strength training according to 5BX plan (Five Basic Exercises) of the Royal Canadian Air Force							
Florian et al. 2013[114]	Aerobic exercises - treadmill Strength exercise - arm and leg exercises. Repetition: one set of 10 per exercise Breathing exercise - associated with arm raising Repetition one set of 10	In-patient (Department of Pulmonary Rehabilitation of the Pereira Filho Ward)	3 times/week (90 min each session)	12 weeks	Supervised by two physical therapists	NR	Strength exercise - initial load of 30% of one repetition maximum testing Aerobic exercise - beginning at 60% of the speed of the 6MWT	Strength exercise - the load was increased by 0.5 kg every 7 sessions according to the patient tolerance Aerobic exercise - progressive protocol every 6 min until reaching 30 min. The speed was increased by 0.3 km/h every 7 sessions
Gloeckl et al. 2012[97]	**High-intensity interval training group** - cycling: 30-second at 100% of PWR alternating with 30 seconds of rest (0% of PWR) **Moderate intense continuous training group** - cycling: 10 to 30 min	In-patient	5 to 6 times/week	3 weeks	NR	NR	**High-intensity interval training group** - 100% PWR **Moderate intense continuous training group** - 60% PWR	**High-intensity interval training group** - exercise time per session increased from 12 to 36 min **Moderate intense continuous training group** - exercise time increased per session
Gross et al. 2017[98]	**Intervention group** - yoga **Control group** - no exercise	In-patient + Telephone base	NR	8 weeks	An instructor showed the poses in the in-person session	NR	NR	NR
Hayes et al. 2012[99]	**Intervention group** - aerobic exercise: stationary cycling for 15 min and treadmill for 15 min - strength exercise: 3 upper limb and 3 lower limb strengthening exercises using weight machines and free weights. 2 sets of 10 repetitions **Control group** - aerobic exercise (mobilization program): diary with record of walking program All participants in the exercise group also participated in the "mobilization program" on the days they did not attend the gym	In-patient (physiotherapy gym) + home-based (after hospital discharge)	**Intervention group** 3 times/week (1 hour) **Control group** Advise to walk 5 times/week	8 weeks	NR	NR	Aerobic exercise - stationary cycling: 50% VO2 reserve - treadmill: speed of 60% of average during the 6MWT	**Intervention group** Aerobic exercise - when able to perform the exercise continuously for 15 min, reporting a Borg RPE of 13, the workload was them progressed by 10% **Control group** Mobilization protocol - increase the walk to 60 min, maintaining an intensity of level 13 on the Borg RPE
Jastrzebsk et al. 2013[115]	Nordic walking exercise training - with ski poles	In-patient (2 weeks) + home-based (4 weeks)	NR	12 weeks	Supervised during hospital-based	NR	NR	NR
Karapolat et al. 2013[107]	Aerobic exercise Strength exercise - involving UE and LE muscle groups Flexibility exercises - range of motion, stretching exercise	In-patient	3 times/week	8 weeks	Supervised by a physiotherapist	NR	Aerobic exercise 60%-70% maximal oxygen consumption test (pVO2), ratings of perceived exertion 12-14, 30 min/ session	NR

	Breathing exercises Exercise sessions with duration of 90 min						Strengthening exercise 250-500g, upper/lower extremities, 8 muscles	
Kenn et al. 2015[116]	Endurance training - 10 to 20 min Strength training - 30-45 min, 3 sets of 20 repetitions Breathing exercises Coughing exercises	In-patient (rehabilitation center)	Resistance training: 5 to 6 times/week Others not reported	5 weeks	Supervised	Strength training: Individually tailored Other intervention: NR	Endurance exercise - at 60% of PWR Strength exercise - four to six exercises with 3x20 maximum tolerated load	NR
Laoutaris et al. 2011[100]	**Intervention group** - aerobic exercise: advised to walk every day, bike or treadmill for 30-45 min (at home) - high-intensity inspiratory muscle training (in the hospital) **Control group** - aerobic exercise: advised to walk every day for 30-45 min	In-patient + home-based	**Intervention group** 3-5 times/week IMT: 2-3 times/week	10 weeks	NR	NR	Aerobic exercise - moderate intensity of 12–14 of the Borg scale IMT - at 60% of MIP	NR
Li et al. 2013[75]	Aerobic - arm ergometer - cycle ergometer - treadmill training Strength exercise - biceps, triceps, quadriceps, hamstrings and hip muscles Total duration of the session was 1.5 to 2 hours	In- patient (pulmonary rehabilitation program)	3 times/week	10 weeks	Supervised by 2 physical therapists and 1 physical therapy assistant	NR	NR	Aerobic exercise - depending on patient's symptoms, increase duration up to 20 min
Limongi et al. 2014[101]	**Intervention Group** (illustrative manual) - strength exercise: abdominal muscles - breathing exercises: awareness of diaphragmatic - isometric exercise: diaphragmatic diaphragmatic breathing - inspiratory muscular training: threshold IMT - mobilization: elevation of upper limbs with a bat associated with All exercises were performed in 3 sets of 15 repetitions **Control group** no exercise	Home-based	7 times/week	12 weeks	NR	Individually at home	- isometric exercise: weight of 1 kg - respiratory exercise: 70% load according to the MIP	NR
Limongi et al. 2016[102]	**Intervention Group** (illustrative manual) - strength exercise: abdominal muscles	Home-based	7 times/week	12 weeks	Supervised at distance monthly	Individually at home	- diaphragmatic isometric exercise: 1kg of weight	NR

	- breathing exercises: awareness of diaphragmatic - isometric exercise: diaphragmatic with the patient in the supine position and weight placed on the diaphragm muscle - inspiratory muscular training: threshold - mobilization: elevation of upper limbs with the help of a bat **Control group** - no exercise All exercises were performed in 3 sets of 15 repetitions							
Manzetti et al. 1994[103]	**Intervention group** - aerobic exercise: treadmill, bicycle ergometer, light aerobic exercises and - strength exercise: light upper extremity weight Training for 30 min **Control group** - no exercise	NR	twice a week	6 weeks	Exercise supervised by physiotherapist	NR	Aerobic exercise - initial exercise intensity was determined from the incremental exercise study - workload either just above anaerobic threshold or achieved 80% of maximal ventilation	Aerobic exercise - adjusted according to tolerance
McAdam-De Marco et al. 2019[108]	**Intervention group** -breathing exercise: diaphragmatic - swiss ball exercise: balance, core stability, pillar strength, and range of motion - trampoline exercise: motor skills, balance, and coordination - strength exercise: weights or elastic stretch band - aerobic exercise: treadmill, bike, and elliptical Each session was 40 min long with 20 min of exercises of their choice **Control group** - standard care (details not reported)	Out-patient (Johns Hopkins outpatient Physical Medicine and Rehabilitation center) + home-based	7 times/week	Maximum 76 sessions	Supervised by a physiotherapist assistant	Individualized	NR	NR
Ochman et al. 2018[109]	**Intervention group** - aerobic exercise: nordic walking with poles **Control group** - did not receive a dedicated exercise program	In-patient + home-based	Not reported	12 weeks (The study was divided into 2 cycles, each lasting 6 weeks)	First 2 weeks supervised by physiotherapist Next 4 weeks not supervised (at home)	NR	NR	NR

Pehlivan et al. 2018[104]	**PR + IMT group** - aerobic exercise: treadmill walking, stationary bicycle, arm ergometer. Sets of 15 min each with three exercise modalities - strength/ endurance exercise: dumbbell and free weight bags for biceps, triceps, quadriceps, hamstring and hip muscles. Between 8 and 12 repetitions for 1 to 2 sets/session - home exercise program: breathing exercises, local expansion exercises, diaphragmatic breathing and pursed lip breathing, free walking, upper and lower extremity strengthening exercises with Thera-Band - inspiratory muscle training for 15 min **PR group** -aerobic exercise: treadmill walking, stationary bicycle, arm ergometer. Sets of 15 min each with three exercise modalities -strength/ endurance exercise: dumbbell and free weight bags; for biceps, triceps, quadriceps, hamstring and hip muscles. Between 8 and 12 repetitions for 1 to 2 sets/session -home exercise program: breathing exercises, local expansion exercises, diaphragmatic breathing and pursed lip breathing, free walking, upper and lower extremity strengthening exercises with Thera-Band	In-patient (Pulmonary Rehabilitation center) + home-based	-Supervised PR: 2 days/week (all patients) - Home exercise program: 3 days/week (all patients) -Inspiratory muscle training: 15 repetitions, twice a day, 5 days/week (only PR + IMT group)	12 weeks	Just the home exercise program that wasn't supervised	- Aerobic exercise: group -Strengthening/ endurance exercise: not reported - Home exercise program: not reported - Inspiratory muscle training: not reported	IMT - 30% of the maximum inspiratory pressure value obtained as a result of the mouth pressure measurement	Aerobic exercise - gradually increased taking the severity of dyspnea perception and fatigue ratio as the basis IMT - increased from 30% to 60%
Singer et al. 2018[117]	- aerobic exercise: walking, sit to stands, tandem walking - strength exercise: wall push-ups Same exercise program for Phase 1 and 2	In-patient + home-based	aerobic exercise: 7 times/week; Other exercises: 3 times/week	8 weeks	Phase 1- supervised Phase 2-weekly phone check-in by trained coordinator	Phase 1- Study coordinator performed assessments and training Individualized nutrition counseling session done by registered dietitian	Aerobic exercise - 65%-75% of each participant's maximum exercise capacity Strength exercise - based on baseline SPPB frailty score	NR
Williams et al. 2019[118]	**Level 1** - Functional endurance exercise/aerobic: frog squat, rock press, lunge, bear crawl; 20 s of	Home-based	NR	12 weeks	First 6 weeks: weekly phone call by chief investigator	Individually tailored	- Started at level 1	- Increasing the levels of difficulty: 1 to 5

	each exercise 40 s rest; 5 circuits; total 20 min **Level 2** - Functional endurance exercise/aerobic: frog squat, rock press, lunge, bear crawl; 30 s of each exercise 30 s rest; 5 circuits; total 20 min **Level 3** - Functional endurance exercise/aerobic: frog squat, rock press, lunge, bear crawl; 40 s of each exercise 20 s rest; 5 circuits; total 20 min **Level 4** - Functional endurance exercise/aerobic: frog squat, rock press, lunge, bear crawl, side bear crawl; 40 s of each exercise 20 s rest; 4 circuits; total 20 min **Level 5** - Functional endurance exercise/aerobic: frog squat, rock press, lunge, bear crawl, side bear crawl, kick sit; 40 s of each exercise 20 s rest; 4 circuits; total 24 min							- Walking program: increase daily step count by 200–500 steps each day every week

Legend: ET- exercise training; NR- not reported; min- minutes; IMT- Inspiratory Muscle Training; MIP- maximal inspiratory pressure; MVC- maximal voluntary contraction; PR- pulmonary rehabilitation; RPE- perceived exertion; 6MWT- six-minutes walking test; km- kilometer; PWR- peak work rate; tMBSR- telephone-adapted Mindfulness-based Stress Reduction; tSupport- telephone-based support; VO_2- oxygen consumption; LTx- lung transplant, kg- kilogram; PR- pulmonary rehabilitation; SPPB- *short physical performance battery.*

2.6.1 QUALITY OF STUDIES

The quality assessment of RCTs is presented in Table 5 and for non-RCTs and pre-post studies in Table 6. Three[100, 101, 103] of the 8 RCTs were deemed to be at high risk of bias. For the non-RCTs and pre-post studies, no trial was classified as "excellent" in regard of the quality. Eleven[75, 106, 108, 110, 111, 113-118] of the 15 studies were classified as "good", three[105, 109, 112] as "fair" and one[107] as "poor" quality.

The average score of the CERT checklist of the 23 included studies was 7.43 ± 3.07 points out of a total of 19 (table 7). Figure 2 shows the frequency of CERT items that were included in the articles. Item 1 (type of exercise equipment), item 4 (supervised or unsupervised) and 13 (detailed description of the exercise intervention for example number of exercise repetitions/set/sessions, session duration and program duration) were the most described items. On the other hand, item 15 (decision rule for determining the starting level at which people start an exercise program) and 16b (intervention delivered as planned) were the least described items.

2.6.2 PRIMARY OUTCOMES

2.6.2.1 Acceptance and Safety

The proportion of participants that accepted to participate in the included studies over the number of participants approached ranged from 16% to 100%, with a median of 97% (tables 2 and 3).

From the 23 included articles, 15 trials reported on adverse events[97-99, 103-105, 107-109, 112, 113, 115-118]. None of these trials mentioned any adverse events occurring during the study period (tables 2 and 3).

Table 5 – Risk of Bias assessment using the Cochrane tool

	Sequence generation	Allocation concealment	Blinding (participants/ personnel)	Blinding of outcomes	Incomplete outcome data	Selective reporting	Other sources of bias	Result
Gloeckl et al. 2012[97]	Unclear	Low	High	Low	Low	Low	Low	Low
Gross et al. 2017[98]	Unclear	Low	High	Low	Low	Low	Low	Low
Hayes et al. 2012[99]	Low	Low	High	Low	Low	Low	Low	Low
Laoutaris et al. 2011[100]	High	High	High	Low	Low	Low	Low	High
Limongi et al. 2014[101]	Unclear	Unclear	High	Unclear	Unclear	High	Unclear	High
Limongi et al. 2016[102]	Low	Low	High	Unclear	Low	Low	Low	Low
Manzetti et al. 1994[103]	Unclear	Low	High	Low	Low	Low	High	High
Pehlivan et al. 2018[104]	Low	Low	High	Low	Low	Low	Low	Low
≥3 UNCLEAR → UNCLEAR >1 HIGH RISK → HIGH RISK OTHER COMBINATION → LOW RISK								

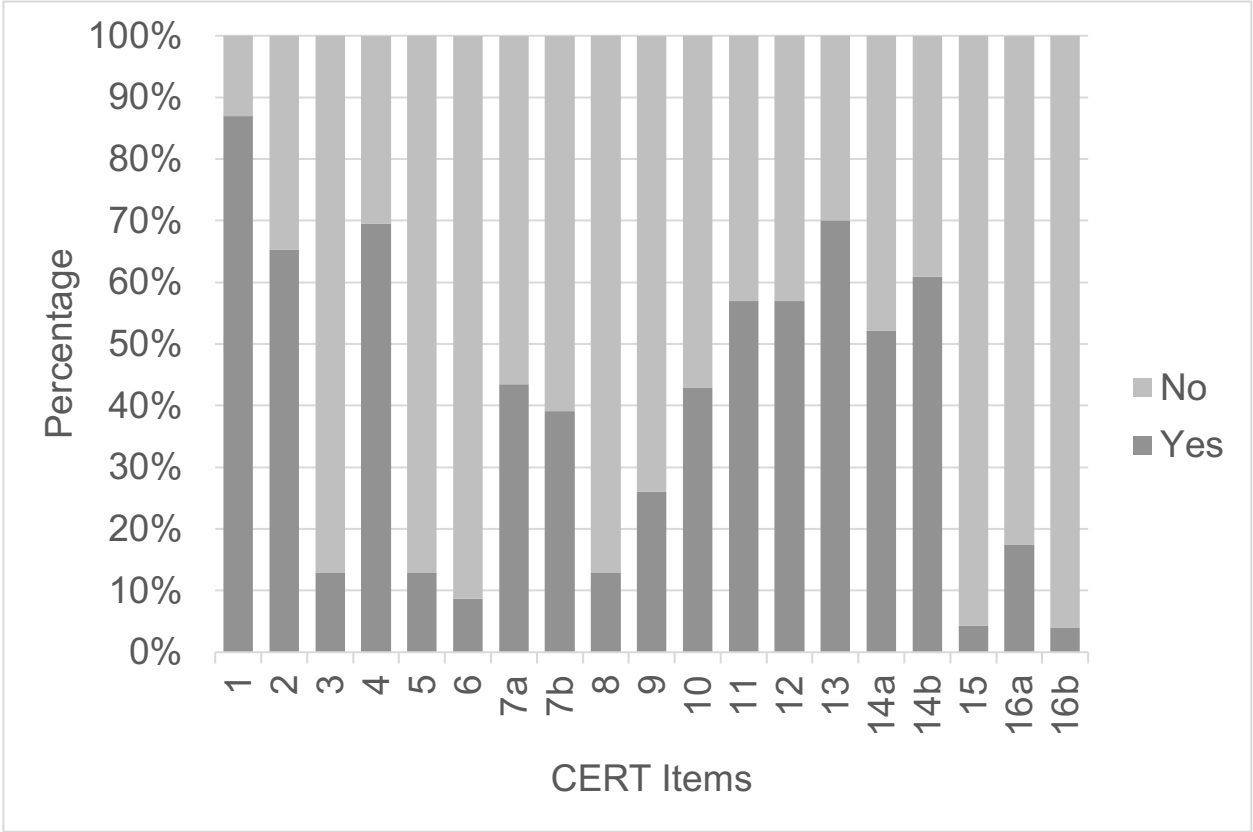
Table 6 – Downs and Black quality assessment score

	Ben-Gall et al. 2000[105]	**Byrd et al. 2019**[110]	**Cahalin et al. 1997**[111]	**Dean et al. 2011**[112]	**Debette-Gratien et al. 2015**[113]	**De-Jonge et al. 2001**[106]	**Florian et al. 2013**[114]	**Jastrzebski et al. 2013**[115]	**Karapolat et al. 2013**[107]	**Kenn et al. 2015**[116]	**Li et al. 2013**[75]	**McAdams-DeMarco et al. 2019**[108]	**Ochman et al. 2018**[109]	**Singer et al. 2018**[117]	**Williams et al. 2019**[118]
Reporting	7	9	10	8	10	10	9	8	7	10	9	10	9	10	10
External Validity	0	3	2	1	2	3	3	3	0	2	3	3	0	2	3
Bias	3	5	4	3	4	5	5	3	4	5	4	4	4	3	5
Confounding	2	4	3	1	3	2	3	3	1	4	3	3	3	3	3
Power	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Total Score	12/23	21/24	19/24	13/24	19/23	20/24	20/23	17/23	12//24	21/24	19/24	20/24	16/23	19/23	21/24
Percentage	52%	87%	79%	54%	83%	83%	87%	74%	50%	87%	79%	83%	70%	83%	88%
Quality levels of Downs and Black scores: excellent (90 to 100%), good (69 to 89%), fair (51 to 68%), and poor (50% or less)															

Table 7 – CERT items per trial

Study		CERT Items																		Score
#		1	2	3	4	5	6	7a	7b	8	9	10	11	12	13	14a	14b	15	16a	16b	
1	**Ben-Gal et al. 2000**[51]	🟢	🟢	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🟢	🔴	🟢	🟢	🟢	🔴	🔴	🔴	6/19
2	**Byrd et al. 2019**[56]	🟢	🟢	🟢	🟢	🔴	🔴	🔴	🟢	🔴	🔴	🟢	🔴	🔴	🟢	🔴	🔴	🔴	🔴	🔴	7/19
3	**Cahalin et al. 1997**[57]	🟢	🔴	🔴	🔴	🟢	🔴	🟢	🟢	🔴	🔴	🔴	🔴	🔴	🟢	🟢	🟢	🔴	🟢	🔴	8/19
4	**Dean et al. 2011**[58]	🟢	🟢	🔴	🟢	🔴	🔴	🔴	🟢	🔴	🔴	🔴	🟢	🔴	🟢	🟢	🟢	🔴	🔴	🔴	8/19
5	**Debette-Gratien et al. 2015**[59]	🟢	🟢	🟢	🟢	🔴	🔴	🟢	🔴	🔴	🔴	🟢	🟢	🟢	🟢	🟢	🟢	🔴	🔴	🔴	11/19
6	**De-Jonge et al. 2001**[52]	🟢	🟢	🔴	🟢	🔴	🔴	🟢	🟢	🔴	🔴	🔴	🔴	🔴	🟢	🟢	🟢	🔴	🔴	🔴	8/19
7	**Florian et al. 2013**[60]	🟢	🟢	🔴	🟢	🔴	🔴	🟢	🟢	🔴	🔴	🟢	🔴	🟢	🟢	🟢	🟢	🔴	🔴	🔴	10/19
8	**Gloeckl et al. 2012**[43]	🟢	🔴	🔴	🔴	🔴	🔴	🟢	🟢	🔴	🔴	🟢	🟢	🔴	🟢	🟢	🟢	🔴	🔴	🔴	8/19
9	**Gross et al. 2017**[44]	🔴	🟢	🟢	🟢	🔴	🔴	🔴	🔴	🔴	🟢	🟢	🟢	🟢	🟢	🔴	🔴	🔴	🔴	🔴	8/19
10	**Hayes et al. 2012**[45]	🟢	🔴	🔴	🟢	🔴	🔴	🟢	🟢	🔴	🟢	🔴	🟢	🟢	🟢	🔴	🟢	🔴	🔴	🔴	9/19
11	**Jastrzebski et al. 2013**[61]	🟢	🟢	🟢	🔴	🔴	🔴	🟢	🔴	🔴	🔴	🔴	🟢	🟢	🔴	🔴	🟢	🔴	🔴	🔴	7/19
12	**Karapolat et al. 2013**[53]	🔴	🟢	🔴	🟢	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🟢	🟢	🔴	🔴	🔴	🔴	🔴	4/19
13	**Kenn et al. 2015**[62]	🟢	🔴	🔴	🟢	🔴	🔴	🔴	🔴	🔴	🔴	🟢	🟢	🟢	🟢	🟢	🟢	🔴	🔴	🔴	8/19
14	**Laoutaris et al. 2011**[46]	🟢	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🟢	🟢	🔴	🔴	🟢	🟢	🔴	🟢	🔴	🔴	🔴	6/19
15	**Li et al. 2013**[18]	🟢	🟢	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	2/19
16	**Limongi et al. 2014**[47]	🟢	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🟢	🟢	🔴	🟢	🔴	🔴	🔴	4/19
17	**Limongi et al. 2016**[48]	🟢	🔴	🔴	🟢	🔴	🔴	🔴	🔴	🟢	🟢	🟢	🔴	🟢	🔴	🟢	🔴	🔴	🔴	🔴	7/19
18	**Manzetti et al. 1994**[49]	🟢	🟢	🔴	🔴	🔴	🔴	🟢	🔴	🔴	🔴	🟢	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	4/19
19	**Mc-Adam et al. 2019**[54]	🟢	🟢	🔴	🟢	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🟢	🟢	🔴	🟢	🔴	🔴	🔴	🔴	6/19
20	**Ochman et al. 2018**[55]	🔴	🟢	🔴	🟢	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🟢	🔴	🔴	🔴	🔴	🔴	🔴	🔴	3/19
21	**Pehlivan et al. 2018**[50]	🟢	🟢	🔴	🟢	🔴	🔴	🔴	🟢	🔴	🟢	🔴	🟢	🔴	🟢	🟢	🟢	🔴	🟢	🔴	10/19
22	**Singer et al. 2018**[63]	🟢	🟢	🔴	🟢	🟢	🟢	🟢	🔴	🔴	🔴	🟢	🟢	🟢	🔴	🔴	🔴	🔴	🟢	🟢	11/19
23	**Williams et al. 2019**[64]	🟢	🔴	🔴	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🔴	16/19
Average score: 7.43±3.07 out of 19 **Legend:** CERT - Consensus on Exercise Reporting Template																					

Figure 2 - Percentage of studies that described the items of the Consensus on Exercise Reporting Template (CERT)



CERT items = 1. type of exercise equipment; 2. qualifications, expertise and/or training of the staff; 3. performed individually or in a group; 4. supervised or unsupervised; 5. adherence to exercise is measured and reported; 6. motivation strategies; 7a. decision rule(s) for determining exercise progression; 7b. how the exercise program was progressed; 8. description of each exercise to enable replication; 9. detailed description of any home program component; 10. non-exercise components; 11. type and number of adverse events; 12. setting in which the exercises are performed; 13. detailed description of the exercise intervention; 14a. describe whether the exercises are generic (one size fits all) or tailored; 14b. detailed description of how exercises are tailored to the individual; 15. decision rule for determining the starting level at which people start an exercise programme; 16a. adherence or fidelity to the exercise intervention is assessed/measured; 16b. describe the extent to which the intervention was delivered as planned (Yes = item correctly described; No = item not described or description was not clear

2.6.2.2 Maximal exercise capacity

Seven trials assessed maximal exercise capacity using VO_{2peak} (2 RCTs[99, 100], 3 non-RCTs[105-107], and 2 pre-post studies[75, 113]). The two RCTs[99, 100] reported no improvement in VO_{2peak} in the intervention group[100] compared to the control group[99, 100]). However, the control groups in these two RCTs included a component of exercise. All three non-RCTs[105-107] reported a statistically significant increase in VO_{2peak} within the intervention group only. Similarly, both pre-post studies[75, 113] showed a statistically significant increase in VO_{2peak} post intervention (tables 2 and 3).

2.6.2.3 Functional exercise capacity

Fourteen studies used the six-minute walk test (6MWT) (5 RCTs[97, 99, 100, 103, 104], 2 non-RCTs[105, 109], and 7 pre-post studies[75, 110, 113-117]), and one pre-post study[118] used the incremental shuttle walk test (ISWT) to assess functional exercise capacity (tables 2 and 3). In 4 RCTs[97, 99, 100, 103] there was no statistically significant improvement in six-minute walking distance in the intervention group compared to the control group, however three of them[97, 103, 104] showed a within group improvement in the outcome (in both groups). Four[97, 99, 100, 104] of the 5 RCTs included an exercise component in the control group. The two non-RCTs[105, 109] showed a statistically significant improvement in 6MWT in the intervention group. The majority of the pre-post studies (n=5)[110, 113-116] that used the 6MWT showed significant increase in the test performed after the intervention. The study that used the ISWT[118] also showed a statistically significant increase in this test after the intervention.

2.6.2.4 Health-related quality of life

Thirteen studies[75, 97-102, 107, 109, 113-116] reported on HRQoL (tables 2 and 3). The short form-36 (SF-36) questionnaire was the most utilized tool, being reported by eleven[75, 97, 99, 101, 102, 107, 109,

43

[113-116] studies (table 8). The majority of RCTs and non-RCTs that included the SF-36 questionnaire (n=6 studies) did not show a statistically significant difference between the intervention and control groups in any of the domains. Most pre-post studies (n=3 studies) showed a statistically significant increase in some domains (e.g. social functioning, vitality, physical and mental component summary) (table 8).

The Minnesota Living with Heart Failure questionnaire[100], EQ-5D[75, 118], and the SF-12[98] were used to assess HRQoL in 4 studies. Out of 2 RCTs[98, 100], only one[98] showed an increase in the intervention group when compared to control (mental component summary of the SF-12 questionnaire). In the two pre-post studies[75, 118] which used the EQ-5D, one[118] showed no statistically difference pre/post intervention and the other study[75] showed an improvement in HRQol post intervention.

Table 8 – SF-36 questionnaire

Author, Year	Organ	Physical Functioning	Role Physical	Role Emotional	Mental Health	Social Functioning	Bodily Pain	General Health	Vitality	Physical Component Summary	Mental Component Summary
RCTs/Non-RCTs											
Gloeckl et al. 2012[97]	Lung	NR	NR	NR	NR	NR	NR	NR	NR	**ND**	**ND**
Ochman et al. 2018[109]	Lung	NR	NR	NR	NR	NR	NR	NR	NR	↑	**ND**
Hayes et al. 2012[99]	Heart	**ND**	**ND**	NR	**ND**	**ND**	**ND**	**ND**	**ND**	NR	NR
Karapolat et al. 2013[107]	Heart	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	NR	NR
Limongi et al. 2014[101]	Liver	**ND**	**ND**	**ND**	**ND**	**ND**	NR	**ND**	**ND**	NR	NR
Limongi et al. 2016[102]	Liver	**ND**	NR	NR	**ND**	NR	NR	**ND**	NR	NR	NR
Pre-post											
Florian et al. 2013[114]	Lung	↑	NR	NR	NR	↑	NR	NR	↑	NR	↑
Jastrzesk et al. 2013[115]	Lung	NR	NR	NR	NR	↑	NR	NR	NR	↑	NR
Kenn et al. 2015[116]	Lung	NR	NR	NR	NR	NR	NR	NR	NR	↑	↑
Li et al. 2013[75]	Lung / Lung-Heart	NR	NR	NR	NR	NR	NR	NR	NR	**ND**	↓
Debette et al. 2015[113]	Liver	NR	NR	NR	NR	NR	NR	NR	NR	**ND**	**ND**

Legend: ↑ - Statically significant increase, ↓ - Statically significant decrease NR - Not Reported, ND - No statistically significant difference

2.6.3 SECONDARY OUTCOMES

2.6.3.1 Respiratory Muscle Strength

Four studies (3 RCTs[101, 102, 104] and 1 pre-post study[111]) measured respiratory muscle strength (MIP and MEP). Two out of the three RCTs[101, 104], reported a statistically significant increase in MIP and MEP in the intervention group compared to the control group. The pre-post study[111] also showed a statistically significant increase in MIP and MEP after the intervention (tables 2 and 3).

2.6.3.2 Upper and Lower Limb Muscle Strength

Two pre-post studies[112, 117] assessed upper limb muscle strength using a handgrip dynamometer. No significant change in upper limb muscle strength after the intervention was observed in either of the studies. Lower limb muscle strength was measured in only one pre-post study[113]. A statistically significant increase after the intervention was reported (tables 2 and 3).

2.6.3.3 Frailty

One pre-post study[117] assessed frailty using the Short Physical Performance Battery and the Fried Frailty Phenotype (tables 2 and 3). No statistically significant change in these outcomes was reported after the intervention.

2.6.3.4 Symptoms of Fatigue and Dyspnea

One RCT[98] measured overall fatigue using The Fatigue Short Form, and no statistically significant difference was observed between the intervention and control groups.

Three studies assessed dyspnea (1 RCT[104], 1 non-RCT[109], and 1 pre-post study[110]) using the Medical Research Council Dyspnea Scale[104, 109], the Baseline Dyspnea Index[109], and/or the San Diego Shortness of breath Questionnaire[110]. In the RCT[104], no significant change in dyspnea between groups was reported. Ochman et al.[109] (non-RCT), reported a decrease in dyspnea in the

intervention group compared to the control group. In the pre-post study by Byrd et al.[110], no significant decrease in dyspnea was observed after the intervention (tables 2 and 3).

2.6.3.5 Anxiety and Depression

Three trials measured anxiety (1 RCT[98], 1 non-RCT[107], and 1 pre-post study[110, 118]). Two studies used The State-Trait Anxiety Inventory[98, 107], and one study[118] used the Hospital Anxiety and Depression tool. No statistically significant improvement in anxiety was reported in any of the articles (tables 2 and 3). Four studies assessed depression (1 RCT[98], 1 non-RCT[107], and 2 pre-post study[110, 118]) using the Center of Epidemiology Studies Depression [98, 110], Hospital Anxiety and Depression tool[118], and the Beck Depression Inventory[107]. Only one study[110] found a statistically significant improvement in anxiety post-intervention (tables 2 and 3).

2.6.3.6 Sleep Quality

One RCT[98] measured sleep quality using the Pittsburgh Sleep Quality Index and reported no statistically significant difference between the intervention and control groups.

2.6.3.7 Post-Transplant Outcomes

Only two articles[75, 108] assessed post-transplant outcomes. Mc-Adams et al.[108] (non-RCT), assessed hospital length of stay post-transplant and reported a reduction in post-surgery days in the hospital in the intervention group when compared to patients who had received standard care. Li et al.[75] (pre-post retrospective study), reported about discharge disposition and length of stay post-transplant. They reported that an increase of 100 in the 6MWT pre-transplant was associated with a decrease of 2.6 days in the median length of stay post-transplant (tables 2 and 3).

2.6.3.8 Adherence

One trial[117] reported on adherence. Singer et al.[117] (pre-post study), reported the percentage of activities completed per day and the percentage of days exercised per week.

Adherence was assessed using an App called Aidcube and a Fitbit activity tracker. The authors reported a moderate adherence, with an average of 60% of the patients completing the exercise regimen.

2.7 DISCUSSION

The findings of this systematic review revealed that exercise interventions are acceptable and safe for SOT candidates. The effects of exercise on exercise capacity and HRQoL in this population are less clear. The body of research evaluating our secondary outcomes (e.g. muscle strength, frailty, symptoms of fatigue, dyspnea, anxiety and depression, sleep quality and post-transplant outcomes) was very small. Most of the studies included heart and lung transplant candidates.

2.7.1 ACCEPTANCE AND SAFETY

We found a high acceptance rate of the exercise interventions among the included studies (median of 97%) which is in line with the review by Wallen et al. [48]. Higher acceptance rates were observed in the studies that included heart and lung transplant candidates. This may be because exercise training is an established non-pharmacological treatment option for patients with advanced heart[119] or lung[120, 121] diseases and research evidence in this field is still emerging for individuals with advanced kidney[122] and liver[123] diseases awaiting transplantation. Therefore, during the course of their treatment, patients with advanced heart and lung diseases may receive more information about the importance of exercise in the management of their disease compared to patients with liver and kidney diseases and be more likely to accept to participate in these programs.

Despite the large variation in the type of exercises that were offered, no adverse events were reported in any of studies (15/23) that mentioned this outcome. However, and as noted by

Wallen et al.[48], we found that the included studies poorly defined adverse events and failed to elucidate the assessment strategies used for this outcome. This lack of information impacts on the interpretation of the studies' results regarding safety, as it is not clear if the authors omitted the occurrence of adverse events or simply did not observe any. Information about the safety of the exercise intervention is important as many healthcare professionals may not feel confident in prescribing exercise or counseling about physical activity in this population[124, 125] because many SOT candidates are frail[126] and may be very sick in the pre-transplant period. It is important to notice that as part of the transplant list process, patients must have had their risk stratified before starting the exercise interventions so participants in the included studies are a selective population.

2.7.2 EXERCISE CAPACITY

The effects of exercise interventions on maximal or functional exercise capacity were not consistent. While most of the non-RCTs (n=5)[105-107, 109] and pre-post studies (n=7)[75, 110, 113-116] demonstrated improvements in maximal or functional exercise capacity, almost all RCTs studies (4 out of 5)[97, 99, 100, 103] failed to do so when comparing the intervention with the control groups. This result is consistent with the findings of Wallen et al.[48] This finding may reflect the fact that the control groups, in the majority of the RCTs, included some type of exercise (e.g. walking, IMT, exercise with lower aerobic intensity, and other aerobic exercises) which may have promoted an effect on exercise capacity. However, when reviewing the results of maximal exercise capacity within groups (intervention and control) in the two RCTs[99, 100], the results continued to be inconsistent. Even though both studies included an exercise component in the control group, just one[99] showed improvement in both groups. However, for functional exercise capacity, the scenario was the opposite. The lack of difference between groups could be explained by the fact that both the intervention and control groups improved their scores. Of the 4 RCTs[97, 99, 100, 103]

that failed to show a statistically significant difference between groups, three[97, 103, 104] had showed improvements within groups (intervention and control), and one[100] showed improvement (no statistically significant) within the intervention group.

Another explanation could be related to the duration of the interventions. The studies[99, 100] that did not observe a significant difference of maximal exercise capacity, offered an exercise program that lasted 8 and 10 weeks respectively while four[75, 105, 106, 113] out of five studies[75, 105-107, 113] that reported statistically significant improvements in the same outcome offered an exercise program for longer than 10 weeks. This difference suggests that longer programs may be more effective in improving maximal exercise capacity in this patient population. Similarly, for functional exercise capacity, the duration of the intervention might have impacted the results. The studies[75, 97, 99, 100, 103, 117] that showed no improvement in functional exercise capacity offered an intervention of less than 10 weeks of length while all programs[104, 105, 109, 113-115, 118] with an exercise intervention of at least 12 weeks showed a statistically significant improvement in this outcome. Byrd et al.[110] and Kenn et al.[116], both pre-post studies, were exceptions since they showed a statistically significant improvement in functional exercise capacity even though the length of their programs was 4.6 and 5 weeks respectively. However, this hypothesis is difficult to confirm without a meta-analysis.

2.7.3 HRQOL

The majority of the RCTs and non-RCTs included in this review did not show an improvement in HRQoL in the intervention group compared to the control, which is in line with the findings of Wallen et al.[48]. It is not clear why the exercise interventions in this review failed to show an improvement in HRQoL considering that exercise training is supposed to improve physical function which seems to be the aspect that is most affected in their lives[127, 128]. The fact

that the RCTs included an exercise component in the control groups might also have played a role in this lack of significance. Other explanations could be the lack of statistical power to detect differences in HRQoL and the potential poor quality of the exercise programs. With the poor description of the exercise interventions it is difficult to evaluate the quality and appropriateness of the exercise programs included in the studies.

2.7.4 SECONDARY OUTCOMES

Very few studies examined our secondary outcomes of interest. More information on muscle strength, frailty, symptoms of dyspnea, fatigue, anxiety, and depression would have provided us a better idea of the effects of exercise programs beyond exercise capacity. Lately, there has been an increased interest in the evaluation of frailty in SOT candidates[49] since frailty has been shown to be associated with the waiting list time and post-transplant mortality as well as hospital re-admissions[129-132]. In our review, only one[117] study included frailty as an outcome. Singer et al., in a pre-post exercise study of lung transplant candidates included the Short Physical Performance Battery (SPPB) as a surrogate outcome for frailty. The authors found a trend towards improvement in the SPPB score (7 out of 13 patients were able to improve their scores) but no statistically significant improvement was seen. Exercise training can decrease frailty in older adults[133] and individuals with chronic diseases[134-137] and should be considered in future exercise trials in SOT candidates[49].

An important advantage of offering exercise pre-transplant is the potential effect that it may have on post-transplant outcomes[84-92]. We identified only two studies[75, 108] that examined post-transplant outcomes in our systematic review. Mc-Adams et al.[108], in small a pilot pre-post study (n=24) found a decrease in hospital length of stay post-transplant in the intervention group (compared to standard care) in patients waiting for kidney transplantation. Li et al.[75] in a

retrospective study offered a hospital-based exercise to lung and heart-lung transplant candidates and found that improvement in the 6MWT pre-transplant was associated with a decrease in hospital length of stay post-transplant. Although these are promising results, larger trials are needed to confirm the effects of exercise pre-transplant on post-transplant outcomes.

The strengths of our systematic review are the inclusion of studies involving all organ groups and the rigorous methodological process that was used. The main limitations of this systematic review are the methodological heterogeneity of the included studies (particularly in terms of characteristics of exercise interventions and study design), the low methodological quality of the studies, the small number of RCTs and small number of articles in liver and kidney transplant recipients which affects the generalizability of the findings. These factors prevented the authors from conducting a meta-analysis and it also made it difficult to interpret the results related to the effectiveness of the exercise programs in SOT candidates. The included studies also scored poorly on the CERT checklist which evaluates the quality of the reporting of the exercise interventions. The lack of specific information on the characteristics of the training programs leads to difficulties in the replication of the programs by researchers and implementation by clinicians.

Moving forward, more well-conducted RCTs with larger sample size and adequately powered for multiple outcomes are needed in order to establish the effectiveness of exercise programs in SOT candidates. More studies including pancreas, kidney, and liver transplant candidates are also needed. Moreover, the authors should follow the CERT checklist when preparing their manuscripts to ensure a high-quality description of the exercise interventions in order to be reproducible.

In conclusion, our findings suggest that exercise training is safe and acceptable to SOT candidates. The effects on exercise capacity, HRQoL and other outcomes such as muscle strength,

frailty, symptoms of fatigue, dyspnea, anxiety, depression, sleep quality, and post-transplant outcomes remain unclear. This lack of evidence is probably due to the poor methodological quality of the published studies.

2.8 CONCLUSION

In conclusion, our findings suggest that exercise training is safe and acceptable to selective SOT candidates. The effects on exercise capacity, HRQoL and other outcomes such as muscle strength, frailty, symptoms of fatigue, dyspnea, anxiety, depression, sleep quality, and post-transplant outcomes remain unclear. This lack of evidence is probably due to the poor methodological quality of the published studies.

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2.10 AUTHORS CONTRIBUTIONS

Pesce de Souza, F and Janaudis-Ferreira, T: Designed the study; Pesce de Souza, F, Massierer, D, Raje, UA, Tansey, CM: Participated in data collection and analysis; Boruff, J: Performed the literature search; Pesce de Souza, F: Worked on drafting the article; Janaudis-Ferreira, T: Gave critical feedback on the article; Massierer, D and Tansey, CM,: Participated in the revision of the article; Some of the funding was secured by Edith Strauss.

2.11 COMPETING INTERESTS

The authors declare that they have no competing interests that could have affected the outcome of this review.

Chapter 3 - MANUSCRIPT 2: Feasibility, safety, and effectiveness of a home-based pre-habilitation program implemented to individuals awaiting kidney transplantation

3.1 PREFACE TO MANUSCRIPT 2

Regardless of the large number of studies investigating the effectiveness of exercise intervention in chronic kidney disease, results of Manuscript 1 showed an important literature gap. There are a very limited number of studies focusing on exercise for kidney transplant (KT) candidates, and especially that consider a home-based exercise intervention as an option. In order to assess the feasibility, safety, and effectiveness of implementing a home-based pre-habilitation exercise program in this population, that has not been fully investigated, this feasibility study presented in Manuscript 2 was created.

Manuscript 2 was the first study to examine the feasibility and effectiveness of exercise fully delivered as a home-based intervention and implemented exclusively to KT candidates. This manuscript also makes recommendations for the refinement of future iterations of the intervention based on the findings of this study.

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3.3 ABSTRACT

Introduction: Kidney transplantation (KT) is the preferred and most common treatment for end-stage kidney disease. Generally, kidney transplant candidates are frail and exhibit a decrease in physiologic reserve. Exercise training is an evidence-based strategy that improves exercise capacity, muscle strength, and health-related quality of life (HRQoL). There is limited information about home-based exercise programs for individuals awaiting KT. The aim is to assess the feasibility, safety, and effectiveness of implementing a 12-week home-based pre-habilitation exercise program in KT candidates. **Methods**: Primary outcome of interest was feasibility, and the secondary were safety and effectiveness (functional exercise capacity, physical activity, HRQoL, lower-extremity function and frailty). The feasibility study was composed of a home-based intervention that consisted of simple exercises (arm, leg, and walking). **Results:** The eligibility and refusal rate for the study was 75%, and 53.5%, respectively. Four participants out of eight completed the intervention. High satisfaction and good adherence (average of 24.86±12.81 sessions completed) were reported. Three adverse events occurred during the study period. Pre-intervention, the average score for distance walked in the 6MWT was 384.6±140.9 meters, and the daily step average count was 3369±1234 steps. Symptom/problem list, effects of kidney disease, burden of kidney disease, and mental health were either maintained or improved in the post-intervention assessment. Two participants maintained and one improved their lower-extremity function. Of the three participants that completed the post-intervention assessment, two had an improvement on the frailty indicator and one participant maintained the pre-frail status. **Conclusion:** A home-based pre-habilitation exercise program is feasible and safe in KT candidates, and preliminary evidence shows a trend in improvement of HRQoL, lower-extremity function and frail status.

Key words: home-based, pre-habilitation, kidney transplantation.

3.4 INTRODUCTION

End-stage kidney disease (ESKD) affects approximately 2 million people worldwide[138]. Kidney transplantation (KT) is the preferred and most common treatment choice for ESKD both in terms of survival and quality of life[9], and it confers a significant personal benefit to the patient and an economic benefit for society[139].

Individuals with EDKD have reduced health-related quality of life (HRQoL), are commonly frail[140] and present impairments such as muscle wasting[141], reduced cardiopulmonary fitness and physical functioning[142]. These impairments are strongly associated with increases in the risk of delayed graft function, a longer hospital length of stay, early hospital readmission[131, 143, 144], and pre/post-transplant mortality and morbidity[145].

Pre-habilitation is the process of enhancing patient functional capacity prior to surgery with the objective of improving tolerance for the upcoming physiological stressor[146]. Widely used in surgical populations, such as elective abdominal surgery, total knee replacement/arthroplasty, abdominal aortic aneurysm surgery, coronary artery bypass surgery, and colorectal cancer surgery, exercise-based pre-habilitation has been shown to improve patients' level of physical activity and functional exercise capacity as well as contribute to reduce postoperative recovery time and a faster return to functional ability[40-47, 147]. Current evidence supports the benefits of exercise in patients with chronic kidney disease, demonstrating that aerobic and resistance exercises improve aerobic capacity, cardiovascular function, walking capacity, muscle strength and HRQoL[50, 148]. However, the majority of these studies offered an inpatient/outpatient program or exercise training during dialysis, which may be costly, difficult to implement and may not be practical for the patients. Time and travel were also identified as important barriers for KT candidates on the waiting list[98] and additionally outpatient exercise programs on non-dialysis days may be a burden to patient

schedules[122]. Despite the strong evidence concerning the benefits of exercise in people with chronic kidney disease, there is limited information on the feasibility of implementing this type of intervention to individuals awaiting KT.

The main objective of this study was to assess the feasibility and safety of implementing a 12-week home-based pre-habilitation program to KT candidates. The secondary objective was to assess preliminary effectiveness of this intervention on functional exercise capacity, physical activity, HRQoL, lower-extremity function and indicators of frailty in KT candidates. The third objective was to make recommendations for the refinement of future iterations of the intervention based on the findings of this study.

3.5 METHODS

3.5.1 DESIGN

This was a pre-post feasibility study, with quantitative and qualitative assessment.

3.5.2 SETTING, POPULATION & RECRUITMENT STRATEGY

Potential participants (patients who were listed or were in the process of being included on the list for KT at the McGill University Health Centre) were identified by a transplant coordinator. Potential participants were introduced to the research coordinator (FP) and approached at the transplant clinic (one-by-one) or at educational sessions (delivered in a group by the transplant coordinator to educate and prepare kidney transplant candidates for the transplant process). After a brief overview of the study, an eligibility questionnaire was provided. If eligibility was confirmed, and patients were willing to participate in the study, they were given the consent form. On the first in-person visit, any remaining questions related to the consent form were clarified, and pre-intervention assessment (physical assessment, questionnaires), and explanation/demonstration of all exercises that consisted the program were performed.

3.5.3 INCLUSION & EXCLUSION CRITERIA

Inclusion criteria: i) Patients with ESKD who were over the age of 18, classified as pre-frail (1-2 points), frail (3-4 points) or very frail (5 points) in the modified Fried's frailty phenotype score and who were accepted or were in the process of being accepted to enter in the deceased or living donor KT waiting list of the McGill University Health Centre for first-time transplantation or re-transplantation; ii) English or French speakers; iii) Patients willing to give informed consent. We excluded patients who: i) were participating in other research studies; ii) who had any cardiovascular, musculoskeletal (important weakness that made impossible to the patient to perform the exercises proposed in the protocol), mental or respiratory conditions that prevented participation in physical exercises (the surgeons determined whether or not the patient was approved to participate in the exercise program); iii) patients participating in any structured exercise program; iv) patients classified as robust (0 points) on their Fried's frailty phenotype score.

3.5.4 INTERVENTION - DELIVERY STRATEGY & OVERVIEW

The exercises were performed at home, three times per week, on non-dialysis days (if performing hemodialysis). The program lasted for 12 consecutive weeks and included three exercises requiring minimal resources: walking, squats, and push-ups. Information about how to perform the exercises were delivered by the research coordinator, who has a background in Physiotherapy, on the first in-person visit. In addition, participants received a booklet with pictures and explanations on how to perform the exercises, and a diary to note their exercise performance and progression (Appendix 1). The research coordinator conducted weekly phone calls (Appendix 2). These calls used a semi-structured interview to ensure participants' adherence to the exercises, to answer any questions, to gather information about their exercise performance, to solicit their

feedback on the program and if needed to make changes. Moreover, participants were sent a weekly reminder by text message containing the time of the appointment and to provide encouragement and motivation.

3.5.5 INTERVENTION – DESCRIPTION OF THE HOME-BASED PROGRAM

Details/instructions and images about the exercise can be found in Appendix 1.

3.5.5.1 AEROBIC EXERCISE – WALKING PROGRAM

Participants were asked to walk on a treadmill (if available), on the street, or at home. Prior to the exercise intervention participants were asked to wear a Piezo RxD activity monitor for seven consecutive days and keep their normal routine, with the objective of having a pre-intervention daily basis step count measure. After these first seven days, the participants were instructed to wear the activity monitor only when going to perform the walk program. They started the walk with a 5-minutes slow walk (warm-up) and progress to a moderate-intense level (maintaining 12-14 score in the rating of the perceived exertion - Borg scale[149]) until they achieved their step goal.

The progression of the step goal was evaluated weekly during the phone call and was calculated as following: (a) participants who walked $\leq$ 5,000 steps per day in the pre-intervention measure, had their step goal increased by 10% weekly; (b) participants who walked between 5,000 - 8,000 steps per day, had their step goal increased by 5% weekly; (c) those who walked between 8,000 - 10,000 steps per day, had their step goal increased by 2.5% weekly; (d) those walking > 10,000 steps were encouraged to maintain their level of physical activity. If the perceived exertion rate (Borg scale) remained the same or improved during exercise performance, the number of steps was increased; if the perceived exertion rate worsened, no increase was made; if the perceived exertion rate worsened for two weeks in a row, the steps were decreased by the same amount as the increase[150]. When participants forgot to use the rating of perceived exertion (Borg scale), the

level of difficulty of the walk was asked during the weekly phone call. If the participant classified the walk as easy (could have walked more), then the number of steps was increased, and if the participant mentioned any extreme fatigue or difficulty on walking, no increase or a decreased by the same amount as the increase was made. The aim for all participants was to reach 10.000 steps per training day.

An instruction sheet with options and tips to maintain the walking program during fall and winter seasons (seasonal barrier) was attached to the booklet with the objective of keeping participants' daily step count. As a consequence of the self-isolation caused by the COVID-19 pandemic, part of the walking program was modified to be performed exclusively inside their house.

3.5.5.2 RESISTANCE EXERCISE – SQUATS

Participants were instructed to perform squats using a chair as a support. Following the recommendations of the American College of Sports Medicine[151], all participants started the exercises with two sets of ten repetitions, three times per week in non-dialytic days (if applicable). Participants were instructed to start performing the Chair Squat (more support) and advancing to the Touch Squat (less support). Progression of these exercises were gradually achieved by adding sets and/or the number of repetitions of exercises, up to a maximum of 3 sets of 12 repetitions per session. If the maximum number of sets and repetitions were reached by the participant, the number of exercise sessions was increased (number of times per week or per day)[151]. All the progression was tailored to each individual and was done by the researcher coordinator. Participants were instructed to use the modified version of the Borg scale (Category-Ratio)[152], to keep record of their muscle fatigue (legs) before and after the exercise. The Borg scale was used

as an instrument to help the research coordinator determinate the necessity of the progression of the exercise. A 2-3 minutes rest interval was suggested between each set.

3.5.5.3 RESISTANCE EXERCISE – PUSH-UPS

Participants were instructed to perform push-ups in three different ways. All participants started the intervention with the push-up against the wall and were asked to progress to a modified form until they were able to safely perform the full form. The push-up exercises followed the same recommendations as the American College of Sports Medicine[151] and were performed with the same number of sets, repetitions, rest intervals and frequency described above in the Squats exercise. The Borg scale (Category-Ratio) was also used to keep record of their muscle fatigue (arms) before and after the exercise.

3.5.5.4 JUSTIFICATION FOR THE CHOICE OF THE EXERCISE

The choice of number and type of exercises for this study (only three types of exercises: walking, squats and push-ups), was based on the fact that medium to intense exercise can be too aggressive and possibly harmful to patients waiting for surgery and can consume their energetic reserve left[45]. Carli et al.[45] in a RCT examining the effects of a structured pre-habilitation regimen to optimize recovery of functional walking capacity after surgery, reported that their sham group which received a light exercise program (walking and breathing,) had a greater clinical meaningful improvement in walking capacity during the pre-habilitation and post-operative periods, when compared to their bike/strengthening program that was offered to the intervention group. The period of 12 weeks was chosen based on a previous study[153], which was able to show a change in daily steps and metabolic parameters in kidney recipients after a 12 week pedometer-based walking program.

3.5.6 DEMOGRAPHIC INFORMATION

The following information was collected: age, sex, employment status, marital status, education level, body mass index (BMI), the primary cause of renal disease, time since diagnosis, creatinine level, whether the participants are on dialysis or not and if so, when dialysis started, which type of dialysis, the number of days and on which days of the week dialysis occurred. In addition, whether the participant has an arteriovenous fistula or not (if so, since when and in which arm). Finally, whether there is any other intervention (i.e. diet, psychology sessions, etc.) in which participants may have been involved was registered. All information was gathered using a standardized questionnaire (Appendix 3), during the in-person interview, or from a medical chart prior to intervention.

3.5.7 OUTCOME MEASURES

Outcomes measured were performed by the same research coordinator during all phases of the study. Pre-intervention assessment was performed at the Centre for Innovative Medicine at the McGill University Health Centre, and all post-intervention assessments (after 12 weeks) were performed by video and/or phone due to social distancing measures of the COVID-19 pandemic.

3.5.7.1 FEASIBILITY

The primary outcome of this study was feasibility, and it focused on the (a) evaluation of recruitment capability and resulting sample characteristics, (b) evaluation and refinement of data collection procedures and outcome measures, (c) evaluation of the acceptability and suitability of the intervention and study procedures, (d) evaluation of the resources and ability to manage and implement the study and intervention. These topics were based on Orsmond et al.[59] feasibility study guide and modified to fit the purpose of the study. More details on each item and how they were assessed is provided in Appendix 4. In addition to the feasibility outcomes suggested by Orsmond et al.[59] (Appendix 4), we conducted weekly structured phone interviews (Appendix 2)

to establish the feasibility of the intervention and the need for any change to the exercise protocol. These phone interviews included questions about how they felt in general; if they performed the exercises; if they encountered any difficulty in performing the exercises; if they needed to interrupt the exercise for any reason; how they felt after completing the exercise session; if they were motivated to continue the exercises; and if any adverse event occurred. After the 12 weeks of intervention, an acceptability scale adapted from a semantic differential scale[154] (Appendix 5) was applied via phone or email.

3.5.7.2 SAFETY

Safety was assessed weekly by phone, recording the number of adverse events occurred during the time the pre-habilitation exercise program was ongoing. Adverse events were categorized as either "related or unrelated to the intervention". Adverse events that occurred during the assessment or exercise period were categorized as related to the intervention. In addition, adverse events were also considered "related to the intervention" if participants reported any joint pain during the proposed exercises, or severe muscle soreness during the exercises and one or two days after the exercises. Otherwise, all other adverse events were classified as unrelated to the intervention.

3.5.7.3 EFFECTIVENESS

3.5.7.3.1 Functional exercise capacity

The gold standard method to evaluate maximal exercise capacity is the peak oxygen consumption (VO_2 peak) which has been identified as a strong survival predictor in ESKD[155]. However, the cost of obtaining the equipment to measure the VO_2 peak is a barrier faced by many research centers[156]. The 6 minutes walking test (6MWT) has been shown to be a viable and safe alternative to the gold standard test[157-159] and has been shown to be strongly correlated with the

VO_2 peak. It has been widely used in patients with chronic diseases[160-163]. Thus, the 6MWT is a low cost, valid and an excellent sub-maximum effort test that is representative of daily life activities[164], and is easy to perform[165, 166].

We followed the American Thoracic Society (ATS) guidelines for conducting the 6MWT[167]. Briefly, the test was performed in an enclosed, unobstructed corridor of at least 33 meters, with cones positioned to mark a 30-meter path. Patients did two walks with at least 30 minutes of rest between each one. During the test, oral encouragement was done following the ATS recommendations[167]. The best result of the 2 tests was used for analysis (Appendix 6).

As a consequence of the COVID-19 pandemic and social distancing measures, the functional exercise capacity was assessed only in the pre-intervention assessment.

5.7.3.2 Physical activity

To access the level of physical activity, we used a validated[168] activity monitor device (the Piezo RxD). Participants were instructed to wear the device for 7 consecutive days before starting the exercise program (pre-intervention assessment) and also for 7 days after the 12-week intervention (post-intervention assessment). Step counts (average of steps) were analyzed. Although many activity monitors have been used in research, the Piezo Rx device is the most validated instrument in Canada[168], and is the only device approved by Health Canada. The Piezo Rx device is also more accurate at measuring steps compared to other activity monitors. In a study by Colley et al.[169], the Piezo Rx had an overall coefficient of determination value of R2 = 0.99 (P <0.001) compared to the criterion method of manually counting steps.

3.5.7.3.3 Health-related quality of life

Health-related quality of life was measured using the Kidney Disease Quality of Life Short Form version 1.3 (KDQoL-SF) instrument (Appendix 7), a self-report measure developed especially for individuals with kidney disease and those on dialysis[170]. It includes both generic (36 items) and disease-specific (43 items) components for the assessment of HRQOL. The generic part uses the 36-Item Short-form Health Survey (SF-36), a well-known questionnaire of QoL. KDQoL-SF has been validated and is widely used around the world[171-174]. This questionnaire has disease-targeted items, that focus on particular health-related concern such as: Symptom/problems (12 items), Effects of kidney disease on daily life (8 items), Burden of kidney disease (4 items), Work status (2 items), Cognitive function (3 items), Quality of social interaction (3 items), Sexual function (2 items), and Sleep (4 items)[170]. The KDQoL-SF also includes three additional quality of life domains, for instance, Social support (2 items), Dialysis staff encouragement (2 items), and Patient satisfaction (1 item).

3.5.7.3.4 Lower-extremity function

The Short Physical Performance Battery (SPPB) was used to measure overall lower-extremity function. The SPPB is a widely used test battery[175] in which low scores have a high predictive value of disability in Activities of Daily Living (ADLs)[176, 177], loss of mobility[178], hospitalization[179], duration of stay in the hospital[180], admission to nursing facilities[175], and death[181-183].

A detailed description is provided in Appendix 8. The SPPB includes three tests: the 4-meter gait speed, the five timed repetitive chair stands, and a balance test which includes standing in three different positions (Side-by-Side Stand, Semi-Tandem Stand, and Tandem Stand). Each measurement can be scored from 0-4. A score of 4 indicates the highest level of performance and 0 the inability to complete the task. In the end, a summary of all scores was calculated and it

ranged from 0 (the worst performers) to 12 (best performers). The cut-off of ≤ 10 points was used to indicate impairment in lower extremity[184-186], and change of 1 point in the SPPB score was considered the Minimal Clinically Important Difference (MCID)[187].

3.5.7.3.5 Frailty indicator

Frailty indicators were assessed using the modified Fried frailty phenotype[188]. A detailed description of each item is described in Appendix 9.

A phenotype of frailty is identified by the presence of three or more of the following components:

- Weight loss: obtained from the patient;

- Weakness: an assessment based on the handgrip strength measurement (interpretation of results takes into account sex and BMI). The measurement of handgrip strength with dynamometer (Jamar; Hydraulic Hand Dynamometer) was conducted according to standard procedures recommended by the American Society of Hand Therapists (ASHT)[189]. The participants were instructed to sit upright on a height-adjustable chair with their feet supported. The tested arm was positioned on the rest of the chair with, the shoulders slightly abducted (~10°) and neutrally rotated, the elbow in 90° of flexion, the forearm in 0° between pronation and supination, and the wrist in a neutral resting position. The participants were instructed to maintain that position during the completion of the test. Both hands were measured starting with the dominant hand. Three measures of each hand were measured with a rest break of 30 seconds between each attempt. Each hand received a 1 min rest break before proceeding to the next handle size. Participants were asked to squeeze continuously and with their maximum strength for 2–3 s. A verbal statement ("Squeeze as hard as you can!") was made to encourage the person to perform maximally during the tests. The average of three tests was calculated and used in the analysis.

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- Exhaustion: self-reported information based on two questions from the Center for Epidemiological Studies Depression (CES-D) scale[190].

- Slow gait: the 4 meters walk test was used to analyze the walking time. This test was already assessed by the SPPS test, and the same result will be used.

- Low physical activity: energy expenditure weekly rate calculated on the basis of a question from the Minnesota Leisure Time Activity Questionnaire[191, 192] (Interpretation of the results adjusted for sex).

Each indicator can have 0 or 1 as a score, resulting in a total of maximum 5 points, where 0 is being robust, 1-2 pre-frail, 3-4 frail and 5 very frail. For this study, patients were categorized based on the frailty score and changes in each individual indicator were analyzed separately as one estimator of responsiveness of the intervention.

Weakness was not assessed post-intervention due to social distancing measures of the COVID-19 pandemic.

3.5.8 DATA ANALYSIS

As described by Birkett and Day[193], a minimum sample size of 10 participants for a pilot/feasibility study should allow some investigation of the objectives. It is important to highlight that our aim was not to estimate population results, but to just have preliminary data and to anticipate some results for a future pilot-randomized control trial (RCT). A sample of 30 participants was aimed for, and from this total, counting dropouts, we estimated that around 10 participants would enroll until the end of the 12 weeks of intervention for reasons related to the waiting list for transplantation.

Descriptive statistics (proportions, percentages, SD, mean) were used to characterize the sample. Barriers, symptoms, rating of the intervention and complains were described by the

participants and used to report on the feasibility and safety of the intervention. To examine and analyze the effectiveness of the intervention, the observed difference between pre-intervention and post-intervention were presented as raw number, mean, standard deviation and percentage of change.

3.6 RESULTS

3.6.1 PARTICIPANTS CHARACTERISTICS

The demographics and clinical characteristics of the patients are shown in table 1. A total of four participants out of eight had completed the exercise program intervention (Figure 1). In general, the three groups (consented to the study, completed the pre-intervention assessment, and completed the 12 weeks of exercise) were similar in terms of characteristics. Of those kidney transplant candidates who completed the pre-intervention assessment (n=8), 37.5% were female, the mean age was 61.1±13.74 years, 62.5% had diabetes as primary diagnosis, 75% were performing hemodialysis, the average time in dialysis was 2.25±0.9 years, 37.5% were frail and also 37.5% presented a lower-extremity impairment.

3.6.2 FEASIBILITY

No barriers were encountered during the recruitment process. The eligibility rate for the study was 75% (15 eligible /20 who accepted to participate in the study), and the refusal rate for participation considering both recruitment strategies was 53.5% (75% when patients were approached in the educational class and 15 % when approach as done one-on-one at the transplant clinic) (Figure 1). The eligibility criteria were inclusive, and only patients who would probably not benefit from the exercise intervention (e.g. active and robust in the frailty indicator scale) were excluded. Two participants underwent transplantation during the study (weeks 3 and 5) and therefore did not completed the exercise program.

All outcomes were collected as intended during the pre-intervention assessment. The pre-intervention assessment was delivered in one day as planned in the majority of the participants, except for two participants due to their medical condition (too tired to perform the physical tests on same day), and one had a transportation/schedule issue. Seven out of eight participants rated the pre-intervention assessment as "not difficult" to be performed. All participants stated that they would not change any aspect of the assessment process.

The research coordinator experienced some difficulties reaching the participants by phone in order to obtain their weekly feedback and training progression, especially toward the end of the 12 weeks. The main complaint of the participants was that the process of filling out the diary was time-consuming. Three out of seven participants reported difficulty in synchronizing the activity monitor.

Regarding the progression of resistance exercises, most participants were unable to perform the modified form of the push-ups (option 2) and none were able to perform the full form of the push-ups (option 3). The maximum frequency and intensity achieved were three sets of twelve repetitions, 4 times a week. In the walking program, the maximum daily average steps achieved was six thousand steps, and the expected daily average steps ranged from 939 to 7310. One participant in week 10 replaced the walking part of the intervention for cycling (on a stationary bike).

The participants unanimously stated that performing a home-based exercise intervention was a good idea, pleasant, safe, easy, helpful and simple. The adherence was good with an average of 24.86±12.81 sessions completed out of 36 sessions (minimum goal), representing 69% adherence.

Table 1 - Characteristics of participants			
	Consented (n= 11)	**Completed Pre-intervention Assessment (n= 8)**	**Completed 12 weeks of exercise training (n= 4)**
Age *(years) [mean±SD]*	57.45±13.97	61.1±13.74	61.25±6.1
Sex, *n(%)*			
Female	6(54.54)	3(37.5)	1 (25)
Male	5(45.45	5(62.5)	3 (75)
BMI *(kg/m^2)[mean±SD]*	28.68±5.8	28.36±5.73	27.26±5.98
Education level, *n(%)*			
Some high school or less	-	3(37.5)	1(25)
Some college	-	1(12.5)	0(0)
Graduate high school	-	2(25)	1(25)
Graduated college	-	1(12.5)	1(25)
Graduate university	-	1(12.5)	1(25)
Employment status, *n(%)*			
Unemployed	-	1(11.11)	0 (0)
Employed	-	2(22.22)	2(50)
Retired	-	6(66.66)	2(50)
Marital status, *n(%)*			
Single	-	2(25)	0(0)
Married	-	6(75)	4(100)
Type of Dialysis*, n(%)*			
Hemodialysis	7(63.63)	6(75)	2(50)
Peritoneal	3(27.27)	2(25)	2(50)
None	1(9.1)	0(0)	0(0)
Primary Diagnosis*, n(%)*			
Diabetes	7(63.63)	5(62.5)	3(75)
Cancer			
Myeloma	1(9.1)	1(12.5)	0(0)
Renal Carcinoma	1(9.1)	1(12.5)	1(25)
Polycystic kidney disease	1(9.1)	1(12.5)	0(0)
Hypertension	1(9.1)	0(0)	0(0)
Time on dialysis *(years)*	2.09±1.0	2.25±0.9	2.5±1
Creatinine level *(µmol/L)*	767.9±375.6	837.87±422.8	-
Frailty Indicator, %	-	37.5	33
Lower-Extremity Impairment, %	-	25	0

BMI - Body Mass Index
Creatinine level was not measured post-intervention due to the COVID-19 pandemic social distancing measure.
Frailty indicator – participants that scored >3 at the Fried frailty phenotype; Lower-extremity impairment – scores ≤ 10 in the Short Physical Performance Battery

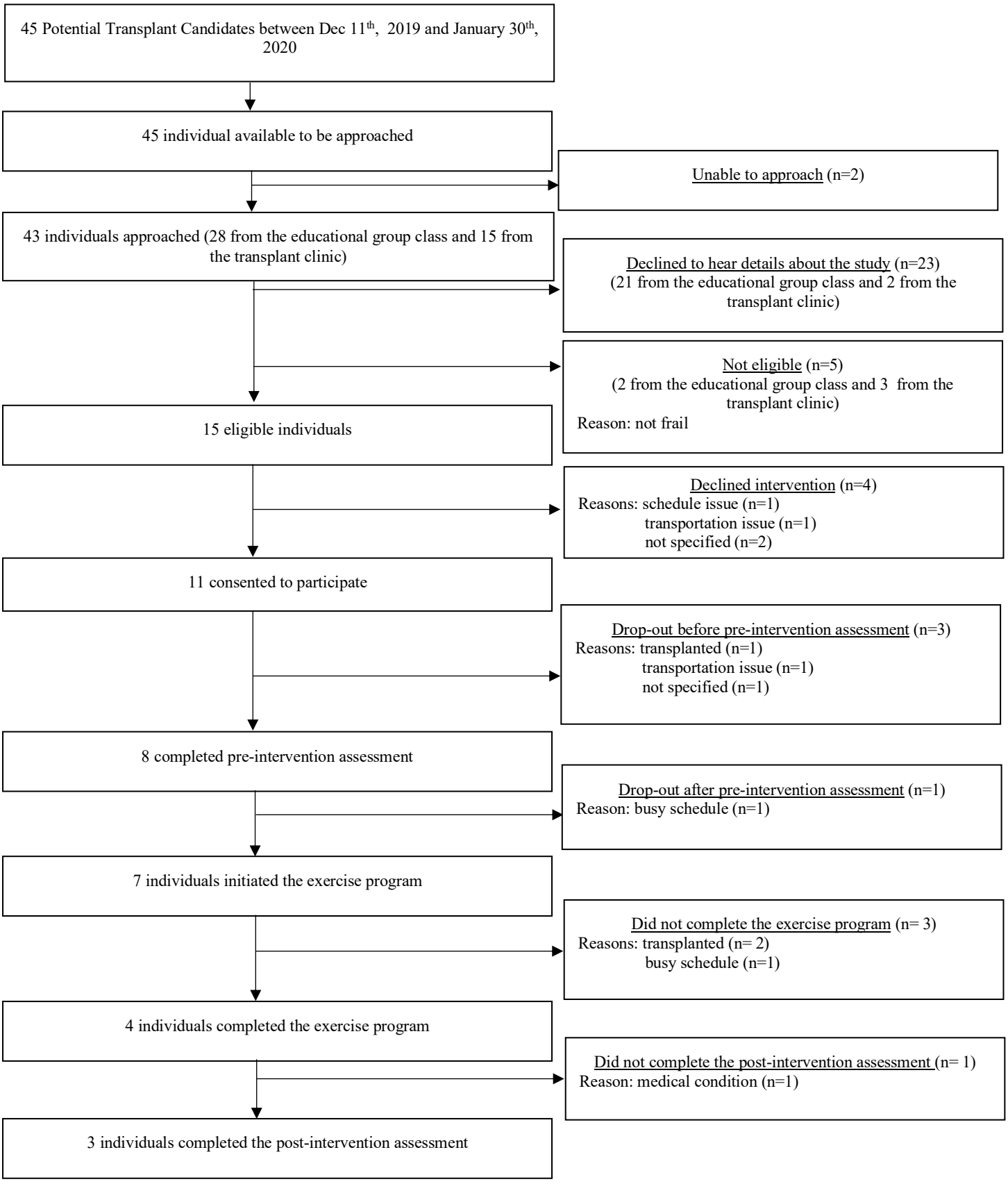

Figure 1 - Flow Chart of patient inclusion during study period

3.6.3 SAFETY

Three adverse events occurred during the study period. The events [knee pain (n=2) and back pain (n=1)] were classified as related to the exercise intervention.

3.6.4 EFFECTIVENESS

3.6.4.1 FUNCTIONAL EXERCISE CAPACITY

The average score in the 6MWT pre-intervention assessment was 384.6±140.9 meters. The percentage of the normative value (calculated using the formula by Hill et al.[194]) ranged from 28% to 108%, with a mean of 58±0.25%. Only one participant had a score higher than their normative value when adjusted for age and gender (Table 2). Post-intervention assessment was not conducted due to the social distancing measures during COVID-19 pandemic.

3.6.4.2 PHYSICAL ACTIVITY

The daily step average count in the pre-intervention assessment was 3369±1234 (Table 3). The pre- and post-intervention daily step average count of the participants that completed the intervention was 3593±204 and 3133±519 respectively; with an average decrease of 460 daily steps (12.8%) (Figure 2).

3.6.4.3 HEALTH-RELATED QUALITY OF LIFE

Compared to the pre-intervention scores, physical health component was the only domain that showed a decrease in the mean score post-intervention (Table 4). The mean score of symptom/problem list, effects of kidney disease, burden of kidney disease and mental health was either maintained or improved in the post-intervention assessment.

3.6.4.4 LOWER-EXTREMITY FUNCTION

The mean score in the SPPB test for all participants in the pre-intervention assessment (n=8) was 10.62±1.50 (Table 5). The three participants that completed the intervention, exhibited

a pre-intervention mean score of 11.66±0.57 and 12±00 post-intervention, representing 2.91% increase. Two participants maintained the same score of 12 and one improved from 11 to 12 points (Figure 3).

3.6.4.5 FRAILTY INDICATOR

In the pre-intervention assessment, the mean total score in the Fried frailty phenotype for all the participants (n=8) was 2.25±1.39 out of 5 points (pre-frail), and for the participants that completed the exercise intervention (n=4) was 2±1 (pre-frail) (Table 6). Of those participants who completed the post-intervention assessment (n=3), two had an improvement on the frailty indicator (pre-frail to non-frail, and frail to non-frail) and one participant maintained the pre-frail status when compared to pre-intervention assessment. The classification of frailty post-intervention was based on the assumption that the weakness score would be equal to zero (not assessed post-intervention due to social distancing measures during the COVID-19 pandemic).

Table 2 - 6MWT values pre-intervention

Participant	Distance Walked pre-intervention (meters)	% of Normative Value
1	414	49%
2	496	68%
3	454	64%
4	368	55%
5*	575	108%
6	180	30%
7	410	65%
8*	180	28%
Mean±SD	384.6±140.9	58±0.25

*Transplanted before completing the intervention
The % of normative value was adjusted to age and gender using the formula by Hill et al.[194]
Post-intervention assessment was not performed due to social distancing measures of the COVID-19 pandemic.

Table 3- Changes in Physical Activity (daily average step counts)

Participant	Pre-intervention (n=7)	Post-intervention (n=2)	Change (%)	Comment
1	4834	-	-	Drop-out before 12 weeks
2	3738	3501	-237(-6.34)	
3	3449	2766	-683(-19.80)	
4	2197	-	-	Lost the activity monitor
5	4807	-	-	Transplanted before completing the intervention
6	1556	-	-	Did not complete the PA post-intervention assessment
7	-	-	-	Drop-out before completing the PA pre-intervention assessment
8	3004	-	-	Transplanted before completing the intervention
Mean±SD	3369±1234	3133±519	-460(-12.8)†	

† Difference of change between pre- and post-intervention assessment only including participants that completed the intervention.

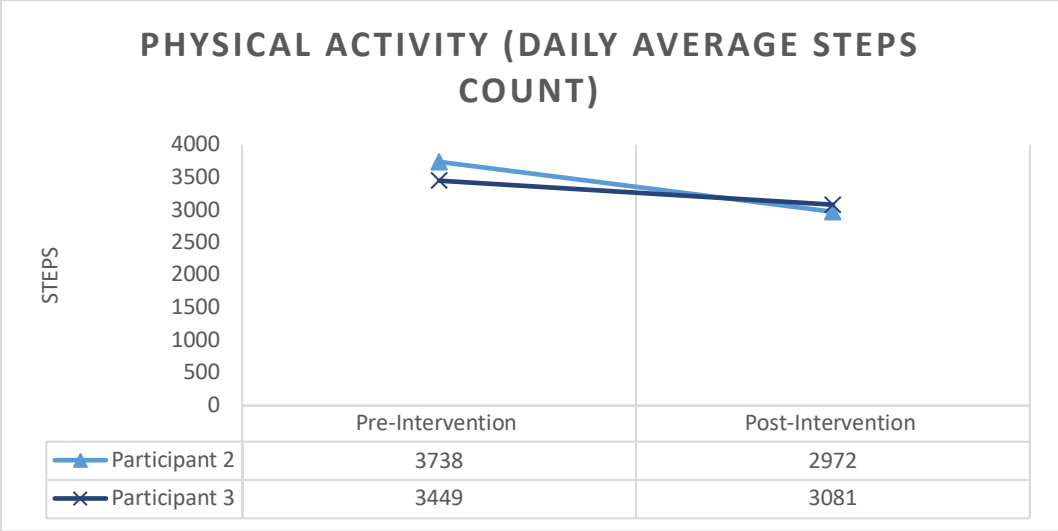

Figure 2 - Comparison of daily step count of the participants that completed the exercise intervention

Table 4 - Changes in the KDQOL

Participant	Symptom/ problem list (SPMD)			Effects of kidney disease (EKD)			Burden of kidney disease (BKD)			Physical Health Composite (PCS)			Mental Health Composite (MCS)		
	Pre-Intervention	Post-Intervention	Change (%)	Pre-Intervention	Post-Intervention	Change (%)	Pre-Intervention	Post-Intervention	Change (%)	Pre-Intervention	Post-Intervention	Change (%)	Pre-Intervention	Post-Intervention	Change (%)
1	100	-	-	100	-	-	37.5	-	-	46.4	-	-	41.8	-	-
2	97.9	93.7	-4.2(-4.2)	84.3	84.3	0(0)	50	43.7	-6.3(-12.6)	42.2	41.3	-0.9(-2.1)	62.2	53.6	-8.6(-13.8)
3	91.6	89.5	-2.1(-2.2)	90.6	75	-15.6(-17.2)	12.5	62.5	+50(+400)	55.5	36.5	-19(-34.2)	51.8	58.6	+6.9(+13.1)
4	70.8	83.3	+12.5(+17.6)	15.6	31.2	+15.6(+100)	0	6.25	+6.25(+100)	51.7	43.4	-8.3(-16.0)	41.1	51.7	+10.6(+25.7)
5*	91.6	-	-	81.2	-	-	75	-	-	46.7	-	-	57.44	-	-
6	79.1	-	-	90.6	-	-	100	-	-	35.2	-	-	59.7	-	-
7	62.5	-	-	31.2	-	-	43.7	-	-	32.36	-	-	32.1	-	-
8*	72.92	-	-	46.8	-	-	25	-	-	32.7	-	-	63.2	-	-
Mean±SD	83.30±13.85	88.83±5.23	+2.07(+2.89)†	67.53±31.69	63.5±28.35	0 (0)†	42.96±32.63	37.48±28.63	+16.65 (+79.93)†	42.84±8.76	40.4±3.53	-9.4 (-18.87)†	52.16±11.53	54.63±3.56	+2.93(+5.66)†

SPMD - Symptom/problem list, EKD - Effects of kidney disease, BKD - Burden of kidney disease, PCS - Physical Health Composite, MCS – Mental Health Composite,
*Transplanted before completing the intervention, † Difference of change between pre- and post-intervention assessment only including the three participants that completed the post-intervention assessment.
Colour: green – increase, yellow – no change, red – decrease from pre-intervention assessment
KDQOL scores range from 0 to 100 in each domain. The higher the score the better is the HRQoL.
PCS score close to 30 is suggestive of extremely poor overall health[(195)].
SPMD score of 70 or > is suggestive of relative low symptom burden[(195)].

Table 5 - Changes in SPPB score

Participant	Gait Speed		Balance		Chair Stand		Total score		
	Pre-Intervention	Post-intervention	Pre-Intervention	Post-intervention	Pre-Intervention	Post-intervention	Pre-Intervention	Post-intervention	Change(%)
1	4	-	3	-	2	-	9	-	-
2	4	4	4	4	3	4	11	12	+1(9)
3	4	4	4	4	4	4	12	12	0 (0)
4	4	4	4	4	4	4	12	12	0 (0)
5*	4	-	3	-	4	-	11	-	-
6	4	-	4	-	4	-	12	-	-
7	3	-	3	-	4	-	10	-	-
8*	4	-	2	-	2	-	8	-	-
Mean±SD	3.87±0.35	4±0	3.37±0.74	4±0	3.37±0.91	4±0	10.62±1.50	12±0	+0.34 (+2.91)†

*Transplanted before completing the intervention. † Difference of change between pre- and post-intervention assessment only including participants that completed the intervention.

SPPB Maximum score of 4 in each section, with a total of maximum 12 points.

No change or increase are considered a positive effect.

Scores ≤ 10 indicates impairment in lower extremity[184-186]

MCID of 1.0 [187].

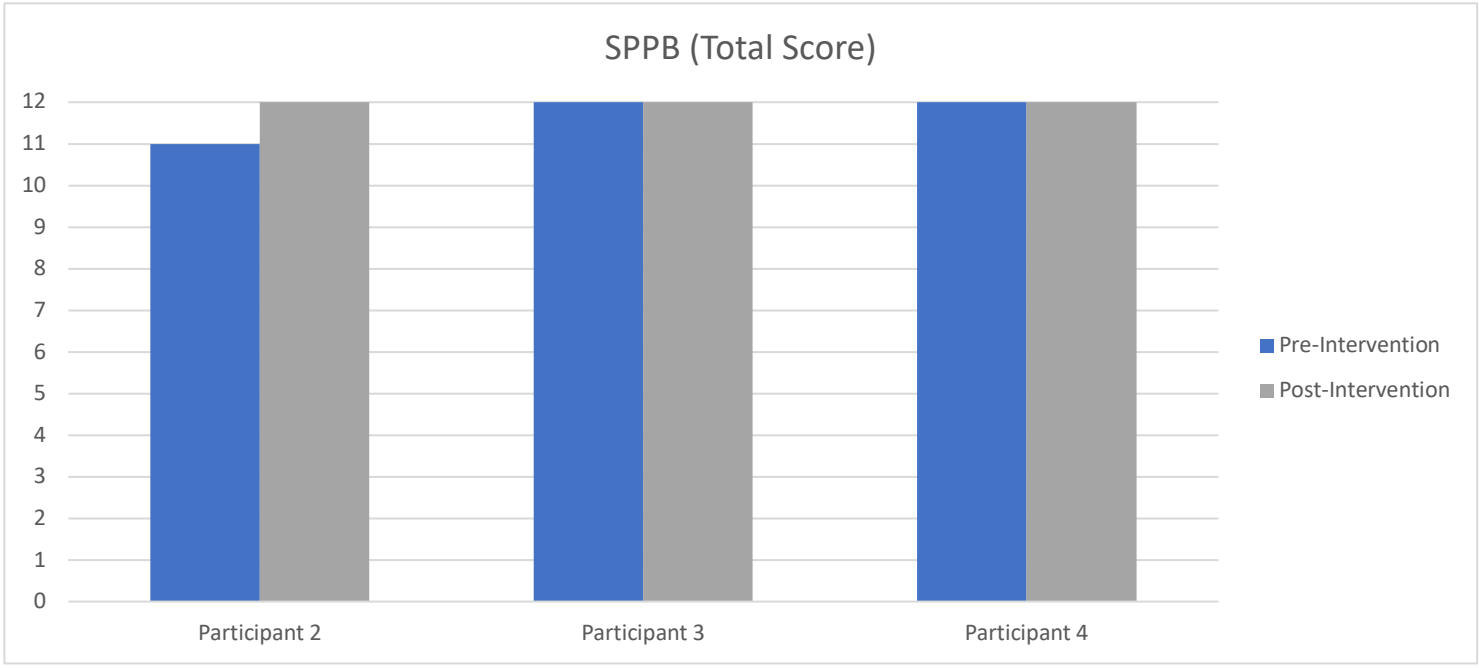

Figure 3 - Comparison Short Physical Performance Battery total score of participants that completed the exercise intervention

Table 6 - Change in frailty indicators score (Fried frailty phenotype)

Participant	Weakness		Weight Loss		Exhaustion		PA's Level		Gait Speed		Total Score	
	Pre-Intervention	Post-Intervention	Pre-Intervention	Post-Intervention	Pre-Intervention	Post-Intervention	Pre-Intervention	Post-Intervention	Pre-Intervention	Post-Intervention	Pre-Intervention	Post-Intervention
1	0	-	1	-	1	-	1	-	0	-	3/5 Frail	-
2	1	-	0	0	0	1	1	0	0	0	2/5 Pre-frail	1/4 Pre-frail
3	0	-	0	0	0	0	1	0	0	0	1/5 Pre-frail	0/4 Non-frail
4	1	-	0	0	1	0	1	0	0	0	3/5 Frail	0/4 Non-frail
5*	0	-	0	-	1	-	0	-	0	-	1/5 Pre-frail	-
6	0	-	0	-	0	-	1	-	0	-	1/5 Pre-frail	-
7	1	-	1	-	1	-	1	-	1	-	5/5 Frail	-
8*	1	-	0	-	1	-	0	-	1	-	2/5 Pre-frail	-
Mean± SD											2.25±1.39	0.3±0.57

Observation: Weakness was not assessed in the post-intervention due to social distancing measures of the COVID-19 pandemic. For this reason, the post-intervention score was out of 4 points and not 5. The classification of frailty in the post-intervention was based on the assumption that there was no impairment (score 0) on weakness.
Legend: 0-no for impairment, 1-yes for impairment, *Transplanted before completing the intervention.
Total score: non-frail (score 0), pre-frail (score 1–2) and frail (score 3–5).

3.7 DISCUSSION

To our knowledge, this is the first study to assess the feasibility and safety of implementing a home-based pre-habilitation exercise program for kidney transplant candidates. Previous studies[108, 196] including this population, delivered the exercise intervention in an out-patient supervised setting and in-patient with the addition of home-exercises.

3.7.1 FEASIBILITY AND SAFETY

When considering the sample studied, our population characteristics were in line with previous studies[108, 196] of KT candidates in terms of age, BMI, sex, and time in dialysis. Our study had a very high eligibility rate (75%), demonstrating that the eligibility criteria were inclusive. However, we observed a high refusal rate (53%), The refusal rate was higher (75% vs 15%) when the recruitment was done in a group setting (educational classes pre-transplant), indicating that the optimal approach to maximize acceptance is using a one-on-one strategy (e.g. recruit from the transplant clinic). The most common reasons for declining participation were transportation issues to attend the assessment sessions and lack of time to perform the exercises and/or attend the assessment sessions. Patients who declined participation reported that hemodialysis (3 times per week) and doctor's appointments (especially when they were in the process to be listed for transplantation) took up most of their time.

We observed good adherence, with an average of 69% (24.86 of 36 sessions) of the intervention completed and a high acceptability of the exercise program among patients who completed the 12-week intervention. Even though our study had a small sample size, these initial findings suggest that delivering the exercise program at home might be a good strategy to reduce the well-known barriers of exercise interventions in people with chronic diseases, such as transportation limitations and lack of time. As reported in previous studies in CKD[197-199], phone

calls with feedback and encouragement are key components to achieve a high adherence rate, which was also found to be a successful strategy in our study.

We encountered difficulty in progressing the push-up exercises, however, patients were able to correctly perform option 1 (push-up against the wall) and the progression was made by increasing the number of sets and repetitions.

Two participants underwent transplantation during the course of our study (week 3 and week 5 of the intervention), which brings into question the optimal length of our intervention. Recently, our group performed a systematic review [200] which demonstrated that the duration of the exercise interventions in KT candidates varies between 8 and 10 weeks. For other organs, the intervention duration varies from 3-12 weeks (lung), 4-24 weeks (heart), and 12 weeks (liver), confirming the lack of consensus on the optimal length for exercise training in transplant candidates. Lorenz et al.[196] concluded that an 8-week exercise intervention was optimal to promote improvements to their 21 patients (KT candidates and CKD patients). Offering an intervention during the entire waitlist period would be ideal but perhaps not as feasible. This has not been considered in any of the studies in KT candidates but would provide a platform for constant follow up and assessment post-transplant.

Three patients reported adverse events [knee (n=2) and back pain (n=1)] which were related to musculoskeletal issues. Previous studies[108, 196] showed that exercise interventions are safe for KT candidates. The interventions in these studies were delivered in an outpatient context, where patients were supervised by healthcare professionals during the performance of the exercise program. In our home-based program, we only offered one in-person session to explain the exercises, and these minor adverse events may have occurred because patients were performing the exercises incorrectly. To avoid these musculoskeletal issues, more than one supervised session

(in-person or by videocall) is strongly recommended to ensure proper performance of the exercises.

3.7.2 EFFECTIVENESS

We observed that the mean distance walked in the 6MWT of our eight participants in the pre-intervention assessment was 58% of the predictive value, demonstrating a strong impairment in their functional exercise capacity. This is concerning as shorter distances walked in the 6MWT represents a greater probability of death in ESKD patients[201]. Unfortunately, due to the social distancing measures of the COVID-19 pandemic, we were unable to perform the 6MWT post-intervention.

Comparing our results to studies that evaluated hemodialysis patients, our patients had lower physical activity levels pre-intervention when compared to other populations[201, 202], averaging at 100 steps less. We also identified a decline in the mean step count in the two participants who completed the assessment of the physical activity post-intervention, in comparison to pre-intervention values. This result can be explained by the fact that participants had a considerable reduction in following the walking program when the COVID-19 outbreak started (March 2020), negatively impacting their physical activity routine. However, all four participants that finished the 12-week of intervention had their step goal higher than the pre-intervention value before the COVID-19 outbreak occurred. In a previous study, McAdams-DeMarco et al.[108] showed that exercise interventions pre-transplant had a positive impact on physical activity levels in KT candidates.

We observed a positive mean change in the symptom/problem list, burden of kidney disease, and MCS domains of the KDQoL-SF questionnaire. These results are in line with the findings of Katherine et al. which showed improvement in burden of kidney disease, effect of

disease, and MCS domains in hemodialysis patients who completed an exercise intervention[203]. Our population presented lower scores pre-intervention in the burden of the disease, and effect of the disease domains, and higher scores on symptoms/problem list, MCS and PCS domains than other studies in hemodialysis patients[203-205]. It is still not clear why our exercise intervention failed to show an improvement in physical function, considering that this domain is the most affected aspect in their lives, and the most likely to improve with exercise training[206].

In terms of lower-extremity function (measured by the SPPB), in the pre-intervention assessment, two out of three participants scored 12 points (the maximum), suggesting that these patients might not present lower-extremity impairments or that this tool might not be sensitive enough to detect the impairments in this specific population (ceiling effect). In line with other studies, our findings demonstrated that the majority of CKD patients do not present with severe lower extremity function (scores <10) when measured by the SPPB [207-209]. We observed that all three patients who had their post-intervention score assessed, either maintained or improved their scores by 1 point, which is the minimal clinically important difference. Our findings align well with Lorenz et al.[196], where they showed a significant increase on SPPB score after the exercise intervention in kidney transplant candidates. Due to the small sample size, future studies are needed to better understand the utilization of this tool in this specific population.

In terms of frailty status in the patients who completed the post-intervention assessment (n=3), we observed a positive change in two patients (pre-frail to non-frail and frail to non-frail), and a maintenance of pre-frailty status in the third patient. This demonstrates that our intervention was able to either maintain or improve frailty status in KT candidates. This finding is important as frailty is correlated to higher chances of being removed from the transplant waiting list and to higher mortality rates while on the waiting list[210].

3.7.3. STRENGTHS AND LIMITATIONS

The main strengths of this study were the comprehensive assessment of the feasibility of conducting the study and delivering the intervention, appropriate eligibility criteria and the high acceptance of the exercise program. Limitations of the study include high refusal rate, low completion rates and the lack of post-transplant outcomes. To address the high refusal rate, a one-on-one recruitment approach should be considered for future studies. Informing patients about the importance of exercise in the pre-transplant education sessions might also improve the acceptance rate for exercise interventions in kidney transplant candidates but approaching then individually after the education session may improve the acceptance rate. Performing the pre- and post-intervention assessments via video conferencing call and/or scheduling the assessments near the patient's medical appointments would address the reasons for refusal and loss of follow-up. For future trials, delivering an exercise intervention for the duration of their time on the waiting list and setting shorter assessment time points, (e.g. every 4 weeks) would be a better strategy to decrease the loss of follow-up. Another approach could be to deliver a shorter intervention (e.g. 8 weeks) and promote a maintenance program after this period. The difficulty in progressing the push-up exercise could be addressed in future studies with the addition of another version that is easier to be performed, for instance, inclined push-up using a chair and knee support before progressing to the modified version (only knee support). Considering that the main goal of exercise-based pre-habilitation is to improve patients' quality of life and physical function pre-transplant as well as optimize recovery post-transplant, inclusion of post-transplant outcomes would have been of great value. However, the focus of this study was on the feasibility of the intervention and conducting the research study rather than on the effectiveness of the intervention. Lastly, the COVID-19 pandemic affected the data collection process, preventing us from

conducting important post-intervention measures such as the 6MWT and the handgrip strength test. The pandemic also contributed to a significant reduction in the walking program performance, which may have affected the results of this study. Nevertheless, we were able to observe a trend in improving most of the outcomes, ultimately providing a foundation and guidance for future studies in this field of research.

3.8 CONCLUSION

In conclusion, this feasibility study suggests that a home-based pre-habilitation exercise program is feasible and safe in KT candidates. This study also suggests that exercise intervention may be effective in improving HRQoL, lower extremity function and frail status, however, this should be evaluated in deep in future studies. The effectiveness of the home-based pre-habilitation exercise program on functional exercise capacity and physical activity levels is also unclear. Our findings provide guidance and support for future pre-habilitation studies for KT candidates which could include post-transplant outcomes.

3.9 ACKNOWLEDGEMENT

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3.10 AUTHORS CONTRIBUTIONS

FPS: Designing the study, writing and researching protocol, creation of data extraction forms, data collection and extraction, interpreting the data, data analysis, table and figure creation, writing and revision of the manuscript. DM: Assisting in the data collection process, providing critical revisions that were important for the intellectual content of the project and manuscript. JT,

FC, and SP: Providing feedback on the study design and protocol. NM, JES, and JFJ: Providing feedback on the study design, protocol, and critical revisions that were important for the intellectual content. TJF: Conceiving and designing the study, interpreting the data, assisting with drafting the manuscript, providing critical revisions that were important for the intellectual content, and approving the final version of the manuscript. TJF is the senior author and guarantor of this study.

3.11 COMPETING INTERESTS

The authors declare that they have no competing interests that could have affected the outcome of this review.

CHAPTER 4 - SUMMARY, DISCUSSION AND CONCLUSION

4.1 SUMMARY OF FINDINGS

This thesis sought to: 1) synthesize evidence on safety, acceptability, and effectiveness of exercise interventions in solid organ transplant candidates (SOT); 2) generate preliminary results on the feasibility of implementing a home-based exercise program to patients waiting for kidney transplantation (KT), and 3) provide recommendations to improve the field of exercise prescription in SOT.

Regarding the first objective of this thesis, the first manuscript presented a comprehensive overview of the evidence for exercise interventions in SOT candidates and highlighted the gaps that should be addressed in future research. Exercise interventions were found to be safe and acceptable by SOT candidates. While most randomized controlled trials (RCTs) did not report significant effects of exercise training on health-related quality of life (HRQoL) and exercise capacity likely because most of these RCTs included a control group that offered an exercise training, there were positive results in studies using other designs. In these studies, an increase in maximal and functional exercise capacity post-intervention was reported (measured by VO_{2peak} and 6-minute walking distance, respectively), however, few studies showed improvement in HRQoL.

Manuscript 2 addressed the second objective of this thesis and drew upon what was concluded in manuscript 1, that more evidence for exercise interventions in KT candidates was needed. Manuscript 2 generated promising results concerning the feasibility of implementing a

12-week home-based exercise program to KT candidates. The process of recruitment and pre-intervention assessment were found to be in general successful, and few barriers were encountered. The inclusion criteria were considered appropriate and the program had good adherence and high acceptance rate. Three musculoskeletal adverse events occurred, and they were mainly related to inappropriate ways of performing the prescribed exercises. There were some indications that the exercise intervention may improve HRQoL, lower-extremity function, and change frail status of the patients. However, the effectiveness of the exercise intervention in improving functional exercise capacity could not be evaluated and the effectiveness on physical activity levels is still unclear.

The third objective of this thesis was to provide recommendations to improve the field of exercise prescription in SOT. Both the first and second manuscripts contributed to identifying barriers and gaps in the literature as well as providing recommendations on how they should be addressed. These recommendations are described in detail in the "recommendations for future research" section. An overall summary of the thesis findings can be found in Table 1.

Table 1 – Summary of the thesis findings	
Objectives	**Findings**
Manuscript 1	
Determine the acceptance and safety of exercise interventions in SOT candidates	Acceptance ranged from 16% to 100% with a median of 97%. The interventions were safe, with no adverse events occurring.
Determine the effects of exercise interventions on exercise capacity and HRQoL in SOT candidates	Effects of exercise training on exercise capacity and HRQoL are still unclear mainly due to the lack of significant findings among RCTs.
Determine the effects of exercise interventions on muscle strength (respiratory, lower and upper limb), frailty, symptoms of fatigue and dyspnea, anxiety, depression, sleep quality and post-transplant outcomes in SOT candidates	There was not enough information to determine the effects of exercise intervention on these outcomes. Most of the studies included only heart and lung transplant candidates.
Manuscript 2	
Assess the feasibility and safety of implementing a 12-week home-based pre-habilitation program in KT candidates	The 12-week home-based exercise intervention was feasible, had a high eligibility rate (75%) and patients accepted the program. Adjustments to the protocol (e.g. additional supervised sessions) will be needed to ensure that patients can perform the exercises correctly and in a safe manner.
Assess the effectiveness of this intervention on functional exercise capacity, physical activity, HRQoL, lower-extremity function and indicators of frailty in KT candidates	There was preliminary evidence showing a trend in improvement in HRQoL, lower-extremity function and frail status. Functional exercise capacity could not be evaluated, and it is still not entirely clear if a 12-week exercise intervention is effective in improving physical activity levels in KT candidates.
Make recommendations for the refinement of future iterations of the intervention based on the findings of this study	Addition of supervised sessions in the beginning of the program to ensure that patients perform the exercises correctly or supervision by video; aerobic and resistance exercise should be part of the exercise intervention with a minimum frequency of three times a week; the exercise intervention should be tailored to each patient's need ; the progression of the exercise should be done carefully and slowly, keeping in mind the patient's limitations.
Legend: SOT - solid organ transplant, HRQoL - health-related quality of life, RCT – randomized control trial, KT- kidney transplant	

4.2 DISCUSSION

The results of this thesis contributed to the body of knowledge in the field of exercise-based pre-habilitation in SOT candidates by: a) demonstrating that exercise intervention in SOT candidates are safe, acceptable, and feasible to be implemented; b) showing promising improvements in maximum and functional exercise capacity, HRQoL, frailty indicators and lower-extremity function post-exercise intervention; c) bringing to light points to be addressed in future studies.

Despite the variety in the type of exercise training in SOT candidates, the exercise interventions, in general, were found to be safe, acceptable, and feasible for implementation. The lack of studies reporting on adverse events, highlight the need for better quality in reporting this outcome. With the implementation of home-based exercise programs, safety is the main concern and in-person sessions prior to starting the unsupervised interventions at home or the use of video calls to supervise the exercise training is strongly recommended to reduce the number of possible adverse events and assure the quality of the exercise performance. The high acceptance rate and positive feedback on the exercises training indicate that exercise interventions are feasible and should be implemented in KT candidates.

This thesis demonstrated a positive trend towards improvement in outcomes such as HRQoL, maximal and functional exercise capacity, frailty, and lower-extremity function in SOT candidates. The majority of the studies in SOT candidates delivered a mix of aerobic exercise and resistance training at least three times a week and showed improvements in these outcomes especially in studies featuring a pre-post design. Among the RCTs, the interventions did not show difference between groups, mainly due to the comparison group that were often also offered an exercise intervention, showing once more that any exercise intervention brings benefit to the patient.

The ultimate goal of exercise pre-rehabilitation in this population is to improve patients' physical fitness pre-transplant and enhance their recovery after transplantation. However, studies often do not include outcomes related to the post-transplant phase, probably due to the challenges of offering an exercise intervention for the time of the waiting list, which can be extensive. In addition, frailty, symptoms of fatigue and dyspnea, anxiety, depression, and sleep quality are important outcomes that are related to general health and prognosis but are not often explored in studies with SOT candidates.

The limited number of studies in certain organ groups (e.g. pancreas, kidney, and liver candidates), contributed negatively to the understanding of the effectiveness of the exercise interventions in SOT candidates. Transplant candidates have similar impairments independent of the organ group in question, however, it is still not clear if all patients have the same response to exercise interventions, and if there is a need to tailor and address some specific impairments that each organ group might have.

The optimal exercise intervention is often debated in the area of pre-habilitation. The length of the intervention is an important challenge especially in SOT candidates; the waiting list period varies by transplant center and organ type, and a shortened intervention might guarantee the completion of the exercise program before transplantation. However, a short exercise intervention might not be enough to bring benefits to patients. Ideally, the exercise should be delivered during the entire period that the patient is waiting for transplantation, but this might not be appropriate in a hospital-based setting. Home-based exercise intervention serves as a potential strategy to address this problem, which should be explored more fully.

4.3 RECOMMENDATION FOR FUTURE RESEARCH

Both manuscripts provided a wealth of information for researchers to advance this field. Manuscript 1 summarized evidence for exercise interventions in SOT candidates and identified gaps in the literature. Recommendations for future research that arose from this work were: 1) more studies that provide higher levels of evidence (e.g. RCTs); 2) larger sample size are needed; 3) more studies that include other organ groups (e.g. pancreas, kidney, and liver); 4) better quality reporting of exercise intervention to facilitate knowledge translation to clinical practice; 5) the prioritization of outcomes, such as, frailty, symptoms of fatigue, dyspnea, anxiety, depression, and sleep quality for better understanding of the large-scale effects of exercise intervention; 6) the inclusion of post-transplant outcomes (e.g. hospital length of stay, intensive care unit length of stay, time on mechanical ventilation, allograft function and mortality) to determine the potential effects of pre-habilitation longitudinally; 7) a clear description of the classification and report of adverse events, especially in unsupervised interventions to provide reliable information on safety. The recommendations that arose from Manuscript 2 were: 1) supervision of the home-based exercise by video or addition of supervised sessions in the beginning of the program to ensure that patients perform the exercises correctly; 2) aerobic and resistance exercises should be part of the exercise intervention; 3) outcome measures should be carefully selected to avoid ceiling effect; 4) planning of remote assessment to avoid issues in case of future pandemics; 5) consideration of a shorter intervention (e.g. 8 weeks) followed by a maintenance component.

4.4 CONCLUSION

Exercise interventions are mainly safe, acceptable, and feasible to be implemented into practice in the pre-transplant phase. Initial evidence suggests improvement in exercise capacity, HRQoL, frailty status and lower-extremity function in KT candidates.

CHAPTER 5 - BIBLIOGRAPHY

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CHAPTER 6 - APPENDICES

6.1 APPENDIX 1- HOME-BASED PRE-HABILITATION PROGRAM

Contact
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Home-based pre-habilitation Program

EXERCISE PROGRAM

WALKING PROGRAM

+

RESISTANCE EXERCISES

PUSH-UPS + SQUATS

Where: At home

How often: 3 times per weeks

Any day of the week? On non-dialytic day /can be in consecutive days or not

EXERCISE GUIDE

General Instructions

- Perform the exercises 3 times per week ONLY on non-dialytic days

- Choose a time during the day when you usually feel good to do your exercise program.

- Do not perform exercises on an empty stomach, immediately after a meal or just before going to bed.

- These exercises can be done in one session or in many sessions throughout the day, according to your tolerance.

- Plan enough time for a warm-up before the exercises and a cool down after you have finished the exercises.

- If possible, always have a bottle of water with you. Keep yourself hydrated.

Emergency plan / Symptoms of exercise intolerance

Always pay attention to the signs of your body during all day (not just when performing the exercise

Specially: Significant respiratory distress, Visual problems, Extreme fatigue, Dizziness / Vertigo, Nausea / Vomiting, Whiteness, Cramps, and Palpitations

Remember

- It is important to lower the intensity of exercise at the onset of even **ONE** of the symptoms listed above.
  - For the walking program: reduce the pace of walking or take a break.
  - For squats and push-ups exercises: take a pause (even if in the middle of the set)
- **If the symptoms do not disappear** despite the decrease in intensity: **Stop the activity totally** and rest until the symptoms are **completely** gone.
- **If any of these symptoms recurs frequently: Consult the person responsible (research team)** to adjust your exercise program.
- **If your symptoms (even during rest) do not get better or are getting worse** consider calling your family doctor or even going to the ER.
- **If you feel that you are in extreme dangerous** don't hesitate to call 911 immediately.

REPORT ANY SYMPTOM OR CHANGE IN THE EXERCISE PROGRAM (PAUSES FOR EXAMPLE) TO THE RESEARCH TEAM IN OUR WEEKLY PHONE CALL.

WALKING PROGRAM

PEDOMETER - PIEZO

FIRST WEEK:
- WEAR THE DEVICE DURING ALL DAY (STARTING WHEN YOU WAKE UP AND FINISHING WHEN YOU GO TO BED) AND KEEP DOING YOUR NORMAL ACTIVITIES
- DO NOT START TO DO THE PUSH-UP AND SQUATS
- **CAUTION !!!!!!** THE DEVICE IS **NOT** WATERPROOF, SO YOU NEED TO TAKE IT OUT TO TAKE A SHOWER FOR EXAMPLE

SECOND WEEK UNTIL THE END OF THE PROGRAM:
- WEAR THE DEVICE ONLY AT THE TIME THAT YOU PREPARED TO PERFORM THE WALKING PROGRAM
- TAKE OUT THE DEVICE WHEN YOU FINISH THE WALK (WHEN YOU ACHIEVE YOUR STEP GOAL OR WHEN YOU CAN'T WALK ANYMORE)
- WHEN YOU FINISH YOUR WALK PROGRAM, LEAVE THE DEVICE IN A NON-MOVING SURFACE (IN A DRAWER, ON A TABLE), AND NEVER IN A MOVING SURFACE (IN A BACKPACK OR INSIDE A CAR)

HOW TO SYNCHRONIZE YOUR PEDOMETER:
- DOWNLOAD THE APP "PIEZO"
- TURN ON THE BLUETOOTH
- OPEN THE APP "PIEZO"
- PRESS THE  BUTTON (THE LAST ON THE RIGHT) UNTIL THE NUMBER OF THE DEVICE APPEARS ON YOUR PHONE SCREEN (5 TO 10 SECOND)

WHEN TO SYNCHRONIZE YOUR PEDOMETER:

- WEEKLY (AFTER YOU COMPLETED THE 3 DAYS OF EXERCISE)

WALKING PROGRAM – PEDOMETER

Baseline – First Week

Record your daily steps. At the end of the week, add up your steps for the 7 days and divide by 7 to get a daily step average.

Date started: __/__/__							
	Sun	Mon	Tu	Wed	Thu	Fri	Sat
Number of Steps							

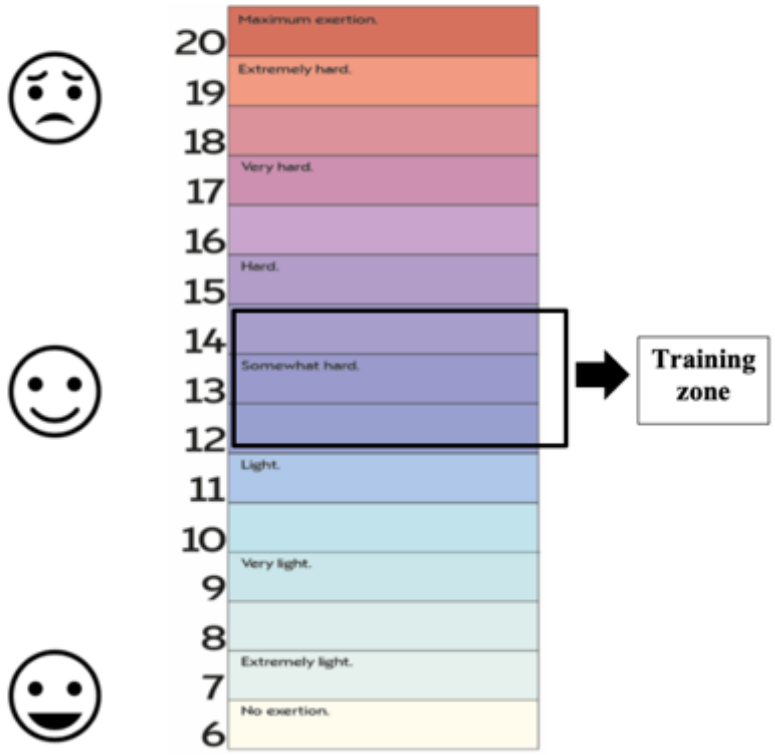
Total Steps for Week 1: _____ ÷ 7 = _____ Daily Step Average/Baseline

BORG – RATING OF PERCEIVED EXERTION (RPE)

This scale is to be used just for the **Walking Program**

This scale measures how are your exhaustion **before**, **during** and **after** the **exercise**

Use it as a guide to safely keep up the intensity of your exercise



WALKING PROGRAM – PEDOMETER

OBS: You will be doing the walking program only 3 days of the week.

Instruction: Slow walk to warm up for around 5 minutes. After that, you can walk at the speed you prefer. Walk continuously until you achieve your goal or until you feel that you can't do it anymore. You are allowed to make small breaks during the walk. Write down the information in your diary below.

Reminder: Always keep an exercise level between 12 and 14 on the Borg Scale (RPE) during your walk.

Week __ - Date: __/__/__					**Goal: _____ steps per day**		
	Sun	Mon	Tu	Wed	Thu	Fri	Sat
Total Duration (min)							
Number of Steps							
Perceived effort (Borg scale)	**Before**	**Before**	**Before**	**Before**	**Before**	**Before**	**Before**
	After	**After**	**After**	**After**	**After**	**After**	**After**

Week ___ - Date: __/__/__					**Goal: _____ steps per day**		
	Sun	Mon	Tu	Wed	Thu	Fri	Sat
Total Duration (min)							
Number of Steps							
Perceived effort (Borg scale)	**Before**	**Before**	**Before**	**Before**	**Before**	**Before**	**Before**
	After	**After**	**After**	**After**	**After**	**After**	**After**

Strategies and options to walking program

- If you live in an apartment building
  - Go up and down the stairs until you reach your daily goal
- If you live in a house
  - Walk inside the house or in the backyard until you reach your daily goal
- Other option
  - Go to a shopping mall, grocery store, or department store (by car) and walk around there until you reach your daily goal
  - Check near your residence or work to see if there is any community centre where you could walk (indoor or treadmill)

GENERAL INSTRUCTION TO RESISTANCE EXERCISES – PUSH-UP AND SQUAT

Important: you will perform JUST **ONE** type of Push-up + **ONE** type of Squat
The progression to another type of push-up and squat will be done by the research coordinator weekly or when necessary.
The exercises should be performed **3 times/week**. Rest 2-3 minutes between each set.

BORG – Category-ratio (CR)

This scale is to be used just for the **resistance exercises** (push-up and squat)

This scale measures muscle fatigue (arms for the push-up and legs for squats) **before** and **after exercising**

0	Nothing at all
0.5	Very, very slight
1	Very slight
2	Slight (light)
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	
10	Very, very severe

PUSH-UPS EXERCISE

Push-up Against the Wall

Instruction: Place hands at shoulder height on a wall. Stand slightly angled towards the wall. Keeping your back straight, bend your elbows to allow your upper body to come closer to the wall.

Reminder: Keep your neck in line with your spine. Make sure to fully extend your arms.

Modified Push-up

Instruction: Put both hands on the floor and push yourself up from the knees.

Reminder: Try to keep the body in a straight line.

Full Push-up

Instruction: Pull both your hands on the floor, keeping your hands in the same line as your shoulders. Extend your legs and place your toes on the floor with your back straight. Push up, extending your elbows and lower yourself flexing them.

Reminder: Make sure to **fully** extend your arms. Always go down slowly.

SQUAT EXERCISE

Chair Squats

Instruction: Sit at the edge of the chair with your legs at an angle of 90 degrees. Stand up without using your hand if possible.

Reminder: Always keep your legs at an angle of 90 degrees. Your feet should not move at the beginning of the movement.

Touch Squats

Instruction: Stand relatively close to the edge of the chair (facing away from it). Slowly lower your body to a sitting position.

Reminder: Do not fully sit on the chair.

RESISTANCE EXERCISE JOURNAL

Legend: Sets → How many sets you performed Reps → How many repetitions you performed

Remember: Perform JUST **ONE** type of Push-up + **ONE** type of Squat

Week __ – Date: __/__/____ Number sets: _____ Number repetitions: _____

	Sun		Mon		Tu		Wed		Thu		Fri		Sat	
Exercises	sets	reps	sets	reps	sets	reps	sets	reps	sets	reps	sets	reps	sets	reps
Wall Push-up														
Modified Push-up														
Full Push-up														
Chair Squat														
Touch Squat														

	Sun		Mon		Tu		Wed		Thu		Fri		Sat	
Exercises	Borg		Borg		Borg		Borg		Borg		Borg		Borg	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Wall Push-up														
Modified Push-up														
Full Push-up														
Chair Squat														
Touch Squat														

6.2 APPENDIX 2 – INTERVENTION'S FEEDBACK

ID: _____ Date: ___/___/___

Questions:

1. In the last week, how did you feel in general ?

_____

2. In the last week, did you perform the exercises of the book? If no, the reasons why

_____

3. In the last week, did you have any difficulty in doing the exercises or any question about it? if yes, please explain?

_____

4. In the last week, did you feel that you needed to interrupt your exercises. If yes, for which reason?

_____

5. In the last week, how did you feel after finishing the exercises? (probing questions: Exhausted, ok, could continue to do more exercises) ?

_____

6. Do you feel motivated to continue to perform the exercises? If not, how we could do to improve it?

_____

7. During this last week, did some adverse event occurred related to the exercises?

_____

6.3 APPENDIX 3- DEMOGRAPHIC/ MEDICAL QUESTIONNAIRE

Name: _____ Phone number (for contact):_____

Email (for contact):_____ Date: ___/___/___ ID:_____

Demographic Questionnaire Items

Age: __ Sex: Female □ Male □ **Gender:** Woman □ Man □ Prefer not to answer □ Other □___

Area of residence: _____

Employment status: Employed □ Unemployed □ Retired □ Other □ _____

Marital status: Single □ Married □ Divorced □ Widowed □ Other □ _____

Education Level: Some high school or less □ Some college □ Graduated high school □

Vocational/technical school □ Graduated college □ Post-graduate study □

Medical/ Physical Questionnaire Items

Height: _____ Weight:_____ BMI: ____ Primary cause of renal disease _____

Time since diagnostic: _____ Dialysis: YES □ NO □ **When dialysis started:** _____

Arteriovenous Fistula: YES □ NO □ If yes, since when? ___If yes, which arm? Left □ Right □

Type of dialysis: Hemodialysis □ Peritoneal □ **Days on dialysis** _____

Other Items

Are you on a special diet that has been prescribed by a nutritionist or by a doctor?

YES □ NO □ _____

Do you currently receive a psychological support/ treatment?

YES □ NO □ _____

Are you involved in any other intervention?

YES □ NO □ _____

6.4 APPENDIX 4 - FEASIBILITY OBJECTIVES AND MEASUREMENT'S TOOL

a) evaluation of recruitment capability and resulting sample characteristics	Eligibility rate
	Recruitment rate and time to recruit
	Drop-out before sign consent form
	Drop-out before intervention start
	Refusal rate
	Feasibility and suitability of eligibility criteria (inclusive or restrictive)
	Obstacles to recruit (reasons for refusal)
	Participants characteristics from medical chart, interviews and measurement
b) evaluation and refinement of data collection procedures and outcome measures	Feasibility and suitability of the data collection procedures (participants understand the questions and procedures or no need for adjustments during the process or not)
	Feasibility and suitability of the amount of data collection (participants were able to complete the data collection or not / reasonable amount of time to complete or created a burden)
	Missing data (%, reasons why it is missing, which data is missing)
	Report of barriers of collecting data (reasons from research coordinator and patients)
	Interview face-to-face – pre-intervention assessment's feedback (Appendix 10)
c) evaluation of the acceptability and suitability of the intervention and study procedures	Weekly phone call - intervention's feedback
	Acceptability Scale - patient's feedback post-intervention
	Description of research coordinator and patient's claims/ barriers about the program and how the intervention was modified if needed
	Adherence of the intervention by analysing the diary and phone calls
	Drop-out during intervention
	Drop-out before post-intervention assessment
	Time participating in the intervention before transplantation (weeks)
d) evaluation of the resources and ability to manage and implement the study and intervention	Barriers reported after the end of the study (budged/ equipment/ research coordinator skills and training /data entry and analysis)
	Time was enough or not to conduct the study
	Progression of the exercise program

6.5 APPENDIX 5 - ACCEPTABILITY OF THE HOME-BASED PRE-HABILITATION PROGRAM

ID: _____ Date: ___/___/___

A. Have a home-based exercise intervention was:

Bad idea	-3	-2	-1	0	1	2	3	**Good idea**
Annoying	-3	-2	-1	0	1	2	3	**Pleasing**
Unsafe	-3	-2	-1	0	1	2	3	**Safe**
Difficult	-3	-2	-1	0	1	2	3	**Easy**
Useless	-3	-2	-1	0	1	2	3	**Helpful**
Complex	-3	-2	-1	0	1	2	3	**Simple**

B. My family and friends liked that I engaged in this home-based pre-habilitation program.

Disagree	-3	-2	-1	0	1	2	3	**Agree**

C. I see the need for a home-based pre-habilitation program in my life.

Disagree	-3	-2	-1	0	1	2	3	**Agree**

D. I think I benefited from this home-based pre-habilitation program.

Disagree	-3	-2	-1	0	1	2	3	**Agree**

E. I felt confident to perform all exercises without assistance.

Disagree	-3	-2	-1	0	1	2	3	**Agree**

F. It was easy to learn how to perform the exercises of the program.

Disagree	-3	-2	-1	0	1	2	3	**Agree**

G. I intend to follow the home-based pre-habilitation exercises even after the end of the program.

Disagree	-3	-2	-1	0	1	2	3	**Agree**

H. I would recommend this home-based pre-habilitation program to others.

Disagree	-3	-2	-1	0	1	2	3	**Agree**

I. The number of exercises in the program was enough.

Disagree	-3	-2	-1	0	1	2	3	**Agree**

J. The length of the program was enough.

Disagree	-3	-2	-1	0	1	2	3	**Agree**

6.6 APPENDIX 6 – 6-MINUTES WALKING TEST

ID# _____ Date: ___/___/___

Walk # 1	Baseline	After
Heart Rate		
Blood Pressure		
BORG (dyspnea / overall fatigue)	/	/

- Stopped or paused before 6 minutes? YES ___ NO___
- Other symptoms at end of exercise:

  _____
- Total distance walked in 6 minutes: _____ meters

30	420
60	450
90	480
120	510
150	540
180	570
210	600
240	630
270	660
300	690
330	720
360	750
390	780
Final partial lap:	

Walk # 2	Baseline	After
Heart Rate		
Blood Pressure		
BORG (dyspnea / overall fatigue)	/	/

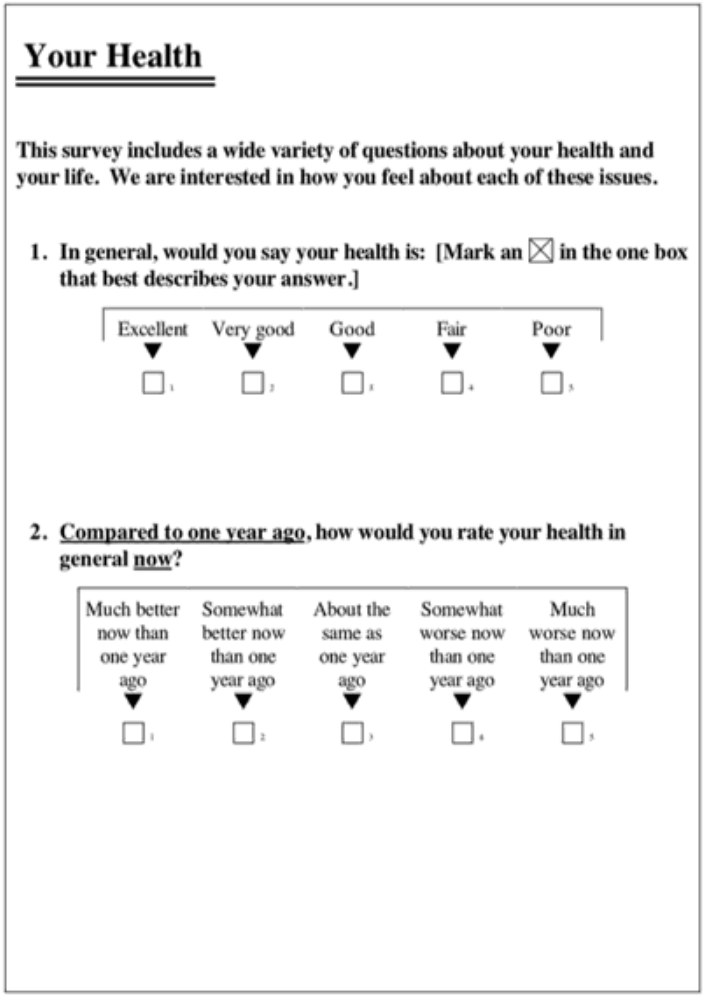
- Stopped or paused before 6 minutes? YES ___ NO___
- Other symptoms at end of exercise:

  _____
- Total distance walked in 6 minutes: _____ meters

30	420
60	450
90	480
120	510
150	540
180	570
210	600
240	630
270	660
300	690
330	720
360	750
390	780
Final partial lap:	

6.7 APPENDIX 7 - KIDNEY DISEASE AND QUALITY OF LIFE (KDQOL-SFTM 1.3)

ID: _____ Date: ___/___/___



Your Health

This survey includes a wide variety of questions about your health and your life. We are interested in how you feel about each of these issues.

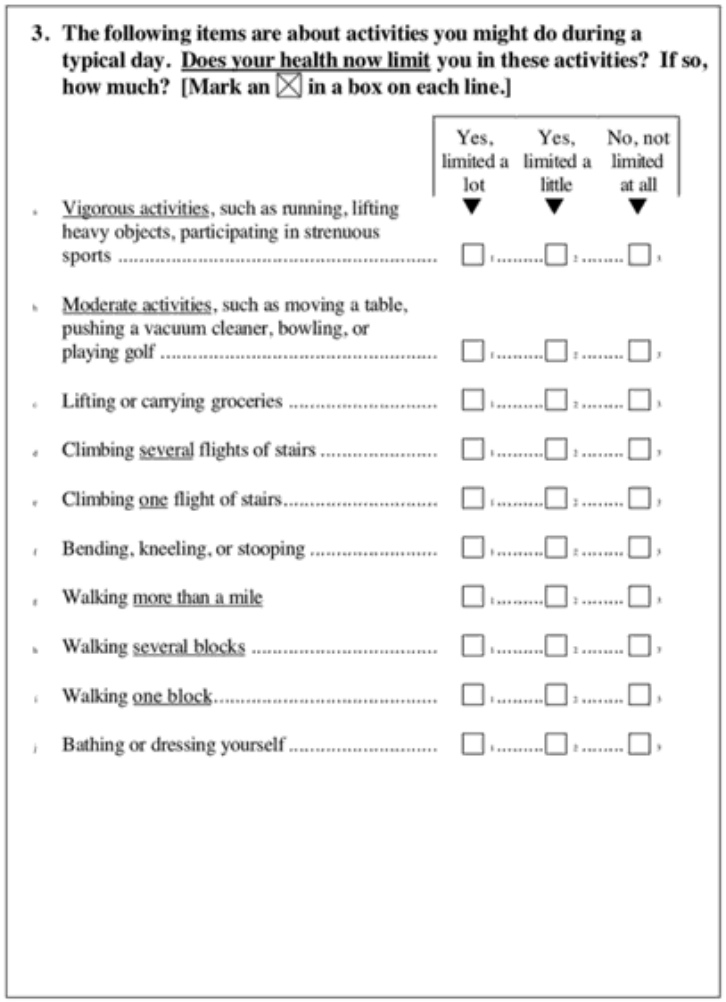
1. In general, would you say your health is: [Mark an ☒ in the one box that best describes your answer.]

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Page 1



3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? [Mark an ☒ in a box on each line.]

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c. Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d. Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e. Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f. Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g. Walking more than a mile	☐ 1	☐ 2	☐ 3
h. Walking several blocks	☐ 1	☐ 2	☐ 3
i. Walking one block	☐ 1	☐ 2	☐ 3
j. Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

Page 2

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	Yes	No
a. Cut down the amount of time you spent on work or other activities	☐ 1	☐ 2
b. Accomplished less than you would like	☐ 1	☐ 2
c. Were limited in the kind of work or other activities	☐ 1	☐ 2
d. Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	Yes	No
a. Cut down the amount of time you spent on work or other activities	☐ 1	☐ 2
b. Accomplished less than you would like	☐ 1	☐ 2
c. Didn't do work or other activities as carefully as usual	☐ 1	☐ 2

Page 3

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks…

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of pep?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
b. Have you been a very nervous person?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
c. Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
d. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
e. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
f. Have you felt downhearted and blue?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
g. Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
h. Have you been a happy person?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
i. Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

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10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. Please choose the answer that best describes how true or false each of the following statements is for you.

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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Your Kidney Disease

12. How <u>true</u> or <u>false</u> is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. My kidney disease interferes too much with my life	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Too much of my time is spent dealing with my kidney disease	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I feel frustrated dealing with my kidney disease	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. I feel like a burden on my family	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

13. These questions are about how you feel and how things have been going during the <u>past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the <u>past 4 weeks</u>…

	None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
a. Did you isolate yourself from people around you?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
b. Did you react slowly to things that were said or done?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
c. Did you act irritable toward those around you?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
d. Did you have difficulty concentrating or thinking?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
e. Did you get along well with other people?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
f. Did you become confused?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

14. During the past 4 weeks, to what extent were you bothered by each of the following?

	Not at all bothered	Somewhat bothered	Moderately bothered	Very much bothered	Extremely bothered
a. Soreness in your muscles?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Chest pain?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Cramps?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Itchy skin?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e. Dry skin?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f. Shortness of breath?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g. Faintness or dizziness?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h. Lack of appetite?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i. Washed out or drained?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
j. Numbness in hands or feet?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
k. Nausea or upset stomach?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
l. (Hemodialysis patient only) Problems with your access site?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
m. (Peritoneal dialysis patient only) Problems with your catheter site?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Effects of Kidney Disease on Your Daily Life

15. Some people are bothered by the effects of kidney disease on their daily life, while others are not. How much does kidney disease bother you in each of the following areas?

	Not at all bothered	Somewhat bothered	Moderately bothered	Very much bothered	Extremely bothered
a. Fluid restriction?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Dietary restriction?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Your ability to work around the house?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Your ability to travel?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e. Being dependent on doctors and other medical staff?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f. Stress or worries caused by kidney disease?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g. Your sex life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h. Your personal appearance?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

The next three questions are personal and relate to your sexual activity, but your answers are important in understanding how kidney disease impacts on people's lives.

16. Have you had any sexual activity in the <u>past 4 weeks</u>?

(Circle One Number)

No .....1 → If no, please skip to Question 17

Yes 2

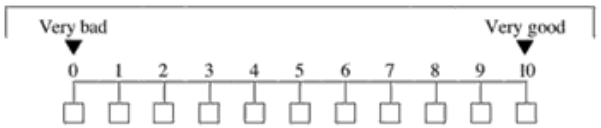
How much of a problem was each of the following in the <u>past 4 weeks</u>?

	Not a problem	A little problem	Somewhat of a problem	Very much a problem	Severe problem
a. Enjoying sex?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Becoming sexually aroused?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

17. For the following question, please rate your sleep using a scale ranging from 0 representing "very bad" to 10 representing "very good."

If you think your sleep is half-way between "very bad" and "very good," please mark the box under the number 5. If you think you sleep is one level better than 5, mark the box under 6. If you think your sleep is one level worse than 5, mark the box under 4 (and so on).

On a scale from 0 to 10, how would you rate your sleep overall? [Mark an ☒ in one box.]



18. How often during the <u>past 4 weeks</u> did you...

	None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
a. Awaken during the night and have trouble falling asleep again?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
b. Get the amount of sleep you need?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
c. Have trouble staying awake during the day?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

19. Concerning your <u>family and friends</u>, how satisfied are you with...

	Very dissatisfied	Somewhat dissatisfied	Somewhat satisfied	Very satisfied
a. The amount of time you are able to spend with your family and friends?	☐ 1	☐ 2	☐ 3	☐ 4
b. The support you receive from your family and friends?	☐ 1	☐ 2	☐ 3	☐ 4

20. During the <u>past 4 weeks</u>, did you work at a paying job?

Yes	No
☐ 1	☐ 2

21. Does your health keep you from working at a paying job?

Yes	No
☐ 1	☐ 2

22. Overall, how would you rate your health?

Worst possible (as bad or worse than being dead) — Half-way between worst and best — Best possible

0 1 2 3 4 5 6 7 8 9 10

Satisfaction With Care

23. Think about the care you receive for kidney dialysis. In terms of your satisfaction, how would you rate the friendliness and interest shown in you as a person?

Very poor	Poor	Fair	Good	Very good	Excellent	The Best
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

24. How true or false is each of the following statements?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. Dialysis staff encourage me to be as independent as possible	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Dialysis staff support me in coping with my kidney disease	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

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6.8 APPENDIX 8 - SHORT PHYSICAL PERFORMANCE BATTERY PROTOCOL AND SCORE SHEET

BALANCE TESTING

A. Feet together
Held for 10 sec ❒ 1 point
Not held for 10 sec ❒ 0 points
Not attempted ❒ 0 points
Number of seconds held if less than 10 sec: _____
Reasons why did not attempt test or failed (number): ___

B. Semi-Tandem Stand
Held for 10 sec ❒ 2 point
Held for 3 to 9.99 sec ❒ 1 point
Held for < than 3 sec ❒ 0 points
Not attempted ❒ 0 points
Number of seconds held if less than 10 sec: _____
Reasons why did not attempt test or failed (number): ___

C. Tandem Stand
Held for 10 sec ❒ 1 point
Not held for 10 sec ❒ 0 points
Not attempted ❒ 0 points
Number of seconds held if less than 10 sec: _____
Reasons why did not attempt test or failed (number): ___

Scoring Balance Test
Total: / 4

GAIT SPEED TEST

Scoring Gait speed Test	
1st Time: _____ 2nd Time: _____	**Total: / 4**

CHAIR STAND TEST

Single Chair Stand Test	
A. Safe to stand without help	YES ❒ NO❒
B. Results:	- Stood without using arms ❒ - Used arms to stand ❒ - Test not completed ❒
C. Reasons why did not attempt test or failed	Number:

Repeated Chair Stand Test	
A. Safe to stand without help	YES ❒ NO❒
B. Time to stand five times	Time: _____sec
C. Reasons why did not attempt test or failed	Number:

Scoring the Chair Test
Total: / 4

SPPB

Total Scoring SPPB
Total: /12

6.9 APPENDIX 9 - MODIFIED FRIED'S FRAILTY PHENOTYPE

ID: **DATE:** **Fried's Frailty Phenotype**	Score
Weight loss **Question:** "In the last year, have you lost more than 10 pounds (≥4.5 kg) unintentionally (i.e., not due to dieting or exercise)?" If yes, then frail for weight loss. Yes=1, No =0 OR **Calculated weight loss:** (Weight in previous year – current measured weight)/(weight in previous year) = K **Interpretation:** If K ≥ 0.05 and the subject does not report that he/she was trying to lose weight (i.e., unintentional weight loss of at least 5% of previous year's body weight), then frail for weight loss = Yes.	
Exhaustion **Question:** "How often in the last week did you feel this way?" (a) I felt that everything I did was an effort _____ b) I could not get going _____ **Response options:** 0 = rarely or none of the time (<1 day), 1 = some or a little of the time (1–2 days), 2 = a moderate amount of the time (3–4 days), or 3 = most of the time **Interpretation:** Having "2" or "3" as an answer to either of these questions are categorized as frail by the exhaustion criterion. Yes=1, No =0	
Physical Activity **Question:** Frequency of mildly energetic, moderately energetic and very energetic physical activity. *(*i.e.: walking, chores (moderately strenuous), mowing the lawn, raking, gardening, hiking, jogging, biking, exercise cycling, dancing, aerobics, bowling, golf, singles tennis, doubles tennis, racquetball, calisthenics, swimming. **Response options:** ≥3 times per week, 1-2 times per week, 1-3 times per month, hardly ever/never **Interpretation:** Hardly ever/never for very energetic physical activity AND for moderately energetic physical activity = frail. Yes=1, No =0	
Weakness **Interpretation:** Grip strength in the lowest 20% at baseline, adjusted for gender and BMI, will be considered as weak. Yes=1, No =0	

Right Hand	Average:
1st measure	Score:
2nd measure	Score:
3rd measure	Score:
Left Hand	Average:
1st measure	Score:
2nd measure	Score:
3rd measure	Score:

Gait speed **Interpretation:** Gait speed of longer than 5 seconds to walk 4 metres (<0.8 m/s). Yes=1, No =0 **1st Time:** _____ **2nd Time:** _____	
TOTAL	

6.10 APPENDIX 10 - FEEDBACK MEASUREMENT QUESTIONNAIRE

ID: _____ Date: ___/___/___

1- How would you rate this part of the study? (Measuring all the physical components and questionnaires?)

Excellent_____ Good_____ Not bad _____ Exhausting_____

If possible, give the reasons:

_____

_____

2- Would you change something if you could? If yes, what would you change? (i.e.: length of the measurements, order of the measurements, make in two days and not in one, etc.)

_____

_____

_____

3- Did you have any difficult during the performance of the tests that you have done today? If yes, which one? What was the difficulty?

_____

_____

_____