Brief report

The association between objectively measured physical activity and the prevalence of comorbidities in lung transplant recipients

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Abstract

Introduction

Lung transplant recipients are often physically inactive and are at risk of developing comorbidities. We investigated whether objectively measured physical activity was associated with the prevalence of comorbidities.

Methods

Physical activity (accelerometry) and the presence of cardiovascular disease, symptoms of depression and anxiety, diabetes, dyslipidaemia, hypertension, lower extremity artery disease, muscle weakness, obesity and osteoporosis were assessed in 108 lung transplant recipients. Patients were divided into four groups based on daily step count.

Results

A cohort of 108 patients (60±7 years, 51% male, 20±14 months since transplantation) was included. Active patients (>7500 steps/day) had significantly fewer comorbidities (4 comorbidities) compared to severely inactive patients (<2500 steps/day, 6 comorbidities) and muscle weakness and high symptoms of depression were less prevalent. Severely inactive patients had significantly more cardiovascular comorbidities compared to all other groups. No other significant differences were observed.

Conclusion

Physically active lung transplant recipients have fewer comorbidities, lower prevalence of muscle weakness and fewer symptoms of depression compared to very inactive patients.

Introduction

Engaging in physical activity (PA) positively impacts cardiovascular, musculoskeletal, metabolic, mental health and all-cause mortality in the general population [1]. A translation of the public health guidelines of the World Health Organization for PA (150 minutes of moderately intense aerobic activity per week) resulted in a recommendation of 7000 to 10000 steps per day [2].

Lung transplant (LTX) recipients are less active than the healthy population and seldom meet these PA guidelines [3]. Research suggests that the normal PA guidelines should apply to LTX recipients since no specific PA guidelines exist [4]. Additionally, LTX recipients are prone to develop comorbidities. One year after LTX, diabetes, osteopenia, hypertension and hyperlipidaemia are reported in 24%, 33%,72% and 49% of the patients, respectively. After five years, the prevalence increases to 32%, 80% 95% and 81% [5, 6]. Whereas it is not clear that these comorbidities were already present before LTX we do know that all aforementioned comorbidities are linked to a lack of PA in the healthy population [7]. The only study reporting on the link between physical activity and comorbidity in lung recipients investigated the additional effect of increased PA through rehabilitation on the incidence of hypertension and concluded that LTX recipients with extremely sedentary behaviour had higher arterial blood pressure [8].

The present study aimed to investigate whether inactive lung transplant recipients exhibit more comorbidities than active patients and whether there is an association between the level of PA and specific comorbidities in LTX recipients. To answer this research question the present study measured physical activity objectively, using accelerometery, the recommended way to capture the activity level of an individual, and collected a broad spectrum of comorbidities (based on objective measures combined with self-report).

Methods

Design and population

This investigation reports on the baseline data of a randomised controlled trial, approved by the Ethics Committee Research UZ/KU Leuven (s62426), Clinicaltrials.gov NCT 04122768. This study is in compliance with the ISHLT ethics statement. Patients were recruited at the University Hospitals of Leuven, Belgium between November 2019 and October 2022 and provided written informed consent before enrolment. The eligibility criteria were derived from the aforementioned randomized controlled trial: patients at least six months and maximum four years after a first double LTX at UZ Leuven, Belgium, aged ≥ 30 years and able to handle a smartphone were informed about the study. Exclusion criteria were a diagnosis of cystic fibrosis, a multi-organ or second solid-organ or bone

marrow transplantation, musculoskeletal problems not allowing for a normal gait pattern, chronic rejection of the allograft before inclusion, or a life expectancy of less than one year.

Physical Activity

All patients wore a triaxial accelerometer on the lower back to measure PA (Dynaport Movemonitor, McRoberts BV, The Hague, the Netherlands) for seven consecutive days during waking hours. Data were aggregated by day using proprietary algorithms (McRoberts). At least two days with a minimum of eight hours of wearing time were considered valid [9]. Data of week and weekend days were included in the analysis [9]. Pulmonary function tests were performed according to the European Respiratory Society guidelines and results are shown as percentages of normal reference values [10] .

Comorbidities

Comorbidities were assessed based on specific criteria and measurements. A comorbidity was considered present if the corresponding measurement exceeded the defined threshold or the patient was prescribed relevant medication.

The patient was considered to have a *cardiovascular disease* if a) he/she had a documented history of cardiac surgery; or b) one of the following medications was prescribed: antiaggregant or anticoagulation. Symptoms of depression and anxiety were evaluated using the Hospital Anxiety and Depression Scale. A score of 8 points or higher indicated a possible diagnosis of depression or anxiety [11]**.** *Diabetes* was diagnosed if a) fasting blood glucose ≥ 126 mg/dL; or b) Haemoglobin A1c > 6.5%; or c) one of the following medications was prescribed: insulin or oral antidiabetics [12]. *Dyslipidaemia* was diagnosed if a) high-density lipoprotein < 40 mg/dL for males and < 50 mg/dL for females; or b) Low-density lipoprotein ≥ 100 mg/dL; or c) statins were prescribed [13]. The patient was diagnosed with *arterial hypertension* if a) the systolic blood pressure, measured in a seated position after 5-10 minutes of rest, exceeded the cut-off of 140 mmHg; or b) one of the following medications was prescribed: diuretics, beta-blockers, ACE inhibitors, sartans or calcium antagonists [14]. *Lower extremity artery disease* was diagnosed when the ankle brachial index (ABI) was below the cut-off of <0.9 [15]. The ABI was measured in supine position after 5-10 minutes of rest and is the ratio between the systolic blood pressure in the ankle and the highest systolic blood pressure of the arms with the lowest ratio chosen for assessment. Isometric Quadriceps force was measured in a seated position of 90° hip and 60° knee flexion (Biodex System II, Biodex Corporation, New York, USA). The best out of three maximum voluntary isometric contractions of the musculus Quadriceps was taken. Patients with an isometric Quadriceps force below 80% of the predicted value were classified as having *muscle weakness* [16]. *Obesity* was evaluated using body mass index (BMI) and waist circumference [17, 18]. A BMI greater than 30 kg/m² or a waist circumference greater than 102 cm for males and 88 cm for

females, both measured in a standing position at the level of the umbilicus, were considered indicative of obesity. *Osteoporosis* was determined by conducting a DEXA scan to measure the T-score at the femur neck or lumbar spine [19]. The lowest T-score was taken into account, where a T-score below -2.5 indicated the presence of osteoporosis. Self-reports of diagnosed comorbidities were also considered.

Statistics

Patients were divided into four groups based on their average daily step count. The following easily-applicable Tudor Locke cut-offs were chosen: <2500 steps/day (A), 2500-4999steps/day (B), 5000-7499 steps/day (C) and ≥7500 steps/day (D) [2]. Missing data for comorbidities were judged as missing at random due to technical problems. ANOVA and Kruskal-Wallis analyses were performed to compare the four groups for differences in characteristics and number of comorbidities. Chi^2 test was used to compare differences in the prevalence of each comorbidity among the four groups. Statistical significance was set at $p<0.05$ for comparing patient characteristics and adjusted to $p<0.017$ for the Chi^2 test with Bonferroni correction for multiple testing. Results are shown as mean±SD or proportions unless otherwise indicated. The analyses were performed using SAS (V.9.4, SAS Institute, Cary, North Carolina, USA). As a sensitivity analyses, the analyses were repeated dividing patients based on PA tertiles.

Results

A cohort of 108 patients was included: 60±7 years, 51% male, 94±25% predicted FEV_1, 54±10% predicted DL_{CO}. Figure 1 shows the flowchart with the group allocation. Patients achieved a mean of 5070±2832 steps/day. Patient characteristics of the whole group and the four groups separately are provided in Table 1.

DL_{CO} was significantly lower in the least active group (group A <2500 steps/day) compared to the other groups. Time since transplantation was lower in group A compared to group C (p=0.042). Most groups were inactive and significant differences were only present between those active and those severely inactive. Severely inactive patients had more comorbidities compared to the active patients (p=0.001) (Table 1). Figure 2 summarizes the prevalence per comorbidity across the groups. Severely inactive patients were more often diagnosed with muscle weakness (p=0.003 and p=0.013 for group comparisons A vs D and B vs D, respectively) and symptoms of depression (p=0.009 for group comparison A vs D). A similar finding for cardiovascular comorbidities was observed ($p<0.017$ for group comparison A vs B-C-D). No other statistically significant differences were found. The sensitivity analysis provided very similar results (data not shown).

Discussion

This study confirms that comorbidities are highly prevalent in LTX recipients. We also confirmed that most patients are physically inactive after LTX. LTX recipients with the lowest PA have more comorbidities compared to physically active patients. More specifically, muscle weakness, symptoms of depression and cardiovascular comorbidities are significantly more prevalent in severely inactive patients. The inactive group was transplanted more recently, when still a lower prevalence of comorbidities is expected. Despite this, our results show that these severely inactive patients have the most comorbidities, which strengthens our hypothesis.

Whereas, our cross-sectional data cannot infer a causal association, given the high prevalence of comorbidities, future research may offer the potential to enhance PA, which might reduce the incidence or worsening of these comorbidities and their associated mortality. Previous research suggested that LTX recipients who increased PA through pulmonary rehabilitation including activity coaching and high intense exercises, improved blood pressure levels compared to more sedentary patients [8].

The present study is unique because it reports on the association between objectively measured physical activity and the relation with a broad range of comorbidities in a large sample of lung recipients. However, some limitations have to be acknowledged. While the inclusion of 108 participants can be considered reasonable, no sample size calculation was performed for these analyses. Additionally, the subsequent division into four groups resulted in reduced statistical power. Hence, the analysis was restricted to a comparison to the group with the lowest PA as a reference group. Second, data on lower extremity artery disease and osteoporosis were missing due to technical issues (n=20 and n=5, respectively). Third, the group size was not equal, as the allocation was done based on a priori determined PA levels. However, despite this limitation, this classification does provide a realistic picture of the distribution of PA among these patients using meaningful cut-offs when considering previous research findings [3]. The sensitivity analysis comparing patients divided based on tertiles of PA provided largely similar results. Next, previous research showed that PA levels of patients before LTX are lower than PA levels after LTX. Our study could not confirm this, as PA was only measured after LTX [8, 20, 21]. Lastly, causal relationships could not be investigated since this study has a cross-sectional design. If investigated in an RCT, such research may lead to evidence-based guidelines to guide PA advice after solid organ transplantation.

Conclusion

Our results confirm that LTX recipients who are severely physically inactive have more comorbidities compared to active patients. Specifically, more muscle weakness, symptoms of depression and cardiovascular comorbidities were observed. Prospective studies are needed to investigate the impact of re-activation post LTX on incidence of comorbidities.

Statements

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Statement of Ethics

This study reports on the baseline data of a randomised controlled trial, reviewed and approved by the Ethics Committee Research UZ/KU Leuven, approval number s62426. All patients provided written informed consent before enrolment.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author contributions

AB, GMV, RV, WJ, TT and HD participated in the conceptualisation, design and protocol development of the RCT. SB, AB and MW collected the data. SB, TT and HD analysed and interpreted the data. All authors contributed to the draft of the work or revised it critically for important intellectual content and approved the final version to be published.

Data Availability Statement

Data cannot be shared publicly because of patient confidentiality according to the Belgian law. New analyses are available on reasonable request from the author or UZ Leuven Ethical Committee (ec@uzleuven.be).

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Figure Legends

Fig. 1: Study flowchart

Fig. 2: Overview of prevalence of comorbidities in lung transplant recipients, categorized in four groups based on physical activity level. Y-axis: Comorbidities; x-axis: % of patients diagnosed with the comorbidity. Coloured bars: activity level, based on daily step count. A vs D, B vs D, A vs B-C-D: comparison between groups A and D, B and D, A and B-C-D respectively