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Original Paper

Physical Performance and Clinical Outcomes in Dialysis Patients: A Secondary Analysis of the Excite Trial

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Key Words
Physical performance • Six-minute walking test • Chronic kidney disease • Dialysis • Clinical outcomes

Abstract
Background/Aims: Scarce physical activity predicts shorter survival in dialysis patients. However, the relationship between physical (motor) fitness and clinical outcomes has never been tested in these patients. ***Methods:*** We tested the predictive power of an established metric of motor fitness, the Six-Minute Walking Test (6MWT), for death, cardiovascular events and hospitalization in 296 dialysis patients who took part in the trial EXCITE (ClinicalTrials.gov Identifier: NCT01255969). ***Results:*** During follow up 69 patients died, 90 had fatal and non-fatal

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cardiovascular events, 159 were hospitalized and 182 patients had the composite outcome. In multivariate Cox models - including the study allocation arm and classical and non-classical risk factors - an increase of 20 walked metres during the 6MWT was associated to a 6% reduction of the risk for the composite end-point (P=0.001) and a similar relationship existed between the 6MWT, mortality (P<0.001) and hospitalizations (P=0.03). A similar trend was observed for cardiovascular events but this relationship did not reach statistical significance (P=0.09). ***Conclusions:*** Poor physical performance predicts a high risk of mortality, cardiovascular events and hospitalizations in dialysis patients. Future studies, including phase-2 EXCITE, will assess whether improving motor fitness may translate into better clinical outcomes in this high risk population.

Introduction

Physical activity and physical performance are notoriously poor in patients with end-stage kidney disease (ESKD) [1], a population with an extremely high risk of death and cardiovascular events [2]. Even though representing strictly related phenomena, physical activity and physical performance are separated entities with different metrics. Physical activity, i.e. physical engagement in daily activities, is a well-established predictor of mortality and cardiovascular events in the general population [3] and in pathological conditions such as diabetes [4] and coronary artery disease [5] and in end stage kidney disease (ESKD) as well [6-9]. To our knowledge, the relationship between actual physical performance, i.e. the objectively measured ability to perform well standardized physical efforts, and clinical outcomes in ESKD has been investigated just in a small study with a very limited number of major clinical events (just 21 deaths) [10]. The Six-Minute Walking Test (6MWT) is an established test to assess physical performance in frail elderly patients [11], and this test has been applied in clinical studies in various conditions, such as heart failure [12, 13] and chronic obstructive pulmonary disease (COPD) [14].

The EXCITE (EXerCise Introduction To Enhance Performance in Dialysis) study, is a large, multicentre, randomized trial whose phase – 2 (clinical outcomes and hospitalization) is still in progress. This study tests the effectiveness of an easy-to-implement program of physical training in dialysis patients. We have taken the opportunity of the EXCITE study to investigate the relationship between actual physical performance, as assessed by the Six-Minutes Walking Test, on mortality, cardiovascular events and hospitalizations in dialysis patients.

Patients and Methods

The study protocol was approved by the ethical committee of our institution. All participants gave informed consent before enrolment.

Patients

The EXCITE Study is a multicentre randomized controlled trial on the effectiveness of exercise in improving physical performance and the quality of life (phase-1) and in reducing adverse clinical outcomes (mortality, cardiovascular events and hospitalizations) (phase-2) in dialysis patients. This trial is registered in ClinicalTrials.gov (Identifier: NCT01255969). In this secondary analysis, we included 296 dialysis patients who performed the 6MWT at baseline. These patients had been on regular dialysis (HD or PD) for a median time of 44 months (inter-quartile range: 26-83). Haemodialysis patients (n=247) were being treated with standard bicarbonate dialysis with non-cellulosic membrane filters of various type. PD patients (n=49) were either on 4 standard exchanges day (n=11) or on continuous cycling peritoneal dialysis (n=38). Two hundred and six patients were treated with various anti-hypertensive drugs (76 on mono-therapy with calcium channel blockers, ACE inhibitors, sartans, alpha or beta blockers, clonidine, furosemide, 65 on double

therapy, 44 on triple therapy and 21 patients on quadruple and quintuple therapy with various combinations of these drugs). The main demographic, somatometric, clinical and biochemical characteristics of the study population are detailed in Table 1.

Table 1. Main demographic, somatometric and clinical characteristics in the study population and correlates of Six-Minute Walking Test (6MWT).

	Whole group (n=296)	6MWT correlation coefficient (P)
Age (years)	65±13	**-0.57 (<0.001)**
BMI (kg/m^2)	25±5	-0.04 (0.63)
Male sex n. (%)	201 (68)	**0.21 (<0.001)**
Current smokers n. (%)	48 (17)	-0.04 (0.52)
Past smokers n. (%)	72 (26)	
Diabetics n. (%)	60 (21)	**-0.20 (0.001)**
On anti-hypertensive treatment n. (%)	206 (73)	0.004 (0.95)
Dialysis vintage (months)	44 (26-83)	-0.03 (0.58)
With cardiovascular comorbidities* n. (%)	226 (76)	**-0.26 (<0.001)**
Systolic Blood Pressure (mmHg)	128±20	0.07 (0.27)
Diastolic Blood Pressure (mmHg)	69±11	**0.38 (<0.001)**
Cholesterol (mg/dL)	164±38	-0.08 (0.23)
Hemoglobin (g/dL)	11.0±1.9	0.11 (0.07)
Albumin (g/dL)	3.9±0.4	**0.22 (0.001)**
hsCRP (mg/L)	0.7(0.4-2.6)	**-0.16 (0.03)**
Calcium (mg/dL)	8.7±1.4	-0.06 (0.31)
Phosphate (mg/dL)	4.9±1.5	**0.22 (<0.001)**
NYHA Class 0 n. (%)	124 (44)	**-0.21 (<0.001)**
NYHA Class 1 n. (%)	95 (34)	
NYHA Class 2 n. (%)	40 (14)	
NYHA Class 3 n. (%)	20 (7)	

* Angina, arrhythmia, myocardial infarction, coronary surgery, angioplasty, other heart surgery, claudicatio, amputations, peripheral surgery, stroke, TIA, heart failure.
Data are expressed as mean ± SD. median and inter-quartile range or as percent frequency, as appropriate.

Laboratory measurements

Blood sampling was performed after an overnight fast. In haemodialysis patients, blood was always drawn in the morning hours (8 am – 12 am) during a mid-week day (brief dialysis interval). Serum cholesterol, albumin, calcium, phosphate, C-Reactive Protein (CRP) and haemoglobin measurements were made using standard methods in the routine clinical laboratory.

Six-Minute Walking Test

Physical performance was assessed at baseline with the Six-Minute Walking Test (6MWT). This test consists in a 6 minute-walk along a marked walkway on a hard, flat surface, at the maximum speed that each patient can maintain. The goal of this test is to walk as far possible in six minutes. During the walk, the patient is allowed to stop and rest whenever he/she wants, and the number of interruptions are carefully recorded by an operator. At the end of the test, the fatigue perceived by the patient is classified by the Borg Scale, a simple method that allows to rate the perceived exertion by using a scale from 0 (no exertion) to 10 (maximum exertion).

Study end-points

In this secondary analysis of EXCITE, a composite end-point including mortality, fatal and non-fatal cardiovascular events and hospitalizations was the main study end-point. Cardiovascular events were classified as follows: stroke (ischemic or haemorrhagic) documented by computed tomography, magnetic resonance imaging and / or clinical and neurological evaluation; transient ischemic attacks (TIA); myocardial infarction confirmed by serial changes of ECG and cardiac biomarkers; ECG-documented angina episodes; heart failure, diagnosed according to criteria by the AHA guideline [15]; ECG documented arrhythmia; peripheral ischemia or amputations; unexpected, sudden death highly suspected as of cardiac origin. Hospitalizations were classified in cardiovascular and non-cardiovascular using information included in the hospital records. Cause of death was assessed by 3 independent physicians. In doubtful cases, diagnosis was attributed by consensus. During the review process, involved physician used all available medical information, including hospitalization forms and medical records. In case of death occurred at home, family members and/or general practitioners were interviewed to better understand the circumstances surrounding death.

Statistical analysis

Data were expressed as mean ± standard deviation (normally distributed data), median and inter-

quartile range (non-normally distributed data) or as per cent frequency (categorical data). The Person correlation coefficient was used to describe correlates of 6MWT variable. The independent correlates of 6MWT were identified by correlation analysis and by multiple linear regression. Tested variables included age, gender, smoking, cardiovascular comorbidities, diabetes, antihypertensive therapy, Body Mass Index (BMI), dialysis vintage, systolic and diastolic blood pressure, cholesterol, albumin, C-reactive protein, calcium, phosphate, haemoglobin and NYHA class. All variables which correlated with 6MWT (with P<0.05) were jointly introduced into the same model. Survival analyses were performed by using bivariate and multivariate Cox regression models. In close parallelism with the strategy used for the identification of independent correlates of 6MWT (see above), in the multiple Cox Regression model we included all univariate correlates of the combined end point (with P < 0.05). Statistical analysis was performed by using standard statistical packages (SPSS for Windows, Version 20, Chicago, Illinois, USA; STATA for Windows, Version 13, College Station, Texas, USA).

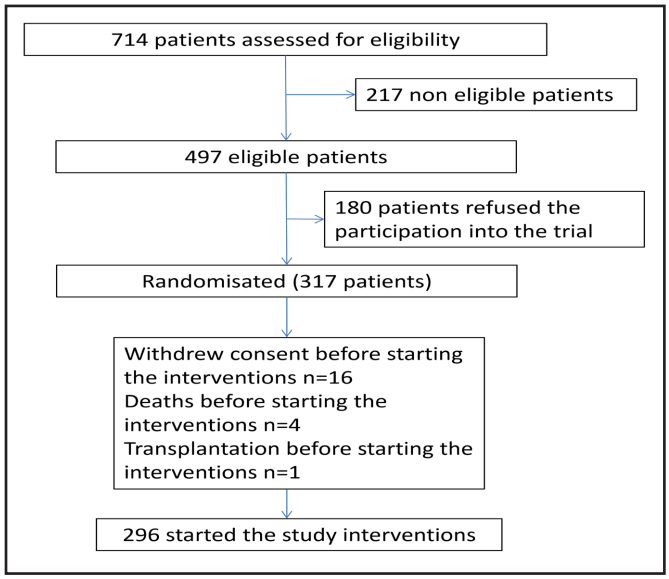

Fig. 1. Flow diagram of the patients enrolled into the study (patients randomised to the physical exercise program or to standard care).

Results

The flow-chart describing the recruitment basis of the study population and the subsequent selection process, from eligibility to randomisation, is reported in Fig. 1 and the baseline characteristics of patients randomised to the study intervention are described in Table 1. Enrolled patients had a mean age of 65 year. Sixty-eight of them were male, 17% were current smokers, 26% were past smokers. Twenty-one per cent of patients were diabetics and 76% had cardiovascular comorbidities.

Correlation analyses

Baseline 6MWT, expressed as number of meters walked in 6 minutes, significantly correlated with age (ρ= -0.57, P<0.001), gender (ρ= 0.21, P=0.001), cardiovascular comorbidities (ρ= -0.24, P<0.001), diabetes (ρ= -0.20, P=0.001), diastolic blood pressure (ρ= 0.38, P<0.001) albumin (ρ= 0.22, P=0.001), phosphate (ρ= 0.22, P<0.001), CRP levels (ρ= -0.16, P=0.03) and NYHA class (ρ= -0.21, P<0.001). In a multiple linear regression analysis including all univariate correlates of 6MWT, only age (beta= -0.55), gender (beta= 0.16), and cardiovascular comorbidities (beta= -0.17) maintained an independent association with 6MWT (P≤0.02).

Survival analyses

The median follow up was 3.3 years (interquartile range: 2.7-3.5 years). During this period, 69 patients died, 90 had fatal or non-fatal cardiovascular events, 159 were hospitalized. Overall, 182 patients had the composite end-point death/cardiovascular events/hospitalizations. In a bivariate Cox regression model, including the allocation arm as covariate, an increase of 20 meters walked during the 6MWT significantly (P<0.001)

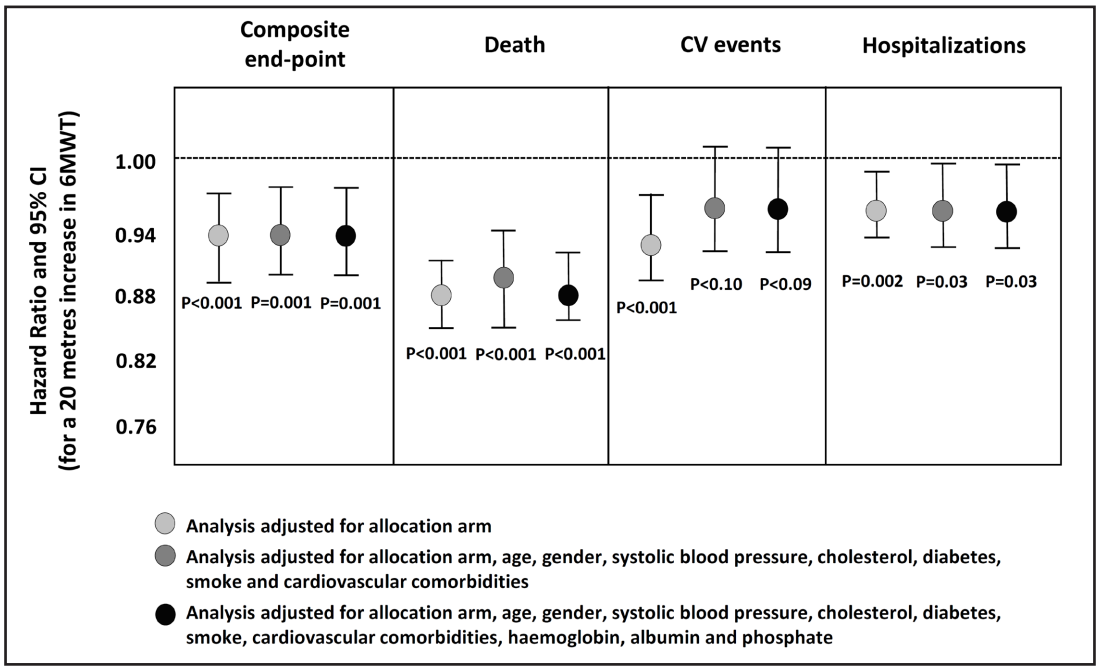

Fig. 2. Hazard ratio and 95% CI associated to an increase of 20 walked metres during the six-minute walking test (6MWT) for the composite end-point (A), all-cause mortality (B), fatal and non-fatal cardiovascular (CV) events (C) and hospitalizations (D).

reduced the risk of the composite end-point by 6%. Similar results were obtained in bivariate analyses of the individual end-points. In these models, an increase of 20 meters significantly reduced all-cause death by 12% (P<0.001), fatal and non-fatal cardiovascular events by 7% (P<0.001), and all-cause hospitalizations by 4% (P=0.002). The relationship between physical performance and the combined end-point was confirmed in a model adjusting for age, gender, systolic blood pressure, cholesterol, diabetes, smoking, cardiovascular comorbidities and allocation arm (HR: 0.94, CI: 0.91-0.98, P=0.001) (Fig. 2). By the same token, physical performance by 6MWT predicted all-cause death (HR: 0.89, CI: 0.84-0.94, P<0.001) and hospitalizations (HR: 0.96, CI: 0.92-0.99, P=0.03). A similar trend was observed for CV events, but this relationship did not reach statistical significance (HR: 0.96, CI: 0.91-1.01, P=0.10). Forcing risk factors peculiar to ESKD (haemoglobin, albumin and phosphate) into the model did not modify these relationships (Fig. 2).

Discussion

This study shows that 6MWT, a test commonly used to measure exercise capacity and motor fitness, predicts the risk for mortality, cardiovascular events and hospitalizations in chronic kidney disease patients on dialysis.

Physical activity, either measured by questionnaires [16, 9] or by accelerometers [17] or pedometers [18], is about 50% less in dialysis patients than in age and sex matched individuals. In the Dialysis Outcomes and Practice Patterns Study (DOPPS), self-reported activity was an independent predictor of death and exercising at least once a week predicted a 27% risk reduction [19]. Similar results emerged from the Wave 2 study of the United States Renal Data System (USRDS) [7] and in a study based on accelerometry [8].

While physical activity estimates engagement in daily activities, metrics of physical performance provide objective measures of motor fitness. As such, metrics of physical

performance looking at walking speed like Six-Minute Walking Test (6MWT), measure cardio-respiratory endurance, muscle endurance and strength as well as balance and coordination. The 6MWT has been applied in the whole age spectrum [19, 20] at population level and in several conditions, including chronic congestive heart failure [13, 21] and other cardiac conditions [22], COPD [14] and in hereditary diseases like cystic fibrosis [20]. This test has prognostic relevance because it predicts clinical outcomes in several categories of patients including elderly patients undergoing coronary artery bypass grafting [23] and patients with chronic heart failure treated with cardiac resynchronization [24]. Whether this test of motor fitness predicts mortality in dialysis patients has never been investigated. In this study, we found coherent correlations between physical performance (6MWT) and some factors which have an obvious influence on health status, such as age, gender, cardiovascular comorbidities, NYHA class, diabetes, diastolic blood pressure and other parameters [25-29]. However, only age, gender and cardiovascular comorbidities maintained an independent association with the 6MWT suggesting that these factors are major determinants of motor fitness in dialysis patients. According to our working hypothesis that physical performance measured by the 6MWT holds prognostic value in dialysis patients, we found that this test is a strong predictor of mortality, cardiovascular events and hospitalizations in this population. More specifically, in adjusted analyses, we observed a reduction of 6% in the combined outcome for each increase of 20 walked meters, and a reduction of 12% and 4% for all cause death and hospitalization. Thus our data extend to the dialysis population observations made in other conditions [23, 24] and underscore the relevance of objective measures of motor fitness in assessing the overall risk profile of dialysis patients.

Future studies, including phase-2 of EXCITE, will assess whether interventions aimed at improving physical fitness may translate into better clinical outcomes, including better physical performance, longer survival and reduced rate of cardiovascular events and hospitalizations in dialysis patients.

Disclosure Statement

The author of this article confirm that there are no conflicts to interest.

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