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ORIGINAL ARTICLE

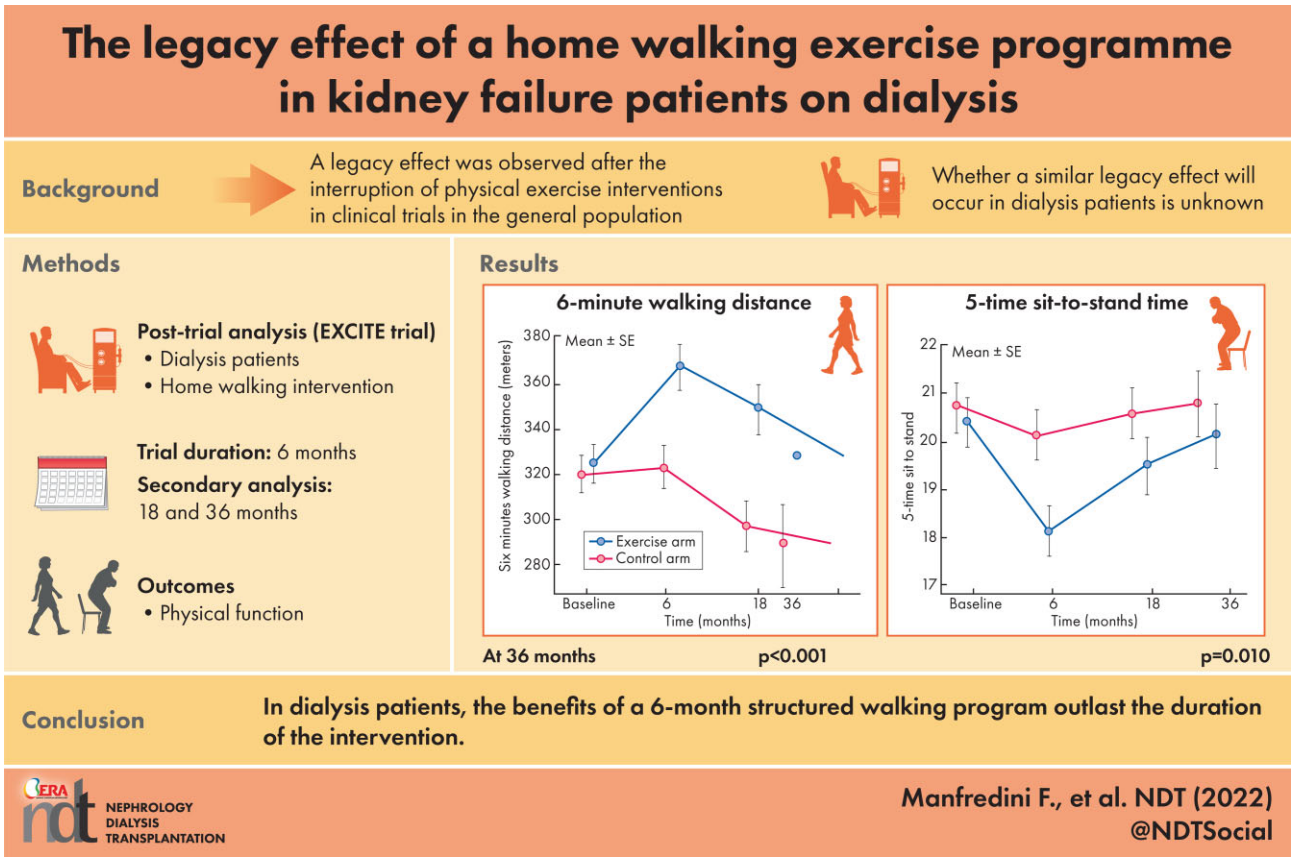
The legacy effect of a home walking exercise programme in kidney failure patients on dialysis

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GRAPHICAL ABSTRACT



ABSTRACT

Background. The EXerCise Introduction To Enhance performance (EXCITE) trial (*J Am Soc Nephrol* 28: 1259–1268, 2017) in dialysis patients showed that a 6-month home walking exercise programme improves physical function and two dimensions of the Kidney Disease Quality of Life Short Form (KDQOLSF-SF^{TM}) questionnaire. Whether improvements in physical function achieved by exercise interventions

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KEY LEARNING POINTS

What is already known about this subject?

- A legacy effect, i.e. an effect observed after the interruption of the key intervention in clinical trials, was also observed in trials testing physical exercise interventions in the general population.
- Whether such an effect also occurs in patients with chronic kidney failure is unknown.

What this study adds?

- In the frame of a 6-months randomized clinical trial testing a walking exercise programme in chronic kidney failure patients on dialysis, the gain in walking distance achieved at 6th month in the exercise group was maintained for up to 36 months.
- These results indicate that the legacy effect of physical exercise programmes described in the general population also occurs in the kidney failure population.

What impact this may have on practice or policy?

- The benefit of a walking training programme in patients with chronic kidney failure outlasts the duration of the intervention and postpones the unrelenting loss of walking performance which naturally occurs in this population.

are maintained in the long term has never been tested in the dialysis population.

Methods. In this post-trial study embedded in the EXCITE trial, we tested the response to the 6 min walking test (6MWT) and the 5-time Sit-To-Stand (5STS) tests and the KDQOLSF-SF^{TM} from the 6th month (end of the trial) to the 36th month.

Results. Among the 227 patients of the EXCITE trial cohort, 162 underwent at least three out of four testing visits (baseline, 6, 18 and/or 36 months) contemplated by the study protocol and 89 during all four testing visits. In the primary analysis by the linear mixed model, the gain in walking distance achieved in the 6th month in the exercise group [between-arms difference: +36 m, 95% confidence interval (CI): 22–51, $P < .001$] was maintained at the 18th month (between-arms difference: +37 m, 95% CI: 19–57, $P < .001$) and reduced to 23 m (95% CI: −4 to 49 meters, $P = .10$) at the 36th month. Overall, the post-trial difference in walking distance trajectories between the two study arms was highly significant ($P = .004$). Furthermore, the walking distance changes at the 6th ($r = 0.34$, $P = .018$) and 18th month ($r = 0.30$, $P = .043$) were directly related to the number of structured exercise sessions completed during the trial (i.e. the first 6 month). No such effect was registered in the response to the 5STS or in quality of life as measured by the KDQOLSF-SF^{TM}.

Conclusions. In dialysis patients, the benefits of a 6-month structured walking programme outlast the duration of the intervention and postpone the loss of walking performance which naturally occurs in this population, but does not affect the quality of life (QoL) and the response to the STS test.

Keywords: chronic kidney failure, dialysis, exercise, 6-minute walking test, sit to stand test, quality of life

INTRODUCTION

Sedentariness and poor physical functioning are common among kidney failure patients maintained on chronic dialysis and are associated with a high death risk [1–3] and poor quality of life (QoL) [4–6].

Regular exercise improves physical performance in dialysis patients [4–7], and rehabilitation outcomes and related physical and mental symptoms are considered as priorities by patients [8, 9]. In a meta-analysis by Clarkson *et al.* [7], including 27 randomized clinical trials in patients with kidney failure, regular exercise improved physical performance in these patients and the improvement was independent of exercise modality (cycling on a stationary cycle ergometer, treadmill, ground walking or weight lifting) and study setting (centre-based intra-dialysis or off-dialysis, or home-based). In these trials the duration of the exercise intervention was brief, lasting on average 15 weeks (range 8–26 weeks) [7] and, in general, with short-term observation. Information on the long-term effects of exercise-based interventions in kidney failure is very sparse and purely observational [10–12]. Whether improvements in physical function achieved by exercise interventions are maintained in the long term has never been tested in the dialysis population.

In the EXerCise Introduction To Enhance performance in dialysis patients (EXCITE) trial [6], a simple, home-based, 6-month walking exercise programme improved the degree of fitness in chronic kidney disease (CKD)-5D patients [6] as well as the cognitive and social interaction dimensions of the kidney disease component of the Kidney Disease Quality of Life Short Form (KDQOLSF-SF^{TM}) in patients randomized to the active arm of the trial as compared with those allocated to the control arm. By protocol, this trial contemplated systematic exercise testing after the end of the trial, up to the 36-month.

In this post-trial study embedded in the EXCITE trial, we tested the response to the 6 min walking test (6MWT) and the 5-time Sit-To-Stand (5STS) tests and the KDQOLSF-SF^{TM} from the 6th month (end of the trial) to the 36th month. Herein we describe the long-term effects of the 6-month walking exercise intervention on physical function and on QoL.

MATERIALS AND METHODS

The original protocol of the EXCITE trial was approved by the Ethics Committees of Renal Units ($n = 9$ Italian Centres) participating in the study and written informed consent was obtained from each participant. The Ethical Committee of the Coordinating Centre is that of 'Grande Ospedale Metropolitano Bianchi-Melacrino-Morelli' of Reggio Calabria, Italy (Committee's reference number: CE150157). The trial was

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registered in ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT01255969) on 8 December 2010.

Study design

EXCITE was a multicentre randomized, controlled clinical trial in dialysis patients testing the effect on physical performance of a personalized, home-based, low-intensity programme of walking exercise (exercise group) (see: of https://www.youtube.com/watch?v=ki8YX_t-0jA,5) versus usual care (control group, receiving just generic advice to maintain an active lifestyle). The intervention was well-structured and involved a progressive, individually profiled, increase in walking exercise [6]. The main outcome measures in this trial were the 6-min walking distance expressed in meters (6MWD) covered during the 6MWT, the 5STS and QoL as measured by the KDQOLSF-SF^{TM} questionnaire [6]. The walking cadence (steps/min) to be maintained at home was dictated by an easily available metronome (Seiko DM50; Seiko Ltd, Japan) which was distributed to all participants. Exclusion criteria were physical or clinical limitations or a high degree of fitness, i.e. the ability to walk a distance of 550 m in 6 min during the standard walking test [6]. All eligible patients were recruited between November 2009 and February 2011. This secondary analysis focusses on the subgroup of patients that had at least one post-trial testing session at 18 and/or 36 months.

Post-trial observation

After the end of the 6-month trial, patients randomized in the active arm of EXCITE were advised to remain active by performing one walking session of at least 10 min at a self-selected walking speed during the dialysis interval up to the 18th month (unstructured part of the exercise programme). Thereafter, up to 36th month, they were given just generic advice to maintain an active lifestyle, like the control group. A training diary was provided to each patient to register their walking sessions up to the 18th month. Total walked sessions were collected for the active group during the structured phase of the study (from baseline to the 18th month) but not thereafter. Patients in the control group were given just generic advice to maintain an active lifestyle.

Assessment of physical function

The assessment of physical function (6MWT and 5STS), from baseline up to the 36th month, was always performed by the same operators of the rehabilitation team (Department of Neuroscience and Rehabilitation, University of Ferrara, Italy).

During the trial execution, the testing sessions were always arranged on a non-dialysis day, 24 h after the dialysis session, either in the morning (between 7 a.m. and 1 p.m.) or in the afternoon (between 2 p.m. and 6 p.m.). Functional capacity testing in both study arms (exercise and control groups) was performed at baseline, and after 6, 18 and 36 months.

Quality of life

QoL was measured at the same time points of functional capacity testing by the Kidney Disease Quality of Life Short Form (KDQOLSF) instrument, short form, version 1.3 (KDQOLSF-SF^{TM}) in the version translated into Italian and specifically validated in a sample of Italian CKD patients. Whenever needed, the compilation of the replies to the KDQOLSF^{TM} was helped by nurses unaware of the treatment allocation of patients.

Statistical analyses

Data are expressed as mean and standard deviation (normally distributed data), median and interquartile range (non-normally distributed data), or as percentage frequency (categorical data) and comparisons between groups were made by independent *t*-test (normally distributed data), Mann–Whitney U test (non-normally distributed data) or chi-squared test (categorical data), as appropriate. To account for multiple testing a Bonferroni correction was applied.

In the primary analysis, we included all patients that took part in the EXCITE trial, including those who completed the 6-month trial ($n = 227$) and those who had the post-trial observation with at least one long-term visit, i.e at three testing sessions (baseline, 6 months and at 18 and/or 36th months; $n = 162$). The between-groups comparisons of the evolution over time of 6MWD and 5STS and the various dimensions and summary measures of the KDQOLSF^{TM} questionnaire were investigated by the linear mixed model (LMM). In LMMs (having the repeated measurements of the two physical performance tests as dependent variables), we introduced as covariates the allocation arm (active group versus control group), the number of visits and the interaction term between the allocation arm and the number of visits. By LMMs analysis, at 6, 18 and 36 months, we derived the estimated within-arm changes from baseline of the three key study outcomes (namely, 6MWD, 5STS and QoL metrics) and the corresponding 95% confidence interval (CI) and *P*-values. For the 6MWD, we also calculated the cumulative probability of an increase in walking distance >20 m at 6, 18 and 36 months. In this analysis, data were compared by the log-rank test. Furthermore, Spearman's rank correlations between the exercise sessions completed during the trial and the changes in 6MWD at the 6th, 18th and 36th month were performed.

Data analysis was performed using a standard statistical package (SPSS for Windows, version 22; IBM SPSS, Chicago, IL, USA).

RESULTS

The original population was composed of 227 patients who completed the EXCITE trial, i.e. patients that underwent physical performance tests both at baseline and after 6 months. The complete flow diagram of the EXCITE trial was reported elsewhere [2] and the same flow diagram is now given as Supplementary data, Fig. S1. The flow diagram of the trial of patients actually entered in the EXCITE trial, is presented in Fig. 1. A total of 47 patients in the exercise arm and 22 in the control arm did not complete the 6-month trial. In all,

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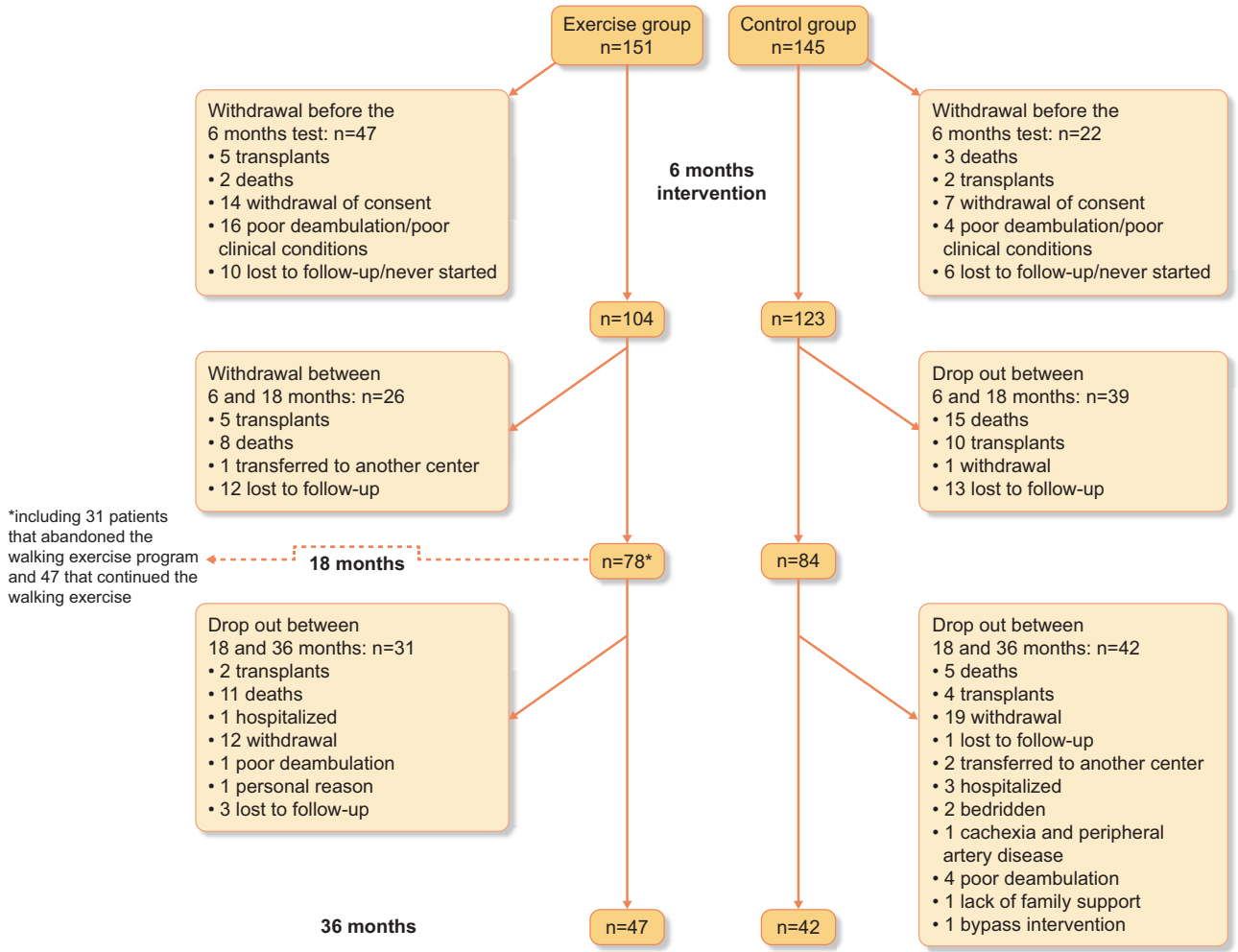


FIGURE 1: Study flow of the EXCITE study cohort from baseline to the 36th month.

26 patients in the exercise arm and 39 in the control arm exited the study for various reasons between the 6 and the 18 months and 31 and 42 between the 18 and the 36 months. A total of 162 patients underwent at least three testing visits (baseline, 6, 18 and/or 36 months) and 89, all four testing visits contemplated by the study design. Patients with three or four visits did not differ from those with only two visits (the two in-trial visits) as for demographic, clinical and biochemical data (see Table 1, all $P > .90$ by the LMM). Patients in the active arm of the trial with three or more visits did not materially differ from those in the control arm for as for demographic, clinical and biochemical data (Supplementary data, Table S1).

Exercise adherence during post-trial observation (from the 6 to the 18 month)

A total of 31 patients in the exercise group did not perform any exercise session, whereas the remaining 46 patients performed at least one training session per week, on average 173 ± 94 sessions per patient.

Longitudinal evolution of 6MWD and STS tests

The changes over time of mean values (and 95% CI) of 6MWD and 5STS test, by study arms, are shown graphically in Fig. 2. At the 6th month (end of the trial) and at the 18th month (1 year after the trial ended) a highly significant increase in walking distance was observed in patients of the active arm (6th month versus baseline, +39 m, 95% CI: 28 to 50 m, $P < .001$; 18th month versus baseline, +18 m, 95% CI: 5 to 32 m, $P = .008$). At the same time points no significant change was observed in patients of the control arm (6th month versus baseline, +3 m, 95% CI: −7 to 13 m, $P = .58$; 18th month versus baseline, −19 m, 95% CI: from −32 to −6 m, $P = .004$). At the 36th month, the walking distance did not significantly differ from baseline in patients of the active arm (36th month versus baseline, 10 m, 95% CI: 29 to 9 m, $P = .31$) whereas it reduced in those of the control arm (36th month versus baseline, −33 m, 95% CI: −53 to −14 m, $P = .001$). The between arms difference in walking distance changes at the 6th month (active group versus control group, +36 m, 95% CI: 22–51 m, $P < .001$) maintained almost identical at the 18th month (active group versus control group, +37 m, 95% CI: 19 to 57, $P < .001$). At 36th month it was still nominally higher (+23 m, 95% CI: −4 to 49 m) in the active group but the difference was not significant ($P = .10$). Overall, the post-trial difference in walking distance trajectories between the two study arms was highly significant ($P = .004$) (Fig. 2).

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Table 1. Demographic, clinical and biochemical data of patients that did not participate into the post-trial observation, patients that underwent at least three visits and those that underwent all four testing visits; for no variable was a statistically significant difference was registered (all $P > .90$ by the LMM)

	Patients with 2 visits ($N = 227$)	Patients with 3 visits ($N = 162$)	Patients with 4 visits (completers) ($N = 89$)
Number			
Age (years)	64 ± 13	64 ± 13	62 ± 12
Male gender, *n* (%)	66	68	65
Haemodialysis/CAPD (*n*)	192/35	141/21	77/12
BMI (kg/m^2)	26 ± 5	26 ± 5	26 ± 5
Smoking (0 = no; 1 = yes)	19%	17%	17%
Diabetes (0 = no; 1 = yes)	18%	16%	16%
Systolic BP (mmHg)	129 ± 18	130 ± 18	131 ± 17
Diastolic BP (mmHg)	71 ± 11	71 ± 11	72 ± 11
Heart rate (beats/min)	74 ± 9	74 ± 9	73 ± 8
Total cholesterol (mg/dL)	165 ± 39	164 ± 40	167 ± 42
Triglycerides (mg/dL)	133 (99–194)	130 (96–186)	135 (99–198)
Haemoglobin (g/dL)	11.3 ± 1.5	11.3 ± 1.5	11.5 ± 1.5
Albumin (g/dL)	3.8 ± 0.4	3.8 ± 0.4	3.9 ± 0.4
Calcium (mg/dL)	8.8 ± 0.7	8.8 ± 0.7	8.9 ± 0.7
Phosphate (mg/dL)	4.8 ± 1.5	4.8 ± 1.6	5.0 ± 1.5
PTH (pg/mL)	263 (156–414)	259 (163–404)	281 (167–418)
Creatinine (md/dL)	9.9 ± 2.7	10.1 ± 2.6	10.2 ± 2.8
Glycaemia (mg/dL)	106.1 ± 50.3	106.4 ± 54.6	103 ± 34
Urea (mg/dL)	150 ± 41	151 ± 41	156 ± 40
CRP (mg/L)	5.0 (3.0–9.0)	5.0 (3.0–9.0)	4.9 (2.5–9.0)
Stroke/transient ischaemic attack, *n* (%)	11	9.3	4
Anginal episodes, *n* (%)	12	10	10
Arrhythmia, *n* (%)	10	9	8
Heart failure, *n* (%)	16	18	16
Peripheral vascular disease, *n* (%)	10	10	8
History of neoplasia, *n* (%)	20	23	23
Anti-hypertensive therapy, *n* (%)	73	73	75
Assisted deambulation, *n* (%)	3	3	1
Independent deambulation, *n* (%)	97	97	99

CAPD, continuous ambulatory peritoneal dialysis; BMI, body mass index; BP, blood pressure; PTH, parathyroid hormone; CRP, C-reactive protein.

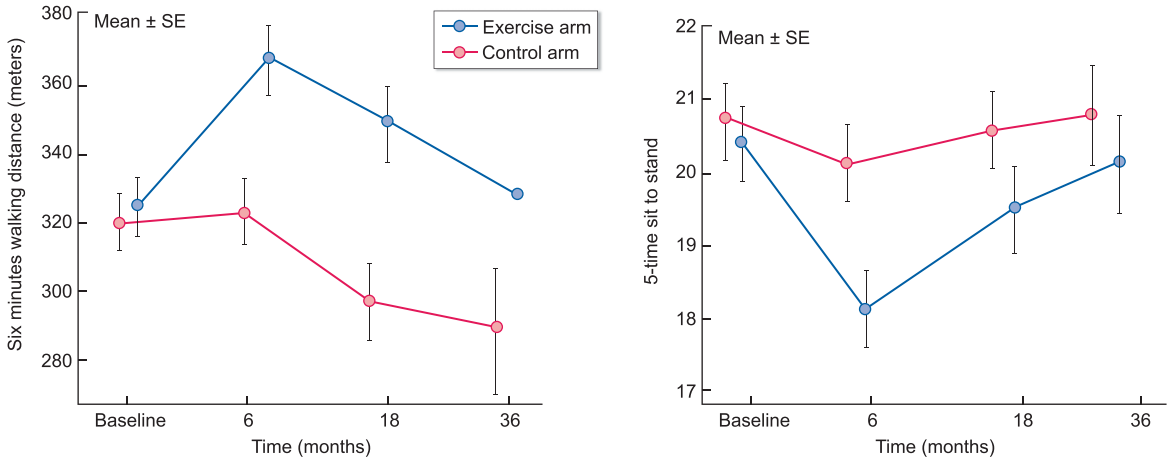


FIGURE 2: Post-trial response to the 6MWT and to the 5STS tests at the end of the EXCITE trial (6 month) and at 18 and 36 months. Data were analysed by the Linear Mixed Model.

Like the 6MWT, also the 5STS test improved at the 6-month in the active arm (within-arm, $P < .001$) but remained almost unchanged in the control arm (Fig. 2). However, from 6th month onward in the post-trial observational analysis, the response to this test did not differ ($P = .15$).

Relationship between exercise sessions completed and variations of performance

As shown in Fig. 3, among patients in the active arm with at least three visits there was a significant relationship between the number of structured exercise sessions completed during

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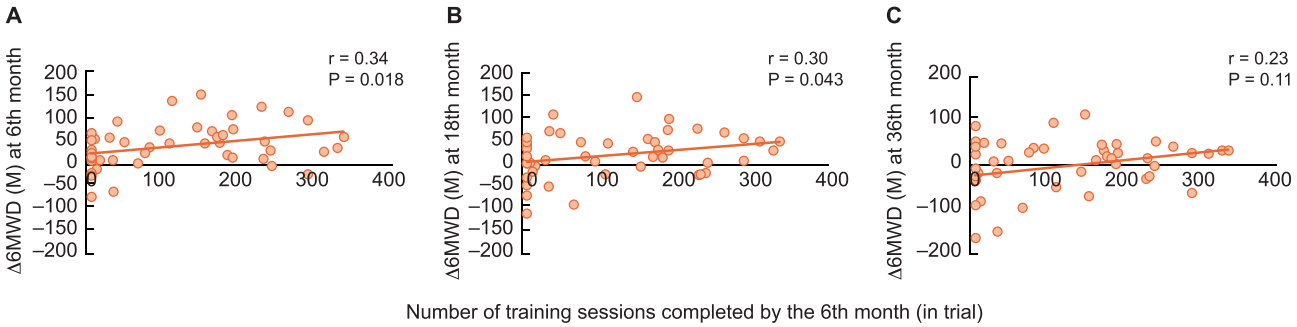


FIGURE 3: Rank correlations between training sessions completed during the trial (the first 6 months) and variations of 6MWD at 6 (**A**), 18 (**B**) and 36 (**C**) month respect to baseline.

the trial (the first 6 months) and 6MWD changes between the baseline value and the value at the 6th month (upper panel, $r = 0.34$; $P = .018$). The same relationship was also observed for 6MWD changes between baseline and the 18th month ($r = 0.30$; $P = .043$). A similar tendency existed also for changes between baseline and the 36th month but the association failed to achieve statistical significance ($r = 0.23$; $P = .11$).

Longitudinal evolution of quality of life in the study

The kidney disease, the physical function and the mental functioning components of the QoL questionnaire (KDQOLSF^{TM}) in the two study arms across time are summarized in Supplementary data, Table S2 and S3. Overall, the evolution over time of the mental component score (MCS) and physical component score (PCS) did not significantly differ between patients in the active and control arms.

DISCUSSION

This post-trial study in the frame of the EXCITE trial shows that the gain in walking distance at 6 months achieved during the trial in patients in the active arm gradually reduce over time and at 3 years the walking distance re-attained the baseline value. In the control group, the walking distance worsened throughout the observation period and at 3 years it was substantially less than at baseline. Overall, the walking performance in patients in the active arm remained much higher than in those in the control arm up to 3 years. The more favourable trajectory in the intervention group indicates that the benefits of a walking training programme outlast the duration of the intervention and postpone the unrelenting loss of walking performance which naturally occurs in this population.

The persistence of a treatment effect beyond the actual intervention period, the legacy effect, is a well known phenomenon. was noted in clinical trials in type 2 diabetic patients. In the United Kingdom Prospective Diabetes Study (UKPDS), patients with type 2 diabetes mellitus who had received intensive glucose therapy, notwithstanding an early post-trial loss of glycaemic differences, continued to have a reduced microvascular risk and clear-cut risk reductions for myocardial infarction and death during 10 years of post-trial follow-up [13]. Long-term post-trial observations in randomized controlled trials in hypertensive subjects showed that patients treated with antihypertensive agents maintain a long-term benefit after discontinuation of therapy [14]. Similarly, in the Modification of Diet in Renal Diseases trial (MDRD) patients assigned to a low blood pressure target during the trial showed a 32% risk reduction for a composite endpoint including death and kidney failure across the 7 years post-trial [15]. A legacy effect was also observed in trials testing physical exercise interventions. In the Studies Targeting Risk Reduction Interventions through Defined Exercise (STRRIDE) trial in middle-aged sedentary, overweight or obese subjects, 10 years after an 8 months exercise training intervention the decline in cardiorespiratory fitness and in metabolic parameters went along with the training intensity during the 8-month intervention [16]. Accordingly, in the present analysis we found (Fig. 3) that adherence to the training (number of walking sessions performed during the 6-month trial) in haemodialysis patients associated with changes in walking distance not only at 6 months but also at 18 and tendentially also at 36 months. The fact that the walking distance did not worsen during the trial in the control arm probably depends on the general recommendation given to patients of this arms to maintain an active lifestyle. The recommendation given at the end of the trial to patients in the active arm to maintain just one walking session per day at a self-selected speed during the inter-dialysis interval was followed by 60% ($n = 47$) of patients, while the remaining did not perform any exercise. The changes in walking distance over time were very similar in these sub-groups and both maintained a walking distance longer than that of patients in the control group. The difference among control patients and patients in the active arm at 18 and 36 months was 33 m and 19 m, respectively. Such a difference may be of clinical relevance because in a previous observational analysis of EXCITE, a 20-m longer walking distance associated with a 12% reduction in all-cause ($P < .001$) and a 7% reduction in the risk for fatal and non-fatal cardiovascular events ($P < .001$) [17]. Overall, this is a favourable long-term outcome in a population exposed to deconditioning, like patients with chronic kidney failure [18]. The long-term persistence of exercise effects was selective for the walking distance because the improved response to the STS test registered at 6 month was not maintained thereafter. The 6MWT is a sub-maximal exercise test reflecting aerobic capacity and endurance [19] and the training programme tested in EXCITE was precisely based on a structured walking exercise. The 5STS test is a

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test of leg strength [20] and the walking exercise usually does not specifically target the response to this test. The fast reversibility of the exercise effects in the absence of specific training stimuli [21] and the uraemia-related sarcopaenic stress [22] may explain a different long-term response in the 5STS test. The two tests are weakly to moderately associated in healthy subjects [23] and in patients with chronic diseases, like bronchopulmonary disease [24]. Likewise, the benefit of the exercise programme on the cognitive and the social interaction dimension of the kidney disease components of the KDQOLSF-SF^{TM} questionnaire observed at 6 months in the EXCITE trial [6] was not maintained beyond the 6th month and there was no overall between group difference in the physical and mental component scores of the same questionnaire throughout the post-trial observation. Like patients that participated in the EXCITE trial, older adults reporting a decrease in exercise do not maintain the initial level of QoL at follow-up [25].

The study has limitations. Even though patients who participated in the post-trial observational study had similar demographic and clinical characteristics as compared with the original population of the EXCITE trial, these patients represent a selected population and results in this group cannot be generalized. Only a minority of patients (30/151 patients, i.e. only 20%) who entered the active arm of the trial, actually maintained the reduced exercise they were advised to perform post-trial. This observation underscores the difficulty of maintaining a home-based exercise intervention in the long term in dialysis patients. On the other hand, the results in this subgroup of adherent patients were identical to those of patients originally allocated to active arm who stopped exercising at the end of the trial, suggesting that the observed benefit beyond the 6th month could be a legacy of the structured intervention applied during the trial. Therefore, a 6-month period of home exercise may produce long-term benefits in dialysis patients as was observed in middle-aged sedentary, overweight or obese subjects, 10 years after an 8-month exercise training intervention [16].

In conclusion, in dialysis patients, the benefits of walking performance of a home-based walking training programme outlast the duration of the intervention and postpone the loss of walking performance which naturally occurs in this population. Findings in this study underscore the potential of physical exercise programmes in the dialysis population and are a strong call for long-term studies testing these interventions based on clinical endpoints including mortality and the risk for hospitalization.

SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

AUTHORS' CONTRIBUTIONS

The trial was conceived by F.M. and C.Z. The design of the trial and of the post-trial observations was done by C.Z., G.T. and F. Manfredini G.T., G.D. and C.T. performed the statistical analysis. F. Manfredini and C.Z. prepared the first draft of the article which was critically read by F. Mallamaci, G.T., G.D., C.T. and N.L. C.Z. prepared the final version of the manuscript which was eventually approved by all authors.

FUNDING

This study had no funding.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

APPENDIX

Rossella Baggetta, Davide Bolignano, Silvio Bertoli, Daniele Ciurlino, Lisa Rocca-Rey, Antonio Barillà, Yuri Battaglia, Renato Rapanà, Alessandro Zuccalà, Graziella Bonanno, Pasquale Fatuzzo, Francesco Rapisarda, Stefania Rastelli, Fabrizio Fabrizi, Piergiorgio Messa, Luciano De Paola, Luigi Lombardi, Adamasco Cupisti, Giorgio Fuiano, Gaetano Lucisano, Chiara Summaria, Michele Felisatti, Enrico Pozzato, Anna Maria Malagoni, Pietro Castellino, Filippo Aucella, Samar Abd ElHafeez, Pasquale Fabio Provenzano and Luigi Catizone all collaborated on the EXCITE trial.

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