

Intradialysis exercise in haemodialysis patients: effective but complex and costly

Carmine Zoccali ^{1,2,3}, Fabio Manfredini⁴, Mehmet Kanbay⁵ and Francesca Mallamaci^{6,7}

¹Renal Research Institute, New York, NY, USA

²Institute of Biology and Molecular Genetics, Ariano Irpino, Italy

³Associazione Ipertensione, Nefrologia e Trapianto Renale (IPNET) c/o Unità Operativa di Nefrologia, Dialisi e Trapianto Renale, Grande Ospedale Metropolitano di Reggio Calabria, Reggio Calabria, Italy

⁴Department of Neuroscience and Rehabilitation, University of Ferrara, Ferrara, Italy

⁵Department of Medicine, Division of Nephrology, Koc University School of Medicine, Istanbul, Turkey

⁶Unità Operativa di Nefrologia, Dialisi e Trapianto Renale, Grande Ospedale Metropolitano di Reggio Calabria, Reggio Calabria, Italy

⁷Institute of Clinical Physiology-Reggio Calabria Unit, National Research Council of Italy, Reggio Calabria, Italy

Correspondence to: Carmine Zoccali; E-mail: carmine.zoccali@icloud.com

Exercise modulates various health outcomes, ranging from cardiorespiratory fitness and musculoskeletal health to mental well-being and cognitive function. Regular physical exercise can attenuate the risk of chronic diseases and improve longevity. Physical activity is recommended by the Centers for Disease Control and Prevention [1] and other major health agencies to prevent obesity, type 2 diabetes, heart disease, many types of cancer, depression and anxiety and dementia. Lack of physical activity is a hallmark of chronic kidney disease (CKD), particularly in kidney failure patients requiring dialysis, a condition plagued by sedentarism, fatigue, decreased physical function and poor quality of life (QoL). Deficient resources and infrastructure to support exercise programs, particularly in low-resource settings, are major hindrances for exercise programs in the dialysis population.

An evaluation of exercise counselling practices among nephrologists in 2001 showed that only a small proportion of clinicians counselled patients about exercise [2]. That notwithstanding, physical activity has been formally recommended since 2005 by the Kidney Disease Outcomes Quality Initiative guidelines, but the application of exercise programs in dialysis patients is restricted to a minority of dialysis centres and the issue remains an unmet clinical need.

Exercise interventions can be delivered during dialysis by using a cycling apparatus placed into the dialysis bed or properly associated to a dialysis chair or prescribed to be done at home. The type of exercise can be aerobic (e.g. cycling during dialysis or walking in a home-based program), resistance [e.g. weightlifting, stretching elastic bands and other interventions that can be done during haemodialysis (HD) or at home] or a combination of the two (aerobic and resistance exercises).

WHAT IS KNOWN?

The number of randomized trials testing intradialysis exercise by far exceeds that of trials testing home-based programs, and cycling is the most applied aerobic exercise in intradialysis pro-

grams. A recent network meta-analysis [3] identified 78 studies in >3000 patients comparing the efficacy of intradialysis versus home exercise. In this meta-analysis, combined training was the intervention with the best performance to increase the maximum rate of oxygen (VO_2max) our body can use during exercise. Inflammation measured by C-reactive protein decreased significantly but modestly with both resistance training (mean difference between the exercise and the control arm -2.6 mg/l) and aerobic training (-1.4 mg/l). Kt/V and the physical component of the 36-item Short Form QoL questionnaire (SF-36) improved significantly but quite modestly in the aerobic training arms as compared with the control arms. Globally, no intradialytic exercise modality was superior to others or comparable home-based exercise modalities for improving the outcomes included in the meta-analysis. Independent of being intradialysis or home based, exercise interventions lasting >12 weeks and interventions of moderate–vigorous intensity improved functional capacity more than interventions <12 weeks or of just moderate intensity. In brief, wherever delivered, physical exercise programs bring benefits to dialysis patients.

Observational analyses [4] in the EXCITE trial (EXercise Introduction To Enhance Performance in Dialysis; NCT01255969) [5] database, a trial that tested the effectiveness of home-based walking exercise, showed that an increase of 20 walked meters during the 6-minute walking test (6MWT) goes along with a 6% reduction in the risk of a composite endpoint including all-cause death, cardiovascular events and hospitalization ($P = .001$) [4]. A thorough per-protocol analysis of the EXCITE trial extended over the 3 years following the end of the trial showed that walking exercise reduces the risk for hospitalization [6] and postpones the decline of walking capacity in dialysis patients [7]. Large trials testing the effect of exercise intervention on major clinical outcomes, like mortality and cardiovascular events, and the impact of improvements in physical performance on QoL in the dialysis population remain an absolute priority for clinical research. Thus nephrologists should make every effort to participate in large-scale trials and start applying physical exercise programs in their dialysis units.

Table 1: Comparison of the resources employed in the PEDAL and EXCITE trials.

Aspect	PEDAL trial	EXCITE trial
Personnel	One 0.6 FTE physiotherapy assistant per 12–20 participants (on average 16 participants). In PEDAL, 379 patients were tested at baseline and 243 at 6 months. On average, the population across the trial can be estimated to be ≈311 patients. Therefore, 190 0.6 FTE physiotherapy assistants were needed in PEDAL.	One 0.2 FTE physiotherapy trainee ^a per 296 participants. In EXCITE, a second 0.2 FTE physiotherapy trainee was involved to ensure continuity and accelerate training and testing.
Supervisor	1 FTE supervisor per 80 participants. For the 311 (average) patients overseen across the PEDAL trial, 4 FTE supervisors were needed.	1 FTE senior physiatrist (professor of physiotherapy) overseeing the trial (296 patients) remotely. Occasionally available for telephone contacts with nephrologists or trial participants.

FTE: full-time equivalent.

^aThis figure results from a time calculation considering the training of the 151 participants in the active arm of the trial (20 minutes per patient, for a total of 50 hours) plus the time for testing (30 minutes per patient with 296 patients at baseline and 227 patients at 6 months, for a total of 523 tests, i.e. 261 hours). The total time (training 50 hours + testing 261 hours) is 301 hours. The yearly FTE of physiotherapy trainees is 1760 hours. Hence the FTE needed in the EXCITE trial was 0.17 (rounded off to 0.2 FTE). These estimates do not include the cost of travel for the physiotherapy trainees (two visits for each of the 13 nephrology units that participated in the EXCITE trial).

WHAT DID THE DiaTT TRIAL REVEAL?

The recent multicentre, interventional, cluster randomized controlled DiaTT (Dialysis Training Therapy) trial included 1211 German HD patients with a mean age of 65.9 years from 24 dialysis centres from a single non-profit kidney care provider (Kuratorium für Dialyse und Nierentransplantation) with a 12-month follow-up period. This clinical trial evaluates the role of intradialytic three-times-per-week supervised endurance (bed-cycle ergometer) and resistance exercise training (elastic bands, exercise balls, dumbbells) lasting for 60 minutes per session compared with the standard of care [8]. Remarkably, DiaTT enrolled about one-third of all patients included in the recent network meta-analysis by Ferrari *et al.* [3]. The primary outcome in this trial was the change in the 60-second sit-to-stand test (STS60, a test that is part of a family of various tests based on the same activity, the STSs) between baseline and 12 months. STSs are used to evaluate lower body strength at the population level, are simple to perform and are easily implemented in patients with mobility problems by trained, non-medical personnel.

A total of 917 patients were included in the final analysis of the trial (exercise intervention, $n = 446$; usual care, $n = 471$). At 12 months, the STS60 repetitions improved from 16 to 19 in the exercise group but declined from 16 to 15 in the usual care group ($P < .0001$). Of note, the between-group difference in the 6MWT, a secondary outcome in the DiaTT (37.5 m), was very close to that registered in the EXCITE trial (39 m). The physical summary score and vitality subscale of the SF-36 showed a favourable trend in the exercise group compared with the control group. The median days spent in the hospital were two per year and five per year in the exercise and usual care group, respectively. Mortality and dialysis-specific adverse events were not affected.

WHERE DO WE STAND?

In essence, the DiaTT demonstrated that a well-concerted intervention contemplating intradialysis cycling, an aerobic type of exercise, and resistance training with elastic bands, exercise balls and dumbbells achieves the same benefits registered in the EXCITE trial, a trial that tested a simple, easy to implement, home-based walking exercise intervention that had both the 6MWT and 5 times sit to stand to sit (5STS) as primary outcomes.

Like in DiaTT, in EXCITE the 5STS improved in the exercise arm as compared with the control arm. Thus these trials, the largest performed so far focusing on intradialysis and home exercise, respectively, recapitulate findings in the Ferrari *et al.* [3] network meta-analysis showing that, wherever delivered, exercise favourably impacts physical performance.

The substantially similar results of the DiaTT and EXCITE trials raise the problem of which type of intervention (during dialysis or at home) is logistically preferable in the dialysis population. The DiaTT trial required trained exercise therapists and entailed substantial cost and labour to implement intradialysis exercise, an intervention difficult to organize at times because of space and staff shortages. Even if motivated, nephrologists find it hard to maintain intradialysis exercise programs. The reality is that exercise programs, be they intradialysis or at home, are very scarcely applied in European nephrology centres. In a systematic survey on this problem in European countries, I asked leading nephrologists in Germany, the UK, Belgium, Spain and Italy to make a gross estimate of nephrology centres that maintain an exercise program in dialysis patients in their countries and the response was invariably 'less than 10%'. The DiaTT trial was possible because of generous funding by the Innovation Fund of the Federal Joint Committee of Germany (Innovationsfond des Gemeinsamer Bundesausschuss, grant 01NVF17052). The investigators of the DiaTT trial estimate that the cost for personalized training in Germany would be ≈€25 per session per person (<https://www.eurekalert.org/news-releases/995624>), i.e. ≈€3500 per year if intradialysis exercise is anticipated for all dialysis sessions. This cost is ≈15% of the yearly cost of HD per se in Germany (€23 341) [9]. Starting an intradialysis exercise program implies a not trivial initial investment for the nephrology unit because the cost of the cycling apparatus is ≈€7000 per dialysis bed/chair plus the maintenance cost [10].

Thanks to the application and competence of Kirsten Anding-Rost and the other DiaTT investigators and the generous funding by Innovationsfond des Gemeinsamer Bundesausschuss, DiaTT has been an unquestionably successful trial. However, without statutory health insurance recognition in Germany, this program is difficult to maintain. Cost-effectiveness analyses of the trial are still unavailable. A similar trial, the PrEscription of intraDialytic exercise to improve quAlity of Life (PEDAL) trial [11] enrolled 379 HD patients and 243 of these completed the 6-month

intervention. In contrast with the DiaTT trial, PEDAL did not register any significant improvement in QoL or in VO₂max or other physical performance measures. Although less than in DiaTT, the costs of delivering the PEDAL intervention were also substantial (US\$598–1092 per participant per year). The staff requirements for ensuring the intradialysis exercise program in PEDAL are summarized in Table 1 and compared with those needed for the walking exercise in the EXCITE trial. This head-to-head comparison clearly shows that the resources needed for a walking exercise program are just a small fraction of those needed for an intradialysis exercise program.

Thus, if we are to promote physical exercise in the dialysis population, a home-based program like the one applied in the EXCITE trial seems to be a simpler, far more cost-effective approach. The training in the EXCITE trial required no special equipment and it can be done almost anywhere. In the EXCITE trial, only amputees and patients unable to stand were excluded. Even for patients with handicaps, with proper assistance, walking can be a social activity, allowing individuals to walk with the help of family members or friends, which can make the exercise more enjoyable and sustainable in the long term. Finally, walking is a weight-bearing exercise that can help prevent bone disease progression in kidney failure patients.

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CONFLICT OF INTEREST STATEMENT

None declared.

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