**Original Article**

**Effects of Graded Exercise Training on Functional Capacity, Muscle Strength, and Fatigue after Renal Transplantation: A Randomized Controlled Trial**

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**ABSTRACT.** Successful renal transplantation (RT) recipients suffer residual muscle weakness, fatigue, and low functional capacity. A safe, feasible, structured, early graded exercise training to improve functional capacity, muscle strength, and fatigue is the need of the hour. The aim of the study is to assess the effectiveness of graded exercise training on the functional capacity, muscle strength, and fatigue after RT. It is a randomized controlled trial conducted at a tertiary care hospital from January 2012 to December 2016. This trial included 104 consented, stable renal transplant recipients without cardiopulmonary/neuromuscular impairment. They received either routine care (51) or graded exercise training (53) for 12 weeks after randomization. The functional capacity, isometric quadriceps muscle strength, and fatigue score were measured at baseline, six, and 12 weeks later to induction. The outcomes of the study and control groups were analyzed using the t-test, Wilcoxon signed-rank test, ANOVA, and Pearson’s correlation. For all analyses, *P* <0.05 was fixed acceptable. The functional capacity improved by 147 and 255 m, the muscle strength by 6.35 and 9.27 kg, and fatigue score by 0.784 and 1.781 in the control and the study group (SG), respectively, significantly more in the SG. Functional capacity had a positive and negative correlation with muscle strength and fatigue, respectively (*P* <0.05). The graded exercise training significantly improved the functional capacity, fatigue levels, and muscle strength after RT.

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**Introduction**

Renal transplantation (RT) has improved patient survival in end-stage renal disease.¹ However, even after successful RT patients suffer from reduced muscle strength, fatigue, and myopathy.²⁻⁴ The lowered physical fitness, effort tolerance, and muscle strength with
fatigue affect the functional capacity. RT recipients also are noted to have hypoactive lifestyle, physical fatigue, and impaired peak exercise performance similar to other solid organ transplants, implicating the need for the structured rehabilitation program.\textsuperscript{5-8} Many recommendations support regular physical activity and exercise along with titration of medications to improve functional abilities and to overcome the barriers of rehabilitation.\textsuperscript{9-14} The regulation of intensity and progression of exercises remains a challenge due to the hypertensive, nonlinear responses and muscle weakness.\textsuperscript{15,16} The follow-up is good in the early phase and hence initiating early, graded exercise training would be a feasible and effective way to ameliorate the physical impairments.\textsuperscript{9,14,17}

### Subjects and Methods

This randomized controlled trial with blinding of outcome measurement was done on 104 Post RT recipients [control group (CG) - 51 and study group (SG) - 53] during January 2012 and December 2016 with institutional ethics committee (IEC-NI/11/DEC26/83) approval and the retrospective registration with CTRI (CTRI/2017/11/010601). RT recipients with vitals instability, surgical complications, acute renal rejection, and pre-existing neuromuscular deficits were excluded from the study. The patients with age (18–65 years), both genders, willing to participate were allocated to either control or SG by restricted random sampling (unequal block randomization, eight to 10 in each block, Figure 1). All the participants received standardized medical care as per their requirements including induction therapy, immune suppression, and pulse steroids.

A structured, graded exercise training protocol after RT (SET-adjuvant RT) was framed as per the ACSM guidelines\textsuperscript{18} and expert opinion. The contents of training protocol were validated and found to be clinically safe. The CG received routine hospital care, including chest physiotherapy, breathing exercise, incentive spirometer training, and graded ambulation as per patient tolerance. The SG got trained in three phases (Table 1). The phase I training included graded ambulation, strength...
training with the use of gravity and own body weight. The study group was assessed for 10 repetitions maximum (RM) of the muscle quadriceps, a key muscle for ambulation. Phases II and III had exercises involving resistance training (50% to 80% of 10 RM), flexibility exercises and aerobic conditioning (walking/bicycle pedalling) as per rating of perceived exertion (RPE) on the Borg scale in graded manner. The exercise intensity was progressively increased with RPE (range 6–9) during 1st week to RPE (range 9–13) during 10–12 weeks. Resistance was increased in graded manner at rate of 5% to 10% of the previous load as per tolerance every week during follow-up. The resisted exercise was avoided in the fistula/cannulated extremity. The SG patients underwent supervised, graded exercise training twice a week with phone call reminders. The study participants did the trained exercises at home for two more days and details were noted in the exercise log. The exercise log was maintained by the patient/caretaker to improve the adherence to protocol. The outcomes were measured at three-time points (T1-Baseline - before discharge, T2 - at the end of 6 weeks, T3 - at the end of 12 weeks after allocation).

Outcome measures

The functional capacity was quantified by the distance walked in the six-minute walk test, as per the American Thoracic Society Guidelines. It is a safe, widely used self-paced submaximal exercise with the ability to predict mortality and the clinical outcomes after transplantation. The isometric quadriceps muscle strength (IQMS) was measured with standardized dynamometer. The fatigue was measured with fatigue severity score, used in many neuro-musculoskeletal dysfunctions and also in RT patients.

Data Analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) statistical software version 15.1 (SPSS Inc, Chicago, IL, USA) with 0.05 as the level of confidence. The normality of data was verified using Shapiro–Wilk test. The within and between-group comparison of the functional capacity was analyzed with paired and unpaired t-test, respectively. The IQMS and fatigue levels were compared between the groups using Mann–Whitney U-test. The test of repeated measures of ANOVA with Bonferroni correction was

| Table 1. Description of exercises in the control and study group. |
|-----------------------|------------------|
| **Control group** | **Study group** |
| **Phase I (From randomization up to 3 weeks)** | Also received graded gravitational stress and limb leverage increased for strengthening, RPE based ambulation in progression (6–11); resistance up to 50% of 10 RM |
| Chest physiotherapy, breathing exercises, use of incentive spirometer, limb movements, ambulation as tolerated by the patient | |
| **Phase II (3 to 6 weeks after training)** | Graded aerobic exercises (Walking/treadmill walk/bicycle ergometer training); resisted exercises - 50–65 of 10 RM% flexibility exercises; RPE-guided progression in exercise volume (RPE: 9–14) |
| Home exercises with self-paced walking; gradual participation in ADL | |
| **Phase III (6-12 weeks after training)** | Progressive, graded aerobic exercises (Walking/treadmill walk/bicycle ergometer training); resisted exercises: 65–85 of 10 RM% flexibility exercises; RPE-guided progression in exercise volume (RPE: 9–14) |
| Home-based increase in activities; self-paced walking as tolerated by the patient | |

RM: Repetition maximum, RPE: Rating of perceived exertion, ADL: Activities of daily living.
used to compare within the groups for outcomes with repeated measures. Pearson’s correlation was used to determine the correlation between the measured outcomes.

### Results

The groups were similar in their baseline characteristics and outcomes measured at the start of trial (Table 2). After the graded training, the functional capacity, IQMS and fatigue score improved in the SG significantly than the CG at six weeks as well 12 weeks, \( P \leq 0.05 \) (Table 3). There was a significant improvement within the SG on repeated measures of functional capacity, muscle strength, and fatigue. The mean difference in the improvement of the functional capacity, muscle strength was found to be more in the SG from baseline to six weeks, while fatigue score improved more between six and 12 weeks, even though both the groups had significant changes at all measurements (Table 4). The muscle strength (IQMS) had a positive relationship with the functional capacity at all measurements (Figures 2 and 3). The fatigue

### Table 2. Demographic and clinical characteristics of the study participants.

| Characteristics       | Control group | Study group |
|------------------------|---------------|-------------|
| Age (years)            | 35.08 (8.78)  | 36.24 (8.66)|
| Gender                 |               |             |
| Male                   | 48 (78.7)     | 47 (77)     |
| Female                 | 13 (21.3)     | 14 (22.1)   |
| Body Mass Index        | 22.21 (2.20)  | 22.59 (1.75)|
| Comorbidities          |               |             |
| Diabetes               | 22 (36.1)     | 16 (31.1)   |
| Hypertension           | 23 (62.3)     | 21 (65.6)   |
| Type of transplantation|               |             |
| LRRT                   | 45 (73.8)     | 47 (77)     |
| DDRT                   | 16 (26.2)     | 14 (23)     |
| Renal parameters       |               |             |
| BUN                    | 20.41 (1.81)  | 20.21 (1.87)|
| Serum creatinine       | 2.20 (0.435)  | 2.23 (0.520)|
| Hemoglobin             | 10.4 (0.875)  | 10.2 (0.882)|

Units in number (percentage), others as mean (SD). LRRT: Live related-renal transplantation; DDRT: Deceased donor renal transplantation, BUN: Blood urea nitrogen; SD: Standard deviation.

### Table 3. Comparison of functional capacity, muscle strength, and fatigue between groups.

| Measured Outcomes | Control group Mean(SD) | Study group Mean(SD) | Mean difference (CI) | \( P \) |
|-------------------|-------------------------|----------------------|----------------------|--------|
| Functional capacity (SMWD) |                     |                      |                      |        |
| Baseline (T1)     | 252 (33.7)              | 249 (41.33)          | 13 (10.88, 16.15)    | 0.7a    |
| Post training (T2)| 318 (48.72)             | 386 (86.91)          | 68 (42.38, 92.90)    | 0.001a  |
| Post training (T3)| 399 (70.74)             | 504 (102.17)         | 105 (73.40, 136.45)  | 0.001a  |
| Muscle strength (IQMS) |                  |                      |                      |        |
| Baseline (T1)     | 2.40 (0.305)            | 2.39 (0.521)         | 0.007 (0.145, 0.160) | 0.922a  |
| Post training (T2)| 5.78 (0.551)            | 7.96 (1.029)         | 2.18 (0.150, 2.481)  | 0.001a  |
| Post training (T3)| 8.75 (1.52)             | 11.66 (1.166)        | 2.91 (0.244, 3.401)  | 0.001a  |
| Fatigue (FSS)     |                        |                      |                      |        |
| Baseline (T1)     | 60.33^a                 | 62.33^a              |                      | 0.714^b |
| Post training (T2)| 86.93^a                | 36.07^a              |                      | 0.001^a |
| Post training (T3)| 83.49^a                | 39.51^a              |                      | 0.001^a |

^aMean rank; ^aUnpaired \( t \)-test ^aWilcoxon signed rank test. SMWD: Six-minute walk distance (meters), IQMS: Isometric quadriceps muscle strength (Kilograms), SD: Standard deviation, CI: Confidence interval unpaired \( t \)-test, FSS: Fatigue severity score.
Table 4. Comparison of functional capacity, muscle strength, and fatigue before and after training within the groups.

| Functional capacity | Control group (n=61) | Study group (n=61) | P* |
|---------------------|----------------------|---------------------|----|
|                     | T1       | T2       | T3       | T1       | T2       | T3       | Time | Group |
| SMWD (m)            | 251.71 (33.71) | 318.05 (48.73) | 399.08 (70.74) | 249.06 (41.33) | 385.69 (86.91) | 504.03 (102.18) | <0.001 <0.001 |
| Mean difference     | 66.34a | 81.03b | 147.37c | 136.62a | 118.34b | 254.97c | <0.001 <0.001 |
| Muscle strength     | Control group (n=61) | Study group (n=61) | P* |
|                     | T1       | T2       | T3       | T1       | T2       | T3       | Time | Group |
| IQMS (Kg)           | 2.40 (.303) | 5.78 (.551) | 8.75 (1.51) | 2.39 (.521) | 7.96 (1.03) | 11.66 (1.17) | <0.001 <0.001 |
| Mean difference     | 3.38a | 2.97b | 6.35c | 5.57a | 3.70b | 9.27c | <0.001 <0.001 |
| Fatigue             | Control group (n=61) | Study group (n=61) | P* |
|                     | T1       | T2       | T3       | T1       | T2       | T3       | Time | Group |
| FSS                 | 5.66 (.386) | 5.49 (.222) | 4.88 (.326) | 5.68 (.404) | 4.97 (.403) | 3.90 (.944) | <0.001 <0.001 |
| Mean difference     | 0.175a | 0.609b | 0.784c | 0.71a | 1.07b | 1.781c | <0.001 <0.001 |

Data are expressed as mean (SD); T1 Baseline, T2 6 weeks, T3 12 week. *ANOVA Repeated measures with Bonferroni corrections. aDifference between baseline and 6 weeks, bDifference between 6th and 12th weeks, cDifference between baseline and 12th week; F Wilks’ Lambda; η² partial Eta squared. SMWD: Six-minute walk distance, m: meters, IQMS: Isometric quadriceps muscle strength, Kg: Kilograms, FSS: Fatigue severity score, SD: Standard deviation.

score had a significant negative correlation with functional capacity at the six and 12 weeks post-intervention (Figures 4 and 5).

**Discussion**

The functional capacity in SG improved significantly than the CG. The natural upsurge in energy levels, could have resulted in improvement in the CG also. The recommended functional capacity of 680 m in healthy participants was attained by the SG in this trial. The minimal clinically important difference of 86 m reported in pulmonary conditions, was well achieved in the present study. The functional capacity in post-RT recipients was reported as 318 ± 136 m with a range of 0–750 m. In the present study, SMWD has improved from 252 and 249 to 399 and 504 m in the control and SGs, respectively, which is almost equivalent to the previous finding. The increase in physical activity participation, increased appetite, recovery from uremic symptoms, and reduction in psychological symptoms, including the need for dialysis, were the possible reasons for the improvement after RT. Interestingly, this study includes early intervention after RT up to three months, which have elicited good improvement in functional capacity. The early training with follow-up with graded training has remained a possible reason for the significant improvement in the functional capacity.

The muscle strength has remained an important determinant in physical activity participation. The quadriceps muscle is known for its role in influencing the walking ability of an individual. The reduction in muscle strength was described in post-RT as in chronic kidney diseases. The relationship between the impaired quadriceps muscle strength and gait performance in RT cites the need for muscle strengthening. There was a significant improvement in IQMS in the SG, which shows the effectiveness of the
Figure 2. Correlation between functional capacity and muscle strength at baseline after renal transplantation.

Figure 3. Correlation between functional capacity and muscle strength at 12 weeks after renal transplantation.

Figure 4. Correlation between Functional capacity and fatigue at 6 weeks after renal transplantation.
protocol. The muscle strengthening after RT was shown as a safe and useful method in improving physical performance and peak oxygen uptake in post-RT patients. The role of resistance training in improving muscle nutrition and physical function is known. The functional capacity improved with a strong correlation with six-minute walk distance in this study, as noted before.

Fatigue remains a multifactorial problem with physical and mental causes and its improvement leads to overall wellbeing. Fatigue remained as the major outcome of intervention as well to a measure of general wellbeing. The improvement of fatigue implies the indirect psychological wellness associated with better muscle activation, physical performance, and social participation. The negative relationship with the functional capacity illustrates its functional impact. The need for exercise training to improve fatigue was reported before. A recent study has shown successful RT recipient still have low QOL with fatigue, which supports the need of graded exercise training. The exercise training had positive outcomes on the quality and quantity of sleep and lipid profiles, which were associated with improvement in fatigue.

All the participants received standardized medications by the renal physicians as per their individual needs. The present study explores the effects of the early intervention and hence medication effects need to be explored by long-term follow-up of the participants. Thus, we can conclude that the use of graded exercise-based rehabilitation with strength training provides significant clinical benefits at the early and crucial post-operative period after RT.

**Presentation at a Meeting**

Part of the study presented at International Symposium on Exercise Science Research in February 2015 at Manipal Academy of Higher Education, Manipal University, Manipal, India.

**Conflict of Interest:** None declared.

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Date of manuscript receipt: 10 August 2018.
Date of revised copy receipt: 19 October 2018.
Date of final acceptance: 21 October 2018.