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**Clinical Trials Study**

# Renal function and physical fitness after 12-mo supervised training in kidney transplant recipients

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## Abstract

### AIM

To evaluate the effect of a 12-mo supervised aerobic and resistance training, on renal function and exercise capacity compared to usual care recommendations.

### METHODS

Ninety-nine kidney transplant recipients (KTRs) were assigned to interventional exercise (Group A;  $n = 52$ ) and a usual care cohort (Group B;  $n = 47$ ). Blood and urine chemistry, exercise capacity, muscular strength, anthropometric measures and health-related quality of life (HRQoL) were assessed at baseline, and after 6 and 12 mo. Group A underwent a supervised training three times per week for 12 mo. Group B received only general recommendations about home-based physical activities.

### RESULTS

Eighty-five KTRs completed the study (Group A,  $n = 44$ ; Group B,  $n = 41$ ). After 12 mo, renal function remained stable in both groups. Group A significantly increased maximum workload ( $+13$  W,  $P = 0.0003$ ),  $\dot{V}O_2$  peak ( $+3.1$  mL/kg per minute,  $P = 0.0099$ ), muscular strength in plantar flexor ( $+12$  kg,  $P = 0.0368$ ), height in the countermovement jump ( $+1.9$  cm,  $P = 0.0293$ ) and decreased in Body Mass Index ( $-0.5$  kg/m<sup>2</sup>,  $P = 0.0013$ ). HRQoL significantly improved in physical function ( $P = 0.0019$ ), physical-role limitations ( $P = 0.0321$ ) and social functioning scales ( $P = 0.0346$ ). No

improvements were found in Group B.

## CONCLUSION

Twelve-month of supervised aerobic and resistance training improves the physiological variables related to physical fitness and cardiovascular risks without consequences on renal function. Recommendations alone are not sufficient to induce changes in exercise capacity of KTRs. Our study is an example of collaborative working between transplant centres, sports medicine and exercise facilities.

**Key words:** Kidney transplant recipients; Renal function; Supervised exercise; Aerobic exercise; Muscle strength

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**Core tip:** This paper shows that developing a supervised exercise protocol for kidney transplant recipients is a useful and safe non-pharmacologic contribution to usual after-transplant treatments, which can improve the physiological variables related to physical fitness and cardiovascular risks without consequences on renal function. Our study is an example of collaborative working between transplant centres, sports medicine and exercise facilities, aimed to apply the concepts of "exercise is medicine".

Roi GS, Mosconi G, Totti V, Angelini ML, Brugin E, Sarto P, Merlo L, Sgarzi S, Stancari M, Todeschini P, La Manna G, Ermolao A, Tripi F, Andreoli L, Sella G, Anedda A, Stefani L, Galanti G, Di Michele R, Merni F, Trerotola M, Storani D, Nanni Costa A. Renal function and physical fitness after 12-mo supervised training in kidney transplant recipients. *World J Transplant* 2018; 8(1): 13-22 Available from: URL: <http://www.wjgnet.com/2220-3230/full/v8/i1/13.htm> DOI: <http://dx.doi.org/10.5500/wjt.v8.i1.13>

## INTRODUCTION

Kidney transplantation is considered the gold standard of treatment for most patients with end-stage renal disease, nevertheless kidney transplant recipients (KTRs) are characterized by long-term clinical complications and high risk of cardio-vascular disease (CVD).

In addition to the traditional CVD risk factors (e.g., hypertension, dyslipidaemia, diabetes mellitus) other non-traditional factors influence the high incidence of cardiovascular events (e.g., duration of prior dialysis, graft function after transplantation, elevated inflammatory markers, proteinuria, toxic effects of immunosuppressant drugs, bone mineral metabolism abnormalities and vascular calcifications). However, among all these risk factors, the lack of physical exercise and a sedentary lifestyle seem to play crucial roles<sup>[1]</sup>.

There is mounting evidence that physical exercise reduces the risk of all-cause mortality<sup>[2,3]</sup> and it is



effective in the primary and secondary prevention of CVD in the general population<sup>[4]</sup>. Physical activity is also considered a key element in the prevention and management of chronic diseases<sup>[5]</sup>, including Chronic Kidney Disease (CKD).

After transplantation, patients are expected to be more active than before because their uremic syndrome is corrected and they do not have to do haemodialysis treatment<sup>[6]</sup>. However, their cardiorespiratory fitness remains reduced by 30% in comparison with matched control subjects<sup>[7]</sup>. Only in selected cases they can achieve results comparable to a healthy population<sup>[8]</sup>, but not all patients increase their physical activity after transplantation; thus, the majority of KTRs maintain a sedentary lifestyle, often associated with an increase in body fat and weight gain<sup>[9]</sup>.

Whether exercise can positively affect outcomes in KTRs has only been addressed in few studies<sup>[4]</sup>, with a small number of subjects and with different types, intensity and durations of interventions lasting almost always not more than six months<sup>[10,11]</sup>. In some studies, exercise was carried out tightly at home without direct supervision and with a partial adherence to the intervention<sup>[6]</sup>. Furthermore, few studies have investigated the effect of a combined aerobic and resistance training<sup>[4]</sup>, and the effect of these protocols on kidney function is rather unknown.

In this paper, we present some clinical and fitness outcomes of a 12-mo study conducted on KTRs, with the aim to evaluate the potential effects of supervised exercise combining aerobic and resistance training.

## MATERIALS AND METHODS

### *Organisational model*

We introduced a project, based on a model of cooperation among: (1) Transplantation specialists (surgeons and nephrologists), who selected patients suitable for physical activity; (2) sports physicians who prescribed a personalised exercise programme based on the results of functional assessment tests; (3) exercise specialists who supervised the patients performing the prescribed programme. This organisation aims to check the patients from clinical and functional perspectives and to identify facilities in their home districts where patients can easily perform their training programmes under supervision<sup>[12,13]</sup>.

### *Study design*

This is a multicentre, controlled, prospective, non-randomised study that considered the enrolment of KTRs patients with clinical and functional stabilities.

Inclusion criteria were the 18-60 years age range, and at least six months after organ transplantation; exclusion criteria were orthopaedic limitations, psychiatric or neurological disorders, proteinuria within nephrotic range, poor compliance to treatment and any cardiovascular contraindication to exercise testing

and training.

Patients were divided into an interventional exercise group (Group A), in which personalised training was supervised, and a usual care group (Group B), in which some exercise indications were given without a specific prescription and supervision. All subjects received individualised counselling by the transplant centre regarding the protocol, and the inclusion in Group B was based on logistic and organisational grounds (patients living in regions not taking part in the project or living in areas without sports medical centres or an accessible gyms). This is the practical reason why we adopted a non-randomised design of our study.

Blood chemistry and urinalysis, complete blood count, and a cardiac evaluation were performed by the transplantation centres to assess the exclusion criteria. After the administration of the SF-36 questionnaire to evaluate Health-Related Quality of Life (HRQoL), the patients were sent to the sports medicine centre to perform the functional assessment tests for exercise capacity, muscle strength, and body composition.

Based on the results of these tests, the sports physicians prescribed a tailored training programme only for Group A. Then, patients in Group A were sent to a certified gym to start the prescribed training under the supervision of exercise specialists, while patients in Group B, as usual, were provided general information to encourage regular physical activities at home but no specific prescription and supervision were given.

Both groups were checked at baseline ( $T_0$ ), six ( $T_6$ ) and 12 mo ( $T_{12}$ ) from the enrolment. The trial did not envisage any change in the immunosuppressive treatment (Table 1).

Written informed consent was obtained by the patients before inclusion, according to the procedures approved by the Ethics Committee. This trial was registered in the ISRCTN registry (Trial ID: ISRCTN66295470) and was conducted in compliance with the ICH Guidelines for Good Clinical Practice, the Helsinki Declaration and national rules regarding clinical trial management.

### *Supervised training intervention (Group A)*

The exercise prescription included sessions of aerobic and resistance training. The total duration of each session was one hour, with a frequency of 3 times per week for 12 mo. In every session, the aerobic training was performed on a stationary bike and was administered with an intensity corresponding to the lactate aerobic threshold<sup>[14]</sup>, previously assessed by the incremental cycling test at  $T_0$  for the first six months and at  $T_6$ , for the subsequent period. The intensity was continuously monitored by heart rate monitors (Polar, Finland) allowing the patients to maintain a constant heart rate (HR) corresponding to the aerobic threshold during the aerobic training.

In the same session, the subsequent resistance training consisted of two sets of 20 repetitions at 35% of one Repetition Maximum (1RM) for each muscle

**Table 1 Pathologies leading to renal disease and transplantation**

Underlying disease	Group A (n = 44)	Group B (n = 41)
Glomerulonephritis	10	6
Nephroangiosclerosis	6	7
Polycystic kidney disease	8	10
End-stage kidney disease	10	5
Alport syndrome	2	2
IgA nephropathy	6	0
Nephrotic syndrome	2	0
Multicystic renal dysplasia	0	4
Interstitial nephritis	0	2
Haemolytic uraemic syndrome	0	4
Vasculitis polyangiitis	0	1

group of the upper (elbow flexors, elbow extensors, shoulder abductors) and lower limbs (knee extensors, plantar flexors). The training intensity at 35% of 1RM was chosen to increase local muscle endurance considering that KTRs are novice individuals for strength training where learning proper form and technique is paramount<sup>[15,16]</sup>. Resistance training was not performed with the upper limb with arterio-venous fistula. Warm-up, cool-down and stretching exercises were included in all training sessions. The intensities of aerobic and strength trainings were adjusted after the T<sub>6</sub> assessment.

#### **Non-supervised home-based exercise intervention (Group B)**

At T<sub>0</sub> and T<sub>6</sub> patients in Group B were provided general information to encourage regular physical activities at home, as usual by the transplant centre, but no specific prescription and supervision were given.

The International Physical Activity Questionnaire (IPAQ) short-version<sup>[17]</sup> was administered only to Group B at the three-time points to evaluate the level of physical activity through nine items that provide information on the time spent walking, in vigorous- and moderate-intensity activity and in sedentary activity. This questionnaire assessed the actual level of daily physical activity and thus reduce the bias between the two groups.

#### **Primary outcomes**

##### **Renal function, lipid values and blood chemistry:**

In both groups, creatinine (mg/dL) using the Jaffé method, estimated glomerular filtration rate (eGFR) using the chronic kidney disease epidemiology collaboration (CKD-EPI) equation, proteinuria (mg/1000 mL) using the turbidimetry method reported in g/24 h calculating 24-h urine collection were collected to check the renal function at T<sub>0</sub>, T<sub>6</sub> and T<sub>12</sub>.

Total cholesterol and triglycerides were measured from venous blood sample using flow cytometry and light-scattering methods to evaluate lipid metabolism. Haemoglobin and glycaemia values were also measured.

**Exercise capacity:** Exercise capacity was assessed by

an incremental cycling exercise starting from a 5-min unloaded cycle and increasing by 20 W every four minutes until the subject was unable to continue. A 12-lead electrocardiogram was monitored continuously throughout the test. At each step a capillary blood sample from the earlobe was taken to measure blood lactate concentration (YSI 1500-Sport; Yellow Springs, United States) to estimate the workload corresponding to aerobic and anaerobic thresholds, conventionally declared at 2 and 4 mmol/L of lactate, respectively<sup>[14]</sup>. Systolic and diastolic blood pressures were measured with sphygmomanometers at rest, at each step and at the third minute of recovery.

Oxygen uptake (V'O<sub>2</sub>) was determined continuously using an open-circuit spirometry system (Sensor Medics, Anaheim, United States), and the V'O<sub>2</sub> at the highest tolerated workload was determined and was referred to as V'O<sub>2</sub> peak (mL O<sub>2</sub>/kg per minute).

**Muscular strength and power:** A leg press (Technogym, Cesena, Italy) and free weights were utilised to assess the dynamic muscular strength of the lower and upper limbs (knee extensors, plantar flexors, elbow flexors, elbow extensors and shoulder abductors). The 1RM strength was calculated using an indirect method consisting of 7 to 12 repetitions with submaximal loads<sup>[18]</sup>.

The general strength was measured using a handgrip dynamometer (Lafayette, IN, United States).

The power of the lower limbs was measured indirectly from the fly time of a countermovement jump (CMJ) and was expressed as maximum displacement (m) of the centre of mass during fly (Optojump, Microgate, Italy).

#### **Secondary outcomes**

**BMI and body composition:** Body mass index (BMI) was calculated using the ratio between weight and square height (kg/m<sup>2</sup>).

Fat mass (FM) percentage was determined using the Jackson and Pollock body density equation considering seven skinfolds in both men and women (abdominal, thigh, triceps, bicep, subscapular, suprailiac, chest) measured with a Harpenden calliper<sup>[19]</sup> at T<sub>0</sub>, T<sub>6</sub> and T<sub>12</sub>.

**Health-related quality of life:** The 36-Item Short Form Health Survey (SF-36, Medical Outcomes Trust) was used to evaluate self-reported domains of health status<sup>[20]</sup> completed by the patients independently at T<sub>0</sub>, T<sub>6</sub> and T<sub>12</sub>.

#### **Statistical analysis**

The sample size to assess eventual differences in exercise capacity, muscular strength, renal function, BMI and HRQoL was determined using the Software G-Power (version 3.1.9.2) with an alpha level of 0.01 and a power of 0.90. All descriptive data are presented as the mean ± standard deviation (SD). Linear mixed

**Table 2** Immunosuppressive and other therapies in both groups

	Tacrolimus	Cyclosporine	Steroid therapy	Purine synthesis inhibitors	(mTOR) inhibitors	Anti-hypertensive therapy	Beta-blockers	Insulin therapy	Statin	Ezetimibe
Group A, <i>n</i> = 44	28 (64%)	12 (27%)	35 (80%)	33 (75%)	7 (16%)	33 (75%)	18 (44%)	1 (2%)	14 (34%)	2 (5%)
Group B, <i>n</i> = 41	27 (66%)	10 (24%)	30 (73%)	34 (83%)	5 (12%)	30 (73%)	18 (44%)	2 (5%)	18 (41%)	2 (5%)

models were used to assess the effects of time and group on dependent variables, with T<sub>0</sub> and Group B set as the base categories. Random intercepts were used for individual subjects. Significance was set at  $P < 0.05$ , and the raw coefficients for the fixed effects and interactions are reported with 95%CI. The statistical analysis was performed using R software for Windows (v. 3.2.3).

## RESULTS

### Subjects

Ninety-nine KTRs were recruited by nine transplant centres between January 2011 and June 2015. Fifty-two patients were included in Group A, and 47 in Group B. Eight patients from Group A decided to withdraw and were considered dropouts. The causes were economic problems and lack of motivation ( $n = 4$ ) or work conflicts ( $n = 4$ ). In Group B, six patients did not show up to the functional assessments during the follow-up.

Forty-four KTRs from Group A (21 female and 23 males, mean  $\pm$  SD age  $47 \pm 12$  years, mass  $69 \pm 14$  kg, BMI  $24.1 \pm 4.3$  kg/m<sup>2</sup>, time from transplant  $5.5 \pm 7.1$  years, dialysis vintage  $36 \pm 35$  mo, range 1-156) and 41 KTRs from Group B (13 female and 28 males, age  $49 \pm 9$  years, weight  $75 \pm 13$  kg, BMI  $25.5 \pm 4.4$  kg/m<sup>2</sup>, time from transplant  $3.6 \pm 4.0$  years, dialysis vintage  $33 \pm 34$  mo, range 1-144) were analysed. There were no significant differences between groups regarding: age ( $P = 0.35$ ), BMI ( $P = 0.16$ ), time from transplant ( $P = 0.11$ ), and dialysis vintage ( $P = 0.42$ ). The only significant difference was found for body mass ( $P = 0.02$ ).

Pathologies leading to renal disease and immunosuppressive therapies of the patients are shown in Tables 1 and 2 respectively.

### Exercise program adherence

In Group A, the exercise program adherence, defined as a total number of exercise sessions completed as proportion of total possible number of session (144 sessions) during the 12-mo period was  $93\% \pm 6\%$ . None adverse events were reported.

### Primary outcomes

Creatinine tended to decrease in Group A at T<sub>12</sub> and increase in Group B at the same time, but the results were not significant. No significant changes were found in eGFR or proteinuria in either group. Average triglyceride and cholesterol levels showed

slight changes at T<sub>12</sub> in both groups which were not significant (Table 3).

Only three patients (one in group A and two in group B) were diabetic under insulin therapy (Table 2). In both groups, glucose values were always  $< 126$  mg/dL without significant changes between the three-time points.

Diastolic and systolic blood pressures were similar ( $P > 0.05$ ) in the two groups at rest, at the maximum workload and after three minutes of recovery, at T<sub>0</sub>, T<sub>6</sub> and T<sub>12</sub> (Table 3). The only significant difference was found between groups for systolic blood pressure at the third minute of recovery, that was always lower in Group A ( $P = 0.0489$ ).

Group A showed a significant average improvement in maximum workload and V'O<sub>2</sub> peak at T<sub>6</sub> ( $P = 0.0010$ ,  $P = 0.0370$ ), and the levels continued to increase at T<sub>12</sub> ( $P = 0.0003$ ,  $P = 0.0099$ ) compared to Group B (Table 3).

The maximum HR, anaerobic threshold workload and corresponding HR significantly increased at T<sub>12</sub> ( $P < 0.05$ ) in Group A compared to Group B. In Group B, we found a significant decrease in the anaerobic threshold HR from T<sub>0</sub> to T<sub>12</sub> ( $P = 0.0434$ ). No additional significant differences were found in Group B at T<sub>6</sub> and T<sub>12</sub> in any variables (Table 3).

Group A showed a significant average improvement in lower limb strength and power expressed by an increase in plantar flexor muscle strength ( $P = 0.0368$ ) and CMJ ( $P = 0.0293$ ) at T<sub>12</sub> compared to Group B. No significant differences were found in Group B at T<sub>12</sub> in any variable (Table 3).

Group A showed a significant improvement in the handgrip test at T<sub>12</sub> ( $P < 0.05$ ) compared to Group B (Table 3).

Group B showed a significant increase in elbow flexor, elbow extensor and shoulder abductor strength (respectively,  $P < 0.05$ ) at T<sub>6</sub>, but the levels remained below the values of Group A (Table 3).

No changes were found in Group B in the level of daily physical activity assessed by IPAQ, which remained at a low level ( $< 600$  MET per minute per week) at the 12 mo follow-up. Theoretical IPAQ calculated from the exercise protocol performed by Group A was  $< 600$  METper minute per week at baseline, and  $> 600$  METper minute (range 1215-1413 MET per minute) per week at T<sub>6</sub> and T<sub>12</sub> ( $P < 0.01$ ).

### Secondary outcomes

Group A showed a significant decrease in BMI at T<sub>12</sub> ( $P = 0.0013$ ) and fat mass percentage at T<sub>6</sub> ( $P = 0.05$ )



**Table 3** Mean  $\pm$  SD of exercise capacity and blood chemistry

	Group A (n = 44)			Group B (n = 41)		
	T <sub>0</sub>	T <sub>6</sub>	T <sub>12</sub>	T <sub>0</sub>	T <sub>6</sub>	T <sub>12</sub>
Maximum workload (W)	95 $\pm$ 36	107 $\pm$ 38 <sup>a</sup>	108 $\pm$ 41 <sup>c</sup>	102 $\pm$ 32	102 $\pm$ 30	98 $\pm$ 34
V'O <sub>2</sub> peak (mL/kg per minute)	22.8 $\pm$ 8.3	25.6 $\pm$ 9.0 <sup>a</sup>	25.9 $\pm$ 7.5 <sup>c</sup>	21.6 $\pm$ 6.8	22.6 $\pm$ 6.6	21.5 $\pm$ 6.4
HR max (bpm)	142 $\pm$ 24	142 $\pm$ 22	145 $\pm$ 22 <sup>c</sup>	133 $\pm$ 22	134 $\pm$ 23	131 $\pm$ 22
Diastolic BP at rest (mmHg)	80 $\pm$ 8	80 $\pm$ 8	78 $\pm$ 6	81 $\pm$ 9	82 $\pm$ 8	82 $\pm$ 8
Diastolic BP at V'O <sub>2</sub> peak (mmHg)	85 $\pm$ 11	83 $\pm$ 12	82 $\pm$ 13	84 $\pm$ 10	81 $\pm$ 13	80 $\pm$ 11
Diastolic BP at 3' recovery (mmHg)	75 $\pm$ 9	76 $\pm$ 8	75 $\pm$ 9	78 $\pm$ 10	79 $\pm$ 9	78 $\pm$ 8
Systolic BP at rest (mmHg)	126 $\pm$ 14	126 $\pm$ 12	125 $\pm$ 11	130 $\pm$ 16	126 $\pm$ 15	127 $\pm$ 13
Systolic BP at V'O <sub>2</sub> peak (mmHg)	183 $\pm$ 26	183 $\pm$ 21	185 $\pm$ 25	181 $\pm$ 26	181 $\pm$ 27	178 $\pm$ 30
Systolic BP at 3' recovery (mmHg)	128 $\pm$ 17	129 $\pm$ 14	131 $\pm$ 16	136 $\pm$ 16	136 $\pm$ 21	135 $\pm$ 20
Body mass index (kg/m <sup>2</sup> )	24.1 $\pm$ 4.3	24.0 $\pm$ 4.3	23.6 $\pm$ 4.5 <sup>c</sup>	25.5 $\pm$ 4.4	25.3 $\pm$ 4.0	25.8 $\pm$ 4.5
Fat mass (%)	21.1 $\pm$ 9.0	19.8 $\pm$ 8.3 <sup>a</sup>	20.7 $\pm$ 7.9	20.0 $\pm$ 7.8	18.9 $\pm$ 6.5	19.8 $\pm$ 8.1
Aerobic threshold workload (W)	53 $\pm$ 23	60 $\pm$ 29	60 $\pm$ 27	53 $\pm$ 21	62 $\pm$ 27	57 $\pm$ 25
Aerobic threshold HR (bpm)	113 $\pm$ 20	108 $\pm$ 19	112 $\pm$ 18	103 $\pm$ 16	103 $\pm$ 19	103 $\pm$ 16
Anaerobic threshold workload (W)	84 $\pm$ 30	94 $\pm$ 37	91 $\pm$ 31 <sup>c</sup>	89 $\pm$ 32	97 $\pm$ 38	88 $\pm$ 36
Anaerobic threshold HR (bpm)	131 $\pm$ 21	130 $\pm$ 23	134 $\pm$ 18 <sup>c</sup>	125 $\pm$ 20	125 $\pm$ 21	120 $\pm$ 19 <sup>e</sup>
Knee extensors right (kg)	87 $\pm$ 38	93 $\pm$ 40	98 $\pm$ 39	55 $\pm$ 27	61 $\pm$ 26	60 $\pm$ 24
Knee extensors left (kg)	80 $\pm$ 36	93 $\pm$ 40	95 $\pm$ 42	51 $\pm$ 23	60 $\pm$ 25	58 $\pm$ 23
Plantar flexors right (kg)	70 $\pm$ 34	76 $\pm$ 29	82 $\pm$ 27 <sup>c</sup>	62 $\pm$ 35	69 $\pm$ 27	65 $\pm$ 23
Plantar flexors left (kg)	70 $\pm$ 33	77 $\pm$ 29	79 $\pm$ 28	64 $\pm$ 34	71 $\pm$ 24	67 $\pm$ 24
Counter movement jump (cm)	24.0 $\pm$ 10.0	26.4 $\pm$ 10.2	25.9 $\pm$ 9.3 <sup>c</sup>	21.5 $\pm$ 9.4	22.9 $\pm$ 10.2	20.9 $\pm$ 10.2
Handgrip right (kg)	30.8 $\pm$ 13.1	33.2 $\pm$ 12.2	32.3 $\pm$ 11.9 <sup>c</sup>	36.3 $\pm$ 9.5	35.9 $\pm$ 9.8	34.2 $\pm$ 9.6
Handgrip left (kg)	29.3 $\pm$ 13.6	30.7 $\pm$ 11.7	30.6 $\pm$ 11.7 <sup>c</sup>	35.1 $\pm$ 9.3	34.4 $\pm$ 9.7	32.7 $\pm$ 10.2
Elbow flexors Right (kg)	8.8 $\pm$ 2.7	9.4 $\pm$ 2.8	9.7 $\pm$ 2.8	8.0 $\pm$ 3.4	9.4 $\pm$ 3.1 <sup>e</sup>	9.4 $\pm$ 3.5
Elbow flexors Left (kg)	8.7 $\pm$ 3.2	9.6 $\pm$ 3.4	9.6 $\pm$ 3.1	7.3 $\pm$ 3.4	8.6 $\pm$ 2.7 <sup>e</sup>	8.7 $\pm$ 3.5
Elbow extensors right (kg)	5.8 $\pm$ 2.0	6.5 $\pm$ 2.3	6.9 $\pm$ 2.3	5.1 $\pm$ 2.2	6.1 $\pm$ 2.1 <sup>e</sup>	6.0 $\pm$ 2.1
Elbow extensors left (kg)	5.7 $\pm$ 2.0	6.5 $\pm$ 2.4	6.8 $\pm$ 2.4	4.9 $\pm$ 2.3	5.6 $\pm$ 1.8 <sup>e</sup>	5.7 $\pm$ 1.9
Shoulder abductors (kg)	5.3 $\pm$ 2.2	6.3 $\pm$ 2.5	6.4 $\pm$ 2.3	4.2 $\pm$ 2.7	5.2 $\pm$ 2.1 <sup>e</sup>	5.4 $\pm$ 2.7
Creatinine (mg/dL)	1.26 $\pm$ 0.38	1.27 $\pm$ 0.41	1.21 $\pm$ 0.29	1.37 $\pm$ 0.48	1.32 $\pm$ 0.50	1.42 $\pm$ 0.47
eGFR (mL/min per 1.73 m <sup>2</sup> )	59.4 $\pm$ 19.3	58.0 $\pm$ 19.6	62.6 $\pm$ 21.8	56.3 $\pm$ 21.2	58.1 $\pm$ 17.8	52.9 $\pm$ 17.4
Proteinuria (g/24 h)	0.41 $\pm$ 0.51	0.34 $\pm$ 0.46	0.52 $\pm$ 0.63	0.45 $\pm$ 0.57	0.48 $\pm$ 0.59	0.61 $\pm$ 0.44
Haemoglobin (g/dL)	12.8 $\pm$ 1.8	12.3 $\pm$ 1.7	12.6 $\pm$ 1.6	12.1 $\pm$ 1.8	12.5 $\pm$ 1.9	12.8 $\pm$ 1.5
Triglycerides (mg/dL)	122 $\pm$ 42	117 $\pm$ 41	117 $\pm$ 47	138 $\pm$ 69	131 $\pm$ 57	132 $\pm$ 59
Cholesterol (mg/dL)	196 $\pm$ 37	186 $\pm$ 52	200 $\pm$ 43	195 $\pm$ 33	193 $\pm$ 31	188 $\pm$ 34

In Group A: <sup>a</sup> $P < 0.05$  between T<sub>0</sub> and T<sub>6</sub>, <sup>c</sup> $P < 0.05$  between T<sub>0</sub> and T<sub>12</sub>; In Group B: <sup>e</sup> $P < 0.05$  between T<sub>0</sub> and T<sub>12</sub>. BP: Blood pressure; HR: Heart rate; eGFR: Estimated glomerular filtration rate.

compared to Group B (Table 3).

In HRQoL, significant improvements were found in Group A in physical function scale at T<sub>6</sub> ( $P = 0.0082$ ) and continued to increase at T<sub>12</sub> ( $P = 0.0019$ ), in role-physical and social functioning scales at T<sub>12</sub> ( $P = 0.0321$ ,  $P = 0.0346$ ) compared to Group B, in which we found no significant changes in any scales (Table 4).

## DISCUSSION

The main result of this study is that in selected KTRs, a programme of 12 mo of supervised training performed one hour, three times per week in certified gyms does not affect the renal function, leading to significant improvement in aerobic fitness, muscle strength and HRQoL, with a significant decrease of BMI. Furthermore, the proposed organizational model led to a high exercise program adherence, *i.e.*, to a positive change in lifestyle.

The KTRs included in Group B who received only general information to promote regular physical activity at home, without a specific supervision, did not show any improvement in physical fitness outcomes,

indicating a low adherence to non-supervised home-based physical activity. This demonstrated that without a direct or indirect supervision (*e.g.*, follow-up by calls or e-mails), patients tend to not carry out physical activity even if it is recommended by the physician.

van Adrichem *et al.*<sup>[21]</sup> highlighted how perceived barriers of physical activity in KTRs such as physical limitations, lack of energy, and comorbidities cannot be omitted. Moreover, the lack of specific counselling by physicians about the benefits of physical activity is a critical issue. However, in the present study we recorded a dropout rate of 15% in Group A and 13% in Group B. Painter *et al.*<sup>[6]</sup> reported a dropout rate of 33% at one year in their exercising group of patients who performed home-based training with regular phone follow-up. Greenwood *et al.*<sup>[22]</sup> in their 12-wk study reported a dropout of 7 on 20 KTRs (35%) in both aerobic and resistance training supervised groups. Most of these patients reported difficulties attending classes following return to work after transplantation. Riess *et al.*<sup>[4]</sup> reported a dropout of 2 out of 16 (13%) on their 12-wk study in the supervised exercise group and 1 out of 15 (7%) in the home based usual care

**Table 4 Mean  $\pm$  SD of 36-Item Short Form Health Survey questionnaire scales**

	Group A (n = 44)			Group B (n = 41)		
	T <sub>0</sub>	T <sub>6</sub>	T <sub>12</sub>	T <sub>0</sub>	T <sub>6</sub>	T <sub>12</sub>
Physical function	84 $\pm$ 20	91 $\pm$ 11 <sup>a</sup>	92 $\pm$ 12 <sup>c</sup>	89 $\pm$ 10	86 $\pm$ 20	86 $\pm$ 23
Role physical	83 $\pm$ 25	88 $\pm$ 21	96 $\pm$ 15 <sup>c</sup>	91 $\pm$ 19	91 $\pm$ 19	86 $\pm$ 24
Bodily pain	80 $\pm$ 24	80 $\pm$ 22	89 $\pm$ 20	86 $\pm$ 19	84 $\pm$ 22	84 $\pm$ 22
General health	63 $\pm$ 20	67 $\pm$ 21	68 $\pm$ 20	64 $\pm$ 21	67 $\pm$ 19	66 $\pm$ 17
Vitality	67 $\pm$ 16	70 $\pm$ 15	69 $\pm$ 19	67 $\pm$ 18	69 $\pm$ 14	68 $\pm$ 14
Social function	75 $\pm$ 19	80 $\pm$ 20	83 $\pm$ 17 <sup>c</sup>	82 $\pm$ 19	78 $\pm$ 21	78 $\pm$ 21
Role emotional	85 $\pm$ 24	91 $\pm$ 20	90 $\pm$ 22	93 $\pm$ 16	96 $\pm$ 15	93 $\pm$ 17
Mental health	75 $\pm$ 16	75 $\pm$ 16	74 $\pm$ 19	74 $\pm$ 18	77 $\pm$ 16	74 $\pm$ 16

<sup>a</sup>P < 0.05 between T<sub>0</sub> and T<sub>6</sub>; <sup>c</sup>P < 0.05 between T<sub>0</sub> and T<sub>12</sub>.

group. O'Connor *et al.*<sup>[23]</sup> in an un-supervised period of self-managed physical activity reported an attrition rate of 30% at the 12 mo time point that confirms a low exercise adherence without supervision.

Compliance with the treatment is a common barrier of health programmes based on exercise even if transplant recipients who have experienced a supervised exercise programme supported that it was beneficial to health and well-being<sup>[24]</sup>. Social, cognitive, personality, environmental, and socio-economic factors, unrelated to the recommended guidelines, seem to be of greater importance in considering behavioural adherence issues<sup>[25]</sup> in KTRs. To improve physical exercise programme compliance and longer-term outcomes, strategies to diversify and stimulate exercise training or change elements of training like introduce specific tracking devices designed for KTRs should be examined. Anyway, data from our study clearly show that recommendations alone are not sufficient to induce a change in lifestyle and physical fitness. On the other hand, the supervised training for long periods is costly and cannot be proposed for all the transplanted patients, so it is urgent to study new solutions, starting from the cooperation between transplantation, sports medicine, and exercise specialists.

Renal function data, expressed as creatinine, eGFR and proteinuria, were compatible with the framework of patients of a select population undergoing successful renal transplantation. The proposed training protocol had no negative effects on the renal function in the medium term and, more in detail, creatinine values tended to decrease in Group A and to increase in Group B at the same time, but the results were not significant after 12 mo. The tendency to decrease of creatinine and eGFR in Group A can be considered as positive effect of physical exercise and needs specific studies. Patients in Group A did not show any significant increase in muscle mass after 12 mo of resistance training such as to affect creatinine and eGFR, probably because of the low intensity of the resistance training.

To the best of our knowledge, 12 mo of observation period is one of the longest in the literature with reference to aerobic and resistance trainings; however, it is a relatively short-time period and further studies

with larger populations are necessary to understand the long-term effects of exercise or sedentary lifestyle on the renal function of KTRs.

Regarding exercise capacity, in Group A we observed a 12% increase of V'O<sub>2</sub> peak at T<sub>6</sub>. Similar results were obtained by van den Ham *et al.*<sup>[26]</sup> in 33 KTRs after 12 wk of combination of endurance and strength training in which V'O<sub>2</sub> peak increase of 10% (from 21.6  $\pm$  6.3 to 23.8  $\pm$  6.1 mL/kg per minute). Riess *et al.*<sup>[4]</sup> reported an increase of V'O<sub>2</sub> peak (from 20  $\pm$  9 to 23  $\pm$  10 mL/kg per minute) after 12 wk of supervised endurance training (three times/week) on cycle ergometer at 60%-80% of V'O<sub>2</sub> max involving 16 patients.

In a study of eight KTRs, Romano *et al.*<sup>[27]</sup> utilised a supervised interval training technique for 10 wk, 40-min sessions for three times per week. They reported an increase of 13% of V'O<sub>2</sub> peak.

Another intervention was published by Kempeneers *et al.*<sup>[28]</sup> who trained 16 KTRs for six months in preparation for the National Transplant Games. Their mean V'O<sub>2</sub> peak rose from 29.0  $\pm$  7.8 to 37.5  $\pm$  4.8 mL/kg per minute, with an increase of 27%.

In the other hand, Painter *et al.*<sup>[6]</sup> prescribed an individualised home-based exercise training programme in 54 KTRs, consisting on 30 min, four times per week of training at an intensity corresponding to 60%-80% of maximal HR. Patients were contacted every two weeks by phone to assess progress and adherence to the programme and to adjust it as needed. After six months, V'O<sub>2</sub> peak increased from 24.0  $\pm$  7.5 to 27.8  $\pm$  11.0 mL/kg per minute (+ 16%) and to 30.1  $\pm$  10.3 mL/kg per minute (+ 25%) after 12 mo.

We can conclude that the aerobic training in KTRs leads to a substantial increase in aerobic power<sup>[29]</sup>. In most cases, the type of training meets the minimal clinically significant difference of 3.5 mL/kg per minute (*i.e.*, 1 metabolic equivalent), which is associated with improved outcomes in CVD. However, Riess *et al.*<sup>[4]</sup> after 12 wk of endurance training were unable to demonstrate any change in resting small or large arterial compliance, peak exercise systemic vascular resistance and Framingham Risk Assessment Score, indicating that exercise intensity and overall duration are probably the most critical factors affecting CVD risk

profile.

Our study did not reveal significant differences in blood pressure between the two groups, both showing normal blood pressure at rest, during and after maximal incremental exercise. This may be explained by the tightly controlled anti-hypertensive regimes in post-transplant care, as previously reported in other studies<sup>[23]</sup>.

Reduced general muscular strength has been related to an increased risk of all-cause of cardiovascular mortality<sup>[30]</sup> and the handgrip test values are a recognised marker of health status<sup>[31]</sup>. In our study, the handgrip test values improved after six months of training and significantly improved after 12 mo, whereas in the Group B we found a trend in reduction in strength, even if it was not significant. Moreover, in the Group A the muscular strength of the lower limbs improved, and the power of the lower limbs increased after 12 mo. This increase in maximal strength and CMJ values may be associated with both neural adaptations and muscle trophism improvement<sup>[32]</sup>. This finding is consistent with prior studies<sup>[6]</sup>.

In relation to anthropometric measures, the 12-mo supervised programme combining aerobic and resistance training was effective in reducing BMI<sup>[33]</sup> and fat mass in Group A, with a non-significant reduction in fat-free mass (-2%). However, in our study, the lipid profile remained the same; 39% of patients were taking a statin or ezetimibe as a regular drug (Table 2), which would make further improvement in the lipid profile unlikely. Moreover, the patients did not receive a diet programme.

Regarding quality of life, we found significant improvement in Group A in the self-perception of physical function, role-limitation to physical activity and social function. The KTRs in the usual care group (Group B) did not show any improvement in HRQoL scores. This finding confirms that supervised exercise training led to a better self-perception of quality of life<sup>[34]</sup>.

The association of aerobic and resistance training was safe; no acute cardiovascular event, renal graft-related or serious adverse events due to endurance or strengthening exercises were recorded. The inclusion in the protocol of the CMJ test did not have any consequence to the musculoskeletal system, indicating that KTRs can safely perform supervised power exercises<sup>[35]</sup>. The accurate selection of the patients and the cardiovascular assessment at T<sub>0</sub> certainly contributed to these findings.

The present study has some limitations. First, it is a non-randomised study; we included the patients in the usual care group (Group B) on logistic and organisational grounds. Therefore, the two groups were different in baseline assessments of body mass.

Another limit is due to the workloads chosen for the aerobic and strength trainings. We adopted a steady state aerobic exercise protocol at intensity corresponding to the lactate aerobic threshold. Different

training protocols, *i.e.*, interval training, or different duration of the sessions could be more effective. Furthermore, it is possible that with a higher percentage of 1RM and with a different progressive strengthening protocols the improvements would be higher, especially when training the upper limbs. The fact that the upper limb with the arteriovenous fistula was not trained, for safety precautions, also affected the final strength results. Furthermore, we checked both groups after 6 mo of training, so probably a more frequent adjustment in the prescription of the relative intensity of trainings would lead to better functional outcomes in Group A or would give further motivations in Group B.

The anthropometric assessment by the skinfolds technique has some limitations and probably it would be possible to detect significant changes with more precise methods (*i.e.*, dual energy X-ray absorptiometry). Another limit is that we administered the IPAQ only to Group B to reduce the bias between the two groups, but it was impossible to make any direct comparison with Group A.

Finally, patients included in our study were carefully selected and were thus not representative of the entire KTRs population. Furthermore, the prescribed exercise program was based on blood tests and other measurements that are not routinely performed in gyms and cannot be universally applied, so the generalizability of the results is limited.

Despite some limitations, this paper shows that developing a supervised exercise protocol for KTRs is a useful and safe non-pharmacologic contribution to usual after-transplant treatments, which can improve the physiological variables related to physical fitness and cardiovascular risks without consequences on renal function. Our study is an example of collaborative working between transplant centres, sports medicine and exercise facilities, aimed to apply the concepts of "exercise is medicine".

Further studies with longer follow-up and larger populations are necessary to understand the strategies that will improve adherence to training programmes, control costs and lead to steady and durable lifestyle changes in KTRs.

## ARTICLE HIGHLIGHTS

### Research background

Kidney transplant recipients (KTRs) are characterised by long term clinical complications and high risk of cardiovascular disease. After transplantation, physical activity is considered a key element in the prevention and management of chronic diseases, however the majority of KTRs maintain a sedentary lifestyle, often associated with an increase of body fat and weight gain. Whether exercise can positively affect outcomes in KTRs has only been addressed in few studies, with a small number of subjects and with different types, intensity and durations of interventions lasting almost always not more than six mo. Furthermore, few studies have investigated the effect of a combined aerobic and resistance training, and the effect of these protocols on kidney function is rather unknown. In this paper, we present some clinical and fitness outcomes of a 12-mo study conducted on KTRs, with the aim to evaluate the potential effects of supervised exercise combining aerobic and resistance training.

## Research frontiers

Developing a supervised exercise protocol for KTRs is a useful and safe non-pharmacologic contribution to usual after-transplant treatments, which can improve the physiological variables related to physical fitness and cardiovascular risks without consequences on renal function. Further studies with longer follow-up and larger populations are necessary to understand the strategies that will improve adherence to training programmes, control costs and lead to steady and durable lifestyle changes in KTRs.

## Innovations and breakthroughs

Selected KTRs can safely perform training protocols lasting 12 mo, with association of aerobic and resistance exercises.

## Applications

The collaboration between transplant centres, sports medicine centres and exercise facilities is effective to prevent the low adherence to suggested and/or prescribed physical activity.

## Terminology

Oxygen uptake ( $\dot{V}O_2$ ) at the highest tolerated workload was referred to as  $\dot{V}O_{2\text{peak}}$  (mL $\dot{O}_2$ /kg per minute).

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