<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Importance of physical capacity and the effects of exercise in heart transplant recipients</td>
<td>Yardley M, Gullestad L, Nytrøen K</td>
</tr>
<tr>
<td>23</td>
<td>In vitro intracellular IFNγ, IL-17 and IL-10 producing T cells correlates with the occurrence of post-transplant opportunistic infection in liver and kidney recipients</td>
<td>Boix F, Llorente S, Eguía J, Gonzalez-Martinez G, Alfaro R, Gallián JA, Campillo JA, Moya-Quiles MR, Minguela A, Pons JA, Muro M</td>
</tr>
</tbody>
</table>
World Journal of Transplantation
Volume 8 Number 1 February 24, 2018

EDITORS FOR
THIS ISSUE

NAME OF JOURNAL
World Journal of Transplantation

ISSN
ISSN 2220-3230 (online)

LAUNCH DATE
December 24, 2011

FREQUENCY
Bimonthly

EDITOR-IN-CHIEF
Maurizio Salvadori, MD, Professor, Renal Unit, Careggi University Hospital, Florence 50139, Italy

EDITORIAL BOARD MEMBERS
All editorial board members resources online at http://www.wjgnet.com/2220-3230/editorialboard.htm

EDITORIAL OFFICE
Xiu-Xia Song, Director

WJT | www.wjgnet.com

EDITORS FOR
THIS ISSUE

Responsible Assistant Editor: Xiang Li
Responsible Electronic Editor: Ruo-Feng Li
Proofing Editor-in-Chief: Lian-Sheng Ma
Responsible Science Editor: Li-Jun Cui
Proofing Editorial Office Director: Xiu-Xia Song

COPYRIGHT
© 2018 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non-commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT
All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS
http://www.wjgnet.com/bpg/gerinfo/204

ONLINE SUBMISSION
http://www.f6publishing.com

ABOUT COVER
Editorial Board Member of World Journal of Transplantation, Robert M Aris, MD, Professor, Division of Pulmonary and Critical Care Medicine, University of North Carolina, Chapel Hill, NC 27599, United States

AIM AND SCOPE
World Journal of Transplantation (World J Transplant, WJT, online ISSN 2220-3230, DOI: 10.5500) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJT covers topics concerning organ and tissue donation and preservation; tissue injury, repair, inflammation, and aging; immune recognition, regulation, effector mechanisms, and opportunities for induction of tolerance, thoracic transplantation (heart, lung), abdominal transplantation (kidney, liver, pancreas, islets), transplantation of tissues, cell therapy and islet transplantation, clinical transplantation, experimental transplantation, immunobiology and genomics, and xenotransplantation. The current columns of WJT include editorial, frontier, diagnostic advances, therapeutics advances, field of vision, mini-reviews, review, topic highlight, medical ethics, original articles, case report, clinical case conference (Clinicopathological conference), and autobiography.

WJT is now indexed in PubMed, PubMed Central.

AIM AND SCOPE
World Journal of Transplantation is now indexed in PubMed, PubMed Central.
Renal function and physical fitness after 12-mo supervised training in kidney transplant recipients

Giulio Sergio Roi, Giovanni Mosconi, Valentina Totti, Maria Laura Angelini, Erica Brugin, Patrizio Sarto, Laura Merlo, Sergio Sgarzi, Michele Stancari, Paola Todeschini, Gaetano La Manna, Andrea Ermolao, Ferdinando Tripi, Lucia Andreoli, Gianluigi Sella, Alberto Anedda, Laura Stefanì, Giorgio Galanti, Rocco Di Michele, Franco Merni, Manuela Trerotola, Daniela Storani, Alessandro Nanni Costa

Giulio Sergio Roi, Department of Education and Research, Isokinetic Medical Group, Bologna 40123, Italy
Giovanni Mosconi, Maria Laura Angelini, Department of Nephrology and Dialysis, Morgagni-Pierantoni Hospital, Forlì 47121, Italy
Valentina Totti, Rocco Di Michele, Franco Merni, Department of Biomedical & Neuromotor Sciences, University of Bologna, Bologna 40121, Italy
Valentina Totti, Associazione Nazionale Emodializzati, Dialisi e Trapianto, Milano 20121, Italy
Erica Brugin, Department of Cardiovascular, Sports Medicine, Noale 30033, Italy
Patrizio Sarto, Laura Merlo, Sports Medicine, ULSS Company 9, Treviso 31100, Italy
Sergio Sgarzi, Michele Stancari, Sports Medicine, Regional Hospital of Bologna, Bologna 40121, Italy
Paola Todeschini, Gaetano La Manna, Department of Nephrology and Dialysis, S. Orsola Hospital, Bologna 40121, Italy
Andrea Ermolao, Sports Medicine Unit DIMED, Department of Medicine, University of Padua, Padua 35100, Italy
Ferdinando Tripi, Lucia Andreoli, Sports Medicine, Regional Hospital of Modena, Modena 41100, Italy
Gianluigi Sella, Sports Medicine, Regional Hospital of Ravenna, Ravenna 48121, Italy
Alberto Anedda, Sports Medicine, Regional Hospital of Parma, Parma 43121, Italy
Laura Stefanì, Giorgio Galanti, Department of Experimental and Clinical Medicine, School of Sports Medicine, University of Florence, Sports Medicine Centre, Florence 50100, Italy
Manuela Trerotola, Daniela Storani, Alessandro Nanni Costa, Italian National Transplant Centre, Rome 00161, Italy

ORCID number: Giulio Sergio Roi (0000-0002-0738-4460); Giovanni Mosconi (0000-0002-1027-1619); Valentina Totti (0000-0003-0646-778X); Maria Laura Angelini (0000-0002-5606-7218); Erica Brugin (0000-0001-8377-9467); Paola Todeschini (0000-0003-0528-4527); Gaetano La Manna (0000-0001-5473-8551); Andrea Ermolao (0000-0002-0546-1514); Alberto Anedda (0000-0002-1235-0716); Laura Stefanì (0000-0002-2981-0424); Giorgio Galanti (0000-0002-2054-8650); Rocco Di Michele (0000-0003-2771-7661); Franco Merni (0000-0002-6012-4596); Alessandro Nanni Costa (0000-0002-9350-9521).

Author contributions: Roi GS and Mosconi G have participated in research design, drafting the paper, performance of the research and critical revision of the paper; Totti V and Angelini ML has participated in drafting the paper, performance of the research and critical revision of the paper; Brugin E, Sarto P, Merlo L, Sgarzi S, Stancari M, Todeschini P, La Manna G, Ermolao A, Capone S, Tripi F, Andreoli L, Sella G, Anedda A, Stefanì L, Galanti G and Trerotola M have participated in the performance of the research and data collection; Di Michele R and Merni F have participated in drafting the paper, data analysis and statistics; Nanni Costa A has participated in research design and in the performance of the research.


Clinical trial registration statement: This study is registered at http://www.isrctn.com/ISRCTN66295470. The registration identification number is ISRCTN66295470.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.
CONFLICT-OF-INTEREST STATEMENT: Dr. Nanni Costa has nothing to disclose.

DATA SHARING STATEMENT: No additional data are available.

OPEN-ACCESS: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

MANUSCRIPT SOURCE: Unsolicited Manuscript

Correspondence to: Alessandro Nanni Costa, MD, Doctor, Italian National Transplant Centre, Istituto Superiore di Sanità, Viale Regina Elena 299, Roma 00161, Italy. daniela.storani@iss.it
Telephone: +39-06-49904040
Fax: +39-06-49904101

Received: October 31, 2017
Peer-review started: November 1, 2017
First decision: November 30, 2017
Revised: December 6, 2017
Accepted: December 28, 2017
Article in press: December 28, 2017
Published online: February 24, 2018

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), VO2 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/m2, 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

| The Author(s) 2018. Published by Baishideng Publishing Group Inc. All rights reserved.

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”.


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[13].

There is mounting evidence that physical exercise reduces the risk of all-cause mortality[2,3] and it is
 effective in the primary and secondary prevention of CVD in the general population\(^9\). Physical activity is also considered a key element in the prevention and management of chronic diseases\(^5\), 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\(^6\). However, their cardiorespiratory fitness remains reduced by 30% in comparison with matched control subjects\(^7\). Only in selected cases they can achieve results comparable to a healthy population\(^8\), 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\(^9\).

Whether exercise can positively affect outcomes in KTRs has only been addressed in few studies\(^4\), with a small number of subjects and with different types, intensity and durations of interventions lasting almost always not more than six months\(^10,11\). In some studies, exercise was carried out tightly at home without direct supervision and with a partial adherence to the intervention\(^6\). Furthermore, few studies have investigated the effect of a combined aerobic and resistance training\(^4\), 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\(^12,13\).

**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.

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 gym). 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\(^14\), 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
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. 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 T6 assessment.

Non-supervised home-based exercise intervention (Group B)
At T0 and T6 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 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, and creatinine (mg/dL) using the Jaffè method, estimated glomerular filtration rate (eGFR) were measured. In both groups, creatinine (mg/dL) using the Jaffè method, estimated glomerular filtration rate (eGFR) 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. Systolic and diastolic blood pressures were measured with sphygmomanometers at rest, at each step and at the third minute of recovery.

Oxygen uptake (VO2) was determined continuously using an open-circuit spirometry system (Sensor Medics, Anaheim, United States), and the VO2 at the highest tolerated workload was determined and was referred to as VO2-peak (mL O2/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.

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/m²).

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, suprailliac, chest) measured with a Harpenden calliper at T0, T6 and T12.

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 completed by the patients independently at T0, T6 and T12.

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
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 ± SD age 47 ± 12 years, mass 69 ± 14 kg, BMI 24.1 ± 4.3 kg/m², time from transplant 5.5 ± 7.1 years, dialysis vintage 36 ± 35 mo, range 1-156) and 41 KTRs from Group B (13 female and 28 males, age 49 ± 9 years, weight 75 ± 13 kg, BMI 25.5 ± 4.4 kg/m², time from transplant 3.6 ± 4.0 years, dialysis vintage 33 ± 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% ± 6%. None adverse events were reported.

Primary outcomes

Creatinine tended to decrease in Group A at T12 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 T12 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 T6, T12 and T18 (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 VO₂peak at T6 (P = 0.0010, P = 0.0370), and the levels continued to increase at T12 (P = 0.0003, P = 0.0099) compared to Group B (Table 3).

The maximum HR, anaerobic threshold workload and corresponding HR significantly increased at T12 (P < 0.05) in Group A compared to Group B. In Group B, we found a significant decrease in the anaerobic threshold HR from T6 to T12 (P = 0.0434). No additional significant differences were found in Group B at T6 and T12 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 T12 compared to Group B. No significant differences were found in Group B at T12 in any variable (Table 3).

Group A showed a significant improvement in the handgrip test at T12 (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 T6, 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 MET per minute per week at baseline, and > 600 MET per minute (range 1215-1413 MET per minute) per week at T6 and T12 (P < 0.01).

Secondary outcomes

Group A showed a significant decrease in BMI at T12 (P = 0.0013) and fat mass percentage at T6 (P = 0.05)
comparing to Group B (Table 3).

In HRQoL, significant improvements were found in Group A in physical function scale at T0 ($P = 0.0082$) and continued to increase at T12 ($P = 0.0019$), in role-physical and role-social functioning scales at T6 ($P = 0.0321$, $P = 0.0346$) 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 not to carry out physical activity even if it is recommended by the physician.

van Adrichem et al. [21] 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. [6] 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. [22] 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. [3] 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 3

<table>
<thead>
<tr>
<th></th>
<th>Group A ($n = 44$)</th>
<th>Group B ($n = 41$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum workload (W)</td>
<td>95 ± 36</td>
<td>102 ± 32</td>
</tr>
<tr>
<td>$V'\text{O}_2$ peak (mL/kg per minute)</td>
<td>22.8 ± 8.3</td>
<td>21.6 ± 6.8</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>142 ± 24</td>
<td>133 ± 22</td>
</tr>
<tr>
<td>Diastolic BP at rest (mmHg)</td>
<td>80 ± 8</td>
<td>81 ± 9</td>
</tr>
<tr>
<td>Diastolic BP at $V'\text{O}_2$ peak (mmHg)</td>
<td>85 ± 11</td>
<td>84 ± 10</td>
</tr>
<tr>
<td>Diastolic BP at 3' recovery (mmHg)</td>
<td>79 ± 9</td>
<td>78 ± 10</td>
</tr>
<tr>
<td>Systolic BP at rest (mmHg)</td>
<td>126 ± 14</td>
<td>130 ± 16</td>
</tr>
<tr>
<td>Systolic BP at V'CO$_2$ peak (mmHg)</td>
<td>183 ± 26</td>
<td>181 ± 26</td>
</tr>
<tr>
<td>Systolic BP at 3' recovery (mmHg)</td>
<td>128 ± 17</td>
<td>136 ± 16</td>
</tr>
<tr>
<td>Body mass index (kg/m$^2$)</td>
<td>24.1 ± 4.3</td>
<td>25.3 ± 4.4</td>
</tr>
<tr>
<td>Fat mass (%)</td>
<td>21.1 ± 9.0</td>
<td>20.0 ± 7.8</td>
</tr>
<tr>
<td>Aerobic threshold workload (W)</td>
<td>53 ± 23</td>
<td>53 ± 21</td>
</tr>
<tr>
<td>Aerobic threshold HR (bpm)</td>
<td>87 ± 38</td>
<td>55 ± 27</td>
</tr>
<tr>
<td>Anaerobic threshold workload (W)</td>
<td>84 ± 30</td>
<td>89 ± 32</td>
</tr>
<tr>
<td>Anaerobic threshold HR (bpm)</td>
<td>131 ± 21</td>
<td>125 ± 20</td>
</tr>
<tr>
<td>Knee extensors right (kg)</td>
<td>87 ± 38</td>
<td>55 ± 27</td>
</tr>
<tr>
<td>Knee extensors left (kg)</td>
<td>80 ± 36</td>
<td>51 ± 23</td>
</tr>
<tr>
<td>Plantar flexors right (kg)</td>
<td>70 ± 34</td>
<td>62 ± 35</td>
</tr>
<tr>
<td>Plantar flexors left (kg)</td>
<td>70 ± 33</td>
<td>64 ± 34</td>
</tr>
<tr>
<td>Counter movement jump (cm)</td>
<td>24.0 ± 10.0</td>
<td>21.4 ± 9.4</td>
</tr>
<tr>
<td>Handgrip right (kg)</td>
<td>30.8 ± 13.1</td>
<td>36.3 ± 9.5</td>
</tr>
<tr>
<td>Handgrip left (kg)</td>
<td>29.3 ± 13.6</td>
<td>35.1 ± 9.3</td>
</tr>
<tr>
<td>Elbow flexors Right (kg)</td>
<td>8.8 ± 2.7</td>
<td>8.0 ± 3.4</td>
</tr>
<tr>
<td>Elbow flexors Left (kg)</td>
<td>8.7 ± 3.2</td>
<td>7.3 ± 3.4</td>
</tr>
<tr>
<td>Elbow extensors right (kg)</td>
<td>5.8 ± 2.0</td>
<td>5.1 ± 2.2</td>
</tr>
<tr>
<td>Elbow extensors left (kg)</td>
<td>5.7 ± 2.0</td>
<td>4.9 ± 2.3</td>
</tr>
<tr>
<td>Shoulder abductors (kg)</td>
<td>5.3 ± 2.2</td>
<td>4.2 ± 2.7</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.26 ± 0.38</td>
<td>1.37 ± 0.48</td>
</tr>
<tr>
<td>eGFR (mL/min per 1.73 m$^2$)</td>
<td>59.4 ± 19.3</td>
<td>56.3 ± 21.2</td>
</tr>
<tr>
<td>Proteinuria (g/24 h)</td>
<td>0.41 ± 0.51</td>
<td>0.45 ± 0.57</td>
</tr>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>12.8 ± 1.8</td>
<td>12.1 ± 1.8</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>122 ± 42</td>
<td>138 ± 69</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>196 ± 37</td>
<td>195 ± 33</td>
</tr>
</tbody>
</table>

In Group A: $P < 0.05$ between T0 and T6, $P < 0.05$ between T6 and T12. In Group B: $P < 0.05$ between T0 and T12. BP: Blood pressure; HR: Heart rate; eGFR: Estimated glomerular filtration rate.
group. O’Connor et al.\(^{[23]}\) 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 it was beneficial to health and well-being\(^{[29]}\). Social, cognitive, personality, environmental, and socio-economic factors, unrelated to the recommended guidelines, seem to be of greater importance in considering behavioural adherence issues\(^{[25]}\) 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\(_\text{peak}\) at T6. Similar results were obtained by van den Ham et al.\(^{[26]}\) in 33 KTRs after 12 wk of combination of endurance and strength training in which V'O\(_\text{peak}\) peak increase of 10% (from 21.6 ± 6.3 to 23.8 ± 6.1 mL/kg per minute). Riess et al.\(^{[2]}\) reported an increase of V'O\(_\text{peak}\) peak (from 20 ± 9 to 23 ± 10 mL/kg per minute) after 12 wk of supervised endurance training (three times/week) on cycle ergometer at 60%-80% of V'O\(_\text{max}\) involving 16 patients.

In a study of eight KTRs, Romano et al.\(^{[27]}\) 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\(_\text{peak}\) peak.

Another intervention was published by Kempeneers et al.\(^{[28]}\) who trained 16 KTRs for six months in preparation for the National Transplant Games. Their mean V'O\(_\text{peak}\) rose from 29.0 ± 7.8 to 37.5 ± 4.8 mL/kg per minute, with an increase of 27%.

In the other hand, Painter et al.\(^{[6]}\) 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\(_\text{peak}\) increased from 24.0 ± 7.5 to 27.8 ± 11.0 mL/kg per minute (+ 16%) and to 30.1 ± 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\(^{[29]}\). 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.\(^{[2]}\) 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.

### Table 4 Mean ± SD of 36-Item Short Form Health Survey questionnaire scales

<table>
<thead>
<tr>
<th>Group</th>
<th>T0</th>
<th>T6</th>
<th>T12</th>
<th>T0</th>
<th>T6</th>
<th>T12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical function</td>
<td>84 ± 20</td>
<td>91 ± 11</td>
<td>92 ± 12</td>
<td>89 ± 10</td>
<td>86 ± 20</td>
<td>86 ± 23</td>
</tr>
<tr>
<td>Role physical</td>
<td>83 ± 25</td>
<td>88 ± 21</td>
<td>96 ± 15</td>
<td>91 ± 19</td>
<td>91 ± 19</td>
<td>86 ± 24</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>80 ± 24</td>
<td>80 ± 22</td>
<td>89 ± 20</td>
<td>86 ± 19</td>
<td>84 ± 22</td>
<td>84 ± 22</td>
</tr>
<tr>
<td>General health</td>
<td>63 ± 20</td>
<td>67 ± 21</td>
<td>68 ± 20</td>
<td>64 ± 21</td>
<td>67 ± 19</td>
<td>66 ± 17</td>
</tr>
<tr>
<td>Vitality</td>
<td>67 ± 16</td>
<td>70 ± 15</td>
<td>69 ± 19</td>
<td>67 ± 18</td>
<td>69 ± 14</td>
<td>68 ± 14</td>
</tr>
<tr>
<td>Social function</td>
<td>75 ± 19</td>
<td>80 ± 20</td>
<td>83 ± 17</td>
<td>82 ± 19</td>
<td>78 ± 21</td>
<td>78 ± 21</td>
</tr>
<tr>
<td>Role emotional</td>
<td>85 ± 24</td>
<td>91 ± 20</td>
<td>90 ± 22</td>
<td>93 ± 16</td>
<td>96 ± 15</td>
<td>93 ± 17</td>
</tr>
<tr>
<td>Mental health</td>
<td>75 ± 16</td>
<td>75 ± 16</td>
<td>74 ± 19</td>
<td>74 ± 18</td>
<td>77 ± 16</td>
<td>74 ± 16</td>
</tr>
</tbody>
</table>

\(^{[1]} P < 0.05\) between T0 and T6; \(^{[2]} P < 0.05\) between T1 and T0.
corresponding to the lactate aerobic threshold. Different steady state aerobic exercise protocol at intensity the aerobic and strength trainings. We adopted a organisational grounds. Therefore, the two groups in the usual care group (Group B) on logistic and is a non-randomised study; we included the patients contributed to these findings.

This finding confirms that supervised exercise training in the protocol of the CMJ test did not have any improvement in Group A in the self-perception of social function. The KTRs in the usual care group (Group B) did not show any improvement in HRQoL scores. The association of aerobic and resistance training was effective in reducing BMI 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.

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. The accurate selection of the patients and the cardiovascular assessment at T₀ 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 limitation is that we administered the IPAQ only to the KTRs with an arteriovenous fistula, and thus 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.
Effects of a supervised exercise after kidney transplantation

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 suggested to and/or prescribed physical activity.

Terminology
Oxygen uptake (VO2) at the highest tolerated workload was referred to as VO2 peak (mLO2/kg per minute).

ACKNOWLEDGMENTS
The authors gratefully acknowledge Paola Di Ciaccio, Claudia Carella, Claudia Ferraro and Carlo Donati for their cooperation in the project.

REFERENCES
23 Schoo E, Gustav T, Barbalinardo C, Rodrigues N, Zameni Y,


33 Lee DC, Sui X, Artero EG, Lee IM, Church TS, McAuley PA, Stanford FC, Kohl HW 3rd, Blair SN. Long-term effects of changes in cardiorespiratory fitness and body mass index on all-cause and cardiovascular disease mortality in men: the Aerobics Center Longitudinal Study. *Circulation* 2011; 124: 2483-2490 [PMID: 22144631 DOI: 10.1161/CIRCULATIONAHA.111.084222]


P- Reviewer: Pham PT, Stavroulopoulos A  S- Editor: Cui LJ  L- Editor: A  E- Editor: Li D