Influence of physical activity on cardiorespiratory fitness in children after renal transplantation

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Abstract
Background. Cardiorespiratory fitness is significantly reduced in children with end-stage renal disease. The role of renal transplantation in improving cardiorespiratory fitness has not been thoroughly investigated.

Methods. In this work, we wanted to assess whether, in children after a successful renal transplant, the amount of weekly physical exercise affects cardiorespiratory fitness and left ventricular mass (LVM). The study was conducted on 16 children after renal transplantation and 36 matching healthy controls. Four groups were formed according to the weekly amount of physical exercise; all children received an echocardiogram and underwent a treadmill exercise test according to the Bruce protocol.

Results. Cardiorespiratory fitness is worst in renal transplant children with a weekly physical exercise < 3 h; renal transplant children with a physical exercise of 3–5 h per week attain a cardiorespiratory fitness comparable to controls with a sedentary lifestyle (<3-h exercise per week); healthy controls with a weekly physical exercise of 3–5 h per week show the highest levels of cardiorespiratory fitness; the LVM assessed via echocardiography follows the same pattern.

Conclusions. In children with a successful renal transplant, a weekly physical exercise of 3–5 h significantly improves the cardiorespiratory fitness and the LVM, up to the level of matching healthy controls with a sedentary lifestyle (<3 h exercise per week).

Keywords: cardiovascular risk factors; child; physical activity; renal transplant

Introduction

Long-term outcomes of paediatric renal transplants have improved dramatically over the last two decades and presently, renal graft survival at 1 and 5 years is >80 and 60%, respectively [1, 2].

Poor physical activity is one of the major components of the lower health-related quality of life in children with end-stage renal disease (ESRD) and after renal transplantation compared to healthy age-matched peers [3–5]. The neuromuscular, metabolic and cardiopulmonary deficits related to ESRD are mostly responsible for poor physical activity in these patients [6] and in renal transplant children, an important role is played by increased fat mass, a side effect of the immunosuppressive therapies. However, an important role could also be played by reduced attention to physical activity and by poor training [7].

In adults, cardiorespiratory fitness is reduced before kidney or liver transplantation [8, 9]; exercise capacity increases soon after transplantation [10], but the improvement is not sustained at 1 year after transplantation in the absence of continuous training [11].

Low cardiorespiratory fitness is an independent predictor of mortality from all causes and specifically death from cardiovascular disease [12–14]. In the general paediatric population and in children after renal transplantation, physical exercise prevents or delays the development of cardiovascular complications, promotes weight control and reduces anxiety improving the child’s body image and mood [15, 16].

Little is known, however, about the correlation between amounts of regular physical exercise and exercise tolerance threshold and cardiovascular complications. Using the treadmill exercise test and assessing the ventricular mass by echocardiography, we aimed to test for cardiorespiratory fitness in a number of children after successful kidney transplantation, relating the level of fitness to the amount of regular physical exercise and comparing the findings with matching healthy controls.

Materials and methods

We enrolled 52 children. Sixteen (14 males, 2 females) children had received a renal transplant for ESRD. At the time the study was conducted, their mean age was 16.03 ± 2.45 years. All patients were >24 months
post-transplantation, had no reported episodes of rejection for at least 3 years and before transplantation had been on extracorporeal dialysis for <1 year. Their renal function had been stable since transplantation and had been re-assessed at enrolment. All kidney transplant recipients were on triple immunosuppressive therapy: 13 with cyclosporine A, prednisone and mycophenolate and 3 with tacrolimus, prednisone and mycophenolate mofetil.

The remaining 36 (28 males and 8 females; mean age 14.68 ± 2.94 years) were healthy and constituted the control group.

Informed consent was obtained from both the parents of each child. The protocol conforms to the guidelines of the Declaration of Helsinki and was approved by the ethical committee of the involved institution [17].

All of the children enrolled in the study had lung function tests within normal limits, and blood pressure below the 90th centile on ambulatory blood pressure monitoring [18], none of the children were on anti-hypertensive drugs. None of the subjects, both studies and controls, had physical or cognitive handicaps.

Sport activity for children in our post-transplant follow-up programme is economically supported by a non-profit organization (nuovArmonia).

A standardized paediatric questionnaire was administered to all children for investigating the time dedicated weekly to physical activity [19]. On the basis of the questionnaire, the children were divided into inadequately active (<3 h of physical activity per week) and adequately active (3–5 h of physical activity per week) according to Crocker et al. [19]. This test has been found to have adequate test–retest reliability and reasonable validity when compared with other objective measures of physical activity [20, 21]. In accordance with the guidelines of the American Heart Association [22] which recommend at least 30 min of moderate-to-vigorous physical activity during the school day for all children and youths, we considered a total of 3 h minimum activity per week to be adequate.

**Parameters evaluated**

None of the patients included in the study protocol had contraindications to exercise testing (ATS/ACCP statement 2003) [23].

Eligibility to executing a maximal incremental exercise was assessed in all patients and controls: the evaluation was comprehensive of an echo-to-exercise testing (ATS/ACCP statement 2003) [23].

In control groups with inadequate physical activity, res-piratory and HR rate in the transplant group were higher in inadequately active controls (P < 0.0002) and adequately active (P < 0.0073) exercise. However, it was similar than in both inadequately active controls (P < 0.0002) and adequately active (P < 0.0073) exercise. It was similar than in both inadequately active controls (P < 0.0002) and adequately active (P < 0.0073) exercise. It was similar than in both inadequately active controls (P < 0.0002) and adequately active (P < 0.0073) exercise.

The null hypothesis was that all the groups in the study came from the same distribution.

The Mann–Whitney U-non-parametric test was used to examine the differences of the same parameter between two groups. In Figure 1, these data are reported as dots, boxes and whisker plot. The boxes summarize the distribution of points at each factor level. The ends of the boxes are the 25th and 75th quintiles. The line across the middle of the boxes identifies the median sample value. The whiskers extend from ends of the box to the outermost data point that falls within the distances computed: upper quartile + 1.5 (interquartile range) and lower quartile – 1.5 (interquartile range).

A P-value < 0.05 was considered statistically significant.

**Results**

Compared with the healthy controls, renal transplant recipients did not show significant differences in terms of age, weight, BMI and resting SBP and DBP (Table 1). On the contrary, height was significantly lower in the study group. HR and respiratory rate in the transplant group were higher than in controls but lower than the 90th centile for sex, age and height (Table 1).

**Grouping according to weekly physical exercise**

The children were sorted into four groups by hours spent weekly on physical activity: 10 post-transplant children with inadequate physical exercise (<3 h/week, Tx inadequately active), 3, 6 post-transplant children with adequate physical exercise (3–5 h/week, Tx ≥ 3), 20 controls with adequate physical exercise (3–5 h/week, control (C) ≥ 3) and 16 controls with inadequate physical exercise (<3 h/week, C < 3).

**Renal function in post-transplant children**

Glomerular filtration rate was similar in all post-transplant children, regardless of physical activity (Tx inadequately active 93.1 ± 22.21 versus Tx adequately active 91.83 ± 23.82 mL/min/1.73 m²; P NS, not significant).

**General comparison of the groups**

The four groups are similar for weight, BMI, SBP and DBP (Table 2). However, the height was higher in controls with adequate physical activity than in controls whose activity was found to be inadequate and height of transplanted children with inadequate physical activity was significantly lower than both control groups.

HR was significantly lower in adequately active controls than in both inadequately active controls (P < 0.0002) and post-transplant children with inadequate (P < 0.002) or adequate (P < 0.0073) exercise. However, it was similar between post-transplant patients with adequate physical exercise and inadequately active controls.

In control groups with inadequate physical activity, respiratory rate is lower than in the post-transplant group with adequate physical activity.

**Physical activity and exercise tolerance**

The peak respiratory and HRs during the treadmill test were significantly lower in both post-transplant groups than in all controls (Table 3).
**Physical activity and fitness in renal transplant children**

**Echocardiographic evaluation**

The LVM of controls with adequate activity is significantly smaller than all other groups (C > 3 = 29.66 ± 5.22 g/m²·7; C < 3 = 41.85 ± 9.00 g/m²·7; Tx > 3 = 42.40 ± 19.70 g/m²·7; Tx < 3; 66.83 ± 21.59 g/m²·7) (Figure 1).

Interestingly, the LVM is not significantly different between well-exercised post-transplant children and poorly exercised controls.

**Discussion**

Chronic renal disease has a progressive negative impact on cardiorespiratory fitness that is not ameliorated and is even worsened by peritoneal dialysis or haemodialysis [7, 8, 10, 27]. It makes the patient unable to perform regular satisfactory physical exercise. It is not clear how renal transplantation in children, the most satisfactory therapy for chronic ESRD, improves VO₂ and cardiorespiratory fitness. Aparicio López et al. [27] have already reported how renal transplantation improves the ability of a child suffering from ESRD to do physical exercise but not equal to the performance of a healthy matching control. Painter et al. [28] state that renal transplantation per se does not improve exercise capacity over pre-transplant levels. Others reported partial improvement of VO₂ max after renal transplantation [29]. As oxidative metabolism of skeletal muscles and erythrocytes may only be partially restored after renal transplantation, it is difficult for these individuals to attain levels of fitness similar to matched healthy controls [30–32].

VO₂ max is an indicator of the ability of the cardiopulmonary system to meet increased metabolic demand [29, 33] and therefore, it expresses the ability to perform physical exercise. During physical exertion, an individual with low VO₂ max will experience early muscular exhaustion and will therefore be unable to perform an adequate regular physical activity.

In fact, low cardiorespiratory fitness expressed as VO₂ max and measured with the treadmill test is a reliable risk predictor for sudden cardiac death [34]. It has been reported that cardiorespiratory fitness can improve with regular physical exercise [34]. Also in adolescents, aerobic fitness plays a positive role in reducing the cardiovascular risk and related mortality [35] and improving overall well-being and health-related quality of life [5].

This is the most important in transplant patients, cardiovascular accidents being among the main causes of death after a successful renal transplant [36, 37].

Our crossover study shows that physically active transplanted children reach a fitness level comparable to sedentary healthy controls and better to that of sedentary transplanted children. The exercise time on treadmill test before muscular exhaustion increases with regular exercise and at the same time VO₂ max/kg improves as expected. Our data add the evidence that regular physical exercise is effective also in reducing the LVM. As the cardiac mass is a known risk factor of cardiovascular disease [38], its reduction is a measurable indicator of improvement. It is worth noting that in our study population, the BMI was always below the 85th centile: the influence of BMI on the ventricular mass was therefore negligible.

**Table 1. Age, height, weight, BMI, resting systolic and diastolic pressure, resting cardiac and respiratory rate of patients and controls**

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 36)</th>
<th>Transplant children (n = 16)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>28/8</td>
<td>14/2</td>
<td>–</td>
</tr>
<tr>
<td>Age (years)</td>
<td>14.68 ± 2.94</td>
<td>16.03 ± 2.45</td>
<td>NS</td>
</tr>
<tr>
<td>Height (SDS)</td>
<td>−0.37 ± 0.79</td>
<td>−1.69 ± 0.82</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Weight (SDS)</td>
<td>−0.11 ± 0.90</td>
<td>−0.71 ± 1.09</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (SDS)</td>
<td>0.11 ± 0.90</td>
<td>0.20 ± 1.24</td>
<td>NS</td>
</tr>
<tr>
<td>SBP (SDS)</td>
<td>0.30 ± 0.82</td>
<td>0.56 ± 1.17</td>
<td>NS</td>
</tr>
<tr>
<td>DBP (SDS)</td>
<td>0.70 ± 0.52</td>
<td>0.98 ± 0.74</td>
<td>NS</td>
</tr>
<tr>
<td>HR (beats per minute)</td>
<td>78.50 ± 10.56</td>
<td>93.81 ± 16.08</td>
<td>0.0012</td>
</tr>
<tr>
<td>Respiratory rate (acts per min)</td>
<td>20.22 ± 1.35</td>
<td>23.65 ± 6.70</td>
<td>0.022</td>
</tr>
</tbody>
</table>

*M/F = males/females; NS = Not significant. A P < 0.05 was considered statistically significant.*

**Left Ventricular Mass (LVM)**

Kruskal Wallis test \(p < 0.0001\)

Fig. 1. Left ventricular mass (LVM) in controls (C) and transplanted children (Tx) divided according to adequate (>3) or inadequate physical activity (<3). (A P < 0.05 was considered statistically significant.)

VO₂ max/kg was significantly higher in controls with adequate physical exercise than in the other three groups; it did not differ significantly between well-exercised post-transplant children and controls with a sedentary lifestyle; it was lower than in any other groups in post-transplant patients with inadequate physical exercise.

Endurance on physical exercise during the stress test was high in controls with adequate physical training and progressively and significantly lower in controls with inadequate physical activity, in adequately exercising transplant children, to reach the lowest level in transplant children with inadequate physical activity. The peak SBP during the stress test in transplanted children with inadequate physical activity was significantly lower than in both control groups. All other differences in blood pressure were not statistically significant.

During the stress test, the DBP decreased significantly in controls with adequate physical activity compared to all other groups, while all other inter-group differences did not reach significance.
Table 2. Age, height, weight, BMI, resting systolic and diastolic pressure, resting cardiac and respiratory rate in controls (C) and transplanted children (Tx) divided according to adequate (>3) or inadequate physical activity (<3)*

<table>
<thead>
<tr>
<th></th>
<th>Controls, inadequately active (n = 16)</th>
<th>Controls, adequately active (n = 20)</th>
<th>Transplant children, inadequately active (n = 10)</th>
<th>Transplant children, adequately active (n = 6)</th>
<th>Kruskal–Wallis test, P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>13/3</td>
<td>15/5</td>
<td>10/4</td>
<td>4/2</td>
<td>NS</td>
</tr>
<tr>
<td>Age</td>
<td>15.00 ± 2.84</td>
<td>14.53 ± 1.86</td>
<td>16.00 ± 3.48</td>
<td>16.55 ± 2.25</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (SDS)</td>
<td>-0.28 ± 0.86</td>
<td>0.02 ± 0.93</td>
<td>-0.31 ± 1.24</td>
<td>-0.51 ± 1.12</td>
<td>NS</td>
</tr>
<tr>
<td>Height (SDS)</td>
<td>-0.68 ± 0.65</td>
<td>0.13 ± 0.82</td>
<td>-1.86 ± 0.66</td>
<td>-1.83 ± 1.07</td>
<td>&lt;0.0002</td>
</tr>
<tr>
<td>BMI (SDS)</td>
<td>-0.001 ± 0.92</td>
<td>0.19 ± 0.93</td>
<td>-0.59 ± 1.58</td>
<td>0.75 ± 0.74</td>
<td>NS</td>
</tr>
<tr>
<td>SBP (SDS)</td>
<td>-0.009 ± 0.94</td>
<td>0.55 ± 0.63</td>
<td>0.45 ± 1.69</td>
<td>0.54 ± 0.53</td>
<td>NS</td>
</tr>
<tr>
<td>DBP max effort (SDS)</td>
<td>0.82 ± 0.68</td>
<td>0.61 ± 0.35</td>
<td>1.40 ± 0.58</td>
<td>0.82 ± 0.95</td>
<td>NS</td>
</tr>
<tr>
<td>HR max effort (beats per minute)</td>
<td>192.68 ± 9.63</td>
<td>197 ± 6.83</td>
<td>160.66 ± 23.78</td>
<td>170.30 ± 17.35</td>
<td>&lt;0.0002</td>
</tr>
<tr>
<td>RR max effort (acts per minute)</td>
<td>32.62 ± 7.2</td>
<td>53.07 ± 6.84</td>
<td>40.20 ± 6.3</td>
<td>41.48 ± 8.41</td>
<td>NS</td>
</tr>
<tr>
<td>Exercise time (min)</td>
<td>11.69 ± 1.13</td>
<td>13.72 ± 1.34</td>
<td>7.69 ± 2.00</td>
<td>10.35 ± 0.99</td>
<td>0.0052</td>
</tr>
<tr>
<td>VO2max/kg</td>
<td>32.62 ± 2.53</td>
<td>41.90 ± 5.66</td>
<td>24.79 ± 1.99</td>
<td>29.59 ± 4.28</td>
<td>0.0001</td>
</tr>
<tr>
<td>SBP max effort (mmHg)</td>
<td>4.56 ± 1.05</td>
<td>4.01 ± 0.87</td>
<td>2.88 ± 0.58</td>
<td>5.17 ± 1.91</td>
<td>0.014</td>
</tr>
<tr>
<td>DBP max effort (mmHg)</td>
<td>-0.44 ± 0.53</td>
<td>0.68 ± 0.44</td>
<td>0.24 ± 1.12</td>
<td>0.10 ± 0.80</td>
<td>0.0004</td>
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Mann–Whitney U-test

<table>
<thead>
<tr>
<th></th>
<th>C &lt; 3 versus C &gt; 3</th>
<th>Tx &lt; 3 versus Tx &gt; 3</th>
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<th>C &lt; 3 versus C &gt; 3</th>
<th>C &lt; 3 versus C &gt; 3</th>
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</thead>
<tbody>
<tr>
<td>Height</td>
<td>0.048</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0.0013</td>
<td>0.001</td>
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<tr>
<td>HR rest</td>
<td>0.0002</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0.0073</td>
<td>NS</td>
</tr>
<tr>
<td>Respiratory rate rest</td>
<td>NS</td>
<td>NS</td>
<td>0.044</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

* = number of subjects; M/F = males/females; NS = not significant. A P < 0.05 was considered statistically significant.

Table 3. Values of the parameters measured at the maximal physical effort, in controls (C), and transplanted children (Tx) divided according to adequate (>3) or inadequate physical activity (<3)*

<table>
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<th>C &lt; 3 versus C &gt; 3</th>
<th>C &lt; 3 versus C &gt; 3</th>
<th>C &lt; 3 versus C &gt; 3</th>
<th>C &lt; 3 versus C &gt; 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR max effort</td>
<td>NS</td>
<td>NS</td>
<td>0.0044</td>
<td>0.001</td>
<td>0.002</td>
<td>0.0011</td>
</tr>
<tr>
<td>HR max effort</td>
<td>NS</td>
<td>NS</td>
<td>0.0022</td>
<td>0.0004</td>
<td>0.0015</td>
<td>0.0001</td>
</tr>
<tr>
<td>Exercise time</td>
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<td>0.0016</td>
<td>0.0002</td>
<td>0.0001</td>
<td>0.005</td>
<td>0.0001</td>
</tr>
<tr>
<td>VO2max/kg</td>
<td>0.0001</td>
<td>0.0048</td>
<td>0.0001</td>
<td>0.0001</td>
<td>NS</td>
<td>0.0015</td>
</tr>
<tr>
<td>SBP max effort</td>
<td>NS</td>
<td>NS</td>
<td>0.0064</td>
<td>0.0098</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>DBP max effort</td>
<td>0.0001</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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</table>

*RR = respiratory rate; NS = not significant. A P < 0.05 was considered statistically significant.

In the observed population, no patient attained levels of physical fitness comparable to healthy controls. However, this could be due to the number of participants being too small to adequately correct for potential confounding factors such as gender or pubertal stage.

In conclusion, our pilot study shows how renal transplanted children benefit from physical activity and how 3- to 5-h weekly exercise is an important threshold for a significant improvement in cardiorespiratory fitness. Adequate cardiorespiratory fitness has proved beneficial in improving the quality of life and decreasing the risk for cardiovascular diseases and accidents. Therefore, resumption of adequate physical exercise after successful renal transplantation should be strongly encouraged.

Conflict of interest statement. None declared.

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