# Can Solid-Organ–Transplanted Patients Perform a Cycling Marathon? Trends in Kidney Function Parameters in Comparison With Healthy Subjects

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## ABSTRACT

**Background.** Few solid-organ–transplanted patients (TP) perform regular sport activity. Poor data are available on the safety of intense and prolonged physical exercise on this population. The aim of the study was to evaluate kidney function parameters in a group of TP in comparison with healthy volunteers (HV) involved in a long-distance road cycling race: length 130 km and total uphill gradient, 1871 m.

**Methods.** Nineteen TP were recruited: 10 renal, 8 liver, and 1 heart and compared with 35 HV. Renal function parameters, namely, creatinine, estimated glomerular filtration rate (eGFR), urea, uric acid, urine specific gravity, microalbuminuria, and proteinuria were collected and their values were compared the day before the race (T1), immediately after crossing the finish line (T2), and 18 to 24 hours after the competition (T3).

**Results.** No adverse events were recorded. At baseline, TP showed lower values of eGFR ($69 \pm 22$ versus $87 \pm 13$ mL/min/1.73 $m^2$), lower urine specific gravity ($1015 \pm 4$ versus $1019 \pm 6$), and higher microalbuminuria ($56 \pm 74$ versus $8 \pm 15$) and proteinuria values ($166 \pm 99$ versus $74 \pm 44$) (in mg/L). At T2 in both groups, renal function parameters showed the same trends: decline of eGFR ($54 \pm 19$ versus $69 \pm 15$ mL/min/1.73 $m^2$) and rise in protein excretion. At T3, functional parameters returned to baseline, except for urine specific gravity values remaining stable in TP ($1018 \pm 6$) and growing higher in HV ($1028 \pm 4$).

**Conclusions.** Selected and well-trained organ-transplanted patients can perform an intensive exercise, displaying temporary modifications on kidney function parameters comparable to healthy subjects, despite differences related to baseline clinical conditions and pharmacological therapies.

RELATIONSHIPS between physical activity and cardiovascular health have been well established [1,2]. Despite this evidence, however, the vast majority of transplanted patients remain sedentary, even though cardiovascular morbidity is one of the most important and recurrent cause of mortality and morbidity. Transplant physicians do not prescribe routinely physical activity as a therapeutic tool, either. This behavior is partly due to the lack of knowledge regarding the safety in this specific subgroup of patients, in particular about intensive

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exercise. Modification on glomerular filtration and proteinuria during exercise are known in the general population [3,4] but little experience is available about the possible dose-related risk of kidney injury during sporting activity in solid-organ–transplanted patients [5]. There are poor data about the functional kidney adaptations that occur during intense and prolonged physical exercise in patients receiving immunosuppressive therapy with nephrotoxic effects [6,7].

The aim of this paper was to contribute in describing functional kidney changes in prolonged and intense exercise and their possible implications in any additional risks of kidney injury. Renal function parameters were recorded in a group of solid-organ–transplanted patients and compared with healthy subjects involved in a long-distance road cycling race.

## METHODS

### The Race

The length of the race was 130 km; total uphill gradient, 1871 m; uphill riding, 50 km over 4 hills; downhill riding, 46 km; and flat terrain, 34 km. The temperature was 12.6 °C at the start and 18.9 °C at noon.

### Inclusion and Exclusion Criteria

We included male subjects who usually practice cycling and voluntarily participated in the race. The healthy volunteers (HV), used as a control group, were amateur cyclists informed by the organization of the study through a newsletter who reported no significant clinical problem, with blood pressure (BP) values within the normal range (<140/80 mm Hg). Solid-organ–transplanted patients (TP) were enrolled with the support of ANED Sport (Associazione Nazionale Emodializzati, Dialisi e Trapianto), an association involved in promoting physical activity after transplantation. Patients were transplanted at least 1 year previously and were between 18 and 80 years of age, with good blood pressure control (BP <140/80 mm Hg), and they all had gone through a preliminary evaluation for their eligibility to perform physical activity: ergometric and cardiac function tests for assessing the likelihood of cardiovascular events (detection of eventual silent heart disease) as previously described [7].

Exclusion criteria included unstable cardiovascular pathology and diabetes.

### Protocol

1. Baseline overall medical assessment of all the subjects, with collection of anamnestic data, information on drug therapy, measurement of resting heart rate and BP; questionnaire investigating the level of training carried out throughout the year and in preparation for the race expressed as amount of training workouts per week and hours of training for each session;
2. Collection of venous blood (30 mL) and urine (30 mL) samples at time 1 (T1) (the day before the race), time 2 (T2) (immediately after crossing the finish line), and time 3 (T3) (18–24 hours after competing);
3. Amount of fluid ingestion (mL) during the race was recorded at T2.

**Table 1. Demographic Historical Characteristics**

| | Transplanted Patients (n = 19) | Healthy Volunteers (n = 35) |
|---|---|---|
| Organ transplanted | | |
| Single kidney | 10 | 0 |
| Liver | 8 | |
| Heart | 1 | |
| Time from transplant (years) | 9.3 ± 5.1 | / |
| Age (years) | 52 ± 9 | 50 ± 10 |
| BMI (kg/m$^2$) | 23.7 ± 1.7 | 24.1 ± 2.3 |
| Immunosuppressive therapy | | |
| Tacrolimus/cyclosporine | 15 | None |
| Steroids | 8 | |
| Mycophenolic acid | 8 | |
| Everolimus | 4 | |
| Hypertension therapy | 14 | 1 |
| Anti-hypertensive therapy | | |
| ACE inhibitors | 7 | 1 |
| β-Blockers | 7 | |
| Calcium channel blocker | 1 | |
| Workouts per week (n) | 3.3 ± 1.7 | 2.8 ± 1.1 |
| Training time for each session (hours) | 2.8 ± 0.8 | 2.8 ± 0.8 |

Continuous variables are expressed as means ± standard deviation; categorical variables as absolute numbers.
Abbreviation: BMI, body mass index.

**Table 2. Baseline Renal Function Results**

| | Transplanted Patients (n = 19) | Healthy Volunteers (n = 35) | *P* Value |
|---|---|---|---|
| Creatinine (mg/dL) | 1.08 ± 0.36 | 0.93 ± 0.14 | NS |
| eGFR (MDRD) (mL/min/1.73 $m^2$) | 69 ± 22 | 87 ± 13 | .01* |
| Urea (mg/dL) | 47 ± 14 | 38 ± 8 | .03* |
| Uric acid (mg/dL) | 5.8 ± 1.3 | 4.7 ± 0.9 | .01* |
| Urine specific gravity (densimetry) | 1015 ± 4 | 1019 ± 6 | .01* |
| Microalbuminuria (mg/L) | 56 ± 74 | 8 ± 15 | <.001* |
| Proteinuria (mg/L) | 166 ± 99 | 74 ± 44 | <.001* |

Data are expressed as means ± standard deviation.
Abbreviations: NS, not statistically significant; eGFR (MDRD), estimated glomerular filtration rate calculated from serum creatinine using the Modification of Diet in Renal Disease Study equation.
*$P < .005$.

4. Assessment of possible adverse events during or after the race at T2 and T3.

### Renal Function Parameters

1. In blood samples: creatinine (mg/dL) with Jaffè method, estimated glomerular filtration rate (eGFR) with Modification of Diet in Renal Diseases formula (isotope dilution mass spectrometry method, mass spectrometry isotope dilution calibrated) in mL/min/1.73 $m^2$, urea (mg/dL) with urease and glutamate dehydrogenase, and uric acid (mg/dL) with enzymatic colorimetric test.
2. In urine samples: urine specific gravity (densitometry), microalbuminuria (mg/L) (nephelometry), and proteinuria (mg/1000 mL) (turbidimetry).

The protocol was approved by an ethics committee, and informed consent was obtained from all the patients.

### Statistical Analysis

Data are presented as mean ± standard deviation. After verifying the assumptions of normality and homoscedasticity, differences between TP and HV were analyzed by means of Mann-Whitney *U* test or *t* test according to the type of the data distribution. One-way analysis of variance for independent samples was used to compare the mean values for the quantity of training questionnaire and the fluid ingestion during the competition between TP and HV groups. Significance was set at *P* less than .05. Statistical analyses were carried out with the use of software R, version 3.0.3.

## RESULTS

We recruited 19 TP: 10 renal, 8 liver, 1 heart, and 35 HV as control a group. All the participants completed the race. No adverse events were recorded in either group during or after the race at T2 and T3. The race time was within a range from 4 hours, 37 minutes, to 10 hours, with no significant differences between the two groups. The amount of fluid ingestion during the race was comparable between the groups: HV, 2533 ± 1067 versus TP, 1957 ± 652 mL at T2.

### Baseline

The characteristics of the study population at baseline are reported in Tables 1 and 2. TP and HV were similar for age (TP, 52 ± 9 versus HV, 50 ± 10 years) and quantity of training expressed as amount of training workouts per week (TP, 3.3 ± 1.7 versus HV, 2.8 ± 1.1) and hours of training for each session. TP had more need for antihypertensive therapy (TP, 14/19 versus HV, 1/35 subjects), and inhibitors of the renin-angiotensin system were used by 7 of 19 TP and 1 of 35 HV subjects. TP were also receiving immunosuppressive therapy, 15 of them with calcineurin inhibitors, which was absent in the HV group. TP showed significantly lower renal function parameters at baseline that was detected by eGFR values (TP 69 ± 22 versus HV 87 ± 13 mL/min/1.73 $m^2$, $P = .01$) and altered values of uric acid,

**Table 3. Renal Function Blood Values at T1, T2, and T3**

| | Creatinine (mg/dL) | eGFR (mL/min/1.73 $m^2$) | Urea (mg/dL) | Uric Acid (mg/dL) |
|---|---|---|---|---|
| Transplanted patients (n = 19) | | | | |
| T1 | 1.08 ± 0.36 | 69 ± 22 | 47 ± 14 | 5.8 ± 1.3 |
| T2 | 1.35 ± 0.46 | 54 ± 19 | 66 ± 17 | 7.2 ± 2.1 |
| T3 | 1.20 ± 0.40 | 68 ± 27 | 62 ± 17 | 6.8 ± 2.1 |
| Healthy volunteers (n = 35) | | | | |
| T1 | 0.93 ± 0.14 | 87 ± 13 | 38 ± 8 | 4.7 ± 0.9 |
| T2 | 1.16 ± 0.22 | 69 ± 15 | 61 ± 11 | 6.9 ± 1.5 |
| T3 | 1.00 ± 0.14 | 84 ± 14 | 55 ± 8 | 6.0 ± 0.9 |

Data are expressed as media ± standard deviation.
Abbreviations: eGFR, estimated glomerular filtration rate; T1, the day before the race; T2, immediately after crossing the finish line; T3, 18 to 24 hours after competition.

**Table 4. Renal Function Urine Parameters at T1, T2, and T3**

| | Urine Specific Gravity (densimetry) | Microalbuminuria (mg/L) | Proteinuria (mg/L) |
|---|---|---|---|
| Transplanted patients (n = 19) | | | |
| T1 | 1019 ± 6 | 8 ± 15 | 74 ± 44 |
| T2 | 1021 ± 6 | 39 ± 48 | 133 ± 83 |
| T3 | 1028 ± 4 | 13 ± 24 | 103 ± 49 |
| Healthy volunteers (n = 35) | | | |
| T1 | 1015 ± 4 | 56 ± 74 | 166 ± 99 |
| T2 | 1017 ± 5 | 259 ± 324 | 420 ± 384 |
| T3 | 1018 ± 6 | 41 ± 59 | 141 ± 130 |

Data are expressed as means ± standard deviation.
Abbreviations: T1, the day before the race; T2, immediately after crossing the finish line; T3, 18 to 24 hours after competition.

urea, pathological proteinuria, and albuminuria, isosthenuria, as shown in Table 2.

### Trends in Renal Parameters

The changes at T2 were similar in the 2 groups, with an increase of creatinine, uric acid, urea, urinary protein excretion, and urine specific gravity and a significant decrease of eGFR. At T3, the values of creatinine, eGFR, microalbuminuria, and proteinuria returned to baseline values in both groups, whereas urea and uric acid values remained higher than the average. Percentage changes from baseline and at T2 and T3 on creatinine, eGFR, uric acid, urea, microalbuminuria, and proteinuria were comparable between groups. At T3, urine specific gravity values had a different trend: in TP it remained stable, whereas in the HV it further increased (Tables 3 and 4).

## DISCUSSION

Physical activity is an important tool for cardiovascular disease prevention in the general population [8]; similar data are also emerging in transplant recipients [9]. In these patients, sport activity can facilitate a full social reintegration and improve the perception of well-being [10,11].

The results of this study suggest that organ-transplanted patients with no cardiovascular contraindications, well-trained and capable to keep a hydration status, were able to complete the route without adverse events.

In our population, TP had a baseline renal impairment (single kidney transplant or calcineurin inhibitor therapy) that was not aggravated by the intensive exercise in the short period. During exercise, trends in blood and urine parameters in TP were fully comparable to HV: they temporarily worsened at T2, due to the known modifications occurring in intense exercise, and returned to baseline values at T3, in accord with physiological findings in the healthy sporting population [4,12].

In our previous experience (unpublished data), we collected data of microalbuminuria and proteinuria in patients with solid-organ transplant who practiced sports activities for at least 3 years of recording stability over time from baseline.

A special note is deserved by the trends in urine specific gravity; this is the only parameter in which TP differ from HV: in the TP group, kidney function seems to fail in concentrating urine during the race (at T2), and the difference in urine concentration is, once again, more evident 18 to 24 hours after the race (at T3). This is feasibly due to tubular impairment and may be affected by immunosuppressive drugs: fluid intake was comparable between the groups during the race, but fluid ingestion between T2 and T3 was not recorded.

## CONCLUSIONS

Well-trained TP with no cardiovascular contraindications can safely participate in a long-distance road cycling race without acute signs of kidney damage.

Our data do not reveal contraindications to sports regarding the preservation of renal function, but this is one of the preliminary studies. Further long-term investigations on larger populations are needed to confirm the safety of the sport activity.

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