Inflammatory and Adipose Response in Solid Organ Transplant Recipients After a Marathon Cycling Race

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ABSTRACT

Background. Organ transplant recipients frequently have chronic inflammation, with a weighty impact on cardiovascular risk. These patients can benefit from exercise, although the role of intense training is unclear. We evaluated the effect of a 130-km cycling race on inflammatory cytokines and adiponectin levels in transplant recipients.

Methods. Circulating interleukin (IL)-6, tumor necrosis factor (TNF)-α, interferon (IFN)-γ, and adiponectin were assayed in 35 healthy subjects vs 19 transplant recipients (10 kidney, 8 liver, 1 heart), matched for sex, age, body mass index, and preparation workout. The determinations were performed before the race, at the end, and after 18 to 24 hours. Baseline values of 32 sedentary transplant recipients also were evaluated to explore the possible chronic impact of lifestyle.

Results. All cyclists had 6- to 8-fold increased IL-6 levels after the race that decreased, without returning to baseline, the day after. Conversely, serum TNF-α and IFN-γ showed a progressive increase starting during physical performance and enduring for the next 18 to 24 hours in healthy subjects, whereas they were unchanged over time in cyclists with transplants. In transplant recipients who did not perform exercise, all of the analytes were significantly higher in comparison to basal levels of physically active subjects.

Conclusions. Our data suggest that clinically stable and properly trained transplant recipients can safely perform and progressively benefit from exercise, even at a competitive level. The changes in inflammation parameters were temporary and parallel with those of the healthy subjects. The comparison with sedentary transplant recipients revealed an overall amelioration of inflammatory indexes as a possible effect of regular physical activity on systemic inflammation.

PHYSICAL activity has been proven to have many important positive cardiovascular effects in the general population [1]. In the last few years, accumulating evidence has suggested that patients with solid organ transplants can also benefit from regular exercise, especially for the prevention of cardiovascular disease, osteoporosis, and joint and bone pathology, and for the recovery of physical ability and psychological wellbeing [2–6]. In 2008, the Italian National Transplant Centre launched the project "Transplant… and now Sport" aimed to spread the awareness of the importance of physical activity in organ transplant recipients. The project developed a model of cooperation between transplantation doctors, sports physicians, physical education specialists, and patient associations, such as

This paper is dedicated to the memory of Jonah Lomu, a sport champion, a rugby legend and a kidney transplant recipient.

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ANED (Associazione Nazionale Emodializzati, Dialisi e Trapianto). The research plan is focused on the concept of exercise as a nonpharmacological therapy to be administered using a patient-tailored approach, able to counteract some common posttransplantation complications frequently associated with chronic subclinical inflammation. Previous results from the project have indicated that regular physical activity is able to bring significant benefits to the clinical, physiological, and psychological status of organ transplant recipients [4–7]. However, little is known about the exercise load and intensity level that may be safely applicable to the transplant population. Recently we evaluated the effects of a 130-km road cycling race ("Novecolli Life" project) on the changes in renal function parameters in solid organ transplant recipients. Our data showed a transient increase of serum creatinine and proteinuria immediately after the end of the race and a successive rapid decline to the baseline levels measured at rest in the following 18 to 24 hours [5].

Given the role of inflammation in atherosclerosis and cardiovascular risk after transplantation, we investigated the impact of the same long-distance road cycling competition on the inflammatory cytokines interleukin (IL)-6, tumor necrosis factor (TNF)-α, interferon (IFN)-γ, and adiponectin in kidney, liver, and heart transplant recipients compared with healthy control subjects.

MATERIALS AND METHODS

Subjects

This study recruited 35 healthy subjects and 19 organ transplant recipients, all male, to participate in the short route of the Nove Colli road cycling race held in the Romagna region of Italy. The path covered by the participants was 130 km, including 4 hills with 1871 meters of altitude drop. The maximum riding time allowed was 7.5 hours, respecting an overall average not exceeding 25 km/h.

The healthy control subjects were leisure and amateur cyclists invited by the organization of the competition through a newsletter. They were between 18 and 72 years old, normal weight, and normotensive, except one of them who was under angiotensin-converting enzyme inhibitor treatment (Table 1). Each subject who agreed to take part in the study provided a medical certificate of fitness for participation in competitive cycling events.

The group of organ transplant patients, enrolled with the support of ANED Sport, consisted of 10 kidney recipients, 8 liver recipients, and 1 heart recipient. All of them voluntarily decided to participate in the race, were between 18 and 72.9 years old, were of normal weight, were at least 1 year posttransplantation with stable renal function (Table 1), and had previous physical preparation through usual practice of road cycling. They had gone through a preliminary evaluation for their eligibility to undertake structured programs of physical activity, according to an algorithm based on ergometric and cardiac function tests for assessing the likelihood of cardiovascular events (detection of eventual silent heart disease), and personalization of exercise loads [7]. The immunosuppressive regimen was calcineurin inhibitors in 15 patients, in 8 of them associated with steroid therapy, inhibitors of DNA synthesis in 8 patients, and mTOR inhibitors in 4 patients. They had good blood pressure control achieved by treatment with angiotensin-converting enzyme inhibitors, beta-blocker therapy, or calcium channel blockers (Table 1). Only 1 patient experienced posttransplantation malignancy. None of the participants in both groups had diabetes mellitus or major cardiovascular events in the 2-year period prior to enrolment.

Table 1. Demographic Characteristics and Biochemical, Therapeutic, and Transplant-Related Parameters

	Healthy Cyclists at Baseline (n = 35)	Transplanted Cyclists at Baseline (n = 19)	Sedentary Transplant Recipients (n = 32)
Age, y	50.0 ± 10.0	52.1 ± 9.0	54.5 ± 7.4
Body mass index, kg/m^2	24.1 ± 2.3	23.7 ± 1.7	24.8 ± 3.2
Systolic blood pressure, mm Hg	120 ± 14	130 ± 12	135 ± 11
Diastolic blood pressure, mm Hg	80 ± 7	86 ± 8	83 ± 6
Transplanted organ			
Single kidney		10	32
Liver		8	0
Heart		1	0
Type of organ donation (kidney)			
Cadaveric/living		9/1	27/5
Time from transplant, y		9.3 ± 5.1	7.4 ± 6.6
Serum creatinine, mg/dL	0.96 ± 0.13	1.43 ± 0.90	1.66 ± 0.70
Estimated glomerular filtration rate, mL/min/1.73 m^2	90.7 ± 27.4	72.4 ± 26.0	61.4 ± 23.7
Immunosuppressive therapy			
Tacrolimus/cyclosporine		15	24
Steroids		8	14
Mycophenolic acid		8	12
Everolimus		4	7
Antihypertensive therapy			
Angiotensin-converting enzyme inhibitors	1	7	12
β-blockers	0	7	11
Calcium channel blockers	0	1	2
Acute rejection episodes, number (%)		2 (10.5%)	4 (12.5%)
Previous malignancy, number (%)		1 (5.3%)	2 (6.2%)

Continuous variables are expressed as media ± standard deviation, categorical variables as absolute numbers or percentages.

The study was carried out in accordance with the Declaration of Helsinki, the ICH (International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) Guidelines for Good Clinical Practice, and national rules and regulations regarding clinical research. A written informed consent was obtained before inclusion, in accordance with the procedures approved by the Ethical Committees of the Italian Institute of Health.

Study Design

All subjects who took part in the study underwent a preliminary overall evaluation consisting of (1) physical examination including measurement of blood pressure and resting heart rate, (2) data collection for anamnesis, clinical history, and information on drug therapies, (3) administration of a questionnaire to assess subjective perceptions of the Health-Related Quality of Life with the SF-36, as previously described in detail by our group [6], along with the preparation training schedule followed during the year. The

experimental protocol included specimen collection at 3 time points: the day before the race (T1), immediately after the race (T2), and 18 to 24 hours after the race (T3). Additionally, the total volume of fluid ingested and the possible occurrence of adverse events also were recorded.

To investigate the chronic effects of exercise on inflammatory status, we successively recruited a third group of 32 kidney transplant recipients with a sedentary lifestyle matched for sex (all male), age, body mass index (BMI), time from transplantation, blood pressure, distribution of immunosuppressive therapy, and frequency of major posttransplantation complications (Table 1), and then compared their circulating levels of cytokines and adiponectin with those measured at the baseline (T1) of the physically active subjects (healthy control subjects and transplant patients) who had participated in the race.

Luminex Analysis of Inflammatory Cytokines and Adiponectin

Blood samples were collected in BD Vacutainer clot activator tubes, centrifuged at 1500 $\times g$ for 15 minutes within 4 hours of venipuncture, and sera were kept at frozen at -70°C until analysis. A multiplex assay was carried out for the simultaneous quantification of serum cytokines (IL-6, TNF-α, and IFN-γ) and adiponectin using commercially available kits (MILLIPLEX MAP Human Cytokine/Chemokine Magnetic Bead Panel, catalog #HCYTOMAG-60K, kit lot #2423458; MILLIPLEX MAP Human Adipokine Magnetic Bead Panel 1, catalog #HADK1MAG-61K, kit lot #2423457, Millipore Corp., Billerica, MA), according to the manufacturer's instructions. Determination of cytokines and adiponectin were done in 2 separate experimental sessions because of the orders of magnitude differences in the expected concentration ranges (pg/mL for cytokines and μg/mL for adiponectin). The assay sensitivities (minimum detectable concentrations) were 0.9 pg/mL for IL-6, 0.7 pg/mL for TNF-α, 0.8 pg/mL for IFN-γ, and 11 pg/mL for adiponectin. The coefficients of variation (CV%) were as follows: 2.0% intra-assay and 18.3% interassay for IL-6, 2.6% intra-assay and 13.0% interassay for TNF-α, 1.6% intra-assay and 12.0% interassay for IFN-γ, 4% intra-assay and 10% interassay for adiponectin. Concentrations were calculated using a 7-point standard curve obtained by serial dilutions, and finally the plates were read on the Luminex MAGPIX system (Luminex, Austin, TX), and data were analyzed through the Analyst 5.1 PLUS software (Millipore).

Statistical Analysis

Continuous variables are given as mean ± standard deviation if normally distributed or median with interquartile range if non-normally distributed. For the evaluation of the acute effects of physical exercise, the changes in circulating cytokine levels over time (baseline T1 vs T2 and T3) were computed in each group using a Friedman test. Differences between healthy subjects and transplanted cyclists at each time were then analyzed by means of nonparametric Mann-Whitney *U* test. For examining the variations related to the chronic effects of sport on inflammatory and adipose response, the values at baseline (T1) of circulating IL-6, TNF-α, IFN-γ, and adiponectin in healthy and transplanted cyclists were compared with those of the group of sedentary transplant recipients using Kruskal-Wallis test, followed by a Tukey test to check for pairwise differences between the groups. Multiple linear regression analysis was used to evaluate the correlations between age, BMI and blood pressure and the serum markers of inflammatory and adipose response, after adjusting for laboratory test variables. Analysis was conducted using the SPSS (IBM SPSS Statistics, version 20.0; SPSS Inc., Chicago, IL). A 2-sided value of $P < .05$ was regarded as statistically significant.

RESULTS

All participants completed the route within comparable times (average about 6 hours) without reporting adverse events during or after the race. Likewise, there were no significant differences in the total fluid volume ingested throughout the competition (2533 ± 1067 mL vs 1957 ± 652 mL; P = NS) and in the amount of previous preparation training, expressed as number of workout sessions per week and exercise duration for each session.

Acute Effects of Exercise on Inflammatory Cytokine Levels

Table 2 reports the results of the Friedman test for the comparison within each group of serum levels of inflammatory cytokines IL-6, TNF-α, and IFN-γ at the different times: T1 vs T2 vs T3. Table 3 illustrates the differences assessed using a Mann-Whitney *U* test in circulating

Table 2. Levels of Circulating Inflammatory Cytokines TNF-α, IL-6, and IFN-γ in Healthy Subjects and Organ-Transplanted Cyclists at Three Different Time Points

	Median [IQR1–IQR3]	*P* Value
Healthy cyclists (n = 35)		
IL-6, pg/mL		
T1	2.17 [1.62–2.91]	<.001*
T2	16.70 [9.54–25.05]	
T3	3.26 [2.64–6.35]	
TNF-α, pg/mL		
T1	10.32 [9.63–14.12]	<.001†
T2	12.52 [11.09–14]	
T3	12.60 [11.09–15.49]	
IFN-γ, pg/mL		
T1	191.01 [182.05–208.65]	<.001†
T2	220.1 [201.90–231.18]	
T3	211.08 [194.90–241.95]	
Transplanted cyclists (n = 19)		
IL-6, pg/mL		
T1	3.10 [2.54–5.11]	<.001*
T2	16.97 [8.09–25.42]	
T3	6.29 [3.52–12.28]	
TNF-α, pg/mL		
T1	20.12 [11.72–26.43]	NS
T2	14.00 [12.93–26.86]	
T3	17.61 [11.09–32.36]	
IFN-γ, pg/mL		
T1	204.26 [190.96–212.99]	NS
T2	220.03 [201.9–228.99]	
T3	248.11 [201.90–294.33]	

Data are given as median and IQR. Changes in cytokine levels over time were assessed using a Friedman test, with the limit for statistical significance set at $P < .05$.

Abbreviations: TNF-α, tumor necrosis factor alpha; IL-6, interleukin 6; IFN-γ, interferon gamma; IQR, interquartile range; T1, day before the race; T2, immediately after the race; T3, 18 to 24 hours after the race.

*T1<T3<T2.

†T1<T2,T3.

Table 3. Levels of Circulating Inflammatory Cytokines TNF-α, IL-6, and IFN-γ in Healthy Subjects vs Organ-Transplanted Cyclists at Three Different Time Points

	Healthy Cyclists (n = 35)	Transplanted Cyclists (n = 19)	
	Median [IQR1-IQR3]	Median [IQR1-IQR3]	*P* Value
IL-6, pg/mL			
T1	2.17 [1.62–2.91]	3.10 [2.54–5.11]	.002
T2	16.70 [9.54–25.05]	16.97 [8.09–25.42]	NS
T3	3.26 [2.64–6.35]	6.29 [3.52–12.28]	.049
TNF-α, pg/mL			
T1	10.32 [9.63–14.12]	20.12 [11.72–26.43]	<.001
T2	12.52 [11.09–14]	14.00 [12.93–26.86]	.016
T3	12.60 [11.09–15.49]	17.61 [11.09–32.36]	NS
IFN-γ, pg/mL			
T1	191.01 [182.05–208.65]	204.26 [190.96–212.99]	NS
T2	220.1 [201.90–231.18]	220.03 [201.9–228.99]	NS
T3	211.08 [194.90–241.95]	248.11 [201.90–294.33]	NS

Data are given as median and IQR, and the differences in cytokine levels between the 2 groups at each time point were assessed using a Mann-Whitney *U* test, with the limit for statistical significance set at $P < .05$.

Abbreviations: TNF-α, tumor necrosis factor alpha; IL-6, interleukin 6; IFN-γ, interferon gamma; IQR, interquartile range; T1, day before the race; T2, immediately after the race; T3, 18 to 24 hours after the race.

cytokine values between the 2 groups (healthy vs transplanted cyclists) for each time point: T1, T2, and T3.

IL-6 serum levels were found to be 6- to 8-fold increased in both healthy subjects and transplanted cyclists immediately after the race (to a higher extent in the healthy subjects), and then declined, without returning to the baseline levels, within the following 18 to 24 hours (Table 2). The comparison between groups at the different times, shown in Table 3, revealed significantly higher IL-6 values in transplanted cyclists at T1 ($P = .002$) and T3 ($P = .049$). Circulating TNF-α levels displayed a progressive increase over time (T1 < T2 < T3, $P < .001$) in the healthy subjects, whereas they remained quite stable in transplant recipients (P = NS) (Table 2). However, TNF-α levels were higher in the transplanted cyclists compared to the healthy ones at each experimental time, but not significantly at T3 (T1: $P = <.001$; T2: $P = .016$; T3: P = NS) (Table 3). Similarly, serum IFN-γ showed increasing values in the healthy subjects starting during the physical performance and enduring 18 to 24 hours after the end of marathon cycling (T1 < T2 < T3, $P < .001$). Conversely, the transplanted patients had no significant variations in IFN-γ levels related to the physical performance. When comparing the 2 groups of cyclists at the different times (Table 3), the concentration of circulating IFN-γ did not differ significantly in the healthy subjects vs transplant recipients at T1, T2, and T3 (P = NS).

Chronic Effects of Exercise on Inflammatory Cytokine and Adiponectin Level

The chronic effects of exercise on inflammatory and adipose response were investigated comparing the values at baseline (T1) of circulating IL-6, TNF-α, IFN-γ, and adiponectin in the 2 groups of physically active subjects who participated in the race with a matched group of 32 sedentary transplanted patients. Table 4 reports the results of the Kruskal-Wallis test used to analyze the differences between the 3 groups. Significantly higher levels of circulating IL-6, TNF-α, and IFN-γ and serum adiponectin were found in sedentary transplant recipients in comparison to the values measured at baseline in healthy and transplanted cyclists (for IL-6, TNF-α, and IFN-γ, $P < .001$; for adiponectin, $P = .030$).

Correlation of Age, BMI and Blood Pressure with Cytokine and Adiponectin Serum Level

For each group, multiple linear regression analyses were performed to assess the possible correlations of age, BMI, and blood pressure with each serum marker of inflammatory and adipose response as dependent variables. As expected, in the healthy cyclists higher BMI values correlated negatively with adiponectin levels and positively with IL-6 ($r = -0.232$, $P = .045$; $r = 0.240$, $P = .039$, respectively), even after adjusting all clinical parameters tested (Fig 1). Likewise, it was observed that in the physically active transplant recipients who participated in the race, BMI was inversely correlated with serum adiponectin values ($r = -0.571$, $P = .021$) (Fig 1C).

DISCUSSION

This study was undertaken in the framework of a broader project, named "Transplant… and now Sport", aimed to encourage physical exercise after transplantation. The

Table 4. Levels of Circulating Inflammatory Cytokines TNF-α, IL-6, IFN-γ, and Adiponectin Levels in Healthy Cyclists at Baseline vs Transplanted Cyclists at Baseline vs Sedentary Transplant Recipients

	A. Healthy Cyclists at Baseline (n = 35)	B. Transplanted Cyclists at Baseline (n = 19)	C. Sedentary Transplant Recipients (n = 32)	
	Median [IQR1–IQR3]	Median [IQR1–IQR3]	Median [IQR1–IQR3]	*P* Value
IL-6, pg/mL	2.17 [1.62–2.91]	3.10 [2.54–5.11]	8.75 [6.98–11.86]	<.001*
TNF-α, pg/mL	10.32 [9.63–14.12]	20.12 [11.72–26.43]	37.18 [20.11–85.53]	<.001*
IFN-γ, pg/mL	191.01 [182.05–208.65]	204.26 [190.96–212.99]	287.44 [266.47–294.33]	<.001†
Adiponectin, μg/mL	3.97 [3.03–7.35]	3.92 [2.34–5.7]	13.09 [6.37–25.49]	.030†

Data are given as median and IQR. The differences in cytokine levels among the 3 groups at each time were assessed using a Kruskal-Wallis test, with the limit for statistical significance set at $P < .05$.

Abbreviations: TNF-α, tumor necrosis factor alpha; IL-6, interleukin 6; IFN-γ, interferon gamma; IQR, interquartile range.

*A<B,C.

†A,B<C.

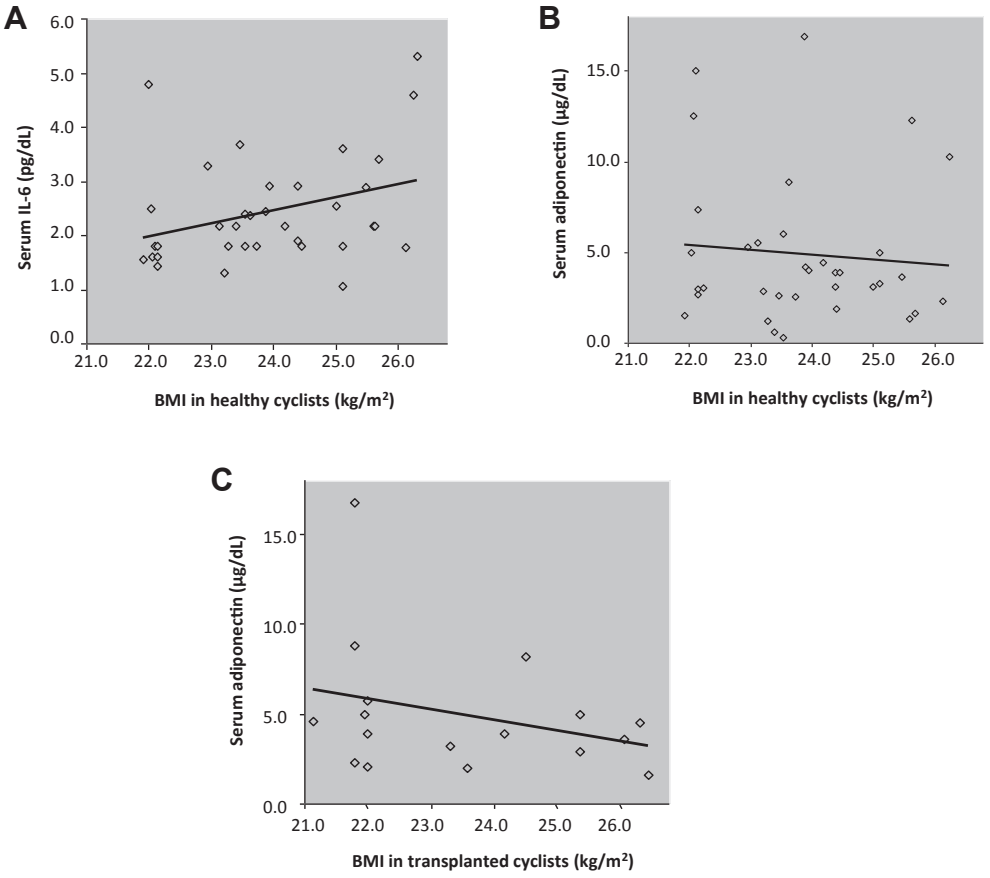

Fig 1. Scatter plots and regression line showing the significant correlations between (**A**) body mass index (BMI) and interleukin (IL)-6 levels in healthy cyclists; (**B**) BMI and adiponectin levels in healthy cyclists; (**C**) BMI and adiponectin levels in transplanted cyclists. In (**A**), $r = -0.232$, $P = .045$; in (**B**), $r = 0.240$, $P = .039$; in (**C**), $r = -0.571$, $P = .021$.

results obtained over the years have proven that medium- to high-intensity exercise can be safely performed by transplanted patients if properly trained and clinically stable. We evaluated the impact of a 130-km road cycling race on inflammatory cytokines and adiponectin in kidney, liver, and heart transplant recipients. The current concept indicates inflammation as the main driving force underlying the pathogenesis of cardiovascular disease, which over recent decades has become the most frequent among the known causes of death after organ transplantation [8,9]. The elevated cardiovascular burden of transplant recipients is feasibly related to the progressive accumulation of atherogenic risk factors during the clinical history of these patients. In addition, after organ transplant a further contribution to the overall cardiovascular risk is given by the chronic use of some immunosuppressive drugs having a negative impact on some common cardiovascular risk factors, such as diabetes, hypertension, hyperlipidemia [10].

Despite the acknowledged effects of regular physical activity in reducing chronic low-grade inflammation [11], in the short-term, prolonged exercise (>2.5 hours) is known to elicit the release of inflammatory mediators into the bloodstream, particularly IL-6 and C-reactive protein [12,13]. Our data on the acute effects of the physical performance on IL-6 levels revealed a comparable course between healthy and transplanted cyclists, although the latter displayed higher serum values at each time point, perhaps because of a different baseline clinical condition. The parallel trend observed in both groups, reaching a zenith immediately after the race followed by a rapid decline in the successive 18 to 24 hours, is consistent with a number of studies reporting that IL-6 is the first cytokine to appear in the circulation during and immediately after exercise: this increase has been minimally attributed to proliferation/mobilization of neutrophils and monocytes [14], and increased production by adipose tissue [15], brain [16], and peritendon tissue [17]. Actually it was firstly reported several years ago that the contracting skeletal muscle is the major contributor of exercise-induced release of specific cytokines, called myokines [18]. This hypothesis is also corroborated by an experimental model on horses that revealed an activation of proflogistic cytokine genes, including IL-6, TNF-α, and IFN-γ in muscle biopsies collected immediately after exercise and at 0.5, 1, 2, 6, and

24 hours after incremental loads of workout [19]. It has been proposed that the initial trigger for the IL-6 upregulation is a drop in muscle glycogen content, together with an increase in intracellular calcium levels and formation of reactive oxygen species [13]. The release of IL-6 into the circulation during exercise induces either an increase in serum levels of anti-inflammatory cytokines IL-10 and IL-1 receptor antagonist (IL-1RA), or the release of cortisol from the adrenal glands, which may signify an adaptation to stress upon resolution of inflammation [20]. The impact of acute exercise on TNF-α and IFN-γ is less clear in the general population, and to the best of our knowledge, there are no available studies to date in transplant recipients. In our transplanted cyclists, both cytokines remained quite unchanged during and after the physical performance, whereas the healthy subjects showed a trend toward an increase over time starting with the race and enduring for the next 18 to 24 hours. A study by Ostroswki et al. on cytokine response to strenuous physical activity during the Copenhagen marathon reported an increase of circulating pro-inflammatory cytokines IL-6, TNF-α, and IL-1β, counteracted by a compensatory release of cytokine inhibitors (IL-1ra, sTNF-r1, and sTNF-r2) and the anti-inflammatory cytokine IL-10, which may be viewed as a mechanism of defense against exercise-induced myocyte injury [21]. The analogous variations over time of IL-6 levels in healthy and transplanted cyclists might indicate that chronic immunosuppression does not impair this protective mechanism of IL-6 gene activation with the subsequent anti-inflammatory cascade in physically active transplant recipients. On the other hand, our findings on the different behavior of TNF-α and IFN-γ between the 2 groups of cyclists are more difficult to interpret, and the relatively small number of patients prevents us from drawing any firm conclusions about a possible attenuated cytokine response in transplant recipients. Moreover, in our protocol the anti-inflammatory cytokines were not assayed, and this might represent a limitation in the current study design that needs to be addressed in the future.

A further interesting finding emerged from the evaluation of chronic effects of regular physical exercise when we compared the baseline values of inflammatory cytokines and adiponectin in the healthy and transplanted subjects who participated in the race with those of a matched group of sedentary transplanted patients. All serum parameters analyzed were found to be significantly increased in transplant recipients who did not perform any regular exercise in comparison to both groups of physically active subjects. For cytokine profiles, our observation agrees with current knowledge based on several previous studies, proving an association between physical inactivity and low-grade systemic inflammation in different populations: healthy subjects as well as patients with one or more cardiovascular risk factors [22,23]. Different mechanisms have been proposed to explicate the antiflogistic effects of regular exercise, and feasibly one key contributor in promoting a beneficial environment is the reduction in visceral fat mass, which is generally accompanied by an increase in anti-inflammatory adipokines [24]. Our findings are only partially in line with this model because in spite of the significant reduction of all inflammatory cytokines in physically active subjects, they unexpectedly revealed lower adiponectin levels in comparison to sedentary transplant recipients. Adiponectin is an adipokine generally known to have protective features in cardiovascular homeostasis, and has been inversely associated with visceral adipose tissue and the risk of insulin resistance, diabetes, and metabolic syndrome [25]. Studies in animals and humans have proven that 3 weeks or more of regular exercise is needed to induce upregulation of adiponectin and adiponectin receptor 1 genes in adipose tissue, whereas acute physical efforts do not seem to affect their mRNA expression in the short term [26,27]. For this reason, we did not observe significant changes in circulating adiponectin levels during or after the race, thus the data concerning the acute effects of exercise on adiponectin have not been described here. Indeed, in both groups of cyclists, the healthy and the transplanted, higher BMI values correlated negatively with adiponectin levels, but we did not find this association in sedentary transplant recipients, who also showed surprisingly high adiponectin serum levels. This puzzling result might be explained in the light of more recent scientific evidence that seems to controvert the role of adiponectin as a protective cardiovascular molecule [25]. Although this paradigm seems to be valid for the general adult and middle-aged population, in the last decade accumulating epidemiological data have introduced the "adiponectin paradox", supporting the contrasting hypothesis that high circulating adiponectin levels are independent predictors of cardiovascular events in specific categories of patients at increased cardiovascular risk [28].

In conclusion, this study suggests that transplanted patients in good clinical condition, with a well-tolerated immunosuppressive therapy and proper training, can benefit from physical activity, even at a competitive level. Marathon cycling induced some changes in inflammation parameters that were transient and superimposable between physically active healthy and transplanted cyclists. The comparison with sedentary transplant recipients revealed a significant lowering in the circulating concentrations of certain proflogistic indexes as a possible effect of sporting activities on systemic inflammation.

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