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EXERCISE AND SPORT FOR HEALTH IN SOLID ORGAN TRANSPLANT RECIPIENTS

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Contents

ABSTRACT

Is well known that physical activity reduces rate of cardiovascular and all-cause mortality in the general population. A growing number of studies showed physical activity beneficial effects also in the population of transplanted recipients. However, most of those investigations present limits such as a short-medium follow up term. Few data are available on exercise effectiveness on kidney and liver transplant recipients and the correlation between practising exercise and the lipid profile and renal function. Additionally, the knowledge on the amount of safe training for sport competitions for this population is limited. This thesis aims to increase the knowledge on the type of exercise and training adapted for transplant recipients and its relative effects on aerobic capacity, strength and quality of life. Moreover, correlation between exercise and blood pressure parameters in solid organ transplant are considered for safeguard of the graft function.

This thesis consists of two lines of study: the first part, from Chapter 2 to Chapter 5, focuses on the effects of exercise in kidney and liver transplant recipients by health pathways. The second part focus on the theme of the sport in solid organ transplant recipients. In detail, **Chapter 2** aims to investigate the renal function and the physical fitness after 12 months of supervised aerobic and resistance training in kidney transplant recipients, compared with not supervised home-based physical activity. In **Chapter 3**, we analyzed the physical condition, metabolic profile and quality of life in liver transplant recipients after 12 months of supervised combined training with major focus on the relationship between physical activity and glycemia, an important marker to control the diabetes. The results of these studies can provide information on the beneficial effects of combined exercise and also identify the type of safe exercise to prescribe for the kidney and liver transplant population. These indications are intended to encourage the healthcare world to refer pre-and post-transplant patients to follow a healthy lifestyle including regular exercise for the prevention of cardiovascular diseases, representing the first cause of post-transplantation death. To obtain more adherence in the prescription of exercise in transplant patients the study described in **Chapter 4** is aimed to promote the network created in Emilia-Romagna region (Italy) in which transplant centers, sports medicine centers and certified gyms collaborate to encourage the practice of prescribed and controlled exercise in pre- and post-transplant patients. **Chapter 5** presents a longitudinal analysis of cardiovascular risk factors in active and sedentary

kidney transplant recipients. This study is the fruit of the collaboration between the College of Applied Health Sciences – University of Illinois at Chicago and the ANED onlus (patient association) in which blood parameters and blood pressure levels were recorded for 3 consecutive years comparing active with sedentary transplanted population. The sample size is small and therefore it is not representative of the whole population of transplanted patients but can set the basis for future studies. The aim of the study described in **Chapter 6** is related to the sports activity in transplanted recipients and focus on the effects of combined strength and endurance training on exercise performance in kidney transplant cyclists and runners. In the literature there are few studies on the effects of endurance sports in transplanted athletes and this study represents a starting point to break down the prejudice that "transplantation" and "sport" cannot coexist. Finally, **Chapter 7** shows other research activities conducted during the Doctorate. In particular, focused on sport in transplant recipients, a case study was conducted to evaluate the high level cycling performance 10 years after cardiac transplantation. Moreover, two studies related to the active recovery was conducted, thanks to the skills learned during the experience at Integrative Physiology Laboratory – College of Applied Health Sciences – University of Illinois at Chicago, evaluating the muscular thickness. The general discussion of the primary findings of all of the chapters is described in **Chapter 8** where methodological considerations and future directions for healthcare and secondary prevention in this population are also discussed.

Chapter 1

General introduction

Exercise and sport in solid organ transplant recipients

Introduction

Organ transplantation is clearly a medical and surgical invasive procedure, which makes permanent modifications to the patient's lifestyle; nevertheless, while in many cases there is no possibility of physical activity, for another sizable number of patients there are no limitations.

Transplantation surgery consists of replacing the sick organ, and therefore no longer functioning, with a healthy organ, of the same kind, which originates from another individual: the donor. The majority of organs are taken from a non-living donor (cerebral death caused by traumatic or cerebrovascular events). In some cases the donor can be living, for example in a kidney transplantation or part of the liver, since it is possible to live with a single kidney or even with part of the liver. Surgical techniques have developed quickly until today. Heart, liver and lung transplants are lifesaving operations, while kidney transplantation is a valid therapeutic alternative for sick people who would otherwise have to undergo life-long dialysis. Pathologies which result in a transplant are many and can have a chronic or acute course. For example, the most common reasons for a liver transplant are chronic evolutive diseases (hepatitis C, hepatitis B, alcoholic cirrhosis) or several types of tumours, pathologies which affect the short-medium term survival of the patient (average 1-2 years). Other pathologies such as fulminant hepatitis, arisen for other reasons in a previously healthy liver, have a very rapid course, and can cause death within a few days or weeks, if no transplant is performed. The causes that lead to a heart transplant are related to the development of cardiac insufficiency, mostly as a result of coronary pathologies, myocarditis, accumulation diseases (e.g. amyloidosis) or cardiac malformations which are the first cause of transplants in childhood. In nephropathies, a transplant is the therapeutic solution for the majority of the chronic forms of end-stage renal insufficiency in patients who often have a long history of haemodialysis or peritoneal dialysis, treatments which implicate important limitations in the social and working sphere. In short, the majority of patients arrive to the transplant after a progressive illness, which inevitably and considerably compromises their overall physical conditions, and their ability to perform physical, sporting and working activities.

Exercise in solid organ transplant recipients

Physical activity is defined as any bodily movement which involves an energy expenditure and can be categorized into activity that occurs during sleep and during leisure, including exercise [1].

In healthy population physical activity level is significantly and positively correlated with physical capacity and muscle strength and is an important determinant of physical functioning [2, 3].

Solid organ transplant is the therapeutic option for patients with end stage organ failure of the heart, lungs, pancreas, liver and kidney.

Post-transplant care usually takes long time before the patient returning at a normal life. In transplanted population physical activity declines by the first month post-transplantation, likely related to the surgical procedure and recovery. Subsequently, physical activity increases by approximately 30% within the first year after transplant compared to pre-transplant patients but this trend is not maintained over time, and a plateau is reached with no significant changes in the 5 years post-transplantation [4].

In general, after transplantation, 80% of transplanted population continues to be very sedentary and only 20% reports moderate to regular physical activity. Solid organ transplant recipients typically report a low physical activity, low energy levels and fatigue [5].

Weight gain, diabetes, hypertension and metabolic syndrome are predominant features after transplantation [6-8] and are associated with cardiac events and graft loss [9]. In general, after transplantation, a reduction in exercise capacity and muscle strength occurs, combined with an increasing risk of cardiovascular disease (CVD), metabolic complication and sarcopenia [10,11]. Low physical activity is strongly associated with increased risk for cardiovascular and all-cause mortality in transplant recipients [12]. A study conducted by Zelle et al. [13] showed the association between physical activity, muscle mass and mortality in renal transplant recipients confirmed the importance of encouraging patients to practice regular to moderate physical activity recognized as an important component in the management of patients, also pre-transplantation (Figure 1).

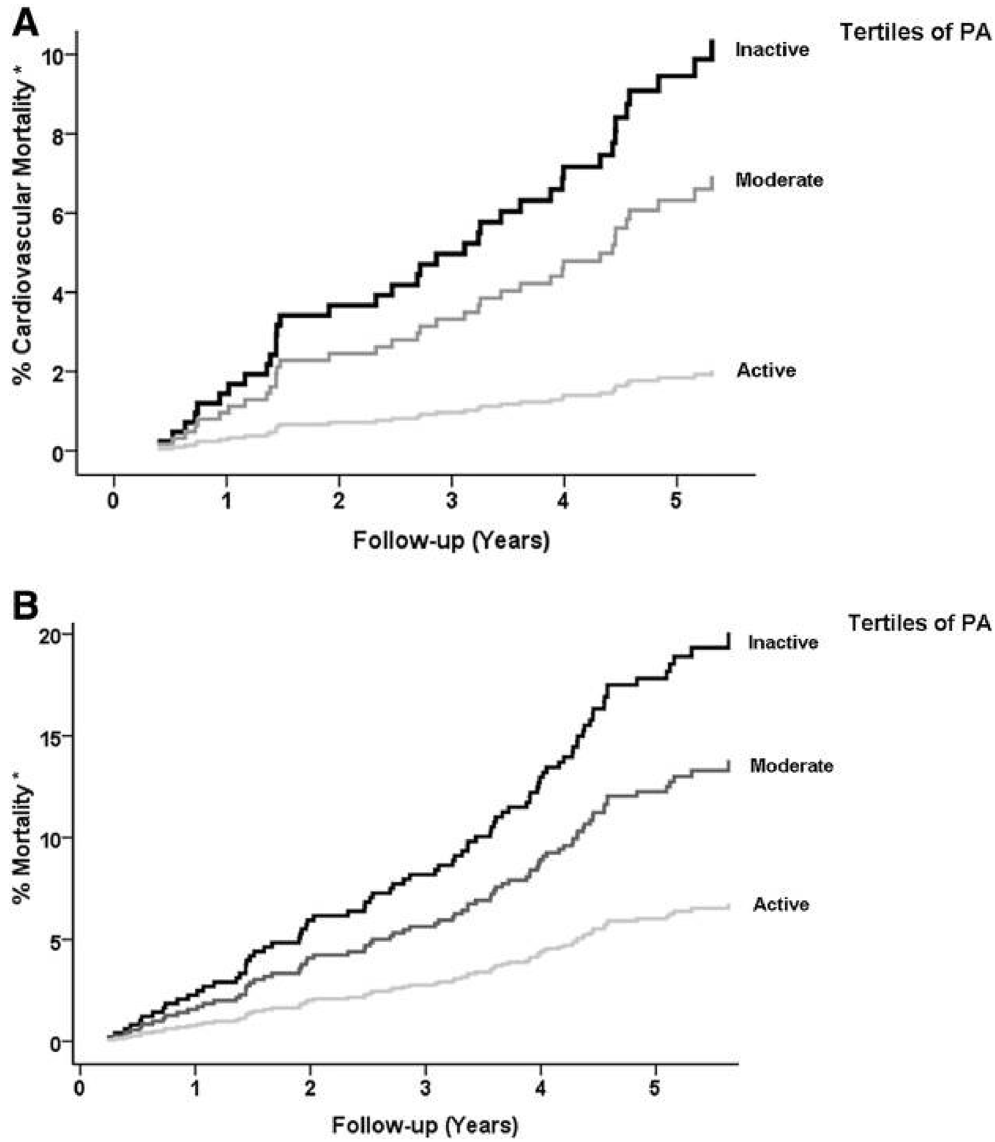

Figure 1: (A) Kaplan-Meier curves of cardiovascular mortality according to gender-stratified tertiles of PA. *Adjusted for age ($P < 0.001$). (B) Kaplan-Meier curves of mortality according to gender-stratified tertiles of PA. *Adjusted for age ($P < 0.001$). Figure reproduced with permission from the Clinical Journal of the American Society of Nephrology, all rights reserved [(13)].

Some studies showed that the level of physical activity may independently predict mortality [(14,15)]. Myers et al. showed that in normal subjects and in subjects with cardiovascular diseases the percentage of survival was higher in those individuals with higher level of physical activity expressed in METs (metabolic equivalents). Improvement of 1 MET in exercise capacity gives a 12% increase in survival (Figure 2) [(16)].

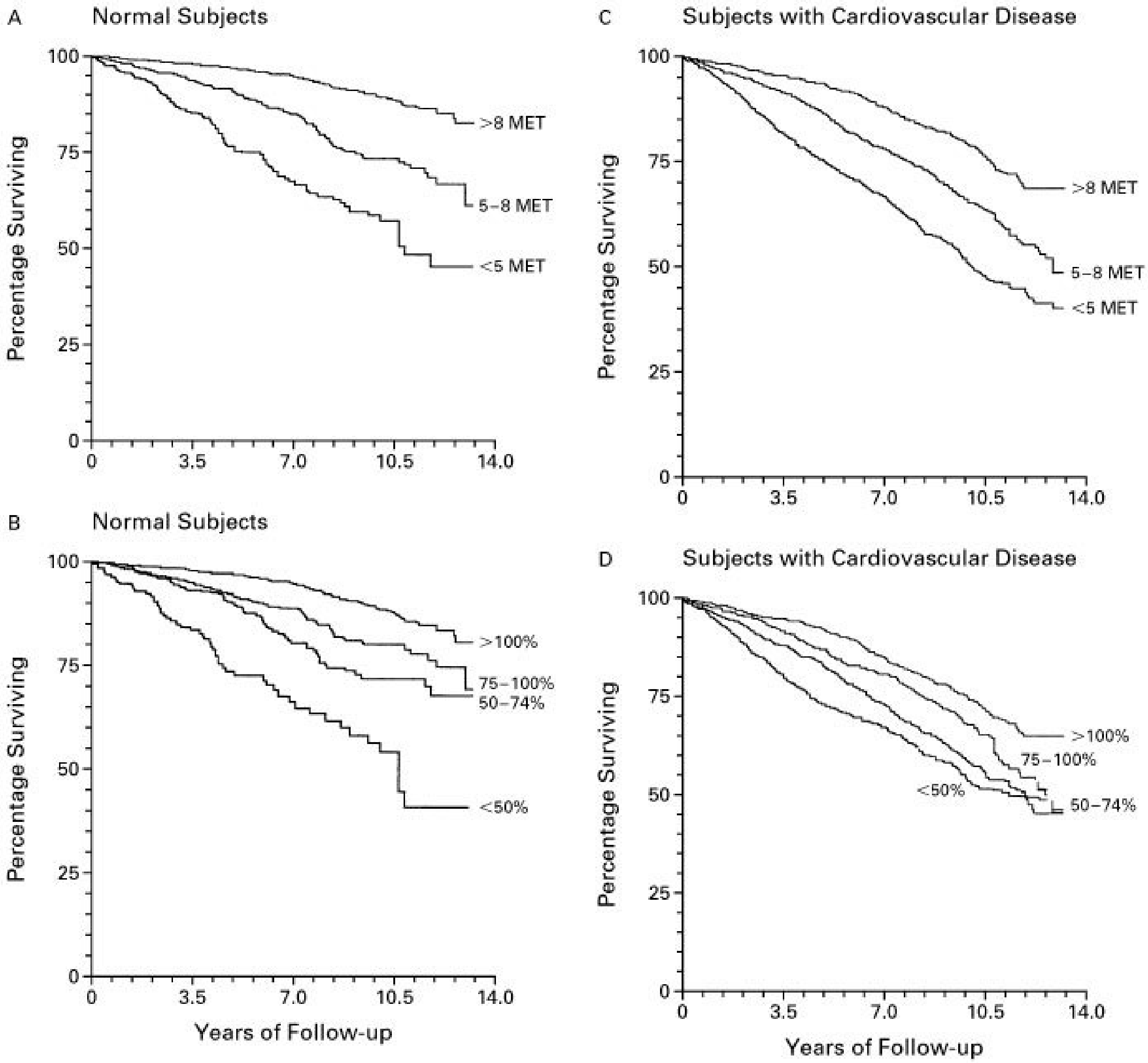

Figure 2: Survival Curves for Normal Subjects Stratified According to Peak Exercise Capacity expressed in MET (metabolic equivalents) (Panel A) and According to the Percentage of Age-Predicted Exercise Capacity Achieved (Panel B) and Survival Curves for Subjects with Cardiovascular Disease Stratified According to Peak Exercise Capacity expressed in MET (metabolic equivalents) (Panel C) and According to the Percentage of Age-Predicted Exercise Capacity Achieved (Panel D). Figure reproduced with permission from the New England Journal of Medicine, Massachusetts Medical Society (United States), all rights reserved [16].

Increased physical activity can improve general health, cardiovascular capacity through improved blood pressure, serum lipids, insulin sensitivity and inflammation [17-21].

In addition, immunosuppressive therapy and chronic steroid treatment contribute to the development of dysmetabolism, reduce muscle mass resulting in less physical activity after transplantation [22,23].

Immunosuppressive medication as calcineurin inhibitor-related neurotoxicity can cause debilitating visual, psychological, central and sensorimotor symptoms and compromise muscular function, increasing perceived fatigue associated also with functional impairment, obesity and lower quality of life (24-26).

CVD remains the leading cause of graft loss, morbidity and mortality among transplant recipients. United States Renal Data System (USRDS) showed that the CVD is the first cause of death with functioning graft in transplant recipients (Figure 3). These data are confirmed from other European databases (27, 28).

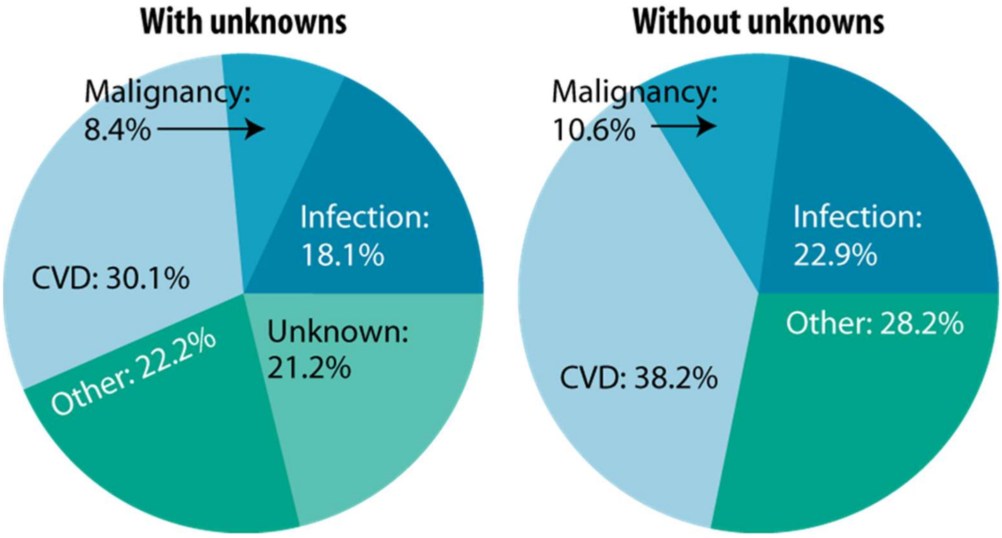

Figure 3: Causes of death among U.S. transplant recipients with a functioning graft (first-time, kidney-only transplant recipients, age 18 & older & transplanted 1997–2006, N=14,169). Figure reproduced with permission from United States Renal Data System (USRDS) 2008 ADR, all rights reserved (27).

Reducing mortality from cardiovascular diseases is indicated as an important goal in improving long-term survival in transplant recipients.

To date studies have shown that exercise has beneficial effects on metabolic profile, overweight, hypertension; all these factors modifiable through the practice of regular and structured exercise for cardiovascular prevention in these patients and interfere with the clinical and functional outcomes of the transplant patients (29-34). Indeed exercise is a promising intervention tool for long-term preservation of renal function (35), but studies so far are based on small samples and short periods of follow up. Physical inactivity in transplant recipients may be consequence of impaired allograft function. In this regard, Gordon et al. showed that physical activity was found to be significantly associated with kidney function with eGFR ~ 8mL/min/1.73 m^2 higher in physically active patients compared with sedentary people [36].

In the literature, studies showed that supervised combined aerobic and strength training was safe and effective in terms of aerobic workload, muscle strength and glucose metabolism among stable transplant recipients. Beyer et al. showed a 3-fold increase in aerobic workload [37] and Krasnoff et al. demonstrated a significant increase of exercise capacity in supervised liver transplant recipients [38]. Notably, supervised training was highly beneficial for muscle strength. Moreover, studies showed beneficial association between physical exercise and quality of life, especially in the general health, vitality and mental health domains. In addition, physical activity has a positive effect on the weight control.

Regarding exercise capacity, Van der Ham et al. [39] in 33 KTRs after 12 weeks of combination of endurance and strength training, observed a 10% increase of V'O2 peak (from 21.6±6.3 to 23.8±6.1 mL/kg/min). Riess et al. [40] reported an increase of V'O2 peak (from 20±9 to 23±10 mL/kg/min) after 12 weeks of supervised endurance training (three times/week) on cycle ergometer at 60-80% of V'O2 max involving 16 patients.

In a study on eight KTRs, Romano et al. [41] used a supervised interval training program for 10 weeks, 40-minute sessions for three times per week. They reported an increase of 13% of V'O2 peak. Another intervention was published by Kempeneers et al. [42] who trained 16 KTRs for six months in preparation for the National Transplant Games. Their mean V'O2 peak rose from 29.0±7.8 to 37.5±4.8 mL/kg/min, with an increase of 27%. In the other hand, Painter et al. [43] prescribed an individualised home-based exercise training programme in 54 KTRs, consisting on 30 minutes, 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'O2 peak increased from 24.0±7.5 to 27.8±11.0 mL/kg/min (+16%) and to 30.1±10.3 mL/kg/min (+25%) after 12 months.

Regarding muscle strength, studies showed an increase in maximal strength and counter movement jump values may be associated with both neural adaptations and muscle trophism improvement [44].

To confirm the results in the literature, this thesis investigates the renal function and the physical fitness after 12 months of supervised aerobic and resistance training in kidney transplant recipients, compared with not supervised home-based physical activity (Chapter 2). Furthermore, in Chapter 3, we analyzed the physical condition, metabolic profile and quality of life in liver transplant recipients after 12 months of supervised combined training with major focus on the relationship between physical activity and glycemia, an important marker to control the diabetes. The results of these studies can provide information on the beneficial effects of combined exercise and also identify the type of safe exercise to prescribe for the kidney and liver transplant population.

Despite this, evidence shows that many transplant recipients do not meet the recommended physical activity level requirements from the World Health Organization (WHO) to practice at least 150 minutes per week of moderate-intensity aerobic exercise or 75 minutes per week of vigorous intensity aerobic activity [(2)].

In addition to the main barriers perceived by transplant recipients as lack of time, the lack exercise guidelines and the fear of movement are associated with lower levels of physical activity (Figure 4) [(45)].

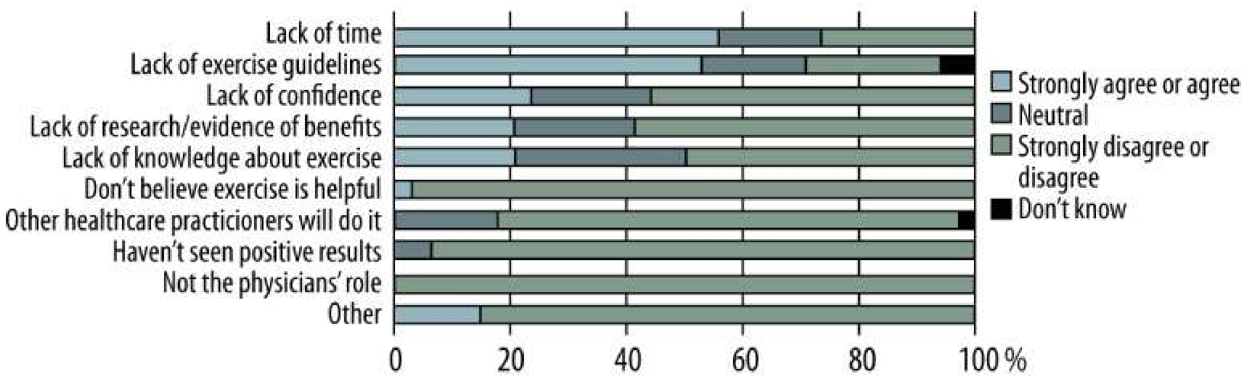

Figure 4: Distribution of barriers perceived by transplant recipient physicians. Figure reproduced with permission from the Annals of Transplantation, International Scientific Information, (USA) on behalf of the Polish Transplantation Society (Poland), all rights reserved [(45)].

Physicians have a responsibility to emphasize the importance of physical activity to their patients. In a study conducted by Pang et al. three-quarters of patients reported that physician either said nothing about exercise or did not specify the amount of type of exercise. Moreover, a lack of clinician guidance has also emerged in the physicians' standard educational curricula system. In the other hand "physician recommendation" alone are not sufficient to induce a long-lasting change in lifestyle and physical fitness in transplanted patients. Incorporation exercise knowledge into medical education curricula system and establish an easy referral system to exercise specialists and a network for exercise prescription might help the transplanted population to know better the benefits of regular physical activity and encourage the adoption of active lifestyles [45]. To obtain a lifestyle change with adherence to the prescription of exercise in transplant patients our study presented in Chapter 4 is aimed to promote the network created in Emilia-Romagna region (Italy) in which transplant centers, sports medicine centers and certified gyms collaborate to encourage the practice of prescribed and controlled exercise in pre- and post-transplant patients. This model could be disseminated and used also in other countries. Further studies with long follow-up and large populations are necessary to understand the effects of different types of training (e.g. combined training, high intensity interval training, etc.) and possible strategies that will improve adherence to training programs, control costs and lead to steady and durable lifestyle changes in transplant recipients.

Sports for transplant recipients

The debate on the possibility of performing a sporting activity, including competitions, by individuals who have undergone a solid organ transplant (heart, liver, lung, kidney, pancreas), is very topical and poses important and delicate questions. Indeed, the collective imagination sees the transplant patient as a delicate and fragile individual, to whom it is not recommended to practice physical activity and sports due to possible risks of cardiovascular complications, infections and traumas [(46,47)].

The most significant international event dedicated to transplant recipients who wish to participate in sports activities is the World Transplant Games (WTG), which are held every two years, and include a summer and a winter edition. The first summer edition of the WTG was held in Portsmouth (England) in 1978 [(48)], while the first winter edition of the Games was held in 1994 in Tignes, France. The World Transplant Games Federation (WTGF) was founded in 1987, and it currently counts 70 member Countries [(49)]. The importance of this sporting movement has ensured that in 2009 the WTGF was recognized by the International Olympic Committee (IOC), and the WTGF today adheres to the code of conduct of the World Antidoping Agency (WADA). A first study was conducted by Kempeneers et al. in 1990 [(50)], who trained 16 kidney transplant recipients for six months to participate in the WTG, achieving an increase in V'O2peak, measured during an incremental test on the treadmill, reaching an average of 7.5±4.8 mLO2/kg/min with a 27% increase. A study conducted in 1996 on 128 participants to the United States Transplant Games, showed that those who trained at least 3 times per week for at least 30 minutes per session, at an intensity defined as "a little difficult", showed a V'O2peak corresponding to 101% compared with that of controls on same age non-transplant recipients, while transplant recipients who did not train obtained only a 73% value [(51)]. The study also highlighted that active individuals presented higher scores in several scales of the SF-36 questionnaire (physical activity, limitation of physical role, body pain, general health, vitality and social activities). In the occasion of the 2011 WTG in Gothenburg (Sweden), a study was conducted on English-speaking participants to investigate the state of psychological wellness [(52)]. From that study, it emerged that only 19% of participants had not practiced a sport before the transplant, while all others practiced sports at various levels (elite 11%; sub-elite 14%, competitive 24% and recreational 32%). The level of education was high (63% university; 32% secondary school) and 63% had a job which could be defined white-collar, with a stable social-economic status which allowed them to afford the expenses to organize their transfer to the WTG (all the athletes participate at their own expense). 50% of participants were kidney transplant recipients followed by liver transplant recipients (22%) and heart transplant recipients (12%). The average time from the transplant was 9.9±7.3 years. The sports practiced the most were: athletics (27%), swimming (15%), golf (10%) and cycling (10%). These transplant recipients were interested and motivated to participate in the games for their personal satisfaction and as a result of the positive perception of their state of health, with evident effects on their self-esteem and mood, reduction in state and trait anxiety, ability to respond to stress and improve sleep. These results confirm that transplant recipients can return to their normal life and, despite several risk factors, can take part in sporting activities in considerable safety [(48)]. The study conducted in the participants to the US Transplant Games showed a lower body mass index (BMI) and percentage of adipose tissue than in sedentary transplant recipients [(51)]. In general, the BMI of transplant recipients who practice sport is often lower than 25 kg/m^2 (normal weight) and almost always below 28 kg/m^2 [(53-54)] which is a reference value that is widely associated to mortality for cardiovascular events and with several types of tumors [(55)]. This allows to classify the majority of transplant recipients who practice sport as individuals at a relatively lower risk of cardiovascular problems compared with sedentary transplant recipients [(56)]. The majority of transplant recipients who practice sport are able to walk at least 10 thousand steps a day, equivalent to an energy expenditure of 300 kcal [(57)], and corresponding to the quantity of physical exercise useful to prevent obesity and reduce the risk of suffering from a first heart attack [(58,59)]. The energy expenditure of transplant recipients of different organs has been measured with portable appliances (Sensewear Armband) within 24 hours, during the participation in alpine skiing, cross-country skiing, road cycling competitions and several track and field specialties, in the context of the Italian National Transplant Games. The energy expenditure within the 24 hours is 25% higher than that of healthy sedentary individuals. The transplant athletes were able to withstand physical activity greater than 3 METS for 197±112 minutes, with peaks of activity which ranged from moderate to intense [(57)].

Königsrainer et al. presented an investigation on 22 heart, liver and kidney transplant recipients, who participated to a road cycling race (Euregio Cycling Tour) which is held across the Austrian and Italian alps in three legs, respectively of 140, 90 and 102 km. The transplant recipients in stable immunosuppression conditions and with a normally functioning organ were able to complete the course trouble-free during and after the race and with performances comparable to those of the control subjects [(60)].

A study conducted during the Winter Games for transplant recipients in Italy, which involved 11 kidney transplant recipients, 4 liver transplant recipients and one heart recipient, has shown that it is possible to recover the ability to use the lactacyd anaerobic metabolism together with the technical abilities to succeed in participating in a giant slalom race in a mountainous environment (42 gates, height difference of 160 m, departure altitude 1600 m asl, air temperature -8°C). Even the gifts of explosive power, determined with the high jump test from a stationary position with a counter movement, were comparable to those of the normal sedentary population (55).

In 1985, it was reported the first case of a 45 years old heart transplant recipient who completed the Boston Marathon, in less than six hours (61). In those years, Kavanagh et al. studied the metabolic implications in a heart transplant recipient after having run half a marathon in 2 h 26 min; the same study showed a significant increase in lactacidemia and blood creatine phosphokinase, and in creatinine and urine urea. These variations were comparable to those of the healthy control corridors, but highlighted several differences in the kidney function due to immunosuppressive therapy (62). Douglas et al. have published the case of a 45 years old heart transplant recipient who began to train for the first time after their transplant for 10-15 hours a week, succeeding in taking part in a triathlon (1.5 km swim, 40 cycle, 10 race) nine months after the transplant, with a time of 4 hours and 12 minutes. Holter monitoring performed for the entire duration of the race showed an average heart rate of 144 bpm (range 139-162 bpm) without significant alterations in the heart rhythm. The myocardial contractility indexes were transitorily altered and returned to the normal values within 24 hours, as it happens in normal individuals. The electrolytes and the muscular enzymes also had a normal trend in the post-race phase (63). Richard et al. have recorded the heart rate of 14 heart transplant recipients involved in a 600 km running race between Paris and La Plagne, a relay race with teams of eight athletes each. The transplant recipients (between 19 and 59 years old; BMI between 18 and 28 kg/m2, V'O2peak between 23.3 and 50 mL/kg/min) had trained regularly for 36±24 months for 4±2 times a week at an intensity of between 4 and 8 METS. For each, the fraction of race was established on the basis of their individual abilities and was included between 10 and 30 minutes with average speeds between 8 and 14 km/h. The average heart rate during the race was between 146 and 201 bpm (mean 179±14 bpm) and was significantly higher than that recorded in the same individuals at the end of maximal incremental tests performed at the cycle ergometer and treadmill. During the race no electrocardiographic alterations were recorded suggesting no pathologic alterations of the rhythm or ischemic phenomena [61]. A bilateral lung transplant recipient, affected by cystic fibrosis, at the age of 32, at a distance of 15 months from the transplant (V'O2max 31.9 mL/kg/min), took part in the New York Marathon finishing it in 7h18'50", trouble-free and with transitory modifications of hematochemical parameters, comparable to those of normal individuals [64]. A 45 year old, ex-triathlete, heart transplant recipient, took part in a 10 km race competition 4 months after transplantation [65]. Haykowsky and Tymchak reported the case of a 44 year old transplant recipient who was able to complete half an Ironman triathlon (1.9 km swim, 90 km cycle and 21,097 km race or rather half a marathon) in 6h28', 18 years after the transplant, improving the following year (6h15'), and to take 3h02' to cut the finishing line of an Olympic triathlon (1.5 km swim, 40 km cycle, 10 km run). This athlete trained 2-3 times a week and showed a maximum aerobic power of 59 mL/kg/min [66]. Patterson and Walton published the case of a 39 year old cyclist (maximum aerobic power 58 mL/kg/min), who underwent a heart transplant after having suffered an acute myocardial infarction at the end of a race. This athlete was able to withstand a more aggressive than usual post-transplant rehabilitation which, after 13 days, led him to walk for 45 minutes at 4.8 km/h with a heart rate below 140 bpm; after 31 days to walk, run or cycle without time restrictions with a heart rate lower than 150 bpm. 47 days after surgery, he was able to do 2-3 bike training sessions per week, of 80 km each, without restrictions. His maximum aerobic power after 12 months from the transplant was 36.5 mL/kg/min [67]. Kidney function was studied in a group of transplant recipients (11 kidney, 5 liver, 2 heart, 2 bone marrow) who took part in a gran fondo cycling road race (Novecolli: length 130 km, overall height difference of 1871 m, average time taken by the transplant recipients 6h36'49"±1h15'14"). The transplant recipients in good clinical conditions and adequately trained, were able to tackle intense and prolonged physical exertion, with transitory modifications of the kidney function which reduced within 24 hours from the end of the race, comparable to those of the healthy control individuals [68]. It should be observed that professional athletes dedicate at least 3-4 hours a day at least 6-7 times a week for several years to preparing for competitions, while the number of weekly training sessions of transplant athletes varies from 1 to 7, with an average of 2-3 training sessions a week, independently of the sport practiced for a total of 6.8±3 hours/week, for a significant part of the year [68]. In actual fact, a group of 12 heart transplant recipients who trained for two years at an intensity corresponding to the aerobic threshold, for 7-20 hours a week, to prepare for the European Championships for heart and lung transplant recipients in 2002, achieved results which the authors call "exceptional" in terms of performances at the ergometric test: maximum workload 255±47 W, V'O2max 45.2+6.9 mL/kg/min [69]. The time differences dedicated to the training can certainly affect the result, but the differences in performances can also be due to other factors. Genetic predisposition plays a particularly important role in determining high level performances, but the type of training, motivation and nutrition can also contribute [70]. Furthermore, for transplant patients, the duration and the effects of the disease which have led to the transplant, the characteristics of the transplanted organ, the physical post-transplant and, above all, the effects of immunosuppressive therapy, should also be considered. The sporting performance is also developed starting from suitable muscular trophism, which is known to be influenced by diet and exercise [70]. The patients affected by chronic illnesses present a form of resistance to anabolism, which is worsened by immunosuppressive drugs that have different inhibitory effects on the control mechanisms of anabolism in the various tissues of the organism [71]. Regular strength training seems able to reset this resistance to anabolism and to improve the anabolic response induced by food [72]. To investigate this aspect, the Chapter 6 of this thesis focused on the effects of combined strength and endurance training on exercise performance in kidney transplant cyclists and runners. In the literature there are few studies on the effects of endurance sports in transplanted athletes and this study represents a starting point to break down the prejudice that "transplantation" and "sport" cannot coexist.

To date in the literature studies on organ transplanted athletes are missing and therefore it is appropriate to study this aspect to understand the effects of a specific endurance sport training in transplant athletes on sports performance.

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Effects of exercise in kidney and liver transplant recipients: the health pathways

Chapter 2

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

The results presented in this chapter were partially taken from a large multicenter study involving 99 patients, already published in World Journal of Transplantation.

World J Transplant. 2018; 8(1):13-22.

ABSTRACT

Aim

Kidney transplant recipients (KTRs) are characterized by reduced physical fitness and higher risk for cardiovascular disease. This study evaluated the effect of a 12-month supervised aerobic and resistance training, on renal function, exercise capacity and blood pressure compared to usual care recommendations.

Methods

Sixty-six KTRs were assigned to interventional exercise (Group A; n=35) and a usual care cohort (Group B; n= 31). Blood and urine chemistry, exercise capacity, muscular strength, anthropometric measures, blood pressure and health-related quality of life (HRQoL) were assessed at baseline, and after 6 and 12 months. Group A underwent a supervised training three times per week for 12 months. Group B received only general recommendations about home-based physical activities.

Results

Sixty-six KTRs completed the study (Group A, n=35; Group B, n=31). After 12 months, renal function remained stable in both groups. Group A significantly increased maximum workload (+10 W, P=0.003), V'O2 peak (+3.1 mL/kg/min, P=0.050), anaerobic threshold workload (+7 W, P=0.032), general muscular strength (+2 kg, P=0.004), height in the countermovement jump (+2.0 cm, P=0.049) and decreased in Body Mass Index (-0.4 kg/m2, P=0.015). HRQoL significantly improved in physical function (+9, P=0.010), physical-role limitations (+22, P=0.028), bodily pain (+12, P=0.035) and social functioning scales (+7, P=0.047). No improvements were found in Group B. During the incremental cycling test, diastolic blood pressure at peak decreased in both group over time (-7 mmHg, P=0.008). No changes were found in mean arterial pressure and pulse pressure in both group.

Conclusions

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 centers, sports medicine and exercise facilities.

INTRODUCTION

Kidney transplantation is considered the gold standard of treatment for most patients with end-stage renal disease, and 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)(1). In particular, systolic (SBP) and diastolic blood pressure (DBP) are associated with heart failure and CVD in KTRs. It is worth noting that increased blood pressure (BP) and reduced renal function are independent predictors of cardiovascular risk and end-organ damage(2). Mean arterial pressure (MAP) that is considered an indicator of perfusion to vital organs, and pulse pressure (PP), are considered an independent predictors of cardiovascular disease (CVD)(3). Prospective studies in a variety of populations have convincingly demonstrated a substantial excess rate of development of CVD in proportion to the degree of elevation in BP(4).

However, among all these risk factors, the lack of physical exercise and a sedentary lifestyle seem to play crucial roles(1).

There is mounting evidence that physical exercise reduces the risk of all-cause mortality(5,6) and it is effective in the primary and secondary prevention of CVD in the general population(7). Physical activity is also considered a key element in the prevention and management of chronic diseases(8), 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(9). However, their cardiorespiratory fitness remains reduced by 30% in comparison with age-matched control subjects(10). Only in selected cases they can achieve results comparable to a healthy population(11), 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(12).

Whether exercise can positively affect outcomes in KTRs has only been addressed in few studies(7), with a small number of subjects and with different types, intensity and durations of interventions lasting almost always no more than six months(13,14). In some studies, exercise was carried out tightly at home without direct supervision and with a partial adherence to the intervention(9). Furthermore, few studies have investigated the effect of a combined aerobic and resistance training(7), and the effect of these protocols on kidney function and blood pressure is rather unknown.

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

METHODS

Organisational Model

We introduced a project, based on a model of cooperation among: i) transplantation specialists (surgeons and nephrologists), who selected patients suitable for physical activity; ii) sports physicians who prescribed a personalised exercise programme based on the results of functional assessment tests; iii) 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(15,16).

Study Design

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

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

Patients were divided into an interventional exercise group (Group A), in which personalised training was supervised, and a usual care group (Group B), in which some exercise indications were given without a specific prescription and supervision. All subjects received individualised counselling by the transplant centre regarding the protocol, and the inclusion in Group B was based on logistic and organisational grounds (patients living in areas without sports medical centres or an accessible gyms). This is the practical reason why we adopted a non-randomised design of our study.

Blood chemistry and urinalysis, complete blood count, and a cardiac evaluation were performed by the transplantation centres to assess the exclusion criteria. After the administration of the SF-36 questionnaire to evaluate Health-Related Quality of Life (HRQoL), the patients were sent to the sports medicine centre to perform the functional assessment tests for exercise capacity, blood pressure, 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 months (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 months. In every session, the aerobic training was performed on a stationary bike and was administered with an intensity corresponding to the lactate aerobic threshold[(17)]. 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[(18,19)]. Resistance training was not performed with the upper limb with arterio-venous fistula. Warm-up, cool-down and stretching exercises were included in all training sessions. The intensities of aerobic and strength trainings were adjusted after the T_6 assessment.

Non-Supervised Home-Based Exercise Intervention (Group B)

At T_0 and T_6 patients in Group B were provided general information to encourage home-based physical activities but no specific prescription and supervision were given.

The International Physical Activity Questionnaire (IPAQ) short-version[(20)] 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 to reduce the bias between the two groups.

PRIMARY ENDPOINTS

Renal Function, Lipid Values and Blood Chemistry

In both groups, creatinine (mg/dL) using the Jaffè method, estimated glomerular filtration rate (eGFR) using the chronic kidney disease epidemiology collaboration (CKD-EPI) equation, proteinuria (mg/1000mL) using the turbidimetry method reported in g/24hour calculating 24-hour urine collection were collected to check the renal function at T_0, T_6 and T_{12}.

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

Exercise Capacity and Blood Pressure

Exercise capacity was assessed by an incremental cycling exercise starting from a 5-minute unloaded cycle and increasing by 20 W every four minutes until the subject was unable to continue. A 12-lead electrocardiogram was monitored continuously throughout the test. At each step a capillary blood sample from the earlobe was taken to measure blood lactate concentration (YSI 1500-Sport; Yellow Springs, USA) to estimate the workload corresponding to aerobic and anaerobic thresholds, conventionally declared at 2 and 4 mM of lactate, respectively[17]. Oxygen uptake (V'O_2) was determined continuously using an open-circuit spirometry system (Sensor Medics, Anaheim, USA), and the V'O_2 at the highest tolerated workload was determined and was referred to as V'O_2 peak (mLO_2/kg/min). During the incremental cycling test SBP and DBP were repeatedly collected at baseline, at the peak and during the recovery in both groups at T_0, T_6 and T_{12} using a manual sphygmomanometer (HEINE GAMMA® G7, Germany). For recording accurate measurements of BP we used standard procedures in according with the AHA guidelines[21]. The patients were asked to avoid caffeine, exercise and smoking for at least 30 minutes before the test. The limb used to measure BP was supported, the BP cuff was at heart level using the correct cuff size and deflating the cuff slowly. To minimize error and provide more accurate estimation of BP an average of 2 to 3 BP measurements were recorded. The average pulse pressure (PP) (SBP-DBP) and the mean arterial pressure (MAP) ([(PP)/3] + DBP) were calculated.

Muscular Strength and Power

A leg press (Technogym, Cesena, Italy) and free weights were used 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[22]. The general strength was measured using a handgrip dynamometer (Lafayette, IN, USA). The power of the lower limbs was measured indirectly from the flight time of a countermovement jump (CMJ) and was expressed as maximum displacement (m) of the centre of mass during fly (Optojump, Microgate, Italy).

SECONDARY ENDPOINTS

BMI and Body Composition

Body Mass Index (BMI) was calculated using the ratio between weight and square height (kg/m^2).

Fat mass percentage (FM%) was determined using the Jackson & Pollock body density equation considering seven skinfolds in both men and women (abdominal, thigh, triceps, bicep, subscapular, suprailiac, chest) measured with a Harpenden caliper[23] at T_0, T_6 and T_{12}.

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[24] completed by the patients independently at T_0, T_6 and T_{12}.

STATISTICAL ANALYSIS

The required sample size 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 models were used to assess the effects of time and group on dependent variables, with T_0 and Group B set as the base categories. Random intercepts were used for individual subjects. Significance was set at $P < 0.05$, and the raw coefficients for the fixed effects and interactions are reported with 95% confidence intervals. The statistical analysis was performed using R software for Windows (v. 3.2.3).

RESULTS

Subjects

Sixty-six KTRs were recruited by six transplant centres between January 2011 and June 2015. Thirty-five KTRs from Group A (17 female and 18 males, age 46±12 yrs, weight 69±14 kg, BMI 24.3±4.4 kg/m^2, time from transplant 6.3±7.7 yrs, dialysis vintage 43±42 months, range 1-156) and 31 KTRs from Group B (11 female and 20 males, mean±SD age 50±10 yrs, mass 77±14 kg, BMI 26.1±4.8 kg/m^2, time from transplant 3.9±4.5 yrs, dialysis vintage 31±30 months, range 1-120) were analysed. There were no significant differences between groups regarding: age (P=0.10), BMI (P=0.16), and dialysis vintage (P=0.42). The only significant difference was found for time from transplant (P=0.028)

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

UNDERLYING DISEASE	**Group A (n=35)**	**Group B (n=31)**
Glomerulonephritis	10	6
Nephroangiosclerosis	7	5
Polycystic kidney disease	8	10
End-stage kidney disease	10	5

Table 1: pathologies leading to renal disease and transplantation.

	Tacrolimus	Cyclosporine	Steroid therapy	Purine Synthesis inhibitors	(mTOR) inhibitors	Anti-Hypertensive therapy	Beta-blockers	Insulin therapy	Statin
Group A n=35	22 (64%)	9 (27%)	28 (80%)	26 (75%)	6 (16%)	26 (75%)	5 (14%)	1 (2%)	12 (34%)
Group B n=31	17 (66%)	6 (24%)	19 (73%)	22 (83%)	3 (12%)	19 (73%)	11 (44%)	1 (5%)	11 (41%)

Table 2: immunosuppressive and other therapies in both groups.

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-month period was 93±6%. No adverse events were reported.

Primary outcomes

Creatinine tended to decrease in Group A at T_{12} and to increase in Group B at the same time, but the differences were not significant. No significant changes were found in eGFR or proteinuria in either group. Average triglyceride and cholesterol levels showed slight changes at T_{12} in both groups which were not significant (Table 3). Glucose values were <126 mg/dL at the three-time points in both groups (Table 3).

	Group A (n=35)			Group B (n=31)		
	T_0	**T_6**	**T_{12}**	**T_0**	**T_6**	**T_{12}**
Creatinine (mg/dL)	1.30±0.37	1.33±0.41	1.34±0.44	1.53±0.75	1.53±0.57	1.52±0.66
eGFR (mL/min/1.73m^2)	59.4±19.3	58.0±19.6	62.6±21.8	56.3±21.2	58.1±17.8	52.9±17.4
Proteinuria (g/24h)	0.41±0.51	0.34±0.46	0.52±0.63	0.45±0.57	0.48±0.59	0.61±0.44
Haemoglobin (g/dL)	12.8±1.8	12.3±1.7	12.6±1.6	12.1±1.8	12.5±1.9	12.8±1.5
Triglycerides (mg/dL)	124±43	123±42	122±47	154±78	134±67	143±65
Cholesterol (mg/dL)	199±38	187±56	204±45	199±35	189±24	187±36

Table 3: mean±SD of blood chemistry.

Group A showed a significant average improvement in maximum workload and V'O_2 peak at T_{12} (P=0.003, P=0.050) compared to Group B. The maximum HR and anaerobic threshold workload significantly increased at T_{12} (P <0.05) in Group A compared to Group B. No significant differences were found in Group B at T_6 and T_{12} in any of the variable (Table 4).

	Group A (n=35)			Group B (n=31)		
	T_0	**T_6**	**T_{12}**	**T_0**	**T_6**	**T_{12}**
Maximum workload (W)	101±50	109±44	111±51*	93±26	94±25	90±28
V'O_2 peak (mL/kg/min)	23.9±8.3	25.8±9.5	26.3±7.8*	19.5±6.0	20.6±5.6	19.6±5.1
HR max (bpm)	143±24	143±22	145±20*	130±22	128±20	126±20
Body Mass Index (kg/m^2)	24.3±4.4	24.2±4.4	23.9±4.9*	26.1±4.8	25.8±4.4	26.4±4.8
Fat Mass (%)	21.3±9.4	19.7±8.8	21.0±8.6	20.8±8.1	19.2±7.1	20.7±9.0
Aerobic threshold workload (W)	56±32	57±29	59±28	51±20	57±24	53±25
Aerobic threshold HR (bpm)	113±21	109±19	112±18	99±20	100±17	100±19
Anaerobic threshold workload (W)	87±41	92±37	94±46*	81±24	85±34	77±29
Anaerobic threshold HR (bpm)	131±23	131±24	129±30	122±20	119±18	117±18
SBP baseline (mmHg)	125±14	118±32	118±32	131±17	122±28	123±27
DBP baseline (mmHg)	79±8	79±8	78±7	81±10	81±8	82±9
PP baseline (mmHg)	46±12	46±10	47±11	50±14	45±13	45±12
MAP baseline (mmHg)	94±9	94±8	94±7	99±9	97±10	97±10
SBP peak (mmHg)	183±27	184±22	184±26	184±28	182±26	181±28
DBP peak (mmHg)	83±11	83±13	80±13*	83±10	77±19	79±11*
PP peak (mmHg)	100±28	102±20	103±24	100±27	104±24	104±24
MAP peak (mmHg)	116±13	117±14	115±15	116±13	116±11	113±14
SBP recovery (mmHg)	129±18	130±13	131±16	138±18	138±22	138±20
DBP recovery (mmHg)	74±9	75±8	74±10	78±10	77±9	77±8
PP recovery (mmHg)	55±17	55±11	57±17	61±18	61±20	61±19
MAP recovery (mmHg)	93±10	93±9	93±10	99±11	99±9	97±10

Table 4: mean±SD of exercise capacity and blood pressure during the incremental cycling test. *P<0.05 between T_0 and T_{12}.

During the incremental cycling test, DBP at peak exercise intensity decreased in both group over time (-7 mmHg, P=0.008). No changes were found in mean arterial pressure and pulse pressure in both group at baseline, peak and during the recovery after the test over time (Table 4).

Group A showed a significant average improvement in power expressed by CMJ (P=0.049) at T_{12} compared to Group B. No significant differences were found in Group B at T_{12} in any variable (Table 5).

Group A showed a significant improvement in the handgrip test at T_{12} (P=0.004) compared to Group B (Table 5).

	Group A (n=35)			Group B (n=31)		
	T_0	**T_6**	**T_{12}**	**T_0**	**T_6**	**T_{12}**
Knee Extensors Right (kg)	83±40	89±40	94±39	53±25	56±25	57±24
Knee Extensors Left (kg)	76±37	90±41	90±39	49±22	56±24	56±24
Plantar Flexors Right (kg)	72±37	75±30	80±29	60±35	62±24	61±23
Plantar Flexors Left (kg)	70±36	75±30	77±30	64±33	66±22	64±24
Counter Movement Jump (cm)	24.4±11.0	27.3±10.9	26.4±10.2*	18.8±9.0	20.3±10.9	18.5±10.0
Handgrip Right (kg)	35.3±14.0	36.8±14.4	36.3±14.5*	35.7±10.5	33.4±7.8	31.9±8.1
Handgrip Left (kg)	30.7±13.9	33.8±12.2	33.0±11.0*	35.2±11.5	32.3±8.5	30.6±9.1
Elbow Flexors Right (kg)	8.8±2.9	9.6±3.4	9.7±2.9	7.8±3.4	8.9±3.1	9.4±5.0
Elbow Flexors Left (kg)	8.8±3.4	9.6±3.7	9.7±3.2	6.8±3.1	8.9±5.3	9.5±7.0
Elbow Extensors Right (kg)	6.2±3.2	6.9±4.0	6.8±2.4	5.0±2.4	5.8±2.1	5.8±2.3
Elbow Extensors Left (kg)	6.2±3.3	7.1±4.1	7.0±2.4	4.4±1.8	5.3±1.7	5.4±1.8
Shoulder abductors (kg)	5.1±2.3	6.2±2.6	6.2±2.2	3.8±2.1	4.7±1.7	4.6±2.0

Table 5: mean±SD of muscular strength and power. *$P<0.05$ between T_0 and T_{12}.

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/min per week) at the 12 months follow-up. Theoretical IPAQ calculated from the exercise protocol performed by Group A was <600 MET/min per week at baseline, and >600 MET/min (range 1,215-1,413 MET/min) per week at T_6 and T_{12} (P <0.01).

Secondary outcomes

Group A showed a significant decrease in BMI at T_{12} (P=0.015) compared to Group B (Table 4).

In HRQoL, significant improvements were found in Group A in physical function scale at T_{12} (P=0.010), in role-physical, bodily pain and social functioning scales at T_{12} (P=0.028, P= 0.035, P=0.047) compared to Group B, in which we found no significant changes in any scales (Table 6).

	Group A (n=35)			Group B (n=26)		
	T_0	T_6	T_{12}	T_0	T_6	T_{12}
Physical Function	84±20	91±11	92±12*	89±10	86±20	86±23
Role Physical	83±25	88±21	96±15*	91±19	91±19	86±24
Bodily Pain	80±24	80±22	89±20*	86±19	84±22	84±22
General Health	63±20	67±21	68±20	64±21	67±19	66±17
Vitality	67±16	70±15	69±19	67±18	69±14	68±14
Social Function	75±19	80±20	83±17*	82±19	78±21	78±21
Role Emotional	85±24	91±20	90±22	93±16	96±15	93±17
Mental Health	75±16	75±16	74±19	74±18	77±16	74±16

Table 6: mean±SD of SF-36 questionnaire scales. *$P<0.05$ between T_0 and T_{12}.

DISCUSSION

The main result of this study is that in selected KTRs, a programme of 12 months 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 and to a positive change in lifestyle.

The KTRs included in Group B who received only general information to promote regular physical activity at home, without a specific supervision, did not show any improvement in physical fitness outcomes, indicating a low adherence to non-supervised home-based physical activity. This demonstrated that without a direct or indirect supervision (e.g. follow up by calls or e-mails), patients tend to not carry out physical activity even if it is recommended by the physician.

Van Adrichem et al.[25] 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.[9] 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.[26] in their 12-week study reported a dropout of 7 out of 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.[7] reported a dropout of 2 out of 16 (13%) in their 12-week study in the supervised exercise group and 1 out of 15 (7%) in the home based usual care group. O'Connor et al.[27] in an un-supervised period of self-managed physical activity reported an attrition rate of 30% at the 12 month time point that confirms a low exercise adherence without supervision.

Compliance with the treatment is a common barrier of health programmes based on exercise even if transplant recipients who have experienced a supervised exercise programme supported that it was beneficial to health and well-being [28]. Social, cognitive, personality, environmental, and socio-economic factors, unrelated to the recommended guidelines, seem to be of greater importance in considering behavioural adherence issues [29] 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.

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. To the best of our knowledge, 12 months of observation period is one of the longest in the literature with reference to aerobic and resistance training; however, it is a relatively short time period and further studies with larger samples 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 6-10% increase of $V'O_2$ peak at T_{12}. Similar results were obtained by Van der Ham et al.[30] in 33 KTRs after 12 weeks of combined endurance and strength training in which $V'O_2$ peak increase of 10% (from 21.6±6.3 to 23.8±6.1 mL/kg/min). Riess et al.[7] reported an increase of $V'O_2$ peak (from 20±9 to 23±10 mL/kg/min) after 12 weeks of supervised endurance training (three times/week) on cycle ergometer at 60-80% of $V'O_2$ max involving 16 patients.

In a study of eight KTRs, Romano et al.[31] used a supervised interval training technique for 10 weeks, 40-minute sessions for three times per week. They reported an increase of 13% of $V'O_2$ peak.

Another intervention was presented by Kempeneers et al.[32] who trained 16 KTRs for six months in preparation for the National Transplant Games. Their mean V'O_2 peak rose from 29.0±7.8 to 37.5±4.8 mL/kg/min, with an increase of 27%.

In the other hand, Painter et al.[9] prescribed an individualised home-based exercise training programme to 54 KTRs, consisting on 30 minutes, 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_2 peak increased from 24.0±7.5 to 27.8±11.0 mL/kg/min (+16%) and to 30.1±10.3 mL/kg/min (+25%) after 12 months.

We can conclude that the aerobic training in KTRs leads to a substantial increase in aerobic power[33]. In most cases, the type of training meets the minimal clinically significant difference of 3.5 mL/kg/min (i.e., 1 metabolic equivalent), which is associated with improved outcomes in CVD. However, Riess et al.[7] after 12 weeks of endurance training were unable to demonstrate any change in resting small or large arterial compliance, peak exercise systemic vascular resistance and Framingham Risk Assessment Score, indicating that exercise intensity and overall duration are probably the most critical factors affecting CVD risk profile. In our study diastolic blood pressure at peak recorded during the incremental cycling test significantly decreased over time in both group demonstrating that practicing regular physical activity, both mild or moderate, supervised or not, can decrease blood pressure and prevent diastolic dysfunction. This finding is confirmed by Roberts et al. that have shown a significant decrease in DBP after home-based exercise[34]. Otherwise, when the diastolic pressure becomes increased, the likelihood of severe coronary artery disease is increased[35].

Reduced general muscular strength has been related to an increased risk of all-cause of cardiovascular mortality[36] and the handgrip test values are a recognised marker of health status[37]. In our study, the handgrip test values improved after 12 months, whereas in the Group B we found a trend in reduction in strength, even if it was not significant. Moreover, in the Group A the muscular strength of the lower limbs improved, and the power of the lower limbs increased after 12 months. This increase in maximal strength and CMJ values may be associated with both neural adaptations and muscle trophism improvement[38]. This finding is consistent with prior studies[9].

In relation to anthropometric measures, the 12-month supervised programme combining aerobic and resistance training was effective in reducing BMI[39] in Group A. However, in our study, the lipid profile remained the same; 34% 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 improvements in Group A in the self-perception of physical function, role-limitation to physical activity, bodily pain 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[40].

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[41]. The accurate selection of the patients and the cardiovascular assessment at T_0 certainly contributed to these findings.

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

Another limit is due to the workloads chosen for the aerobic and strength training. We adopted a steady state aerobic exercise protocol at intensity corresponding to the lactate aerobic threshold. Different training protocols, i.e. interval training, or different duration of the sessions could be more effective. Furthermore, it is possible that with a higher percentage of 1RM and with a different progressive strengthening protocols the improvements would be higher, especially when training the upper limbs. The fact that the upper limb with the arteriovenous fistula was not trained, for safety precautions, also affected the final strength results. Furthermore, we checked both groups after 6 months of training, so probably a more frequent adjustment in the prescription of the relative intensity of training would lead to better functional outcomes in Group A or would give further motivations in Group B.

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

Finally, patients included in our study were carefully selected and were thus not representative of the entire KTRs population.

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 samples 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.

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Chapter 3:

Physical condition, glycemia, liver function and quality of life in liver transplant recipients after a 12-month supervised exercise program

The results presented in this chapter were partially taken from a large multicenter study that involved 39 patients, accepted for publication in Transplantation Proceedings.

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ABSTRACT

Background and aims

Despite the excellent long-term outcomes in liver transplant (LT) recipients, several medical complications related to lifestyle represent still an issue. This study examined the effects of a 12-month supervised aerobic and strength training on the aerobic capacity, muscle strength, metabolic profile, liver function and quality of life in a cohort of LT recipients.

Methods

LT recipients with stable liver function were assigned to interventional exercise (group A) or usual care (group B). Aerobic capacity, muscle strength, metabolic profile, liver and kidney function, and health-related quality of life were assessed at baseline, after 6 and 12 months. Group A attended supervised training sessions 3 times per week for 12 months. Group B received general recommendations about home-based exercise.

Results

Twenty-two patients (72.5%, M/F 23/6, mean age 52±8 years) from 4 Italian LT Centers in Emilia-Romagna Region were analyzed. Baseline characteristics were similar between groups except for BMI and time from LT. No episode of acute rejection nor increase of transaminases occurred. Maximum workload, aerobic threshold workload and BMI increased in both groups over time, but fasting glucose significantly decreased in group A (94±16 vs 89±14 mg/dl; p=0.047) and increased in controls (90±6 vs 93±5 mg/dl, p=0.04). Upper limb and general muscle strength increased only in supervised LT recipients. Physical functioning, vitality and general health domains significantly improved after physical exercise.

Conclusions

Supervised combined training was safe and effective in increasing aerobic capacity, muscle strength and quality of life and in improving glucose metabolism in stable LT recipients.

INTRODUCTION

Even if short-term outcomes and survival rates after orthotopic liver transplantation (LT) have improved over time, exceeding 80% and 72% at 1 and 5 years [1, 2], there have been no appreciable improvements in long-term survival [3]. This might be due to several medical complications, often related to lifestyle, which represent still an issue in the long-term medical care.

LT recipients are at higher risk of developing metabolic complications, chronic kidney disease, bone loss and sarcopenia, which are associated with cardiovascular diseases (CVD) [4, 5]. Long-term immunosuppression, but also a sedentary lifestyle, often associated with a gradual weight gain, weakness and fatigue represent modifiable risk factors [6]. Even if exercise capacity and muscle strength improve after LT, they remain significantly lower than age and sex-matched people without solid organ transplant [7, 8]. The role of physical exercise on LT recipients has only been addressed in few studies, which were conducted on small samples, and considered different types, intensity and durations of interventions that lasted no more than 24 weeks [9-12]. Furthermore, few studies [10, 12] have investigated the effect of combined aerobic and strength training on aerobic capacity, strength, metabolic profile, and kidney and liver function. The beneficial role of physical activity has been demonstrated also on health-related quality of life (QoL), which significantly improves after transplant, but often remains far from the expected results [13-15].

Thus, this study aimed to evaluate the role of a 12-month combined aerobic and strength training on aerobic capacity, strength, metabolic profile, liver function and HRQoL in stable LT recipients.

METHODS

This was a multicenter, controlled, non-randomized study. From January 2011 to June 2015, a total of 22 adult patients were prospectively enrolled from 4 LT Centers in Emilia Romagna Region, Italy. Inclusion criteria were: age between 18-60 years; previous LT (> 6 months) with stable clinical and functional status (e.g.: absence of liver related complications in the previous six months, including episodes of acute rejection, increase of serum transaminases 2xULN). Exclusion criteria were: combined transplantation; re-LT; physical limitations to exercise; psychiatric or severe debilitating neurological disorders; non-adherence; cardiovascular contraindications to exercise testing and training. Written informed consent was obtained for all patients before their enrolment in accordance with procedures approved by participating centers' ethical Committees. This trial was listed in the ISRCTN registry (Trial ID: ISRCTN66295470) and conducted in accordance with the ICH Guidelines for Good Clinical Practice, the Helsinki Declaration, and Italian legislation on the conduction of clinical trials.

After individualized counseling from the transplant Centers regarding the protocol, patients were assigned to one of two groups: an interventional exercise group (group A), in which personalised aerobic and strength training was prescribed and supervised; and a usual care group (group B), in which patients received general exercise recommendations without any specific supervision. Inclusion in group B was based on logistic grounds (patients living in areas without sports medicine centers or local gyms). A multidisciplinary group comprising transplantation hepatologists, sports physicians, and exercise specialists was actively involved in monitoring graft function and identifying facilities outside the medical setting where patients can easily complete their training programs under the supervision of exercise specialists.

All patients enrolled were referred to a sports medicine center for functional tests to assess their aerobic capacity, muscle strength, and body composition. Based on the results of these tests, the sports physicians prescribed a tailored combined aerobic and strength training program. Group A conducted the exercise program in a certified gym under the supervision of exercise specialists instead group B practiced home-based exercise without supervision.

Evaluation of liver, kidney and metabolic profile

Liver function was assessed in both groups at T_0, T_6 and T_{12}; kidney function was expressed as the estimated glomerular filtration rate (eGFR), calculated using the CKD-EPI creatinine equation [16]. Lipid profile (total cholesterol, HDL and triglycerides) was measured using flow cytometry and light-scattering methods. Glucose metabolism was assessed based on standard fasting blood glucose measurement. Systolic (SBP) and diastolic blood pressure (DBP) was measured repeatedly at T_0, T_6 and T_{12} in both groups, at each clinical assessment, using a manual sphygmomanometer (HEINE GAMMA® G7, Germany) according to current guidelines [17].

Body composition

At T_0, T_6 and T_{12}, fat mass (%), total body weight (kg), and body mass index (BMI; kg/m^2) were assessed in both men and women, using the Jackson & Pollock body density equation, a weighing machine, and a Harpenden caliper, measuring seven skinfolds (abdominal, thigh, triceps, bicep, subscapular, supra-iliac, chest)[18].

Aerobic capacity

Aerobic capacity was assessed with an incremental cycling exercise starting from a 5-minute unloaded cycle and increasing by 20 W every 4’ until the patient was unable to continue. A 12-lead EKG was obtained 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, USA). This was used to estimate the workload corresponding to the aerobic and anaerobic thresholds, conventionally set at 2 and 4 mM of lactate, respectively [(19)]. During testing, maximal oxygen consumption (VO_{2peak}) was recorded using an open-circuit spirometry system (Sensor Medics, Anaheim, USA).

Muscle strength

Free weights and a leg press (Technogym, Cesena, Italy) were used to assess dynamic muscular strength in the upper and lower limbs (elbow flexors, elbow extensors, knee extensors, plantar flexors). One-repetition maximum (1RM) strength was calculated using an indirect method involving 7 to 12 repetitions with submaximal loads [(20)]. General strength was measured using a handgrip dynamometer (Lafayette, IN, USA).

Exercise intervention

The prescribed exercise included sessions of combined aerobic and strength training. Each session lasted one hour and was scheduled 3 times per week for 12 months. At each session, aerobic training was performed on a stationary bike for 30’, administered at an intensity corresponding to the lactate threshold [(19)]. The intensity was monitored continuously using heart rate monitors (Polar, Finland) so that patients could keep a constant heart rate (HR) corresponding to their aerobic threshold.

During the same session, subsequent strength training consisted of 2 sets of 20 repetitions at 35% of 1RM for each muscle group of the upper and lower limbs (single joint exercises of the elbow flexors, elbow extensors, plantar flexor, knee extensor). This training intensity was chosen assuming that LT recipients were naïve at strength training [(21, 22)]. Warm-up, cool-down, and stretching exercises were included in all training sessions. The intensity of the aerobic and strength training was adjusted after the T_6 assessment. Adherence to the exercise program was measured as the proportion of completed sessions.

Health-related quality of life

The SF-36 questionnaire was used to assess self-reported health status [(23)] through 8 different items: physical functioning, role limitations due to physical health, bodily pain general health, vitality, social functioning, role limitations due to emotional health, and mental health. Questionnaires were completed independently by patients at T_0, T_6 and T_{12}.

Statistical analysis

The required sample size was ascertained using the Software G*Power (version 3.1.9.2) with an alpha level of 0.01, and a power of 0.90. Continuous and categorical variables were expressed as mean±SD and frequencies, as appropriate. Repeated-measures analysis of variance (ANOVA) were used to assess the effects of time and group, and their interaction on the dependent variables. Statistical significance was set at $p<0.05$. The statistical analysis was performed using SPSS, Version 20 (IBM, SPSS Inc., Chicago).

RESULTS

Twenty-two LT recipients were enrolled at 4 Emilia-Romagna (Italy) LT Centers and 1:1 assigned to groups. All of them (M/F 16/6, mean age 52±7 years, n.12 in group A and n. 10 in group B) completed the study. Hepatitis C related cirrhosis was the main indication to LT. Fourteen patients (63.6%) were receiving calcineurin inhibitors and mycophenolic acid and 8 patients (36.3%) calcineurin inhibitors monotherapy. No changes on immunosuppression therapy occurred during the study. Baseline characteristics were similar between groups in terms of age, gender, indication to LT, liver and kidney function, eGFR, fasting glucose, serum cholesterol and triglycerides (each p=ns, Table 1). Cohorts differed on baseline BMI (group A vs group B: 25.2±3.4 vs 26.1±5.4; p= 0.046), and time since LT (1.0±0.4 vs 2.7±1.8 years; p=0.040). In group A, adherence to the exercise program (144 sessions in all) during the 12-month period was 89±6%, without adverse events. The level of physical activity remained unaltered (<600 MET/min a week) at the 12-month follow-up in group B.

Liver, kidney and metabolic profile

Liver function remained stable during the study period in both groups; no episodes of acute rejection nor increase of serum transaminases occurred. Renal function remained unaltered in both groups; no patients had an eGFR<60 ml/min (Table 1). Regarding metabolic profile, fasting blood glucose decreased in group A (T_0 vs T_{12} 94±16 vs 89±18 mg/dl; p=0.047) and increased in group B (T_0 vs T_{12}: 90±6 vs 93±5 mg/dl; p=0.04) over time. Nevertheless, there was no significant decrease on other metabolic variables.

	Group A (n=12)			Group B (n=10)		
	T_0	T_6	T_{12}	T_0	T_6	T_{12}
EXERCISE AND BODY COMPOSITION						
Maximum workload (W)	100±46	107±42	110±36*	86±33	94±34	96±39*
Aerobic threshold workload (W)	56±32	69±28	69±30*	42±20	49±22	49±22*
Fat mass (%)	22±5	23±3	23±4	25±8	24±10	25±8
Body mass index (kg/m^2)	25.2±3.4	25.6±3.3	26.0±3.8*	26.1±5.4	26.2±6.0	27.5±6.4*
V'O_2 peak (mL/kg/min)	22.0±8.5	22.7±7.6	24.1±7.9	21.3±5.8	22.5±6.3	21.1±7.7
Plantar flexors (kg)	97±51	113±46	109±45*	82±29	89±31	93±39*
Handgrip (kg)	42±13	44±15	45±16§	35±9	34±9	33±12§
Elbow extensors (kg)	8±3	9±3	9±3§	6±2	6±2	6±2§
METABOLIC PROFILE						
Fasting glucose (mg/dL)	94±16	92±18	89±14§	90±6	90±6	93±5§
Triglycerides (mg/dL)	147±64	149±74	155±84	104±37	112±36	125±61
Total cholesterol (mg/dL)	166±32	170±33	163±31	162±21	167±24	165±19
HDL (mg/dL)	54±14	56±9	45±8	50±11	52±8	51±13
Systolic blood pressure (mmHg)	122±13	120±10	119±10	129±17	129±17	129±17
Diastolic blood pressure (mmHg)	77±10	76±10	76±10	80±14	80±14	80±14
LIVER AND KIDNEY FUNCTION						
Total bilirubin (mg/dL)	0.5±0.3	0.6±0.3	0.5±0.2	0.6±0.2	0.8±0.6	0.7±0.5
Aspartate aminotransferase (U/L)	23±10	22±5	22±7*	26±17	24±10	21±11*
Alanine aminotransferase (U/L)	22±9	20±9	20±10	32±24	26±15	26±14
Gamma-glutamyl-transpeptidase (U/L)	28±36	27±36	38±48	26±16	28±16	31±15
eGFR (mL/min/1.73m^2)	81±18	84±19	84±16	87±20	84±20	83±19

Table 1: Physical conditions, metabolic profile, liver and kidney function at baseline (T_0), and after 6 (T_6) and 12 (T_{12}) months. Data are expressed as mean±SD. $^{§}p < 0.05$ time x group interaction between groups; $^{*}p<0.05$ time effect between groups.

Exercise capacity, muscle strength and body composition

A significant time effect was found for aerobic threshold workload (P=0.001) and maximum workload (P=0.015).

Parameters regarding lower limb muscle strength improved over time in both groups (p=0.024), whereas general strength (p=0.050) and upper limb muscle strength significantly increased only in supervised LT recipients (elbow extensors P=0.036). Lastly, BMI increased in both groups over time, whereas fat mass remained unchanged.

Health-related quality of life

Some items pertaining to the SF36 questionnaire were not similar between groups, thus we compared intra-individual changes at baseline and at T_{12}. In the supervised cohort, physical functioning, general health and vitality items significantly improved, whereas they decreased in controls (Table 2).

	Group A (n=17)			**Group B (n=12)**		
	T0	**T6**	**T12**	**T0**	**T6**	**T12**
Physical functioning	83±16	86±19	86±16§	82±18	82±18	77±19§
Role limitations due to physical health	59±50	63±46	69±37	42±52	42±52	43±50
Bodily pain	78±23	77±26	77±26	54±6	55±6	51±10
General health	59±17	59±22	71±18§	61±13	60±19	43±21§
Vitality	59±24	64±18	66±21§	65±15	63±15	45±9§
Social functioning	70±22	84±20	83±18	83±19	87±19	66±19
Role limitations due to emotional health	54±50	67±44	50±47	67±58	67±58	44±51
Mental health	68±20	76±15	78±15	73±20	74±22	50±6

Table 2: SF-36 scores domains. § P<0.05 time x group interaction between groups.

DISCUSSION

The present study showed that a 12-months supervised combined aerobic and strength training was safe and effective in terms of aerobic workload, muscle strength and glucose metabolism among stable LT recipients. Data are in accordance with those reported by Beyer et al.[24], who showed a 3-fold increase in aerobic workload, and with those reported by Krasnoff et al.[12], who demonstrated a significant increase of exercise capacity in supervised LT recipients**.** Notably, we noticed that supervised training was highly beneficial for upper limb muscle strength, which significantly improved in trained group whereas decreased in controls. This could be explained with the fact that, even if LT recipients are generally advised to walk and to return to a normal lifestyle after surgery [10], they usually are not able to adequately strengthen their upper limbs.

An increase in BMI is common after LT especially in the post-operative months, due to lack of physical exercise and immunosuppressant medications [12, 25]. We confirmed this trend in our cohort of stable LT recipients, even if we did not notice an increase in % fat mass over time. This could be explained by the fact that time from LT was longer and baseline BMI was higher than in other studies. An optimal post-transplant intervention would probably require a multidisciplinary approach, including nutritional counseling, immunosuppression minimization when available, exercise and behavioral interventions [9].

It is well known that metabolic complications occur soon after LT, being associated with cardiovascular diseases [5, 26]. Metabolic abnormalities can be prevented or reversed by regular physical exercise. The beneficial role of physical exercise on glucose metabolism is well known among general population [27], and once again confirmed in our cohort of LT recipients, where fasting glucose gradually decreased in exercise group whereas increased in controls. Nevertheless, lipid profile showed no significant improvement over time in both cohorts, pointing out that other factors (as diet, immunosuppressant regimens) should be adequately managed.

Lastly, we confirmed the beneficial association between physical exercise and HRQoL, especially for physical condition, general health and vitality domains. This would suggest that LT recipients benefit from strength and endurance training under professional supervision, also in terms of motivation, self-perception, social inclusion, in everyday life [15, 28].

This study has some limitations that need to be acknowledged. First, absence of randomization; patients were grouped because of logistic grounds (e.g., distance from a gym), however cohorts were comparable in terms of age, gender, and liver function at enrolment. Second, the small sample size could give a picture which is partly representative of the whole LT population.

Despite these limitations, this study showed that a supervised combined aerobic and strength training in stable LT recipients can be a useful and safe non-pharmacological tool, improving physiological variables related to patients' physical conditions, glucose metabolism, and quality of life, without impairment on liver and kidney function.

Further studies with a longer follow-up, larger population, and different types of training are needed to clarify better strategies to improve adherence to training programs and keep costs manageable so that exercise programs can be included as a standard treatment for LT recipients.

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Chapter 4

The promotion of pre and post-transplant physical exercise in Emilia-Romagna region: the network of the program "transplantation, physical activity and sport"

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ABSTRACT

Introduction

Following the positive experience of the national project "A transplant...and now it's time for Sport", the Transplant Reference Center of the Emilia-Romagna Region has pursued the promotion of pre- and post-transplant physical exercise by developing a network.

Methods

The path involved the Transplant Centers and Operative Units (UU.OO) who wanted to target transplant and waiting list patients, clinically stable, to perform personalized exercise through a program (supervised or not) prescribed by a specialist in sports medicine.

With the collaboration of the Collective Prevention and Public Health Service the network was established, consisting of the Sports Medicine Centers and the Gyms that promote health (PS-AMA). To implement the network, training courses for all the professionals involved (doctors, nurses, exercise specialists) and operational meetings in the Transplant Centers-Nephrology Units with Patients' Associations have been organized.

Results

To date there are 14 transplant centers and UU.OO, 9 sports medicine centers and 45 PS-AMA involved in this network. Seven training courses were organized with the participation of 193 health professionals. From January 2016, there have been 65 transplanted patients and 5 patients on waiting list who practiced prescribed exercise. Of these, 45 carried out supervised exercise in PS-AMA, whereas 25 performed autonomous exercise. Each patient is monitored every 6 months. No problems related to the exercise performance were recorded.

Conclusions

The development of a network of professionals and associations is the key element to raise awareness on physical activity among transplanted and waiting for transplant patients, reducing the pathologies associated with a sedentary lifestyle.

INTRODUCTION

The World Health Organization (WHO) identified physical inactivity as the fourth leading risk factor for global mortality. Physical inactivity levels are increasing in many countries with major implications for the prevalence of non-communicable diseases (NCDs) and the general health of the population worldwide.

The Global Recommendations on Physical Activity for Health (at least 150 minutes of moderate-intensity aerobic physical activity throughout the week) are primary prevention of NCDs [(1)].

Transplant recipients are at higher risk of developing metabolic complications, bone loss and sarcopenia, which are associated with cardiovascular diseases (CVD) [(2, 3)]. Long-term immunosuppression, but also a sedentary lifestyle, often associated with a gradual weight gain, weakness and fatigue represent modifiable risk factors [(4-6)]. Even if exercise capacity and muscle strength improve after transplant, they remain significantly lower than those in age and sex-matched people without solid organ transplant [(7, 8)].

Physical exercise in the pre-transplant period is correlated to better physical function and improved outcomes, including both reduced all-cause and cardiovascular mortality risk, and graft survival in transplant recipients [(9-11)].

The beneficial role of physical activity has been demonstrated also on health related quality of life (HRQoL) in transplant patients [(12)].

In the transplant world, both in the pre- and post-transplant, there are also psychological and logistic barriers that limit access to physical activity programs [(13-15)].

In addition, the limited existence of guidelines on physical activity for pre- and post- transplant patients highlight the need for the development of a Regional network encouraging the transplanted population and waiting list patients to an active lifestyle for the prevention of NCDs [(1)].

Thanks to the positive results of the national study protocol "A Transplant…and Now it's time for Sport" which demonstrated the beneficial effects of prescribed and supervised physical exercise in transplant recipients by creating a collaborative network between Transplant Centers, Sports Medicine Centers and Gyms [(12, 16, 17)]; the Transplants Reference Center of the Emilia-Romagna Region (CRT-ER) has implemented the local network, creating an *ad hoc* program to promote the exercise both in the pre and post-transplant called "Transplantation, Physical Activity And Sport".

METHODS

The local network is based on a model of cooperation between Regional Transplant Centers- Operative Units, Sport Medicine Centers, and accredited Gyms that promote health for adapted physical activity (PS-AMA) together with Patients' Associations that promote the regional program.

(a) Transplant physicians select clinically stable transplanted and waiting list patients. (b) Sport physicians perform functional tests (aerobic capacity and muscle strength), and prescribe a personalized exercise program. HRQoL is also recorded. Each patient can decide to do the exercise program indoor (in PS-AMA with supervision) or outdoor (with app support, without supervision). (c) Exercise Specialists working in the PS-AMA (graduates and postgraduates in physical education) support the prescribed exercise by supervising the activity. All patients are monitored every 6 months at sports medicine centers. Regular clinical follow-up continues at the Transplant Centers-UU.OO as routine (Figure 1).

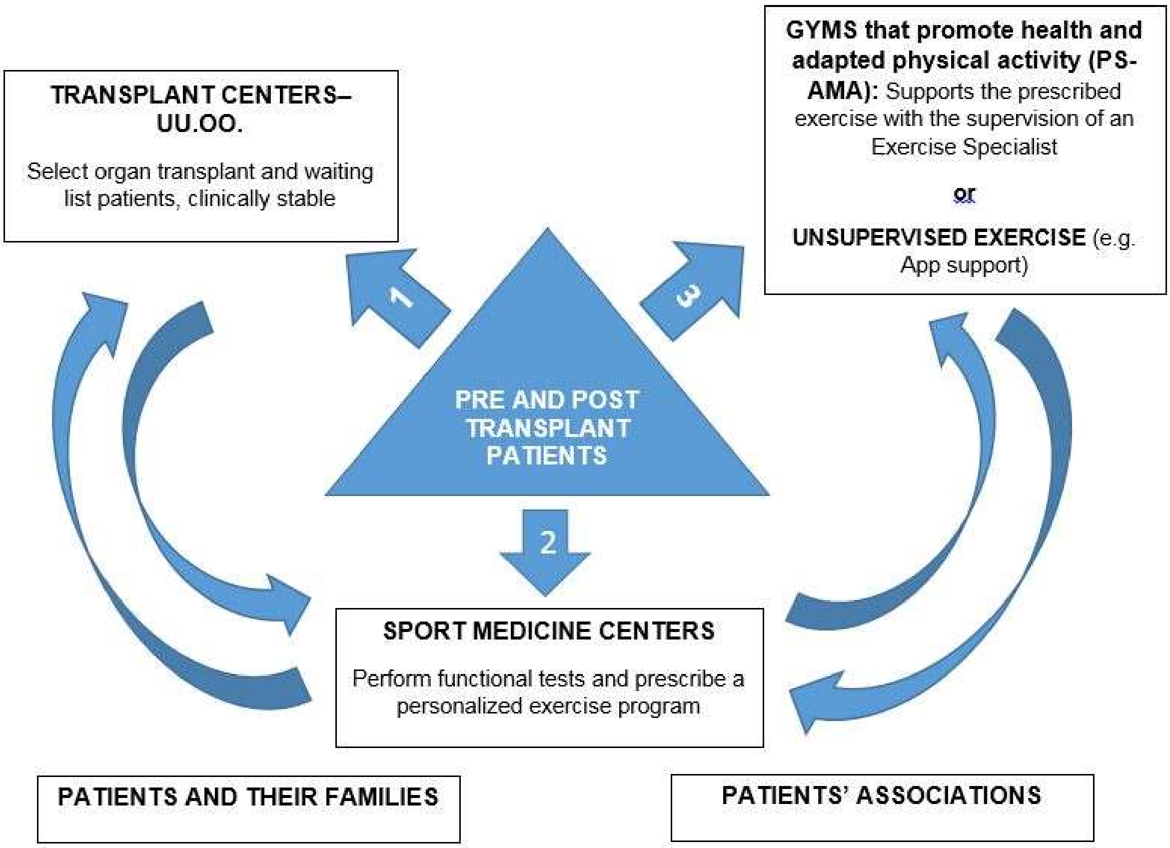

Figure 1: the network of the program "Transplantation, Physical Activity and Sport" for the promotion of pre and post transplantation exercise in Emilia-Romagna Region.

This network aims to check the patients from the clinical (transplant center) and functional (sports medicine units) point of view, but also to identify facilities in their home districts where patients can easily perform their training programs.

The collaboration with the Public Prevention and Collective Health Service of the Emilia-Romagna Region was of pivotal importance. The Resolution of the Regional Council (DGR) 2127 of 5 December 2016, has promoted the development of exercise programs for transplant and waiting list patients; has accredited PS-AMA throughout the regional territory; established that the exercise is made on prescription (thus enabling patients in the pre- and post-transplant to be exempt from paying a ticket for specialist visits at sports medicine centers). To implement the network and the accession of all the personnel involved in this network (doctors, nurses, exercise specialists) a number of training courses and direct meetings with the Transplant Centers-UU.OO and Patients' Associations have been organized in all the Provinces of the Region.

In addition, a devoted information campaign was organized in collaboration with the Emilia-Romagna Region through the distribution of leaflets describing the program, including the program in the CRT-ER service card and presenting it at national and international conferences.

RESULTS

To date there are 11 transplant centers-UU.OO, 9 sports medicine centers and 45 PS-AMA involved in this network. Seven training courses were organized with the participation of 193 health professionals (24 nephrologists, 9 hepatologists, 30 sports physicians, 45 nurses, 85 exercise specialists). At least 3 health operators for each transplant center-UU.OO were involved. In particular, to motivate patients and increase adherence in the program, nursing staff have been involved in collaboration with the medical team in monitoring the transplant and waiting list patients. From January 2016 to December 2018, there were 65 transplanted patients (46 renal, 14 liver and 5 lung transplantations) and 5 patients on the waiting list (for renal transplantation) who did prescribed physical activity (Table 1).

TRANSPLANT CENTERS- UU.OO.	IN WAITING LIST FOR RENAL TRANSPLANTATION	RENAL TRANSPLANTATION	LIVER TRANSPLANTION	LUNG TRANSPLANTION
BOLOGNA	0	5	13	1
FERRARA	0	8	0	0
MODENA	2	2	0	0
FORLI'- CESENA	3	31	1	4
TOTAL	**5**	**46**	**14**	**5**

Table 1: patient enrollment on the Regional Program from January 2016 to December 2018. Thirty-three and 10 patients have reached 6 and 12 months of observation, respectively.

Of these, 45 carried out supervised physical exercise in accredited PS-AMA, 25 performed autonomous exercise. Each patient was monitored every 6 months. The number of patients included in the path is increasing. At this moment 33 and 10 patients have reached 6 and 12 months of observation, respectively. Preliminary data showed a satisfying adherence to prescribed exercises and improved perceived HRQoL. No particular problems related to physical activity have been recorded.

DISCUSSION

The development of a network of professionals (physicians, nurses, exercise specialists) together with Patients' Associations has resulted to be the key element for motivating transplant and waiting list patients to be physically active by encouraging them to an active life and reducing the risk of developing pathologies associated with a sedentary lifestyle.

The creation of a multi-professional network promotes cultural growth related to the importance of physical exercise in populations with chronic diseases and increased risk of cardiovascular disease. The identification of paths and places where physical exercise can be practiced helps the overcoming of both the psychological and logistic barriers faced by the patients and their families.

The possibility to access to an unsupervised exercise programs also enlarges the potential number of participants and allows the resolution of the problems of economic sustainability related to the practice of exercise programs in the gyms. Furthermore, overweight or dysmetabolic organ donor candidates could be included in physical activity programs, as a therapeutic tool.

The Italian National Transplant Center aims to extend this network to all Italian regions. The regional and national prevention plans will be able to support the implementation of the physical activity prescription programs for patients with chronic conditions in which pre- and post-transplant patients are included.

The promotion of pre and post-transplant physical exercise, in order to be effective, should be encouraged by physicians and nurses from the Transplant Centers-UU.OO who routinely see the patients during follow-ups and which have a great influence on their decisions in terms of changes of lifestyle, exercising and following a healthy diet.

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Chapter 5

Longitudinal analysis of cardiovascular risk factors in active and sedentary kidney transplant recipients

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ABSTRACT

Background

Despite the beneficial effects of physical activity on cardiovascular risk factors in Kidney Transplant Recipients (KTRs), the long-term effects of exercise are rather unexplored in this population, so we performed a multi-year observational study comparing renal function and cardiovascular risk factors of Active KTRs (AKTRs) and Sedentary KTRs (SKTRs).

Methods

Complete blood count, blood chemistry, blood pressure, and anthropometric measures from 30 AKTRs and 24 SKTRs were collected yearly for an observation period of three years.

Results

Significant differences were found in Body Mass Index (BMI; P=0.043) between groups at baseline with lower values in AKTRs. Significant interactions were found: a) for BMI (p=0.006) where AKTRs decreased and SKTRs increased over time; b) for creatinine (p=0.006) and eGFR (p=0.050) where AKTRs showed stable renal function while SKTRs exhibited a decline; c) for proteinuria (p=0.015), glucose levels (p=0.004) and uric acid (p=0.013) where AKTRs decreased and SKTRs increased over time; d) for triglycerides (p=0.014), with a decrease in AKTRs and a clinically relevant increase in SKTRs over time.

Conclusions

Our findings indicate that regular weekly exercise training may counteract the increased cardiovascular risks and may also maintain graft function in KTR.

INTRODUCTION

Kidney transplantation is a preferred life-saving treatment for people with end stage renal failure. Nevertheless, the incidence and prevalence of cardiovascular disease (CVD) are four to six times higher in kidney transplant recipients (KTRs) than in the general population [(1, 2)]. Sustaining or improving quality of life and physical functioning as well as reducing morbidity from CVD are primary goals currently being addressed [(3)]. In KTRs, 38% of all deaths are linked to a CVD, often despite a functioning graft [(4, 5)]. High risk of CVD in KTRs is partly based on the high prevalence of modifiable CVD risk factors, such as diabetes, dyslipidemia and hypertension [(6)]. However, other factors may also be involved, particularly those that influence systemic inflammation, including graft rejection, infection and use of immunosuppressive medications [(7)].

Creatinine and estimated glomerular filtration rate (eGFR) are important markers of renal function [(8)] and are considered independent predictors of mortality [(9)]. An eGFR below 60 mL per minute per 1.73 m^2 is considered a risk factor for both new and recurrent CVD in the general population and in people at increased risk for cardiovascular events [(10, 11)]. Percentage change in eGFR between the first and third year post-transplant is significantly predictive of patient survival and a decline in eGFR of ≥30% is associated with a 2.2-fold increase in death compared with in those with stable eGFR [(12)].

Systolic (SBP) and Diastolic Blood Pressure (DBP) are associated with heart failure and CVD in KTRs. It is worth noting that increased Blood Pressure (BP) and reduced renal function are independent predictors of cardiovascular risk and end-organ damage [(13)]. Prospective studies in a variety of populations have convincingly demonstrated a substantial excess rate of development of CVD in proportion to the degree of elevation in BP [(14)].

Emerging research also demonstrates that sedentary behaviour and low level of physical activity in KTRs are predictive of CVD and premature mortality [(15)]. Physical activity is associated with improved graft function [(16)], reduction in the risk of CVD [(17)], metabolic disease and diabetes [(18)], and aids weight gain reduction following successful kidney transplantation [(19)]. However, only 28.5% of nephrologists prescribe exercise for their patients and only 4.3% inform patients about benefits of exercise [(20)]. While some patients avoid a sedentary lifestyle due to physical constraints, others do not perform physical exercise due to lack of motivation or support and feelings of helplessness [21, 22]. Conversely, there are KTRs who practice regular physical activity and even take part in sport competitions without negative effects [23, 24, 25].

In a recent review by Takahashi et al. it has emerged that the potential beneficial effects of physical activity on renal function and cardiovascular risk factors in KTRs has been investigated up to a time frame of 12 months [26]. Despite that, long-term effects of exercise are still largely unexplored in this population.

The purpose of this study was therefore to perform a multi-year observation of renal function and cardiovascular risk factors in active KTRs compared to sedentary KTRs. In particular, the aim of this study was to describe if regular active lifestyle may have beneficial effects on reducing some cardiovascular risk factors over a three-year period.

METHODS

This is an observational cohort study that considered the enrolment of clinically and functionally stable Active (AKTRs) and Sedentary (SKTRs) kidney transplant recipients. Complete blood count, blood chemistry tests, blood pressure, and anthropometric measures (weight and height) from 30 AKTRs and 24 SKTRs were collected during an observation period of three years with a 12±1months interval between each observation. Participants were enrolled from two clinically distinct populations. Between January 2013 and November 2016 AKTR were recruited from the Italian national association of kidney transplanted sportsmen (i.e. ANED Sport Associazione Nazionale Emodializzati, Dialisi e Trapianto), which every year organizes the national transplant games in partnership with the World Transplant Games Federation (WTGF). SKTRs were recruited from the Nephrology and Dialysis Department of the Sant'Orsola-Malpighi University Hospital, Bologna, Italy, during routine care management visits. Patients in both groups were selected according to the eligibility criteria consisting in age range of 45-51 years, between 6-8 years after organ transplantation, completed 20-30 months of dialysis before transplantation, non-smoking patients without recent episode (at least 3 months) of rejection and treatment. Exclusion criteria were clinical instability, orthopaedic limitations, psychiatric or neurological disorders and proteinuria within the nephrotic range. SKTRs were defined as patients with low level of physical activity (weekly physical activity <150 minutes); AKTRs were defined as patients with a level of weekly physical activity ≥150 minutes as recommended by the American College of Sport Medicine and the World Health Organization to promote and maintain health for adults [27, 28]. In both groups, physical activity levels were self-reported during standardized interviews.

All study procedures have been reviewed by the Ethics Committee of the Polyclinic Sant'Orsola-Malpighi University Hospital, Bologna, Italy and have therefore been performed in accordance with the ethical standards laid down in an appropriate version of the 2000 Declaration of Helsinki as well as the Declaration of Istanbul 2008. All participants gave their informed consent prior to their inclusion in the study.

Complete blood count and the blood chemistry tests

Blood samples were taken in both groups under clinically stable conditions (i.e., not recent fever episodes), and in AKTR at least 24 hours after exercise.

The following laboratory tests (ADVIA 2120, Haematology System, Siemens, Erlangen, Germany) were evaluated on all KTRs yearly: creatinine (mg/dL) measured using the Jaffè method [29, 30], estimated glomerular filtration rate (eGFR) assessed using the modified diet in renal disease (MDRD) formula: GFR ($mL/min/1.73\ m^2$) = $186 \times (S_{cr}/88.4)^{-1.154} \times (\text{age})^{-0.203} \times (0.742$ if female) (IDMS method, mass spectrometry isotope dilution calibrated) [31]; proteinuria assessed using urine protein electrophoresis; triglycerides, High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL) and total cholesterol were measured using flow cytometry and light-scattering methods to evaluate lipid metabolism, glucose levels were recorded using standard fasting blood glucose. Blood sampling was done in a seated position and fasting state (at least 10-12 hours fasting).

Body mass index

Body weight was recorded, and height was measured using a calibrated stadiometer. Body Mass Index (BMI) was calculated using the ratio between weight and height (kg/m^2) across a three-year period in both groups.

Blood pressure

SBP and DBP were repeatedly collected across the study period in both groups using a manual sphygmomanometer (HEINE GAMMA® G7, Germany). For recording accurate measurements of BP we used standard procedures in according with the AHA guidelines [32]. The patients were asked to avoid caffeine, exercise and smoking for at least 30 minutes before measurement. Every patient sat quietly for 5 minutes before a measurement was taken, the limb used to measure BP was supported, the BP cuff was at heart level using the correct cuff size and deflating the cuff slowly. To minimize error and provide more accurate estimation of BP an average of 2 to 3 BP measurements were recorded. The average Mean Arterial Pressure (MAP) ([(SBP - DBP)/3] + DBP) and Pulse Pressure (PP) were calculated.

Active vs sedentary behaviour

Active and sedentary behaviours were recorded through a standard interview where patients reported the type of exercise (walking, running, swimming, etc.) and the amount of physical activity expressed in number of sessions per week and the total time per session (training volume).

Statistical methods

All descriptive data are presented as the mean ± standard deviation. Baseline comparisons between active and sedentary groups were performed using Student's *t*-test or Chi-squared test. Repeated measures analyses of covariance (ANCOVAs) with one within subject factor (time) and one between subject factors (group), and age as covariate were used. This analysis allows for testing of the main effects of group and main effect of time, as well as the interaction of group by time. It is this interaction that indicates whether the change over time is determined by group (active vs sedentary). Bonferroni corrected post-hoc tests were used to assess significant main or interaction effects. Statistical significance was set at $p<0.05$. The statistical analysis was performed using SPSS, Version 20 (IBM, SPSS Inc, Chicago).

RESULTS

The baseline characteristics and non-modifiable risk factors (prior dialysis, time from transplantation, family history of CVD) of the two groups are presented in Table 1. Considering the modifiable risk factors, fifteen AKTRs and seventeen SKTRs respectively were hypertensive, all treated with beta-blockers. At baseline, a higher BMI was observed in SKTRs compared to AKTRs (p=0.043). None of the participants in either group had diabetes, dyslipidemia, respiratory disease or peripheral vascular disease. No major cardiovascular events occurred before and after transplantation. All KTRs were on regular immunosuppressive therapy. Immunosuppressive drug treatment consisted of corticosteroids in all KTRs, cyclosporine and azathioprine in thirty subjects (eighteen from AKTRs, twelve from SKTRs) and tacrolimus and mycophenolate mofetil in twenty-four KTRs (thirteen from AKTRs, eleven from SKTRs).

GROUPS	**Active Kidney Transplant Recipients N=30**	**Sedentary Kidney Transplant Recipients N=24**
Race	30 Caucasian	24 Caucasian
Sex	4 F_26 M	6 F _18 M
Age (years)	45±12	51±14
Dialysis Vintage (months)	28.7±21.2	21.0±14.0
Time Post-Transplant (years)	6.8±5.7	6.9±6.2
Family history of CVD	5 M	5 M_1 F
Original kidney disease		
Glomerulonephritis	10	7
Polycystic kidney disease	8	9
End-stage kidney disease	10	6
IgA nephropathy	2	1
Nephrotic syndrome	0	1

Table 1. The baseline characteristics (mean ± SD) of the two groups.

Table 2 shows the BMI, urine parameters, blood parameters, blood pressure data and physical activity levels collected over the study period.

A significant time x group interaction was found for BMI (p=0.006), with AKTRs decreasing and SKTRs increasing over time. There was a significant time x group interaction for creatinine (p=0.006). Indeed, AKTRs showed stable renal function while SKTRs showed reductions in renal function indicated by increases in creatinine over time. A similar interaction was observed for eGFR (p=0.050) where AKTRs showed an increase and SKTRs showed a decline. Furthermore, a significant interaction was found for proteinuria (p=0.015) and uric acid (p=0.013), with AKTRs showing a decrease and SKTRs an increase over time.

A significant time x group interaction was found for glucose levels (p=0.004), with AKTRs decreasing and SKTRs increasing fasting blood glucose. Furthermore, a significant group x time interaction was found for triglycerides (p=0.014), with a decrease in AKTRs and a clinically relevant increase in SKTRs over time that exceeded the normal reference values. No significant between-group differences or interactions were observed for total cholesterol, HDL, LDL, SBP, DBP, MAP and PP.

	Active Kidney Transplant Recipients N=30			**Sedentary Kidney Transplant Recipients N=24**		
	T1	**T2**	**T3**	**T1**	**T2**	**T3**
BMI (kg/m²)	23.8±2.7*	23.8±2.6	23.7±2.8§	25.6±3.9*	25.8±4.3	26.1±4.1§
CREATININE(mg/dL)	1.4±0.5	1.4±0.5	1.3±0.4§	1.4±0.5	1.5±0.5	1.5±0.6§
PROTEINURIA (mg/24h)	184±92	164±85	146±82§	235±124	236±104	252±124§
eGFR (mL/min/1.73mq)	60.3±17.6	60.8±16.9	63.0±17.1§	58.4±19.3	57.7±19.1	56.6±19.1§
URIC ACID (mg/dL)	6.6±1.3	6.3±1.5	6.3±1.3§	6.1±1.3	6.1±1.4	6.4±1.2§
GLUCOSE (mg/dL)	91±11	84±8	83±9§	95±9	93±9	95±10§
TRIGLYCERIDES (mg/dL)	125±88	127±60	107±44§	158±62	169±65	183±76§
CHOLESTEROL (mg/dL)	186±37	214±43	192±28	233±41	234±44	228±47
HDL (mg/dL)	60±15	58±15	57±14	61±9	59±8	60±7
LDL (mg/dL)	102±24	104±31	92±18	110±25	111±25	111±22
SBP (mmHg)	128±15	125±11	125±10	135±11	136±13	135±11
DBP (mmHg)	79±9	79±9	77±8	83±7	83±5	84±6
MAP (mmHg)	92±21	91±20	90±20	100±8	101±7	101±7
PP (mmHg)	47±13	44±12	46±11	59±17	60±18	58±18
Physical activity level (minutes/week)	391±241*	394±220	392±221	57±38*	55±34	55±31

Table 2: BMI, renal function, lipid profile, blood pressure and physical activity levels as mean±SD at three years of observation (T1, T2, T3) in the two groups. * $P<0.05$ between groups at T1; § $P<0.05$ time x group interaction between groups.

DISCUSSION

The main finding of this study was that selected KTRs who practice regular physical activity show stable renal function over a three-year period, with all examined parameters remaining within normal reference values. Conversely, KTRs who had a sedentary lifestyle increased creatinine levels and proteinuria over time exceeding normal reference values across the observation period with a worsening of renal function and a consequent decrease in eGFR (Table 2).

Additionally, we found that glucose levels and triglycerides decreased in active KTRs across the study period but increased in sedentary KTRs across the same time. These findings support the current literature showing the positive effect of physical activity on maintaining regular glucose levels and reducing triglycerides both in the general population and in people at increased risk for cardiovascular events as KTRs [33, 34]. Furthermore, it was demonstrated that in KTRs physical activity is protective against cardiovascular risk factors as diabetes, hypertension and metabolic syndrome in KTRs [35]. Our data are in agreement with these previous findings and showed that cardiovascular risk factors are associated with physical activity and may worsen in sedentary KTRs in the long term. Regarding BMI, KTRs who practice regular physical activity exhibited significantly lower BMI over time compared with sedentary KTRs, who exhibited increased BMI over the three-year time period. This result supports the findings of Ejerblad et al., that maintaining a healthy weight is protective for the renal function and reduces the risk of cardiovascular disease [36].

In a prospective study of 4,011 adults performed by Robinson Cohen et al., both energy expenditure in leisure-time physical activity and exercise intensity were found to be inversely associated with rapid kidney function decline (loss > 3.0 mL/min/1.73 m^2 per year in eGFR), indicating that even vigorous-intensity activities may be protective for patients with CKD and after transplantation [37]. Our data are in support of these findings, but also indicate that not being physically active actually increases deterioration of kidney function. In our study, the physical activity level was recorded in both groups once a year during the three-years study period, indicating that AKTRs who maintained a high levels of physical activity reflected beneficial effects on renal function and metabolic profile compared to SKTRs who remained sedentary over the three years period of time, showing a decline of renal function (Table 2). This study has some limitations. Firstly, we recruited a rather small sample size and the participant cohorts were enrolled from two distinct population groups. Furthermore, the sedentary group was older (± 6 years). This was probably due to the fact that young patients usually have a more active lifestyle than older patients, so it has not been possible to recruit a sufficient number of young sedentary KTRs, although a difference of 5-10 years can be considered not clinically relevant in our patient groups. There was also a potential interviewer bias to estimate individual physical activity due to the absence of a specific questionnaire to assess the level of weekly physical activity (self-reported interviews only). About the selection process, the eligibility criteria were very strict for age and years post transplantation considering that the most representative transplant population are 45-51 years-old, with time from transplant of 6-8 years, in which the incidence of cardiovascular diseases increases. Furthermore, KTRs included in our observational study were carefully selected in relation to the inclusion and exclusion criteria and were thus not representative of the entire KTRs population.

Despite these limitations, our study is the first to show longer term (three years) effects of regular physical activity on renal function, lipid profile and blood pressure compared to sedentary behaviours in KTRs. Our findings support the concept that in KTRs regular weekly training may counteract cardiovascular risks typically experienced in this patient population, may promote health, and may support maintenance of renal function in KTRs.

Future studies should investigate the economic impact of practicing regular physical activity and the potential cost savings of physical activity in solid organ transplanted patients. Further studies should also be aimed to understand if AKTRs experience less long-term CVD and fewer hospital readmissions compared to their sedentary counterparts.

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Sport in solid organ transplant recipients

Chapter 6

Effects of combined strength and endurance training on exercise performance in kidney transplant cyclists and runners

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ABSTRACT

This case series describes the effects of combined strength and endurance training on selected performance parameters in competitive kidney transplant recipient cyclists (CKTRs) and runners (RKTRs).

Eight CKTRs and four RKTRs completed a 6-month training period. The workload at aerobic and anaerobic thresholds, the energy cost (EC) of cycling or running and the peak instantaneous power (PIP) were assessed at baseline (T_0) and after 6 months (T_6). Exercise training adherence, renal function and lipid profile were also recorded.

At T_6, the workloads at aerobic and anaerobic thresholds were overall improved in both CKTRs (11.5 to 17.5 W) and RKTRs (0.03 to 0.53 km/h). EC was also improved in both groups (-0.21 mL/min/kg), PIP improved on average by 90 N. Cholesterol and triglycerides slightly decreased, with average changes of -17.5 and -4.7mg/dL, respectively.

These findings showed that combined training is well tolerated and may improve sport performance in kidney transplant cyclists and runners.

INTRODUCTION

Kidney transplantation is the standard treatment for end-stage renal disease and can offer a new independence from the disease process. After transplantation, engaging in regular physical activity is recommended for improving health [(1)]. Furthermore, participation to recreative and competitive sports activities is increasingly common among kidney transplant recipients (KTRs). Totti et al. showed that transplant recipients practicing football are able to attain energy expenditure levels and quality of life similar to healthy controls [(2)]. Moreover, it was shown that well-trained KTRs can safely participate to a long-distance road cycling race without acute signs of kidney damage and can benefit from physical activity, even at a competitive level [(2-4)].

The increasing interest on the benefits of physical activity in transplant recipients has led to a number of studies showing the effects of different exercise training programs on health and exercise capacity in this population [(5)]. Nevertheless, most studies focused on sedentary or moderately active transplant recipients, while still little is known on how training affects the physical performance in transplanted competitive athletes.

Conditioning programs including a combination of strength and endurance training are known to impact performance-related parameters such as running or cycling economy and the power output associated to the maximum oxygen uptake in healthy competitive cyclists and runners [(6)]. While this kind of training may be used also by competitive KTRs, some aspects specific of that population might lead to a sub-optimal training stimulus and adaptation. Indeed, reduced muscle mass and strength are common conditions during dialysis and muscle wasting is major clinical problem due to the dialysis [(7)]. As a consequence, perceived muscular fatigue may be increased with possible inability to maintain a given force or power output [(8)]. Furthermore, immunosuppressive therapy as cyclosporine reduces oxidative activity and capillarity of some muscles, possibly contributing to reduce exercise tolerance [(9)]. The long-term systematic combination of immunosuppressive drug and glucocorticoid therapy may also induce muscle atrophy and bone loss [(10)].

To investigate the impact of combined strength and endurance training in competitive KTRs athletes, the purpose of the present case series study was to assess the effects of a tailored training program on a selection of performance parameters on kidney transplant cyclists and runners.

CASES REPORT

Participants

CKTRs and RKTRs were recruited from a national association who organize sport events for transplant recipients (ANED Sport – Associazione Nazionale Emodializzati, Dialisi e Trapianto). The following inclusion criteria were used: age 18-60 years, at least 6 months after organ transplantation and regularly trained. Exclusion criteria were orthopaedic limitations, psychiatric or neurological disorders, proteinuria within nephrotic range, sedentary lifestyle and any cardiovascular contraindication to exercise testing and training. Twelve KTRs [8 male cyclists (CKTRs), 4 male runners (RKTRs)] provided informed consent before inclusion according to the procedures approved by the local Ethics Committee and following all the guidelines for experimental investigation required by the institutions. The study conformed to the policy statement with respect of Declaration of Helsinki. Subjects were informed about the nature of the research and the assurances of anonymity.

Outcome Measures

Information on medical illness, pathologies leading to renal disease, dialysis vintage and medications were collected using structured questionnaires.

Renal function and lipid profile were recorded from the last medical visit from each participant.

Fat mass percentage (FM%) was determined by the Jackson & Pollock equation using seven skinfolds (abdominal, thigh, triceps, bicep, subscapular, suprailiac, chest).

In relation to the practiced sport, an incremental cycling or treadmill exercise protocol were used to determine the aerobic and anaerobic thresholds. For cyclists, the cycling exercise protocol started with a workload of 25-50 W increased by 50 W every 3 minutes, while, for runners, the treadmill exercise protocol started with a speed of 10-12 km/h and was increased by 1 km/h every 4 minutes. At every stage, a capillary blood sample from the earlobe was taken to measure blood lactate concentration (YSI Model 1500 Sport Lactate Analyzer; Yellow Springs Instrument Co, Yellow Springs, Ohio, USA) to estimate the workload associated to the aerobic and anaerobic thresholds, corresponding to 2 and 4 mM of lactate, respectively. The test was ended when lactate was > 4mM. The perceived fatigue of the lower limbs was recorded at each step using 0-10 visual analogue scale. The oxygen consumption (VO_2) was measured in the first stage of the test to determine the energy cost of cycling/running using an open-circuit spirometry system (Sensor Medics Corp., Anaheim, CA, USA), which was calibrated before each test. Respiratory gases were analysed for volume and fractions of oxygen and carbon dioxide, and the steady state VO_2 expressed in terms relative to body mass (mLO_2/kg/min) averaged over the final 2 minutes of the stage, was used to calculate the EC. Finally, a countermovement jumps (CMJ) were performed on a dual-force platform system (Kistler Instruments Ltd., Farnborough, United Kingdom). The peak instantaneous power (PIP) of the lower limbs during the jump was considered as the outcome measure. Training volume was recorded by direct interviews before the tests. Adherence to the exercise program and eventual adverse events were also recorded.

Training Intervention

After testing, a tailored exercise training was given to each participant. Each training program included 3 sessions/week of aerobic exercise (cycling or running) and 2 sessions/week of strength exercises that included isometric squats (4 series per 10 seconds), lunges (3 series of 10 repetitions) and plantar flexors (3 series of 10 repetitions). Warm-up, cool-down and stretching exercises were included in each training sessions. All KTRs were contacted after 3 months by phone to assess progress and adherence to the program. The same testing protocol was repeated after 6 months.

RESULTS

The demographic and clinic characteristics of the participants are shown in Table 1. All KTRs were assuming regular immunosuppressive therapy. The exercise program adherence, defined as compliance in executing the assigned exercise program (total number of session n=72) during the 6-

month period was met by 7 out of 8 CKTRs and 3 out of 4 RKTRs. The training volume showed increases of +479 minutes/week in CKTRs and +344 minutes/week in RKTRs at T_6. No adverse events were reported.

No changes were observed for FM% that remained stable in both groups at T_6. The workloads associated to the aerobic and anaerobic threshold showed improvements in CKTRs by 11.5 to 17.5W and in RKTRs by 0.03 to 0.53 km/h at T_6 (Figure 1). Fatigue tolerance was slightly increased (+0.9 and +0.5 in CKTRs and RKTRs respectively). Furthermore, in both groups, a higher workload at the end of the test was observed at T_6 (on average, +21.8W in CKTRs, +0.6km/h in RKTRs).

PIP showed improvements of +82N in CKTRs and +104N in RKTRs, respectively. As expected, VO_2 showed a reduction in both groups (-0.46 and -0.23 VO_2 mL/min/kg in CKTRs and RKTRs respectively), indicating a slightly improved economy at T_6 (Figure 2).

Renal function and glucose remained stable, cholesterol and triglycerides showed a slight reduction in both groups (-17.5mg/dL and -4.7mg/dL respectively) at T_6 (Table 2).

	CKTRs								**RKTRs**			
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**1**	**2**	**3**	**4**
Dialysis vintage ***(Months)***	126	72	0	66	96	24	13	48	48	24	6	7
Age ***(Years)***	54	45	44	40	49	51	50	61	33	50	45	60
Time from transplant ***(Years)***	15	3	6	5	17	4	12	22	4	10	7	17
BMI ***(Kg/m²)***	24.7	26.5	23.1	24.1	22.4	22.3	22.4	30.5	23.7	20.6	22.6	22.7
Pathologies leading to renal disease	Glomerulonephritis	Polycystic kidney disease	Glomerulonephritis	Glomerulonephritis	Glomerulonephritis	Glomerulonephritis	Nephropathy	Polycystic kidney disease	Glomerulonephritis	Polycystic kidney disease	Glomerulonephritis	Glomerulonephritis

Table 1: Demographic and clinical characteristics, immunosuppressive therapies of cyclists (cktrs) and runners (rktrs) kidney transplant recipients.

Legend: - - - Runners ---- Cyclists

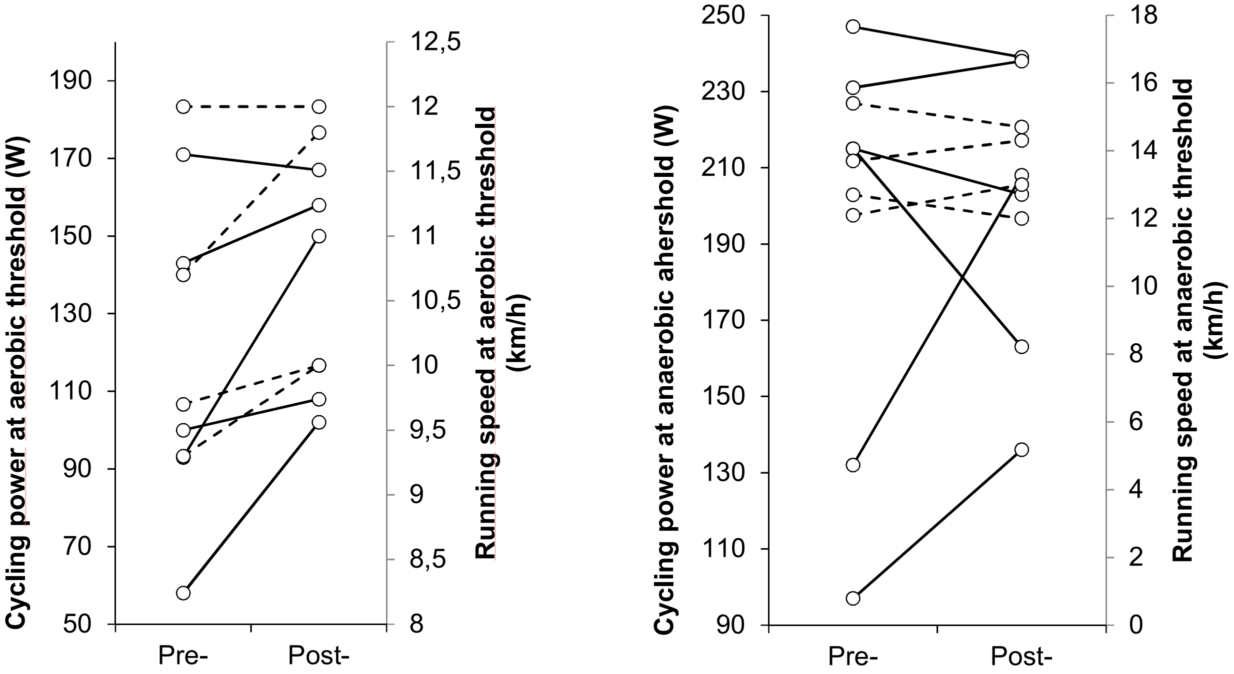

Figure 1: scatterplot of cycling power and running speed at aerobic [95% CI diff standard: 0.12 - 0.76 ($p<0.05$)] and anaerobic thresholds [95% CI diff standard: -0.25 - 0.55 (ns)] pre and post training in kidney transplant recipients cyclists and runners respectively.

Legend: - - - Runners ---- Cyclists

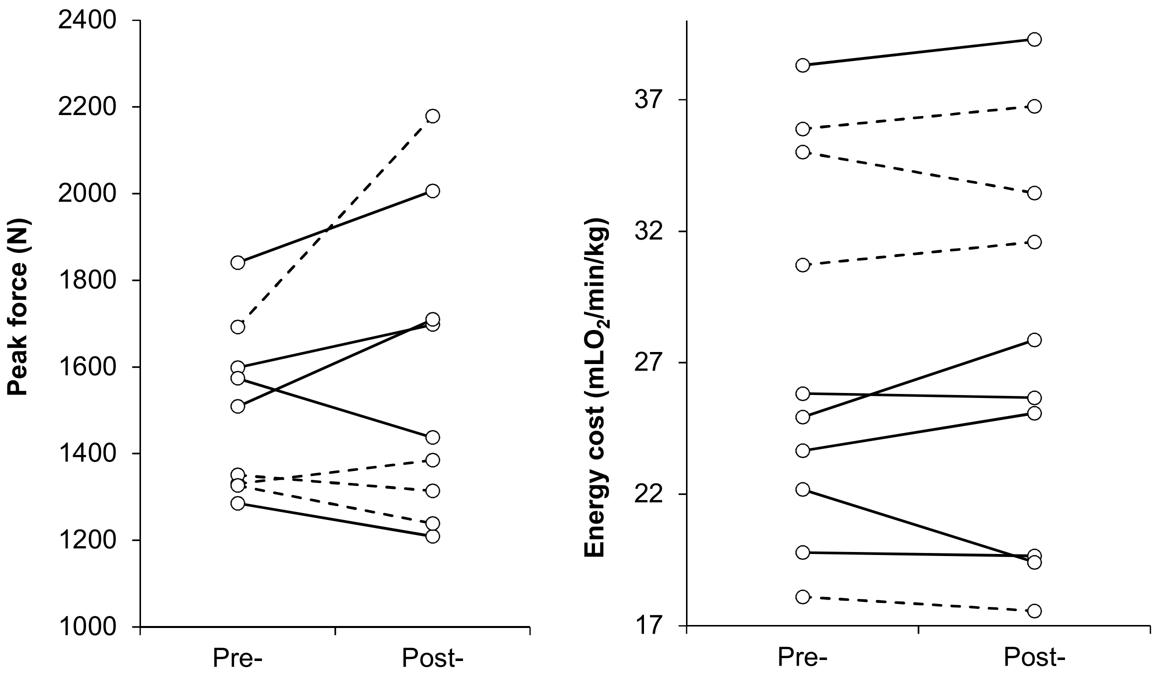

Figure 2: scatterplot of peak force (N) [95% CI diff standard: -0.27 a 1.03 (ns)] and energy cost (mLO_2/min/kg) [95% CI diff standard: -0.14 a 0.16 (ns)] in kidney transplant recipients cyclists and runners pre and post training.

		CKTRs								RKTRs			
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**1**	**2**	**3**	**4**
Fat mass *%*	T_0	11.9	17.5	8.6	20.6	11.2	15.0	8.5	23.3	18.0	7.6	21.8	11.2
	T_6	12.5	22.9	9.7	17.3	13.1	13.7	8.8	23.8	20.2	8.5	19.4	10.0
Training volume *min/week*	T_0	120	240	720	1620	540	234	552	720	240	150	180	480
	T_6	180	480	480	2880	1620	720	600	1620	240	100	270	600
Energy cost *VO2 mL/min/kg*	T_0	19.79	22.18	23.66	23.99	24.53	24.93	25.83	18.10	30.72	35.01	35.89	38.31
	T_6	19.66	19.41	25.08	22.01	22.07	27.87	25.67	17.56	31.59	33.45	36.76	39.30
S2 - Workload *Watt-km/h*	T_0	171	100	143	100	165	93	168	58	9.7	9.3	12.0	10.7
	T_6	167	108	158	136	172	150	145	102	10.0	10.0	12.0	11.8
S4 - Workload *Watt-km/h*	T_0	247	215	231	176	211	132	215	97	12.1	12.7	13.7	15.4
	T_6	239	163	238	203	226	208	203	136	13.0	12.0	14.3	14.7
Max workload *Watt-km/h*	T_0	250	250	250	200	250	200	250	125	12	13	14	15
	T_6	250	250	300	200	300	250	250	150	13	13	14.5	16
Perceived muscle fatigue	T_0	5	5	4	0	6	6	4	4	5	5	3	0
	T_6	5	5	5	0	7	7	5	7	4	5	2	0
Peak instantaneous power *N*	T_0	1598	1841	1574	1659	1504	1509	1285	-	1330	1351	1692	1326
	T_6	1698	2006	1437	1810	1759	1710	1209	-	1385	1314	2178	1239
Total Cholesterol *mg/dL*	T_0	178	220	237	261	195	211	230	217	173	174	168	171
	T_6	161	222	200	244	170	193	160	210	164	165	164	172
Triglycerides *mg/dL*	T_0	87	280	99	199	55	249	115	93	126	145	61	145
	T_6	87	282	98	157	37	250	105	90	166	122	60	144
Creatinine *mg/dL*	T_0	1.58	1.68	1.84	1.10	1.34	1.82	1.70	1.05	0.92	1.30	1.00	1.31
	T_6	1.54	1.56	1.88	1.07	1.47	1.89	1.48	1.05	0.89	1.43	1.00	1.23
eGFR *mL/min/1.73mq*	T_0	49	47	43	79	60	42	46	76	101	62	86	59
	T_6	50	51	42	81	54	40	50	76	104	55	86	64
Glucose *mg/dL*	T_0	65	85	85	114	101	100	99	91	79	84	90	79
	T_6	71	76	87	116	92	107	102	85	81	77	79	83

Table 2: fat mass, training volume, performance parameters, perceived muscle fatigue, lipid profile and renal function in cyclists (cktrs) and runners (rktrs) kidney transplant recipients at baseline (t0) and after 6 months of training (t6).

DISCUSSION

This case series showed that competitive KTRs were able to complete a 6-month training including 3 sessions/week of aerobic exercise and 2 sessions/week of strength exercises without any evident adverse effects. Moreover, the athletes showed overall improvements in the workload associated to the aerobic and anaerobic thresholds and maximum workload, with a slightly decrease of perceived muscle fatigue. Also, the PIP showed improvement at T_6 in most athletes, as a possible effect of strength exercises on the power of lower limbs in KTRs. Chan et al. showed that KTRs were mostly capable of generating muscular power similar to healthy subjects, corroborating that fatigue is not explained by deficits in the muscular and cardiovascular systems [11]. The same mechanisms were showed in elite healthy cyclists where adding strength training to endurance training can increase strength and rate of force development as appear in CKTRs [12]. In this study, the energy cost of cycling or running showed a slight improvement in both groups, consistently with the effects of combined endurance and strength training in healthy cyclists and runners [12]. Montero et al. showed that exercise programs including strength training improve the energy cost and shows a superior effect compared with endurance training alone [13]. The present findings confirm that, despite the intake of immunosuppressive therapies often associated with glucocorticoid, KTRs may improve the exercise performance by combined endurance and strength training, counteracting the side effects of the pharmacological therapies and may reduce the muscle atrophy and weakness. Furthermore, immunosuppressive therapy seems to have no inhibitory effect on the physiological factors related to the aerobic and muscular metabolism.

A limitation of this study is the absence of a specific questionnaire to assess the exercise program adherence, as we used self-reported interviews.

The outcomes of this case series demonstrate that combined endurance and strength training is overall well tolerated and may improve sport performance in cyclist and runners KTRs, with a response comparable to non-transplanted healthy competitive athletes. These findings can help design future studies to determine the optimal training load to improve performance and reduce fatigue in KTRs practicing different sports disciplines.

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Chapter 7

Other research activities

HIGH LEVEL CYCLING PERFORMANCE 11 YEARS AFTER CARDIAC TRANSPLANTATION

Grazzi G, Totti V, Myers J, et al. Int J Sports Exerc Med 2018, 4:102

ABSTRACT

Introduction: Exercise training is recommended for heart transplant recipients (HTR). However, how training late after cardiac transplantation (CTX) may influence exercise tolerance is not well defined.

Methods: The patient was diagnosed with arrhythmogenic right ventricular cardiomyopathy at 13 years of age, and underwent CTX due to progression of heart failure at 34 years. Exercise training began 3 weeks after CTX and progressively increased in volume and intensity. Eleven years after CTX he performed a maximal cardiopulmonary exercise test (CPX), followed by participation in nine one-day road cycling races over an eight-month period, representing a total of 1594 km and 30642 m altitude gain. One race was monitored using a wearable device, which recorded power output (W), and heart rate (HR).

Results: The study period was uneventful, with no evidence of arrhythmias or myocardial damage. $V'O_2$peak (47.2 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$) was 113% of age-predicted maximum. Maximal heart rate (HR, 161 bpm) and oxygen pulse (18.8 mL·bpm) were 92% and 118% of age-predicted respectively. HR, W, and relative $V'O_2$ at ventilatory threshold (VT) and the respiratory compensation point (RCP) were 128 bpm, 120 W, and 75% $V'O_2$peak, and 142 bpm, 155 W, and 86% $V'O_2$peak respectively. The W/$V'O_2$ ratio was ~80 watt·liter $V'O_2^{-1}{\cdot}min^{-1}$. The race was completed in 7 hours and 56 minutes, finishing 2841st of 4449 competitors, at an average of 141 bpm and 162 W. During the race, he remained between the VT and RCP (moderate-to-high intensity) for 4 hours and 2 minutes and spent 2 hours and 19 minutes above RCP (high-to-severe intensity).

Conclusion: Remarkable aerobic capacity and exercise tolerance are possible a decade after CTX, likely because of central and peripheral adaptations.

UPPER-BODY RESISTANCE EXERCISE REDUCES TIME TO RECOVER AFTER A HIGH-VOLUME BENCH PRESS PROTOCOL IN RESISTANCE-TRAINED MEN

Bartolomei S, Totti V, Griggio F, et al. J Strength Cond Res. 2019 Mar 4.

ABSTRACT

The aim of this study was to compare the effects of active and passive strategies on the recovery response after a high-volume bench press protocol. Twenty-five resistance-trained men (mean ± SD: age = 25.8 ± 3.6 years; body mass = 87.1 ± 12.1 kg; and height = 177.4 ± 4.9 cm) performed a high-volume bench press session (8 sets of 10 reps at 70% of 1 repetition maximum). Subsequently, they were randomly assigned to an active recovery (AR) group (n = 11) or to a passive recovery (PR) group (n = 14). Active recovery consisted of light bench press sessions performed 6 hours and 30 hours after the high-volume exercise protocol. Muscle performance (bench throw power [BTP] and isometric bench press [IBP]) and morphology (muscle thickness of pectoralis major [PECMT] and of triceps brachii [TRMT]) were measured before exercise (baseline [BL]), and at 15-minute (15P), 24-hour (24P), and 48-hour (48P) post-exercise. Post-exercise recovery of both maximal strength and power was accelerated in AR compared with PR. Both BTP and IBP were significantly ($p < 0.001$) reduced at 15P and 24P in PR, whereas changes were significant ($p < 0.001$) at 15P only in AR. PECMT was still significantly ($p = 0.015$) altered from BL at 48P in PR, whereas changes were significant ($p < 0.001$) at 15P only in AR. No significant interactions ($p > 0.05$) between PR and AR were detected for TRMT and muscle soreness. The present results indicate that AR enhances the recovery rate after high-volume exercise sessions and may be included in resistance training programs to optimize muscle adaptations.

A COMPARISON BETWEEN THE RECOVERY RESPONSES FOLLOWING AN ECCENTRICALLY LOADED BENCH PRESS PROTOCOL VS. REGULAR LOADING IN HIGHLY TRAINED MEN

Bartolomei S, Totti V, Nigro F, et al. Journal of Human Kinetics volume 68/2019, 131-140.

ABSTRACT

The purpose of this study was to compare the physiological responses of a single bout of an eccentric accentuated bench press protocol (120% of 1RM in the eccentric phase/80% in the concentric phase; [120/80]) versus a regular high-intensity exercise protocol (80%/80%; [80/80]) in resistance-trained men. Eleven men (age = 25.6 ± 3.9 y; body mass = 84.6 ± 11.2 kg; body height = 176.4 ± 3.9 cm) with 6.3 ± 3.4 y of resistance training experience performed each protocol in counterbalanced, randomized order. Isometric, isokinetic and ballistic tests were performed at the bench press (IBPF, ISOK and BTP, respectively) at baseline (BL), 15-min (15P), 24-h (24P), and 48-h (48P) post-exercise for each testing session. In addition, muscle thickness of the pectoralis major (PecMT) was measured at the same timepoints via ultrasound. Significantly greater reductions in BTP ($p < 0.001$), peak force during both ISOK ($p = 0.005$) and IBPF ($p = 0.006$) at 15P were detected in 120/80 compared to 80/80. BTP was still significantly ($p = 0.009$) impaired at 48P following the 120/80 protocol, while no differences were noted following 80/80. PecMt was significantly elevated following both 120/80 and 80/80 ($p < 0.05$) at 15P, but significant differences between the trials were present at 15P and 24P ($p = 0.005$ and $p = 0.008$, respectively). Results indicated that heavy eccentric loading during the bench press exercise caused greater performance deficits than a bout of traditionally loaded high intensity resistance exercise. Power performance appears to be more influenced by the 120/80 protocol than isometric peak force. Eccentrically loaded exercise sessions should be separated by at least 48 hours to obtain a complete recovery of the initial muscle morphology and performance.

Chapter 8

General discussion

EXERCISE IN SOLID ORGAN TRANSPLANT RECIPIENTS

The main result of this thesis is that in selected renal and liver transplant recipients, a program of 12 months of supervised combined training (aerobic and strength) performed one hour, three times per week in certified gyms does not affect the renal function, and leads to significant improvements in aerobic fitness, muscle strength and quality of life, with a trend of reducing BMI but with heterogeneous outcomes based on the type of transplant. An increase in BMI is common after transplantation especially in the post-operative months, due to lack of physical exercise and immunosuppressant medications [(1, 2)]. An optimal post-transplant intervention would probably require a multidisciplinary approach, including nutritional counseling, immunosuppression minimization when available, exercise and behavioral interventions [(3)]. Renal function data were compatible with the framework of patients of a select population undergoing successful transplantation. The proposed training protocol had no negative effects on the renal function in the medium term.

Regarding exercise capacity, in supervised groups we observed a 6-10% increase of $V'O_2$ peak after 12 months. Similar results were observed by Van der Ham et al.[(4)] in 33 KTRs after 12 weeks of combination of endurance and strength training in which $V'O_2$ peak increased of 10% (from 21.6±6.3 to 23.8±6.1 mL/kg/min). Riess et al.[(5)] reported an increase of $V'O_2$ peak (from 20±9 to 23±10 mL/kg/min) after 12 weeks of supervised endurance training (three times/week) on cycle ergometer at 60-80% of $V'O_2$ max involving 16 patients.

In a study on eight KTRs, Romano et al.[(6)] used a supervised interval training technique for 10 weeks, 40-minute sessions for three times per week. They reported an increase of 13% of $V'O_2$ peak.

Another intervention was presented by Kempeneers et al.[(7)] who trained 16 KTRs for six months in preparation for the National Transplant Games. Their mean $V'O_2$ peak rose from 29.0±7.8 to 37.5±4.8 mL/kg/min, with an increase of 27%. Data are in accordance with those reported by Beyer et al.[(8)], who showed a 3-fold increase in aerobic workload, and with those reported by Krasnoff et al.[(9)], who demonstrated a significant increase of exercise capacity in supervised liver transplant recipients.

In the other hand, Painter et al.[(10)] prescribed an individualized home-based exercise training program in 54 KTRs, consisting on 30 minutes, 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, $V'O_2$ peak increased from 24.0±7.5 to 27.8±11.0 mL/kg/min (+16%) and to 30.1±10.3 mL/kg/min (+25%) after 12 months.

We can conclude that the aerobic training in transplant recipients leads to a substantial increase in aerobic power[11].

Regarding strength, we noticed that supervised training was highly beneficial for upper limb muscle strength, which significantly improved in trained group whereas decreased in controls. This could be explained with the fact that, even if transplant recipients are generally advised to walk and to return to a normal lifestyle after surgery [12], they usually are not able to adequately strengthen their upper limbs.

It is well known that metabolic complications occur soon after transplantation, being associated with cardiovascular diseases [13,14]. Metabolic abnormalities can be prevented or reversed by regular physical exercise. The beneficial role of physical exercise on glucose metabolism is well known among the general population [15], and once again confirmed that fasting glucose gradually decreased in exercise group whereas it increased in controls in transplanted populations. Nevertheless, lipid profile showed no significant improvements over time, pointing out that other factors (as diet, immunosuppressant regimens) should be adequately managed.

Lastly, we confirmed the beneficial association between physical exercise and quality of life, especially for physical condition, general health and vitality domains. This would suggest that transplant recipients benefit from strength and endurance training under professional supervision, also in terms of motivation, self-perception, social inclusion, in everyday life [16 17].

Another important finding of this thesis was that active transplant recipients who practice regular physical activity (150 minutes/week of moderate-intensity aerobic exercise) show stable renal function over a three-year period, with all examined parameters remaining within normal reference values. Conversely, patients who had a sedentary lifestyle increased creatinine levels and proteinuria over time exceeding normal reference values across the observation period with a worsening of renal function and a consequent decrease in eGFR. Additionally, we confirmed that glucose levels and triglycerides decreased in active patients across the 3-year period but increased in sedentary patients across the same time. These findings support the current literature showing the positive effect of physical activity on maintaining regular glucose levels and reducing triglycerides both in the general population and in people at increased risk for cardiovascular events as transplant recipients [18, 19]. Our data are in agreement with these previous findings and showed that cardiovascular risk factors are associated with physical activity and may worsen in sedentary kidney transplant recipients in the long term. Regarding BMI, patients who practice regular physical activity exhibited significantly lowered BMI over time compared with sedentary people, who exhibited increased BMI over a three-year time period. This result supported the findings of Ejerblad et al. that maintaining a healthy weight is protective for the renal function and reduces the risk of cardiovascular disease [(20)].

In a prospective study of 4,011 adults performed by Robinson Cohen et al., both energy expenditure in leisure-time physical activity and exercise intensity were found to be inversely associated with rapid kidney function decline (loss > 3.0 mL/min/1.73 m^2 per year in eGFR), indicating that even vigorous-intensity activities may be protective for patients with CKD and after transplantation [(21)]. Our data are in support of these findings, but also indicate that not being physically active actually increases deterioration of kidney function. Further studies are needed to investigate the effects of different types of training (e.g. high-intensity interval training - circuit training, etc.) on physical conditions to try to prescribe different types of exercise and thus increase the motivation towards exercise.

STRATEGIES TO INCREASE THE COMPLIANCE WITH THE EXERCISE IN PRE-POST TRANPLANTATION

The proposed organizational model (Transplant Centers, Sport Medicine Centers, Certified Gyms with supervision by Exercise Specialists) led to a high exercise program adherence, with a consequent positive change in lifestyle. Patients who received only general information to promote regular physical activity at home, without a specific supervision, did not show any improvement in physical fitness outcomes, indicating a low adherence to non-supervised home-based physical activity. This demonstrated that without a direct or indirect supervision (e.g. follow up by calls or e-mails), patients tend to not carry out physical activity even if it is recommended by the physician. The lack of specific counselling by physicians about the benefits of physical activity is a critical issue.

Compliance with the treatment is a common barrier of health programs based on exercise even if transplant recipients who have experienced a supervised exercise program supported that it was beneficial to health and well-being [(22)]. Social, cognitive, personality, environmental, and socio-economic factors, unrelated to the recommended guidelines, seem to be of greater importance in considering behavioural adherence issues [(23)] in transplant recipients. To improve physical exercise program compliance and longer-term outcomes, strategies to diversify and stimulate exercise training or change elements of training like introducing specific tracking devices (e.g. Apps) designed for transplant recipients should be examined. Anyway, data from this thesis clearly show that recommendations alone are not sufficient to induce a change in lifestyle and physical fitness. The development of a network of professionals (physicians, nurses, exercise specialists) together with Patients' Associations has resulted to be the key element for motivating transplant and waiting list patients to be physically active by encouraging them to an active life and reducing the risk of developing pathologies associated with a sedentary lifestyle.

The creation of a multi-professional network promotes cultural growth related to the importance of physical exercise in populations with chronic diseases and increased risk of cardiovascular disease. The identification of paths and places where physical exercise can be practiced helps the overcoming of both the psychological and logistic barriers faced by the patients and their families.

The possibility to access to an unsupervised exercise programs certainly enlarges the potential number of participants and allows the resolution of the problems of economic sustainability related to the practice of exercise programs in the gyms. The use of dedicated apps could be a way to supervise the physical exercise by the physicians or the exercise specialists without the patient physically accessing the gym.

SPORT IN SOLID ORGAN TRANSPLANT RECIPIENTS

This thesis showed that competitive kidney transplant recipients were able to complete a 6-month training including 3 sessions/week of aerobic exercise and 2 sessions/week of strength exercises without any evident adverse effects. The present findings confirm that, despite the intake of immunosuppressive therapies often associated with glucocorticoid, kidney transplant recipients may improve the exercise performance by combined endurance and strength training, counteracting the side effects of the pharmacological therapies and may reduce the muscle atrophy and weakness. Transplant recipient athletes showed overall improvements in the workload associated to the aerobic and anaerobic thresholds and maximum workload, with a slightly decrease of perceived muscle fatigue. Also, the power of lower limbs showed improvement after 6 months in most transplanted athletes, as a possible effect of strength exercises. Chan et al. showed that kidney transplant recipients were mostly capable of generating muscular power similar to healthy subjects, corroborating that fatigue is not explained by deficits in the muscular and cardiovascular systems [(24)]. The same mechanisms were showed in elite healthy cyclists where adding strength training to endurance training can increase strength and rate of force development as it appears in cyclists kidney transplant recipients [25]. Furthermore, the energy cost of the transplanted athletes showed a slight improvement, consistently with the effects of combined endurance and strength training in healthy cyclists and runners [25]. Montero et al. showed that exercise programs including strength training improve the energy cost and shows a superior effect compared with endurance training alone [26]. There is evidence of solid organ transplant recipients who have been able to return to their sport at the same level as that before the illness which had led to the transplant, succeeding also in competing on a par with healthy athletes of the top level or of the same Master category. In solid organ transplant recipients, the principal risks connected with practicing sports are those of infection and cardiovascular risk, due to the side-effects of immunosuppresive therapy. And yet, we have been unable to find cases in literature which show a clear relationship between practicing sports and infectious diseases or side effects of immunosuppressive therapy, including cardiovascular diseases. Those who practice sport deal with the risk of infection by means of suitable prophylactic measures which range from personal hygiene to vaccinations [27-29]. The risk caused by immunosuppressive therapy is dealt with primarily with personalised exercise used as a drug [30,31] as well as with adequate pharmacological support therapies [28]. Though no epidemiological data exist in this respect, the risk of trauma does not appear to be substantially different from that encountered by non-transplant athletes and it does not appear to imply dangers for the transplanted organ, even in several contact sports. In this respect it should be noted that there is evidence of athletes who have returned to practicing their sport trouble-free, but we are not aware of data on athletes who have reported negative consequences on the transplanted organ due to practicing sport. Instead, we have recorded several cases of athletes who have not been able to continue to train for more or less long periods because of complications occurred to the function of the transplanted organ, which are not attributable to physical activity and sports, but rather to typical problems that follow a transplant, including rejection. In actual fact, the transplant recipients who present important psycho-physical consequences due to the chronic pathology which has led to the transplant or who manifest important forms of rejection or side-effects of immunosuppressive therapy, not only are unable to practice sporting activities (training and competing), but their health conditions require frequent therapeutic interventions so these patients present lifestyles which are not likely to be compatible with a physical and sporting activity, even one at the lowest intensity. The fact that there is no data in literature that declares important alterations in organ functions or complications during sports practiced by transplant recipients would confirm this statement which, in any case, requires specific investigation [32,33].

It is necessary to observe that the data and the experiences which we have summarized here show that transplant recipients who practice sports competitively at an amateur or professional level cannot be considered representative of the entire population of transplant recipients, but they do offer us a unique opportunity to become acquainted with and study the higher limits of the possibilities of functional recovery following an organ transplant. This aspect must be considered in order to formulate the criteria for granting suitability for competitive sports, but above all it allows to counteract the preconception that transplants and sports cannot co-exist.

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