The Effects of Exercise and Sport in Solid Organ Transplant Recipients: A Review

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Abstract

Solid organ transplantation is the gold-standard treatment for many with end-organ failure and can offer a new independence from the burden of disease. However solid organ transplant recipients (SOTRs) remain at high risk of cardiovascular disease (CVD), poor quality of life and physical functioning. Increasing physical activity and exercise can improve the health of the general population, however the effects on those with a transplant remain unclear. Intensive exercise and sporting activity has the potential to be beneficial, although there remain concerns particularly around the effects on immune function and the CV system. This review summarises what is known about the effects of exercise on determinants of health in SOTR and then collates the available literature investigating the consequences of intensive exercise and sport on the health of SOTR. There is a paucity of high-quality research, with most evidence being case-studies or anecdotal; this is understandable given the relatively few numbers of SOTR who are performing sport and exercise at a high level. However if suitable evidence-based guidelines are to be formed and SOTR are to be given reassurances that their activity levels are not detrimental to their transplanted organ and overall health, then more high-quality studies are required.

Key Words

Transplants, Rehabilitation, Exercise, Sports

Introduction

Solid organ transplantation offers those with end-stage organ disease an intervention which can transform their lives and is now the gold-standard of care. More patients are successfully undergoing transplants, partly due to advances in surgical techniques, as well as improvements in donor recruitment, organ preservation and immunosuppressive therapies. In the UK there has been a 12% increase in kidney transplants and a rise of 20% from donors after circulatory-death(1). Worldwide there has been a steady increase in solid organ transplants (SOT) with 114,690 estimated to have taken place in 2012, however this is meeting <10% of global need, meaning there is increased emphasis on improving transplant survival(2). Morbidity and mortality following SOT continues to fall and one-year patient and graft survival from cadaveric transplants has increased over the last ten years(3). Therefore the long-term focus is on identifying modifiable risk factors which can be addressed to improve health related quality of life (HRQoL), morbidity and survival.

Exercise has a range of health benefits to the general population including improved HRQoL, reduced CV risk and chronic inflammation. However there are many other factors which need consideration such as the effects of immunosuppression, their underlying disease process and altered body composition which mean that the effects of exercise in the general population cannot be directly translated into solid organ transplant recipients (SOTRs). In addition, many SOTRs wish to either return to, or begin, new sporting activities to improve their health following transplant and this higher intensity exercise may have more unanticipated effects than activity at lower levels.

Competitive Events

The first Transplant Games were held in the UK in 1978(4) with 99 participants from 5 countries. Since then there has been a significant growth in the event with emerging evidence of the benefit of exercise in SOTRs and the publicity surrounding the Games. There are a number of reasons why SOTRs take up sporting activities or exercise, ranging from perceived health benefits to enjoyment. It can be done simply as a hobby or for social reasons but it can also be life-affirming, a celebration of regained health, or a way of showing appreciation to their donor and the health services.

The US Transplant Games (USTG) attracts high-level athletes from across the country who have near age-predicted cardiorespiratory fitness and HRQoL(5). Those more active participants have higher $VO_{2peak}$and lower body fat compared to those who train less intensely(6-8). In a paediatric population, participation at the World Transplant Games (WTG), results in an improvement in habitual activity, with an increase in those achieving healthy CV fitness, abdominal strength and upper body strength compared to controls who do not take part(9).

The location of the WTG has been shown to affect rates of organ donation in that local area(10). Education, awareness and engaging the public through the media have all been shown to increase knowledge of transplantation and affect willingness to donate. However, donation rates are rarely maintained after media coverage ceases.

These highly organised events have the potential to greatly improve our knowledge of the effects of high-intensity exercise on SOTRs and are a potential platform for the development of future research studies. This review article will summarise the current available literature examining the effects of physical activity and exercise on SOTRs.

Solid Organ Transplantation

Patients with chronic kidney disease (CKD), and those on dialysis in particular, have an elevated CV risk compared to the general population(11-13). Kidney transplantation improves survival(14), quality of life(15,16) and reduces CV events(17,18) compared to individuals on dialysis, although outcomes still remain poorer than in the general population(19), with the rate of cardiac death 10-times higher and the annual rate of fatal or non-fatal CV events 50-times that of the general population. It is thought that this is due to traditional CV risk factors which remain, such as hypertension and dyslipidaemia, but non-traditional risks such as immunosuppression(20-22), chronic inflammation(23,24) and altered haemostasis(25-27) also play an important role.

Patients with severe heart failure, understandably, have elevated morbidity and mortality compared to the general population. The most common causes of death include congestive cardiac failure (CCF) and arrhythmias(28). However these numbers have been improving, in part due to the use of left ventricular assist devices (LVAD) which act to delay or prevent the progression to end-organ failure(29). Overall outcomes remain better following heart transplant than LVAD so this still remains the optimum treatment for those with end-stage heart failure(30). Following a heart transplant, patients have an improvement in survival, QoL and exercise capacity, although these measures often do not reach those of their non-transplanted counterparts.

Heart transplant recipients (HTRs) represent a complex population, with several issues needing to be considered when determining their exercise capabilities(31). Prior to transplantation, the donor heart experiences a significant ischaemic time and then subsequently undergoes reperfusion when successfully transplanted into the recipient. Also, the anatomy is not completely restored and during the operation, the heart is surgically denervated and this is not entirely corrected. In the post-operative months, some patients demonstrate signs of partial cardiac re-innervation which may serve to, in part, normalise their responses to exercise. HTRs also often experience diastolic dysfunction. The underlying causes are likely to be multi-factorial including hypertension, episodes of rejection and vasculopathy of the allograft. These factors directly affect the function of the transplant and are likely to influence the response to exercise.

For patients with chronic lung conditions, transplantation offers the chance of improving QoL, morbidity and mortality. In the USA, there are 1572 people currently waiting for a transplant with the most common underlying diagnoses being congenital disease, chronic obstructive pulmonary disease (COPD) and cystic fibrosis(32).

Lung transplantation is a highly complex procedure that carries considerable peri- and postoperative risks. It is a treatment option for patients whose pulmonary function, exercise capacity, and QoL are drastically restricted and predicted 5-year survival is <50%(33). There are three types of lung transplant; single lung transplantation (SLTx), double lung transplantation (DLTx) and simultaneous heart and lung transplantation (HLTx), with the selection depending on the underlying pathology(34).The 1 and 5-year survival rates for SLTxRs and DLTxRs are 77% and 59% respectively(35). Infection (38%), rejection (29%), malignancy (15%) and CVD (10.9%) are the main contributors to morbidity and mortality post-operatively(33) as well as organ specific complications such as obliterative bronchiolitis, all of which may be influenced by physical activity. Post-transplant rehabilitation has recently been the focus, in order to optimise long-term outcomes and promote physical and psychological measures as these still remain impaired despite transplantation(36)with the majority of lung transplant recipients (LTxRs) remaining sedentary 3-6 months post-transplant(37).

Liver transplantation (LivTx) offers those with end-stage liver disease improved morbidity and mortality and is now an established procedure in the developed world, with over 6000 transplants being performed in the United States in 2010(38). Obesity and the development of metabolic syndrome are well-recognised after LivTx, with an increasing BMI seen in the first few years after surgery and 22% of previously normal-weight individuals becoming obese within two years(39). Independent predictors of obesity include episodes of acute rejection and a higher dose of prednisolone. In LivTx recipients (LivTxR), increased BMI at one-year accurately predicts the development of metabolic syndrome(40) and one-third will have CVD at 8-years. Therefore addressing weight gain in the early-post-operative period should be seen as a priority to reduce CVD in the future. LivTx has also been shown to improve markers of QoL including self-reported physical health, daily activities, general HRQoL and social functioning(41).

Cardiovascular System

Regular exercise has positive effects on CV risk in the general population(42), and now the focus has switched to analysing the effect on transplant recipients.

Renal transplant recipients (RTRs) spontaneously increase their activity levels after transplantation and this peaks at one-year despite an initial decrease in the first month post-operatively(43)whereas in the first three months after receiving a heart transplant, HTRs significantly increase their physical activity levels(44) although the effect plateaus after this time. Those transplant recipients who are more physically active have reduced CV risk(45) and this principal has been used in the design of exercise programs aiming to improve a variety of physiological parameters.

Blood Pressure

In RTRs, there are no overall significant effects of exercise on blood pressure (BP)(46,47) with both a supervised six-week aerobic training and a 1 year home-based aerobic program yielding insignificant results in those undergoing the intervention (133/87 at baseline to 132/89 at 12 months) compared to the control group receiving usual care (138/88 to 133/90). Additionally, exercise programs for RTRs do not seem to interact with anti-hypertensive medications either(48) with the number of anti-hypertensives being similar at all time-points and between groups.

In HTRs, exercise has been shown to have equivocal effects on BP. Some studies of supervised moderate intensity exercise for 10-12 weeks demonstrate little effect on either systolic or diastolic BP(49,50) even when combined with strength training(51), with the timing of commencement of the exercise program after transplantation not influencing outcomes. However, high-intensity interval training (HIIT) regimes (16-min interval training with intervals of 4-, 2- and 1-min duration at >80% of VO_{2peak}, separated by a 2-min active rest period) of 12-weeks duration, commenced >12 months after surgery, significantly reduce systolic BP compared to a control group of exercisers who continue to do moderate-intensity activity (50). Additionally, one 6-month study of cycle-based moderate intensity exercise 5 times-a-week at home, reduced both systolic and diastolic BP in the exercisers (143/78 at baseline to 121/69 at 6 months) compared to non-exercising controls (140/77 to 136/77), perhaps suggesting that a longer duration of intervention may be needed to have an effect(52). Hypertension is common in HTRs and beta-blockers have been shown to have an adverse effect on peak heart rate (HR) during exercise and overall exercise capability(53) therefore their use needs to be carefully considered in active HTRs.

In LTxRs, a RCT of 3 months of three times-a-week combined aerobic and resistance training(54) led to a significant improvement in ambulatory 24-hour BP in the intervention group compared to controls. The exercising group maintained their BP at 1 year after transplantation (129/80 pre-transplant and 126/80 at 1 year) whereas the control group experienced worsening hypertension (126/73 to 142/89 $p<0.01$).

Serum Cholesterol

In RTRs, there is no clear consensus as to whether exercise has a beneficial effect on lipid levels as some studies show an improvement(55) and others do not(47,56-58). The only study to show an improvement in total serum cholesterol was based on a Chinese alternative therapy (Don Jeon) for a duration of 9 weeks with 1 once-a-week supervised session and daily activity at home, unfortunately the control group of transplanted patients was not equivalent and therefore it is difficult to draw a meaningful conclusion. The studies which showed no significant improvements in cholesterol profiles included a variety of interventions including combined exercise program and dietary advice(56), supervised(57), and home-based exercise(47,58). Additionally there were also variations in type of exercise with some being solely aerobic(47,59) and others including only strengthening(57) or a combination of both(58). Interestingly, in one study(57) there was a significant increase in total cholesterol in both the exercise group (5.55mmol/L to 6.92mmol/L at 5 weeks $p=0.001$) and the controls (5.40mmol/L to 6.85mmol/L) although this is in part due to a rise in

HDL-cholesterol (1.29mmol/L to 1.67mmol/L in exercisers vs 1.42mmol/L to 1.51mmol/L in controls p=0.05). There was no change seen in triglyceride levels.

In LTxRs, the RCT of combined aerobic and resistance training revealed no significant improvements in total cholesterol (219mg/dL to 191mg/dL at 1 year) compared to controls (169mg/dL to 190mg/dL) or triglycerides (107mg/dL to 159mg/dL vs 86mg/dL to 145mg/dL) (54).

Following LivTx, there is an increase in prevalence of hypertriglyceridaemia and hypercholesterolaemia after 1-year(60) and metabolic syndrome is very common and has been described in 44–58% of patients followed for 6 months after transplantation (61). The development of metabolic syndrome is associated with lower exercise intensity and older age. In addition exercise intensity is inversely related to the development of metabolic syndrome after LivTx suggesting that those who are more active are likely to have improved CV risk factors(62). However an uncontrolled, supervised 12-week combined aerobic and strength training program with lifestyle counselling(63), found that there was actually no improvement in lipid profile with total cholesterol:HDL cholesterol ratio (3.70 to 3.74 after 12-weeks) and LDL cholesterol: HDL cholesterol ratio (2.08 to 2.09) remaining static.

Glycaemic Control

In RTRs, the total amount of physical activity is significantly lower in RTRs with impaired glucose tolerance compared to RTRs with normal glucose tolerance (255 vs 580 minutes/week respectively, P = 0.03) and total physical activity has been identified as an independent predictor of impaired glucose tolerance in all RTRs (p=0.04)(64). A 6-month study of combined lifestyle modification advice and 2-hours endurance exercise per week in RTRs(56) with either new-onset diabetes after transplant (NODAT) or impaired glucose tolerance(IGT) (group 1) versus RTRs with normal glucose tolerance receiving usual care (group 2) revealed a 15% improvement in 2-hr postprandial glucose in group 1 versus 12% deterioration in group 2 (p=0.001). Additionally in group 1, 44% of impaired glucose tolerance patients developed normal glucose tolerance, whereas only 4% developed NODAT and 58% of NODAT patients showed improvement (29% to IGT and 29% to normal). Glucose metabolism deteriorated in group 2 with 14% developing IGT and 3% developing NODAT. Another study of strengthening exercise alone(57), commenced within the first few days after transplantation, showed improvements in glucose levels in both the intervention group (102mg/dL to 83mg/dL at the end of the study) and the control group (108mg/dL to 83mg/dL) which may reflect changes in medications (such as decreased steroid doses).

Three months of 3 times-a-week aerobic and resistance training in LTxRs(54) leads to a trend of reduced rates of overall progression to NODAT (6%) compared to the control group (25%) although this is not significant (p=0.11) and also a reduction in fasting glucose (99mg/dL to 90mg/dL at 1 year vs 88mg/dL to 107mg/dL) however again this is not significant (p=0.13). However in LivTxRs, after a 12-week aerobic and strength exercise program, there was actually a trend towards worsening of glycaemic control (HbA1c 5.40% to 5.60% after the program, p=0.071)(63).

Body Composition

Body Weight and Soft Tissue

Observational studies have shown that those RTRs who are more physically active have lower amounts of body fat(65) however a randomised trial of home-based cardiovascular exercise versus usual care has shown particularly disappointing effects on body composition(48). In fact body weight and BMI increase in both groups from baseline (Intervention: 24.8 to 27.7 at 1-year vs Control: 25.1 to 27.1) and lean body mass remains constant (Intervention: 49.2kg to 49.7kg at 1-year vs Control: 50.1kg to 51.8kg) whilst fat mass rises (Intervention: 20.8kg to 25.8kg at 1-year vs Control: 21.2kg to 27.6kg). Increased habitual activity levels do reduce body fat and increase lean muscle mass in women(66) in some studies but there is no clear link in males. A 7-week isokinetic bicycle-based program focusing on thigh musculature(67), discovered that RTRs taking prednisolone and those who were not both benefitted from increased thigh muscle area (Prednisolone group: $128cm^2$ to $133cm^2$ p=0.01, Non-prednisolone group: $100cm^2$ to $107cm^2$, p=0.005) although there were non-significant changes in both total fat area and overall thigh area.

Previous CCF and reduced pre-transplantation physical activity both contribute to deterioration in overall body composition. In HTRs, a 12-week combined aerobic and strength training program increased total lean tissue mass compared to the control group(51) and 6-months of resistance exercise training alone also had positive results compared to the control group(68). Fat mass significantly increased at 2 months after transplant in both the control (+8.3%) and exercising groups (+7.3%) and 6-months of resistance training restored fat-free mass to levels 3.9% greater than before transplant (p<0.05). Fat-free mass of the control group decreased progressively to levels that were 7% lower than pre-transplant values (p<0.05). However HIIT programs have yet to be proven to be effective in improving body composition(69), with no significant reduction in BMI in the intervention group (27.2 to 26.5 at follow-up) compared to the controls (26.3 to 26.3 p=0.106) or improvement in body fat percentage (Intervention: 26.1% to 25.2% at follow-up versus Control: 24.6% to 25.0% p=0.152).

In LTxRs, a randomised trial of combined aerobic and resistance training did not reveal any positive effects on body weight or BMI in either the intervention group (22.6 to 24.4 at 1-year) or the controls (21.5 to 24.1, p=0.89) with both overall body weight and BMI increasing over time in both groups.

A randomised 10-month home-based aerobic exercise program in combination with dietary advice has been shown to improve lean body mass, although coincidentally, there were also increases in body weight, fat-mass and percentage of body fat(70) , additionally there were issues with adherence to the program, with only 37% following the program as instructed. When this was taken into account, total body weight, lean mass, and fat mass increased in all patients over the study period (p<0.001) with no significant interactions found between the intervention and control groups in any of the body composition variables.

In LivTxRs, a randomised 24-week combined resistance and aerobic based regime based either at home or supervised in a clinical setting(71), resulted in a significant increase in BMI in the supervised exercise group compared to the home-based group and the controls (Supervised: 20.4 to 24.4, Home-based: 22.3 to 22.6, Control: 22.2 to 22.2 p=0.005). This increase was predominantly due to an increase in lean mass in the exercising groups (Supervised: 43.4kg to 48.9kg, Home-based: 41.7kg to 47.0kg, Control: 49.9kg to 45.1kg p=0.009) with a non-significant change in fat mass (Supervised: 13.9kg to 17.5kg, Home-based: 16.4 to 15.6kg, Control: 13.2 to 15.1kg p>0.05). However in another study(63), 3-months combined training in a supervised group setting, resulted in stabilisation of the BMI (29.7 to 30.0 after completion, p-=0.287) and a significant reduction in body fat percentage (33.0% to 31.8%, p=0.049).

Bone Mineral Density

In RTRs, 1-year of home-based aerobic exercise(48) did not influence bone mineral density (BMD) in either the exercisers (0.970g/cm^2 to 0.995g/cm^2 at 12 months) compared to the control group (1.012g/cm^2 to 1.024g/cm^2, $p>0.05$).

In HTRs, a 6-month weekly lumbar extensor and twice weekly upper and lower limb resistance training program(72), found that bone demineralisation occurred early after transplantation, and BMD losses from compartments with trabecular bone, such as the lumbar spine, were greater than BMD losses from regions with cortical bone, such as the femoral neck. BMD losses in the lumbar vertebra were 12% and 15% in the control and training groups, respectively, at 2 months after transplantation. Following the intervention, losses were significantly reduced compared to the control group (-3% vs -16%, $p<0.05$). The main finding of this study was that resistance training was osteogenic and restored BMD toward pre-transplantation levels in HTRs despite continued immunosuppression with glucocorticoids. In contrast, regional BMD in the control group did not indicate any significant recovery toward preoperative levels by 8 months after transplantation. Additionally, a 6-month resistance training program with calcitonin supplementation versus calcitonin alone(73), found that total body BMD did not decrease significantly below pre-transplantation values at 2-months after transplantation in either the calcitonin plus training (–0.5%) or calcitonin reference groups (–1.7%). At 8-months post-transplantation both the calcitonin group (–2.4%) and the calcitonin plus training group (-2.6%) experienced small but significant ($p<0.05$) losses in total body BMD when compared to pre-transplantation values. The magnitude of change in total body BMD at 2 and 8-months after transplantation were comparable in the two groups. This suggests that neither calcitonin nor calcitonin plus mechanical loading were efficacious in preventing small long-term reductions of BMD in non-metabolically active, slow turnover, cortical bone cells of the appendicular skeleton in HTRs.

In LTxRs, prior to commencing the training study(74), both the trained (0.63 to 0.54 g/cm^2 of hydroxyapatite) and control groups (0.62 to 0.53 g/cm^2 of hydroxyapatite) lost significant and comparable amounts (-14.5%) of BMD between study entry and 2 months post-transplantation. After 6-months of weekly lumbar extensor training, the control group lost further lumbar BMD between 2 and 8 months post-transplantation (0.53 to 0.50 g/cm^2 of hydroxyapatite, $p<0.05$), decreasing to values that were 19.5% less than pre-transplantation baseline. Lumbar BMD in the trained group increased significantly (+9.2%) after 6 months (0.54 to 0.60 g/cm^2 of hydroxyapatite) and returned to values that were within 5% of pre-transplantation baseline. The aforementioned resistance training program, in combination with alendronic acid led to a bigger improvement than alendronic acid alone(75) . Lumbar BMD decreased significantly to below pre-transplant baseline at 2-months after transplantation in controls (−12.5%), but not in the alendronate (1.5%) or alendronate + training (1.5%) groups. At 8-months after transplantation, lumbar BMD in controls was 14.1% below baseline ($p<0.05$), but was 1.4% above baseline in alendronate recipients ($p>0.05$). The alendronate + training group showed a significantly increased lumbar BMD with values 10.8% greater than before transplant. This indicates that pharmacological intervention should be prescribed alongside resistance exercise for the greatest benefit in LTxRs.

A 24-week combined resistance and aerobic based regime based either at home or supervised in a clinical setting for LivTxRs(71) found that total BMD did not change significantly in any group from baseline to after completion of the program (Supervised: 1.11g/cm^2 to 1.11g/cm^2, Home-based: 1.21g/cm^2 to 1.11g/cm^2, Control: 1.21g/cm^2 to 1.11g/cm^2). However proximal femoral BMD did differ significantly in the home-based exercise group compared to the controls (Home-based: 0.9 g/cm^2 to 0.8 g/cm^2, Control: 0.9 g/cm^2 to 0.9 g/cm^2, $p=0.017$) although there were no differences in T or Z-scores. Similarly, a randomised home-based cardiovascular exercise and dietary education program, found no difference in BMD between the exercisers (1.14 g/cm^2 to 1.15 g/cm^2) and controls (1.15 g/cm^2 to 1.17 g/cm^2).

Exercise Capacity

Muscle Strength and Function

In RTRs, a thrice-weekly strengthening focused exercise program of 6 months duration(76), found that upper extremities muscle strength increased more in the rehabilitation group (15.99 to 18.56 after completion) compared to the control group (15.89 to 16.88) although this did not reach significance. Similarly, a 7-week isokinetic bicycle-based exercise program investigating outcomes in those on prednisolone compared to those on steroid-sparing regimes(67), found improvements in peak torque (at 60°) in both groups (Prednisolone-free: 236Nm to 289Nm after training completion $p<0.005$, Prednisolone: 207Nm to 237Nm $p<0.005$) and in total work output (at 180°/s (Prednisolone-free: 3563J to 4584J after training completion $p<0.001$, Prednisolone: 2712J to 3587J $p<0.001$). Benefits were also seen in a study of Don Jeon(55), for a duration of 9 weeks with 1 once-a-week supervised session and daily activity at home, where grip strength ($p<0.001$), back muscle strength ($p=0.01$) and sit and reach distance ($p<0.001$) all improved in the intervention group compared to those receiving usual care.

In RTRs 1-year of home aerobic training(48), also resulted in an improvement in peak torque (per body weight) in the intervention group (34.5 ft/lb/kg to 42.5ft/lb/kg) compared to the control group (33.7ft/lb/kg to 37.2ft/lb/kg, $p<0.003$). Furthermore, a study of 24-weeks of treadmill exercise alone(77), revealed that exercise time to exhaustion (12min $p<0.001$) improved and there were also large increases seen in isokinetic muscle function in both the quadriceps and hamstrings ($p<0.001$ to $p<0.0001$) although values were still lower than in the untrained non-transplanted healthy control group. Muscle biopsies showed an unexpected rise in type-2 muscle fibres and low oxidative capacity suggesting that enhanced muscle contractile function is partly responsible for improved overall performance.

In comparison of aerobic training versus resistance training alone in RTRs(78), 12-weeks of twice weekly supervised exercise found an improvement in the isometric quadriceps muscle force in both of the exercising groups (Aerobic: 77.9nM to 81.0nM after 12-weeks, Resistance: 91.2nM to 130.3nM) whereas the control group actual deteriorated (101.0nM to 95.1nM), with a significant difference between the resistance trained group and the controls (p=0.006) A similar pattern was seen in performance in the sit-to-stand 60 test (Aerobic: 24reps to 27 reps, Resistance: 30reps to 37 reps, Control: 26reps to 26reps) where improvements were seen in both intervention groups in comparison to the controls although only the difference between resistance training and controls was significant (p=0.009).

In HTRs, a 6-month study of cycle-based moderate intensity exercise 5 times-a-week at home(52), found that in the training group, physical performance improved significantly, with exercise time (7.65mins to 11.40mins, p<0.01) and maximal workload (75W to 105 W, *p*<0.01) both improving and the anaerobic threshold was reached at higher workloads (50 to 75 W). In the control group, physical performance did not improve with VO_{2peak} (14.33ml/kg/min to 15.60ml/kg/min), exercise time (8.00mins to 8.50mins) and peak workload (70W to 78W) remaining comparable to baseline. Another study of 10-weeks of aerobic exercise 2-3 times per week(49), found a significant increase in peak HR in the exercising group (128bpm to 146bpm) compared to the control group (136bpm to 142bpm, p<0.05) and in duration of the exercise to exhaustion test (Exercisers: 9.2mins to 10.7mins, Control: 8.5mins to 8.8mins, p<0.05).

A 6-month structured aerobic and strength training program designed for HTRs(79) revealed that peak workload increased in the exercisers (59W to 94W) compared to the usual care group (66W to 78W p=0.01) and the duration of exercise performed also improved (Exercisers: 6.9mins to 9.0mins, Controls:7.2mins to 8.3mins p=0.07).

A study of either moderate exercise or a HIIT regime of 12-weeks duration, commenced >12 months after heart transplant(50) found improvements between groups in workload achieved (HIIT: 148W to

162W, Moderate: 155W to 158W, p=0.003) and peak HR (HIIT: 139bpm to 144bpm, Moderate: 140bpm to 141bpm, p=0.027). A second study of HIIT versus usual care(69) also found a significant improvement in peak HR (HIIT: 159bpm to 163bpm, Control: 154bpm to 153bpm, p=0.035) as well as the test duration (HIIT: 10.6mins to 14.1mins, Control:12.2mins to 13.0mins p<0.001) and quadriceps and hamstring strength (HIIT: 394Nm to 402nM, Control: 380nM to 359nM p=0.043).

After LTx, there are significant gains in exercise capacity. In the first 3 months, there is a 60–75% increase in the distance covered in 6 minute walking test (6MWT), with an ensuing plateau in performance(80). However VO_{2max}remains deficient compared to expected levels with a function of 40-60% of predicted achieved(81,82) but there is no overall ventilatory limitation to mild exertion required for daily living(83). Exercise capacity is reduced in both SLTxRs and DLTxRs(84). LTxRs have similar thigh muscle volumes, intramuscular fat infiltration and strength of the quadriceps and hamstrings to those with COPD who have not undergone transplantation. However, quadriceps endurance tends to be lower in LTxRs compared to people with COPD(85). A 12-week study of thrice-weekly cycling(86) found that endurance time was improved in LTxRs to the same extent as healthy subjects but with greater variability between patients (LTxRs: +9min, Healthy Control: +8min, p<0.05). Additionally, muscle strength significantly improved in LTxRs, with similar increases also seen in the healthy controls (LTxRs: +4.6kg p = 0.001, Controls: +3.1kg p=0.047), leading to a recovery of muscle strength as compared with the initial healthy subjects' value. In LTxRs, there were also trends to significant changes in the percentage of type I fibre (+7%, p = 0.10) and the type II fibre diameter (−3µm, p = 0.10).

Three-months of supervised combined aerobic and resistance training(54) resulted in an improvement in performance in the 6MWT at 1-year in the LTxRs undergoing exercise training (56%pred to 86%pred) compared to the controls receiving usual care (51%pred to 74%pred p=0.002) as well as peak workload (Exercisers: 47%pred to 69%pred, Controls: 39%pred to 53%pred, p=0.043) and quadriceps force (Exercisers: 63%pred to 92%pred, Controls: 56%pred to 71%pred, p=0.001). An early intervention of mixed aerobic and strengthening training(87), initiated in the first few weeks after transplant also reported an improvement in performance in the 6MWT (451m at 1 month to 543m at 3 months post-transplantation). Improvements between all time points were statistically significant ($p<0.0001$), although with no control group for comparison it is difficult to make assumptions from this study that LTxRs would not have shown improvement after transplant without the intervention.

In LivTxRs, 10-months of home-based aerobic exercise(70), led to a significant increase in quadriceps strength in the exercising group over time (26.9ft/lb/weight to 32.6ft/lb/weight $p<0.001$) although this was not significantly different to the control group (29.2ft/lb/weight to 32.9ft/lb/weight). Additionally, after 24 sessions of aerobic treadmill-based exercise(88), the exercising group increased their walking distance (Baseline: 453.6m to 582.5m after the program $p<0.05$) compared to the controls receiving usual care (Baseline 516.5m to 517.7m).

A randomised 24-week combined resistance and aerobic based regime based either at home or supervised in a clinical setting(71) revealed no significant improvement in performance in the 6MWT between the supervised exercisers (Baseline: 506.2m to After program: 573.3m), home-based exercisers (491.2m to 550.5m) or the control group receiving usual care (530.9m to 553.6m $p>0.05$) or in the quadriceps strength (Supervised: 506.2Nm to 573.3Nm, Home: 491.2Nm to 550.5Nm, Control: 530.9Nm to 553.6Nm, $p>0.05$). However, a supervised 12-week combined aerobic and strength training program with lifestyle counselling(63) with no control group, did find a non-significant trend towards improvement in quadriceps strength (Baseline 1.3Nm/kg, After program: 1.4Nm/kg $p=0.058$), although improvements in workload (Baseline 1.6W/kg, After program: 1.7W/kg $p=0.004$) and performance in the 6MWT (Baseline: 546.5m, After Program: 578m $p=0.004$) were significant.

Cardiorespiratory Fitness

In RTRs, a 6-month strengthening program(76), discovered that peak expiratory flow rate (PEF) increased significantly in those undergoing strength training (Intervention: 419L/min to 516L/min, Control: 439L/min to 483L/min). One year of home aerobic training(48), also resulted in a significant improvement in age-predicted VO_2 (Intervention: 70.9% to 85.4% at 1-year, Control: 71.6% to 77.4%, $p<0.03$) although peak respiratory exchange ratio did not change (Intervention: 1.32 to 1.35, Control: 1.38 to 1.37 $p>0.05$). Another study of treadmill exercise alone(77), revealed that exercise time to exhaustion (12min $p<0.001$), VO_{2max} (37.5 ml/kg/min $p<0.05$) and maximum ventilation rate (68.5L/min $p<0.05$) all improved. In comparison of resistance or aerobic training versus standard care(48), VO_{2max} increased over time in all groups (Aerobic: 12.3ml/kg/min to 15.1ml/kg/min, Resistance: 14.1ml/kg/min to 16.8ml/kg/min, Control: 11.8ml/kg/min to 12.8ml/kg/min) however significantly greater gains were seen in those who were trained compared to the control group (Aerobic vs Control $p=0.02$, Resistance vs Control $p=0.002$). Nevertheless, in comparison of VO_{2max} between very well-trained RTRs and non-transplanted controls the transplant patients still have decreased mechanical efficiency as reflected by an increased VO_2/treadmill-speed relationship(89).

Observational studies have found that, even in well-trained HTRs, there were still deficiencies in VO_{2max} and treadmill speed and the VO_{2max}/treadmill speed relationship compared to healthy controls(89,90). A 6-month study of cycle-based moderate intensity exercise (52), found that in the training group, VO_{2peak} improved significantly (14.93ml/kg/min to 19.61ml/kg/min, $p<0.001$) compared to the control group (14.33ml/kg/min to 15.60ml/kg/min $p<0.05$) and this is supported by a shorter study of 10 weeks duration of aerobic exercise(49) where VO_{2max} also increased to a greater extent in the exercisers (Intervention: 16.7ml/kg/min to 20.0ml/kg/min, Control: 15.5ml/kg/min to 16.1ml/kg/min, $p<0.05$).

Following a 6-month combined aerobic and strength training program(79)it was observed that VO_{2peak} increased significantly in the intervention group (9.2ml/kg/min to 13.6ml/kg/min) compared to the controls (10.4ml/kg/min to 12.3ml/kg/min, p=0.01).

HIIT training(50) has been found to be more beneficial in HTRs than moderate aerobic exercise in improving VO_{2peak} (HIIT: 23.2 to 28.1ml/kg/min, Moderate: 23.0ml/kg/min to 25.6ml/kg/min, p<0.001). However the respiratory exchange ratio remained unchanged in both the HIIT (1.18 to 1.15) and moderate groups (1.20 to 1.18, p=0.754). These results are supported by another study(69) of 24-weeks of HIIT training where VO_{2peak} also improved significantly in those in the intervention group (27.7ml/kg/min to 30.9ml/kg/min) compared to the controls (28.5ml/kg/min to 28.0ml/kg/min, p<0.001) and the respiratory exchange ratio remains stable (HIIT: 1.07 to 1.08, Control: 1.06 to 1.07, p=0.602).

Following a 12-week, home-based cycling program comparing healthy controls and LTxRs(91), FVC (Forced Vital Capacity) (LTxRs: 78%pred to 82%pred p=0.19, Controls: 109%pred to 109%pred p=0.82) and FEV_1 (Forced Expiratory Volume in the first second) (LTxRs 74%pred to 77%pred p=0.44, Controls: 108%pred to 106%pred p=0.20) remained generally stable in both groups. However VO_{2max} did show a trend for improvement in the LTxRs (63%pred to 68%pred, p=0.07) and increased significantly in the healthy controls (101%pred to 113%pred p=0.02). Similarly, a 12-week study of thrice-weekly home-based aerobic exercise(86) discovered that VO_{2peak} was significantly improved in healthy subjects after the program, although there was only a trend to improvement observed in LTxRs (+0.13 ± 0.22, p = 0.059). Additionally, a 6-week part home-based, part-supervised, aerobic training program(92) found a significant improvement in VO_{2peak} from baseline (18.4ml/kg/min) compared to after training (20.3ml/kg/min p<0.05), although there were no controls for comparison therefore is difficult to conclude that the improvements seen were greater than would have been seen in those receiving usual care.

Following a supervised mixed aerobic and strength training program of the same duration, VO_{2max} showed a non-significant improvement compared to the non-exercising controls (Exercisers: 55%pred to 78%pred, Controls: 47%pred to 63%pred, p=0.082) with FEV_1 also being non-significant (Exercisers: 79%pred to 92%pred, Controls: 69%pred to 89%pred, p=0.615). A mixed endurance and resistance rehabilitation programme (with no control group)(87), completed in the first 12-weeks post lung-transplant, found that both FEV_1 and FVC significantly increased(87) after the training program (p<0.0001). FEV_1 increased from 71% at 1 month to 78% at 2 months and 81% at 3 months. The improvement from 2 to 3 months was not statistically significant. FVC improved from 69% at 1 month to 77% at 2 months and 81% at 3 months with improvements between each time point being statistically significant.

Following LivTx, VO_{2peak}increases by a modest amount(93), however it actually decreases in one-quarter of patients. This persistent impairment of exercise tolerance is principally peripheral in origin but anaemia and beta-blocker treatment should be considered as major aggravating factors(94). A randomised 10-month home-based aerobic exercise program in combination with dietary advice(70) discovered that age-predicted VO_{2peak} increased significantly in the exercising group(71.9%pred to 90.1%pred) compared to the control group receiving usual care (73.2%pred to 83.0%pred p<0.04), although the respiratory exchange ratio did not change in either group from baseline to 12-month assessments (Intervention: 1.11 to 1.10 , Control: 1.12 to 1.11 p>0.05). An uncontrolled, supervised 12-week combined aerobic and strength training program with lifestyle counselling(63) also found that VO_{2peak} increased significantly from baseline (20.9ml/kg/min) to after the intervention (22.4ml/kg/min p=0.031).

Quality of Life and Anxiety and Depression

HRQoL describes the subjective assessment of the impact of disease and its treatment across the physical, psychological and social domains of functioning and well-being(95). There are many factors of HRQoL including satisfaction with life and individual happiness, as well as objective assessments of physical and psychological functioning(96). In research studies involving transplant recipients, the most commonly used method of evaluation of anxiety and depression is the Hospital Anxiety and Depression Scale (HADS)(97). The HADS is a validated screening instrument for the presence of depression and anxiety symptoms, which is widely used in hospital settings, it takes less than 5 minutes to complete and has been shown to be acceptable by the population for which it was designed. The HADS consists of 14 Likert scaled items with two subscales (0–21). Each subscale includes seven items scored on a four-point scale between 0 and 3. Subscale scores of up to 7 are considered normal, whereas scores of 8–10 are regarded as borderline and set as clinical manifestation. Both scales can be interpreted independently from each other. HRQoL is most commonly measured using the internationally validated SF-36 questionnaire(98). Thirty-six items are combined into 8 scales such as physical functions (PF, 10 items), social functions (SF, 2 items), role limitations due to physical problems (RP, 4 items), role limitations due to emotional problems (RE, 3 items), mental health (MH, 5 items), energy and vitality (VIT, 4 items), bodily pain (BP, 2 items), and a general perception of health (GH, 5 items). The subscales can be combined into two summation scales measuring the overall physical and mental HRQoL (a physical component summary and a mental component summary). Sometimes shortened versions of this questionnaire can be use when time constraints apply (for example SF-12 or SF-8).

HRQoL and Anxiety and Depression following Transplantation

HRQoL often does not improve according to expectations, as RTRs often have ongoing physical and psychological issues which persist post-operatively. Diagnoses of psychiatric disorders remain high with some studies reporting a prevalence of 50% with affective disorders, major depression and anxiety being most common at around 5 years post-transplant (99) and those with a cadaveric transplant are more likely to experience anxiety and depression than those who receive a living transplant(100). Using the Spielberg State Trait Anxiety Inventory and the Beck Depression Inventory (BDI), anxiety scores are significantly lower among living transplant recipients (80.2) compared to cadaveric transplant recipients (86.9, p=0.03). There is also a significant relation between depression score and kind of graft donation (Living: 11.6, Cadaveric: 16.4, p<0.005). However HRQoL has been found to improve following renal transplant with a significant improvement in all QoL domains(101). This improvement occurs within the first 6 months after surgery and remains stable following that. Predictors of QoL include number of hospital admissions (representing early morbidity after transplantation), work (representing economic autonomy), and social support.

Following heart transplant, a significant overall improvement in QoL is perceived not only immediately after the operation(102), but also in the long-term(103). However another study found that in the immediate post-transplant period there were no significant differences in adjustment, physical function and employment between HTRs and similar medically managed heart failure patients(104). The long term improvements(103) are apparent in the physical domain, social dimension and psychological dimension. The improvement remains stable up to 5 years post-transplant and is not correlated with age, rejection episodes, preoperative medical parameters, or medication and this is supported by other studies which have also shown improvements in physical functioning(105,106) and perceived quality of life(107,108) in HTRs.

In the first 3 years after heart transplant, survival analysis indicates that cumulative risks for disorder onset are major depression, 25.5%; adjustment disorders, 20.8%, post-traumatic stress disorder (PTSD), 17.0%; and any assessed disorder, 38.3%, with only one case of generalised anxiety disorder(109). PTSD onset is limited almost exclusively to the first year after transplantation. Episodes of major depression (but not anxiety disorders) that occur at 8-36 months post-transplant are more likely than early post-transplant episodes to be treated with psychotropic medications. Factors increasing cumulative risk for post-transplant psychiatric disorder include a pre-transplant psychiatric diagnosis, female gender, longer hospitalisation, more impaired physical functional status and lower social supports from caregivers or family in the peri-operative period. At around 10 years post-transplantation moderate or severe depression is still experienced by around 37% of patients(110), although interestingly around 50% report good or very good satisfaction with QoL and physical health. However the prevalence of depression is negatively associated with physical domain (r = −0.45, p<0.01), social domain (r = −0.49, p<0.05), and psychological domain (r = −0.3, p<0.05). The worst QoL signifies a high prevalence of depression and the subjective assessment of QoL negatively correlates with the prevalence of depression (r = −0.43; p<0.01).

Within the first 2 years following lung transplantation(111), LTxRs report that several symptoms are both frequently occurring and rather distressing such as muscle weakness (occurs in 40%, distressing in 46%, shortness of breath with activity (occurs in 32%, distressing in 36%, and increased hair growth (occurs in 54%, distressing in 29%). At around 5 years after lung transplant, patients demonstrate statistically lower rates of respiratory problems as compared with reference values for patients with COPD(112). Following completion of the SF-36, in the sub-scales of vitality and mental health and the mental component summary scale, LTxRs had scores similar to those of the healthy control population, although the remaining scores were significantly lower. Also, there were no significant differences between the LTxRs and the reported reference healthy population on the anxiety and depression sub-scales. However 10% of the patients showed clinical depression and 12% had clinical anxiety.

Levels of anxiety are higher in those waiting for transplant than in the LivTxR group (7.1 vs 5.6 p<0.05)(113) and the mean score for the depression scale is higher in the waiting group as well (6.5 vs 4.9 p<0.05). Comparing both groups with data from the reference population (mean scores: anxiety: 4.7, depression: 5.1, total score: 9.9) reveals significant differences for anxiety (p<0.001), depression (p<0.05) and the summation score (p<0.001). There are also significantly higher scores for anxiety (p<0.001), depression (p<0.05) and HADS total score (p<0.001) in the group of patients on the waiting list compared to the reference population. However after liver transplant, anxiety scores are significantly higher (p<0.001).

Prior to liver transplantation, half of patients report some level of distress in 14/21 HRQoL determinants whereas 1-year post-operatively they report distress in only 10/21(114). The most commonly reported symptoms causing distress at baseline are fatigue and muscle weakness which are experienced by 98% and 90% respectively, however these are statistically likely to improve at 1-year although 86% remain distressed by fatigue and 79% by weakness demonstrating that these continue to be a substantial problem for these patients. At baseline the Index of Wellbeing is 8.4 and this increases to 11.2 at follow-up which is similar to that of the general population (11.8). Although wellbeing generally improves it does actually decrease after transplantation in around 15% of patients.

<u>Exercise and HRQoL and Anxiety and Depression</u>

One study of active RTRs showed that regular exercise significantly improves different aspects of HRQoL such as social function, general health perception and mental health, compared to their sedentary counterparts(115). Additionally, just 2 hours of exercise per week significantly ameliorates RTRs' self-reported health and fitness condition. The amount of exercise participation also positively correlates to the patient's health and fitness condition with no effect on graft function(116). In RTRs, 10-weeks of thrice-weekly cycling has been shown to improve anxiety (HADS score: Baseline: 9.9 After program: 6.0 p<0.004) and depression (HADS score: Baseline 8.3, After program 5.9 p<0.008) scores in RTRs(117) as well as overall HRQoL as measured by the SF-36 questionnaire (Baseline: 394 After program: 553 p<0.0001) although the authors did not provide a breakdown of the scoring for each component. A 9-week intervention of Don Jeon, with 1 once-a-week supervised session and daily activity at home (55), found reductions in both stress (p=0.03) and uncertainty (p=0.001) compared to the control group and improvements in self-esteem (p<0.001) and overall QoL (p=0.001) although they do not report which questionnaires have been used.

After one-year of home-based aerobic exercise(48), the only scale on the SF-36 questionnaire that approached significant differences between the two groups was the physical functioning scale (Baseline Exercisers: 68.1, Control: 64.1; 12 months: Exercisers: 84.8, Control: 73.2, $P=0.06$). Although both groups improved in the role physical during the 12 months (Baseline Exercisers: 39.0, Control: 54.9; 12 months: Exercisers: 59.4, Control: 60.6), it remained low compared with the general population (average for general population is 83). Both groups improved with time in the physical component summary during the 12 months, (Baseline Exercisers: 40.1, Control: 40.8; 12 months: Exercisers 47.0, Control 44.8, $p<0.0001$), but there were no significant differences between the groups as a function of time. At 12 months, both groups were similar to the general population scores for mental health and the mental component summary; all other scale scores remained lower than the scores reported for the general population.

A 1-year resistance training intervention for 1 hour twice-a-week, with psychological and dietary support, specifically designed for obese RTRs (118), found that the mean SF-36 score at 6 months was significantly higher in the intervention group compared with the control group (583 vs 436 $p=.008$) and the exercisers had improvements in the domains of vitality (Intervention: 53 to 62, Control: 59 to 25, $p<0.05$) and general health (Intervention:39 to 50, Control: 45 to 29 ,$p<0.05$) compared to the controls receiving usual care. This translated positively into job prospects, as overall, at 12-months there was a significantly higher employment rate of 77.7% in the exercise group, compared with 12.5% in the control group ($p=0.02$).

HTRs who participated in an early post-transplant rehabilitation program of supervised cycling or treadmill-walking for 12 weeks showed a significant increase of SF-36 scores in physical functioning (59.7 to 77.0), physical role (21.1 to 38.3), bodily pain (57.4 to 73.6), social functioning (63.6 to 72.8), emotional role (59.2 to 76.3), and mental health (67.1 to 73.4) (119). This study compared the results to patients undergoing coronary artery bypass grafting (CABG) and found that after early post-operative cardiac rehabilitation HTRs showed greater improvement in HRQoL than patients with CABG regardless of lower physical capacity.

Additionally a hospital-based exercise program of combined aerobic and strength training three-times-a-week over an eight-week period, produced a significant improvement in all aspects of the SF-36 questionnaire except for mental health(120), although there was a significant improvement in depressive symptoms as measured by the BDI (7.36 to 5.86 $p<0.05$). However there was no change in symptoms of anxiety as recorded on the Spielberger State-Trait Anxiety Inventory (43.89 to 45.58 $p>0.05$).

A 24-week HIIT program for HTRs(69) found that both groups had high HRQoL scores and there were no significant changes in any of the sum-scores. However, there was a significant difference between the exercisers and the control group on the SF-36 General Health subscale at follow-up (Exercisers: 54 Control: 49, $p<0.05$). As for subjectively improved health, the exercisers reported 65 on the visual analogue scale compared to 26 in the control group ($p< 0.001$).

A 12-week home-based aerobic training program after lung transplantation(86) improved symptoms of dyspnoea (3.6 to 4.2 after training, $p=0.03$) and a there was an observed trend towards decreased fatigue (4.5 to 4.8, $p=0.07$) as measured by the chronic respiratory questionnaire.

A program for LTxRs within the first 12-weeks post-transplant, of mixed aerobic and strengthening training(87), revealed that all HRQoL domains improved from month 1 to 3 when measured using the SF-36. Physical conditioning demonstrated gains up to 3 months (Physical functioning: 46 at baseline to 75 at 3-months, $p<0.05$, Role functioning physical: 31 to 71, $p<0.05$) whereas symptoms related to surgery for example pain (39 at baseline to 62 at 2-months to 66 at 3-months), showed a reduction up to 2 months ($p<0.05$) and then this effect plateaued.

A 3-4 week inpatient intensive rehabilitation program of aerobic and strengthening training for LTxRs around 4.5 years post-transplantation(121) found no significant improvements in HRQoL (SF-

36) could be demonstrated in the either the exercise group of the usual care group. In fact, the groups were found to have an already good HRQoL at the first evaluation visit, as indicated by SF-36 scores >80% of 100% best possible and although there was a slight trend toward increased HRQoL levels, this did not reach statistical significance.

A RCT of 3 months of three times-a-week combined aerobic and resistance training(54) only found a significant improvement in the physical components of the SF-36 when the intervention group were compared with controls (Physical functioning: Intervention: 43 at baseline to 77 after 1-year, Control: 36 to 65 p=0.039. Role functioning physical: Intervention: 31 to 83, Control: 22 to 52 p=0.011).

More physically active LivTxRs have improved general health, physical function, bodily pain and vitality(122). Fatigue is a common problem following LivTx(123) with 60% perceiving themselves to be fatigued or severely fatigued. . Following an uncontrolled twice-a-week, 12-week aerobic and strength rehabilitation program, LivTxRs reported an increase in health-related daily functioning (Sickness Impact Profile-68, 10.39 to 7.94 p=0.007). When assessing HRQoL with the SF-36 only physical functioning (67.5 to 75.3 p=0.007) and vitality (7.8 to 58.1 p=0.019) were statistically significant and the HADS score did not improve for either anxiety (5.5 to 5.4 p=0.929) or depression (5.8 to 5.4 p=0.432). Furthermore, another uncontrolled, supervised 12-week combined aerobic and strength training program with lifestyle counselling(63) found that there was a clinically relevant improvement in fatigue after the intervention (Fatigue Severity Scale 5.5 to 4.9 p=0.014, Visual Analogue scale 63.5 to 50.3 p=0.043 and Checklist Individual Strength 38.5 to 28.0 p=0.007).

A randomised 10-month home-based aerobic exercise program in combination with dietary advice(70) found that only the general health aspect of HRQoL improved (SF-36 Intervention: 54.5 to 65.1, Control: 58.8 to 63.0 p<0.05). This indicates that the increase in general health over time is greater for the exercisers than for those receiving usual care. All other physical scales increased in both groups (p<0.05) but the change was not significantly different between the exercisers and controls. Of the mental scales only mental health showed a significant group by time interaction (Exercisiers:78.5 to 83.4, Control: 79.3 to 77.9, p=0.009) with the increase being greater over time in the exercising group. Vitality and social functioning increased in both groups (p<0.001) at 12-months.

Sporting Performance Following Transplantation

Renal Transplant

High intensity exercise and sport have not been extensively investigated in transplant recipients, with most publications being case report or small-scale studies.

A study of RTRs, performed at the WTG(124), determined that the average energy expenditure was 3376±739 kcal/day, corresponding to 43.7±13.6 kcal/kg per day, which is 25% higher than those of age-matched inactive healthy subjects. The transplant recipients were also able to perform activity at an intensity level greater than three times the resting MET for 197±112 min suggesting that SOTRs are capable of taking part in sustained moderate-vigorous activity. However the RTRs did perform at a lower level compared to age-matched best performances of nationally competitive healthy athletes. Following a complicated post-transplant recovery a previously competitive swimmer has managed to complete a successful rehabilitation programme and return to swimming(125), taking part in several WTG and gaining many medals and records. Although transplant patients are performing at a lower level than healthy athletes, with a structured training program there is potential for them to return to performance levels which match their non-transplanted counterparts with adequate training, motivation and nutrition. Another example of a RTR returning to competition with non-transplanted athletes is seen in a case study of a professional boxer(126). Within three years of transplantation he had returned to regular training and commenced protein supplements to improve his body composition. Despite recommendations from physicians he continued to box professionally and has had no adverse effects to his graft function.

Heart Transplant

A patient, who developed cardiac failure due to dilated cardiomyopathy, underwent a cardiac transplant(127) and as part of his rehabilitation he was introduced to tennis. At 22-months post-transplant he was able to match the aerobic capacity of an age-matched member of the general population. He went on to participate successfully at the WTG and has managed to maintain his physiological function a decade later at his most recent assessments. Furthermore, an elite cyclist who experienced heart failure following a myocardial infarction (MI) received a heart transplant 4 months later(128,129). He resumed training after 1 month and underwent maximal exercise testing. Prior to his MI, his VO_{2max} was 58ml/kg/min, this remained reduced at both 6 and 12-months post-transplant, although there were significant improvements over time. These results imply that if an individual is physically fit prior to their transplant then this may positively impact on their subsequent work capacity. In active HTRs it may be beneficial to introduce a more intensive rehabilitation program so that they can return to competition faster.

It is difficult to predict which patients chronotropic incompetence will affect. A young HTR experienced a severely reduced exercise capacity with a workload of only 56% predicted(130),with the major contributor an insufficient HR response to activity. She had a pacemaker implanted and this significantly improved her physical performance, resulting in her winning several medals at the European Heart and Lung Transplant Games. This demonstrates that chronotropic incompetence can be successfully treated and it does not necessarily limit subsequent athletic performance.

Further case-reports have shown that, following an intensive endurance training program, HTRs are able to improve maximal power, oxygen consumption, resting and submaximal HR and ventilator anaerobic threshold(131). One such report featured a HTR who completed the Boston marathon in less than six hours with no observed complications(131) and the second successfully competing for an intercollegiate conference championship soccer team(132). Additionally, in endurance-trained HTRs(133), graded exercise does not alter levels of malondialdehyde in either HTRs or healthy controls and there is also no difference in glutathione peroxidase activity or vitamin E levels suggesting that exercise to fatigue does not promote an increase in oxidative stress in the blood of HTRs.

Heart and Lung Transplant

A patient with cystic fibrosis successfully underwent a HLTx(134). One year after surgery, exercise capacity was slightly reduced due to cardio-circulatory rather than ventilatory limitations. In the 10-years after transplantation he took part in strenuous training in order to compete in sports events for transplant patients. Exercise testing revealed better-than-normal aerobic and ventilatory capacity as characterized by a noticeably high oxygen uptake, oxygen pulse and delayed onset of ventilatory anaerobic threshold. This suggests that patients who have had a HLTx are capable of achieving high levels of physical fitness and can perform well in competitive environments. Therefore, those patients who are motivated to return to intense physical activity should be encouraged, as their maximal physical capabilities are often not reached by conventional rehabilitation.

Sporting Performance in an Extreme Environment

Performance in an extreme environment has been assessed by studying RTRs whilst trekking in the desert(135). There were minimal differences between transplant and healthy-controls for BP, hydration status, walking velocity and intensity of physical activity. The selected transplant patients, who had a creatinine clearance>55ml/min, showed a near-normal physical performance and acclimatisation to the extreme conditions of the desert environment which suggests that performance of RTRs can be maintained even in challenging environmental conditions. Moreover, 6 LivTxRs and 15 healthy controls participated in a trek up Mount Kilimanjaro in Tanzania, with an ascent of 5895m(136). Most of the participants successfully completed the trek (83% LivTxRs vs 84.6% controls). Of those who were unable to complete the climb, the LivTxR reported physical exhaustion and the two controls developed gastroenteritis and cerebral oedema respectively. Overall, there was no difference in physical performance, perceived exertion or altitude sickness between groups. However both experienced reduced oxygen saturations and a rise in BP and HR as altitude increased. The only significant difference was the development of hypertension in LivTxRs at

3950m. This study provides evidence that LivTxRs can safely participate in strenuous physical activity at high altitude, as their adaptive responses are similar to the control participants with few adverse events seen.

Risks of Exercise and Sport

There are risks to the transplant recipients of a return to sport, although documented adverse events are mostly linked to traumatic events. One RTR developed a traumatic lymphocoele following direct trauma from a squash ball(137) requiring marsupialisation of the lymphocoele in the peritoneal cavity although the patient recovered fully despite being very unwell initially. Additionally, following intense gym sessions and heavy lifting, a RTR reported anuria(138). Investigations revealed a haematoma secondary to a spontaneous pseudocapsular bleed or intense activity. Following evacuation of the blood clots in theatre, the patient began to pass urine and has made a full recovery.

Infection remains a concern in transplant recipients and, as exercise can be detrimental to the immune system, it should be considered when athletes who are already immunosuppressed are training intensely(139). After cycling in an 81km event, 10 RTRs and 10 healthy-controls underwent simulated exposure to pathogens(140). Analysis revealed an oppositional pattern of gene expression in RTRs compared to controls. In addition, in RTRs several apoptotic genes were over-represented whereas immune response genes were seen more commonly in controls. RTRs also had a significantly lower relative increase in neutrophils following the bout of exhaustive exercise(141).

In HTRs, one study discovered that lymphocyte subpopulations do not change during or after a six-week cycling exercise intervention(142),with only slight, non-significant, increases in total T cells, activated T cells, cytotoxic T cells and the T4+/T8+ ratio. Additionally, levels of immunosuppression in the bloodstream, episodes of rejection and infections are also unaffected. Another supervised 8-week aerobic program found there is no effect on plasma markers of inflammation (C-reactive protein, IL-6, TNF-α)(143). However the control group (HTRs receiving usual care) did have a significant rise in TNF-α following completion suggesting that activity does have a role in improving inflammation in HTRs.

Many individuals who receive a SOT, regard it as an opportunity to embark on a new healthier lifestyle or to re-engage with sporting activities they enjoyed prior to their transplant. There are many opportunities for SOTRs to partake in competitive sporting events and they are often able to achieve a fitness level near to that of the general population. Although the intensive training and exercise that they participate in is usually well-tolerated there are potential issues which may arise and therefore the benefits of exercise cannot simply be considered as for the general population. The effects of immunosuppression and the known increase in CV risk means that undertaking physical training may result in abnormal responses of the immune and CV systems to exercise. Given the paucity of research, and that it has been highlighted as a top research priority by a panel of transplantation and sports experts(144), further studies need to be conducted, so that evidence-based guidelines can be produced for this complex population, ensuring the best possible outcomes whilst limiting adverse events.

Conclusions and Recommendations

This review explores the benefits of structured exercise programs on the health of SOTRs. Incorporation of exercise into the routine post-operative care of transplant recipients should be strongly considered due to the improvement in many aspects of wellbeing in these patients and the absence of significant complications or side-effects.

Cardiovascular System

Exercise programs of combined aerobic and strength training of at least 3 months duration seem to be most effective at reducing BP in HTRs and LTxRs, with HIIT being a promising alternative. However RTRs seem to gain less benefit and this may be in part due to their underlying disease process and suboptimal renal function. Cholesterol and triglyceride levels do not appear to be augmented by exercise, with transplant recipients experiencing increases over time regardless of activity. LivTxRs, who are more likely to experience metabolic syndrome, did however have static total cholesterol:HDL cholesterol after training and this may represent a slowing of the progression of hypercholesterolaemia. Glycaemic control in RTRs is improved by a 6-month combined lifestyle education and endurance exercise program and LTxRs achieve benefit after 3-months of combined training. However LivTxRs experience worsening of glycaemic control despite 12-weeks of exercise and this again reflects the complexities of treating those with increased risk of metabolic syndrome, LivTxRs may benefit from longer interventions or modification of the training program to include dietary and lifestyle advice.

Body Composition

Both aerobic and combined resistance and aerobic training programs of at least 12-weeks duration are effective in increasing lean muscle mass, however there are few improvements seen in fat mass and overall body weight and BMI. Even when dietary advice has been incorporated into the programs, there have been no additional benefits observed. BMD decreases in transplant recipients post-operatively, predominantly due to immunosuppression and steroids, and this decline is reduced by targeted lumbar resistance training of at least 6-months duration. The greatest benefit is seen when combined with alendronic acid, although calcitonin supplementation is not effective. Results have been less promising in improving femoral BMD and also in LivTxRs, and this requires further investigation.

Exercise Capacity

Interventions comprising of aerobic or combined aerobic and resistance exercise have consistently been shown to improve workload and muscle strength. Durations of between 12-weeks and 12-months and both home-based and supervised training have been effective in all types of transplant recipient. These improvements are also translated into a significant improvement in physical performance in a variety of tests such as the 6MWT and the capacity to exercise until exhaustion.

In RTRs, HTRs and LivTxRs aerobic, resistance or combined training leads to consistent gains in aerobic capacity with improvements being seen in home-based and supervised programs and also in durations of between 10-weeks and 1-year, with frequencies of between 2 and 5 times-a-week. However LTxRs generally see minimal improvement in FVC, FEV_1, VO_{2max} in comparison to transplant recipients receiving usual care in studies of 12-weeks duration, irrespective of supervision. This is a reflection of their underlying disease status and they may require longer interventions to see a benefit. In HTRs, HIIT is more effective than moderate continuous exercise in improving exercise capacity and this could be a potential area of further investigation in other transplant recipients, particularly LTxRs.

Quality of Life

The most commonly used measures of HRQoL and anxiety and depression are the SF-36 and HADS respectively. In general there is an improvement in the overall SF-36 score and in particular physical functioning, vitality and general health in all types of transplant recipients, with changes being seen following supervised, inpatient and home-based exercise of varying types. Measures of mental health prove more variable, with no clear trend emerging with regards to which type of exercise intervention is most beneficial. Similarly, when anxiety and depression are assessed, a short 10-week program of cycling for RTRs significantly improved both anxiety and depression, whereas an 8-week combined program for HTRs showed only a statistically significant improvement in depressive symptoms and in LivTxRs, 12-weeks of aerobic and strength training failed to show an improvement in either anxiety or depression. Structured exercise programs may be useful in improving anxiety and depression and more importantly they are not detrimental to mental health.

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Conflict of Interest

J. Neale, A.C Smith and N.C Bishop declare that they have no conflict of interest.

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