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Health-related fitness and quality of life following steroid withdrawal in renal transplant recipients

Patricia L. Painter, K.S. Topp, J.B. Krasnoff, D. Adey, A. Strasner, S. Tomlanovich, and P. Stock

Department of Physiological Nursing, University of California at San Francisco, San Francisco, California; Graduate Program in Physical Therapy, University of California at San Francisco, San Francisco, California; Division of Nephrology, Department of Medicine, University of California at San Francisco, San Francisco, California; and Division of Transplantation, Department of Surgery, University of California at San Francisco, San Francisco, California

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Background. Exercise capacity increases significantly soon after transplantation; however, over time it does not further improve and patients remain low compared to normal levels. The limitations to exercise following transplantation have not been identified, but may be related to immunosuppression therapy regimens that include prednisone.

Methods. We studied health-related fitness measures (cardiorespiratory fitness, muscle strength, and body composition) and quality of life in renal transplant recipients randomized into two groups: those using standard maintenance immunosuppression, including prednisone therapy ($N = 14$); and those undergoing rapid withdrawal of steroids using Simulect® [interleukin-2 (IL-2) receptor inhibitor] ($N = 9$). Testing was done at 3 and 12 months following transplant and the 12-month data were compared to 15 normal sedentary controls.

Results. Compared to those maintained on steroids, the steroid withdrawal group showed greater gains in VO_{2peak} ($P = 0.05$) and quadriceps peak torque ($P = 0.05$) and greater gains in the vitality score and the Physical Composite Scale on the SF-36 questionnaire ($P < 0.05$). At 1 year, all patients had significantly lower exercise capacity compared to the sedentary controls ($P = 0.01$). No differences were observed in body composition, with both patient groups increasing in body weight (primarily body fat) over time. At 12 months, all patients were not different in body fat percentage compared to the sedentary controls.

Conclusion. We conclude that prednisone is not the cause for increased body fat following transplantation; however, it may contribute to lower spontaneous improvements in exercise capacity possibly by limiting increases in muscle strength. The low exercise capacity in all transplant recipients studied at 1 year suggests a need for exercise training to optimize physical functioning following transplant.

Key words: exercise capacity, health-related fitness, renal transplantation, prednisone withdrawal.

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Patients presenting for renal transplantation are limited in their exercise capacity [1–12]. Although exercise capacity improves dramatically soon after successful transplantation [7, 13], patients who remain inactive have markedly reduced exercise capacity at 1 year posttransplant [14, 15]. Kempeneers et al [16] reported that exercise capacity is limited following transplantation by skeletal muscle myopathy, which is not fully corrected with exercise training. Although there are many possible factors contributing to limitations to exercise in patients with end-stage renal disease (ESRD) treated with dialysis [4, 10, 11, 17, 18], cause for persistent limitation following transplant has not been clearly identified. The effects of immunosuppression, specifically glucocorticoids, on muscle function and structure is well documented by Horber et al [19, 20]. It is unclear whether the absence of steroids from maintenance immunosuppressive regimens improve exercise capacity, muscle structure, or muscle function.

Glucocorticoids cause proximal muscle weakness and atrophy. Ultrastructural abnormalities in skeletal muscle include reduced myofibrillar mass, mitochondrial volume, and decreased capillary number. Lower extremities typically are the first affected, demonstrating the first signs of weakness during climbing stairs and rising from chairs. Quadriceps strength is markedly reduced in both kidney and heart transplant recipients [16, 20, 21] and reported to be 80% [20] and 69% [22] of untrained sedentary control subjects. The atrophy of skeletal muscle with administration of glucocorticoids is related to increased amino acid efflux and decreased rates of protein synthesis. Additionally, glucocorticoids may also reduce mitchondrial respiration in skeletal muscle [23–25]. Regardless of the mechanism, it is clear that the atrophy results in reduced muscle function, which could affect overall physical functioning and quality of life [21]. Maintenance steroid therapy may attenuate improvements in

fitness following transplant. The availability of newer, more specific immunosuppression provides the opportunity to withdraw patients from prednisone following transplant and offers the promise of achieving normal levels of fitness.

The purpose of this study is to compare health-related fitness (cardiorespiratory fitness, muscle strength, and body composition) and quality of life over the first year following renal transplantation in patients with rapid elimination of steroids with recipients managed with a standard immunosuppression regimen that includes prednisone.

METHODS

Subjects

Kidney transplant recipients were recruited from the population of approximately 290 patients per year transplanted at the University of California, San Francisco (UCSF). All patients were unsensitized recipients of first cadaveric, living related, or living unrelated donor renal transplants. Sedentary controls were recruited from the hospital staff and the larger community. Recruitment attempted to match controls to the patients for age and activity (i.e., all were physically inactive).

Patients were a part of a larger study being conducted at UCSF studying the efficacy of steroid-free maintenance immunosuppression regimens. This study randomly assigned patients to one of two groups: (*1*) induction therapy with an interleukin-2 (IL-2) inhibitor (Simulect®) and rapid elimination of prednisone versus (*2*) induction therapy and maintenance immunosuppression, including prednisone (see **Prednisone Withdrawal Protocol** below). The investigators were blinded to the prednisone treatment group. The patients signed a separate consent for this study, which was approved by the UCSF Committee on Human Research and the Advisory Committee for the UCSF General Clinical Research, where the studies were completed.

Patients were recruited from the adult renal transplant population (i.e., >18 years of age). Patients were excluded from the rapid elimination of steroid study if they had (*1*) positive T-cell cross match or ABO incompatibility against the donor; (*2*) previous or multiple organ transplants; (*3*) evidence of transplant rejection; (*4*) increased risk for graft rejection; or (*5*) a last panel reactive antibody level greater than 30% at the time of transplantation. Further exclusion criteria included (1) human immunodeficiency virus (HIV) positivity; (*2*) active hepatitis; (*3*) history of malignancy; (*4*) history of myocardial infarction within six months prior to the study; or (*5*) cardiac arrhythmias or other severe or unstable medical conditions. Additional exclusion criteria for the exercise testing study included orthopedic or musculoskeletal disorders that would prevent completion of the exercise testing or any absolute contraindications to exercise testing as established by the American Heart Association [26] or American College of Sports Medicine [27].

Prednisone Withdrawal Protocol

A total of 36 transplant recipients and 15 sedentary control subjects were recruited into the study. The immunosuppression protocol was as follows. All patients (in both groups) received basliximab (Simulect®, Novartis Pharmaceuticals, East Hanover, NJ, USA) (20 mg intravenously) on days 0 and 4, Cyclosporin (Neoral®, Novartis Pharmaceuticals) (4 to 5 mg/kg orally) twice daily starting postoperative day 1 and mycophenolate mofetil (Cellcept®, Roche Laboratories, Nutley, NJ, USA) (1 g orally preoperatively, then 1.0 to 1.5 g orally twice daily starting postoperative day 1). Prednisone was given to all patients at the following doses postoperatively: day 0, 500 mg methylprednisolone (Solumedrol) intravenously; day 1, 250 mg Solumedrol intravenously; and day 2, 125 mg Solumedrol intravenously. Patients randomized into rapid elimination of steroids were decreased to 30 mg at day 4 and were withdrawn at day 5. Those randomized into standard prednisone maintenance therapy were tapered to 20 to 30 mg/day of prednisone over day 4 to day 20. From day 21 to day 90, they were tapered in their final prednisone dose that ranged from 5 to 10 mg/day. This was a standard taper of 5 mg decrease every other week with the final dose determined primarily by body weight. Maintenance immunosuppression for both groups included standard CellCept® dosing (2 to 3 g/day) and Neoral® to maintain trough levels 200 to 250 ng/mL.

Testing

Patients underwent baseline testing at 3 months posttransplant with repeat testing at 12 months posttransplant. The testing was all performed on a single visit and included symptom-limited treadmill exercise testing, isokinetic muscle function testing, body composition analysis, and completion of a quality-of-life questionnaire. Muscle biopsies were also performed, the data of which are presented elsewhere [28].

Cardiorespiratory exercise testing. Symptom-limited exercise testing was performed on a treadmill. Oxygen uptake (VO_2) was determined using a computerized open-circuit spirometry system (Quinton QMC, Bothell, WA, USA), which was calibrated against known gases prior to each test. Expired respiratory gases were analyzed for volume, fractions of oxygen and carbon dioxide, and oxygen uptake was calculated. Peak oxygen uptake (VO_{2peak}) is expressed in terms relative to body weight (mL O_2/kg body weight/minute). Age-predicted VO_{2peak} was determined using formulas reported for sedentary normal individuals by Bruce, Kusumi and Hosmer [29]: VO_{2peak} for males = 57.8–0.445 × age; and VO_{2peak} for females = 42.3–0.356 × age.

The branching protocol [30] was used for testing,

which established a comfortable walking speed, after which the work intensity was increased by increasing grade to achieve approximately 1 metabolic unit increments between stages. The work rate increased every 2 minutes until the subject was unable to continue (volitional fatigue) or until there was indication to discontinue the test (i.e., electrocardiographic changes, inappropriate blood pressure response) [27]. A 12-lead electrocardiogram was monitored continuously throughout the test, and blood pressure was auscultated at every stage. Ratings of perceived exertion (subjective rating of effort) (RPE) were measured at each stage on a 6 to 20 scale [31].

Muscle strength. Quadriceps muscle strength was measured using a computerized isokinetic muscle function testing system (Biodex II, New York, NY, USA). The right leg was attached to a dynamometer allowing for isolation of the quadriceps muscle group. The patient performed maximal effort knee extensions (kicks) at a controlled speed of 180° per second for 20 repetitions. Variables measured for analysis were peak torque (the highest torque developed during the set of repetitions measured in foot pounds) and peak torque per body weight (%).

Body composition. Body composition was determined using dual energy x-ray absorptiometry (DEXA) (Hologic QDR 4500, Bedford, MA, USA). The machine was calibrated daily using known phantoms. The software from a full body scan determined bone mineral density (g/cm^2), lean body mass (g), and fat mass (g). Percent body fat was calculated from the fat mass and total body weight.

Health-related quality of life. The Medical Outcomes Short Form (SF-36) questionnaire was used to evaluate self-reported domains of health status [32]. The SF-36 is a 36-item questionnaire that includes eight components of health-related quality of life: physical functioning (PF), role limitations due to physical health (RP), body pain (BP), general health (GH), vitality (VT), social functioning (SF), role limitations due to emotional health (RE), and mental health (MH). These scales are scored from 0 to 100, with higher scores being more positive (i.e., less pain, less limitation). Normalized scores representing overall physical functioning and mental functioning are calculated from the individual scales and are presented as the physical composite scale (PCS) and the mental composite scale (MCS). The PCS includes the dimensions of PF, RP, BP, GH, VT, and SF. The MCS is composed of the RE and MH and includes elements of the GH, VT, and SF scales as well [33]. The scaling of each of these component scores is around 50 for normal population values. Questionnaires were given to patients following each testing session to be completed independently and returned by mail.

Activity participation. Activity levels were determined by self-report and subjects were classified as active or inactive using the following sequence of questions: Do you exercise regularly? If yes, what type(s) of exercise do you do? How many times per week do you exercise? How long do you exercise per session? How hard do you exert yourself during your exercise (rating 1 to 5). This allowed us to classify patients into active or inactive according to the Surgeon General's Report Guidelines [34]. The classification of active required cardiovascular exercise three or more times per week for at least 30 minutes per session at an intensity described as "somewhat hard" or greater. All others were classified as inactive.

Data analysis

Descriptive statistics (means, standard deviations) were calculated for all continuous variables. Frequencies were generated for other variables. Repeated measures analysis of variance with 1 within factor (time, baseline and 12 months) and 1 between factor (group, standard therapy versus steroid withdrawal) was used to determine differences between the two patient groups over the study time. This analysis allows for testing of the main effects of group and the main effects of time as well as the interaction of group by time. The group by time interaction indicates whether the change over time differs between the groups. Univariate analysis of variance was used to compare the two patient groups at 12 months to the control subjects. This analysis was performed using gender as a covariate since the control group had more females than the patient groups. Statistical significance was set at $P < 0.05$.

RESULTS

Subjects

Since repeated measures analysis of variance only allows for inclusion of those subjects who completed both baseline and 12-month testing, 25 transplant recipients are included in the analysis (10 in the rapid elimination of steroids group and 15 in the standard immunosuppression therapy, including prednisone). Reasons for loss of subjects at the 12-month testing included four lost to follow-up, one transplant rejection, two with medical contraindications to testing at 12 months (foot ulcer and chronic hypotension), two with a change to prednisone in the steroid elimination of steroid protocol, two who refused repeat testing. Two diabetic patients were not included in the analysis. Fifteen sedentary control subjects completed one testing session for comparative analysis. The controls were apparently healthy, with no medical conditions and were not taking any medication. All control subjects were sedentary (i.e., not participating in any regular program of exercise).

Demographics, laboratory values, and immunosuppression medications for those subjects who completed

Table 1. Demographics (mean ± SD)

	Steroid avoidance ($N = 9$)	Standard therapy ($N = 14$)	Sedentary controls ($N = 15$)
Gender (m/f) %	6/3 (66/33%)	11/3 (78/22%)	6/9 (40/60%)
Age *years*	48.3 ± 12.7	46.8 ± 14.4	50.7 ± 6.7
Ethnicy (Number) %			
Caucasian	7 (78%)	7 (50%)	9 (60.0%)
Hispanic	2 (22%)	3 (21.7%)	2 (13.3%)
African American		1 (7.1%)	1 (6.7%)
Asian/Pacific Islander		2 (14.3%)	3 (20%)
Other		1 (7.1%)	
Cause of renal failure			
Glomerulonephropathy	1 (11.1%)	2 (14.3%)	
Hypertension	2 (22.2%)	2 (14.3%)	
IgA nephropathy	2 (22.2%)	1 (7.1%)	
PCKD	—	3 (21.4%)	
Hydronephrosis	1 (11.1%)	—	
Unknown	3 (33.3%)	4 (28.6%)	

PCKD is polycystic kidney disease.

Table 2. Immunosuppression and laboratory values for patient group (mean ± SD)

	Steroid avoidance	Standard therapy
Immunosuppression		
Prednisone *mg/day*		
Baseline	—	13.2 ± 3.5
12 months	—	6.9 ± 2.5[a]
Cyclosporine *mg/day*		
Baseline	472.2 ± 198.6	491.7 ± 223.4
12 months	322.2 ± 148.1[a]	312.5 ± 146.4[a]
Mycophenolate mofetil *mg/day*		
Baseline	1583.3 ± 707.2	1545.1 ± 650.1
12 months	1333.3 ± 559.0	1145.5 ± 694.8
Laboratory values		
Creatinine *mg/dL*		
Baseline	1.44 ± 0.41	1.27 ± 0.41
12 months	1.50 ± 0.52	1.36 ± 0.61
Blood urea nitrogen *mg/dL*		
Baseline	25.3 ± 10.3	29.8 ± 10.7
12 months	26.7 ± 7.9	25.5 ± 10.3
Hematocrit %		
Baseline	34.4 ± 4.2	32.0 ± 12.8
12 months	38.8 ± 7.4[a]	40.2 ± 6.4[a]

[a] $P = 0.01$ compared to baseline

both baseline and 12-month testing and for the sedentary control group are shown in Tables 1 and 2. The patients were not on any medications that would affect the heart rate response to exercise (specifically β blockers). There were no differences in age among the three groups and no differences in laboratory measures of renal function between the two patient groups at either baseline or 12 months.

Body composition

All patients gained weight over the study time period. The weight gained predominantly was fat, as indicated by a significant effect of time in total fat mass ($F_{1,20} = 5.15$; $P = 0.03$) and percent fat ($F_{1,20} = 28.33$; $P < 0.0001$) (Table 3). There was no difference between the patient groups in the increases in fat mass or percent fat over time. At 1 year, both groups of patients had a greater fat mass than the controls regardless of steroid usage ($P < 0.05$), even when controlling for gender differences between groups. The percent fat was, however, not different at 1 year between the patients and the controls. There were no differences in lean body mass over time or between the patient groups and controls at 12 months, even when controlled for gender differences.

Table 3. Body composition (mean ± SD)

	Steroid avoidance	Standard therapy	Sedentary controls
Height *cm*	173.3 ± 7.9	172.6 ± 11.3	168.3 ± 8.9
Weight *kg*			
Baseline	77.5 ± 11.1	78.4 ± 14.4	71.9 ± 11.2[b]
12 months	81.2 ± 12.3[a]	81.5 ± 14.9[a]	
BMI			
Baseline	26.0 ± 4.5	27.1 ± 4.9	25.4 ± 3.7
12 months	27.4 ± 4.8	27.1 ± 4.9	
Total lean mass *kg*			
Baseline	53.7 ± 9.9	54.7 ± 9.8	48.12 ± 7.6
12 months	54.9 ± 11.0	55.9 ± 10.9	
Total fat mass *kg*			
Baseline	27.7 ± 7.9	21.3 ± 8.6	21.6 ± 7.1[b]
12 months	30.7 ± 13.7[a]	24.2 ± 9.6[a]	
% Fat			
Baseline	27.7 ± 7.9	28.4 ± 9.5	29.7 ± 7.4
12 months	30.7 ± 7.6[a]	29.0 ± 9.6[a]	

[a] $P < 0.05$ over time (from baseline to 12 months)
[b] $P < 0.05$ controls vs. all patients at 12 months

Table 4. Physiologic variables at peak exercise (mean ± SD)

	Steroid avoidance	Standard therapy	Sedentary controls
Peak VO_2 *mL/kg/min*			
Baseline	21.5 ± 4.6	25.3 ± 6.5	28.6 ± 3.7[b]
12 months	24.1 ± 6.5[a]	23.7 ± 86.0[a]	
% Age-predicted VO_2			
Baseline	66.6 ± 7.9	72.6 ± 15.0	96.8 ± 17.8[b]
12 months	74.6 ± 11.0[a]	66.2 ± 7.9[a]	
Peak heart rate			
Baseline	139 ± 26	144 ± 25	168 ± 13[b]
12 months	141 ± 2	131 ± 26	
Peak RPE			
Baseline	18.5 ± 1.0	17.4 ± 1.8	17.5 ± 1.9
12 months	17.8 ± 0.9	17.1 ± 2.9	
Respiratory exchange ratio			
Baseline	1.07 ± 0.08	1.06 ± 0.07	1.12 ± 0.07[b]
12 months	1.10 ± 0.07	1.05 ± 0.07	

RPE is rating of perceived exertion.
[a] $P < 0.05$ over time (from baseline to 12 months)
[b] $P < 0.05$ controls vs. all patients at 12 months

Cardiorespiratory fitness

Physiologic data at peak exercise are shown in Table 4. There were no differences at baseline between the patient groups in the VO_{2peak} measurements. Patients

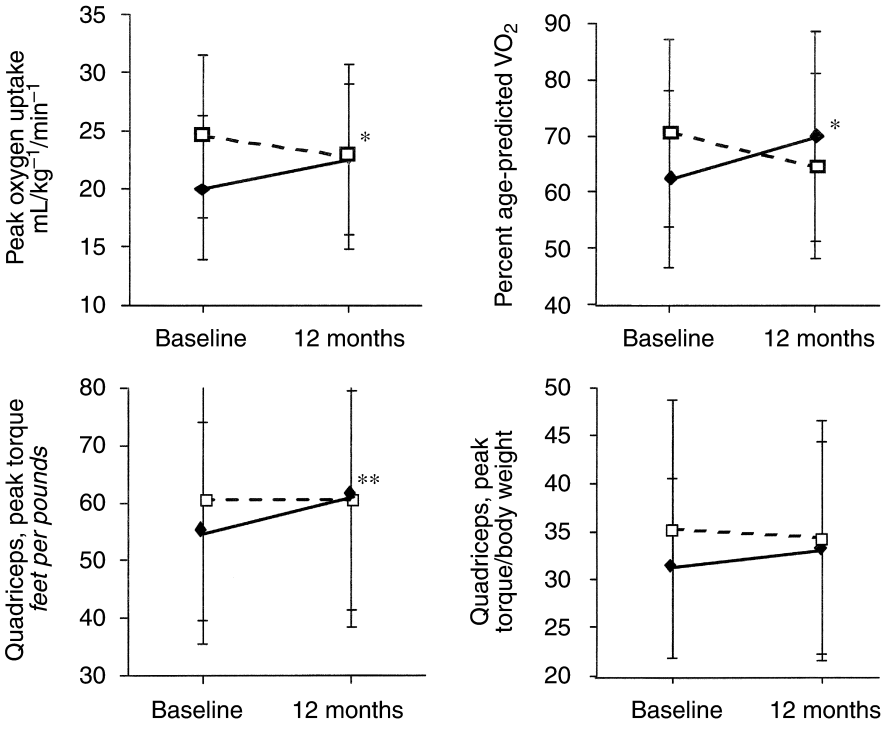

Fig. 1. Changes in fitness measures from baseline to 12 months. Symbols are (□) on prednisone; (◆) off prednisone. *$P < 0.01$, time by group interaction; **$P = 0.05$, time by group interaction.

successfully maintained on steroid-free immunosuppression had significantly greater gains in VO_{2peak} than the standard therapy group (time by group interaction: $F_{1,20} = 7.16$; $P = 0.01$). The standard therapy actually decreased in their VO_{2peak} levels (Fig. 1).

At 1 year posttransplant, all patients remained lower in both VO_{2peak} and in percent of age predicted VO_{2peak} compared to the sedentary control subjects (Table 4).

All transplant recipients achieved a perceived exertion rating (RPE) >17 (which indicates a subjective maximal effort), which was not different than the subjective efforts of the controls. The respiratory exchange ratio (RER) (a physiologic indicator of maximal effort) of >1.0 was also achieved by all patients. However, the RER was significantly lower in all patients at 1 year compared to the controls ($P = 0.007$) (Table 4), suggesting a muscle metabolic limitation to higher levels of exercise in the patients.

Patient heart rates at peak exercise at 1 year were significantly lower than the sedentary controls (Table 4). Patients only achieved 75% to 78% of age predicted maximal heart rates, compared to 98% of age-predicted levels for the controls. Patients were not on any medications that would affect heart rate response to exercise.

Isokinetic muscle function

There were no differences in baseline values for quadriceps peak torque at a contraction speed of 180° per second. There was a significant increase in this measure in all patients over time ($F_{1,20} = 3.89$; $P = 0.05$). There was a significant time by group interaction in this measure, indicating that those on standard therapy did not change over time, but the group maintained on the steroid-free regimen increased in muscle strength ($F_{1,20} = 3.72$; $P = 0.05$) (Table 5) (Fig. 1). The values of peak torque/ body weight were not different over time or between groups over time. There was no difference in the peak torque or peak torque/body weight at 1 year between either of the patient groups and the sedentary control subjects, even when controlled for gender.

Table 5. Isokinetic muscle test variables (mean ± SD)

	Steroid avoidance	Standard therapy	Sedentary controls
Peak torque (foot pounds) *180°/second*			
Baseline	56.1 ± 19.8	60.5 ± 21.8	57.1 ± 15.0
12 months	61.8 ± 23.6[a]	60.5 ± 19.6	
Peak torque/body weight %			
Baseline	32.5 ± 8.8	35.9 ± 13.8	39.1 ± 12.1
12 months	34.3 ± 11.3	34.8 ± 12.5	

[a] Time × group interaction; $P = 0.05$

Health-related quality of life

The scores for the SF-36 questionnaire for the two patient groups are found in Table 6. There were no statistically significant differences between the two groups in any of the scale scores at baseline. Statistically significant time by group interactions were found in the vitality score ($F_{1,19} = 4.02$; $P = 0.048$) and in the Physical Composite Scale ($F_{1,19} = 3.77$; $P = 0.05$). This indicates

Table 6. SF-36 scale scores

Scale score on SF-36	Steroid avoidance	Standard therapy	Sedentary controls
Physical functioning			
Baseline	82.1 ± 17.3	68.3 ± 18.8	95.0 ± 6.5[c]
12 months	89.3 ± 17.6	69.4 ± 23.1	
Role physical			
Baseline	37.5 ± 42.5	50.0 ± 35.4	98.2 ± 6.7[c]
12 months	75.0 ± 40.0[a]	63.9 ± 43.5[a]	
Bodily pain			
Baseline	64.4 ± 20.6	71.9 ± 21.8	91.8 ± 13.9[c]
12 months	75.6 ± 14.3	67.2 ± 26.5	
General health			
Baseline	64.4 ± 20.6	70.0 ± 20.3	80.7 ± 13.1[c]
12 months	64.4 ± 14.3	61.7 ± 18.9	
Vitality			
Baseline	50.0 ± 27.7	69.8 ± 14.6	65.4 ± 22.9
12 months	64.4 ± 22.8[b]	65.6 ± 12.8[b]	
Social functioning			
Baseline	78.1 ± 21.9	73.6 ± 21.1	97.3 ± 7.2[c]
12 months	84.4 ± 17.4	68.0 ± 25.1	
Mental health			
Baseline	86.0 ± 12.1	78.2 ± 14.0	81.7 ± 13.3
12 months	83.5 ± 14.7	80.4 ± 9.6	
Role emotional			
Baseline	66.7 ± 39.8	77.7 ± 37.3	92.8 ± 19.3
12 months	91.7 ± 23.6	77.7 ± 37.3	
Physical composite score			
Baseline	42.0 ± 8.6	42.9 ± 7.5	55.45 ± 2.9[c]
12 months	48.4 ± 8.7[b]	42.6 ± 12.1[b]	
Mental composite score			
Baseline	52.6 ± 9.2	51.9 ± 9.7	53.1 ± 7.6
12 months	56.0 ± 3.4	52.3 ± 9.1	

[a] Effect of time (patients), $P < 0.05$
[b] Time × group (patients) interaction, $P < 0.05$
[c] $P < 0.01$ compared to all patients

a difference in the change over time between the two groups, with the prednisone withdrawal group having greater gains and the prednisone-treated group actually deteriorating in some scale scores or showing no change in others. Trends toward increases over time in the steroid-elimination group with no change or decreases in the standard therapy group were observed in the following scales: bodily pain, role limitations/physical, social functioning, and mental composite score. All patients increased in the role physical scale (effect of time, $F_{1,19} = 5.14$; $P = 0.03$); however, the increase in the steroid minimization group was much greater than that of the standard therapy group. The variation in the scores was high, thus the time by group interaction was not significant.

At 12 months posttransplant, the patients had significantly lower scores on all the physical scales, including the Physical Composite Scale, compared to the sedentary normal controls ($P < 0.003$). The patients did not differ from the controls in any of the mental scale scores except for social functioning ($P < 0.001$) (Table 6).

DISCUSSION

The use of Simulect® induction following renal transplantation has been reported to have no detrimental clinical outcomes and is thought to be another alternative for immunosuppression therapy in unsensitized patients [35, 36]. The irritating side effects and clinical consequences of long-term steroid therapy, as well as the emergence of other more specific immunosuppression, have led to increasing interest in the possibility of steroid-minimizing or steroid-free immunosuppression therapy. This study is the first to document the effects of steroid minimization on health-related fitness. Measures of fitness are important in that they are predictive of all-cause mortality and cardiovascular mortality in the general population [37]. Although no studies have linked fitness to outcomes in transplant recipients, optimization of functioning following transplantation is in the best interest of patients and the transplant community. Limitations to exercise have not been identified in transplant recipients; however, steroid therapy and the resulting muscle dysfunction has been suspected as one of the possible limiting factors [7, 16, 19, 20, 38].

The weight gain following transplant in both patient groups confirms the cross-sectional data presented by Van Den Ham et al [39] who found no differences in body composition between groups of kidney transplant recipients treated with 0, 5, or 10 mg per day of steroids. They also reported no relationship between the cumulative dose of steroids and body composition in this group of 77 renal transplant recipients. It is highly possible that lifestyle factors, specifically physical activity, determine body composition more than steroid doses. Van Den Ham et al [39] found that leisure-time physical activity was positively related with percentage of lean body mass and inversely related with fat mass. We reported that physically active transplant games participants had significantly lower body mass index (BMI) and percent body fat than did those who were physically inactive [14]. However, in an intent-to-treat exercise intervention over the first year posttransplant, we did not find any differences in body composition between the exercise intervention group (33% of whom were not regularly active) and those in the usual care group [15]. However, secondary analysis comparing active versus inactive subjects (regardless of randomization groups) showed a significant trend toward lower BMI and percent fat in the active subjects. There was no dietary intervention in that study and caloric intake was not different between the groups.

This study is limited by the small numbers; however, the observations of statistically significant findings in many of the measurements would not be expected in small numbers. Thus, we think that the fact that statistical significance was observed in repeated measures analysis of variance was particularly impressive and represent real difference in exercise responses over the study time between the two groups. We observed similar decrements in functioning in usual care group (treated with

prednisone) over the first year posttransplant in another study that included a larger number of subjects [15].

The greater increases in peak VO_{2peak} in the patients maintained on the steroid-free regimen suggests that, following renal transplant, there is a greater spontaneous increase in functioning in those not on steroid therapy. The repeated measures analysis of variance is an analysis of change over time between the two groups. Although there was a trend (NS) for the prednisone withdrawal group to have lower values at baseline, the trend of those maintained on prednisone to deterioration in function over 1 year posttransplant is similar to that reported previously in a larger study [15]. Patients maintained on steroids showed a similar trend toward deterioration in functioning over the first year to what we reported in the usual care group of the exercise intervention trial [15]. In that study, the VO_{2peak} at 1 year was significantly higher in the exercise group compared to the usual care group, which had VO_{2peak} values similar to high-functioning dialysis patients. This was also reported in our cross-sectional analysis of active versus inactive transplant games participants [14]. There was no exercise intervention or exercise recommendations given to any subject in the current study. Only two subjects (both in the standard therapy group) reported regular participation in physical activity.

The greater gains in VO_{2peak} could be related to an improvement in muscle functioning, as evidenced by the increased quadriceps muscle strength gains in the steroid avoidance group. Shephard et al [40] reports that lower extremity muscle mass is a determinant of external work performed, thus determining VO_{2peak}. Although our patient group as a whole did not have lower lean mass compared to the control group, there were more males in the patient group than the control group. However, when the comparison with the normals was controlled for gender, there was no difference in lean body mass between the patients and the controls. At the 1-year testing time, the patients not on prednisone in this study had significantly larger muscle fiber size (type IIX) than those on prednisone [28] and showed ultrastructural differences that would suggest facilitated muscle contraction and oxygen utilization. It is possible that the microscopic and ultrastructural changes did not show up in the total lean mass measurements, but could contribute to the differences observed in muscle strength gains and VO_{2peak}.

Exercise capacity could also be limited by a blunted heart rate response to exercise, which is typically seen in patients with ESRD treated with dialysis [3, 4, 8, 17]. This blunted heart rate response observed in both patient groups in this study would limit maximal cardiac output, which is one of the primary determinants of oxygen uptake as defined by the Fick equation (VO_2 = cardiac output $\times$ arteriovenous O_2 difference). Until all determinants of VO_2 are actually measured in this patient group, there is no way to determine the relative contributions of cardiac output and peripheral oxygen utilization.

Measurement of health-related quality of life is difficult, and often the variation in the scale scores necessitates large sample sizes to determine differences between groups. Thus, the striking trends with statistical significance achieved in changes in the vitality score and the overall Physical Composite Scale are impressive, considering the small numbers of subjects in this study. The trends of the physical function scale, the bodily pain, and the significant time by group interactions in the vitality and Physical Composite Scale parallel the physiologic measurements of VO_{2peak} and muscle strength (i.e., improved scores in the steroid avoidance group and either no change or decline in the standard therapy group). Lack of energy is a common complaint in transplant recipients. It may be possible that this overall lack of energy is due to prednisone therapy. Many more subjects are required to confirm the effects of steroid minimization on quality of life; however, it appears in this preliminary study that overall quality of life is improved with steroid elimination.

Although there were significant gains in cardiorespiratory fitness and muscle strength in those patients not on prednisone, it should be pointed out that all the patients remained low in VO_{2peak} compared to the sedentary normal controls. The sedentary normal controls achieved 96% $\pm$ 18% of their age-predicted maximal capacity, compared to only 67% in the patients. Thus, although significantly greater gains were observed in those not taking prednisone, all patients remain low in physical functioning at 1 year posttransplant. Exercise training is thus warranted for this patient group for optimizing functioning following transplant. Given the greater gains in patients not on prednisone (and actual deterioration in those in the standard care), it is possible that those patients not taking prednisone will be able to achieve higher levels of cardiorespiratory fitness and muscle strength with exercise training than those remaining on prednisone.

CONCLUSION

Withdrawal of steroid therapy following renal transplantation results in greater gains in the cardiorespiratory fitness, and muscle strength. It has, however, had no effect on body composition. Lifestyle interventions such as exercise training and dietary modification, which are guidelines for reduction of cardiovascular risk, are necessary for optimizing health-related fitness following renal transplantation.

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Reprint requests to Patricia Painter, Ph.D., Department of Physiological Nursing, University of California at San Francisco, 2 Koret Rd., Box 0610, San Francisco, California 94143-0610.
E-mail: painter@itsa.ucsf.edu

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