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Exercise training ameliorates progressive renal disease in rats with subtotal nephrectomy

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Exercise training ameliorates progressive renal disease in rats with subtotal nephrectomy. To determine the effect of chronic exercise training on renal function in animals with moderate renal insufficiency, rats with 75% renal ablation were either exercise trained by swimming for two months or remained sedentary. Glomerular filtration rate was significantly higher in trained (1.89 ± 0.07 ml/min) than in sedentary rats (1.52 ± 0.11 ml/min). No change was observed in renal blood flow or the degree of hypertension. Proteinuria was reduced in trained (13.6 ± 4.9 mg/24 hr) compared to sedentary animals (33.5 ± 9.2 mg/24 hr). The degree of glomerulosclerosis was much less prominent in trained animals. Plasma, low-density lipoprotein cholesterol-levels and total triglycerides were reduced in trained compared to sedentary rats. This study suggests that chronic exercise training ameliorates the progression of renal disease and improves plasma lipids in rats with moderate renal insufficiency. The mechanism for this improvement in renal function appears to be independent of the influence of systemic blood pressure.

Strenuous exertion in healthy humans produces a significant decline in glomerular filtration rate (GFR) and renal plasma flow (RPF). Both return to pre-exercise values within hours after the cessation of significant physical activity [1, 2]. Similar responses have been observed in other mammals after an acute exercise load [3]. Little information is available regarding the effect of continuous exercise training on renal function in the presence of impaired renal function and/or decreased renal mass [1, 4]. However, in healthy humans, continuous heavy physical exertion has been reported to significantly increase GFR as measured by inulin clearance [5]. Chronically exercised normal rats have been demonstrated to live significantly longer than nonexercised rats [6]. Although the mechanisms responsible for this effect are not clear at present, exercise could prolong longevity by reducing renal glomerulosclerosis and uremia, which are significant causes of mortality in rats.

The purpose of the present study was to determine the effect of chronic exercise training on the rate of progression of renal disease in rats with existing renal impairment due to reduced renal mass (subtotal nephrectomy). The natural history of the renal lesion in this model is well established, initially leading to remnant nephron hypertrophy and then to progressive glomerulosclerosis, hypertension, proteinuria, uremia, and death [7]. The effects of chronic exercise on plasma lipids and lipoprotein lipids were also studied since increased plasma, low-density lipoprotein cholesterol-levels have been proposed to exert nephrotoxic effects [8].

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Methods

Experimental design

Studies were conducted in six–week old, female Sprague–Dawley rats (Charles River Laboratories, Wilmington, Massachusetts, USA) weighing 90 to 110 g on arrival. Animals were housed five or six to a cage with a 12 hour light/dark cycle at 21°C ambient temperature, and free access to water and food (rat chow, containing 22.8% protein; Ralston Purina, St. Louis, Missouri, USA). Several days after arrival, all rats underwent reduction of renal mass. The right kidney was removed and one-half of the left kidney was infarcted by ligation of some of the terminal branches of the renal artery ("1-1/2 subtotal nephrectomy"). This degree of renal ablation was selected to produce a mild to moderate degree of renal impairment which did not lead either to a reduction in physical activity or excessive mortality before the completion of the training period. Surgery was performed under anesthesia with chloral hydrate (36 mg/100 g body wt given intraperitoneally). Animals were allowed to recover for one week after surgery, and baseline systolic blood pressure and urine and plasma creatinine, sodium and urea nitrogen were obtained in awake rats. Urine for protein and creatinine determinations was collected for 24 hours in individual metabolic cages while the rats were fasted but had free access to water. Rats were randomly assigned to either the exercise ($N = 41$) or sedentary group ($N = 37$). The exercise group was subjected to swimming for two hours daily at 37°C as described previously [9]. The sedentary group was handled in an identical manner throughout the course of the study, except swimming was omitted. After one and two months of study, the measurements of systolic blood pressure, urine and plasma creatinine, urea nitrogen, and urine protein were repeated. GFR, RPF, fractional excretion of sodium (FE_{Na}), and filtration fraction (FF) were determined in 26 exercised and 21 sedentary rats from renal clearances of inulin (C_{in}) and para-aminohippuric acid (C_{PAH}) and sodium measurements in urine and plasma after two months of exercise. At the completion of the clearance studies, rats were anesthesized with ether, kidneys were removed, and viable remnant tissue was dissected out, weighed, and fixed in 10% formalin for

Table 1. Effect of exercise training on body and heart weight, hematocrit, blood urea nitrogen, and systolic blood pressure in rats with a remnant kidney

	Body wt		Systolic BP				
	Baseline *g*	2 months *g*	1 month *mm Hg*	2 months *mmHg*	Hct %	Heart wt *g*	CHI
Sedentary	118 ± 2	263 ± 6	150.9 ± 5.9	149.6 ± 5.7	46.8 ± 0.36	0.805 ± 0.034	304 ± 7
Exercise	120 ± 1	280 ± 5	141.6 ± 6.6	145.1 ± 5.8	46.3 ± 0.52	0.918 ± 0.067	326 ± 20
P	NS	<0.05	NS	NS	NS	NS	NS

Values are mean ± SEM. Abbreviations are: Hct, hematocrit; CHI, cardiac hypertrophy index. Data were obtained following 2 months of treatment except where indicated. Baseline body weight was obtained 1 week after renal ablation. The sample sizes in sedentary and exercise groups were 37 and 41 at baseline, 35 and 40 at 1 month, and 21 and 26 at 2 months, respectively. Although 33 rats in the sedentary group and 37 rats in the exercised group were alive at 2 months, the remaining rats were utilized for studies related to the effects of exercise on muscle metabolism in uremia and did not have determinations of clearances or renal histology

[a] For comparison, systolic blood pressure in control rats averaged 118 ± 9 mm Hg

histologic analysis. Rats were exsanguinated and hearts were excised and weighed.

The effect of chronic exercise on plasma lipids and lipoprotein lipid profiles were studied in a separate group of male Sprague–Dawley rats subjected to 1-1/2 subtotal nephrectomy. One week later, rats began exercise training by swimming or remained sedentary [9]. Following two months of treatment, plasma cholesterol fractions and total triglycerides were measured. Sedentary non-uremic animals of the same age and fed the same diet, served as controls.

Clearance studies and blood pressure determination

All clearance studies were performed using standard clearance techniques and calculations in awake rats 24 hours after the last preceding swimming session [10]. Under light ether anesthesia, the tail vein was cannulated for intravenous infusion of 2% inulin and 0.1% para-aminohippurate in 0.9% NaCl. A polyethylene catheter (PE10) was placed in the femoral artery for blood sample collection. A silastic catheter for urine collection was inserted atraumatically into the bladder via urethra. Rats were passively restrained in lucite tube holders and allowed to recover from anesthesia for 40 minutes. A priming dose of 0.97 ml of inulin and PAH solution was given over 2-1/2 minutes followed by a sustained infusion given at 38.8 μl/min. Animals were equilibrated for one hour. After equilibration, urine was collected in three periods of 20 to 30 minutes each. Blood samples were obtained from the femoral artery at the beginning and end of each collection period, and plasma was separated for determination of inulin, PAH, and sodium.

Systolic blood pressure (SBP) was determined by tail artery occlusion pressure (Programmable Sphygmomanometer Pe 300', Narco Bio-Systems, Houston, Texas, USA) in awake rats after prewarming in a chamber with circulating air temperature 38°C for 10 minutes.

Renal function measurements

Inulin and PAH in urine and plasma for clearance calculations were determined using standard, manual colorimetric micromethods [10]. Sodium was determined by flame photometry. Urine protein was measured using the sulfosalicyclic-acid turbidity method [11]. Creatinine and urea nitrogen were measured colorimetrically on Beckman MicroAnalyzers (Beckman Instruments, Fullerton, California, USA). The presence of blood in the urine was determined using Lab-Stix (Miles Laboratories, Elkhart, Indiana, USA).

Histologic analysis

Light microscopy was carried out in a blind fashion on midline saggital sections of remnant kidney stained with para-aminosalicyclic acid. At least 50 consecutive cortical glomeruli were counted. Each glomerulus was assigned into one of five categories based on the degree of detectable morphological damage: "O"—no visible pathologic changes; "I"—mesangial thickening only with no other damage; "II"—appearance of focal areas of proliferative lesion and loop collapse in the glomerulus with or without generalized mesangial thickening; "III"—diffuse proliferative lesions and loop collapse, crescent formation with or without other lesions, some apparently functioning areas of the glomerulus; "IV"—total glomerular collapse, fibrosis/sclerosis, no functional architecture can be identified. The number of glomeruli in each category was expressed as percentage of the total number of glomeruli counted for each rat.

Calculations

Filtration fraction (FF) was calculated as a ratio of C_{in} and C_{PAH}. FE_{Na} was determined as a ratio of sodium concentration in urine and plasma, divided by C_{in}. Cardiac hypertrophy index (CHI) was calculated as a ratio of heart weight to body weight. The data from exercise and sedentary animals were compared for significance using non-paired Student's *t*-test. Paired analysis was utilized when comparing data from the same animals. All values are expressed as means ± standard error of the mean.

Plasma lipids and lipoprotein lipids

Cholesterol and triglycerides in plasma were measured using Technicon AutoAnalyzers (Technicon Instruments Corp., Tarrytown, New York, USA) [12]. Heparin manganese chloride was added to whole plasma to precipitate apoprotein B-containing lipoproteins before measurement of high density lipoprotein (HDL) cholesterol in the supernatant fraction. Very low density lipoprotein (VLDL) was separated from low density lipoprotein (LDL) and HDL by ultracentrifugation at d = 1.006, and LDL cholesterol was calculated as the difference between total cholesterol and the sum of VLDL and HDL cholesterol values.

Table 2. Urine protein excretion, inulin and PAH clearance, filtration fraction and fractional excretion of sodium in 2 month exercised and sedentary rats with a remnant kidney

	UP *mg/24 hr*	C_{in} *ml/min*	C_{in} *g kidney*	C_{PAH} *ml/min*	C_{PAH} *g kidney*	FF *%*	FE_{Na} *%*	Viable kidney *wt*
Sedentary $N = 21$	33.5 ± 9.16	1.52 ± 0.11	1.31 ± 0.11	4.57 ± 0.26	17.63 ± 1.10	33.86 ± 1.66	1.68 ± 0.21	1.23 ± 0.07
Exercise $N = 26$	13.6 ± 4.9	1.89 ± 0.07	1.62 ± 0.08	4.87 ± 0.16	17.95 ± 1.02	39.23 ± 0.87	1.62 ± 0.14	1.22 ± 0.05
P	<0.05	<0.01	<0.05	NS	NS	<0.01	NS	NS

Values are mean ± SEM. Abbreviations are: UP, urine protein; C_{in}, inulin clearance; C_{PAH}, para-aminohippurate clearance; FF, filtration fraction; FE_{Na}, fractional excretion of sodium

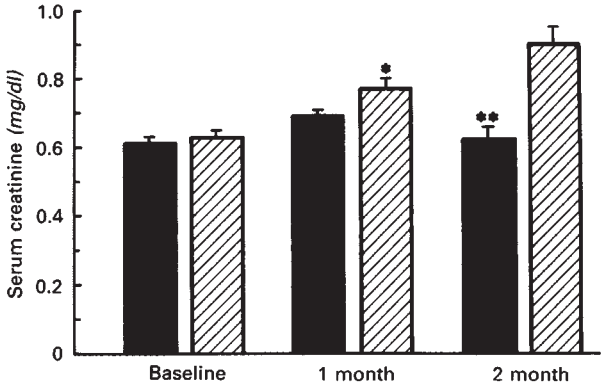

Fig. 1. *Plasma creatinine in sedentary (▨) and trained (■) rats with a remnant kidney before and after 1 and 2 months of treatment.* Values are mean ± SEM. Baseline values were obtained 1 week after nephrectomy and before training was initiated. (*) Trained significantly different from sedentary at 1 month, $P < 0.05$. (+) Trained significantly different from sedentary at 2 months, $P < 0.001$.

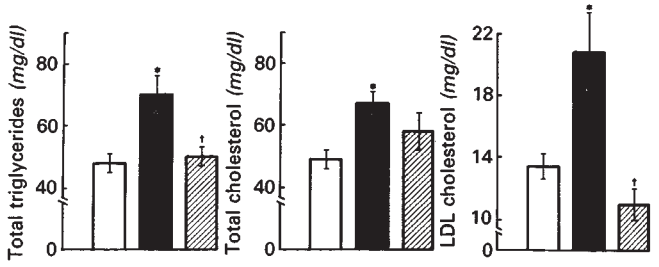

Fig. 2. *Effect of exercise training on plasma total triglycerides, total cholesterol, and low density lipoprotein (LDL) cholesterol in rats with a remnant kidney.* (*) Significantly different ($P < 0.05$) from those obtained in sedentary controls. (+) Values significantly different from those obtained in sedentary azotemic rats. In control rats with normal renal function total triglycerides decreased from 47.7 ± 3.1 in sedentary rats to 45.2 ± 10.7 in exercised rats (not significantly different, $P < 0.10$). Total cholesterol in control rats decreased from 48.6 ± 2.8 in sedentary animals to 41.4 ± 3.1 in exercised rats ($P < 0.05$). Symbols are: (□) sedentary controls; (■) sedentary azotemics; and (▨) trained azotemics.

Results

Rats in both groups developed systolic hypertension but there were no differences in blood pressure between the exercise and sedentary groups throughout the study duration (Table 1). Heart weights were slightly greater in the exercise group but the difference was not statistically significant. CHI for both groups were not different as well, indicating no long-standing differences in the degree of hypertension [13]. Cumulative mortality rates were 9.8% in the exercise and 10.8% in the sedentary group over two months.

Rats in both groups developed mild to moderate azotemia after nephrectomy. Plasma creatinine concentration increased significantly in both groups at one month compared to baseline (Fig. 1) and was greater in the sedentary than exercise group ($P < 0.05$). At two months, plasma creatinine concentration in the exercise group returned to baseline, while that of sedentary rats continued to rise (Fig. 1). The 24-hour urinary creatinine was similar in both groups at baseline and throughout the study (data not shown).

Remnant kidneys in both groups underwent hypertrophy without significant differences in viable renal tissue weight (Table 2). Both groups developed significant proteinuria; protein excretion at two months was twice as high in the sedentary as in the exercise group (Table 2). None of the rats in either group developed hematuria as evidenced by negative dipstick performed on 24-hour collections.

GFR as measured by C_{in} was significantly higher in the exercise group than in the sedentary group whether expressed in absolute terms or per gram of viable remnant renal tissue. RPF, as measured by C_{PAH}, did not differ between the two groups. Filtration fraction was significantly higher in the exercise group (Table 2). The volume status of the extracellular fluid was similar in both groups as evidenced by similar values of hematocrit and FE_{Na} (Table 2).

Histological analysis revealed pathological changes characteristic of remnant kidney nephropathy [10] in a majority of glomeruli in both groups. The prevalence of glomeruli without any appreciable anatomical defects was not different between the groups (Table 3). The degree of glomerular morphological damage was much more pronounced in the sedentary than in the exercise group as evidenced by significantly higher prevalence of glomeruli containing more extensive damage with diffuse proliferative lesions, loop collapse and crescents (Grade III; Table 3). On the other hand, the prevalence of glomeruli with only mesangial thickening present (Grade I) was significantly higher in the exercise group (the prevalence of totally sclerotic glomeruli was higher in the sedentary group but the difference did not reach statistical significance). There was no difference between groups in the prevalence of glomeruli with only focal lesions.

Total triglycerides, total cholesterol, and LDL cholesterol were greater in sedentary azotemic animals than in sedentary controls ($P < 0.05$), (Fig. 2). Training reduced total triglycerides

Table 3. Comparison of severity of pathological changes (%) in glomeruli in remnant renal tissue of sedentary and 2 month exercised rats

	Grade				
	0	I	II	III	IV
Sedentary $N = 21$	2.14 ± 0.45	39.55 ± 2.38	21.36 ± 1.22	32.35 ± 2.55	4.91 ± 1.27
Exercised $N = 26$	3.08 ± 0.60	57.65 ± 2.40	19.28 ± 1.09	17.93 ± 1.89	2.23 ± 0.93
P	NS	<0.01	NS	<0.01	NS

Values are expressed as mean % of total for each grade ± SEM. Grade 0—normal histology; Grade I—mesangial thickening only; Grade II—appearance of isolated areas of glomerular sclerosis and loop collapse; Grade III—scattered areas of sclerosis, loop collapse, microaneurysms, and/or crescents throughout the glomerulus; Grade IV—total glomerular collapse—no viable remaining structures

and LDL cholesterol in azotemic animals ($P < 0.05$), but the reduction in total cholesterol with training was not statistically significant. There was also a significant difference in plasma creatinine levels between sedentary rats, 0.53 ± 0.05 mg/dl, and exercised rats, 0.36 ± 0.04 mg/dl, in this group of animals ($P < 0.02$). The number of sclerosed glomeruli (Grades III and IV) averaged 41.5 ± 3.5% in sedentary male rats ($N = 7$) with a remnant kidney, a value significantly different ($P < 0.01$) from the 20.6 ± 2.1% observed in exercise trained rats ($N = 6$).

Discussion

The results of the present study suggest that chronic exercise training improves GFR, decreases the degree of proteinuria, and lessens the extent of glomerulosclerosis in rats with moderate renal insufficiency due to reduced renal mass. These events took place without a significant change in RPF which led to the higher filtration fraction in the exercise group. Moreover, exercise did not alter the degree of systemic hypertension. The heart weights and the cardiac hypertrophy index did not differ between groups as well, suggesting the absence of differences in long-standing hypertension between sedentary and exercised rats.

It is of interest that after two months, exercise-trained rats with a remnant kidney had a significantly higher body weight than the pair-fed sedentary rats (Table 1). One possibility for this difference in weight is increased intake of protein and calories in the exercised group. However, this apparently was not the case. The mean daily feed intake during the two month period averaged 21.6 ± 0.4 g/day in sedentary rats with a remnant kidney and 21.9 ± 0.9 g/day in exercise-trained rats ($P > 0.30$). The daily protein intakes averaged 4.92 ± 0.1 g in sedentary rats and 4.99 ± 0.2 g ($P > 0.50$) in exercise-trained rats. Thus, although the exercise-trained rats ate a slightly greater amount of food and protein than sedentary rats, the values were not significantly different from each other and the differences in intake between the two groups were minimal.

Another potential explanation for the greater weight in exercise-trained rats may be related to increased muscle mass and increased protein anabolism, perhaps as a consequence of both exercise and improved renal function in this group.

The possibility of increased ECF volume and total body water should also be considered as a potential explanation for the greater weight of exercise-trained rats, since studies in exercise-trained man have shown an increase in ECF volume [5]. Although hematocrit values were similar in both groups of rats (Table 1), suggesting that plasma volume was not different, one cannot exclude an increase in both plasma volume and total, red blood cell-mass in the exercise-trained animals. The finding that systolic blood pressures were not significantly different in the two groups of rats (Table 1) was somewhat surprising. Since renal function was decreased to a greater extent in sedentary rats than in exercise-trained animals, one would expect to find a higher systolic blood pressure in the former group. Although systolic blood pressure was somewhat higher in sedentary rats both at one and two months, the differences in blood pressure between the two groups was not marked. It is possible that expansion of the ECF volume in the exercise-trained group may have masked greater differences in blood pressure between the two groups.

The greater GFR in exercise-trained rats with a remnant kidney is probably due to a greater number of filtering nephrons in this setting, due to amelioration of glomerulosclerosis in these animals as compared to sedentary controls. The decrease in proteinuria would support this concept. An increase in GFR on the basis of ECF volume expansion alone in the exercise-trained rats seems unlikely because ECF expansion would tend to increase proteinuria in animals with a remnant kidney [14]. There was, as shown in Table 2, a decrease in proteinuria in the exercise-trained rats.

Our findings of an increased GFR are in contrast with those obtained in healthy individuals immediately after an acute bout of strenuous exercise, where both GFR and, to a greater extent, RPF fell precipitously [1, 2]. The differences in these results are probably due to the repetitive nature of the exercise and the measurement of GFR and RPF 24 hours after the last bout of exercise in our study. Moreover, in subjects involved in repetitive strenuous activity over several weeks, GFR has been reported to increase by the end of the training period [5].

The proteinuric response to acute exercise is transient [1], while chronic exercise in the present study significantly reduced the proteinuria which develops in rats with a remnant kidney. In a study of children with insulin dependent diabetes, Poortmans, Waterlot and Dorchy [15] showed that two weeks of intense exercise training significantly reduced the degree of proteinuria as measured by both albumin and β_2-microglobulin.

There was no difference in sodium excretion between the two groups in our study, in contrast to the fall in sodium excretion reported in response to an acute workload [16]. This phenomenon may reflect an adaptation to maintain steady-state sodium balance during exercise training in spite of renal insufficiency.

The mechanism responsible for the ameliorating effects of exercise training on renal function in remnant kidney nephropathy is not clear. One possibility is that repeated reductions in

renal blood flow during the exercise sessions serve to protect the remnant kidney from the damage caused by intraglomerular hypertension [17]. Although RPF did not differ between the exercise and sedentary group 24 hours after the last exercise session, RPF has been previously reported to decrease during an acute exercise bout [1].

Another possible mechanism for the improvement in GFR with exercise training in rats with a remnant kidney is a reduction in plasma lipids [8, 18]. Although the evidence is not conclusive, it has been proposed that hyperlipoproteinemia in general, and increased LDL cholesterol levels in particular, can perpetuate the glomerulosclerosis and tubulointerstitial disease of chronic renal failure. In the present study, exercise training reduced total lipids and LDL cholesterol in plasma, thereby suggesting that the reduction in plasma lipids may have contributed to the exercise-related reduction in the progression of the renal disease. On the other hand, the improvement in GFR may have been due to some other mechanism, and this improved renal function may have been responsible for the lower plasma lipids. Indeed, the reduction by exercise training of the elevated muscle proteolysis in chronic renal failure reported earlier [9] may have been due also to the improvement in renal function.

The improvement in GFR by chronic exercise in azotemic animals may be due to changes in coagulation and fibrinolysis [19] induced by exercise. Exercise has been reported to activate fibrinolysis [20, 21], to shorten blood clotting time [22] and to reduce thromboxane production in rat platelets stimulated by thrombin and collagen [23]. Although anticoagulants have been shown to decrease proteinuria and glomerulosclerosis in rats with a remnant kidney [19, 24, 25], it is not clear whether or not exercise may affect the progression of renal disease through effects on blood coagulation.

Exercise training has been shown to improve physical work capacity, glucose and lipid metabolism, hypertension, anemia, and depression in patients with end-stage renal disease on hemodialysis [4, 26]. The lack of improvement in hypertension with exercise in the present study may have been due to the shorter period of training (2 compared to 12 months), the lesser severity of the renal disease, expansion of the ECF space or species differences. Thus, exercise training has been demonstrated to have the potential to prevent or delay many of the medical complications which occur in patients with end–stage renal disease. The present study suggests that exercise training may also reduce the progression of renal disease in moderate renal insufficiency. However, acute and chronic exercise in immune complex glomerulonephritis has been shown to worsen the course of renal disease [27, 28]. This suggests that exercise may affect the function of the diseased kidney in different ways depending on the nature of renal injury.

Our observations indicate that chronic exercise training ameliorates the progression of renal disease in the remnant kidney model. The mechanism for this improvement appears to be independent of the influence of systemic blood pressure. Clearly, additional research is required to elucidate the mechanism(s) responsible for the effects of exercise on renal function in the diseased kidney. The data further suggest that exercise training has the potential to be an important component of the treatment of patients with moderate renal insufficiency.

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