The Physiology and Potential Uses of Carnitine in Maintenance Dialysis Patients

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CAUSES OF IMPAIRED EXERCISE CAPACITY IN ESRD

- Anemia
- Deconditioning
- Cardiovascular dysfunction
- Uremic myopathy(?)
- Carnitine deficiency(?)

EXERCISE TRAINING IN MHD PATIENTS

- Approximately 18 published studies of exercise training involving about 300-400 patients.
- Only 4 of these studies, with 60 patients, were conducted in the rhuEPO era.

EXERCISE TRAINING PROGRAMS IN ESRD PATIENTS

1. Duration of studies: 8 weeks to 12 months.
2. Exercise regimens: Endurance training in all studies, mild strength training (10 min. of low-weight resistance exercise) in one study.
3. Intensity targets: Percent of observed VO_2 peak or maximum heart rate, lactic acid threshold, or perceived exertion ratings.

RESULTS OF EXERCISE TRAINING PROGRAMS

1. VO_2 peak increased in 8/11 studies; in 2/3 studies reporting no increase, exercise was performed at home.
2. Increased lactic acid threshold.
3. Heart rate at submaximal work rate.

BENEFITS REPORTED IN STUDIES OF EXERCISE TRAINING IN ESRD PATIENTS

Increased or improved:
- VO_2 peak
- lower heart rate at submaximal work rate
- Kidney disease quality of life scores
- Hemoglobin
- Muscle strength
- Muscle structure - histology

Decreased
- Blood pressure
- Serum cholesterol
- Serum triglycerides
- Insulin resistance

EXERCISE TRAINING REGIMEN

1. Exercise 3x/week.
2. 5-10 min warm-up and stretching exercises.
3. Pedalling on calibrated, electronically braked, recumbent cycle ergometer (SciFit Pro II) with patient in his usual dialysis chair.
4. Initial exercise at an intensity usually of 50% VO_2 peak for 20 min.
5. Gradual increases in exercise to 40 min with graded increases in work rate intensity.

CHARACTERISTICS OF 12 EXERCISING MHD PATIENTS

Age, years	46 ± 16 (SD)	(range, 34-60)
Duration of HD therapy, months	82 ± 80	(range, 10-289)
Duration of exercise training, weeks	8.25 ± 2.53	(range, 5-12)
Predialysis	**Pre-training**	**End-training**	**P**
Hemoglobin, g/dl	11.8± 2.4	11.8±1.8	NS
Serum creatinine, mg/dl	12.5 ± 3.5	12.4 ± 2.6	NS
Serum urea nitrogen, mg/dl	57 ± 20	59 ± 16	NS
Serum albumin, g/dl	4.08 ± 0.3	4.26 ± 0.31	NS
Serum prealbumin, mg/dl	35.6 ± 9.1	37.9 ± 10.6	NS
Energy, kcal/kg bw *	22.7 ± 4.9	21.9 ± 5.6	NS
Protein, g/kg bw *	0.93 ± 0.26	0.87 ± 0.25	NS

* Determined from 3-day diaries/interviews

EXERCISE CAPACITY IN 12 EXERCISING MHD PATIENTS UNDERGOING EXERCISE TRAINING

	Pre-Training	End-Training	Change (%)	P
Endurance Capacity				
VO_2 peak, ml/min	990 ± 418 (SD)	1133 ± 459	+15	0.06
Work peak, watts	66 ± 32	90 ± 45	+36	0.007
Heart rate peak, beats/min	128 ± 22	140 ± 19	+10	0.001
Endurance time, min	5.5 ± 2.0	13.4 ± 2.6	+142	0.001
End HR peak, beats/min	126 ± 23	135 ± 20	+7	0.032
Anaerobic threshold, ml/min	621 ± 224	718 ± 215	+16	0.037

STRENGTH IN 12 EXERCISING MHD PATIENTS UNDERGOING EXERCISE TRAINING

	Pre-Training	End-Training	Change (%)	P
Muscle Power				
Leg power, watts/kg	1.63 ± 105	1.88 ± 0.71	+ 15	NS
5RM Leg Press, lbs*	422 ±136	482 ±170	+ 14	0.003
Fatigability, Reps at 80% 5RM	19.7 ± 7.2	28.3 ± 12.2	+ 44	0.029
5RM Calf Press, lbs*	283 ± 120	323 ± 137	+ 14	0.02
Travel Stair Climb, sec	2.24 ± 0.46	1.91 ± 0.53	+ 14	0.03
10-meter walk time, sec	4.09 ± 1.16	3.49 ± 1.07	+ 17	0.002
Get-up-and-Go, sec†	7.56 ± 2.43	6.50 ± 1.73	+ 16	0.012

*5 repetitive maximum leg press or calf press. †Arising from a chair and walking.

DAILY NUTRIENT INTAKE OF 12 MHD PATIENTS*

	Pre-training	End-training	P
Energy, kcal	1765 ± 460 (SD)	1695 ± 444	NS
Protein, g	71.0 ± 18.5	68 ± 22	NS
Carbohydrate, g	217 ± 43	203 ± 51	NS
Fat, g	70 ± 31	69 ± 23	NS
Cholesterol, mg	334 ± 152	361 ± 136	NS
Calcium, mg	472 ± 191	510 ± 163	NS
Phosphorus, mg	954 ± 202	965 ± 201	NS
Magnesium, mg	204 ± 39	188 ± 38	NS
Sodium, mg	2831.1 ± 886	2786 ± 1240	NS
Potassium, mg	1847 ± 494	1740 ± 344	NS

*Determined from 3-day dietary diaries and interviews

ANTHROPOMETRY IN 12 EXERCISING MHD PATIENTS UNDERGOING EXERCISE TRAINING

	Pre-training	End-training	P
Weight, kg	78.0 ± 10.8	78.2 ± 10.9	NS
MAMC, cm	33.9 ± 2.9	34.1 ± 2.7	NS
Calf circumference, cm	14.2 ± 1.2	14.4 ± 1.0	< 0.05
Triceps skinfold, cm	19.2 ± 11.0	18.4 ± 10.0	NS
Biceps skinfold, cm	12.2 ± 8.5	12.0 ± 9.1	NS
Subscapular skinfold, cm	24.7 ± 11.7	21.5 ± 8.9	< 0.05
Body fat, %	31.2 ± 10	32.2 ± 7.3	NS
Body fat, kg	24.1 ± 7.8	25.0 ± 6.2	NS
Lean body mass, kg	53.9 ± 10.4	53.2 ± 10.4	NS
Waist/hip ratio	0.90 ± 0.08	0.89 ± 0.07	NS

MAMC: Mid-arm muscle circumference.
Calf Circumference: Circumference of calf at its largest cross-sectional area.

DXA MEASUREMENTS IN 12 EXERCISING MHD PATIENTS

	Pre-training	End-training	P
Lean body mass, kg	49.3 ± 12.5 (SD)	52.4 ± 12.8	<0.005
Bone mineral content (BMC), kg	2.27 ± 0.47	2.2 ± 0.45	NS
Lean body mass + BMC, kg	51.6 ± 12.9	54.6 ± 13.1	<0.005
Fat, kg	23.2 ± 8.7	18.1 ± 8.8	<0.001
Total mass, kg	74.8 ± 11.0	72.7 ± 10.9	<0.001
Percent body fat, %	31.4 ± 11.4	25.2 ± 11.9	<0.001

CARNITINE LEVELS IN 10 EXERCISING MHD PATIENTS

	Pre-training	End-training	Normal Controls
Number of Subjects	10	9	6
Serum, nmol/L			
Total carnitine	46.6 ± 11.5 (SD)	47.0 ± 10.5	51.0 ± 8.2
Free carnitine	31.1 ± 9.1	28.8 ± 8.8	38.2 ± 7.2
Acylcarnitine	15.5 ± 3.5	18.2 ± 4.3*	12.8 ± 4.9
Free/Acylcarnitine	0.52 ± 0.17	0.67 ± 0.2*	0.35 ± 0.18
Acetylcarnitine	10.8 ±2.3	10.4 ± 2.5	11.7 ± 3.0
Vastus Lateralis Muscle, nMol/gm wet wt			
Total carnitine	3250 ± 807	2980 ± 847	3030 ± 1173
Free carnitine	2710 ± 834	2460 ± 686	2459 ± 1101
Acylcarnitine	534 ± 335	516 ± 345	572 ± 228
Free/Acylcarnitine	0.23 ± 0.21	0.21 ± 0.13	0.26 ± 0.12
Acetylcarnitine	496 ±166	45 ±233	1029 ± 385

*Significantly different from pre-training data, P < 0.05.

SKELETAL MUSCLE GENE EXPRESSION IN 8 EXERCISING MHD PATIENTS

The following changes in gene expression were noted:

1. The myostatin mRNA decreased significantly
2. Insulin-like growth factor-1 mRNA increased significantly
3. Insulin-like growth factor receptor mRNA increased significantly
4. The mRNA for several insulin-like growth factor binding proteins increased significantly

SUMMARY

In maintenance hemodialysis undergoing endurance exercise training:

1. There is an increase in endurance exercise capacity and skeletal muscle strength and performance.
2. There is evidence for muscle hypertrophy
3. This is associated with increased gene expression for anabolic hormones and decreased gene expression for the anti-hypertrophic compound, myostatin