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Carnitine metabolism during exercise in patients on chronic hemodialysis

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Carnitine metabolism during exercise in patients on chronic hemodialysis. Patients on hemodialysis (HD) have impaired exercise performance. Carnitine homeostasis is also abnormal in this population. As carnitine is an important cofactor for muscle energy metabolism, exercise performance and skeletal muscle carnitine metabolism were characterized in eight HD patients, and in five age-matched controls. Each patient underwent graded bicycle exercise testing to define maximal performance, and prolonged exercise at 70% of their peak work capacity. Muscle (vastus lateralis) total carnitine content (carnitine plus all acylcarnitines) at rest was lower in HD patients than in controls (2320 ± 1190 vs. 3800 ± 940 nmol/g, $P < 0.05$). In patients on HD, muscle carnitine content was inversely correlated to time on HD ($r = -0.74$, $P < 0.05$), and positively correlated to peak exercise performance ($r = 0.77$, $P < 0.05$). In patients on HD, 8 ± 7% of the muscle carnitine pool at rest was short-chain acylcarnitines (similar to the distribution in controls), but 32 ± 5% of the plasma carnitine pool consisted of short-chain acylcarnitines. With high-intensity exercise in patients on HD, muscle short-chain acylcarnitine content increased from 130 ± 130 to 1380 ± 820 nmol/g ($P < 0.01$). The change in muscle short-chain acylcarnitine content with exercise was correlated with the increase in muscle lactate content ($r = 0.88$, $P < 0.01$). In summary, patients on HD had a lower muscle total carnitine content than control subjects which was correlated to exercise performance. In the HD patients during exercise, the load-dependent changes in muscle metabolism (lactate accumulation, acylcarnitine production) occurred over a constricted range of work loads, but were qualitatively similar to the responses observed in normal subjects.

Patients with chronic renal failure on hemodialysis (HD) have a moderate to severe impairment in exercise performance. The peak oxygen consumption in these patients averages 16 to 20 ml/kg/min [1–5], or approximately 50 to 70% of the age-predicted maximal oxygen consumption in normal subjects [6]. When patients with chronic renal failure perform submaximal exercise, blood lactate concentrations increase at work loads not associated with a change in lactate metabolism in normal subjects [7, 8]. These alterations in peak exercise performance and exercise metabolism in patients with renal failure are associated with a clinically significant reduction in the ability to sustain even moderate levels of activity [9].

The etiology of the marked impairment in exercise capacity in patients with renal failure is unknown, but may be multifactorial. The chronic anemia of renal failure is associated with a reduced exercise capacity [10]. However, an increase in hematocrit with erythropoietin results in only modest improvements in exercise performance [4]. Structural changes in type II (fast-twitch) muscle fibers [11] are associated with muscle weakness which contributes to the exercise impairment [4, 12]. Patients with chronic renal failure also have abnormalities of skeletal muscle metabolism including an impairment in fatty acid oxidation [13], an important pathway for muscle energy production during exercise. Finally, deconditioning and underlying cardiovascular disease in many patients may limit exercise capacity.

Carnitine homeostasis is abnormal in chronic renal failure. Carnitine is required for the mitochondrial oxidation of long-chain fatty acids [14], and also interacts with short-chain acyl-CoA's (intermediates of oxidative metabolism), to reversibly form short-chain acylcarnitines [15]. In normal subjects, skeletal muscle carnitine metabolism changes during exercise in a fashion that is dependent on metabolic state, with an exercise-induced accumulation of short-chain acylcarnitines observed at work loads above the lactate threshold [16, 17]. In patients on hemodialysis, the plasma concentration of short-chain acylcarnitines is increased [1, 13, 18], but changes in tissue carnitine content and metabolism have been less well defined. Muscle carnitine content is decreased in some hemodialysis patients [1, 19–21], but this observation has not been consistently replicated [22, 23]. Further, it is not known if alterations in skeletal muscle carnitine homeostasis and metabolism may be important in the pathophysiology of the poor exercise tolerance in these patients. To evaluate this relationship, muscle and plasma carnitine metabolism was evaluated in patients on hemodialysis at rest and after exercise.

Methods

Subjects

Eight patients with end-stage renal disease on maintenance hemodialysis, and five age-matched control subjects were enrolled. All subjects were initially evaluated with a history and

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physical examination, and a screening exercise test to familiarize them with the testing procedures. Control subjects had no chronic, active diseases, were on no medications, and had a normal physical examination.

Patients on erythropoietin were allowed to continue on this medication as long as the dose and hematocrit were stable and unchanged over the preceding three months prior to enrollment. Patients taking other chronic medications were continued on their drugs, but the doses remained unchanged during the study. Patients whose exercise capacity was limited by symptoms of angina, congestive heart failure, chronic obstructive pulmonary disease or arthritis were excluded. Diabetics were excluded as glycemic control may affect carnitine metabolism [24]. The study was approved by the University of Colorado School of Medicine Human Subjects Committee, and informed consent was obtained from all subjects.

Exercise measurements

All exercise was conducted on an electronically-gaited ergometer (Uniwork ergometer model 845, Quinton Instrument Co., Seattle, Washington, USA) the morning after a dialysis treatment with an average of five days between each test. Rates of oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) were measured at rest and during exercise, using an Ametek metabolic system (Ametek Thermox, Pittsburgh, Pennsylvania, USA). Before each test the analyzers were calibrated with known concentrations of O_2 and CO_2. The respiratory exchange ratio (RER) was calculated as the ratio of $\dot{V}CO_2/\dot{V}O_2$. Arm blood pressure (by auscultation) and heart rate (by an electrocardiogram) were obtained every minute during exercise. Cardiac status was continually monitored throughout the exercise test by 12-lead electrocardiogram. During exercise, perceived exertion was ascertained by the Borg scale with a range of 6 (very, very light) to 20 (very, very hard) [25]. Blood lactate concentrations were measured at rest and during each minute of exercise. A lactate threshold was determined for each patient as the work load and oxygen consumption where blood lactate concentration began to progressively increase over baseline values [9, 26].

Exercise testing validation

The exercise testing methods were initially validated in four subjects on hemodialysis who had a similar age, hematocrit and exercise performance as the patients subsequently enrolled in the biopsy study. In the validation studies, patients performed exercise on four separate occasions to peak exertion using graded ergometer protocols that varied in the progression of work loads. The exercise protocols used in the current studies demonstrated coefficients of variation (within-subject standard deviation divided by the mean) of 4% for peak oxygen consumption, 5% for peak RER, 5% for peak heart rate and 4% for perceived exertion in HD patients. In two of the graded tests in the validation group blood lactate concentration was measured. The coefficient of variation for the lactate threshold (expressed as the percent of peak oxygen consumption) was 5%, whereas the peak blood lactate concentration varied by 29%. Thus, the protocols and instrumentation permitted a highly reproducible assessment of exercise performance and metabolic characterization in this patient population.

Exercise protocols

Eight patients were enrolled to evaluate changes in skeletal muscle carnitine metabolism on chronic hemodialysis. These patients initially performed two graded exercise tests using the 200 kp · m/min, three-minute stage protocol, and the 100 kp · m/min, two-minute stage protocol. Peak exercise time and the lactate threshold were defined from the 200 kp · m/min, three minute stage test, but the peak oxygen consumption, RER, and heart rate were averaged from the two graded tests. Control subjects also performed graded bicycle exercise (200 kp · m/min, 3 min stages) to define a lactate threshold and maximal exercise performance. A "maximal" level of exertion could be defined in control subjects as a plateau in oxygen consumption. Since no plateau in oxygen consumption was observed in HD patients, the performance parameters are described as "peak".

The HD patients were then evaluated during an exercise test at a constant work load that was above the individual's lactate threshold. From these evaluations, a work load was selected for the final study characterizing metabolic parameters. The work load selected ensured that patients would exercise above their lactate threshold (that is, reproducible metabolic state), and that the exercise could be maintained for a defined period without exhaustion.

Physical activity recall

Subjects were asked to recall their major occupational, leisure and home activities over a typical week using a previously validated standard questionnaire [27]. The intensity and duration of each activity were recorded in METs (1 MET = 3.5 ml oxygen/kg/min), and the number of active MET hours per week was calculated (1 MET hour = 1.02 Kcal/kg/hr).

Blood collection and preparation

A 20 g intravenous catheter was placed in a forearm vein, with a three-way stopcock to facilitate blood drawing. Patency of this system was maintained with heparinized saline. For each sample, 5 ml of blood was withdrawn and immediately transferred to a heparinized tube on ice. The blood was centrifuged in chilled tubes at 600 × g for three minutes, with plasma aliquots stored at −80°C until subsequent analysis. Blood for lactate analysis (25 μl) was immediately deproteinized in 3% perchloric acid and stored on ice.

In all subjects, three resting samples of blood were drawn five minutes apart for the analysis of carnitine, acylcarnitines, β-hydroxybutyrate and glucose, with the average results reported as "Rest" values. In patients on hemodialysis studied during the constant-load protocol, additional blood samples were drawn for analysis immediately prior to the end of exercise, and at the end of exercise. The average of the two samples are reported as the "Exercise" value. In the recovery period, blood was also obtained at 5, 15 and 30 minutes after exercise and reported as the "Recovery" values. Blood for the measurement of lactate was drawn every minute during exercise, and five minutes after exercise.

Muscle biopsy

A resting biopsy of the vastus lateralis muscle was performed in the control subjects and in patients on hemodialysis. After a

Table 1. Characteristics of patients on chronic hemodialysis

Subject	Sex/age	Weight *kg*	Dialysis *years*	Etiology	Hct	Erythropoietin Dose *μ*	Erythropoietin Months	PAR
1	M/38	68.6	16.0	Congenital	33%	1000	7	146
2	M/58	70.0	0.5	Hypertension	23%	—	—	180
3	F/25	53.6	6.0	SLE	25%	5000	6	146
4	M/51	85.5	0.6	GN	34%	—	—	119
5	M/60	67.3	10.5	Idiopathic	33%	3600	11	146
6	M/49	72.2	2.8	PKD	33%	—	—	113
7	M/46	66.9	16.0	GN	27%	4000	9	164
8	M/67	66.4	10.5	GN	33%	1600	5	115

Abbreviations are: SLE, systemic lupus erythematosus; GN, glomerulonephritis; PKD, polycystic kidney disease. PAR refers to the physical activity recall questionnaire that records the level of activity in MET hours per week. The erythropoietin dose is in units per dialysis.

3 ml subcutaneous injection of 1% lidocaine, a 5 mm biopsy needle (Bergstrom muscle biopsy cannula, DePuy Inc., Warsaw Indiana, USA) was used to remove approximately 40 to 50 mg of tissue. After constant-load exercise, a second biopsy was performed in the hemodialysis patients through a separate incision, located 5 mm proximal to the site of the resting biopsy. Muscle tissue was immediately frozen in liquid nitrogen and stored at −80°C.

Assay methods

Carnitine was measured by a radioenzymatic assay [28], as previously described [29]. The carnitine concentration in standard solutions was determined by the method of Marquis and Fritz [30]. Samples were prepared in 3% perchloric acid and centrifuged at 10,000 × g for two minutes. The perchloric acid supernatant, which contains carnitine and short-chain acylcarnitines, was assayed for carnitine. An additional aliquot of the supernatant was then subjected to alkaline hydrolysis to convert short-chain acylcarnitines to carnitine, and carnitine was again measured to determine total acid soluble carnitine. Short-chain acylcarnitine concentration (acyl groups less than 10 carbon atoms) was derived from the difference in the concentrations of total acid-soluble carnitine and carnitine in the supernatant. The ratio of short-chain acylcarnitine concentration to total acid soluble carnitine concentrations (SC/TAS) was calculated, and provides a useful marker of changes in carnitine metabolism [15]. Long-chain acylcarnitine concentration (acyl moiety of 10 or more carbons) was measured as carnitine after alkaline hydrolysis of the perchloric acid pellet. Total carnitine refers to the sum of the carnitine, short-chain acylcarnitine and long-chain acylcarnitine concentrations. All assays were performed in duplicate with the average result reported.

Lactate was assayed in deproteinized blood, or muscle, prepared in perchloric acid [31]. Plasma β-hydroxybutyrate was measured by the method of Olsen [32], and glucose by a glucose oxidase method adapted to kit form by Sigma Chemicals (St. Louis, Missouri, USA).

Statistical analysis

Student's *t*-test for paired data, or a within-subjects analysis of variance (ANOVA) for multiple measurements over time was used for within-subject comparisons. An unpaired *t*-test was used to compare results between the control and patient groups. Linear regression was calculated for correlation between variables using the Pearson's product moment correlation coefficient. Data are presented as mean ± SD and analyses considered statistically significant when $P < 0.05$.

Table 2. Peak exercise performance of control subjects and patients on chronic hemodialysis

Peak values	Control	Hemodialysis
Perceived exertion	20 ± 0	19 ± 1
Work load *kp · m/min*	840 ± 90	438 ± 92[a]
VO_2 *ml/kg/min*	25.0 ± 3.0	16.0 ± 2.2[a]
Heart rate *beats/min*	142 ± 14	113 ± 11[a]
RER $\dot{V}CO_2/\dot{V}O_2$	1.12 ± 0.07	1.26 ± 0.07[a]
Blood lactate *mM*	3.7 ± 1.6	2.5 ± 0.8

Subjects were tested on a graded bicycle ergometer protocol to peak exertion. The peak values for rates of oxygen consumption ($\dot{V}O_2$), the respiratory exchange ratio (RER), heart rate and blood lactate concentration and perceived exertion were obtained during the last minute of exercise.

[a] $P < 0.01$ for value in patients on hemodialysis compared to value for controls using an unpaired *t*-test

Results

Patient characteristics

End-stage renal disease was diagnosed in all patients, and was secondary to the diseases listed in Table 1. The patients had been on hemodialysis treatment for an average of 7.9 ± 6.4 years, with a range of seven months to 16 years. Five of the eight patients were receiving stable erythropoietin doses at an average dose of 3000 U/dialysis. Patients on erythropoietin had a similar activity level by physical activity recall and peak oxygen consumption as did the patients not on this medication. The five control subjects were age-matched (48 ± 12 years) with the HD patients (48 ± 14 years). However, controls had higher hematocrits (44 ± 4%) than HD patients (30 ± 4%), and physical activity levels (282 ± 86 MET hr/week) than the HD patients (141 ± 24 MET hr/week).

With graded exercise, all subjects stopped at a perceived exertion level of 19 to 20 on the Borg scale. However, control subjects achieved a greater exercise work load, exercise duration, heart rate and oxygen consumption than the peak values for the hemodialysis patients (Table 2). In the control and HD subjects a lactate threshold was defined during graded exercise to facilitate the evaluation of carnitine metabolism in a reproducible metabolic state [9]. The HD patients had a lactate

Table 3. Plasma and muscle carnitine and acylcarnitine contents at rest in hemodialysis patients

	Plasma μM		Muscle *nmol/g*	
	Control	HD	Control	HD
Carnitine	42.2 ± 8.3	28.7 ± 5.4[a]	3420 ± 910	2190 ± 1190
Short-chain acylcarnitines	6.5 ± 6.4	13.8 ± 4.5[a]	340 ± 190	130 ± 130[a]
SC/TAS ratio	0.13 ± 0.13	0.32 ± 0.05[a]	0.09 ± 0.06	0.08 ± 0.07
Long-chain acylcarnitines	6.0 ± 1.4	5.8 ± 1.9	41 ± 16	21 ± 11[a]
Total carnitine	54.7 ± 7.2	48.3 ± 9.5	3800 ± 940	2320 ± 1190[a]

Patients on hemodialysis (HD) were studied the day following the last dialysis, after an overnight fast. Control subjects were also studied after an overnight fast. Muscle biopsies of the vastus lateralis were performed at rest. The ratio of short-chain acylcarnitine content to total acid soluble carnitine content (SC/TAS ratio) provides an index of the change in acylation of the carnitine pool.

[a] $P < 0.05$ for patients on hemodialysis compared to controls

threshold during graded exercise that occurred at 82 ± 12% of peak oxygen consumption and 75 ± 18% of the peak work load. The average peak blood lactate concentrations were not different between groups ($P = 0.19$), but patients on hemodialysis had a higher RER at peak exercise than control subjects.

Carnitine metabolism at rest

At rest, the patients on hemodialysis had a lower plasma concentration of carnitine, a higher plasma concentration of short-chain acylcarnitines, the ratio of short-chain acylcarnitine concentration to total acid soluble carnitine concentration (SC/TAS ratio) as compared to control subjects (Table 3). The plasma concentrations of long-chain acylcarnitines and total carnitine were similar between groups as was the blood lactate concentration. The plasma concentrations of glucose and β-hydroxybutyrate (Table 4) were within the expected ranges for normal subjects [33–35].

At rest, patients on hemodialysis had lower muscle contents of short-chain acylcarnitines, long-chain acylcarnitines and total carnitine (all $P < 0.05$) as compared to control subjects (Table 3). However, in contrast to the plasma carnitine pool, the skeletal muscle SC/TAS ratio was similar between patients and control subjects. The duration on chronic hemodialysis was inversely correlated with the resting skeletal muscle total carnitine content ($r = -0.74$, $P < 0.05$, Fig. 1). Patients on erythropoietin had a muscle total carnitine content similar to the patients not on this medication (data not shown).

Constant-load exercise in patients on hemodialysis

In patients on hemodialysis, the physiologic and metabolic responses to exercise were determined during a constant-load exercise protocol at an intensity above each individual's lactate threshold. Exercise above the lactate threshold was selected as it is associated with a series of well characterized, qualitative changes in carnitine and fuel metabolism [16, 36]. This exercise test was terminated prior to exhaustion (time to exhaustion at the selected work load determined by previous testing in each individual), with an average duration for the group of 9.4 ± 2.5 minutes. The mean exercise work load was 300 ± 93 kp · m/min, which averaged 68% of the peak work load achieved during the graded protocols. Heart rate during the constant-load protocol averaged 110 ± 17 beats/min, which was 97% of the peak heart rate as determined from the graded tests. The average oxygen consumption during the endurance exercise was 14.7 ± 2.4 ml/kg/min, which was 90% of the peak oxygen consumption.

The systemic metabolic responses to exercise were characterized in the eight hemodialysis patients during the constant-intensity exercise by the respiratory exchange ratio (RER), blood lactate concentration, and the plasma concentrations of glucose, and β-hydroxybutyrate (Table 4). The mean RER at the conclusion of constant-intensity exercise was 1.11 ± 0.08, and the blood lactate concentration was greater than 2.0 mM in all patients (confirming that the work load selected was above the individual's lactate threshold), with an average peak value of 3.3 ± 1.1 mM. During exercise and recovery, the plasma concentration of β-hydroxybutyrate remained unchanged. At rest the plasma glucose concentration was 83.4 ± 15.1 mg/dl which decreased after 15 minutes (74.4 ± 8.4 mg/dl) and 30 minutes (73.9 ± 7.4 mg/dl) of recovery post-exercise.

At the conclusion of the constant-load exercise above the lactate threshold, plasma concentrations of carnitine, short-chain acylcarnitine and long-chain acylcarnitine were unchanged from values obtained at rest (data not shown). In contrast, the muscle carnitine pool was redistributed to short-chain acylcarnitines at the end of the exercise, with the muscle short-chain acylcarnitine content increased to 1510 ± 780 nmol/g. At the end of exercise, the muscle contents of carnitine (1560 ± 720 nmol/g), long-chain acylcarnitines (20 ± 15 nmol/g) and total carnitine (3090 ± 1050 nmol/g) were unchanged from resting values. The muscle SC/TAS ratio increased from 0.08 ± 0.07 at rest to 0.48 ± 0.18 ($P < 0.01$) after exercise, reflecting the accumulation of short-chain acylcarnitines. The muscle lactate content also increased from 1.7 ± 1.2 μmol/g at rest to 5.0 ± 4.7 μmol/g after exercise. The increases in muscle lactate and short-chain acylcarnitine contents during exercise were positively correlated ($y = 179\,x + 793$, $r = 0.88$, $P < 0.01$).

Predictors of exercise performance

The hematocrit in patients on hemodialysis was not correlated with peak exercise time ($r = 0.26$, P = NS) or peak oxygen consumption ($r = 0.04$, P = NS) during the graded test. In contrast, the resting total carnitine content in muscle was correlated with peak exercise duration during the graded test ($r = 0.81$, $P < 0.05$, Fig. 2), but muscle carnitine total content was not correlated with peak oxygen consumption ($r = 0.26$, P = NS).

Discussion

Patients on hemodialysis have a marked impairment in peak and endurance exercise performance [1–5]. Although multiple factors may contribute to this exercise impairment, attempts to correct the low blood oxygen content with erythropoietin improves, but does not normalize exercise performance [4]. In the current study, peak exercise time and oxygen consumption were not related to the degree of anemia. These observations are consistent with the concept that alterations in skeletal muscle metabolism may contribute to the limited exercise performance [1, 37]. In this context, the state of the muscle carnitine pool at rest and with exercise provides a marker of muscle metabolism in these patients.

Table 4. Metabolic parameters during constant-load exercise in patients with chronic renal failure on hemodialysis

	Rest	Exercise	Recovery	
			5 min	15 min
Respiratory exchange ratio ($\dot{V}CO_2/\dot{V}O_2$)	0.86 ± 0.12	1.11 ± 0.08[a]	—	—
Blood lactate *mM*	0.9 ± 0.2	3.3 ± 1.1[a]	3.4 ± 1.3[a]	—
Plasma β-hydroxybutyrate *mM*	0.38 ± 0.15	0.39 ± 0.16	0.38 ± 0.16	0.38 ± 0.16
Plasma glucose *mg/dl*	83.4 ± 15.1	78.1 ± 8.4	77.0 ± 8.6	74.4 ± 8.4[a]

Patients on hemodialysis performed exercise at a constant work load that was at an intensity above their individually determined lactate threshold.

[a] $P < 0.05$ for change in exercise or recovery values compared to rest in patients on hemodialysis

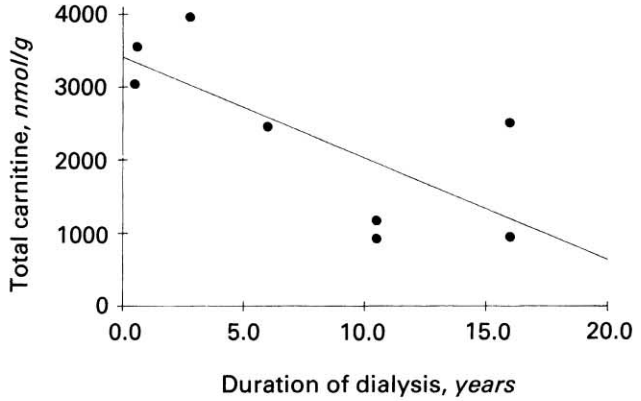

Fig. 1. *Relationship between duration of hemodialysis in patients with chronic renal failure and total muscle carnitine content at rest in the vastus lateralis.* Each point represents an individual patient. The duration of hemodialysis was inversely correlated with the muscle carnitine content ($y = -138\ x + 3409$; $r = -0.74$, $P < 0.05$).

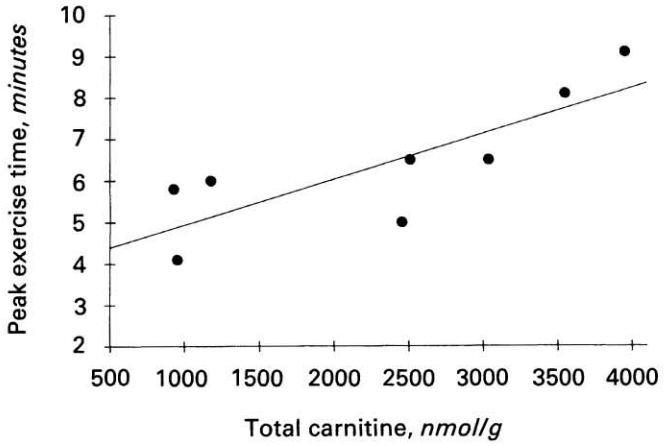

Fig. 2. *Relationship between total muscle carnitine content at rest and exercise performance in patients on hemodialysis.* Each point represents an individual patient. The total muscle carnitine content at rest was positively correlated with peak exercise time on the graded ergometer protocol ($y = 0.0011\ x + 3.84$; $r = 0.81$, $P < 0.05$).

In the present study it was critical to characterize not only the reproducibility of the peak exercise measurements, but also the presence of a lactate threshold, in order to define an exercise intensity for each patient that reflected a specific metabolic state of exercise. Validation studies demonstrated that patients on hemodialysis had peak exercise measurements that were highly reproducible and independent of the type of graded protocol used (**Methods**). A lactate threshold could be defined for each subject that was also reproducible. Peak blood lactate concentrations were in the range previously reported for patients on hemodialysis [12], but were more variable than the threshold values. However, peak lactate concentrations may be influenced by multiple factors such as the type of exercise protocol used and the duration of exercise. Thus, determination of the work load defining the lactate threshold was used to design subsequent protocol work loads, with peak lactate concentrations confirming that the lactate threshold had been exceeded (high intensity exercise).

Carnitine metabolism in hemodialysis patients is characterized by accumulation of short-chain acylcarnitines in plasma, and a decreased plasma unesterified carnitine concentration [20, 21, 38]. This redistribution of the plasma carnitine pool was confirmed in the current studies. However consistent with previous reports [1, 20, 21], there was no accumulation of short-chain acylcarnitines in muscle at rest, and the muscle SC/TAS ratio in the hemodialysis patients was similar to control values and to previously reported values for normal subjects [16]. With exercise HD patients had a large increase in muscle short-chain acylcarnitine content without a similar change in plasma short-chain acylcarnitine concentration. These findings support the concept that changes in muscle carnitine metabolism with exercise are poorly reflected in plasma [16], and that accumulations of short-chain acylcarnitines in the plasma at rest in hemodialysis patients are secondary to alterations in liver [29], or renal carnitine metabolism.

Patients on hemodialysis had lower short-chain acylcarnitine, long-chain acylcarnitine and total carnitine contents in the vastus lateralis muscle at rest as compared to control subjects. Previous reports have shown that the amount of carnitine lost per week from hemodialysis was less than the amount of carnitine excreted by normal subjects over the same time period [39]. More recent data suggest that the total body clearance of both carnitine and acylcarnitines are similar in dialysis patients and healthy subjects [22]. However, the duration of hemodialysis in this study was correlated with a lower total carnitine content in muscle. This finding suggests that hemodialysis is associated with changes in muscle metabolism and carnitine homeostasis that require several years to become manifest as decreased muscle carnitine content.

The muscle total carnitine content at rest was positively correlated with exercise duration on the graded ergometer

protocol suggesting that changes in muscle carnitine homeostasis may serve as a marker of the altered metabolic state of renal failure that is associated with decreased exercise performance. Although speculative, it is possible that the low muscle total carnitine content may play a causal role in impaired exercise performance. Since attempts to improve exercise performance in renal failure patients with carnitine therapy have not met with consistent results [5, 23, 40], the long-term hemodialysis patient with a low muscle carnitine content may represent a subpopulation that would potentially benefit from carnitine supplementation.

Patients on hemodialysis had a normal metabolic response to constant-load exercise above the lactate threshold as defined by progressive increases in blood lactate concentration, and RER values remaining greater than 1.00 [9, 16, 26]. Under these metabolic conditions during exercise, patients on hemodialysis had a redistribution of the total skeletal muscle carnitine pool from unesterified carnitine towards short-chain acylcarnitines. These changes in muscle carnitine metabolism were correlated to the increase in muscle lactate content. In healthy subjects, large amounts of acylcarnitines (particularly acetylcarnitine) accumulate in skeletal muscle during exercise above the lactate threshold [16, 17, 41, 42]. This metabolic-state dependent generation of acylcarnitines may be critical in maintaining normal muscle metabolic regulation during exercise by buffering the acyl-CoA pool [43]. Thus, in hemodialysis patients the expected metabolic transitions to increasing work loads occur during exercise, but over a constricted range of work loads as compared to normal subjects [16, 44].

Consistent with high-intensity exercise in normal subjects [33], patients on hemodialysis had no change in the plasma concentration of β-hydroxybutyrate during exercise. However, plasma glucose concentration was decreased in the hemodialysis patients during the recovery period as compared to pre-exercise values. Patients with chronic renal failure have decreased rates of glucose production and degradation during exercise, suggesting that alterations in glucose homeostasis may occur in these patients [2]. Additionally, impaired fatty acid utilization in renal failure [13] would increase peripheral glucose utilization and decrease hepatic gluconeogenesis.

In conclusion, patients on hemodialysis had a low muscle carnitine content at rest, and a redistribution of the carnitine pool to acylcarnitines during exercise performed above the lactate threshold. The status of the muscle carnitine pool provides a useful probe of altered metabolism during exercise. Further, the decreased muscle total carnitine content provides a marker of the muscle dysfunction during exercise, and may contribute to the poor exercise tolerance in these patients.

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