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Abnormal Increase of Creatine Kinase Plasma Levels following Muscle Exercise in Nephrotic Patients

Key Words
Creatine kinase
Muscle
Nephrotic syndrome

Abstract
Nephrotic syndrome is a protein-wasting disorder affecting total body protein metabolism, often leading to reduction of lean body mass and changes of muscle cell composition. The aim of this study was to investigate the susceptibility to muscle cell damage in nephrotic patients following submaximal physical exercise, by detection of the creatine kinase (CK) plasma level changes. Fourteen patients affected by primary nephrotic syndrome, without chronic renal failure, underwent an exercise test on a cycle ergometer for 20 min at a constant speed (60 rpm). In each subject, the work rate (expressed as watts) was established as 70% of the maximum power theoretically calculated on a sex, age, weight and height basis. CK plasma levels (U/l) were determined before and 1, 3, 6 and 24 h after the exercise. Following exercise, CK plasma levels became higher in nephrotics than in normal controls. That is, the amount of CK increments was greater in nephrotics than in controls from the first hour after the end of exertion. These changes, both as absolute values and as percentage of the basal values, correlate positively to daily urinary protein losses; moreover, an inverse relationship was detected with albumin serum levels. However, no correlation was observed between the amount of plasma CK increases and age, body weight, plasma creatinine, plasma cholesterol or hemoglobin levels. These results demonstrate that a greater than normal increase of CK plasma levels occurs in nephrotics following physical exercise, and that this increment correlates with the severity of urinary protein wasting. This suggests an increased susceptibility to muscle injury in nephrotic patients probably related to protein depletion and/or to modifications of muscle cell metabolism. Further studies are needed to define the pathogenesis of our findings.

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Introduction

The nephrotic syndrome is a protein-wasting disorder that affects hepatic and muscle protein synthesis and catabolism. It has recently been demonstrated that the urinary protein loss stimulates adaptive metabolic responses, namely reduction of protein degradation and postprandial stimulation of protein synthesis, resulting in net protein anabolism. Neutral or positive nitrogen balance can thereby be achieved, provided adequate protein and energy intake is maintained [1]. However, clinical experience suggests that, especially in the case of very high urinary protein excretion, these patients are at risk of malnutrition, reduction of muscle protein content and of lean body mass [2].

Muscle tissue plays a pivotal role in total body protein metabolism and in nephrotics we often observed creatine kinase (CK) plasma levels higher than normal at admission, then abating after some days of bed-sitting. CK is a key enzyme of muscle metabolism that catalyzes the reversible reaction: ADP + P-creatine ↔ ATP + creatine. At rest this enzyme is placed inside the sarcoplasmic membrane. The increment of CK serum levels is regarded as an index of increased membrane permeability and muscle damage [3], both in healthy subjects performing a strenuous exercise [4] and in patients affected by primary myopathy [5].

Therefore, the aim of this study has been to investigate the susceptibility to muscle cell damage in nephrotic patients following submaximal physical exercise, by detection of the CK plasma level changes.

Patients and Methods

This study included patients affected by primary nephrotic syndrome (urinary protein excretion > 3 g/day) without chronic renal failure. Patients older than 65 years, suffering from diabetes, ischemic heart disease, badly controlled hypertension, myopathies, liver diseases, or with familiar history of muscle disorders were excluded. Fourteen consecutive patients (10 m, 4 f, age 44 ± 4 years) entered the study. In this group of patients, urinary protein excretion was 6.1 ± 0.6 g/24 h, serum albumin 2.5 ± 0.1 g/dl, serum total protein 4.8 ± 0.1 g/dl, serum total cholesterol 309 ± 26 mg/dl, serum creatinine 1.1 ± 0.1 mg/dl, hemoglobin 13.4 ± 0.5 g/dl.

Pitting edema of the lower limbs was detectable in the majority of patients, whereas none showed anasarca or pleural effusions. The underlying renal disease was membranous nephropathy in 11 cases, focal glomerulosclerosis in 2 cases and membranoproliferative glomerulonephritis in 1 case. No patient was following steroid, immunosuppressive or lipid-lowering treatments. All the patients were studied at least 1 week after intramuscular injections, muscle trauma or strenuous physical performances. Twelve normal subjects (9 m, 3 f, age 42 ± 5 years) served as controls.

Table 1. Changes of CK plasma levels (U/l) in nephrotics and controls, before and 1, 3, 6 and 24 h after submaximal exercise (mean ± SEM)

	Baseline	1 h	3 h	6 h	24 h
Nephrotics	103±11	146±19	157±17	167±20	149±20
Controls	93±13	102±15	101±16	115±13	98±10
p	NS	NS	<0.05	<0.05	<0.05

The patients and controls underwent an exercise test on a cycle ergometer (BIK by Robert Bosch GmbH for Elettronica Trentina, Italy) for 20 min at a constant speed of 60 rpm. In each subject, the work rate (expressed as watts) was established as 70% of the maximum power theoretically calculated on the basis of sex, age, weight and height. Such a work rate was gradually reached in the first 5 min of exercise. During the exercise, heart rate was continuously monitored (Oximeter; Radiometer, Copenhagen, Denmark) not to exceed the maximal heart rate theoretically calculated.

CK plasma levels were determined at rest and 1, 3, 6 and 24 h after the conclusion of the test, by venous blood samples drawn from the antecubital vein. CK plasma levels were assayed using an enzymatic method (CK IFCC, Boehringer Mannheim, Germany). Serum albumin was determined by a nephelometric procedure. Urinary proteins were measured by the Ponceau red method. The other biochemistry evaluations were performed by means of routine methods employed in our laboratory.

All values are expressed as mean ± SEM. Statistical evaluation was performed using Student's t test for unpaired data and Pearson's linear correlation test. Differences were considered as statistically significant when $p < 0.05$.

Results

Following exercise, CK plasma levels became higher in nephrotics than in normal controls, in face of similar basal values (table 1). In other words, the CK increments were greater in nephrotics than in controls from the first hour after the end of exercise (fig. 1). These changes, both as absolute values and as percentage of the basal values, correlate positively to daily urinary protein excretion in nephrotics (table 2, fig. 2). Furthermore, an inverse linear relationship was detected between CK increases and albumin serum levels either after 3 h ($r = 0.56$, $p < 0.05$) or 6 h ($r = 0.60$, $p < 0.05$) (fig 3). However, no correlation was observed between the amount of plasma CK increase and age, body weight, plasma creatinine, plasma cholesterol or hemoglobin levels of the nephrotic patients.

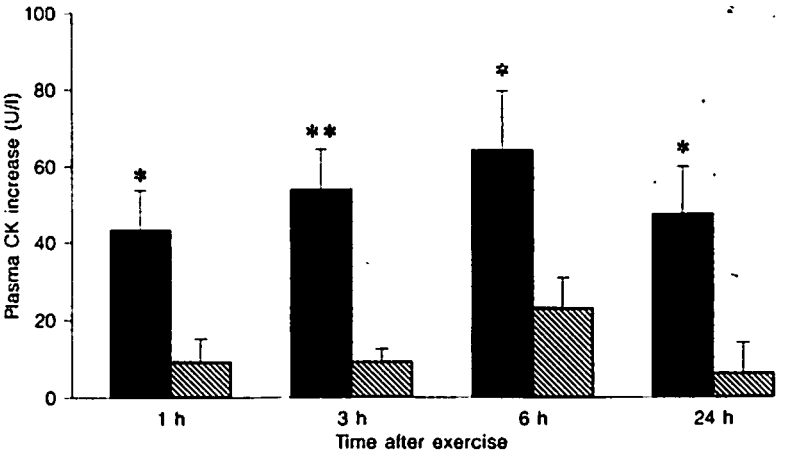

Fig. 1. Plasma CK increments (mean ± SEM), in respect to the basal value, following muscle exercise in nephrotic patients (solid bars) and normal controls (hatched bars). * $p < 0.05$; ** $p < 0.01$.

Table 2. Pearson's linear correlation test between daily urinary protein excretion and plasma CK increases (both as absolute value and as percentage of the basal value) after 1, 3, 6 and 24 h following the end of submaximal muscle exercise (* $p < 0.05$)

X-axis	Y-axis	
Urinary protein excretion	CK increase	% CK increase
1 h after	r: 0.420	r: 0.486
3 h after	r: 0.640*	r: 0.549*
6 h after	r: 0.617*	r: 0.567*
24 h after	r: 0.618*	r: 0.652*

Discussion

The results of the present study demonstrate that a greater than normal increase of CK plasma levels occurs following muscle exercise in nephrotics and that this increment correlates to the severity of the daily urinary protein losses and negatively to the serum albumin concentration. This suggests an abnormal susceptibility to injury of the muscle performing submaximal exercise in nephrotic patients with preserved renal function.

Clinical practice suggests that nephrotic syndrome is often associated with protein depletion. Recently it has been demonstrated that urinary protein losses trigger metabolic changes aimed to conserve body proteins and nitrogen balance [1]. Indeed, a reduction of protein catabolism and an increase of protein synthesis occurs in nephrotic patients together with reduction of dietary amino acid oxidation and their better utilization [1]. However, when massive urinary protein losses override this mechanism or when appropriate compensatory responses to massive protein losses are lacking, protein malnutrition and degradation of body protein stores occurs leading to reduction of lean body mass, since the muscle tissue plays a pivotal role in total body protein metabolism. The evidence of a greater fragility of muscle fiber performing a submaximal exercise, and its relationship to the severity of nephrotic syndrome, focuses the attention to clarify whether the urine protein loss per se or the induced modifications of metabolic processes can account for these findings.

The increment of CK plasma levels is regarded as a marker of increased membrane permeability and muscle damage [3, 4]. The process causing these muscle changes can develop through several stages, being the initial event of physical or of metabolic nature. In the former case, high specific tensions could mechanically disrupt sarcolemma, sarcoplasm reticulum or myofibril as in muscle dystrophy, in which sarcolemma proteins are quantitatively or qualitatively abnormal [6, 7]. In the latter case, an insufficient mitochondrial respiration can cause an abnormal calcium overload triggering muscle fiber disruption [8, 9]. This mechanism occurs in patients affected by metabolic myopathies and in healthy subjects performing strenuous exercise.

A role for interstitial edema in muscle tissue damage can also be taken into account. In fact it could contribute

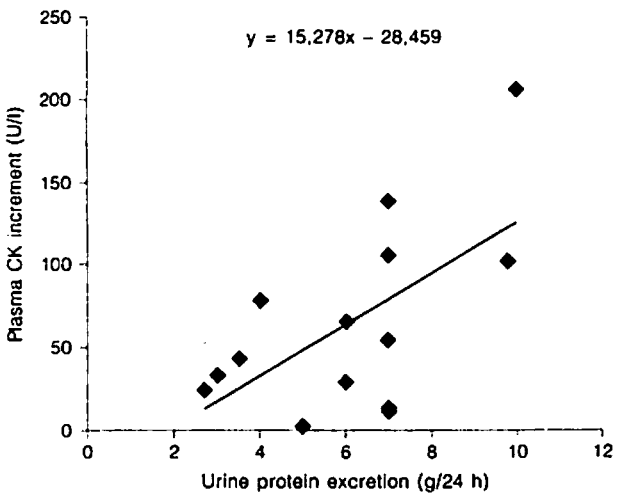

Fig. 2. Correlations between urinary protein excretion and plasma CK changes, 6 h after exercise in nephrotic patients.

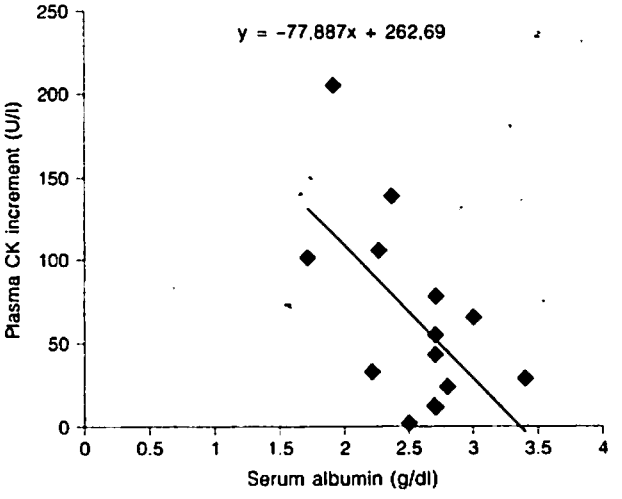

Fig. 3. Correlations between serum albumin concentration and plasma CK changes, 6 h after exercise in nephrotic patients.

to muscle suffering during intense exercise, probably by hindering the metabolic exchanges between muscle cells and the bloodstream. Further studies should be addressed to define the muscle structural and/or functional abnormalities in nephrotic syndrome leading to exercise-induced muscle damage. Physical inactivity has been recommended for a too long time in renal patients, contributing to reduction of body muscle mass and trophism, and to an unsatisfactory life quality in these patients. Actually, physical rehabilitation is a major therapeutic goal in the management of chronic renal patients.

So the question arises as to whether the muscle abnormality found in the studied nephrotics can be favorably affected by regular muscle training or, on the contrary, intense physical activity is really not safe in nephrotic patients even in the absence of renal failure.

In conclusion, our data suggest increased muscle fragility in nephrotics that correlates to the severity of urinary protein wasting. Further studies are needed to define the properties of muscle fibers in nephrotic patients and the mechanisms of the increased susceptibility to muscle damage following submaximal exercise.

References

1 Maroni BJ, Staffeld C, Young VR, Manatunga A, Tom K: Mechanisms permitting nephrotic patients to achieve nitrogen equilibrium with a protein-restricted diet. J Clin Invest 1997;99:2479–2487.

2 Guarnieri GF, Toigo G, Situlin R, Carraro M, Tamaro G, Lucchesi A, Oldrizzi L, Rugiu C, Maschio G: Nutritional state in patients on long-term low-protein diet or with nephrotic syndrome. Kidney Int 1989;36:S195–S200.

3 Van der Muelen JH, Kuipers H, Drukker J: Relationship between exercise-induced muscle damage and enzyme release in rats. J Appl Physiol 1991;71:999–1004.

4 Hortobagyi T, Denahan T: Variability in CK: Methodological, exercise and clinically related factors. Int J Sports Med 1989;10:69–80.

5 Jackson MJ, Round JM, Newham DJ, Edwards RHT: An examination of some factors influencing CK in the blood of patients with muscular dystrophy. Muscle Nerve 1987;10:15–21.

6 Matsumura K, Campbell K: Dystrophin-glycoprotein complex: Its role in the molecular pathogenesis of muscular dystrophies. Muscle Nerve 1994;17:2–15.

7 Hoffman EP, Fischbeck KH, Brown RH, Johnson M, Medori R, Loike JD, Harris JB, Waterston R, Brooke M, Speckt L, Kupsky W, Chamberlain J, Caskey CT, Shapiro F, Kunkel LM: Characterization of dystrophin in muscle-biopsy specimens from patients with Duchenne's or Becker's muscular dystrophy. N Engl J Med 1988;318:1363–1368.

8 Armstrong RB: Mechanism of exercise induced muscle fibre injury. Sports Med 1991;12:184–207.

9 Duan C, Delp MD, Hayes DA, Delp PD, Armstrong RB: Skeletal muscle Ca^{2+} overload and injury from excentric exercise. J Appl Physiol 1990;68:1241–1251.