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# Carnitine deficiency and L-carnitine supplementation in lysinuric protein intolerance

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**Abstract**

The aim of the study was to investigate the prevalence and mechanisms of development of carnitine deficiency in patients with lysinuric protein intolerance (LPI). In our cohort of 37 Finnish patients with LPI, 8 (8-52 years of age) have been diagnosed with hypocarnitinemia. Their free and total serum carnitine levels, acyl carnitine profiles, renal function, diet, and medication were compared with the data from 8 age- and sex-matched patients with LPI not treated with carnitine supplementation. In patients with LPI, hypocarnitinemia was strongly associated with female sex, renal insufficiency, and the use of ammonia-scavenging drugs. Of the 8 hypocarnitinemic patients, 3 complained of muscle weakness, and their symptoms disappeared during carnitine supplementation. Oral lysine supplementation did not correct hypocarnitinemia in our patients. The patients with LPI are at considerable risk for carnitine deficiency. Supplementation of hypocarnitinemic LPI patients with oral L-carnitine improved serum total carnitine values, but the ratio of free and total carnitine remained subnormal in all supplemented patients except one. Furthermore, decreased ratio of free and total serum carnitine was common even in LPI patients with normal total serum carnitine concentration.


## 1. Introduction

Lysinuric protein intolerance (LPI; OMIM 222700) is a rare autosomal recessive defect in the transport of the cationic amino acids that is more prevalent in Finland than elsewhere in the world [1,2]. Lysinuric protein intolerance is caused by mutations in the SLC7A7 gene encoding the $y^+L$ amino acid transporter 1 [3], which lead to defective transport of cationic amino acids lysine, arginine, and ornithine at the basolateral membrane of enterocytes and renal tubular cells and in hepatocytes [4]. Because of defective absorption and increased urinary loss, the plasma concentrations of cationic amino acids are decreased. The deficiency of arginine and ornithine leads to malfunction of the urea cycle and hyperammonemia after dietary loads of protein. Symptoms of LPI include aversion to protein-rich foods, failure to thrive, hepatomegaly and splenomegaly, osteoporosis, and muscle hypotonia [2,5]. The patients are also predisposed to severe complications such as pulmonary alveolar proteinosis and glomerulonephritis [6]. Treatment of LPI is based on protein-restricted diet and meal-time supplementation with oral citrulline, a neutral amino acid and urea cycle intermediate, which is effectively absorbed from the intestine and improves the function of the urea cycle [7].

Carnitine is an essential component in the transport of long-chain fatty acids from the cytosol to the mitochondrial matrix for $\beta$-oxidation [8]. In omnivorous humans, approximately 75% of body carnitine comes from the diet and 25% from de novo biosynthesis [9]. Meat, fish, and dairy products

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Table 1
Characteristics and total and free serum carnitine concentrations of 8 female LPI patients with hypocarnitinemia before and 6 to 12 months after carnitine supplementation (1 g/d)

| Patient | Age (y) | Before carnitine supplementation | | | During carnitine supplementation | | |
|---|---|---|---|---|---|---|---|
| | | Total carnitine (μmol/L) (reference range, 23-62 μmol/L) | Free carnitine (μmol/L) (reference range, 23-52 μmol/L) | Free/total (%) (reference range >80%) | Total carnitine | Free carnitine | Free/total (%) |
| 1a | 10 | 20.4 | B | NC | 47.3 | 31.9 | 67 |
| 2a | 16 | 18.7 | 14.1 | 76 | 29.2 | 22.4 | 77 |
| 3a | 32 | 26.6 | 19.9 | 75 | 53.7 | 37.1 | 69 |
| 4a | 41 | 20.1 | 13.1 | 65 | 29.5 | 14.2 | 48 |
| 5a | 8 | 20.9 | 11.3 | 54 | 57.0 | 47.7 | 84 |
| 6a | 13 | 19.7 | 11.8 | 60 | 35.5 | 26.3 | 74 |
| 7a | 21 | 19.1 | 14 | 73 | 35.9 | 21.2 | 59 |
| 8a | 52 | 22.5 | 14.2 | 63 | 34.7 | 26.6 | 77 |

B indicates below the detection threshold; NC, not calculated.

are the major sources of carnitine in the human diet [10]. Human skeletal muscle, liver, kidney, heart, and brain are all capable of the biosynthesis of γ-butyrobetaine, the immediate precursor of carnitine, from methionine and lysine, but the final conversion from γ-butyrobetaine to L-carnitine takes place only in liver, kidney, and brain. Carnitine is then released into the circulation and imported to other tissues, especially skeletal muscle, which contains more than 90% of total body carnitine [11]. Plasma carnitine concentration is regulated largely by the renal threshold [12]. At normal physiologic plasma concentrations, more than 90% of filtered carnitine is reabsorbed by the kidney [13].

Carnitine deficiency is a frequent secondary complication in patients with inborn errors of fatty acid oxidation or organic acid metabolism [14]. Failure to reabsorb free and acyl carnitines may also result in secondary carnitine deficiency in renal Fanconi syndrome [15]. Secondary carnitine deficiency may present as failure to thrive, recurrent infections, hypotonia, encephalopathy, cardiomyopathy, or nonketotic hypoglycemia. Plasma carnitine deficiency is defined as free carnitine concentration of 20 μmol/L or lower, or an acyl–free carnitine ratio of 0.4 or higher [16]. However, normal plasma carnitine does not rule out deficiency of carnitine in muscle, and muscle biopsy is therefore necessary if carnitine deficiency in tissues is suspected [17].

L-Carnitine supplementation is commonly used in several inborn errors of metabolism, although there is no high-quality evidence of its benefits [18]. Consequently, there has also been disagreement over the proper threshold for medical intervention in hypocarnitinemia associated with these diseases. Two cases where oral carnitine supplementation had a beneficial effect on a patient with hypocarnitinemia associated with LPI have been reported [19,20]. We have screened our patients with LPI for carnitine deficiency and started oral carnitine supplementation with 1 g of L-carnitine (Carnitene/Carnitor, Sigma-Tau Pharmaceuticals, Gaithersburg, MD) per day for those with markedly decreased serum free carnitine concentration and/or clinical symptoms of muscle weakness. The purpose of this study was to investigate retrospectively the role of several clinical factors (meat intake, oral lysine supplementation, and renal function) on plasma carnitine levels of patients with LPI.

## 2. Patients and methods

### 2.1. Patients

Thirty-seven Finnish patients with LPI followed at the Turku University Hospital were routinely screened for carnitine deficiency. All patients, for whom carnitine supplementation (1 g/d) was initiated for diagnosed carnitine deficiency, were included in the study group A (n = 8). All the subjects were female and their ages varied from 8 to 52 years (mean age, 20.8 years). The subjects had been diagnosed with LPI between the ages of 1 and 14 years (average age at diagnosis, 4.5 years). They had been treated with a protein-restricted diet (recommended protein intake, 0.8 g/kg per day for adults and 1 g/kg per day for children) and L-citrulline supplementation (86-182 mg/kg per day). Eight age- and sex-matched LPI patients not on carnitine supplementation were chosen as controls.

The patients received written information about the study and gave written informed consent for testing the acylcarnitine profile. For children younger than 12 years, parental consent was asked, and for patients between 12 and 18 years of age, both parental consent and the consent of the patient were required. The study was approved by the ethics committee of the hospital.

### 2.2. Methods

The data concerning free and total serum carnitine levels, renal function (glomerular filtration rate, serum creatinine, and the quantity of protein excreted in the urine), plasma lysine levels, and possible oral lysine supplementation of the patients were obtained from hospital records. At their routine control visits, the patients were interviewed about possible symptoms of muscle weakness (walking difficulties, inability to participate in sporting activities, clumsiness in children). The mean daily red meat intake was evaluated with a detailed questionnaire, in which the most common meat dishes in Finland were listed. The patients were asked to report both the

Table 2
The use of ammonia-scavenging drugs and lysine hydrochloride supplementation together with observed benzoylcarnitine and phenylacetylcarnitine in acyl carnitine profiling (average of 2 determinations) in 8 patients with hypocarnitinemia (A) and 8 LPI controls without previously diagnosed hypocarnitinemia (B)

A

| Patient | BMI | Dose of sodium benzoate (mg/kg per day) | Dose of sodium phenylbutyrate (mg/kg per day) | Blood sodium benzoylcarnitine (μmol/L) | Blood sodium phenylacetylcarnitine (μmol/L) | Dose of lysine-HCl (mg/kg per day) | Kidney involvement |
|---|---|---|---|---|---|---|---|
| 1a | 15 | – | 333 | 0.11 | 0.27 | 19 | CKD |
| 2a | 19.8 | – | 202 | 0.06 | 0.26 | 18 | CKD |
| 3a | 18 | 111 | – | 0.14 | 0 | 38 | – |
| 4a | 23 | – | – | 0 | 0 | – | CKD |
| 5a | 14.8 | 83 | 106 | 0.17 | 0.37 | 16 | – |
| 6a | 16 | 78 | 85 | 0.13 | 0.08 | 6 | CKD |
| 7a | 25 | – | – | 0.12 | 0 | 41 | ESRD |
| 8a | 21 | 44 | – | 0.17 | 0 | – | ESRD |

B

| Control | BMI | Dose of sodium benzoate (mg/kg per day) | Dose of sodium phenylbutyrate (mg/kg per day) | Blood sodium benzoylcarnitine (μmol/L) | Blood sodium phenylacetylcarnitine (μmol/L) | Dose of lysine-HCl (mg/kg per day) | Kidney involvement |
|---|---|---|---|---|---|---|---|
| 1b | 12.5 | 166 | – | 0.27 | 0 | 24 | – |
| 2b | 19.1 | – | – | 0 | 0 | 26 | – |
| 3b | 27 | – | – | 0 | 0 | 41 | – |
| 4b | 20 | 84 | – | 0.07 | 0 | 20 | – |
| 5b | 13.9 | 200 | – | 0.16 | 0 | – | – |
| 6b | 15.7 | – | 173 | 0.03 | 1.63 | 11 | – |
| 7b | 34.5 | – | – | 0 | 0 | 31 | – |
| 8b | 19 | 20 | – | 0.09 | 0 | 16 | ESRD |

BMI indicates body mass index; CKD, chronic kidney disease; ESRD, end-stage renal disease.

frequency of consumption of each food and the sizes of the servings. Total red meat intake was then calculated using Micro-Nutrica program developed at the Research Centre of the Social Insurance Institution, Turku, Finland.

A venous blood sample for acylcarnitine analysis was taken from all the patients with hypocarnitinemia and from 8 age- and sex-matched LPI patients with normal total serum carnitine concentrations. A drop of blood was then transferred on a filter paper and allowed to dry.

Serum total and free carnitine concentrations were measured from fasting samples with the radioenzymatic assay of Cederblad and Lindstedt [21] as modified by McGarry and Foster [22]. The acyl carnitine profiling was performed from blood spot sample by automated electrospray tandem mass spectrometry as described by Rashed et al [23].

## 3. Results

On carnitine supplementation, total serum carnitine concentrations rose up to the reference range in all the patients (Table 1). However, the ratio of free to total carnitine remained below the reference range in all but one patient. In the control group, 5 of 8 patients had decreased ratio of free to total carnitine, although the total serum carnitine concentrations of all the control patients were within the reference range. Of the 8 patients, 3 had symptoms of muscle weakness before supplementation, and muscle biopsy was taken from 2 of them. Myopathy and fat deposition were seen in one biopsy sample and mild variation of the size of muscle fibers in another. Muscle weakness rapidly subsided after carnitine supplementation had been initiated.

Of the 8 patients with carnitine supplementation, 6 showed variable degrees of renal involvement, from proteinuria and elevated serum concentrations of creatinine and cystatine C to end-stage renal disease in 2 cases. However, most of them had only slightly impaired renal function when hypocarni-

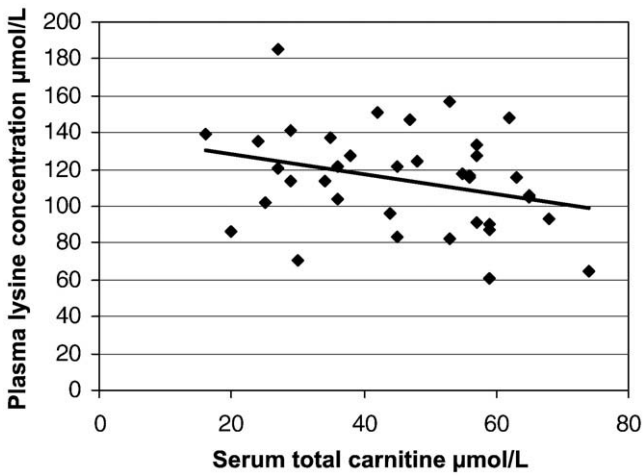


Fig. 1. Serum total carnitine (μmol/L) vs plasma lysine concentration (μmol/L) in 37 Finnish patients with LPI.

Table 3
Characteristics, total and free serum carnitine concentrations, and the use of ammonia-scavenging drugs and lysine in 29 Finnish LPI patients without carnitine supplementation

| ID | Age (y) | Sex | Total carnitine (μmol/L) (reference range, 23-62 μmol/L) | Free carnitine (μmol/L) (reference range, 23-52 μmol/L) | Free/total (%) (reference range >80%) | Sodium benzoate therapy | Sodium phenylbutyrate therapy | Lysine therapy |
|---|---|---|---|---|---|---|---|---|
| 1 | 2 | F | 56.2 | 36.2 | 64 | | | |
| 2 | 8 | F | 25.5 | 18.9 | 74 | x | | x |
| 3 | 9 | F | 40.1 | 30.8 | 77 | x | | x |
| 4 | 12 | F | 45.2 | 37.5 | 83 | x | x | |
| 5 | 20 | F | 28.1 | 28 | 100 | | | x |
| 6 | 24 | F | 46.1 | 39.4 | 85 | | | x |
| 7 | 31 | F | 39.6 | 30.3 | 77 | x | | x |
| 8 | 32 | F | 29.3 | 25.2 | 86 | | | x |
| 9 | 36 | F | 24.8 | 18.5 | 74 | x | | x |
| 10 | 38 | F | 28.3 | 21.1 | 74 | x | | x |
| 11 | 39 | F | 46.8 | 37.1 | 79 | | | x |
| 12 | 40 | F | 41.8 | 30.2 | 72 | x | | x |
| 13 | 46 | F | 44.5 | 36.4 | 82 | | | x |
| 14 | 50 | F | 33.0 | 32.0 | 97 | x | | x |
| 15 | 51 | F | 53.2 | 35.6 | 67 | | | x |
| 16 | 54 | F | 34.1 | 15.1 | 44 | x | | x |
| 17 | 1 | M | 48.4 | 26.9 | 56 | | | x |
| 18 | 23 | M | 54.4 | 47.7 | 88 | | | x |
| 19 | 29 | M | 51.5 | 42.3 | 82 | x | | x |
| 20 | 31 | M | 42.7 | 32.0 | 75 | | | x |
| 21 | 34 | M | 48.1 | 38.4 | 80 | x | | x |
| 22 | 37 | M | 47.4 | 38.9 | 82 | | | x |
| 23 | 37 | M | 64.7 | 53.3 | 82 | x | | x |
| 24 | 41 | M | 66.1 | 47.7 | 72 | | | x |
| 25 | 41 | M | 68.4 | 56.5 | 83 | | | |
| 26 | 43 | M | 54.5 | 46.5 | 85 | x | | |
| 27 | 48 | M | 41.5 | 28.4 | 68 | | | |
| 28 | 51 | M | 46.8 | 36 | 77 | x | | |
| 29 | 62 | M | 38.6 | 26.1 | 68 | x | | x |

tinemia was first diagnosed. In the control group, one patient developed rapidly progressive renal insufficiency during the follow-up. After 1 year of dialysis therapy, her total serum carnitine concentration had decreased from 34.1 to 21.2 μmol/L, with the free to total carnitine ratio of 44%.

There were no significant differences in the consumption of red meat between the patients with hypocarnitinemia and the control group. Six of the 8 patients with hypocarnitinemia and 7 of the 8 control patients received oral lysine hydrochloride supplementation (Table 2). When data from all Finnish patients with LPI followed up at the Turku University Hospital (n = 37) were analyzed, no positive correlation between plasma lysine concentration and serum total carnitine could be observed (Fig. 1). Six of the 8 patients with carnitine supplementation and 15 of the 29 nonsupplemented patients were using ammonia-scavenging drugs. The use of sodium phenylbutyrate was more common in patients with carnitine supplementation than in nonsupplemented patients (50% vs 3%) (Table 3). In acyl carnitine profiling, benzoylcarnitine was detected in the blood samples of all patients receiving sodium benzoate. Both phenylacetylcarnitine and benzoylcarnitine were detected in the patients receiving sodium phenylbutyrate supplementation alone or combined with sodium benzoate (Table 2). The concentration of palmitoylcarnitine was low in all samples, but the significance of this finding is unknown.

## 4. Discussion

Patients with LPI are predisposed to hypocarnitinemia both because of the strong aversion to protein-rich foods, which are the most important source for exogenous carnitine, and because of the deficiency of lysine that may restrict carnitine biosynthesis. Fanconi-type tubulopathy is relatively common in LPI, and renal carnitine loss thus provides another possible pathophysiologic mechanism for carnitine deficiency. However, only some of the patients develop hypocarnitinemia. Because this was a retrospective study, the effect of carnitine supplementation on clinical status was difficult to evaluate as multiple changes were often made to the medication during the follow-up period. Carnitine supplementation normalized the total serum carnitine concentrations in all patients with hypocarnitinemia, but the ratio of free to total serum carnitine remained below the reference range. In this study, all the patients with

hypocarnitinemia were female. On the other hand, high-normal and even supranormal serum total carnitine concentrations have been observed in male patients with LPI. The reason for this is not known to us, although males generally have slightly higher serum carnitine levels than females [24].

In this study, only small differences in the intake of carnitine-rich foods between the patients with and without hypocarnitinemia could be observed. In most patients with LPI, aversion to protein-rich foods prevents them from accepting more than minimal amounts of protein in spite of citrulline supplementation. The diet is often very restricted, and use of nutritional supplements is necessary to ensure adequate intake of nutrients. Chronic lysine deficiency is also common in patients with LPI and may contribute to the carnitine deficiency. However, oral lysine supplementation did not correct hypocarnitinemia in our patients. The lysine doses need to be individually titrated to avoid gastrointestinal side effects [25]. In addition, even the maximum tolerated doses of lysine may insufficiently improve carnitine synthesis, as protein-bound trimethyllysine rather than free lysine is the precursor for carnitine in its biosynthesis. Three of our patients suffered from muscle weakness, a characteristic sign of carnitine deficiency, which subsided during carnitine supplementation. In patients with LPI, however, the clinical signs of hypocarnitinemia may be difficult to notice as they may be masked by low muscle mass and symptoms of the primary disease.

Several patients in both study groups were treated with sodium benzoate, sodium phenylbutyrate, or both to reduce the need for citrulline, as exposure to high plasma concentrations of citrulline may play a role in the development of renal problems associated with LPI. Sodium benzoate increases ammonia nitrogen elimination via conjugation with glycine and excretion as urinary hippurate. In patients with inborn urea cycle disorders, it is effective in reducing and controlling hyperammonemic episodes [26-29]. However, benzoic acid inhibits carnitine biosynthesis and consequently reduces plasma free and acylcarnitine levels [30,31]. L-Carnitine supplementation is therefore recommended to patients who develop hypocarnitinemia during long-term sodium benzoate therapy [32]. Sodium phenylbutyrate, another ammonia-scavenging drug, is oxidized to phenylacetate, which is then conjugated with glutamine and excreted in the urine [33]. In rats, phenylacetic acid effectively inhibits carnitine biosynthesis [34]. In this study, the use of sodium benzoate and sodium phenylbutyrate was strongly associated with elevated concentrations of carnitine esters of benzoic acid and phenylacetic acid in the plasma, suggesting increased loss of free carnitine via conjugation and subsequent decrease in the ratio of free to total carnitine.

In the last few years, an increasing number of Finnish patients with LPI have developed progressive renal disease of indeterminate origin, which has in some cases led to renal failure and kidney transplantation [35]. In this study, renal insufficiency was more common in patients with hypocarnitinemia than in the control group (75% vs 12.5%). However, hypocarnitinemia was generally diagnosed at a time point when renal function was only mildly impaired, suggesting that other mechanisms are involved in the development of carnitine deficiency. In one patient, plasma total carnitine concentration also remained nearly normal despite severe renal insufficiency and only decreased during dialysis. The healthy human kidney acts to conserve the carnitine stores of the body via carrier-mediated tubular reabsorption. Deterioration of kidney function therefore leads to disturbed homeostatic control of the L-carnitine pool in the body [36]. As a low-molecular-weight compound, carnitine is effectively removed from the body by hemodialysis procedure, which lacks the ability to conserve L-carnitine. Hemodialysis also tends to promote a greater acyl- L-carnitine–L-carnitine ratio than the healthy kidney [37]. The patients with end-stage renal disease therefore generally have substantially decreased plasma carnitine concentrations. However, low plasma carnitine concentrations or elevated acylcarnitine-carnitine ratios are not predictive of clinical response to L-carnitine supplementation, and according to the recommendations of the National Kidney Foundation, the detection and diagnosis of dialysis-related carnitine disorder should be based on clinical signs and symptoms (anemia, intradialytic hypotension, cardiomyopathy, muscle weakness, and fatigability) rather than laboratory findings [38]. L-Carnitine supplementation has been shown to be effective adjunctive treatment of hyporesponsive erythropoietin-dependent anemia associated with kidney disease, which has also been a significant problem in patients with LPI [39]. Routine supplementation with L-carnitine might be of value for the patients with renal insufficiency associated with LPI.

In summary, patients with LPI are at considerable risk for carnitine deficiency, which may contribute to their symptoms. In this study, hypocarnitinemia was associated with female sex, chronic nephropathy, and the use of ammonia-scavenging drugs. Supplementation with oral L-carnitine improved serum total carnitine values in hypocarnitinemic patients with LPI, but the ratio of free to total carnitine remained subnormal. Surprisingly, decreased ratio of free to total serum carnitine was also common in female LPI patients with normal total serum carnitine concentration.

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