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Alimentary Tract

L-Carnitine in the treatment of fatigue in adult celiac disease patients A pilot study

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Abstract

Background. Fatigue is common in celiac disease. L-Carnitine blood levels are low in untreated celiac disease. L-Carnitine therapy was shown to improve muscular fatigue in several diseases.

Aim. To evaluate the effect of L-carnitine treatment in fatigue in adult celiac patients.

Methods. Randomised double-blind versus placebo parallel study. Thirty celiac disease patients received 2 g daily, 180 days (L-carnitine group) and 30 were assigned to the placebo group (P group). The patients underwent clinical investigation and questionnaires (Scott-Huskisson Visual Analogue Scale for Asthenia, Verbal Scale for Asthenia, Zung Depression Scale, SF-36 Health Status Survey, EuroQoL). OCTN2 levels, the specific carnitine transporter, were detected in intestinal tissue.

Results. Fatigue measured by Scott-Huskisson Visual Analogue Scale for Asthenia was significantly reduced in the L-carnitine group compared with the placebo group ($p = 0.0021$). OCTN2 was decreased in celiac patients when compared to normal subjects (−134.67% in jejunum), and increased after diet in both celiac disease treatments. The other scales used did not show any significant difference between the two celiac disease treatment groups.

Conclusion. L-Carnitine therapy is safe and effective in ameliorating fatigue in celiac disease. Since L-carnitine is involved in muscle energy production its decreased absorption due to OCTN2 reduction might explain muscular symptoms in celiac disease patients. The diet-induced OCTN2 increase, improving carnitine absorption, might explain the L-carnitine treatment efficacy.

Keywords: Asthenia; Carnitine; Celiac disease; Fatigue; Gluten-free diet

1. Introduction

Celiac disease (CD) is a chronic systemic autoimmune disorder triggered by gluten proteins in genetically predisposed individuals. The disease is characterised by enteropathy with destruction of the small intestine villi, with resulting malabsorption of nutrients [1].

The gluten-related malabsorption may include fatty acids, iron, glucose, electrolytes, vitamins and others. All the above may result in short stature, muscular hypotrophy, iron deficiency anaemia, hypovitaminosis (A, D, K) and a number of gastrointestinal and non-gastrointestinal symptoms [2]. Besides, many adults and children report fatigue at the moment of CD diagnosis [3–6]. Fatigue is a subjective perception that can be defined as difficulty in initiating or sustaining regular activities. In the patient's definition the above symptom can overlap the feelings of tiredness, muscle weakness, depression, fatigability and/or irritability, affect-

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ing the quality of life of the individual. Actually, fatigue is frequently reported in primary care [7] and can also be related to systemic or neuromuscular diseases [8–10].

L-β-hydroxy-trimethyl-ammonium butyric acid (L-carnitine) is a natural compound and it is ubiquitarious in the mammal organisms with different biological functions [11]. The major role of L-carnitine is in the β-oxidation and it is vital for the skeletal and myocardial muscles that utilise lipids as the main source for energy [12]. In humans, it has been demonstrated that carnitine enters the cell through the plasma membrane carnitine family transporters, called OCTN1, OCTN2, OCTN3 and CT2 [13–15]. The carnitine family transporters have different structures and functions [16,17] and are critical in the transport of endogenous amines, some vitamins and several xenobiotics [18]. Among them OCTN2 is the more specific and effective in carnitine absorption [14]. Supporting the importance of OCTN2-mediated intestinal LC absorption in maintaining carnitine homeostasis, there is the onset of carnitine deficiency in subjects with a defective OCTN2-mediated transport [14]. Moreover, experimental studies have shown that in several stress conditions, such as acute ischaemia, diphtheric myocarditis, the decrease of LC tissue levels [20] account for the impaired function of the heart, condition strongly related to fatigue [7]. The deficiency of carnitine in humans is associated with muscle asthenia, easiness to contract infections and cardiomyopathies [19–21]. LC supplementation is relevant for the treatment of the myopathies associated with the above diseases. Indeed, LC has been used for the fatigue treatment in IFNγ hepatitis therapy [22], haemodialysis, [23] cancer chemotherapy [24] and multiple sclerosis therapy [25]. Studies conducted on CD children with malabsorption showed that there is a direct relationship between CD-related symptoms and carnitine blood levels, suggesting that CD is to be considered causative of secondary carnitine deficiency [26–29]. Moreover, in CD children, a gluten-free diet results not only in intestinal mucosa recovery but also ameliorates the carnitine blood levels [27].

The present study aimed to evaluate the effect on fatigue of a long LC treatment in adult celiac patients. Secondary objectives were to evaluate LC effects on psychological status, assessed by the following quality-of-life questionnaires: EuroQoL and SF-36 Health Status Survey, and long-term safety and tolerability, assessed by onset adverse events and standard laboratory tests. As an ancillary study we evaluated OCTN2 levels in intestinal biopsies from CD patients before and after diet and LC treatment.

1.1. Patients and methods

An open randomised study was performed to determine the future study sample size. Ten patients with newly diagnosed CD were randomised: five received treatment with L-carnitine (2 g/day) and five were not treated. Fatigue was evaluated by a Visual Analogue Scale (VAS) before and after 180 days of treatment. Patients receiving LC showed a 25% decrease of VAS score in comparison with untreated patients. With the proposed sample of 30 subjects for each group the study would have had the power of 90% to yield a statistically significant result.

The present study was planned as a single-centre, randomised, double-blind parallel study LC versus placebo, involving 60 consecutive newly diagnosed adult (mean age 32.62 ± 8.60 years) CD patients. The main inclusion criteria were: patients aged 18–45years; with diagnosis of CD due to gluten intolerance, confirmed by the intestinal biopsy showing subtotal villous atrophy, anti-endomysium and atransglutaminase antibody positivity and absence of clinical evidences for depression (Zung Scale score ≤ 27). Exclusion criteria were: acute or previous hepatic or renal failure, acute or previous alterations of cardiopulmonary functionality, concomitant treatment with drugs that could interfere with the protocol evaluation, if the patient was a female of child-bearing potential, she had to agree to follow adequate contraception throughout the study period and to provide a negative pregnancy test, patients included in a clinical trial within 60 days from screening, known as hypersensitivity to LC, patients not able to fill in the quality of life scales and written informed consent, patients unwilling and unable to comply with protocol requirements.

Patients with CD were screened for the above inclusion/exclusion criteria in the Clinical and Experimental Medicine Department of the Federico II University of Naples, Italy. The study was approved by the Ethical Committee of the University Federico II of Naples. The study was conducted according to the ethical principles of the Declaration of Helsinki and the European Guidelines for Good Clinical Practice.

The 60 patients, following a 30-day gluten-free diet which was needed to improve malabsorption and assure a better use of oral route for the treatment, were randomly assigned (by means of a computerised pseudorandom number generation) to one of the two groups below:

- 30 patients were assigned to the L-carnitine group (LC group)
- 30 patients were assigned to the placebo group (P group)

No differences were present in the two groups with respect to age, height, weight, laboratory indices, systolic and diastolic arterial pressure.

Patients were treated with L-carnitine (Sigma-tau, Italy), single-dose vials, 1 g/twice daily, by oral route or similar vials containing placebo according to randomisation code for 180 days. The study protocol was structured in four visits: T-1, enrolment (7 days); T0, starting gluten-free diet (30 days); T1, starting treatment (180 days); T2, last visit.

Forty-seven patients (25 LC group, 22 P group) completed the study up to the second endoscopy (performed at T2) because 10 patients refused to undergo the second endoscopy, and 3 patients dropped out. For the 47 patients data from questionnaires and scales were complete for first visit and last

visit. For each visit the patients were examined according to the protocol as follows.

1.1.1. Physical examination

Patients were submitted to physical examination at visits T-1, T0, T1 and T2; included were measurements of blood pressure (diastolic and systolic, assessed by sphygmomanometer), heart rate, weight, height and body mass index (BMI).

1.1.2. Jejunal biopsies

Four jejunal biopsies at baseline and again at the end of the study (according to procedures adopted at the centre) were performed in order to evaluate the structure of intestinal mucosa and, in one sample, OCTN2 expression. Biopsies were performed at T-1, while they were repeated at T2 only for those patients who accepted. OCTN2 levels in the biopsy samples of jejunal mucosa were investigated by western blotting analysis (see below).

1.1.3. Scott-Huskisson Visual Analogue Scale (VAS) for Asthenia

The VAS is a sample tool that permits patients to rate the severity of their symptoms (in this case of fatigue). It is made up of a single question: *How have you felt in the last week? OR How did you feel last week*? The patients were asked to mark a visual analogical scale consisting of a 10-cm line at the left extreme the sentence: *I never feel tired*, and at the opposite extreme the sentence: *I always feel tired* [3]. Thus, the possible score ranges from 0 to 10. This scale was administered at each visit.

1.1.4. Verbal Scale for Asthenia

The Verbal Scale for Asthenia [31] was administered by the physician in order to quantify patient's physical (eight items) and mental (five items) fatigue. This scale was administered at each visit.

1.1.5. Modified Zung Depression Scale

Modified Zung Depression Scale [30,32] was administered to evaluate patient's anxiety and depression status. The scale is formed by 17 items: 10 items relate to physical and 7 to biological parameters. This scale was administered only at screening visit (T-1), patients whose score was >27 were not included.

1.1.6. SF-36 Health Status Survey

This test consists of multiple-choice answers (eight items) and one single-choice answer (one item) [33,34]. SF-36 Health Status Survey was administered to the patients in order to investigate changes in physical, mental and emotional dimensions at visits T0 and T2.

1.1.7. EuroQoL

EuroQoL is a simple questionnaire designed to evaluate health-related quality of life of the patients [35]. This test records patient's health problems (five items: mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and patient's self-related health status using a graduated scale (from 0 to 100). It was administered at visits T0 and T2.

1.2. Statistical and analytical plans

For each variable, descriptive statistics (mean, S.D., minimum and maximum values) were computed. Statistics were reported for each experimental time T-1, T0, T1, T2 and for the two treatment groups.

For each variable measured at baseline (observation at time T-1, as indicated by the protocol, and observation at time T0, at the end of the diet and before starting treatment), an independent sample *t*-test between LC and P groups was performed in order to verify if the two samples were homogeneous at the beginning of the study and at the beginning of the administration of LC. For non-parametric variables a Mann–Whitney *U*-test was utilised. For all subjects, delta (Δ) was computed as differences between the observations at time T0 and T2 (Δ = value at T2 − value at T0).

In order to verify if there were differences over time for the VAS between LC and P groups and males and females, an analysis of variance for repeated measures with treatment and gender as between factors was performed. For the assessment of the significance of treatment during the time intervals, an independent sample *t*-test between LC and P groups was performed.

For all subjects and for each of the variables indicating the clinical conditions (weight, height, blood pressure, heart rate) Δ was computed as differences between the observation at T0 and T2. To quantify significance of treatment, an independent sample *t*-test between LC and P groups was performed.

At the end of treatment, a chi-square test was performed to evaluate the association between the presence of intestinal atrophy at biopsy and the administration of LC.

Where the total scores of VAS are concerned, non-parametric tests were used. Δ was computed as indicated and the Mann–Whitney *U*-test between LC and P groups was utilised to assess the significance of treatment. For all subjects and for each parameter concerning the quality of life, Δ between values at T2 and T0 was computed and the Mann–Whitney *U*-test between LC and P groups was utilised to assess the significance of treatment. All tests were conducted considering the significance level $p = 0.05$.

1.3. L-carnitine assay

Serum L-carnitine levels have been measured by HPLC–mass spectrophotometric assay according to the technique currently in use in the Sigma-tau laboratory (Tallarico, Rapid Communication in Mass Spectrography, 1998).

Serum levels of total L-carnitine observed in the normal control study group (values ranging from 25.08 to

49.86 μmol/l) were found to be within the normal values reported in the literature.

1.4. OCTN2 assay

Extracts of human intestinal biopsies from control and celiac subjects were analysed by western blotting. Biopsy samples were homogenised in RIPA lysis buffer (0.1% sodiumdodecylsulphate (SDS), 0.5% deoxycholate, 1% Nonidet, 100 mM NaCl, 10 mM Tris–HCl (pH 7.4)) containing a protease inhibitor cocktail, 0.5 mM dithiotreitol and 0.5% phenylmethylsulfonyl fluoride (Sigma, Milan, Italy). Mucosal homogenates from patients as well as normal controls were spun at 140,000 × *g* for 30 min to separate the insoluble material. Protein concentration was determined on the supernatants using Bradford reagent (Bio-Rad). An aliquot of each lysate containing equivalent amounts of protein was separated on a 10% SDS-PAGE and transferred to nitrocellulose membrane (western blot). The transfer buffer consisted of 25 mM Tris, 190 mM glycine, 20% methanol and 0.005% SDS. Membranes were blocked with 5% non-fat dry milk in TBST (150 mM NaCl, 20mM Tris–HCl (pH 7.4) and 0.3% Tween 20), and probed with OCTN2 rabbit primary antibodies (2 mg/ml) which are polyclonal and are against a synthetic peptide corresponding to amino acid residues (YKHNKTPSHTNMLKDGQER) of human OCTN2. Filters were then incubated with horseradish peroxidase conjugated anti-rabbit IgG secondary antibody (Amersham, Milan, Italy) for 1 h at room temperature. Membranes were washed with TBST buffer. The enhanced chemiluminescence reagent was used for detection. Densitometry of autoradiographic bands was analysed using National Institutes of Health (Bethesda, MD) Image 1.62 software.

2. Results

No individual clinically significant abnormality was reported by the investigators and there was no suggestion in the laboratory data of any harmful effect of LC on the measured parameters.

General characteristics of the patients' cohort such as age, gender, anthropometry and vital signs are reported in Table 1. No significant differences were noted for the two treatment groups. In the LC group the compliance was 88.4 ± 8.3%, while in the P group it was 85.9 ± 9.5%. No serious adverse events were registered. The most frequent complains were abdominal cramps and/or diarrhoea in four patients, and skin rash in two patients. Three patients dropped out.

Table 1
Age, gender, anthropometry and vital signs in the cohort under study

	LC group ($N = 30$)	P group ($N = 30$)
Age (years)	33.60 ± 8.50	31.63 ± 8.74
Sex (M/F)	6/24	8/22
Body weight (kg)	57.51 ± 10.31	57.33 ± 9.99
Height (cm)	163.53 ± 6.95	165.10 ± 7.16
Heart rate (bpm)	71.53 ± 8.92	72.68 ± 7.01
Diastolic arterial pressure (mmHg)	68.83 ± 9.44	70.18 ± 7.87
Systolic arterial pressure (mmHg)	110.10 ± 11.70	111.96 ± 11.33

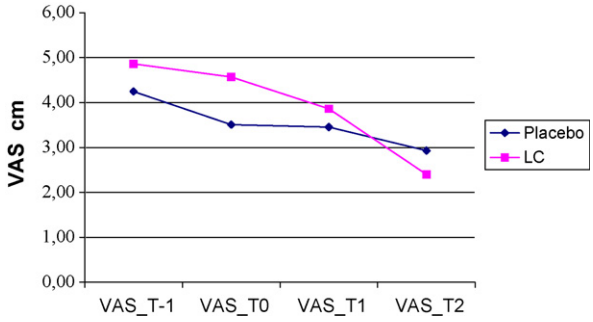

Fig. 1. Trend of values in the VAS scores (in cm) along time in LC group and placebo group. The absolute variation, ΔVAS decreases at T2 more dramatically for LC group (−2.17 ± 2.03 cm) than for the placebo group (−0.57 ± 2.55 cm).

Table 2 shows data of serum carnitine levels in celiac patients before and after treatment (LC or P) and in a group of healthy subjects as the normal control. Serum carnitine levels were significantly different before treatment and after treatment independently from the kind of treatment, although the LC-treated group showed the serum carnitine levels closest to the control group ones.

The main results of the present study is that LC-treated patients reported a significant improvement of the reported fatigue evaluated by VAS scale when compared to the P group. In fact, as reported in Fig. 1, at the end of the 180 treatment days with L-carnitine, there was a reduction of the VAS, expressed in cm, from 4.57 ± 1.98 (T0) to 2.40 ± 1.80 (T2), while the P group started from 3.50 ± 2.09 (T0) arrived at 2.93 ± 1.85 (T2). The absolute variation of VAS decreased more dramatically in the LC group (T2–T0 = −2.17 ± 2.03 cm) then for the P group (T2–T0 = −0.57 ± 2.55 cm). Mean scores of the VAS evalu-

Table 2
Serum L-carnitine levels before and after gluten-free diet and LC or placebo treatment in celiac disease and in a group of normal subjects as control group

	Celiac patients before			
	Diet ($n = 60$)	LC group ($n = 25$)	P group ($n = 22$)	Control group ($n = 30$)
Serum L-carnitine (μmol/l)	25.16 ± 1.09	50.83 ± 4.90	33.71 ± 2.16	47.30 ± 6.18

Student's *t*-test: before diet vs. LC group, $p = 0.001$; before diet vs. P group, $p = 0.0001$; before diet vs. normal controls, $p = 0.0001$; LC group vs. P group, $p = 0.243$; LC group vs. normal controls, $p = 0.257$; P group vs. control group, $p = 0.547$. Student's *t*-test for unpaired data showed significant differences before and after treatment independently from treatment.

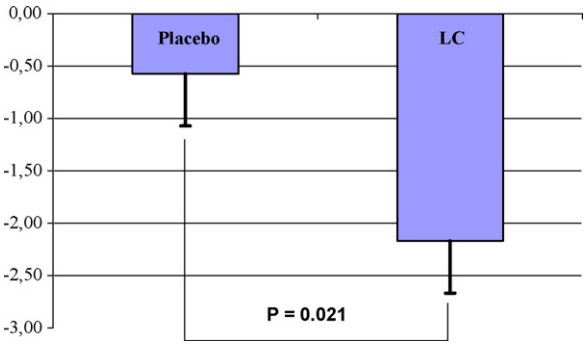

Fig. 2. Comparison of ΔVAS ((difference of VAS score at the end of study and scores at T-1) between LC and P group scores at the end of trial (T2) shows a statistically significant difference ($p = 0.021$).

ations during all visits are shown in Fig. 1. The comparison of ΔVAS (difference of VAS score at the end of study and scores at T-1) between the LC group and the P group showed a statistically significant difference with $p = 0.021$, as reported in Fig. 2.

All the other mean score differences between T2 and T0 for the other questionnaire analyses are shown in Table 3. Although no significant statistical difference was noted for the other scale an improvement trend is evident for all the scores in the LC group.

A general improvement of intestinal mucosal atrophy was observed in all patients, due to the concurrent gluten-free diet, and the analyses performed on the sub-group of 47 patients having evaluation at T-1 and T2 did not show any association between LC treatment and mucosal atrophy grade.

2.1. Detection of OCTN2 on intestinal biopsies

Biopsy specimens were tested for tissue levels of OCTN2, the specific carnitine transporter present on the intestinal epithelial cells. As controls, subjects underwent biopsies for upper gastrointestinal symptoms which resulted normal to endoscopy. The rabbit polyclonal OCTN2-specific antibody detected a protein with an apparent molecular mass of 70 kDa. No OCTN2 cross-reactivity was observed in any specimens tested. The results clearly demonstrated a significant decrease of OCTN2 in specimens obtained from celiac patients when compared to normal subjects (Fig. 3, panel A, upper lanes). Fig. 3 (panel B, upper lanes) shows differences between OCTN2 tissue levels in celiac patients before and after gluten-free diet. Indeed, OCTN2 tissue levels were significantly increased after diet in both celiac groups (+83.25% and + 83.1% in jejunum in P and LC groups, respectively). Means and S.D. of OCTN2 tissue levels (semiquantitative analysis) are shown in Fig. 3 (panel C); there was a significant difference between the OCTN2-relative expression in pre-diet compared to the control group and the post-diet group, in both comparisons ($p < 0.001$).

Table 3
Differences of scores for all scales measured at baseline (T0) and at time T2 (values are expressed as mean ± S.D.)

T2–T0	LC group	P group
VSA total	−5.12 ± 3.73	−3.23 ± 3.9
VSA physical fatigue	−4.52 ± 3.82	−2.41 ± 3.02
VSA mental fatigue	−0.60 ± 1.44	−0.82 ± 1.44
SF-36 physical functioning	13.50 ± 12.15	11.32 ± 24.03
SF-36 social functioning	24.43 ± 27.13	13.13 ± 24.16
SF-36 role limitation due to physical problems	41.67 ± 41.49	18.42 ± 47.76
SF-36 role limitation due to emotional problems	27.78 ± 51.71	26.32 ± 51.62
SF-36 mental health	8.47 ± 16.30	4.00 ± 16.47
SF-36 energy/vitality	14.44 ± 14.13	6.75 ± 16.88
SF-36 pain	10.50 ± 26.27	14.65 ± 23.53
SF-36 general health perception	13.39 ± 17.34	11.32 ± 17.10
EuroQoL	0.09 ± 0.18	0.05 ± 0.20

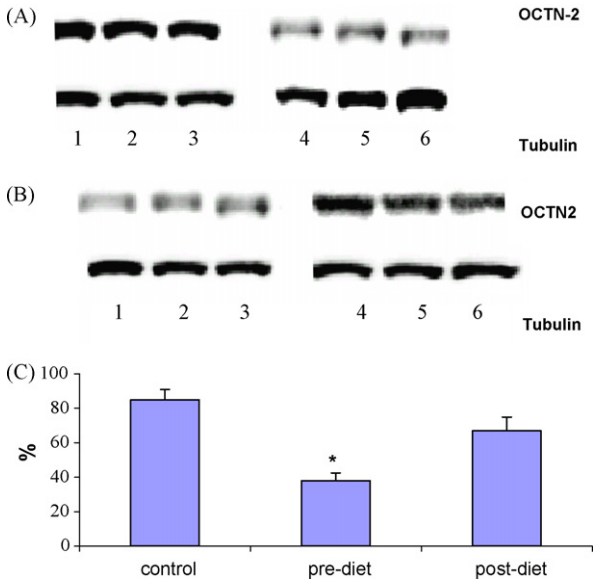

Fig. 3. OCTN2 expression in jejuenal (intestinal) epithelium. Panel A: representative western blot for OCTN2 (upper lanes) and tubulin (lower lanes) expression in normal subjects (lanes 1, 2, 3) and in celiac patients (lanes 4, 5, 6) biopsies. Panel B: representative western blot for OCTN2 (upper lanes) and tubulin (lower lanes) expression in celiac patients biopsies before (lanes 1,2,3) and after (lanes 4,5,6) diet. Panel C: OCTN2 relative expression densitometry. There is significant variation in % expression of OCTN2 relative to tubulin in CD patients biopsy before and after diet; (*) $p < 0.001$.

3. Discussion

In view of the strict links among CD, LC, fatigue and their relationships, the results of the primary outcome of the current study, i.e. improvement of fatigue measured by VAS, confirms our study hypothesis. VAS at the end of the study decreased more significantly both for absolute and percent values in the LC group than in the P group.

Other parameters that also measured patients' well-being such as EuroQoL and SF-36 Health Status Survey were not affected by L-carnitine treatment, although in all scores a trend toward better scores in LC group is noticeable. In our

opinion, these findings are in accordance with the reported VAS results for fatigue since the specificity of the other questionnaires used – EuroQoL and SF-36 Health Status Survey – is actually poor as they have not been originally designed to evaluate fatigue as "the sole symptom". This is fundamental since fatigue remains one of the "primary" limiting symptoms in CD patients' perspective [3]. The findings, however, suggest that a greater number of patients and/or a longer treatment period may increase the significance of the LC effect. It must be considered that, due to the way our protocol was designed, the greatest treatment effect found was related to the gluten-free diet prescribed in both groups, which acted as a major confounder in evaluating LC treatment effects.

Our study failed to demonstrate a significant increase of L-carnitine in the LC group in comparison with the P group. It may be possible that the effect of the main treatment, the gluten-free diet, acted as a confounder in the analysis hiding the drug effect. It must be noted, however, that LC-treated patients showed the serum L-carnitine levels most similar to those of the control group. Moreover, the limited number of patients tested for L-carnitine may affect the significance of the statistical analysis. It must be noted, however, that a recent study showed a marked decrease of circulating acetylcarnitine and a decrease of 11 other carnitine esters in clinically asymptomatic and well-being adult celiac disease patients, and gluten withdrawal alone does not necessarily normalise all elements of the disturbed carnitine homeostasis [37].

The ancillary study on OCTN2 levels in jejunal mucosa demonstrated an effect of gluten-free diet in both groups in terms of increased OCTN2 transporter. OCTN2 is unique in that it transports carnitine with high affinity in Na^+-dependent manner and transports organic cations in a Na^+-independent manner. Mutation in the human OCTN2 gene causes primary systemic carnitine deficiency (SCD;OMIM 212140), an autosomal recessive disease associated with cardiomyopathy, muscle weakness, fasting hypoglycaemia and sudden death. Recently, it was reported that variants of OCTN2 increased susceptibility to Crohn's disease. It has been suggested that these play a role in chronic inflammatory disorders variants by impairing OCTN2 activity [36]. The decrease of OCTN2 tissue levels in celiac patients could explain the reduced carnitine uptake before diet. After diet, the recovery of intestinal mucosa at histology increases carnitine absorption by inducing neo-expression of OCTN2 transporter. Although the pathogenetic meaning of OCTN2 decrease in celiac disease remains unknown, the decrease in carnitine uptake related to OCTN2 might account for muscle weakness. Indeed, OCTN2 increased expression after diet improves carnitine uptake and resolves muscle weakness in celiac patients.

Carnitine homeostasis in celiac disease may be extremely variable just as celiac disease may vary in symptoms from patient to patient. Recently, carnitine deficiency was shown to affect a patient with celiac disease and encephalopathy [38] and in a series of patients with both celiac disease and idiopathic dilated cardiomyopathy [39]. The patients enrolled in the present study did not have any such diseases that can be considered as a severe complication of gluten intolerance. The small series of uncomplicated celiac patients in our study encourage a larger study on the possible benefit of carnitine supplementation in celiac disease patients reporting fatigue. In fact, given that LC is well tolerated and demonstrates clinically relevant effects in patients with CD, the current study suggests that the risk/benefit ratio of LC therapy in patients with CD is favourable. The results of the current study provide good reasons to pursue larger Phase II and III studies for the definite identification of the clinical relevance of LC body levels and LC treatment in patients with CD.

Practice points

- Muscular symptoms and/or chronic fatigue are common findings in celiac disease.
- No treatment has been so far studied for these symptoms.
- A randomised, double-blind versus placebo parallel pilot study demonstrate L-carnitine efficacy and safety in treating fatigue in adult celiac disease.

Research agenda

- Further larger, multicenter, double-blind versus placebo clinical trial is necessary to definitely assess L-carnitine efficacy in treating fatigue of celiac disease patients.
- Carnitine homeostasis in serum and tissue samples of persons with celiac disease should be object of research protocols.

Conflict of interest statement

None declared.

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