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ORIGINAL

L-carnitine supplementation for the management of fatigue in patients with hypothyroidism on levothyroxine treatment: a randomized, double-blind, placebo-controlled trial

Jee Hyun An[1)*], Yoon Jung Kim[1),2)*], Kyeong Jin Kim[1)], Sun Hwa Kim[1)], Nam Hoon Kim[1)], Hee Young Kim[1)], Nan Hee Kim[1)], Kyung Mook Choi[1)], Sei Hyun Baik[1)], Dong Seop Choi[1)] and Sin Gon Kim[1)]

[1)] *Division of Endocrinology and Metabolism, Department of Internal Medicine, Korea University College of Medicine, Seoul, Korea*
[2)] *Division of Endocrinology and Metabolism, Department of Internal Medicine, Hallym University Kangdong Sacred Heart Hospital, Seoul, Korea*

Abstract. Hypothyroid patients experience fatigue-related symptoms despite adequate thyroid hormone replacement. Thyroid hormone plays an essential role in carnitine-dependent fatty acid import and oxidation. We investigated the effects of L-carnitine supplementation on fatigue in patients with hypothyroidism. In total, 60 patients (age 50.0 ± 9.2 years, 3 males, 57 females) who still experienced fatigue (fatigue severity scale [FSS] score ≥ 36) were given L-carnitine (n = 30, 990 mg L-carnitine twice daily) or placebo (n = 30) for 12 weeks. After 12 weeks, although neither the FSS score nor the physical fatigue score (PFS) changed significantly, the mental fatigue score (MFS) was significantly decreased by treatment with L-carnitine compared with placebo (from 4.5 ± 1.9 to 3.9 ± 1.5 *vs*. from 4.2 ± 1.8 to 4.6 ± 1.6, respectively; $P < 0.01$). In the L-carnitine group, 75.0%, 53.6%, and 50.0% of patients showed improvement in the FSS score, PFS, and MFS, respectively, but only 20.0%, 24.0%, and 24.0%, respectively, did so in the placebo group (all $P < 0.05$). Both the PFS and MFS were significantly improved in patients younger than 50 years and those with free T3 ≥ 4.0 pg/mL by treatment with L-carnitine compared with placebo. Additionally, the MFS was significantly improved in patients taking thyroid hormone after thyroid cancer surgery. These results suggest that L-carnitine supplementation may be useful in alleviating fatigue symptoms in hypothyroid patients, especially in those younger than 50 years and those who have hypothyroidism after thyroidectomy for thyroid cancer (ClinicalTrials.gov: NCT01769157).

Key words: L-carnitine, Hypothyroidism, Fatigue, Fatigue severity scale, Wessely and Powell score

PRIMARY hypothyroidism is a relatively common disease, with a prevalence of 0.3%–5.0% [1-3]. Despite apparently adequate thyroid hormone replacement, many hypothyroid patients still experience persistent fatigue and fatigue-related symptoms [4, 5]. In a large community-based study, hypothyroid patients who maintained normal thyroid-stimulating hormone (TSH) levels while receiving thyroid hormone replacement still had significantly more psychological distress than subjects with normal thyroid function [4]. However, the mechanism causing persistent fatigue in these patients remains unclear.

Thyroid hormone is involved in fatty acid oxidation [6]. Inside cells, free fatty acids are converted into acyl-coenzyme A (acyl-CoA) derivatives, which should be transported to the inner mitochondrial membrane for oxidation. Because the outer mitochondrial membrane is impermeable to acyl-CoA, an acylcarnitine transportation system is essential and plays a vital role in the production of energy [7, 8]. Thyroid hormone stimulates carnitine-dependent fatty acid import and oxidation [9-12] and increases carnitine bioavailability [13].

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Correspondence to: Sin Gon Kim, M.D., Ph.D., Division of Endocrinology and Metabolism, Department of Internal Medicine, Korea University Hospital, Korea University College of Medicine, 73 Inchon-ro, Seongbuk-gu, Seoul, Korea.
E-mail: k50367@korea.ac.kr
* The first two authors contributed equally to this study.

Several lines of evidence have shown an association between thyroid hormone and the carnitine system. Thyroid hormone has been shown to promote the urinary excretion of carnitine. A hyperthyroid state was associated with increased urinary carnitine excretion, and hypothyroid patients had decreased urinary carnitine excretion [14]. In another study, there was a significantly decreased total carnitine level in skeletal muscle in hyperthyroid patients *versus* euthyroid individuals, and the carnitine level tended to be lower in hypothyroid patients [15]. Carnitine depletion in hyperthyroidism may be explained by increased fatty acid oxidation due to increased transcription of CPT-1, and carnitine-acylcarnitine translocase in the liver, and decreased carnitine levels in hypothyroidism may be explained by decreased biosynthesis of carnitine [10, 12, 13, 16]. Other studies showed that carnitine inhibited the entry of thyroid hormone into the nucleus in some tissues and suggested that it is a peripheral antagonist of thyroid hormone action [17-19]. These results may appear to contradict earlier studies, but this inhibitory effect may be part of a retro-control loop between thyroid hormone and carnitine.

We hypothesized that the fatigue-related symptoms in hypothyroid patients may be related to the relative deficiency of carnitine in these patients. When hypothyroid patients receive levothyroxine, thyroid hormone would promote carnitine synthesis, but would also accelerate mitochondrial fatty acid oxidation, which uses carnitine. If the consumption of carnitine exceeds its synthesis, it could cause relative carnitine deficiency, which, in turn, could result in fatigability. In this study, we investigated the effects of L-carnitine supplementation on fatigue-related symptoms in these hypothyroid patients.

Materials and Methods

Study design and subjects

This was a 12-week, randomized, double-blind, placebo-controlled trial conducted between May 2012 and August 2013 at Korea University Anam Hospital, Seoul, Korea. The protocol was reviewed and approved by the institutional review board of Korea University Anam Hospital (No. ED11316) and was registered at ClinicalTrials.gov (NCT 01769157).

In total, 77 patients, aged 20–80 years who received adequate levothyroxine treatment for primary hypothyroidism (etiology: chronic autoimmune thyroiditis or postoperative hypothyroidism after total thyroidectomy for treatment of thyroid cancer) but still experienced fatigue or fatigue-related symptoms were screened for this study. Subjects who had received a stable dose of levothyroxine treatment for more than 6 months and had normal blood levels of free T4 (0.79–1.86 ng/dL) and not an elevated TSH level ($\leq$ 4.05 μIU/mL) were eligible. We used a fatigue severity scale (FSS) to evaluate the severity of fatigue and the eligibility criterion was an FSS score of $\geq$ 36 [20]. The exclusion criteria were 1) presence of conditions that might cause chronic fatigue including acute or chronic liver disease (such as hepatitis or liver cirrhosis), anemia (Hb < 12 g/dL), chronic lung disease (chronic obstructive pulmonary disease or asthma), cardiovascular disease (such as heart failure and arrhythmia), acute or chronic kidney disease (Cr > 1.5 mg/dL), endocrine/metabolic disease (such as diabetes), autoimmune disease (such as rheumatoid arthritis, systemic lupus erythematosus, or multiple sclerosis), malignant tumor or infectious disease (such as tuberculosis or HIV), and psychological disorders (such as depression, anxiety disorder, schizophrenia, alcoholism, and eating disorders); 2) use of medications that can affect thyroid hormone production and metabolism; 3) use of health supplements such as red ginseng or multivitamin that started less than 1 month before; and 4) pregnancy or desire to conceive within the study period or breastfeeding. In total, 17 subjects were excluded. The remaining 60 eligible subjects were randomly allocated to the L-carnitine (n = 30) or placebo groups (n = 30) (Fig. 1). The allocation sequence was determined using Random Allocation Software with a block size of 4 (http://mahmoodsaghaei.tripod.com/Softwares/randalloc.html). L-carnitine was given orally in two divided doses per day (three tablets twice per day, 330 mg in each tablet), totaling 1,980 mg for 12 weeks. The trial intervention tablets were produced by Ildong Pharmaceutical Co., Seoul, Korea, and the dosage was based on previous studies [21, 22]. Efficacy, safety, and compliance were evaluated at 12 weeks. Of those enrolled, 28 patients in the L-carnitine group and 25 in the placebo group completed the 12-week treatment (Fig. 1).

Measurement of anthropometric and biochemical parameters

Height and body weight were measured, and body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Waist circumference (WC)

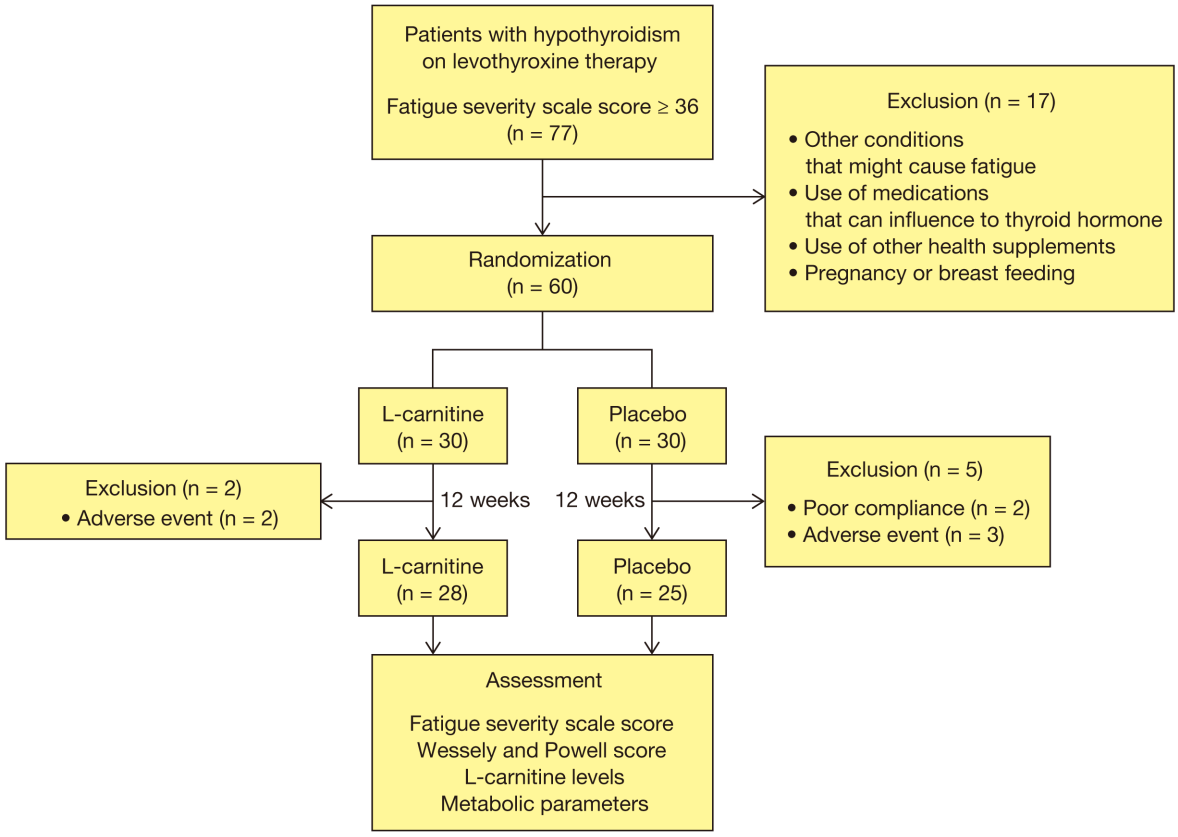

Fig. 1 Flow chart of the study
Eligible participants with primary hypothyroidism and a fatigue severity scale (FSS) score of >36, despite thyroid hormone replacement, were randomly allocated to the L-carnitine (1980 mg per day, $n = 30$) or placebo ($n = 30$) group. Fatigue scores, L-carnitine levels, and metabolic parameters were assessed before and after treatment for 12 weeks.

was measured at the narrowest point between the lower limit of the rib cage and the iliac crest. Blood pressure was recorded three times after the subjects had been in a relaxed state for at least 10 min; a 5-min rest period was given between measurements. Blood samples were acquired between 0800 and 1000 h after overnight fasting, and serum was obtained by centrifugation (1,006 × *g*, 20 min, 4°C). Serum samples were stored at −80°C until analysis. Plasma levels of total and acyl L-carnitine were measured by liquid chromatography tandem mass spectrometry (Xevo TQS; Waters, Milford, MA, USA) [23]. Free carnitine level was calculated as the difference between total and acyl-carnitine levels. Carnitine-deficiency was defined as an acyl-carnitine to free carnitine ratio > 0.4 or free carnitine < 35 μmol/L (male) and < 25 μmol/L (female) [24]. Thyroid function, including TSH, free T4, and T3 levels; fasting plasma glucose; hemoglobin A1c (HbA1c); and lipid and liver profiles were measured. Total fat mass and body fat percent were measured using an InBody 720 (Biospace Co. Ltd., Seoul, Korea).

Efficacy outcomes

The primary outcome was change in the fatigue scores: FSS score (ΔFSS score = final − baseline FSS score) and the Wessely and Powell score, consisting of physical fatigue scores (ΔPFS = final − baseline PFS) and mental fatigue scores (ΔMFS = final − baseline MFS). The FSS score is composed of nine items developed to assess disabling fatigue (see Supplementary Table 1 for a copy of the complete FSS) [20]. The nine items are combined into a total score ranging from 7 to 63: a lower total score indicates less effect of fatigue in everyday life. The Wessely and Powell score consists of two scales measuring physical fatigue (PFS,

eight items scored from 0 [no fatigue] to 2 [highest possible fatigue]; total score range, 0–16) and mental fatigue (MFS, five items scored from 0 [no fatigue] to 2 [highest possible fatigue]; total score range, 0–10) (see Supplementary Table 2 for a copy of the complete Wessely and Powell scheme) [25].

Secondary outcomes were changes in 1) serum L-carnitine levels (total and acyl-carnitine), 2) thyroid function (free T4, free T3, and TSH levels), 3) lipid profiles (serum triglyceride and total, HDL-, and LDL-cholesterol levels, 4) liver profiles (AST and ALT levels), and 5) total fat mass and body fat percent.

Statistical analysis

Sample size determination was conducted for the main outcome variables (FSS score and Wessely and Powell score). Based on a previous study and a power of 0.80 ($p = 0.05$, two-sided) to detect a clinically relevant treatment difference between two balanced arms, a total of 26 patients was required [26]. To account for deviations from the expected effect size and subject withdrawal, we planned to recruit 60 patients (30 patients per arm). All continuous variables were compared using Student's *t*-test or the Mann–Whitney U-test. Categorical variables were compared using the χ^2 test or Fisher's exact test. *P* values of < 0.05 were considered to indicate statistical significance. All analyses were performed using the SAS software (ver. 9.4; SAS Institute, Cary, NC).

Results

Baseline characteristics

Baseline characteristics of the study participants in the L-carnitine and placebo groups are shown in Table 1. The BMI of the L-carnitine group was slightly higher than that of the placebo group (24.7 ± 3.1 *vs*. 22.7 ± 2.8, respectively; $P = 0.048$); however, there was no significant difference in other characteristics between the groups. Mean age was about 50 years, and females represented 93%–97% of each group. The etiology of hypothyroidism was chronic autoimmune thyroiditis in 50%–60% and postoperative hypothyroidism after thyroid cancer in 40%–50%. Neither the FSS score (48.8 ± 8.2 *vs*. 47.9 ± 7.4, $P = 0.931$) nor the Wessely and Powell score (PFS, 8.8 ± 2.9 *vs*. 8.8 ± 3.1, $P = 0.875$; MFS, 4.5 ± 1.9 *vs*. 4.2 ± 1.8, $P = 0.195$) was significantly different between the groups. Serum carnitine and thyroid hormone levels were also similar.

Table 1 Baseline characteristics of the L-carnitine and placebo groups

	L-carnitine	Placebo
Age (years)	49.0 ± 8.2	50.9 ± 9.1
Sex (female,%)	93.3	96.7
Etiology (%)		
Chronic autoimmune thyroiditis	50.0	60.0
Postoperative hypothyroidism	50.0	40.0
Smoking (%)	0	0
Alcohol (glasses/day)	0.29 ± 0.65	0.18 ± 0.33
Systolic blood pressure (mmHg)	118.4 ± 13.0	116.0 ± 12.0
Heart rate (/min)	76.7 ± 7.6	74.0 ± 7.4
Body mass index (kg/m^2)	24.7 ± 3.1*	22.7 ± 2.8
Waist circumference (cm)	82.3 ± 9.5	78.6 ± 8.4
AST (IU/L)	20.9 ± 6.5	22.1 ± 5.3
ALT (IU/L)	19.1 ± 12.9	17.3 ± 7.4
Creatinine (mg/dL)	0.80 ± 0.14	0.77 ± 0.12
HbA1c (%)	5.5 ± 0.4	5.5 ± 0.4
Fasting plasma glucose (mg/dL)	96.1 ± 7.4	95.7 ± 8.7
Total cholesterol	199.7 ± 40.6	189.1 ± 33.3
Triglycerides	107.4 ± 79.5	113.6 ± 43.6
HDL-cholesterol	57.4 ± 14.0	57.3 ± 11.9
LDL-cholesterol	118.0 ± 38.0	106.0 ± 30.7
Body fat (%)	33.1 ± 6.9	31.1 ± 6.7
TSH (μIU/mL)	0.84 ± 1.18	1.04 ± 1.09
Free T4 (ng/dL)	1.43 ± 0.18	1.43 ± 0.19
Free T3 (ng/dL)	3.49 ± 0.58	3.64 ± 0.80
Total carnitine (μmol/L)	66.7 ± 15.9	61.2 ± 13.7
Acyl carnitine (μmol/L)	14.8 ± 7.1	13.4 ± 6.4
Free carnitine (μmol/L)	51.9 ± 8.2	47.8 ± 7.3
Acyl / free carnitine ratio	0.29 ± 0.07	0.28 ± 0.06
Carnitine deficiency (%)	13.3%	16.7%
Fatigue severity scale score	48.8 ± 8.2	47.9 ± 7.4
Wessely and Powell score		
Physical fatigue score	8.8 ± 2.9	8.8 ± 3.1
Mental fatigue score	4.5 ± 1.9	4.2 ± 1.8

AST, aspartate aminotransferase; ALT, alanine aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TSH, thyroid-stimulating hormone. Data are presented as mean ± SD. * $P < 0.05$.

Effect of L-carnitine supplementation on fatigue scores

After 12 weeks of treatment, the serum total and acyl-carnitine levels increased significantly in the L-carnitine group, as expected (from 66.7 ± 15.9 to 84.6 ± 18.9 μmol/L and from 14.8 ± 7.1 to 19.9 ± 9.5 μmol/L, respectively; all $P < 0.05$). There was no significant change in carnitine levels in the placebo group (Supplementary Fig. 1). The primary efficacy outcome, FSS score, and PFS decreased more with the 12-week treatment with L-carnitine than with placebo, but the differences were not statistically significant. However, the MFS decreased significantly by treatment with L-carnitine *versus* placebo treatment (from 4.5 ± 1.9 to 3.9 ± 1.5 *vs*. from 4.2 ± 1.8 to 4.6 ± 1.6; ΔMFS −0.6 ± 1.0 *vs*. +0.4 ± 0.9, $P < 0.01$) (Fig. 2A–C). In the L-carnitine group, 75.0%, 53.6%, and 50.0% of patients showed improvement in the FSS score, PFS, and MFS, respectively; the values were only 20.0%, 24.0%, and 24.0% in the placebo group (all $P < 0.05$) (Fig. 2D–F). Although the changes in the FSS scores after treatment in both groups were not significantly different, the FSS score decreased in the placebo-treated group after 12 weeks (Fig. 2A). It was inferred that 20% of subjects with improved FFS scores (Fig. 2D) showed potent placebo effects. Neither baseline levels nor changes in L-carnitine levels correlated significantly with changes in each fatigue score after adjusting for BMI, age, sex, free T4, cholesterol, ALT, and body fat mass (data not shown).

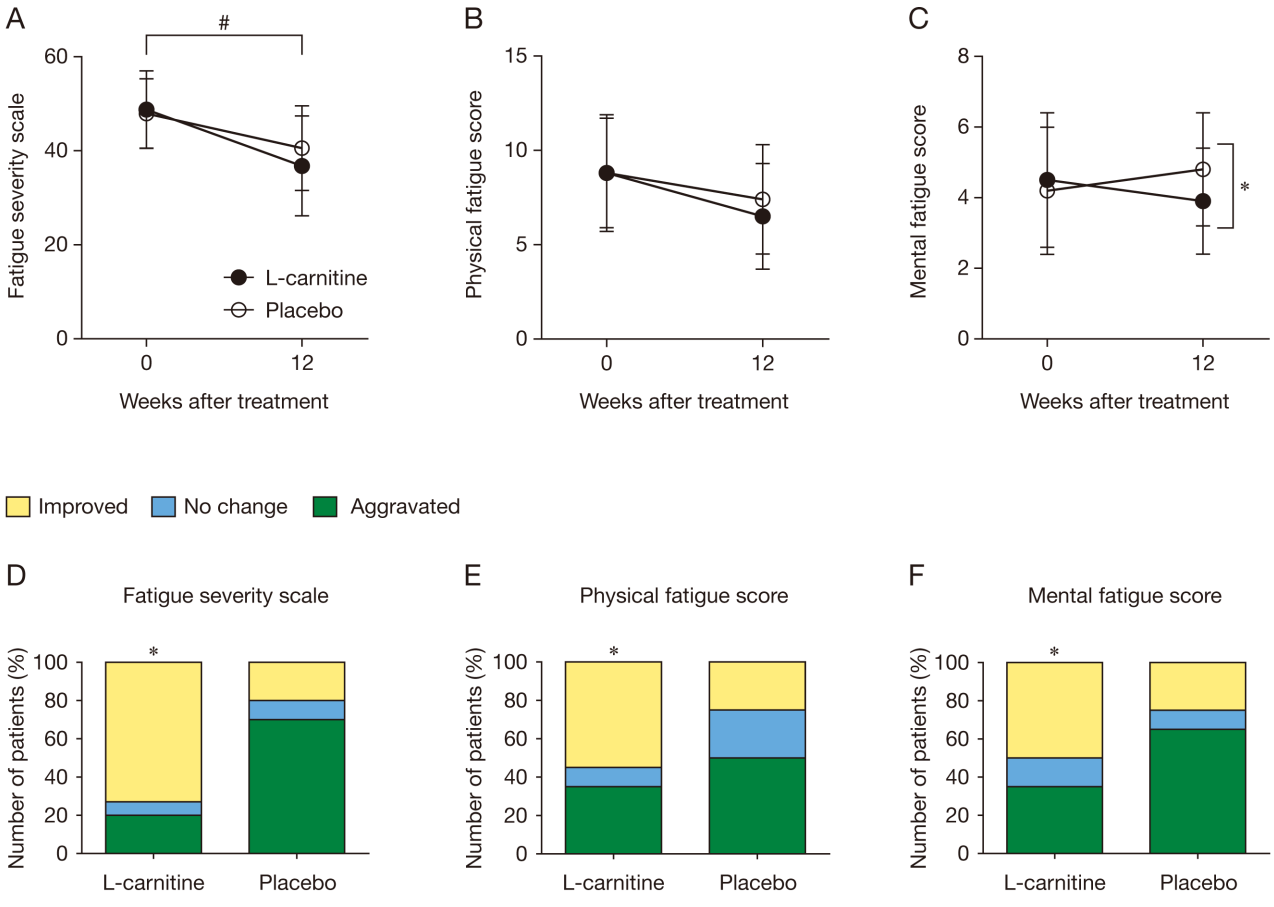

Fig. 2 Effects of L-carnitine supplementation on fatigue scores
Change in (**A**) fatigue severity scale (FSS) score and Wessely and Powell score, consisting of (**B**) physical fatigue score (PFS) and (**C**) mental fatigue score (MFS). Proportion of subjects according to the change in each fatigue score (improved, aggravated, or no change) after 12 weeks of supplementation (**D**, **E**, and **F**). * $P < 0.05$ compared with placebo group. # $P < 0.05$ compared with baseline in each group.

Candidate subjects who had more fatigue-alleviating effects from L-carnitine supplementation

To identify the candidate subjects who had more fatigue-alleviating effects from L-carnitine supplementation, we conducted subgroup analyses according to subject age, etiology of hypothyroidism, thyroid hormone, and carnitine levels (Table 2). Both the PFS and MFS were improved significantly in patients younger than 50 years (ΔPFS, −3.1 ± 2.6 *vs*. −1.0 ± 2.6; ΔMFS, −1.0 ± 1.5 *vs*. +0.4 ± 1.5, all $P < 0.05$) and those with free T3 ≥ 4.0 pg/mL (ΔPFS, −5.1 ± 3.8 *vs*. −0.1 ± 3.4; ΔMFS, −0.4 ± 1.4 *vs*. +0.9 ± 1.5, all $P < 0.05$) by treatment with L-carnitine compared with placebo. Furthermore, the MFS was improved significantly in patients whose serum total carnitine level was ≥ 60.9 μmol/L (ΔMFS, −1.2 ± 1.9 *vs*. +1.0 ± 1.9, $P < 0.05$) and those with hypothyroidism after thyroid cancer surgery (ΔMFS, −0.6 ± 2.2 *vs*. +1.4 ± 2.2, $P < 0.05$) by treatment with L-carnitine *versus* placebo. There was no statistically significant difference in the change in fatigue scores between the L-carnitine and placebo groups when we divided them into subgroups by BMI, body fat mass, free T4/TSH, ALT, or cholesterol levels (data not shown).

Next, to define the characteristics of patients who had shown improvement in fatigue scores after L-carnitine supplementation, we divided the patients according to the response in fatigue scores: the improved and non-improved (stable or aggravated) groups. However, there was no statistically significant difference in the baseline phenotypic characteristics between improved (n = 21) and non-improved (no change or aggravated, n = 7) patients in their FSS score (Table 3). Similar results were obtained for the PFS and MFS (data not shown).

Effect of L-carnitine supplementation on metabolic parameters

During 12 weeks of intervention, BMI, WC, serum glycemic, lipid and liver profiles, and body fat mass were not significantly changed in either group, even after adjusting each baseline value and BMI, revealing significant differences in baseline characteristics. Thyroid function also was not significantly changed in either group (Supplementary Table 3).

Safety and tolerability

The incidence of adverse events was modest (Table 4). L-carnitine was generally well tolerated and produced no severe drug-related adverse events. The incidence of all adverse events did not differ between the groups: 10 of 30 patients (33.3%) in both the L-carnitine and placebo groups. A few subjects discontinued therapy due to adverse events: two in the L-carnitine group (1 nausea and 1 epigastric discom-

Table 2 Effect of L-carnitine supplementation on fatigue scores according to subgroups

	L-Carnitine	Placebo	L-Carnitine	Placebo
	Age < 50 years		Age ≥ 50 years	
	n = 11	n = 13	n = 17	n = 12
ΔFSS	−8.7 ± 11.5	−9.0 ± 11.3	−13.5 ± 12.9	−6.6 ± 11.1
ΔPFS	−3.1 ± 2.6 *	−1.0 ± 2.6	−1.8 ± 3.3	−1.7 ± 4.0
ΔMFS	−1.0 ± 1.5 *	+0.4 ± 1.5	−0.3 ± 1.0	+1.0 ± 1.5
	Total carnitine < 60.9 μmol/L †		Total carnitine ≥ 60.9 μmol/L †	
	n = 11	n = 14	n = 17	n = 11
ΔFSS	−9.7 ± 12.0	−6.7 ± 9.4	−12.1 ± 12.7	−8.8 ± 13.6
ΔPFS	−2.6 ± 3.7	−1.0 ± 2.6	−1.8 ± 2.6	−1.8 ± 4.3
ΔMFS	+0.2 ± 2.4	+0.3 ± 1.5	−1.2 ± 1.9 *	+1.0 ± 1.9
	Postoperative hypothyroidism		Chronic autoimmune hypothyroidism	
	n = 15	n = 12	n = 13	n = 13
ΔFSS	−12.2 ± 11.6	−5.8 ± 9.3	−9.2 ± 11.5	−9.0 ± 11.7
ΔPFS	−2.1 ± 3.0	−1.2 ± 4.2	−2.1 ± 2.4	−1.4 ± 2.7
ΔMFS	−0.6 ± 2.2 *	+1.4 ± 2.2	−0.4 ± 2.1	−0.1 ± 1.1
	Free T3 < 4.0 pg/mL ††		Free T3 ≥ 4.0 pg/mL ††	
	n = 23	n = 18	n = 5	n = 7
ΔFSS	−10.1 ± 12.5	−9.4 ± 11.9	−16.0 ± 10.6	−3.3 ± 7.8
ΔPFS	−1.4 ± 2.5	−1.8 ± 3.3	−5.1 ± 3.8 *	−0.1 ± 3.4
ΔMFS	−0.6 ± 2.7	+0.5 ± 1.8	−0.4 ± 1.4 *	+0.9 ± 1.5

ΔFSS, change in fatigue severity scale score; ΔPFS, change in physical fatigue score; ΔMFS, change in mental fatigue score. † Median value of total carnitine level in study subjects, †† Median value of free T3 level in study subjects.
* $P < 0.05$, reduced fatigue scores compared with other subgroup of subjects within the same treatment group.

Table 3 Comparison of baseline characteristics between improved and non-improved subjects in fatigue severity scale score after L-carnitine supplementation

	Improved $n = 22$	Non-improved $n = 8$
Age (years)	48.7 ± 8.9	49.6 ± 6.6
Sex (female, %)	100	75
Etiology (%)		
Chronic autoimmune thyroiditis	37.5	54.5
Postoperative hypothyroidism	62.5	45.5
TSH (μIU/mL)	0.38 ± 0.45	1.00 ± 1.32
Free T4 (ng/dL)	1.48 ± 0.17	1.42 ± 0.19
Free T3 (ng/dL)	3.63 ± 0.41	3.47 ± 0.64
Total carnitine (μmol/L)	68.0 ± 15.2	63.2 ± 18.5
Acyl-carnitine (μmol/L)	15.9 ± 6.3	11.7 ± 8.6
Free carnitine (μmol/L)	52.1 ± 11.2	51.5 ± 14.3
Acyl / free carnitine ratio	0.31 ± 0.08	0.28 ± 0.09
Carnitine deficiency (%)	13.6%	12.5%
Fatigue severity scale score	49.5 ± 9.0	45.9 ± 6.3
Wessely and Powell score		
Physical fatigue score	8.8 ± 3.2	8.0 ± 2.4
Mental fatigue score	4.5 ± 2.5	4.5 ± 2.0

TSH, thyroid-stimulating hormone. Data are presented as mean ± SD.

Table 4 Safety profile during the 12-week placebo-controlled trial of L-carnitine supplementation in hypothyroid patients on levothyroxine treatment

	L-carnitine	Placebo
Any adverse event, *n* (%)	10 (33.3)	10 (33.3)
Serious adverse event, *n* (%)	2 (6.7) *	1 (3.3) †
Discontinuation of study treatment due to adverse event, *n* (%)	2 (6.7) **	3 (10.0) ††
Adverse events, *n* (%)		
Nausea	3 (10.0)	1 (3.3)
Generalized edema	1 (3.3)	0 (0.0)
Epigastric discomfort	1 (3.3)	0 (0.0)
Fracture	1 (3.3)	0 (0.0)
Memory impairment	1 (3.3)	0 (0.0)
Sore throat	1 (3.3)	0 (0.0)
Headache	1 (3.3)	1 (3.3)
Surgical intervention	1 (3.3)	1 (3.3)
Abdominal pain	1 (3.3)	2 (6.6)
Angina pectoris	0 (0.0)	1 (3.3)
Hypoesthesia	0 (0.0)	1 (3.3)
Gastroesophageal reflux	0 (0.0)	1 (3.3)
Dry mouth	0 (0.0)	1 (3.3)
Chest discomfort	0 (0.0)	1 (3.3)
Dental caries	0 (0.0)	1 (3.3)
Sinus bradycardia	0 (0.0)	1 (3.3)
Laryngitis	0 (0.0)	1 (3.3)
Pruritus	0 (0.0)	1 (3.3)
Urticaria	0 (0.0)	1 (3.3)
Cystitis	0 (0.0)	1 (3.3)
Diarrhea	0 (0.0)	2 (6.6)

* 1 abdominal pain and 1 surgical intervention for left arm implant removal, ** 1 nausea, 1 epigastric discomfort, † 1 surgical intervention for facial trauma, †† 1 abdominal pain, 1 dry mouth, 1 sinus bradycardia.

fort) and three in the placebo group (1 abdominal pain, 1 dry mouth, and 1 sinus bradycardia). Liver, kidney function, and lipid profiles were unchanged in both groups during treatment.

Discussion

In this study, we investigated the efficacy of L-carnitine supplementation on fatigue-related symptoms in hypothyroid patients receiving adequate thyroid hormone replacement. L-carnitine supplementation for 12 weeks alleviated fatigue symptoms in these patients without serious drug-related adverse events. Favorable effects were seen in patient subgroups: those younger than 50 years and those who underwent thyroidectomy for thyroid cancer.

Carnitine supplementation enhances fatty acid oxidation and has been used in patients with muscular hypoxia, angina pectoris, peripheral vascular disease, congestive heart failure, and hemodialysis [7, 26-28]. To our knowledge, this is the first report to show that L-carnitine may be useful in alleviating fatigue symptoms in hypothyroid patients. Given the relatively high prevalence of hypothyroidism in the general population and rapidly increasing number of patients with postoperative hypothyroidism due to thyroid cancer, we believe that the results of our study have important implications for these patients.

Because mitochondria are the key organelles regulating cellular energy metabolism, dysfunction in mitochondria could lead to excess fatigue and other symptoms commonly encountered in chronic diseases. However, clinical trials that investigated the ability of coenzyme Q10 [29, 30], NADH (reduced nicotinamide adenine dinucleotide) [31, 32], and alpha-lipoic acid [33] to improve mitochondrial function have not shown consistent results. L-carnitine is a critical component for mitochondrial fatty acid oxidation, and its supplementation has been shown to improve quality of life and reduce fatigue-related symptoms in patients with chronic kidney disease, cancer, and chronic hepatitis [26, 34-36]. Because thyroid hormone is involved in carnitine-dependent fatty acid import and oxidation, our study was based on a plausible hypothesis in hypothyroid patients. Although we did not investigate the cellular mechanism, the promising results obtained support that a carnitine-related mechanism is involved in fatigue-related symptoms in hypothyroid patients who still experience fatigue while receiving adequate thy-

roid hormone replacement. In addition, these results could be used in the development of a new drug targeting chronic fatigue symptoms, one of the most vague and problematic conditions, not only in hypothyroidism but also in other medical conditions.

After 12 weeks of treatment, the mean FSS score and PFS did not change significantly in the L-carnitine group; however, the proportion of patients who showed improved fatigue symptoms (decreased fatigue scores) was more than 50% of the patients in the L-carnitine group in all FSS score, PFS, and MFS categories, and these were significantly larger than in the placebo group. This may simply be the result of the relatively small number of study subjects with enough power for statistical significance, because the FSS score and PFS were decreased more in L-carnitine group, although not significantly so. Alternatively, the relatively larger increment in the mean fatigue scores in a number of subjects who showed deterioration may have offset the decrease in mean symptom scores in subjects with improvements, even though there were significantly more subjects in the latter group.

To identify subjects who could benefit from L-carnitine supplementation, we divided the study patients into subgroups by age, cause of hypothyroidism, and thyroid hormone and carnitine levels. It would be reasonable to expect that younger subjects, those receiving relatively high doses of thyroid hormone for TSH suppression after thyroid cancer surgery, and those with higher free T3 levels should be more active metabolically and thus will be more prone to have relative carnitine deficiency. From these results, we suggest two potential target groups of patients who may benefit from treatment of fatigue through L-carnitine supplementation: patients younger than 50 years and those who have postoperative hypothyroidism after thyroid cancer. A previous randomized controlled trial reported that L-carnitine supplementation relieves symptoms of iatrogenic hyperthyroidism due to TSH-suppressive effects of levothyroxine treatment [19]. Therefore, the mechanism of the fatigue relieving effect by L-carnitine may be different between subgroups with different thyroid hormone levels. The beneficial effects in those with higher carnitine levels may indicate the possibility that the supplementation dosage of L-carnitine in our study was sub-optimal with regard to deriving sufficient fatigue relieving effects for subjects whose total carnitine levels were < 60.9 μmol/L.

In the L-carnitine supplementation group, we did not find any statistically significant difference in phenotypic characteristics between the improved and non-improved fatigue score subgroups. Furthermore, there was a small number of subjects who had carnitine deficiency and no correlation between change in L-carnitine level and fatigue scores. Fatigue is a vague and subjective symptom that is affected by various personal characteristics and environmental factors, although we evaluate it *via* various objective scores. Furthermore, most subjects were women and the mean age was about 50 years, which is perimenopause, when estrogen levels could be confounding the L-carnitine effect on fatigue symptoms. Further large-scale studies with more variables affecting fatigue symptoms, including estrogen levels, are needed to overcome these confounding factors.

Several previous studies have shown favorable effects of L-carnitine supplementation on metabolic profiles, including lipid and liver parameters [22, 37, 38]. However, in our study, L-carnitine did not affect any metabolic parameter during 12 weeks of treatment. This result also may result from too short a duration of treatment or too few subjects.

In conclusion, L-carnitine produced potentially favorable effects on fatigue-related symptoms after 12 weeks of treatment in hypothyroid patients receiving thyroid hormone replacement, especially in those younger than 50 years and those who had hypothyroidism after thyroidectomy for thyroid cancer. Further larger-scale clinical studies with various dosage forms of L-carnitine are needed, and determining the cellular mechanism of the fatigue-relieving effects of L-carnitine should be a subject of future research.

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Disclosure

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Supplementary Table 1 Fatigue severity scale

Below are several statements regarding your fatigue. By "fatigue" we mean a sense of tiredness, lack of energy, or total body give-out. Please read each statement and choose a number from 1 to 7, where "1" indicates that you completely disagree with the statement and "7" indicates that you completely agree. Please answer these questions as they apply to the past 2 weeks.

	Completely disagree						Completely agree
1. My motivation is lower when I am fatigued.	1	2	3	4	5	6	7
2. Exercise brings on my fatigue.	1	2	3	4	5	6	7
3. I am easily fatigued.	1	2	3	4	5	6	7
4. Fatigue interferes with my physical functioning.	1	2	3	4	5	6	7
5. Fatigue causes frequent problems for me.	1	2	3	4	5	6	7
6. My fatigue prevents sustained physical functioning.	1	2	3	4	5	6	7
7. Fatigue interferes with carrying out certain duties and responsibilities.	1	2	3	4	5	6	7
8. Fatigue is among my three disabling symptoms.	1	2	3	4	5	6	7
9. Fatigue interferes with my work, family, or social life.	1	2	3	4	5	6	7

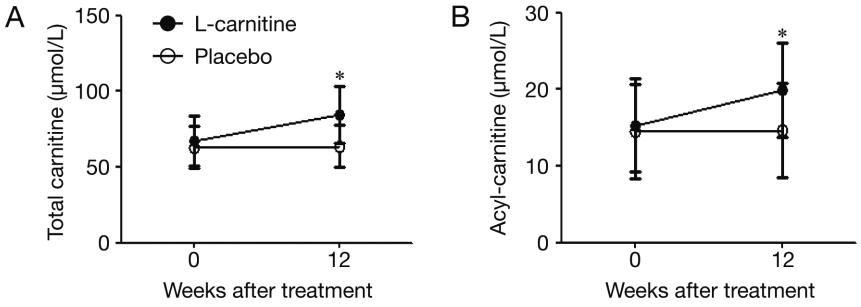
Supplementary Table 2 Wessely and Powell score

A. Physical fatigue score
1. I get tired easily.
2. I need to rest more.
3. I feel sleepy or drowsy.
4. I can no longer start anything.
5. I am always lacking in energy.
6. I have less strength in my muscles.
7. I feel weak.
8. I can start things without difficulty, but get weak as I go on.
B. Mental fatigue score
1. I have problems concentrating.
2. I have problems thinking clearly.
3. I make more slips of the tongue, or have problems finding the correct word.
4. I have problems with eyestrain.
5. I have problems with memory.

Supplementary Table 3 Changes in metabolic parameters in the L-carnitine and placebo groups

	L-carnitine		Placebo	
	Baseline	After 12 wks	Baseline	After 12 wks
Body mass index (kg/m^2)	24.7 ± 3.1	24.8 ± 3.5	22.7 ± 2.8	23.3 ± 2.7
Waist circumference (cm)	82.3 ± 9.5	82.5 ± 9.6	78.6 ± 8.4	79.0 ± 8.7
AST (IU/L)	21.3 ± 5.0	20.9 ± 6.7	22.3 ± 5.5	22.4 ± 5.4
ALT (IU/L)	18.9 ± 13.4	17.9 ± 7.3	18.0 ± 7.7	18.0 ± 7.5
HbA1c (%)	5.4 ± 0.4	5.4 ± 0.4	5.5 ± 0.4	5.5 ± 0.5
Fasting plasma glucose (mg/dL)	95.6 ± 7.3	95.3 ± 6.4	96.9 ± 8.2	95.7 ± 11.3
Total cholesterol (mg/dL)	201.2 ± 41.3	206.8 ± 53.0	190.0 ± 34.7	184.1 ± 31.5
Triglyceride (mg/dL)	107.8 ± 82.3	120.9 ± 55.3	119.2 ± 45.2	117.0 ± 50.0
HDL-cholesterol (mg/dL)	57.9 ± 14.3	54.5 ± 13.6	56.6 ± 12.1	54.9 ± 12.4
LDL-cholesterol (mg/dL)	120.1 ± 28.2	119.6 ± 38.7	108.4 ± 32.2	109.8 ± 24.9
Body fat (%)	33.0 ± 7.1	32.9 ± 6.3	31.8 ± 6.9	31.1 ± 7.5
TSH (μIU/mL)	0.83 ± 1.22	0.92 ± 1.02	0.98 ± 1.10	1.11 ± 1.28
Free T4 (ng/dL)	1.43 ± 0.19	1.42 ± 0.20	1.41 ± 0.19	1.42 ± 0.23
Free T3 (ng/dL)	3.50 ± 0.60	3.31 ± 1.04	3.60 ± 0.83	3.25 ± 0.73

AST, aspartate aminotransferase; ALT, alanine aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TSH, thyroid-stimulating hormone. Data are presented as mean ± SD.



Supplementary Fig. 1 Changes in total and acyl-carnitine levels after 12 weeks of treatment in the L-carnitine and placebo groups
* $P < 0.05$ compared with placebo group.

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