Clinical Nutrition 35 (2016) 826–834

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Randomized control trials

Effect of coenzyme Q_{10} plus nicotinamide adenine dinucleotide supplementation on maximum heart rate after exercise testing in chronic fatigue syndrome — A randomized, controlled, double-blind trial

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ARTICLE INFO

Article history:
Received 26 February 2015
Accepted 10 July 2015

Keywords:
Chronic fatigue syndrome
Maximum heart rate
Pain
Sleep
Nutritional supplements
Coenzyme Q_{10}

SUMMARY

Background & aims: Chronic Fatigue Syndrome (CFS) is a complex condition, characterized by severe disabling fatigue with no known cause, no established diagnostic tests, and no universally effective treatment. Several studies have proposed symptomatic treatment with coenzyme Q_{10} (CoQ_{10}) and nicotinamide adenine dinucleotide (NADH) supplementation. The primary endpoint was to assess the effect of CoQ_{10} plus NADH supplementation on age-predicted maximum heart rate (max HR) during a cycle ergometer test. Secondary measures included fatigue, pain and sleep.

Methods: A proof-of-concept, 8-week, randomized, controlled, double-blind trial was conducted in 80 CFS patients assigned to receive either CoQ_{10} plus NADH supplementation or matching placebo twice daily. Maximum HR was evaluated at baseline and at end of the run-in period using an exercise test. Fatigue, pain and sleep were evaluated at baseline, and then reassessed at 4- and 8-weeks through self-reported questionnaires.

Results: The CoQ_{10} plus NADH group showed a significant reduction in max HR during a cycle ergometer test at week 8 versus baseline ($P = 0.022$). Perception of fatigue also showed a decrease through all follow-up visits in active group versus placebo ($P = 0.03$). However, pain and sleep did not improve in the active group. Coenzyme Q_{10} plus NADH was generally safe and well tolerated.

Conclusions: Our results suggest that CoQ_{10} plus NADH supplementation for 8 weeks is safe and potentially effective in reducing max HR during a cycle ergometer test and also on fatigue in CFS. Further additional larger controlled trials are needed to confirm these findings.

Clinical trial registration This trial was registered at *clinicaltrials.gov* as NCT02063126.

1. Introduction

Chronic Fatigue Syndrome (CFS) is a complex and extremely debilitating condition with no known cause, no established diagnostic tests, and no universally effective therapy. Its symptoms are characterized by extreme disabling fatigue that does not improve with rest, persists for more than six months and cannot be explained by any underlying medical condition. It is associated with other symptoms including muscle pain, sleep dysfunction and cognitive problems. Chronic fatigue may worsen with physical and mental activity, and exercise intolerance is a frequent complaint in most CFS patients [1]. Currently there is no known universally effective treatment for CFS, and the available therapy options focus on symptom relief [2,3]. Coenzyme Q_{10} (CoQ_{10}) and reduced nicotinamide adenine dinucleotide (NADH) are common antioxidant

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http://dx.doi.org/10.1016/j.clnu.2015.07.010

Abbreviations

ATP	adenosine triphosphate
CFS	chronic fatigue syndrome
CoQ_{10}	coenzyme Q_{10}
DBP	diastolic blood pressure
max HR	maximum heart rate
NADH	reduced nicotinamide adenine dinucleotide
PBMC	peripheral blood mononuclear cells
SBP	systolic blood pressure
VO_2	pulmonary oxygen uptake
VCO_2	pulmonary carbon dioxide uptake

supplements with known cardioprotective effects which have been used for several decades as dietary supplements for general health maintenance. The benefits of their administration have been most extensively evaluated in cardiovascular and neurodegenerative conditions [4,6–8]. However, several studies have shown that there is a mitochondrial failure which reduces the rate of adenosine-5-triphosphate (ATP) synthesis, the central agent of energy production in most CFS patients [9–11]. Because CoQ_{10} and NADH increase cellular ATP production via mitochondrial oxidative phosphorylation, their supplementation could help improve fatigue and other symptoms in CFS [12,13]. A previous study by our group showed that oral NADH (20 mg/day) administration for eight weeks was associated with reductions in anxiety and maximum HR after a stress test in 77 Spanish CFS patients [14]. Another placebo-controlled cross-over study in 26 CFS patients found that those who received NADH (10 mg/day) supplementation for 12 weeks obtained more effective symptom relief than those assigned to the placebo (31% vs. 8% respectively) [15]. A study comparing oral NADH supplementation with conventional therapy for 24 months in 31 CFS patients showed a higher effectiveness of NADH (in terms of the reduction in the mean symptom score) over nutritional supplements and psychotherapy [16]. Previous studies have shown that oral NADH administration has a good safety profile, with no observed adverse effects or toxicity [14–17]. For its part, CoQ_{10} supplementation has been evaluated in many illnesses, such as fibromyalgia, with conflicting findings [18]. For instance, an effect on dyspnea and exercise tolerance has been described in patients with congestive heart failure and/or cardiomyopathy and an increased time to exhaustion following two weeks of CoQ_{10} in trained and untrained individuals [4,19,20]. However, the data regarding the effects of CoQ_{10} and NADH supplementation on exercise performance and cardinal symptoms in CFS remain limited and inconsistent. Additionally, no specific assessment of cardiovascular functioning with CoQ_{10} plus NADH supplementation during a stress test in CFS has been performed to date. Our aim was to conduct an 8-week, randomized, double-blind, controlled trial to evaluate the clinical response after CoQ_{10} plus NADH supplementation on cardiovascular function (max HR changes) during an incremental cycle ergometer test, and to assess perceptions of fatigue, pain and sleep disturbances in a sample of CFS patients.

2. Subjects and methods

2.1. Study participants and recruitment

An 8-week randomized, placebo-controlled, double-blind pilot study was conducted at a single tertiary referral center (CFS Clinical Unit, Vall d'Hebron University Hospital, Barcelona, Spain) from January to December 2013. A total of 113 potentially eligible patients were enrolled. At enrollment, 33 patients (29.2%) who failed to satisfy all inclusion criteria or presented one or more exclusion criteria were excluded from the study. The remaining 80 fully eligible patients (70.8%, mean age, 49.2 ± 7.8 years) were included in the study. The reasons for rejection of potentially eligible patients are shown in Fig. 1. Inclusion criteria were female sex, age between 18 and 65 years with a confirmed diagnosis of CFS according to 1994 CDC case criteria. All participants had a resting radial pulse rate between 50 and 100 bpm, systolic blood pressure between 100 and 140 mm Hg and diastolic blood pressure between 50 and 90 mm Hg. Exclusion criteria were contraindication of an ergometer exercise test, participation in other trials in the 30 days prior to inclusion, intake of any drug or banned substances (statins, dietary supplements, anti-hypertension or beta-blocker drugs), pregnancy or breast-feeding, secondary hypertension, hepatobiliary tract disease that might alter CoQ_{10} bioavailability, cardiovascular or pulmonary disorder (unstable angina pectoris, heart failure, life-threatening arrhythmia) that might interfere with maximal exercise testing, and inability to communicate and comply with all study requirements.

2.2. Intervention

Eighty participants were randomized in a double-blind fashion in a 1:1 ratio and assigned to receive either CoQ_{10} plus NADH ($n = 40$) or matching placebo ($n = 40$) in enteric-coated tablets twice daily for 8-weeks, in addition to standard therapy. To allocate participants, we applied a computer-generated list of random-numbers using Stata 9.0 (StataCorp, College Station, TX, USA) statistical software. Participants were instructed to avoid taking any additional supplements containing CoQ_{10}, NADH, phosphatidylserine and vitamin C during the study. Adherence to study medications was assessed by serial measures of CoQ_{10} and NADH levels in peripheral blood mononuclear cells (PBMC) at baseline and following eight weeks of therapy. Patients randomized to the CoQ_{10} plus NADH group received four enteric-coated tablets daily consisting of active ingredients (50 mg of CoQ_{10} and 5 mg of NADH) and excipients (20 mg of phosphatidylserine and 40 mg of vitamin C). Patients randomized to placebo received supplementation comprising four enteric-coated tablets daily without active ingredients and containing only excipients. Both active and placebo tablets, were identical in size, color, opacity, shape, presentation and packaging. All tablets were manufactured and donated by Vitae Natural Nutrition Corporation, S.L. (Sant Cugat de Vallès, Barcelona, Spain). Telephone calls were made at two, four and eight weeks of the intervention to encourage compliance and to record the average number of tablets not taken during the previous month. Participants were supplied with excess tablets. The number of tablets returned and PBMC CoQ_{10} and NADH levels at week 8 were used as a measure of compliance. Evidence of adverse effects of CoQ_{10} and NADH could include insomnia, elevated liver enzymes, rash, nausea, vomiting, epigastric pain, diarrhea, abdominal discomfort, dizziness, photophobia, irritability, headache, and heartburn; however, regardless of the dosage used, few untoward effects have been previously reported. In our study, no serious adverse effects were recorded in any of the 80 randomly assigned subjects. Overall, only 3 patients (3.8%) of the placebo group reported an adverse event, usually moderate and considered unrelated to the study drug. These were abdominal pain and discomfort ($n = 2$), and orthostatic intolerance ($n = 1$). However, these three patients were excluded from the study in order to avoid the influence of these symptoms on the evaluated variables. There were no statistical differences in the number of adverse events between groups ($P = 0.110$). The study was conducted in accordance with the guidelines laid down in the Declaration of Helsinki. The study

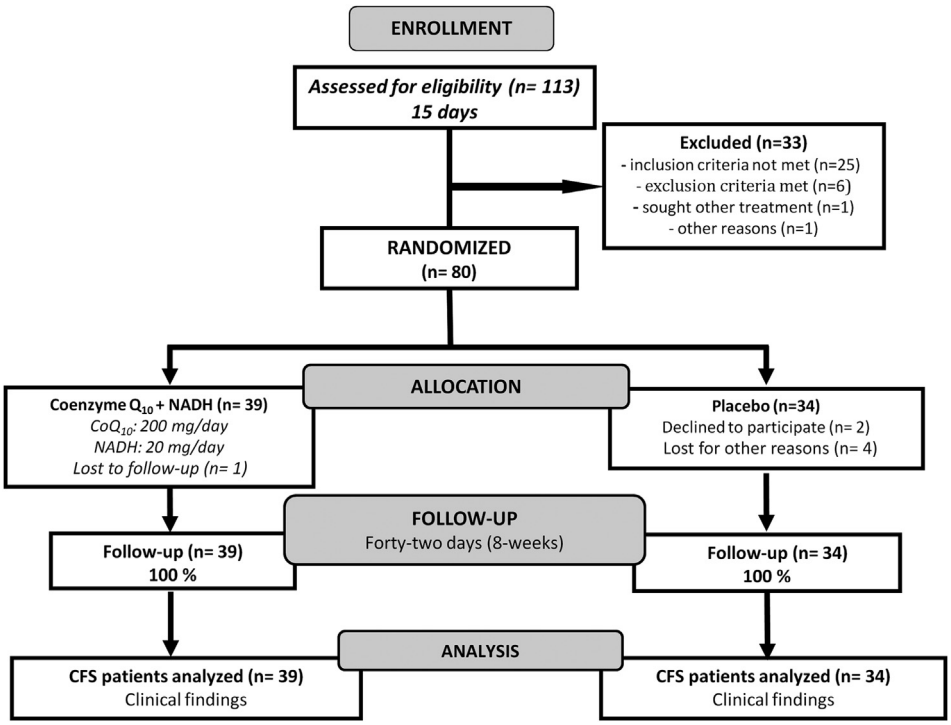

Fig. 1. Flowchart of the study participants. Consolidated Standards of Reporting Trials (CONSORT) flow diagram showing the distribution of the participants from initial assessment to analysis of study data. CFS, Chronic Fatigue Syndrome; CoQ_{10}, Coenzyme Q_{10}; NADH, reduced nicotinamide adenine dinucleotide.

protocol and amendments were approved by Clinical Research Ethics Committee of the Vall d'Hebron University Hospital, Barcelona, Spain. Informed written consent was obtained from each of the study participants.

2.3. Study design

A proof-of-concept, 8-week, randomized, double-blind, placebo-controlled trial was conducted at a single tertiary referral center in order to evaluate the effects of oral CoQ_{10} plus NADH supplementation on max HR changes during an incremental exercise test using a cycle ergometer with continuous monitoring of cardiovascular response and on CFS related symptoms (fatigue, pain and sleep disturbances) in 80 eligible Spanish CFS patients who fulfilled the 1994 CDC case criteria. The patients were evaluated at baseline and at the end of the run-in period (8-weeks) regarding age-predicted max HR functional response with an incremental cycle ergometer test. Changes in fatigue, pain and sleep problems were assessed through patient self-reported questionnaires from baseline to each follow-up visits (at 4- and 8-weeks).

2.4. Primary outcome measure

The protocol-defined outcome measure was to evaluate the max HR changes as measured by an exercise test on a cycle ergometer from baseline to the end of treatment period (8-weeks). The subjects performed a cycle ergometer test against a graded increase in workload, until exhaustion was reached. The exercise tests were performed at a humidity of 40%– 60% and at room temperature (20 °C–22 °C). The subjects were asked to adopt a sitting position on the electromagnetically braked ergometer (Angio, Lode B.V., Groningen, The Netherlands) and, after three to five minutes of adjustment to the position, the test was started. Heart rate was monitored continuously at rest and during exercise. Twelve-lead electrocardiogram and HR were monitored continuously during the test (Cardio Scan v.4.0, DM software, Stateline, Nevada, USA), obtaining HR at each stage of the test. VO_2 peak (L/min) and relative VO_2 peak (ml/kg/min) were measured breath-by-breath with an automatic gas analysis system (Metasys TR-plus, Brainware SA, La Valette-du-Var, France) equipped with a pneumotachometer and making use of a two-way mask (Hans Rudolph, Shawnee, Kansas, USA). Gas and volume calibrations were performed before each test, in accordance with the manufacturer's guidelines. After a four-minute period cycling at 0 W, participants followed a 20 W/min ramp protocol up to exhaustion, which was the maximal test. In a previous study, the exercise capacity stress testing protocol was able to distinguish women with CFS from healthy sedentary controls [21]. The following physiological variables were obtained during the exercise test: pulmonary oxygen uptake (VO_2), pulmonary carbon dioxide output (VCO_2), maximal workload, heart rate (HR), respiratory quotient, arm blood pressure (BP) and perceived exertion based on the Börg scale (scores 6 to 20).

2.5. Secondary outcome measures

Secondary outcome measures included changes in fatigue, pain and sleep problems assessed through validated self-reported questionnaires from baseline to each follow-up visits (4 and 8 weeks). The above symptoms were recorded through patient self-reported assessment scales by trained investigators who supervised compliance. Fatigue was scored using the Fatigue Impact Scale (FIS) [22], a 40-item questionnaire which assesses perceptions of how fatigue affects cognitive, physical and psychosocial functions. This validated, self-administered questionnaire has been used in a number of fatigue-associated diseases, including CFS. Participants rate how these items are affected by fatigue on a five-point scale: 0 (no fatigue) to 4 (severe fatigue). The total score is calculated by adding responses from the 40 questions (range

0–160). Higher scores indicate more functional limitations due to fatigue. Pain was scored using the McGill Pain Questionnaire (MPQ) [23], a validated instrument composed of 15 numerically scaled questions rated from 0 (no pain) to 3 (severe pain). These items measure two dimensions of subjective pain: sensory (11 items) and affective (4 items). Finally, sleep disruption were assessed using the 24-item Pittsburgh Sleep Quality Index (PSQI) questionnaire [24]. Scores are obtained on each of seven components of sleep quality: subjective quality, sleep latency, sleep duration, habitual sleep efficiency, sleep perturbations, use of hypnotic medication, and daytime dysfunction. Each component is scored from 0 to 3 (0 = no problems and 3 = severe problems). Global PSQI score ranges from 0 to 21, with higher scores indicating more sleep problems.

2.6. Sample size and statistical analysis

Efficacy data were analyzed on the basis of an intention-to-treat population approach, which included patients who had been treated for at least 30 consecutive days. Missing values were imputed by the last observation carried forward method. All patients who were randomized were considered for safety analysis. A descriptive analysis for demographic and clinical data was performed on the number of valid cases by means of absolute and relative frequencies, measures of central tendency (mean and median) and dispersion (standard deviations (SD), minimum and maximum). The sample was checked for normal distribution and homogeneity of the variance using the Kolmogorov–Smirnov test and the Levene test, respectively. Since all data were normally distributed, one-factor ANOVA test was used to compare the mean values of variables. A chi-square test (χ^2) or Fisher's exact test were used to assess differences in categorical variables. According to the pre-specified primary analysis plan, treatment effect was assessed as the mean change in the max HR from baseline to 8-weeks (max HR at week 8 minus max HR baseline visit) for each intervention group. Statistical comparison between treatment effects on max HR changes was made by analysis of covariance (ANCOVA) in a model that adjusted for the change in the work-load between baseline and final exercise test. Treatment effect on the secondary outcome measures was calculated (week 4 score minus baseline score, and week 8 score minus baseline score) and differences between groups were evaluated by ANCOVA adjusted by the basal score of the parameter analyzed. Regarding the final sample size, the study detected differences of 5 points in the max HR with a power of 75% at an *alpha*-level of 0.05. For all analyses, a P-value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS, version 18.0 for Windows (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Study participants

An 8-week randomized, placebo-controlled, double-blind trial was conducted at a single tertiary center (CFS Clinical Unit, Vall d'Hebron University Hospital, Barcelona, Spain) from January to December 2013. Figure 1 shows a flowchart of the participants prior to analysis. Dropout was defined as missing data on lost to follow-up visits from baseline. One patient in the CoQ_{10} plus NADH group was lost to follow-up and excluded from the study. In the placebo group, six patients were also excluded, for the following reasons: refusal to participate (n = 2), loss of a cycling ergometer test (n = 1) and adverse effects (n = 3). Therefore, 73 participants [CoQ_{10} + NADH (n = 39) and matching placebo (n = 34)] completed the trial. However, the statistical analyses were performed on the original 80 participants on the basis of an intention-to-treat approach, and missing values for these seven excluded subjects were determined on the basis of the last observation carried forward method. The rate of compliance in the study was high, since 100% of tablets were taken throughout the study in both groups. Additionally, analyses of CoQ_{10} and NADH levels in PBMC at week 8 showed clear differences between the groups [CoQ_{10}: treatment group: 361.8 ± 37 vs. placebo: 155.1 ± 26spmole/mg proteins; P < 0.05 and NADH: treatment group: 247.3 ± 5.1 vs. placebo: 98.2 ± 4.6 pmole/10^6 PBMC; P < 0.001]. Means (±SD) weight, height and BMI of all participants were 70.3 ± 13.3 kg (range 42–106), 1.8 ± 0.1 m (range 1.6–1.9) and 23 ± 4.9 kg/m^2 (range 17–43), respectively. Baseline data on demographic and clinical characteristics, associated comorbid conditions, pharmacological therapy used and baseline CoQ_{10} and NADH levels did not differ significantly between the groups (Table 1).

3.2. Primary outcome measure

Table 2 summarizes the results of main functional physiological variables, before and after an incremental cycle ergometer test at baseline and week 8 of intervention between both randomization

Table 1
Baseline demographic, clinical and laboratory characteristics among 73 chronic fatigue syndrome patients according to treatment assigned at enrollment.

Variable	CoQ_{10} + NADH group (n = 39)	Placebo (n = 34)	*P* value[a,b]
Age, y	49.3 ± 7.1	49.1 ± 8.4	0.96
Duration of fatigue, y	15.4 ± 8.9	14.7 ± 6.2	0.86
Time of symptoms onset, y	33.9 ± 6.8	34.4 ± 2.5	0.68
Body weight, kg	68.5 ± 14.6	72.1 ± 13.7	0.79
Height, m	1.7 ± 0.07	1.8 ± 0.02	0.53
BMI, kg/m^2	23.7 ± 5.2	22.3 ± 2.4	0.93
Type 2 diabetes	5 (13)	4 (12)	0.95
Fibromyalgia	17 (44)	13 (38)	0.91
Irritable bowel syndrome	3 (8)	2 (6)	0.57
Hypothyroidism	6 (15)	4 (12)	0.75
Analgesic/anti-inflammatory drugs	12 (31)	8 (24)	0.73
Antidepressants/anxiolytics	19 (49)	11 (32)	0.41
Hypnotics	6 (15)	4 (12)	0.81
CoQ_{10}, pmole/mg protein	135.8 ± 22	137.2 ± 13	0.53
NADH, pmole/10^6 PBMC	95.3 ± 2.1	96.7 ± 2.4	0.71

Data are expressed as mean ± standard deviation for continuous variables, and categorical variables as number (percentage) for group.
[a] Obtained by using an one-factor ANOVA test for continuous variables.
[b] Obtained by using a chi-square test (χ^2) or Fisher's exact test for categorical variables.

Table 2
Rest and maximum functional physiological data during the incremental cycle ergometer stress test at baseline and week 8 of intervention between randomization arms.

Physical	Week 0		Week 8	
Performance variables	Rest	Maximum test	Rest	Maximum test
HR, bpm				
CoQ_{10} + NADH	81.7 ± 10.1	140.1 ± 15.3	79.0 ± 9.1	136.8 ± 14.2[a]
Placebo	82.6 ± 10.2	140.3 ± 19.8	80.7 ± 9.5	138.7 ± 17.4
Workload, km/h				
CoQ_{10} + NADH	–	92.8 ± 20.7	–	93.2 ± 21.4
Placebo	–	91.9 ± 21.7	–	88.8 ± 19.7
Respiratory quotient				
CoQ_{10} + NADH	0.81 ± 0.05	1.07 ± 0.11	0.83 ± 0.07	1.07 ± 0.1
Placebo	0.82 ± 0.05	1.06 ± 0.09	0.82 ± 0.05	1.08 ± 0.1
VO_2, ml/kg/min				
CoQ_{10} + NADH	4.73 ± 0.92	19.4 ± 4.3	4.63 ± 0.95	18.6 ± 3.2
Placebo	4.91 ± 0.92	19.7 ± 3.3	4.74 ± 0.80	18.6 ± 3.8
VCO_2, l/min				
CoQ_{10} + NADH	0.26 ± 0.05	1.4 ± 0.3	0.25 ± 0.05	1.3 ± 0.3
Placebo	0.27 ± 0.06	1.4 ± 0.3	0.26 ± 0.05	1.4 ± 0.4
Systolic BP, mm Hg				
CoQ_{10} + NADH	119.9 ± 15.6	139.8 ± 19.5	118.1 ± 15.6	136.4 ± 19.3
Placebo	115.9 ± 15.9	135.6 ± 22.2	113.4 ± 13.7	132.9 ± 20.2
Diastolic BP, mm Hg				
CoQ_{10} + NADH	70.1 ± 10.7	72.6 ± 14.1	68.4 ± 11.1	70.2 ± 14.1
Placebo	70.2 ± 11.9	69.7 ± 13.4	67.6 ± 8.17	69.3 ± 10.5

Data are expressed as mean ± standard deviation.
[a] An one-factor ANOVA test was used comparing intragroup maximum HR scores vs. baseline. Statistical significance at $^*P < 0.05$.

groups. For the primary clinical outcome (reduction of max HR change) statistically significant differences were observed in CoQ_{10} + NADH group during the study, with a reduction in max HR after 8 weeks of treatment compared with baseline max HR (136.8 ± 14.2 vs. 140.1 ± 15.3 bpm, P = 0.022). Comparing max HR change at the end of the exercise test from baseline to week 8 between groups, the treatment did not have a significant effect on max HR in study participants. However, as shown in Fig. 2, there was a clear trend towards a greater max HR reduction to week 8 in the treatment group (CoQ_{10} + NADH group: −3.28 ± 8.7 vs. placebo group: −1.82 ± 12.2, F = 3.53; P-trend = 0.225). There were no differences in the change in VO_2, VCO_2, maximal workload, respiratory quotient and arm systolic and diastolic blood pressure from baseline to week 8 (P > 0.05). The perceived effort during the exercise, assessed by the change of the Börg test score from baseline to week 8, did not differ between both intervention groups (CoQ_{10} + NADH group: 0.25 ± 1.35 vs. placebo group: 0.12 ± 1.63, F = 0.15; P = 0.66).

3.3. Secondary outcome measures

Table 3 shows the fatigue and pain scores at baseline, weeks 4 and 8 and the changes between the intervention groups. Patients treated with CoQ_{10} + NADH presented significant reductions in FIS total scores from baseline to 4- and 8-weeks of treatment (P = 0.021 and P = 0.03, respectively). There were also significant differences in mean FIS total score in the placebo group, but only at 4 weeks of treatment compared to baseline (P = 0.04). As shown in Fig. 3, there was a more marked trend towards decrease of the mean FIS total scores and physical, cognitive and psychosocial FIS subscores in the CoQ_{10} + NADH group between baseline and weeks 4 and 8. However, as shown in Table 3, the changes in FIS total score and in physical, cognitive and psychosocial FIS subscores did not differ between the groups from baseline to weeks 4 and 8. On the other hand, a significant decrease in sensory and affective pain perception was observed in the placebo group from baseline to week 8 (21.8 ± 6.0 vs. 17.7 ± 7.4, P = 0.01 and 8.9 ± 3.1 vs. 6.8 ± 3.6, P = 0.01, respectively). The changes in sensory and affective pain perception (treatment effect) from baseline to week 8 were higher in placebo group compared to active group (- 4.35 ± 7.5 vs. 1.59 ± 6.4, P = 0.002 and − 1.94 ± 3.8 vs. 0.41 ± 3.7, P = 0.006, respectively). Finally, Table 4 shows the data for quality of sleep

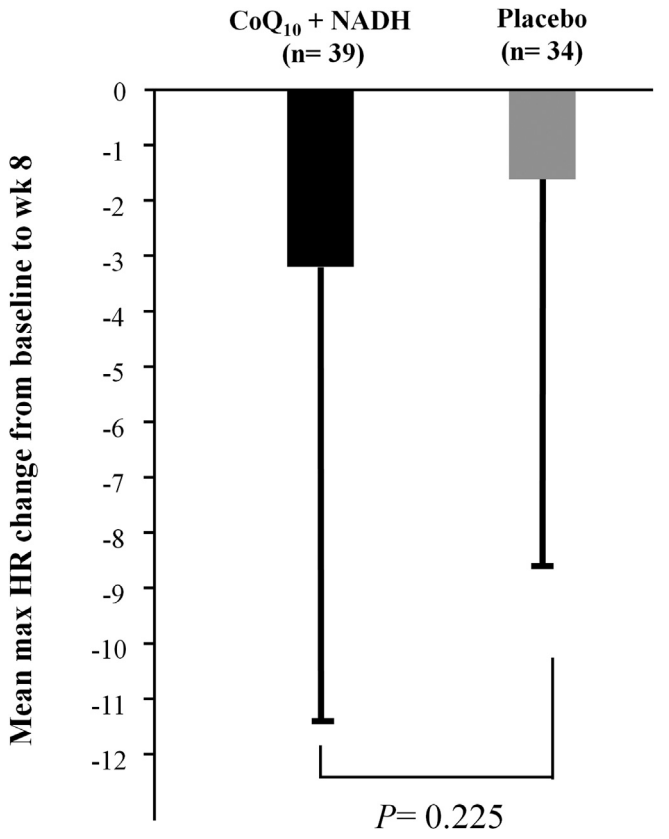

Fig. 2. The changes in participants treated with CoQ_{10} + NADH or placebo were determined on the basis of the changes in max HR during the cycle ergometer test from baseline to week 8. More negative scores indicate more diminishment of the max HR value from baseline.

assessment at baseline, week 4 and 8 and the change from baseline in the two groups. Patients with CoQ_{10} + NADH had fewer sleep disturbances at week 8 ($F = 3.83$, $P < 0.001$) and were taking more hypnotic drugs ($F = -2.75$, $P = 0.008$).

4. Discussion

New therapeutic strategies for CFS are urgently needed since its symptoms cause substantial impairments in patients' quality of life and currently there is no FDA-approved effective treatment. To our knowledge, this is the first randomized, placebo-controlled, double-blind clinical trial to evaluate the potential beneficial effects of oral CoQ_{10} plus NADH supplementation on maximum HR changes in CFS patients performing an incremental cycle ergometer stress test, and also their perceptions of fatigue, pain and sleep disturbances in CFS patients. Our results suggest that CoQ_{10} plus NADH supplementation may have a positive effect on max HR change during the maximal cycle ergometer test and patients' perception of fatigue. Although the differences in the effect of treatment between the two groups were not statistically significant, this may have been due to not enough study power; in view of the positive trend found for the combination of CoQ_{10} plus NADH, we consider that this study should be continued with a larger number of patients in CFS subgroups more homogeneous. CFS patients present multiple symptoms, including physical and mental fatigue, pain and sleep disruption. Some studies have suggested that they show normal resting HR but blunted HR and systolic BP responses during exercise [25,26]. However, other studies have not reported HR reductions, and attribute some of the observed effects to reduced effort [27]. The discrepancies between different studies and treatment outcomes may be due to the heterogeneity of CFS populations (patients' heterogeneous clinical characteristics, study entry case criteria, the role of intervention provider, centre-specific characteristics, co-therapies, comorbidities, study designs, and outcome variability is a critical aspect to consider) and that sample sizes were small. Lack of consistency of outcome measures in intervention trials for CFS might be a function of combining patients into a large heterogeneous group rather than analyzing them within subgroups. The etiology of CFS remains unclear. Several biochemical and immune abnormalities in inflammatory, oxidative and nitrosative stress (O&NS) pathways [28], and recent studies have suggested that mitochondrial disturbances to energy requirements may be associated with the condition's pathogenesis [9]. The reduction in mitochondrial function has been associated with a decreased efficiency of oxidative phosphorylation and a fall in ATP production. Two of these mitochondrial components are CoQ_{10} and NADH. Dysfunctions in these two coenzymes have also been associated with neurodegenerative diseases and cancer [29,30].

Table 3
Fatigue and pain scores at baseline, week 4 and 8 and changes from baseline after of intervention between treatment groups.

FIS and MPQ	CoQ_{10} + NADH (n = 39)	Placebo (n = 34)	*P* value[c]
Fatigue Index Scale-40			
FIS total score[a]			
Basal	131.9 ± 18.9	136.0 ± 16.0	0.32
Week 4	125.4 ± 22.4	127.5 ± 24.9	0.71
Week 8	124.4 ± 23.4	132.3 ± 20.7	0.14
Treatment effect (week 4)[b]	−6.51 ± 17.1	−8.56 ± 23.0	0.83
Treatment effect (week 8)	−7.46 ± 18.6	−3.73 ± 17.5	0.27
Physical			
Basal	34.8 ± 4.2	35.6 ± 4.2	0.36
Week 4	32.3 ± 5.8	33.4 ± 6.4	0.48
Week 8	32.4 ± 5.9	34.2 ± 5.7	0.19
Treatment effect (week 4)	−2.44 ± 4.9	−2.29 ± 6.4	0.73
Treatment effect (week 8)	−2.41 ± 5.2	−1.47 ± 4.8	0.33
Cognitive			
Basal	33.6 ± 5.1	34.6 ± 4.3	0.35
Week 4	31.9 ± 6.1	32.4 ± 6.6	0.72
Week 8	31.4 ± 6.0	33.9 ± 4.9	0.06
Treatment effect (week 4)	−1.69 ± 4.7	−2.21 ± 6.2	0.85
Treatment effect (week 8)	−2.15 ± 5.1	−0.76 ± 5.0	0.11
Psychosocial			
Basal	63.5 ± 10.9	65.7 ± 9.2	0.36
Week 4	61.2 ± 11.9	61.7 ± 12.9	0.86
Week 8	60.6 ± 12.6	64.2 ± 10.9	0.20
Treatment effect (week 4)	−2.4 ± 9.3	−4.1 ± 11.6	0.67
Treatment effect (week 8)	−2.9 ± 10.2	−1.5 ± 8.8	0.37
McGill Pain Questionnaire [2]			
Sensory			
Basal	20.2 ± 4.7	22.1 ± 5.6	0.20
Week-4	19.9 ± 6.6	19.9 ± 8.1	0.98
Week-8	21.8 ± 6.0	17.7 ± 7.4	0.01
Treatment effect (week 4)	−2.6 ± 6.1	−2.2 ± 8.0	0.49
Treatment effect (week 8)	1.59 ± 6.4	−4.35 ± 7.5	0.002
Affective			
Basal	8.5 ± 2.6	8.8 ± 3.1	0.65
Week 4	8.3 ± 3.0	7.7 ± 3.6	0.42
Week 8	8.9 ± 3.1	6.8 ± 3.6	0.01
Treatment effect (week 4)	−0.21 ± 3.4	−1.48 ± 3.4	0.28
Treatment effect (week 8)	0.41 ± 3.7	−1.94 ± 3.8	0.006

Data are expressed as mean ± standard deviation.
[a] On the FIS and MPQ, higher scores indicate greater severity of fatigue or pain perception, respectively. FIS, fatigue index scale; MPQ, McGill pain questionnaire.
[b] Treatment effect was calculated as changes from baseline to week 4 and 8 (last observation minus baseline ones) and reported as adjusted (least squares) means ± SD from the analysis of covariance. Negative numbers in treatment effect scores indicate improvement from baseline.
[c] An ANCOVA test was used for the intergroup statistical analysis.

CoQ_{10} and NADH deficiencies have also been described in patients with CFS and fibromyalgia [9,12,31], and it has also been suggested that serum NADH levels are directly correlated with serum CoQ_{10} concentration in these patients. Several components of the mitochondrial system require diet replacement and this need can be facilitated with natural nutritional supplements [13]. Clinical trials have shown the utility of using oral replacement supplements of CoQ_{10} and/or NADH to significantly reduce the fatigue levels and other symptoms associated with chronic diseases, neuropsychiatric conditions and fibromyalgia [18,32]. However, studies carried out in CFS have included only very small samples and their conclusions are inconsistent [14–16]. Additionally, although combinations of different oral dietary supplements have been proposed, to date no clinical trials with the association of CoQ_{10} plus NADH in CFS have been published [13]. Therefore, we evaluated the combination of CoQ_{10} with NADH in a nutraceutical formulation because it may have a synergistic antioxidant effect. Some studies have suggested that CoQ_{10} or NADH may have a positive effect on max HR change and physical exercise in CFS. A previous study by our group suggested that oral NADH was associated with decreases in max HR after a stress test in a CFS population [14]. Our results partially concur with these previous reports and suggest that the combination of CoQ_{10} and NADH may improve max HR during an incremental cycle ergometer stress test. At present, few studies have been published that analyze the mechanisms by which CoQ_{10} and NADH influence cardiovascular response [15,16,19,20]. It has been suggested that these molecules may modulate the autonomic function by regulating the synthesis of endogenous catecholamines and acetylcholine [10]. It has also been proposed that they can improve the endothelial function and as a consequence increase left ventricular contractility and cardiac function [18]. However, future research are warranted to further clarify the exact mechanisms by which CoQ_{10} and NADH influence cardiovascular function in the general population and in CFS patients. Little information is available on the effect of CoQ_{10} or NADH in fatigue and other CFS associated symptoms. Some studies conclude that NADH had a positive effect on fatigue perception in some patients, although one of them suggested that the effect was limited to the first trimester of the treatment [16]. To our knowledge, no studies published to date have analyzed the efficacy and tolerance of CoQ_{10} plus NADH administration on fatigue levels, pain perception and sleep problems in CFS. In view of our observation of a trend towards a reduction in the perception of fatigue in the group treated with this combination compared to placebo, further studies with larger samples of CFS patients are warranted in order to confirm our findings. The lack of any effect on pain was an unexpected result. Although pain response in CFS patients has not been previously analyzed, a possible effect of CoQ_{10} or NADH on pain perception has been suggested in other pathologies such as fibromyalgia [31]. In view of the study's design, any description of the mechanisms underlying the results would be purely speculative and would need to be confirmed in future studies. It is known that pain is a symptom that can be decreased by the placebo effect. We therefore believe that the group receiving non-active treatment was more sensitive to the placebo effect than the active group, since they were anticipating a certain improvement. Patients receiving active treatment would detect the objective improvement in certain symptoms (mainly fatigue) deriving from CoQ_{10} and NADH and would therefore be less sensitive to the less intense placebo response. For the effect on sleep, the results reported so far are also

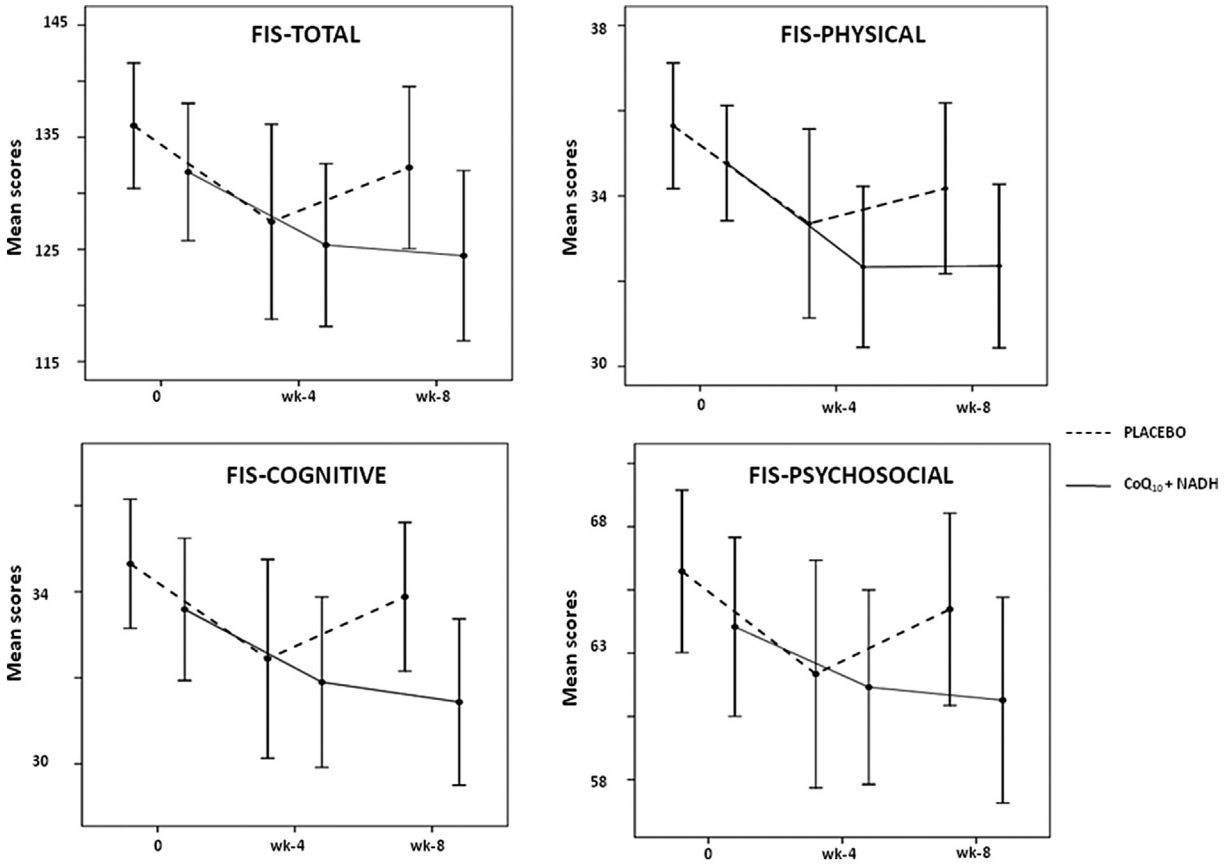

Fig. 3. Changes in FIS scoring during each follow-up visits. Each point on the curve indicates mean FIS scoring. Lower scores means an improvement in the fatigue perception. No significant differences in all the FIS scores were observed between both intervention groups in each study visits.

Table 4
Sleep scores at baseline, week 4 and 8 and change from baseline after intervention in participants who received either CoQ_{10} + NADH or placebo [1].

PSQI[a]	CoQ_{10} + NADH (n = 39)	Placebo (n = 34)	*P* value[c]
Subjective sleep quality			
Basal	2.3 ± 0.7	2.4 ± 0.6	0.30
Week 4	2.3 ± 0.8	2.1 ± 1.0	0.36
Week 8	2.5 ± 0.8	2.4 ± 0.7	0.77
Treatment effect (week 4)[b]	0.03 ± 09	−0.32 ± 1.01 [3]	0.12
Treatment effect (week 8)	0.18 ± 0.9	−0.03 ± 0.8	0.62
Sleep latency			
Basal	2.1 ± 0.7	2.5 ± 0.7	0.04
Week 4	1.95 ± 0.9	2.4 ± 0.8	0.04
Week 8	2.1 ± 0.8	2.4 ± 0.7	0.09
Treatment effect (week 4)	−0.18 ± 0.8	−0.09 ± 0.8	0.63
Treatment effect (week 8)	−0.08 ± 0.8	−0.12 ± 0.7	0.43
Sleep duration			
Basal	1.9 ± 1.0	1.9 ± 0.8	0.93
Week 4	1.8 ± 1.1	1.9 ± 1.0	0.64
Week 8	2.3 ± 1.1	1.9 ± 0.9	0.13
Treatment effect (week 4)	−0.15 ± 0.8	−0.06 ± 0.6	0.57
Treatment effect (week 8)	0.33 ± 1.3	−0.03 ± 0.8	0.12
Habitual sleep efficiency			
Basal	1.8 ± 1.3	2.0 ± 1.3	0.49
Week 4	1.8 ± 1.4	2.0 ± 1.3	0.51
Week 8	2.2 ± 1.2	2.1 ± 1.3	0.56
Treatment effect (week 4)	−0.03 ± 1.3	−0.03 ± 1.1	0.99
Treatment effect (week 8)	0.41 ± 1.4	0.03 ± 1.5	0.38
Sleep disturbances			
Basal	2.2 ± 0.5	2.3 ± 0.6	0.29
Week 4	2.0 ± 0.6	2.2 ± 0.6	0.07
Week 8	2.0 ± 0.5	2.5 ± 0.5	<0.001
Treatment effect (week 4)	−0.18 ± 0.7	−0.06 ± 0.60	0.44
Treatment effect (week 8)	−0.13 ± 0.6	0.18 ± 0.8	0.001
Hypnotic medication use			
Basal	1.8 ± 1.4	2.2 ± 1.3	0.22
Week 4	2.0 ± 1.4	1.7 ± 1.3	0.35
Week 8	2.2 ± 1.3	1.3 ± 1.4	0.008
Treatment effect (week 4)	0.10 ± 1.5	−0.6 ± 1.7	0.070
Treatment effect (week 8)	0.31 ± 1.5	−0.94 ± 1.8	0.002
Daytime disfunction			
Basal	2.5 ± 0.7	2.5 ± 0.7	0.82
Week 4	2.5 ± 0.8	2.3 ± 0.9	0.38
Week 8	2.6 ± 0.7	2.4 ± 0.7	0.24
Treatment effect (week 4)	0.01 ± 0.8	−0.21 ± 0.9	0.31
Treatment effect (week 8)	0.15 ± 0.9	−0.09 ± 0.8	0.18
Global Psqi score			
Basal	14.6 ± 3.4	15.9 ± 3.2	0.10
Week 4	14.2 ± 4.4	14.6 ± 4.4	0.73
Week 8	15.8 ± 4.5	14.9 ± 2.7	0.31
Treatment effect (week 4)	0.41 ± 3.7	1.35 ± 3.2	0.25
Treatment effect (week 8)	−0.03 ± 0.8	−0.03 ± 0.8	0.05

Data are expressed as mean ± standard deviation.
[a] On the PSQI, higher scoring indicates more sleep disturbances. PSQI, Pittsburgh Sleep Quality Index.
[b] Treatment effect was calculated as changes from baseline to week 4 and 8 (last observation less baseline ones), and reported as adjusted (least squares) means ± SD from the analysis of covariance. Negative values on the treatment effect scores indicate improvement from baseline.
[c] An ANCOVA test was used for the intergroup statistical analysis.

inconsistent. A recent clinical trial in a sample of Gulf War veterans concluded that CoQ_{10} (100 mg/day) conferred benefits to physical function and symptoms, but not sleep [32]. Though the differences in the samples should not be overlooked, the findings of that study are in agreement with ours. In our sample, some of the patients also had fibromyalgia and other comorbid conditions frequently associated with CFS. Although there were no differences in these clinical parameters between the two groups, future studies should evaluate the effect of these treatments in more homogeneous subgroups of CFS populations as noted above. Previous reports have suggested that dietary supplements such as CoQ_{10} or NADH are safe and well tolerated [12,14]. Our results confirm these observations and suggest that moderate doses of these molecules can be generally safety and well tolerated added to conventional therapy in CFS. This study has some limitations that should be noted. First, because of the small sample size, the study may have lacked the power to detect statistically significant differences in max HR changes between treatments. However, it was designed as a proof-of-concept trial and we consider that our research can serve as a basis for further studies enrolling larger numbers of participants in order to confirm these findings. The second limitation derives from the origin of the sample. The fact that all patients were recruited from a single tertiary referral center may have increased the proportion of more severe patients and we should be cautious in generalizing the results to patients seen in other medical settings or to the general population. Third, doses and timing were pre-established, and so the dose-response effect cannot be analyzed. It may be useful to consider higher dosages and longer interventions to determine their potential benefit. Finally, it has been stated that ergometric response is influenced by gender; therefore, our results may be conditioned by the lack of men in the sample. However, since CFS is more prevalent in women we preferred to study a more homogeneous and representative sample [21]. Nevertheless, our study had important strengths: 1) few previous studies have analyzed the combination of CoQ_{10} with NADH as nutritional supplement in CFS; 2) the use of a incremental cycle ergometer stress test protocol as an objective measure to evaluate the effect of dietary supplements on max HR change has not been previously analyzed, and very little information is available regarding its effect on fatigue levels, pain perception and sleep disruption; 3) the use of strict inclusion criteria based on 1994 CDC case definition ensures that the participants were appropriately selected and without confounding comorbidities. In conclusion, this 8-week, randomized, double-blind, placebo-controlled trial suggested that the CoQ_{10} plus NADH supplementation may be a safe, well tolerated and potentially useful treatment. Beside, CoQ_{10} plus NADH supplementation improved significantly reducing max HR during the ergometer stress test and also on perceived fatigue in CFS. On the contrary, CoQ_{10} plus NADH supplementation had no positive effect on pain and sleep disturbances between the intervention groups. Larger multicenter trials with longer term follow-up interventions in more homogenous CFS populations are warranted to assess these findings and to produce evidence-based guidelines regarding the potential benefits of antioxidant therapy in CFS and other chronic conditions.

Sources of support

JC-M received financial support from Vitae Natural Nutrition Co., S.L. This study and infrastructure was supported by Vall d'Hebron University Hospital Research Institute, Universitat Autònoma de Barcelona (UAB), Spain. Vitae Natural Nutrition Co., S.L. (Sant Cugat del Vallès, Barcelona, Spain) supplied the Coenzyme Q_{10} plus NADH tablets.

Conflict of interest

The authors have no competing personal or financial interests to declare.

Authors' contributions

The authors' responsibilities were as follows: JC-M: designed research (project conception, development of overall research plan, and study oversight) and wrote the paper. NS-F and LA: contributed to the final content, analyzed and interpreted the data, performed

statistical analysis, helped to write the study and provided critical revision and important intellectual content. MJS: designed/conducted/supervised the study, and participated in the development of the project. NC: provided critical oversight of the project and revisions to the manuscript, and also provided essential reagents and essential materials. MF: conceived and designed the study protocol and provided administrative, technical and material support. TFS: had primary responsibility for final content. JA: participated in the development of the project, had full access to all study data and took responsibility for the integrity of the data and the accuracy of the data analysis. All authors have read and approved the final version of the manuscript.

Acknowledgments

The authors thank all the study participants. We are grateful to Dr Mari Carmen Delicado and Dr Casimiro Javierre (Physiological Sciences Department, Exercise Physiology Laboratory, University of Barcelona, Barcelona, Spain) for performing the cycle ergometer exercise testing. We thank Luisa Aliste for help with the statistical data analysis. We are also grateful to Michael Maudsley for linguistic advice and Dr Eva Balada (Systemic Autoimmune Diseases Unit, Vall d'Hebron Hospital Research Institute, Barcelona, Spain) for their review, critical comments and suggestions on the manuscript.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.clnu.2015.07.010.

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