Original research paper

# Coenzyme Q10 as a treatment for fatigue and depression in multiple sclerosis patients: A double blind randomized clinical trial

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**Objectives:** Multiple sclerosis (MS) is the chronic inflammatory and demyelinating disorder of central nervous system which is accompanied with disability and negative life style changes such as fatigue and depression. The aim of this study is to investigate the effect of coenzyme Q10 (CoQ10) supplementation on fatigue and depression in patients with MS.

**Methods:** We performed a randomized, double-blinded, placebo-controlled trial to determine the effect of CoQ10 supplement (500 mg/day) vs. placebo for 12 weeks. Fatigue symptoms were quantified by means of fatigue severity scale (FSS) and the Beck depression inventory (BDI) was used to assess depressive symptoms.

**Results:** A significant decrease of FSS was observed in CoQ10 group during the intervention ($P = 0.001$) and significant increase of FSS change was observed within placebo group ($P = 0.001$). Repeated measure analysis of variance showed a significant time-by-treatment interaction for FSS (baseline 41.5 ± 15.6 vs. endpoint 45 ± 13.6; $F_{1,45} = 55.23$, $P < 0.001$, $\eta^2 = 0.56$) and BDI (baseline 17.8 ± 12.2 vs. endpoint 20.4 ± 11.4; $F_{1,45} = 40.3$, $P < 0.001$, $\eta^2 = 0.48$), indicating significant decrease of FSS and BDI in CoQ10 group compared to placebo group.

**Conclusion:** Our study suggests that CoQ10 supplementation (500 mg/day) can improve fatigue and depression in patients with multiple sclerosis.

**Keywords:** Coenzyme Q10, Multiple sclerosis, Fatigue, Depression, Treatment



## Introduction

Multiple sclerosis (MS) is the chronic inflammatory and demyelinating disorder of central nervous system (CNS) which is accompanied with disability and negative life style changes.[1] Fatigue and depression are common symptoms in MS patients.[2] The MS council defined fatigue as a lack of physical and or mental energy generated to make useful and desired activities possible. MS-related fatigue appears with heat and intensifies during day time.[3] Although the exact etiology of fatigue is unknown, multi-factorial causes such as autoimmune abnormalities and endocrine disorders are involved.[4] In MS patients, appearance of fatigue is not correlated with degree of nervous system impairment, disability, or subtypes of multiple sclerosis.[5]

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The immune system also has an important role in MS-related depression. Based on some evidence, pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-alpha) induce locomotors retardation, anorexia, weight loss, anxiety, and decreased social exploration.[6] In addition, major depression has a strong relationship with inflammatory response system, and increased number of leucocytes and neutrophils and increased plasma concentration of pro-inflammatory cytokines and receptors have been reported in depression.[7–9] Depression is accompanied by oxidative stress markers such as elevation of malondialdehyde (MDA) as a byproduct of lipid per oxidation.[10] It seems that inflammatory responses in depression result from induction of oxidative and nitrosative stress.

CoQ10 as a potent antioxidant has anti-inflammatory effects and decreases pro-inflammation cytokines


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such as TNF-alpha.[11] Moreover, the neuroprotective property of CoQ10 has been seen in protecting brain cells and neurons against central neurotoxic damages.[12] On the other hand, low plasma levels of CoQ10 have been found in chronic fatigue syndrome[13] and depression.[14] Furthermore, depression is characterized by lower blood levels of other antioxidants such as zinc, vitamin E, and vitamin C.[15–17]

Recently, a study among older adults with bipolar disease showed that high dose supplementation of Q10 (500 mg/day) improved depression.[18] Therefore, CoQ10 with anti-inflammatory and anti-oxidative properties may be considered as an alternative medicine for depression treatment. However, to the best of our knowledge, no research has tested anti-fatigue and anti-depression effect of Q10 in multiple sclerosis patients. We have carried out this study in multiple sclerosis patients in order to examine whether the consumption of high doses (500 mg/day) of Q10 improves depression and fatigue.

## Materials and methods

### *Patient requirement*

The MS patients ($n = 48$) were recruited from multiple sclerosis clinic at Sina Hospital in Tehran. A definite diagnosis of MS was confirmed according to McDonalds *et al.*'s[19] criteria and relapsing-remitting course was ascertained by the treating neurologist using the Lublin *et al.*'s[20] criteria. The study was approved by medical ethics committee of the Tehran University of Medical Sciences and all patients gave written informed consents. Criteria for excluding patients were ongoing clinical relapse, pregnancy and lactation, the use of corticosteroid drugs, occurrence of relapse during the study, patients with disease duration of less than 1 year, other major medical illnesses, and current smokers. We also excluded patients with regular intake of antioxidants, vitamin supplements, antidepressants, or fatigue modulating drugs.

### *Design of the study*

The current study followed the pattern of a randomized double-blinded clinical trial. Forty-eight patients were randomly allocated to two groups: CoQ10 group ($n = 24$) and control (placebo) group ($n = 24$). Among the patients, three women (two in CoQ10 group and one in placebo group) were excluded because of the occurrence of relapse during the study. The study was completed by 22 patients in CoQ10 and 23 patients in placebo group (Fig 1). The patients in CoQ10 group were treated with CoQ10 at doses of 500 mg per day for 3 months, whereas controls received placebo capsules (with the same shape and color of CoQ10 capsules). The medications of MS disease and related symptoms were not changed during the study. Each subject received the capsules (CoQ10 or placebo) at first, fifth and ninth weeks from the onset of the study and adherence to study medications was controlled with weekly phone calls for 12 weeks. On entry and after 3 months, all patients underwent clinical examination using expanding disability status scale (EDSS) by the same neurologist. Participants were instructed to avoid changing their routine physical activity for the duration of the study. We obtained information about patients' dietary intake by using 3-day dietary food records at baseline and endpoint of the study.

### *Anthropometric assessment*

The subjects were asked to be barefoot and wear light clothing. They were asked to stand straight on the electronic weighting scale, and the weight displayed on the screen was recorded. Weight was recorded using Seca Electronic Weighting Scale (Seca, Hamburg, Germany) to the nearest 100 g. Height was recorded using a non-stretchable tape to the nearest 0.1 cm. Body mass index (BMI) was determined by dividing the weight (kg) by the square of height ($m^2$).

### *Fatigue assessment*

Fatigue was defined as a lack of physical or mental energy or a feeling of tiredness.[21] The symptoms of fatigue were quantified by means of fatigue severity scale (FSS) that has been found to be reliable and valid in MS.[22] FSS, the most widely used fatigue rating scale, was administered at baseline and at 12 weeks. FSS consists of nine items with scores on a seven-point scale from one (strongly disagree) to seven (strongly agree) with higher scores, indicating more severe fatigue. The overall score is the mean of the rating from the nine items.[23]

### *Depression assessment*

The Beck depression inventory (BDI) that has been widely utilized to assess depression in MS patients was used to assess depressive symptoms in the current study. It consists of 21 questions of four statements describing symptoms related to depression, each of which is self-rated from zero (absent) to three (severe). Patients choose the one statement from each group that best describes how they have felt during the 'past week up to today'. The score range is 0–63 with higher scores indicating higher intensity. Patients completed the BDI at baseline and at 12 weeks.

### *Statistical analyses*

Discrete variables are shown as numbers and percentages and continuous variables are shown as mean ± standard deviation (SD). The independent $t$ test was used to determine differences between intervention and control groups. Paired-sample $t$ tests were used to determine within group differences (before and

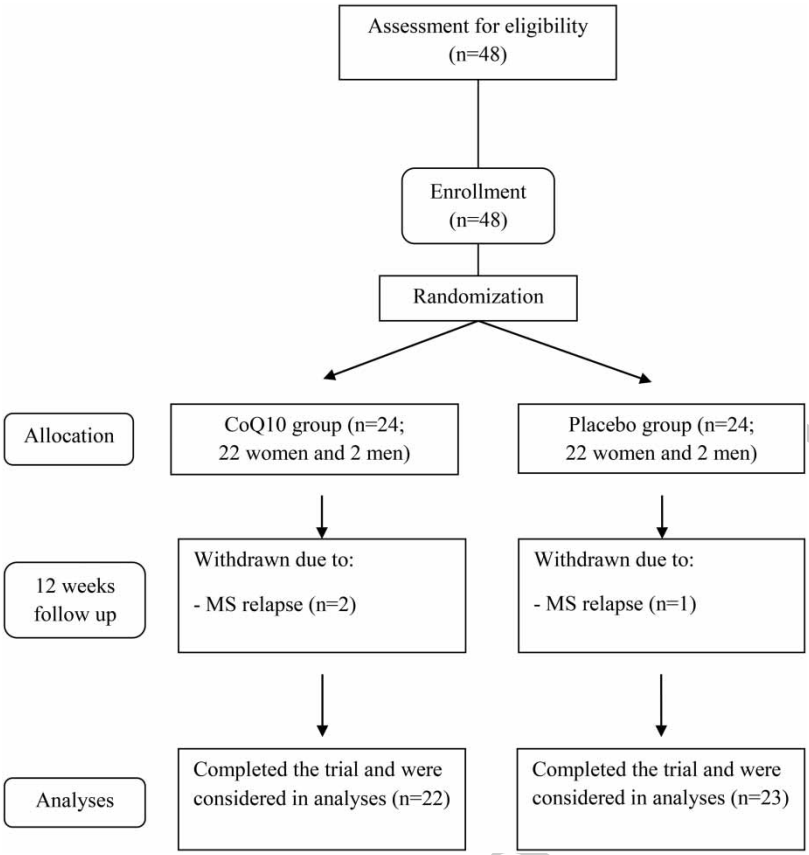


**Figure 1 Study design.**

after intervention). The repeated-measures analysis of variance (ANOVA) was used for determining differences between the two groups over time. This analysis allowed testing for a main effect of treatment (CoQ10 vs. placebo), a time effect (prior to treatment and after 12 weeks of treatment), and the interaction of time by treatment. $P < 0.05$ was considered significant. All statistical analyses were conducted using SPSS version 16 (SPSS Inc., Chicago, IL, USA).

## Results

Forty-five subjects with MS completed the study. Comparing of mean age (33.1 ± 7.6 vs. 30.9 ± 7.7 years) and anthropometric measurements including body weight (66.5 ± 14.8 vs. 63.6 ± 14.2 kg) and BMI (24.4 ± 4 vs. 23.4 ± 4.3 kg/m$^2$) showed no significant differences between the two groups. No significant differences among the groups in mean disease duration and EDSS values at baseline were observed (Table 1). Dietary intake of energy, carbohydrate, protein, fat, vitamin A, vitamin E, and vitamin C were not significantly different between the two groups, nor were within group differences (Table 2). The capsules were well tolerated by patients and no adverse reactions were reported throughout the study.

**Table 1 The basic characteristics of study subjects**

| Parameters | CoQ10 group ($n = 22$) | Placebo group ($n = 23$) |
|---|---|---|
| Mean age (years) | 33.1 ± 7.6 | 30.9 ± 7.7 |
| Gender [*n* (percent)] | | |
| Male | 2 (9.09%)* | 2 (8.69%)* |
| Female | 20 (90.9%)* | 21 (91.3%)* |
| Weight (kg) | 66.5 ± 14.8 | 63.6 ± 14.2 |
| BMI (kg/cm$^2$) | 24.4 ± 4 | 23.4 ± 4.3 |
| EDSS | 1.8 ± 1.2 | 1.9 ± 1.1 |
| Mean disease duration (month) | 52.8 ± 47 | 60.9 ± 51 |
| Mean age of onset (years) | 28.7 ± 8 | 25.8 ± 8 |

Values are means ± SD.
*Values are number (%).

As Table 3 shows, the severity of fatigue and depression were evaluated at baseline and endpoint of the study. Baseline fatigue and depression scores did not differ between CoQ10 and placebo groups. Although a significant decrease of FSS was observed in CoQ10 group during the intervention ($P = 0.001$), significant increase of FSS was observed within placebo group ($P = 0.001$). As expected, after the 12-week intervention, a significant time-by-treatment interaction for FSS with CoQ10 group showed significant FSS decreases (baseline 43.1 ± 10 vs. endpoint 33 ± 12.6), compared to FSS in the placebo group (baseline 41.5 ± 15.6 vs. endpoint 45 ± 13.6; $F_{1,45} = 55.23$, $P < 0.001$, $\eta^2 = 0.56$). Change of BDI within CoQ10 group was observed as a significant decrease ($P = 0.001$). But in the placebo group, we came

**Table 2 Dietary intake of study patients at baseline and endpoint**

| | Baseline | | | Endpoint | | |
|---|---|---|---|---|---|---|
| | CoQ10 group ($n = 22$) | Placebo group ($n = 23$) | $P^*$ | CoQ10 group ($n = 22$) | Placebo group ($n = 23$) | $P^*$ |
| Energy (kcal/day) | 1498 ± 556 | 1609.7 ± 527 | 0.493 | 1525 ± 554 | 1610.3 ± 539 | 0.604 |
| Carbohydrate (g/day) | 183.9 ± 79 | 200.9 ± 80 | 0.481 | 179.8 ± 68 | 204.1 ± 70 | 0.244 |
| Protein (g/day) | 60.5 ± 28.3 | 57.3 ± 26.1 | 0.451 | 62.1 ± 32.6 | 58.4 ± 29.9 | 0.343 |
| Fat (g/day) | 62.2 ± 27.8 | 64.5 ± 23.5 | 0.763 | 65.7 ± 26.2 | 62.5 ± 26.5 | 0.454 |
| Vitamin A (μg/day) | 588.1 ± 990 | 428.6 ± 336 | 0.469 | 366.4 ± 303 | 625.8 ± 685 | 0.111 |
| Vitamin E (mg/day) | 34 ± 21 | 37 ± 18 | 0.615 | 36.2 ± 20 | 33.1 ± 19 | 0.606 |
| Vitamin C (mg/day) | 76.1 ± 82 | 76.9 ± 78 | 0.974 | 48.1 ± 53 | 62.4 ± 40 | 0.317 |
| Zinc (mg/day) | 7.12 ± 3.4 | 6.54 ± 2.7 | 0.529 | 7.27 ± 4.5 | 8.14 ± 6.2 | 0.597 |
| Copper (μg/day) | 0.995 ± 0.44 | 1.015 ± 0.34 | 0.869 | 0.912 ± 0.38 | 2.943 ± 6.64 | 0.160 |
| Iron (mg/day) | 19.4 ± 4 | 16.5 ± 31 | 0.310 | 28.9 ± 4 | 33.7 ± 107 | 0.284 |

Values are means ± SD.
*$P$ values were obtained by comparison of values in the two groups at baseline and endpoint from independent $t$ tests.

across a significant increase of BDI ($P = 0.01$). Repeated measure ANOVA with BDI scores found a significant time-by-treatment effect indicating those who were treated with CoQ10 had significantly reduced BDI scores (baseline 14.3 ± 8.2 vs. endpoint 10.27 ± 7.4), in comparison with those treated with placebo (baseline 17.8 ± 12.2 vs. endpoint 20.4 ± 11.4; $F_{1,45} = 40.3$, $P < 0.001$, $\eta^2 = 0.48$).

## Discussion

To the best of our best knowledge, our study is the first one that assesses anti-depression effect of CoQ10 in multiple sclerosis patients. We found that CoQ10 consumption improved depression. In agreement with our study, Forester *et al*. showed that 1200 mg of CoQ10 lead to reduction in the severity of depression symptoms in older adults with bipolar disorder.[18] Similarly, CoQ10 left antidepressant effects in chronically stressed rats.[24] In this study, different i.p doses of CoQ10 (25, 50, 100, and 150 mg/kg/day) over 3 weeks in rats with restraint stress model of depression reduced glutathione and glutathione peroxidase levels as well as reduction of lipid and DNA oxidative damage markers such as hippocampal nitric oxide, MDA, and 8-hydroxy-2-deoxyguanosine levels. While reduction of CoQ10 and ATP levels and mitochondrial mass happened in depression, elevation of lipid peroxidation has also been reported. According to the role of inflammation and oxidative and nitrosative stress in pathogenesis of multiple sclerosis[25,26] and depression,[27,28] several antioxidants such as CoQ10[29] and lipoic acid[30,31] have been considered as alternative treatment in multiple sclerosis and MS-related depression. In a paper published from our study, we revealed that CoQ10 supplementation (500 mg/day) decreased MDA level and improved antioxidant capacity of multiple sclerosis subjects.[32] Consistent with our findings, Lee *et al*. reported that intake of CoQ10 supplementation (150 mg/day) for 12 weeks in patients with coronary artery disease reduced MDA levels and improved activity of antioxidant enzymes (catalase, superoxide dismutase, and glutathione peroxidase). But low dose of CoQ10 supplementation (60 mg/day) in the other group of this study did not show antioxidant activity.[33]

Depression has the same character in neurodegenerative diseases such as multiple sclerosis, Parkinson, and Alzheimer. Therefore, it is hypothesized that depression is accompanied by inflammation and neurodegeneration in the so-called inflammatory and neurodegenerative hypothesis of depression.[34] Considering this hypothesis, oxidative and nitrosative stress may lead to immunity response and produce immunogenic byproducts such as epitopes. Moreover, oxygen and nitrogen stress causes fatty acid and protein damage. These processes together

**Table 3 FSS and BDI at baseline and endpoint of study**

| | CoQ10 group ($n = 22$) | | | | Placebo group($n = 23$) | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Baseline | Endpoint | Change | $P^*$ | Baseline | Endpoint | Change | $P^*$ | $P^\dagger$ |
| FSS | 43.1 ± 10 | 33 ± 12.6 | −10.09 | 0.001 | 41.5 ± 15.6 | 45 ± 13.6 | 3.4 | 0.01 | 0.001 |
| BDI | 14.3 ± 8.2 | 10.27 ± 7.4 | −4.09 | 0.001 | 17.8 ± 12.2 | 20.4 ± 11.4 | 2.5 | 0.01 | 0.001 |

FSS: fatigue severity scale; BDI: Beck depression inventory.
Values are means ± SD.
*Indicates within-group differences (paired-sample $t$ test).
†Indicates time-by-treatment interaction differences (repeated measure ANOVA).

with damage to DNA and mitochondria may lead to dysfunction of cells, apoptosis, and finally neurodegeneration.[35]

Lowered antioxidant defenses[15] and raised O&NS in multiple sclerosis patients with depression[36] have been revealed by evidence from several studies and the inflammatory base of MS may be involved in depression episodes of MS subjects. Therefore, it is suggested that CoQ10 with several useful properties like acting as cofactor for mitochondria function, antioxidant, and anti-inflammatory activity may suppress the inflammatory and neurodegenerative pathway of depression.

The second finding of our study is that CoQ10 supplementation decreased fatigue in multiple sclerosis patients. Despite several studies conducted concerning the management of fatigue,[37,38] there is little evidence about pathogenesis of fatigue in multiple sclerosis patients. MS is characterized by inflammation, demyelization, and destruction of axons in the CNS. MS patients must recruit more nerve fibers of the brain compared with healthy individuals and this could result in fatigue.[3]

The effect of inflammation has been reported in MS-related fatigue. For example, Flachenechar and colleagues found high levels of TNF-alpha mRNA expression in peripheral blood sample of fatigued subjects compared to no-fatigue participants.[39] Also, the relationship between cytokines and fatigue was not seen to depend on autonomic nervous system activity or disease related factors.

MS-related fatigue may result from demyelination and axon loss in the CNS and immune responses. The longitudinal study conducted by Marie *et al.* found that increase in fatigue during the first 2 years was related to brain atrophy progression in the next 6 years.[40]

On the other hand, MS patients during the relapse phase often report a higher degree of fatigue and also, increase of immune action with higher levels of pro-inflammatory cytokines like TNF-alpha, IL-1, and IL-6.[39,41] These findings are experienced by other research studies, suggesting the remarkable role of inflammation in the pathogenesis of MS-related fatigue.

We hypothesized above that CoQ10 with its anti-inflammation and antioxidant property could improve fatigue in multiple sclerosis. Researchers have investigated the anti-fatigue effect of CoQ10 with different doses in various kind of fatigue. In agreement with our study, daily consumption of CoQ10 (300 mg) improved fatigue sensation and physical performance during fatigue-inducing work load trials. However, dose of 100 mg/day did not have any effect on fatigue. Moreover, daily intake of 70–100 mg of CoQ10 did not show anti-fatigue effects during physical load in healthy volunteers.[42]

Similarly, Cordero and colleagues showed that consumption of CoQ10 supplement (300 mg/day) reduced fatigue in fibromyalgia patients through relief in inflammation and improvement of antioxidant enzymes activities.[43] Although fatigue does seem to increase in relapse episodes and is a main cause of unemployment in multiple sclerosis patients,[5] it is not closely related to physical signs of disability (EDSS) or with MRI markers of disease activity.[41] Therefore, anti-fatigue and depression treatment may improve quality of life in MS patients. It is concluded that anti-fatigue effects of CoQ10 could appear in adequate and high doses of CoQ10 supplement by suppressing pro-inflammatory cytokines and enhancing antioxidant capacity.

## Conclusion

Overall, CoQ10 supplementation (500 mg/day) can improve depression and fatigue in multiple sclerosis patients. The antioxidant and anti-inflammation activity may be considered as one of the main factors responsible for the anti-fatigue and anti-depression effects of CoQ10. Larger and long-term follow-up studies would be necessary to confirm protective effects of CoQ10 against fatigue and depression.

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## Disclaimer statements

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**Conflicts of interest** None.

**Ethics approval** None.

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