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Effect of coenzyme Q10 supplementation on fatigue: A systematic review of interventional studies

Sanaz Mehrabani[a], Gholamreza Askari[b], Maryam Miraghajani[c,d], Rahele Tavakoly[e], Arman Arab[b,*]

[a] Student Research Committee, Department of Clinical Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran
[b] Department of Community Nutrition, School of Nutrition and Food Science, Food Security Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
[c] Cancer Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[d] The Early Life Research Unit, Division of Child Health, Obstetrics and Gynaecology, University of Nottingham, Nottingham, UK
[e] Department of Nutrition, School of Health, Kerman University of Medical Sciences, Kerman, Iran

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ABSTRACT

Aims: A number of studies have examined the beneficial effects of Coenzyme Q10 (CoQ10) on fatigue in different population, but the findings have been inconclusive. Herein, we systematically reviewed available interventional studies to elucidate the overall effects of CoQ10 supplementation on fatigue among adolescent and adult population.

Methods: PubMed, Cochrane's library, Science direct, Scopus, Google scholar and ISI web of science databases were searched for all available literature until April 2018 for studies assessing the effects of CoQ10 supplementation on fatigue. The Cochrane bias assessment tool were used to assess the quality of studies.

Results: A total of 16 studies out of 1316 met our inclusion criteria and included in our systematic review. Among included studies 10 of them showed significant beneficial effects ($p < 0.05$) of CoQ10 supplementation on fatigue status among healthy, fibromyalgia, statin-related fatigue, multiple sclerosis and end-stage heart failure subjects. CoQ10 supplementation could alleviate fatigue, but differences between studies population should be taken into account.

Conclusion: It seems CoQ10 has better therapeutic effects in statin-related fatigue and fibromyalgia patients compared with the other disease related fatigue. Finally, in order to draw a firm link between CoQ10 and fatigue, more clinical trials with adequate sample size and with sufficient follow-up periods are needed.

1. Introduction

Fatigue is a broad term referred to several aspects of human physiology. Possible definition described that fatigue is a problem in starting or maintaining voluntary activity[1] Acute fatigue has been defined as "reversible motor weakness and whole-body tiredness that were predominantly brought on by muscular exertion and was relieved by rest. However, chronic fatigue is a result of acute fatigue accumulation, and it may sometimes be irreversible.[2] In addition, fatigue could be classified as physical and mental[3] Physical fatigue occurs for a variety of reasons: depletion of glycogen and phosphocreatine of muscles, dysfunction of neuromuscular transmission and dysfunction of the calcium pump of sarcoplasmic reticulum.[4] Mental fatigue occurred when people undergo long periods of cognitive activity.[5] It also can be experienced as a pervasive feeling in other diseases such as anemia,[6] chronic fatigue syndrome,[7] cancer,[8] fibromyalgia,[9] multiple sclerosis[10] and HIV.[11] Patients experienced fatigue during rest and lack of energy for doing their daily work.[12]

Many pharmacological and non-pharmacological approaches are used for the management of fatigue. Exogenous dietary factors that were involved in producing energy may act as an anti-fatigue agent such as garlic,[13] quercetin[14] and Coenzyme Q10 (CoQ10).[15] CoQ10 or ubiquinone is a fat-soluble vitamin-like compound with multiple functions.[16] In mitochondria, CoQ10 is found both in the reduced and oxidized state.[17] CoQ10 as a conventional compound for energy metabolism plays an important role in transport of electrons in the inner mitochondrial membrane, convert the energy from fatty acids and carbohydrate to adenosine triphosphate and play an important role in energy producing for muscles.[18,19] It also has antioxidant properties[20,21] which is naturally synthesized by the body and can be taken

* Corresponding author.
E-mail address: arman4369@gmail.com (A. Arab).

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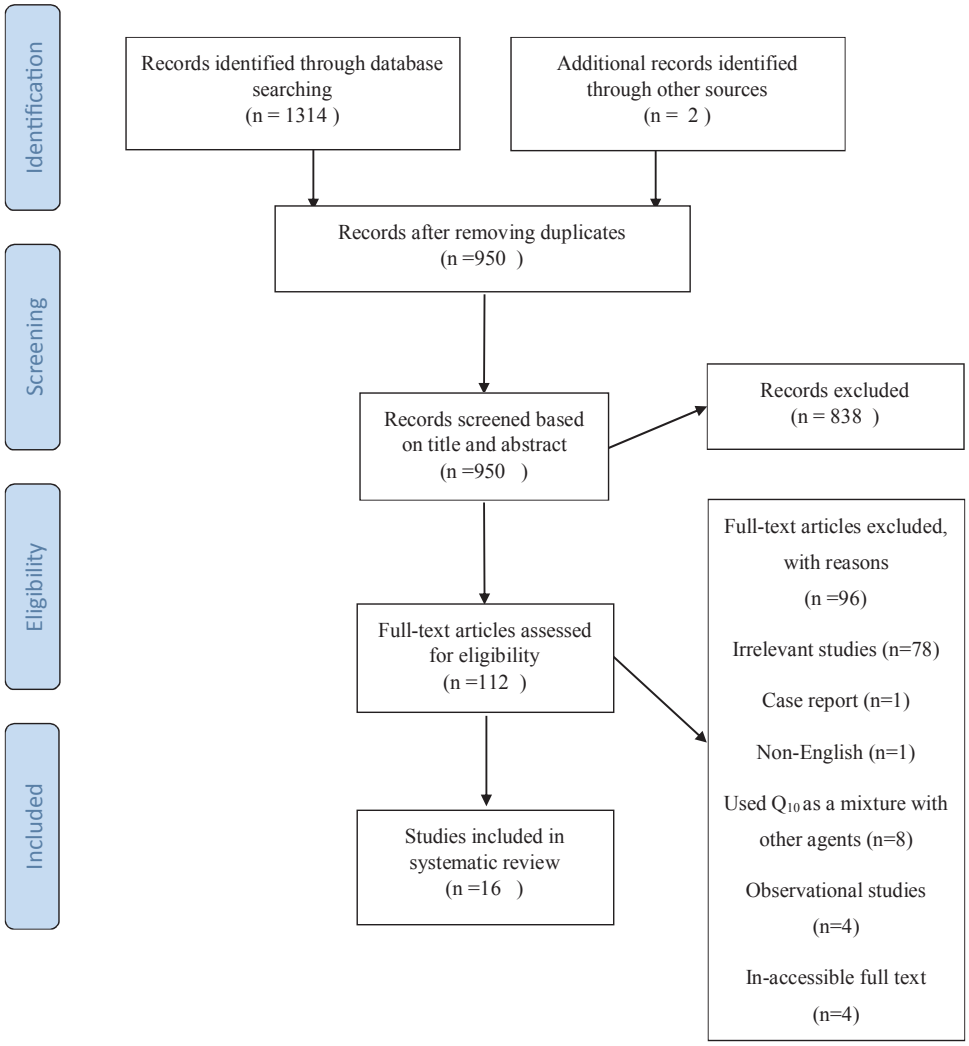

Fig. 1. The flow diagram of study selection.

through diet.[22] CoQ10 deficiency may occur for several reasons such as deficiency of nutrients involving in CoQ10 synthesis, genetic defect in synthesis or utilization of CoQ10 and some disease leading to increase tissue's need for CoQ10[23] Impaired oxidative phosphorylation has been shown in CoQ10 deficiency that led to alternation in mitochondrial metabolism, which plays an important role in progression of some disorders such as reduced physical tolerance and fatigue[24–26] Studies showed that plasma CoQ10 concentration was low in subjects with chronic fatigue syndrome and myopathy.[25,26] Emerging data suggest that consumption of CoQ10 could improve the phosphocreatine recovery by suppression of phospholipase A2. Recent process could alleviate fatigue during exercise[27] Physical activity leads to increase uptake of oxygen. Therefore, high production of ROS may be responsible for muscle damage and physical fatigue as known a peripheral fatigue.[3,28] So, taking CoQ10 as an antioxidant may provide a benefit for fatigue.[29]

Despite these reports, trials have explored this area with varied results[3,15,30–43] As physical fatigue can reduce the quality of life in healthy people, athletes and patients and due to existence of explained gaps between studies, we decided to conduct a systematic review of interventional studies to investigate the effect of CoQ10 supplementation on fatigue among adolescent and adult population.

2. Method and materials

The present systematic review was performed based on the Preferred Reporting Item for Systematic Review and Meta-analysis (PRISMA) statement and was registered on Prospero database (CRD42018096638).

2.1. Data source and search strategy

The comprehensive search was done through PubMed, Scopus, Cochrane's library, Science direct, Google scholar and ISI web of science databases for all available articles until April 2018 with no restriction of language. The search terms were “Coenzyme Q10″, “CoQ10″, “CoQ”, “Ubiquinone”, and “Ubiquinol”, combined with “Fatigue”, “Lassitude” and “Tiredness”. In addition, the cited references of included articles were examined to find any related literature too.

2.2. Inclusion criteria

Articles were considered for inclusion if they reported on original data from an original study examined the effects of CoQ10 supplementation on fatigue status, and were published in English language. Articles were excluded if they were of non-human studies, review articles, case reports, editorials and poster abstracts.

2.3. Data extraction

The following data was extracted for each included article: author name, year of publication, location, sample size, age, study design,

study duration, participants' health status, dose of CoQ10, dietary assessment and fatigue assessment method. To reduce human errors, the data extraction and assessment for each study were separately done by two investigators using a pre-designed data collection check form.

2.4. Study quality

Risk of bias was assessed according to the methods recommended by the Cochrane Collaboration which consisted of seven domains, including random sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other potential sources of bias (Table 2).[44]

3. Result

3.1. The search results

Our initial search through databases identified 1316 articles. After removing of duplicates, remaining 950 papers was reviewed based upon the title and abstract by two independent reviewers. Totally 112 articles were retrieved and reviewed based on full text and finally 16 studies met our inclusion criteria and included in our systematic review. The PRISMA flow diagram summarizes the results of study selection process for this systematic review (Fig. 1).

3.2. Overview of included studies

These included trials were conducted between 2004 and 2016. Participants had a different health condition at aged 13–69 years old in both genders. Between 16 studies included in our systematic review, 4 studies recruited healthy subjects[3,36,37,39] 5 fibromyalgia,[15,31–33,41] 2 statin associated myopathy[34,38] and the others poliomyelitis,[42] multiple sclerosis,[43] end-stage heart failure,[30] chronic fatigue syndrome[35] and breast cancer patients.[40] Three trials were conducted in Japan, [3,35,41] 3 in Spain,[31–33] 2 in United States,[38,40] 2 in Iran [36,43] and the remaining consisted of participants from Korea,[39] Turkey,[37] Italy,[15] Slovakia,[34] Australia[42] and Israel.[30] Eleven studies[30,32,34–36,39–43] had been parallel randomized controlled trial (RCT), and 3 had cross-over design[3,15,37] and 2 were quasi-experimental.[33,38] Among included studies, only 2 examined the dietary intake of participants[36,43] and the others didn't mention anything. Three studies ranked as good,[30,35,42] 1 as fair[15] and the others as poor quality,[3,31–34,36–41,43] respectively. Characteristics of included studies are illustrated in Table 1.

3.3. Findings from systematic review

3.3.1. The effects of CoQ10 supplementation in healthy subjects

The effect of CoQ10 supplementation on fatigue in healthy subjects was examined in 4 clinical trials.

In 2008, Mizuno et al. conducted a randomized controlled trial (RCT) study to evaluate the effects of CoQ10 administration during physical fatigue. In this study, 17 healthy volunteers (37.5 ± 9.9 years old) were randomized to receive 100 or 300 mg/day CoQ10 or placebo during 8 days of fatigue inducing activity. Subjective fatigue measured with visual analog scale (VAS) which revealed significant reduction ($p < 0.01$) in the 300-mg CoQ10–administered group compared with placebo.[3]

In another study, 16 soccer players (21.87 ± 1.58) randomly allocated to receive 300 mg/day CoQ10 or placebo for 1 month. Fatigue status assessed by fatigue index (FI) which failed to show any beneficial effects ($p > 0.05$) of CoQ10 administration on fatigue reduction during exercise.[36]

Another evidence investigated the effects of CoQ10 supplementation on fatigue in obese subjects. In this RCT study, 51 subjects randomly assigned to receive either 200 mg/day CoQ10 or placebo for 3 months. Fatigue assessed by fatigue severity scale (FSS) questionnaire, which did not show any significant reduction ($p = 0.28$) in the intervention group compared with placebo[39]

Regarding the evaluation of the Gokbel et al., analysis by FI did not show any beneficial effects ($p > 0.05$) of supplementation with CoQ10 in reduction of fatigue during exercise. In this RCT study, 15 sedentary men randomized to receive 100 mg/day CoQ10 or placebo for 2 months.[37]

3.3.2. The effects of CoQ10 supplementation in patients with fibromyalgia

The effect of CoQ10 supplementation on fatigue in fibromyalgia subjects was examined in 4 RCT and 1 quasi-experimental study.

In 2012, Cordero et al. conducted a quasi-experimental study and showed a significant reduction ($p < 0.001$) in fibromyalgia patients fatigue, which assessed by Fibromyalgia Impact Questionnaire (FIQ) and VAS. In this study, 35 females (44.8 ± 9 years old) patients recruited and divided into intervention group ($n = 10$) to receive 300 mg/day CoQ10 and control to receive placebo for 3 months.[33]

The effect of CoQ10 was also investigated on clinical and molecular parameters in fibromyalgia. In this RCT study 20 female patients (> 18 years old) with fibromyalgia randomly assigned to either intervention group to receive 300 mg/day CoQ10 or control to receive placebo for 40 days. FIQ was used to assess participant's fatigue and results showed a significant reduction ($p < 0.01$) of fatigue in the intervention group compared to control.[31]

Furthermore, Miyamae et al. evaluated the efficacy of ubiquinol-10 supplementation in patients with juvenile fibromyalgia. In this study, 75 patients (13.1 ± 2.45 years old) randomly allocated intervention group to receive 100 mg/day CoQ10 or control to receive placebo for 3 months. Chalder's Fatigue Scale was used to assess participants fatigue status showed a significant improvement ($p < 0.05$) in the fatigue scores of participants after 3 months.[41]

In another study, 35 female patients (45.75 ± 4.5 years old) recruited and randomly allocated to the intervention group to receive 300 mg/day CoQ10 supplement or control group to receive placebo for 3 months. The results of FIQ score revealed a significant reduction of fatigue ($p < 0.001$) in fibromyalgia patients compared to control.[32]

Results of another study with cross-over design suggested the efficacy of oral supplementation with water-soluble form of CoQ10 among 22 female patients (53 ± 9.1 years old) with fibromyalgia who receive 400 mg/day CoQ10 for 3 months. The results of VAS showed a significant reduced fatigue ($p < 0.05$) in CoQ10 group compared with placebo.[15]

3.3.3. The effects of CoQ10 supplementation in patients with statin-associated myopathy

The effect of CoQ10 supplementation on fatigue in patients with statin-associated myopathy was examined in 2 clinical trials.

In 2013, Fedacko et al. evaluated the benefits of CoQ10 administration in patients with statin associated myopathy. Sixty patients (57.5 ± 10.65) enrolled and randomly allocated to the intervention group to receive 200 mg/day CoQ10 or control to receive placebo for 3 months. The results of VAS revealed significant reduction ($p < 0.01$) in patient's tiredness treated with CoQ10.[34]

Another study was conducted to assess the effects of CoQ10 supplementation combined with statin discontinuation on fatigue. Fifty patients (66 years old) who were on statin drug therapy recruited for this study and discontinued statin therapy and supplemented with 240 mg/day CoQ10 for 22 months. The prevalence of fatigue decreased from 84% on the initial visit to 16% at the end of study, which showed a significant reduction[38]

3.3.4. The effects of CoQ10 supplementation in patients with the other fatigue-related disease

The effect of CoQ10 supplementation on fatigue in patients with

Table 1
Characteristics of included studies.

Author, Year	Location	Sample size	Age (Mean ± SD)	Duration	Study Design	Study Population	DAM	FAM	Dose of Q_{10}	P-value	Result
Mizuno et al., 2008	Japan	8M/9F	37.5 ± 9.9	2 × 8 d	RCT-Cross over	Healthy subjects	–	VAS	100 & 300	< 0.01	Fatigue reduced significantly with 300 mg/d of Q_{10}
Gharahdaghi et al., 2013	Iran	16M	21.87 ± 1.58	1 m	RCT	Healthy subjects	FFQ, 24-h recall, food record	FI	300	> 0.05	NS
Lee et al., 2010	Korea	51 (M & F)	42.6 ± 11.25	3 m	RCT	Healthy subjects	–	FSS	200	0.28	NS
Gokbel et al., 2010	Turkey	15 M	19.9 ± 0.9	2 × 2 m	RCT-Cross over	Healthy subjects	–	FI	100	> 0.05	NS
Cordero et al., 2012	Spain	35F	44.8 ± 9	3 m	Quasi-experimental	Fibromyalgia	–	FIQ, VAS	300	< 0.001 < 0.001	Fatigue reduced significantly
Cordero et al., 2013	Spain	20F	> 18	40 d	RCT	Fibromyalgia	–	FIQ	300	< 0.01	Fatigue reduced significantly
Miyamae et al., 2013	Japan	39 M/38F	13.1 ± 2.45	3 m	RCT	Fibromyalgia	–	CFS	100	< 0.05	Fatigue reduced significantly
Cordero et al., 2012	Spain	35F	45.75 ± 4.5	3 m	RCT	Fibromyalgia	–	FIQ	300	< 0.001	Fatigue reduced significantly
Di Pierro et al., 2016	Italy	22F	53 ± 9.1	2 × 3 m	RCT-Cross over	Fibromyalgia	–	VAS	400	< 0.05	Fatigue reduced significantly
Fedacko et al., 2013	Slovakia	19 M/41F	57.5 ± 10.65	3 m	RCT	Statin-associated myopathy subjects	–	VAS	200	< 0.01	Fatigue reduced significantly
Langsjoen et al., 2005	USA	(50) 58% M/ 42% F	66 (44-84)	22 m	Open-Label study	Statin-associated myopathy subjects	–	–	240	–	Fatigue reduced significantly
Peel et al., 2015	Australia	32 M/69F	69.85 ± 8.3	2 m	RCT	Poliomyelitis	–	MAF FSS	100	0.36 0.74	NS
Sanoobar et al., 2015	Iran	4M/41F	32 ± 7.65	3 m	RCT	Multiple sclerosis	3-day food record	FSS	500	0.001	Fatigue reduced significantly
Berman et al., 2004	Israel	28 M/4F	54.6 (40-67)	3 m	RCT	End-stage heart failure	–	FSS	60	< 0.001	Fatigue reduced significantly
Fukuda et al., 2016	Japan	5M/15F 7M/25F	36.8 ± 6.88 37.15 ± 8.93	2 m 4 m	Open-Label study RCT	Chronic fatigue syndrome	–	CFS	150	> 0.05	NS
Lesser et al., 2013	USA	236F	51 (28-85)	3 m	RCT	Breast Cancer subjects	–	POMS-F FACIT-F LASA-F	300	0.25 0.96 0.26	NS

DAM: Dietary Assessment Method, FAM: Fatigue Assessment Method, VAS: Visual Analog Scale, FI: Fatigue Index, FSS: Fatigue Severity Scale, FIQ: Fibromyalgia Impact Questionnaire, CFS: Chalder's Fatigue Scale, MAF: Multidimensional Assessment of Fatigue, POMS-F: Profile of Mood States-Fatigue, FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue, LASA-F: Linear Analog Scale Assessment – Fatigue, FFQ: Food Frequency Questionnaire.

Table 2
Quality assessment of included studies.

Studies	Random sequence generation	Allocation concealment	Selective reporting	Other bias	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Quality
Mizuno et al., 2008	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Poor quality
Gharahdaghi et al., 2013	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Poor quality
Lee et al., 2010	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Poor quality
Gokbel et al., 2010	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Poor quality
Cordero et al., 2012	High risk	High risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Poor quality
Cordero et al., 2013	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Poor quality
Miyamae et a., 2013	High risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Poor quality
Cordero et al., 2012	Unclear risk	Unclear risk	Low risk	Unclear risk	High risk	Low risk	Low risk	Poor quality
Di Pierro et al., 2016	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Fair quality
Fedacko et al., 2013	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Poor quality
Langsjoen et al., 2005	High risk	High risk	Low risk	Unclear risk	High risk	Unclear risk	Low risk	Poor quality
Peel et al., 2015	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Sanoobar et al., 2015	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Poor quality
Berman et al., 2004	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Fukuda et al., 2016	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Good quality
Lesser et al., 2013	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Poor quality

poliomyelitis, end-stage heart failure, breast cancer, multiple sclerosis and chronic fatigue syndrome was examined in 5 clinical trials.

Peel et al. conducted an RCT study to determine the efficacy of CoQ10 supplementation to alleviate fatigue in the late-onset sequelae of poliomyelitis. One-hundred and one participants (69.85 ± 8.3 years old) randomly assigned to receive 100 mg/day CoQ10 or placebo for 2 months. FSS and Multidimensional Assessment of Fatigue (MAF) were used to assess fatigue status which both failed to show any statistically significant ($p > 0.05$) reduction in fatigue.[42]

Based on another investigation, fatigue symptoms had a significant reduction ($p < 0.001$) in patients with multiple sclerosis (32 ± 7.65 years old) after receiving 500 mg/day CoQ10 for 3 months Fatigue symptoms were quantified by FSS.[42]

Another trial which was conducted by Berman et al. examined the effects of CoQ10 supplementation in patients with end-stage heart failure awaiting cardiac transplantation. In this study, thirty-two patients (54.6 years old) enrolled and randomly assigned to either intervention group to receive 60 mg/day CoQ10 or control to receive placebo for 3 months. The results of FSS revealed significant reduction ($p < 0.001$) in fatigue symptoms in the intervention group compared with control.[30]

However, evaluation of Fukuda et al. did not support the efficacy of CoQ10 supplementation in patients with chronic fatigue syndrome (CFS) using an open-label study and an RCT study. Twenty patients (36.8 ± 6.88 years old) randomly were enrolled in an open-label study and supplemented with 150 mg/day CoQ10 for 2 months. Thirty-two patients (37.15 ± 8.93) with CFS randomly assigned to receive either 150 mg/day CoQ10 or placebo for 4 months in an RCT study. Fatigue status analyzed by CFS, and the results of both study failed to reveal any significant improvements ($p > 0.05$) in fatigue after supplementation with CoQ10.[35]

Similarly, the last study did not show any significant efficacy ($p > 0.05$) for CoQ10 supplementation in fatigue reduction in newly diagnosed patients with breast cancer. In this RCT, 236 females (51 years old) with newly diagnosed breast cancer were enrolled and randomized to receive either 300 mg/day CoQ10 or placebo for 3 months. Fatigue assessed by Profile of Mood States-Fatigue (POMS-F), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) and Linear Analog Scale Assessment – Fatigue (LASA-F).[40]

4. Discussion

To the best of our knowledge, no systematic review has been published to assess the effects of CoQ10 supplementation on fatigue. Therefore, we gathered all the interventional studies, which assessed the efficacy of CoQ10 on fatigue status.

First subgroup included healthy individuals whom CoQ10 supplementation failed to reveal beneficial effects on fatigue [36,37,39] except one study.[3] All the articles in this subgroup ranked as poor quality but based upon the sample size and duration of each study, three papers, which did not show any significant results, had more powerful methodology compared with the other one. Furthermore, it seems that there are not any differences regarding the dosage of administered CoQ10 in healthy subjects. One of the accepted mechanisms in the etiology of fatigue and the effects of CoQ10 in improvements this comorbidity is oxidative stress. Evidence suggests that ROS is responsible for exercise-induced protein oxidation and can be a factor in development of physical fatigue. To protect against oxidative damage caused by exercise, muscle cells contain complex mechanisms of endogenous cell defense to eliminate oxygen species. Additionally, dietary antioxidants, CoQ10, communicate with endogenous antioxidants create a collaborative network of antioxidants[3]

A probable explanation for ineffectiveness of CoQ10 supplementation on fatigue in healthy subjects might be due to the baseline and change percentage of CoQ10 plasma level. That means not only the administered CoQ10 dosage is important, but also it is more important

which CoQ10 could change the level of plasma ubiquinol after study to exert a beneficial impact on fatigue status[3,45]

Second subgroup consists of fibromyalgia patients whom all the papers in this category proved the efficacy of CoQ10 in fatigue reduction.[15,31–33,41] The quality of these studies ranked as low[3,15,30,39] except one.[15] There are several pathophysiological processes described the etiology of fibromyalgia, including oxidative stress, mitochondrial dysfunction, bioenergetics alteration and inflammatory cascades which in all of them AMP-activated protein kinase (AMPK) plays a key regulatory role.[15,32] AMPK is an enzyme evolved in maintaining cellular energy homeostasis and reported to be down regulated in fibromyalgia patients.[31,46] It has been shown *in vitro* and *in vivo* studies that CoQ10 induced AMPK activation and consequently, improves clinical symptoms of fibromyalgia patients[15,38,47] Based upon the results of included studies, it might be a practical guide to administer 300 mg/day CoQ10 in patients with fibromyalgia.

Third subgroup included the effects of CoQ10 supplementation in patients with statin-associated myopathy. Two studies in this section revealed a beneficial effect of CoQ10 in relieving fatigue, which both of them ranked as poor quality studies[34,38] Statin-associated myopathy mechanisms are still unclear, but possibly consist of decreased sarcolemmal cholesterol, reduction in small guanosine triphosphate-binding proteins, increased intracellular lipid production and lipid myopathy, increased myocellular phytosterols, and reduction in mitochondrial CoQ10[48] In more details, statin drugs inhibit hydroxyl-methylglutaryl coenzyme A (HMG-CoA) reductase, a rate-limiting enzyme in farnesyl pyrophosphate and cholesterol synthesis. On the other hand, farnesyl pyrophosphate is essential for CoQ10 biosynthesis and could explain the link between statins and CoQ10 deficiency.[49] Based on included studies it seems CoQ10 supplementation (200 mg/day) is a good choice for patients received statins drug to prevent or relief statin-associated myopathy.[31,36]

The last subgroup consists of CoQ10 supplementation in different pathological condition like: poliomyelitis, multiple sclerosis, end-stage heart failure, chronic fatigue syndrome and breast cancer-related fatigue. These studies were ranked as good[30,35,42] and poor quality[40,43] but lack of sufficient study makes it difficult to draw a firm link between these pathological conditions and CoQ10. Inflammation might be another explanation for disease-related fatigue. It has been shown that TNF-alpha mRNA expression increased in patients suffered from fatigue. CoQ10 has an antioxidant activity which could activate antioxidant enzymes like catalase, superoxide dismutase and glutathione peroxidase. Furthermore, it could decrease the marker of DNA oxidative damage, for example, malondialdehyde and 8-hydroxyl-2-deoxyguanosine.[43]

There are some limitations to this study that should be taken into account. First, significant heterogeneity was present between included studies. Heterogeneity may be explained by different assessment methods of fatigue, different dosage of administered CoQ10 and different populations. Second, most of the included studies were ranked as low quality which this negative point alongside with high between studies, heterogeneity has prevented us from doing meta-analysis.

There is no previous systematic review assessed the beneficial effects of CoQ10 supplementation on fatigue status in different population which this point is our study strength.

5. Conclusion

According to what have been discussed, we found that CoQ10 supplementation could alleviate fatigue but differences between studies population should be taken into account. It seems CoQ10 has better therapeutic effects in statin-related fatigue and fibromyalgia patients compared with the other disease related fatigue. Finally, in order to draw a firm link between CoQ10 and fatigue, more clinical trials with adequate sample size and better methodology should be done.

Conflict of interest

None.

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