Archives of Medical Research 46 (2015) 527–533

ORIGINAL ARTICLE

Effects of Coenzyme Q_{10} Supplementation on Inflammatory Cytokines (TNF-α, IL-6) and Oxidative Stress in Rheumatoid Arthritis Patients: A Randomized Controlled Trial

Hadi Abdollahzad,[a] Mir Amir Aghdashi,[b] Mohammad Asghari Jafarabadi,[c] and Beitollah Alipour[d]

[a]*Students' Research Committee, Faculty of Nutrition, Tabriz University of Medical Sciences, Tabriz,* [b]*Department of Rheumatology, Faculty of Medicine, Urmia University of Medical Sciences, Urmia,* [c]*Road Traffic Injury Research Center,* [d]*Department of Community Nutrition, Faculty of Nutrition, Tabriz University of Medical Sciences, Tabriz, Iran*

Received for publication May 31, 2015; accepted August 25, 2015 (ARCMED-D-15-00393).

Backgrounds and Aims. Overproduction of proinflammatory cytokines is a main trait of rheumatoid arthritis. Coenzyme Q_{10} (CoQ_{10}), an endogenous antioxidant, has shown anti-inflammatory effects in some diseases. In this study we aimed to assess the effects of CoQ_{10} supplementation on cytokines generation and oxidative stress in rheumatoid arthritis.

Methods. In this double-blind, randomized controlled clinical trial, 44 patients with rheumatoid arthritis were recruited. Twenty two patients received 100 mg/day capsules of CoQ_{10} and 22 patients took placebo for 2 months. At the beginning and the end of the intervention, 7 mL of fasting blood was taken from patients to measure malondialdehyde (MDA), total antioxidant capacity (TAC), interleukin (IL)-6 and tumor necrosis factor alpha (TNF-α).

Results. At the end of the study, serum MDA significantly decreased in supplemented group (mean difference = −1.47 nmol/mL; 95% confidence interval (CI), −2.52 to −0.43; $p = 0.008$). CoQ_{10} also suppressed overexpression of TNF-α (difference in median was +1.1 in placebo vs. +0.03 in CoQ_{10} group; $p = 0.033$). There was no significant difference in TAC and IL-6 levels between groups.

Conclusions. This study showed beneficial effects of CoQ_{10} supplementation on inflammatory cytokines and oxidative stress in rheumatoid arthritis patients. © 2015 IMSS. Published by Elsevier Inc.

Key Words: Coenzyme Q_{10} (CoQ_{10}), Ubiquinol, Inflammatory cytokines, Oxidative stress, Rheumatoid arthritis.

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease in which the synovium is the first affected constitution (1). Although each articulation may be involved, symmetrical engagement of small joints in the hands and feet is more common (2,3). The main etiology of the disease is unknown; it appears that environmental factors initiate the immune cells response in genetically predisposed individuals. Stimulation of the immune system leads to secretion of a large number of proinflammatory cytokines (3). Cytokines may be produced by nearly every cell, but mostly act locally on cell receptors and have high potency (4). Their production gives rise to an inflammatory cascade. One of the most important elements in this cascade is overexpression of tumor necrosis factor-alpha (TNF-α). TNF-α causes synovitis, articular destruction and overproduction of other cytokines, especially interleukin (IL)-6 which, in turn, leads to further inflammation and joint degradation (5). Attention

Address reprint request to: Beitollah Alipour, PhD, Department of Community Nutrition, Faculty of Nutrition, Tabriz University of Medical Sciences, East Azarbaydjan, P.O. Box 5166614711, Attar Neyshabouri, Tabriz, Islamic Republic of Iran; Phone: (+98) 41 33357580; FAX: (+98) 41 33340634; E-mail: alipourb@tbzmed.ac.ir or abdollahzad@kums.ac.ir

0188-4409/$ - see front matter.
http://dx.doi.org/10.1016/j.arcmed.2015.08.006

to the role of TNF-α and IL-6 in RA comes from *in vitro* studies where they showed potential for bone and cartilage breakdown (6).

During the inflammation, immune cells (neutrophils) generate pro-oxidant substances such as reactive oxygen species (ROS) (7). In addition, ROS can be generated via mitochondria as a byproduct of electron transport chain (ETC) during adenosine triphosphate (ATP) synthesis (8). ROS, especially mitochondrial ROS (MtROS), is reciprocally implicated in secretion of proinflammatory cytokines (8,9). Regardless of the origin of ROS, it was also associated with DNA, proteins and membrane lipid damage (10). Incessant generation of ROS in involved joints leads to depletion of antioxidant systems (7). Levels of certain antioxidants are lower in both serum (11) and synovial fluid (7) of RA patients compared to healthy persons. These changes all have positive feedback on inflammation and resulting joint erosion.

New treatment strategies based on blockade of cytokine pathways in late stages of RA are progressing. In spite of their benefits, longtime utilization of these blocking agents has indicated side effects (12). Our role as nutritionists is to find nutraceuticals with similarity in function to these agents and with the least disadvantages. It has been demonstrated that antioxidant nutrients exert anti-inflammatory activity (7). Coenzyme Q_{10} (CoQ_{10}) or ubiquinone is a lipid-soluble vitamin-like antioxidant naturally found in the diet and can also be synthesized endogenously by all cells of our body. It is one of the key components in ATP production in ETC. CoQ_{10} protects membranes against oxidation, regenerates and reduces vitamins E and C and enzymatic antioxidant systems, and modulates prostaglandin metabolism (13–16).

Studies in cells (17) and animal models (18) revealed anti-inflammatory effects of CoQ_{10}. Recent studies also indicated the usefulness of this micronutrient against inflammation in coronary artery disease, neurodegenerative diseases and diabetic patients (19–21). To our knowledge, there is no clinical study reporting the effects of CoQ_{10} on inflammation and oxidative stress in RA. For this reason, our research team was encouraged to investigate the effects of oral supplementation with this anti-inflammatory agent on serum concentration of inflammatory biomarkers (TNF-α, IL-6) and oxidative stress in RA patients.

Materials and Methods

Study Design and Ethics Statements

After the ethics committee of Tabriz and Urmia Universities of Medical Sciences approved the study in accordance with the Helsinki Declaration (the ethical codes of study in Tabriz and Urmia were 92113 and umsu.rec.1392.152, respectively), this double-blind, randomized controlled clinical trial was conducted at the Imam Hospital and Sahand Clinics affiliated with Urmia University of Medical Sciences. This study was registered in the Iranian registry of clinical trials (ID: IRCT201311014105N16).

Sample Size and Randomization

With a standard deviation of 1.08 from a previous study (22) to detect the smallest difference in malondialdehyde (MDA) means (0.97 nmol/mL) based on 95% confidence interval and a power of 80%, sample size was determined as 20 patients for each group. In regard to dropout (35%), the sample size was considered to be 27 persons per group. Blocked randomization was run through Random Allocation Software (RAS) to assign patients into two parallel groups (1:1) with four participants in each block.

Recruitment of Patients

According to 1987 American College of Rheumatology (ACR) criteria, 54 RA patients (18–65 years) diagnosed at least 6 months ago with moderate and severe disease activity (DAS 28 >3.2) were recruited from January to June 2014. Patients with a history of diabetes mellitus, renal, liver, thyroid and infectious diseases, smoking, consumption of antioxidants or omega-3 fatty acid supplements in the previous month, persons taking warfarin or oral contraceptive pills, and pregnant or lactating women were excluded. All participants signed informed written consent.

Intervention

Patients received daily a 100 mg capsule of CoQ_{10} (Health Burst Inc., USA) ($n = 27$) or placebo (wheat starch, identical in size, color and shape to supplement) ($n = 27$) for 2 months in addition to their conventional medications (methotrexate, sulfasalazine, hydroxychloroquine, prednisolone). They were asked to take the capsule along with a meal and not to change their usual diet and physical activity during the study. Patients completed 3-day food records during two steps: 1 week prior to beginning and at the final week of the intervention. Dietary intakes were analyzed using modified Nutritionist IV software for Iranian foods.

At least 2 weeks supplementation with 90 mg/day is needed to reach steady state levels of CoQ_{10} in serum (23). Considering that RA patients routinely report to the rheumatologist in the mentioned clinics every 2 months and that the long intervention period may decrease the rate of adherence (24), we designed our intervention using 100 mg/day CoQ_{10} for 2 months. Whereas measuring CoQ_{10} concentration in serum better reveals compliance of intervention, due to budgetary considerations we could not measure its levels in the present study. Adherence to the prescribed interventions was pursued every 14 days

via a phone interview by questioning about side effects and time and number of capsules consumed in a day during the study, at the end of intervention it was also calculated using the following equation:

$$\text{Compliance} = \text{consumed capsules at the end of study} / \text{received capsules at the entry} * 100$$

Biochemical Measurements

Seven mL of venous blood was taken from patients after fasting for 10−12 h at baseline and after 2 months of intervention in the laboratory of Imam Hospital. Two-mL blood samples were used to measure erythrocyte sedimentation rate (ESR) and the remainder was immediately centrifuged to separate serum. Serum samples were stored at −80°C until analysis. Serum IL-6 and TNF-α were assayed by relevant ELISA kit (Human IL-6 ELISA kit and Human TNF-α ELISA kit; Orgenium Inc., Finland). Serum total antioxidant capacity (TAC) was assessed using ELISA Kit (TAC ELISA kit; LDN Labor Diagnostika Nord GmbH and Co. KG, Germany). Spectrophotometric method was used to measure serum MDA by its reaction with thiobarbituric acid (25).

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences v. 16 (SPSS Inc.). Normality of variables was evaluated by Kolmogorov-Smirnov test. Paired sample *t*-test and Wilcoxon were used to examine differences in each group; independent sample *t*-test and Mann-Whitney tested differences between groups. Analysis of covariance (ANCOVA) assessed differences between groups at the end of the study after adjustment for changes of disease duration, medication, and total energy intake. Data were expressed as mean ± standard deviation (SD) for normally distributed variables and median (interquartile range [IQR]) for non-normally distributed variables; $p < 0.05$ was considered significant.

Results

As shown in Figure 1, 45 patients (39 females and six males) completed the study. Because of the low amount

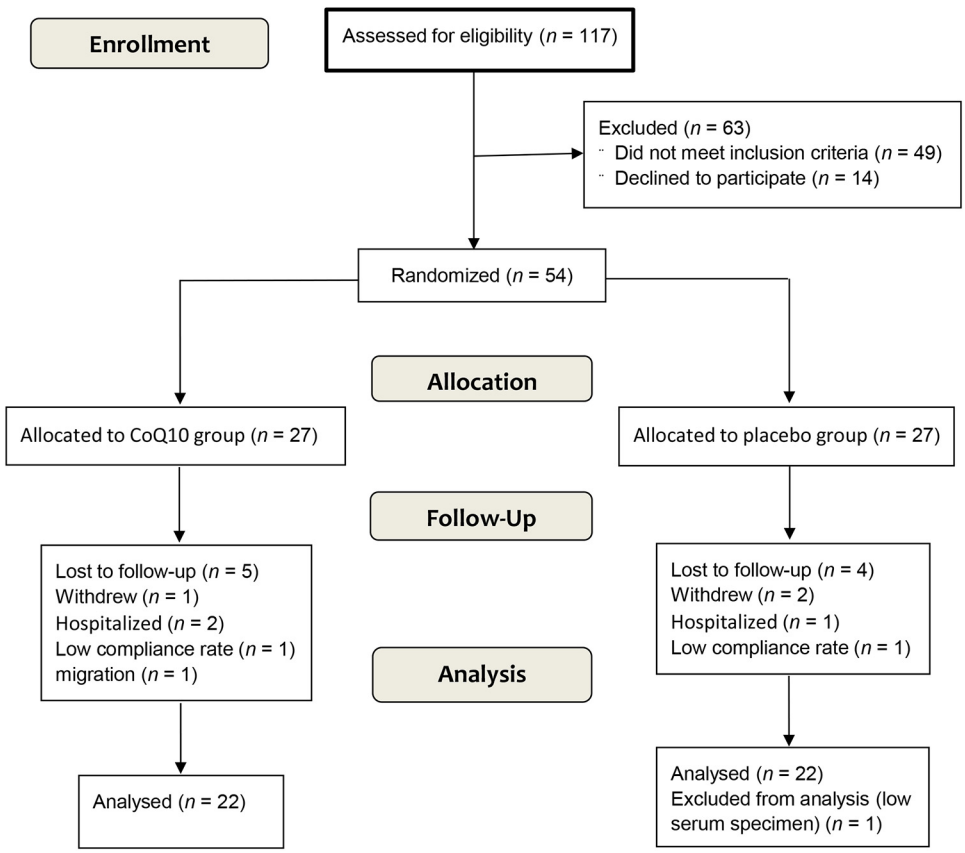

Figure 1. CONSORT flow diagram of supplementation with 100 mg/day coenzyme Q_{10} for 2 months in rheumatoid arthritis patients. (A color figure can be found in the online version of this article.)

Table 1. Some characteristics of RA patients at baseline

Variables	Placebo group (n = 22)	CoQ_{10} group (n = 22)
Age (years)	50.41 ± 11.28	48.77 ± 11.58
Disease duration (years)	6.94 ± 6.50	6.91 ± 5.87
Female (n, %)	20 (87.0)	19 (86.4)
Marital status (n, %)		
Married	21 (95.5)	20 (90.9)
Single	1 (4.5)	2 (9.1)
Physical activity (n, %)		
Low	2 (9.1)	2 (9.1)
Moderate	20 (90.9)	19 (86.4)
High	0 (0)	1 (4.5)
Medications (n, %)		
Methotrexate	21 (95.5)	21 (95.5)
Sulfasalazine	20 (90.9)	20 (90.9)
Hydroxychloroquine	15 (68.2)	14 (63.6)
Prednisolone	20 (90.9)	22 (100)
Folic acid	22 (100)	22 (100)
Calcium D	19 (86.4)	20 (90.9)
Others	14 (63.6)	11 (50)

RA, rheumatoid arthritis.
Data are presented as mean ± standard deviation (SD), number (percentage). There was no significant difference between groups.

of serum specimen, one patient in the placebo group was excluded from analysis. Age and disease duration of participants as mean ± SD were 49.59 ± 11.33 and 6.92 ± 6.12 years, respectively. Some characteristics of patients at the beginning of the study are shown in Table 1 and were not significantly different between placebo and CoQ_{10} groups. Dietary intake of antioxidant nutrients such as β-carotene, vitamins A, C, E, α-tocopherol, zinc, and selenium were assessed and showed no differences between groups at baseline and did not change (except vitamin C) at the end of 2 months (Table 2).

Table 3 shows serum levels of TAC and MDA during the two steps of measurement and their changes throughout the study. MDA concentration in the CoQ_{10} group significantly decreased at the end of the intervention (mean difference = −1.47 nmol/mL; 95% confidence interval (CI), −2.52 to −0.43; p <0.05). CoQ_{10} led to a significant decrease in MDA compared with placebo (p <0.05). IL-6 and TNF-α values as median (IQR) are shown in Table 4. Serum level of TNF-α regarding its baseline value increased significantly in the placebo group (p <0.05). Comparison of the TNF-α changes in patients who received CoQ_{10} supplement and placebo showed a significant difference (median difference was +0.03 vs. +1.1, respectively; p <0.05). In this interventional study, CoQ_{10} supplementation did not reveal any significant effect on serum TAC and IL-6 concentration. Adverse effects of CoQ_{10} were not seen during the intervention.

Discussion

The purpose of the current study was to evaluate the effects of oral CoQ_{10} supplementation on serum concentration of MDA, TAC, IL-6 and TNF-α in RA patients. This study indicated that CoQ_{10} supplementation for 2 months in RA patients led to a significant decrease in MDA compared with placebo. Also, a nonsignificant increase was observed in TAC in both groups. Although the augmentation was larger in the supplemented group than in placebo group (+0.19 vs. +0.14) the difference between groups was not significant.

MDA level as an indicator of free radical-induced injuries or oxidative stress (26) is much higher and antioxidant levels are much lower in RA patients than healthy persons (27). Numerous investigators evaluated effects of CoQ_{10} on oxidative stress and inflammation in other diseases. Lee et al. observed a significant increase in plasma Q_{10}, catalase (CAT), superoxide dismutase (SOD) and a significant decline in serum MDA level after 12 weeks administration of 150 mg/day CoQ_{10} in patients with coronary artery disease (CAD); however, they could not see the same effect using 60 mg/day of CoQ_{10} (26). Also, in their investigations, 300 mg/day CoQ_{10} raised plasma vitamin E and glutathione peroxidase (GP_X) levels in addition to reported effects via 150 mg/day of supplement (28). In

Table 2. Dietary antioxidants intake in RA patients before and after 2 months supplementation with CoQ_{10}

Micronutrients daily intake	Placebo group (n = 22)		CoQ_{10} group (n = 22)	
	Baseline	Endpoint	Baseline	Endpoint
β-Carotene (μg)	614.9 ± 827.2	476.1 ± 598.8	512.5 ± 376.2	511.6 ± 622.7
Vitamin A (μg RAE)	1003.8 ± 901.3	1018.5 ± 782.8	1122.8 ± 762.0	803.9 ± 751.9
Vitamin C (mg)	96.0 ± 53.6	63.4 ± 30.2	109.8 ± 60.4	90.8 ± 53.2
Vitamin E (mg)	2.5 ± 0.9	2.9 ± 1.8	3.8 ± 1.5	3.1 ± 1.4
α-Tocopherol (mg)	6.9 (5.9–8.3)	7.3 (5.3–10.1)	7.8 (6.8–10.1)	7.6 (6.0–10.1)
Zinc (mg)	7.6 ± 2.6	7.9 ± 3.2	8.1 ± 2.7	7.3 ± 2.2
Selenium (μg)	77.5 ± 30.9	86.0 ± 37.6	87.4 ± 40.4	74.0 ± 34.3

RA, rheumatoid arthritis; RAE, retinol activity equivalent.
Data are presented as mean ± standard deviation (SD) except α-tocopherol, which was presented as median (interquartile range). There was no significant difference between (except baseline of vitamin E and endpoint of vitamin C) and within groups.

Table 3. Serum levels of oxidative stress-related markers in RA patients before and after 2 months supplementation with CoQ_{10}

Variables		Placebo group (n = 22)	CoQ_{10} group (n = 22)	p
TAC (mmol/L)	Baseline	0.81 ± 0.47	0.77 ± 0.55	0.790
	End point	0.96 ± 0.47	0.96 ± 0.58	0.744
	p	0.275	0.312	
	Mean changes	0.15 ± 0.62	0.19 ± 0.87	0.847
MDA (nmol/mL)	Baseline	3.07 ± 1.71	3.61 ± 1.51	0.274
	End point	3.16 ± 1.71	2.13 ± 1.44	0.006***
	p	0.755	0.008*	
	Mean changes	0.09 ± 1.39	−1.47 ± 2.36	0.009**

RA, rheumatoid arthritis; TAC, total antioxidant capacity; MDA, malondialdehyde.
Data are presented as mean ± standard deviation (SD).
Data were analyzed by *paired t-test, **Student t-test, and ***ANCOVA test after adjustment for baseline measurements (disease duration, dietary intake, and medication); p value <0.05 was considered significant.

another study, Sanoobar et al., following supplementation with 500 mg/day CoQ_{10} for 12 weeks, found a meaningful decrease in serum MDA and a rise in SOD of multiple sclerosis (MS) patients; however, no effect on TAC was seen. These authors declared that availability of various methods of TAC assessment may be responsible for dissimilarity of their finding from other authors (29). Singh et al. reported that supplementation of 120 mg/day CoQ_{10} in heart disease patients after 4 weeks (30) and 8 weeks (31) led to a significant decrease in MDA, lipid peroxidation [thiobarbituric acid reactive substances (TBARS)], and diene conjugates. A significant increase was also seen in plasma antioxidant vitamins (E, C, A and β-carotene) in these studies. Kumar et al. (32) indicated that daily consumption of carni Q-gel (270 mg CoQ_{10} and 2250 mg L-carnitine) for 12 weeks resulted in elevation of serum Q_{10} and reduction of MDA and TBARS in patients with heart failure. In another study, Farhangi et al. (33) showed no significant change in MDA and TAC after 4 weeks supplementation with 100 mg/day CoQ_{10} in patients with nonalcoholic fatty liver disease.

Table 4. Serum levels of inflammatory markers in RA patients before and after 2 months supplementation with CoQ_{10}

Variables		Placebo group (n = 22)	CoQ_{10} group (n = 22)	p
IL-6 (pg/mL)	Baseline	0.09 (0.05−5.72)	0.45 (0.04−18.15)	0.769
	End point	0.09 (0.06−47.10)	0.07 (0.04−9.32)	0.342
	p value	0.485	0.570	
TNF-α (pg/mL)	Baseline	3.36 (2.21−16.86)	3.36 (1.89−26.79)	0.916
	End point	4.45 (3.41−37.72)	3.39 (1.91−24.25)	0.033**
	p value	0.008*	0.858	

RA, rheumatoid arthritis; IL-6, interleukin 6; TNF-α, tumor necrosis factor-α.
Data are presented as median (interquartile range). Data were analyzed by *Wilcoxon Signed Ranks Test and **Mann-Whitney U test on parameter changes (after-before); p value <0.05 was considered significant.

Effects of CoQ_{10} have been examined in other circumstances. Administration of CoQ_{10} in athletes showed an increase in total antioxidant status (TAS) (34,35), CAT and a reduction in markers of DNA and lipid peroxidation (8-hydroxy-2′-deoxyguanosine [8OhdG], F_2-isoprostane) (35). Consistent with our results, Wang et al. (18) reported that cosupplementation of CoQ_{10} and vitamin E, despite elevation of TAS in baboons, culminated in no significant increase in comparison with vitamin E alone. Furthermore, inhibitory effect of CoQ_{10} on MDA formation has been shown in an *in vitro* study (36).

Serum/plasma elevation of CoQ_{10} levels after oral administration of the supplement (16,26,28,32), negative correlation between ubiquinol and MDA levels shown in observational studies (37,38), and free radical scavenging property of CoQ_{10} (30) may illustrate the likely effects of this antioxidant on MDA status. No effect of CoQ_{10} on TAC concentration may be attributed to its low dose in our study. It must be kept in mind that even though improvement of TAC with supplements is necessary, the extent of safety is not clear and a high increase may induce detrimental results in some conditions (39).

Increasing amount of inflammatory cytokines is the best defined characteristic of RA patients. Numerous approaches (medications and dietary interventions) have been introduced to treat RA patients and ameliorate the situation by reducing the executioner cytokines. We applied supplementation with CoQ_{10} to examine its anti-inflammatory effects claimed in previous reports (18,28). CoQ_{10} suppressed overproduction of TNF-α in CoQ_{10}-treated group and led to a significant change in comparison to placebo group. Although in our study the concentration of IL-6 decreased in the CoQ_{10} group, the reduction was not significant.

The effects of CoQ_{10} on inflammatory cytokines have previously been assessed. In one study in patients with MS, 500 mg/day CoQ_{10} supplementation for 12 weeks decreased serum levels of TNF-α and IL-6; however, there was no significant effect on anti-inflammatory cytokines such as transforming growth factor-beta (TGF-β) and IL-4 (40). In another study, 12-week consumption of carni Q-gel (270 mg/day CoQ_{10} and 2250 mg/day L-carnitine) in patients with heart failure reduced both TNF-α and IL-6 but did not alter IL-10 level (32). Lee et al. (21) found that administration of 60 mg/day CoQ_{10} did not lower plasma IL-6 in coronary artery disease (CAD), but 150 mg/day diminished its level after 12 weeks. Furthermore, in another study the same investigators reported that 300 mg/day CoQ_{10} in addition to IL-6 diminished TNF-α in CAD, whereas it did not change C-reactive protein (CRP) and adiponectin levels (28). Sachdanandam (41) showed that 100 mg/day CoQ_{10} in combination with tamoxifen decreased IL-6 and TNF-α levels in breast cancer patients.

Anti-inflammatory abilities of CoQ_{10} have been studied under other conditions. In agreement with the findings of the present study, Díaz-Castro et al. (35) found that in athletes who demonstrate overproduction of inflammatory cytokines during strenuous exercise, administration of CoQ_{10} reduced overexpression of TNF-α and had no effect on IL-6 values. Supplementation of 100 mg/day CoQ_{10} for 8 weeks in the study by Gökbel and colleagues (42) did not affect TNF-α and IL-6 concentration in healthy males. Lack of effect may be due to the reality that healthy subjects have normal levels of these cytokines. Diminishing effects of CoQ_{10} on TNF-α levels have been reported in animal and in *in vitro* studies by Fouad et al. (43), Schmelzer et al. (44), and Tawfik (45); the last researcher also noted that CoQ_{10} had a significant effect on IL-6 levels. Bauerova et al. (46) indicated that CoQ_{10} in a rat model of rheumatoid arthritis through decrease of lipid and protein oxidation (MDA-adducts, 4-hydroxy-2-nonenal [HNE]-adducts, and carbonyl) and of IL-1α could potentiate antioxidant and anti-inflammatory effects of methotrexate. In a study by Bessler et al. (17), production of IL-6 was not affected by incubation of peripheral blood mononuclear cells with CoQ_{10}, whereas TNF-α secretion significantly declined.

In our study the effect of CoQ_{10} in suppression of TNF-α overexpression without further decrease in IL-6 may be due to the fact that inflammatory cytokine production as previously mentioned is increased in rheumatoid arthritis or due in part to the low dose of supplement or short duration of the intervention. A presumptive mechanism by which CoQ_{10} exerts inhibitory effects on TNF-α secretion can be attributed to its capability in inhibition of nuclear factor-kappa B (NF-κB) signaling pathways (35,47). NF-κB is a family of transcriptional factors with beneficial effects in normal physiology. Dysregulation of NF-κB leads to inflammatory diseases, in particular rheumatoid arthritis and osteoarthritis; therefore, inhibition of NF-κB seems to be a logical objective in the treatment of these diseases (48).

There are at least two limitations to our study. First, we did not assay antioxidant enzymes. Because total antioxidant capacity does not contain all present antioxidants in the defense system and encompasses only free radical scavengers (49), measurement of enzymatic antioxidants will be helpful and can better describe the suitable influences of CoQ_{10} on the defense system. Second, we did not evaluate CoQ_{10} intake in patients because of inadequate information about the amount of this micronutrient in nutritional databanks.

In conclusion, our findings demonstrated that supplementation with 100 mg/day CoQ_{10} for 2 months has an important role in attenuating MDA and TNF-α levels. It appears that oral CoQ_{10} supplement can be applied as an adjunct treatment in rheumatoid arthritis patients. Evaluation of other parameters related to oxidative stress and inflammation including enzymatic and nonenzymatic antioxidants, different metabolites of oxidative stress, anti-inflammatory and other proinflammatory cytokine levels using longer clinical trials with different doses of CoQ_{10} in RA patients may be necessary to confirm results of the present study.

Acknowledgments

This research formed part of the Ph.D. thesis of Hadi Abdollahzad (No. D/38) and was supported by a grant from research vice chancellor of Tabriz University of Medical Sciences (No. 5/97/3196). We thank the research vice chancellor of Urmia University of Medical Sciences and Dr. Seyed Mostafa Seyed Mardani for collaboration in patient recruitment. We express our appreciation to all patients who participated in the study.

References

1. Gibofsky A. Overview of epidemiology, pathophysiology, and diagnosis of rheumatoid arthritis. Am J Manag Care 2012;18:S295–S302.
2. Comeau D, Heaton K, Gordon A. Rheumatology and musculoskeletal problems. In: Rakel RE, Rakel DP, eds. Textbook of Family Medicine. 8th ed. Philadelphia: Elsevier Saunders; 2011. pp. 648–689.
3. Firestein GS. Rheumatoid arthritis: etiology and pathogenesis of rheumatoid arthritis. In: Firestein GS, Budd R, Gabriel SE, et al, eds. Kelley's Textbook of Rheumatology. 9th ed. Philadelphia: Elsevier Saunders; 2012. pp. 1059–1108.
4. Malaviya AM. Cytokine network and its manipulation in rheumatoid arthritis. J Assoc Physicians India 2006;54 Suppl:15–18.
5. Scott DL, Wolfe F, Huizinga TWJ. Rheumatoid arthritis. Lancet 2010; 376:1094–1108.
6. Brennan FM, McInnes IB. Evidence that cytokines play a role in rheumatoid arthritis. J Clin Invest 2008;118:3537–3545.
7. Pattison DJ, Winyard PG. Dietary antioxidants in inflammatory arthritis: do they have any role in etiology or therapy? Nat Clin Pract Rheumatol 2008;4:590–596.
8. Li X, Fang P, Mai J, et al. Targeting mitochondrial reactive oxygen species as novel therapy for inflammatory diseases and cancers. J Hematol Oncol 2013;6:19.
9. Naik E, Dixit VM. Mitochondrial reactive oxygen species drive proinflammatory cytokine production. J Exp Med 2011;208:417–420.
10. Filippin LI, Vercelino R, Marroni N, et al. Redox signalling and the inflammatory response in rheumatoid arthritis. Clin Exp Immunol 2008;152:415–422.
11. Cerhan JR, Saag KG, Merlino LA, et al. Antioxidant micronutrients and risk of rheumatoid arthritis in a cohort of older women. Am J Epidemiol 2003;157:345–354.
12. Tayar JH, Suarez-Almazor ME. New understanding and approaches to treatment in rheumatoid arthritis. Br Med Bull 2010;94:201–214.
13. Kapoor P, Kapoor A. Coenzyme Q10—a novel molecule. J Indian Acad Clin Med 2013;14:37–45.
14. Bentinger M, Tekle M, Dallner G. Coenzyme Q—biosynthesis and functions. Biochem Biophys Res Commun 2010;396:74–79.
15. Turunen M, Olsson J, Dallner G. Metabolism and function of coenzyme Q. Biochim Biophys Acta 2004;1660:171–199.
16. Bhagavan HN, Chopra RK. Plasma coenzyme Q10 response to oral ingestion of coenzyme Q10 formulations. Mitochondrion 2007;7: S78–S88.
17. Bessler H, Bergman M, Blumberger N, et al. Coenzyme Q10 decreases TNF-α and IL-2 secretion by human peripheral blood mononuclear cells. J Nutr Sci Vitaminol 2010;56:77–81.
18. Wang XL, Rainwater DL, Mahaney MC, et al. Cosupplementation with vitamin E and coenzyme Q10 reduces circulating markers of inflammation in baboons. Am J Clin Nutr 2004;80:649–655.
19. Spindler M, Beal MF, Henchcliffe C. Coenzyme Q10 effects in neurodegenerative disease. Neuropsychiatr Dis Treat 2009;5:597.

20. Villalba JM, Parrado C, Santos-Gonzalez M, et al. Therapeutic use of coenzyme Q10 and coenzyme Q10-related compounds and formulations. Expert Opin Investig Drugs 2010;19:535−554.
21. Lee BJ, Huang YC, Chen SJ, et al. Effects of coenzyme Q10 supplementation on inflammatory markers (high-sensitivity C-reactive protein, interleukin-6, and homocysteine) in patients with coronary artery disease. Nutrition 2012;28:767−772.
22. Aryaeian N, Djalali M, Shahram F, et al. The effect of conjugated linoleic acids, vitamin E and their combination on lipid peroxidation in active rheumatoid arthritis. Iran J Public Health 2009;38:79−89.
23. Hosoe K, Kitano M, Kishida H, et al. Study on safety and bioavailability of ubiquinol (Kaneka QH™) after single and 4-week multiple oral administration to healthy volunteers. Regul Toxicol Pharmacol 2007;47:19−28.
24. Jin J, Sklar GE, Oh VMS, et al. Factors affecting therapeutic compliance: a review from the patient's perspective. Ther Clin Risk Manag 2008;4:269−286.
25. Kei S. Serum lipid peroxide in cerebrovascular disorders determined by a new colorimetric method. Clin Chim Acta 1978;90:37−43.
26. Lee BJ, Huang YC, Chen SJ, et al. Coenzyme Q_{10} supplementation reduces oxidative stress and increases antioxidant enzyme activity in patients with coronary artery disease. Nutrition 2012;28:250−255.
27. Chandankhede MS, Gupta MM. Oxidative stress and antioxidant status in patients with rheumatoid arthritis. Int J Biol Med Res 2013;4:3088−3090.
28. Lee BJ, Tseng YF, Yen CH, et al. Effects of coenzyme Q10 supplementation (300 mg/day) on antioxidation and anti-inflammation in coronary artery disease patients during statins therapy: a randomized, placebo-controlled trial. Nutr J 2013;12:142.
29. Sanoobar M, Eghtesadi S, Azimi A, et al. Coenzyme Q10 supplementation reduces oxidative stress and increases antioxidant enzyme activity in patients with relapsing-remitting multiple sclerosis. Int J Neurosci 2013;123:776−782.
30. Singh RB, Wander GS, Rastogi A, et al. Randomized, double-blind placebo-controlled trial of coenzyme Q10 in patients with acute myocardial infarction. Cardiovasc Drugs Ther 1998;12:347−353.
31. Singh R, Niaz M, Rastogi S, et al. Effect of hydrosoluble coenzyme Q10 on blood pressures and insulin resistance in hypertensive patients with coronary artery. J Hum Hypertens 1999;13:203−208.
32. Kumar A, Singh RB, Saxena M, et al. Effect of carni Q-gel (ubiquinol and carnitine) on cytokines in patients with heart failure in the Tishcon study. Acta Cardiol 2007;62:349−354.
33. Farhangi MA, Alipour B, Jafarvand E, et al. Oral coenzyme Q_{10} supplementation in patients with nonalcoholic fatty liver disease: effects on serum vaspin, chemerin, pentraxin 3, insulin resistance and oxidative stress. Arch Med Res 2014;45:589−595.
34. Leelarungrayub D, Sawattikanon N, Klaphajone J, et al. Coenzyme Q10 supplementation decreases oxidative stress and improves physical performance in young swimmers: a pilot study. Open Sports Med J 2010;4:1−8.
35. Díaz-Castro J, Guisado R, Kajarabille N, et al. Coenzyme Q_{10} supplementation ameliorates inflammatory signaling and oxidative stress associated with strenuous exercise. Eur J Nutr 2012;51:791−799.
36. Ahmadvand H, Mabuchi H, Kobayahi J, et al. Effects of coenzyme Q10 on LDL oxidation *in vitro*. Acta Med Iran 2013;51:12−18.
37. Lee BJ, Lin YC, Huang YC, et al. The relationship between coenzyme Q_{10}, oxidative stress, and antioxidant enzymes activities and coronary artery disease. Sci World J 2012;2012:792756.
38. Kaya Y, Çebi A, Söylemez N, et al. Correlations between oxidative DNA damage, oxidative stress and coenzyme Q_{10} in patients with coronary artery disease. Int J Med Sci 2012;9:621.
39. Verit FF, Erel O. Oxidative stress in nonobese women with polycystic ovary syndrome: correlations with endocrine and screening parameters. Gynecol Obstet Invest 2007;65:233−239.
40. Sanoobar M, Eghtesadi S, Azimi A, et al. Coenzyme Q_{10} supplementation ameliorates inflammatory markers in patients with multiple sclerosis: a double blind, placebo, controlled randomized clinical trial. Nutr Neurosci 2014;18:169−176.
41. Sachdanandam P. Antiangiogenic and hypolipidemic activity of coenzyme Q_{10} supplementation to breast cancer patients undergoing Tamoxifen therapy. Biofactors 2008;32:151−159.
42. Gökbel H, Gergerlioğlu HS, Okudan N, et al. Effects of coenzyme Q_{10} supplementation on plasma adiponectin, interleukin-6, and tumor necrosis factor-α levels in men. J Med Food 2010;13:216−218.
43. Fouad AA, Jresat I. Hepatoprotective effect of coenzyme Q_{10} in rats with acetaminophen toxicity. Environ Toxicol Pharmacol 2012;33:158−167.
44. Schmelzer C, Lorenz G, Lindner I, et al. Effects of coenzyme Q_{10} on TNF-α secretion in human and murine monocytic cell lines. Biofactors 2007;31:35−41.
45. Tawfik MK. Combination of coenzyme Q_{10} with methotrexate suppresses Freund's complete adjuvant-induced synovial inflammation with reduced hepatotoxicity in rats: effect on oxidative stress and inflammation. Int Immunopharmacol 2015;24:80−87.
46. Bauerova K, Paulovicova E, Mihalova D, et al. Combined methotrexate and coenzyme Q_{10} therapy in adjuvant-induced arthritis evaluated using parameters of inflammation and oxidative stress. Acta Biochim Pol 2010;57:347−354.
47. Schmelzer C, Lindner I, Rimbach G, et al. Functions of coenzyme Q_{10} in inflammation and gene expression. Biofactors 2008;32:179−183.
48. Roman-Blas J, Jimenez S. NF-κB as a potential therapeutic target in osteoarthritis and rheumatoid arthritis. Osteoarthritis Cartilage 2006;14:839−848.
49. Niki E. Assessment of antioxidant capacity *in vitro* and *in vivo*. Free Radic Biol Med 2010;49:503−515.