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ORIGINAL ARTICLE

Effects of coenzyme Q10 supplementation on matrix metalloproteinases and DAS-28 in patients with rheumatoid arthritis: a randomized, double-blind, placebo-controlled clinical trial

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Abstract

Objectives This study aimed to assess the effect of CoQ10 supplementation on serum matrix metalloproteinases (MMPs) and clinical parameters in rheumatoid arthritis (RA) patients.

Method In this randomized, double-blind, placebo-controlled trial, 54 RA patients who fulfilled the eligibility criteria (18–56 years, diagnosed at least 6 months ago, with DAS-28 > 3.2) were randomly assigned into two groups to receive 100 mg/day CoQ10 ($n = 27$) or placebo ($n = 27$) for 2 months. Serum MMP-1 and MMP-3 levels and clinical status using disease activity score in 28 joints (DAS-28) were assessed before and after supplementation. Data were analyzed using $\chi 2$, independent sample t test, paired t test, Wilcoxon, Mann-Whitney, and analysis of covariance.

Results A significant reduction was observed in both CoQ10 and placebo groups in the medians of serum MMP-1 (0.2 to 0.16, $P < 0.001$), (0.18 to 0.15, $P = 0.001$); swollen joint count (2 to 0, $P < 0.001$), (2 to 0, $P = 0.009$); and the means of DAS-28 (5.01 ± 1.21 to 2.34 ± 0.68, $P < 0.001$), (4.88 ± 0.96 to 4.04 ± 1.36, $P = 0.009$) respectively. Serum MMP-3 level increased significantly in placebo group (2.26 to 2.57, $P = 0.020$), and the MMP-3 changes between groups were significant ($P = 0.027$). Furthermore, significant reductions were only observed in ESR, pain score, and tender joint count in CoQ10 group compared with baseline ($P = 0.001$, $P < 0.001$, and $P < 0.001$, respectively). Significant differences were observed between two groups in DAS-28, pain score, and swollen and tender joint count after the intervention ($P < 0.001$, $P < 0.001$, and $P = 0.012$ and $P < 0.001$, respectively).

Conclusions It seems that CoQ10 may provide a new complementary approach for RA patients.

Key Points
- *CoQ10 supplementation in RA patients attenuated serum MMP-3 level.*
- *CoQ10 supplementation in RA patients improved clinical outcomes and ameliorated disease severity.*
- *CoQ10 may provide a new complementary approach for patients with RA.*

Keywords Clinical parameters · Clinical trial · Coenzyme Q10 · Matrix metalloproteinases · Rheumatoid arthritis

Abbreviations

ANCOVA	Analysis of covariance
BMI	Body mass index
CoQ10	Coenzyme Q10

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DAS-28	Disease activity score-28 joints
DMARDs	Disease-modifying anti-rheumatic drugs
ESR	Erythrocyte sedimentation rate
FIQ	Fibromyalgia Impact Questionnaire
hs-CRP	High-sensitivity C-reactive protein
IL-1β	Interleukine-1β
IL-6	Interleukine-6
MDA	Malondialdehyde
MMPs	Matrix metalloproteinases
MTX	Methotrexate
TNF-α	Tumor necrosis factor-alpha
VAS	visual analogue scale

Introduction

Rheumatoid arthritis (RA) is one of the most common autoimmune disorders that are characterized by inflammation, swelling, tenderness, and progressive destruction of joints, leading to functional disability and increased mortality if left untreated [1]. This chronic disease affects 0.5–1.0% of adults worldwide [2, 3]. The etiology of this systemic disease is unknown; however, several cell types including B lymphocytes, T lymphocytes, macrophages, and fibroblast-like synoviocytes are involved in the pathogenesis of RA. These cells develop systemic and articular inflammation and oxidative stress through excess production of cytokines, chemokines, matrix metalloproteinases (MMPs), adhesion molecules, and reactive oxygen species (ROS) [4]. Furthermore, infiltration of B cells, T cells, and macrophages into the synovial stroma contributes to the synovium proliferation and consequently joint swelling and pain [5]. MMPs are tissue-destroying enzymes which are involved in various pathological processes such as arthritis, cancer, and neurological disorders. Among MMPs, MMP-1 and MMP-3 are key enzymes in RA-related cartilage and bone destruction. Previous studies reported an increased expression of MMP-1 and MMP-3 in serum and synovium in RA. As tissue-destroying enzymes, their activity in synovial fibroblasts, osteoclasts, and chondrocytes help degradation of the extracellular matrix and consequent cartilage and bone destruction in RA joints [6–9].

There are various pharmacologic agents such as analgesics, non-steroidal anti-inflammatory drugs, corticosteroids, biologic response modifiers, and disease-modifying anti-rheumatic drugs (DMARDs) available today to alleviate RA symptoms, but they are accompanied by some side effects [10]. Therefore, interest in adjuvant interventions in particular dietary supplements has been raised. It is important to study whether nutritional agents with potential to attenuate inflammation, oxidative stress, or both have benefits in RA or not.

Coenzyme Q10 (CoQ10) or ubiquinone is a lipid-soluble vitamin-like antioxidant and a crucial component of the oxidation-reduction process in cell membranes. It is naturally found in the diet and can also be synthesized endogenously by all cells in the body [11]. CoQ10 has direct antioxidant action in quenching free radicals or regeneration of tocopherol as well as anti-inflammatory properties [12]. It has been indicated that CoQ10 suppresses TNF-α gene expression in mice and exerts anti-inflammatory effects probably via NF-κB1-dependent gene expression [13, 14]. Findings from in vitro and animal studies showed anti-inflammatory effects of CoQ10 as well as alleviating clinical symptoms [15–19]. In addition, previous studies demonstrated the usefulness of CoQ10 in patients with coronary artery disease, neurodegenerative diseases, diabetes mellitus, and fibromyalgia [20–23].

To the best of our knowledge, there is no study investigating the effect of CoQ10 on clinical status in RA, so we hypothesized that CoQ10 would decrease serum MMPs and improve clinical status. To test the hypothesis, this study was designed to evaluate the effects of CoQ10 supplementation on serum MMPs and clinical parameters in patients with RA.

Methods and materials

Subject selection

This randomized, double-blind, placebo-controlled trial was conducted on patients with RA referred to the outpatient rheumatology clinic of Urmia University of Medical Sciences, Urmia, Iran, according to the 1987 American College of Rheumatology criteria [24], diagnosed at least 6 months ago with moderate and severe disease activity (disease activity score-28 joints (DAS-28) > 3.2), aged 18–56 years from January 2014 to June 2014. Exclusion criteria were any history of diabetes mellitus; renal, liver, thyroid, and infectious diseases; pregnancy and lactation; smoking; consumption of antioxidants or omega-3 fatty acid supplements in the previous month; and taking warfarin or oral contraceptives. Also, any change in medication intake during intervention was considered as exclusion criterion. With a standard deviation of 1.08 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 [25]. The study protocol was approved by the Ethics Committee of Tabriz and Urmia Universities of Medical Sciences (Iran) and registered on the Iranian Registry of Clinical Trials website (code: IRCT201311014105N16). All subjects were made aware of the content of the study and a written informed consent was obtained from each subject.

Study design

The eligible participants were randomly allocated into intervention and placebo groups based on random block

procedure consisting of four subjects per block, produced by Random Allocation Software, version 1.0 (M. Saghaei, Department of Anesthesia, Isfahan University of Medical Sciences, Isfahan, Iran) [26]. A computer-generated random sequence was kept in a remote secure location and administered by an independent third party who was not involved with the clinical conduct of study until all data were collected and verified. Patients and those who involved in enrolling participants, administering interventions, and assessing outcomes were blind to group assignments. The experimental group ($n = 27$) received 100 mg/day CoQ10 capsules (Health Burst Inc., USA) along with a meal for 2 months in addition to their conventional medications (methotrexate, sulfasalazine, hydroxychloroquine, prednisolone). The control group ($n = 27$) received placebo (wheat starch; identical in size, color, and shape to supplement) according to the same regimen and for the same duration. The participants were asked to keep their usual dietary intake and physical activity during the study period. Patients were monitored every 14 days for any side effects of CoQ10 supplementation as well as adherence to the prescribed interventions.

At the onset of the study, all patients underwent routine physical examinations. Body weight was recorded to the nearest 0.1 kg using a Seca scale (Hamburg, Germany) and height was also measured by a non-stretched tape to the nearest 0.1 cm. Body mass index (BMI) was determined as body weight (kg) divided to square of height (meters) [27]. Total energy intake was calculated using a 24-h food record method for 3 days (including 2 weekdays and 1 weekend day) a week before and at the end of supplementation by the Nutritionist IV software program (First Databank Inc., Hearst Corp., San Bruno, CA).

Clinical status assessment

At baseline and after a 2-month intervention, DAS-28 was used for the clinical evaluation of RA, which includes the 28 different joints for calculation (proximal interphalangeal joints, metacarpophalangeal joints, wrists, elbows, shoulders, and knees). The DAS-28 also takes into account the erythrocyte sedimentation rate (ESR) and the visual analogue scale (VAS) score [28]. The VAS used a 100-mm horizontal scale where patients were asked to report the current pain intensity, by placing a line on a VAS scale between "no pain" (0 mm) and "excruciating pain" (100 mm) [29, 30]. The DAS-28 score calculation was performed by the automatic DAS-28 calculator V1.1-beta [31] using the following appropriate formula [32]. The range of the DAS-28 is 0–9.4 and the level of disease activity can be interpreted as remission ($DAS \leq 2.6$), mild ($2.6 < DAS \leq 3.2$), moderate ($3.2 < DAS < 5.1$), or high ($DAS \geq 5.1$) [33].

Biochemical assessment

At the beginning and at the end of the trial period, 5 mL of venous blood samples was collected after an overnight fast of 12 h. The serum samples were separated from whole blood by centrifugation at 3200 rpm for 10 min and were kept at – 80 °C until biochemical analysis. Serum levels of MMP-1 and MMP-3 were determined using human ELISA kits from Boster (Boster Biological Technology Co., Ltd., Pleasanton, CA). Using an ELISA plate reader (Model stat fax 2100, Awareness, Ramsey, MN) at a wavelength of 450 nm, the color changes were measured. All measurements were done following the instructions provided by the manufacturers.

Statistical analysis

Statistical analysis was performed using SPSS version 16.0 software (SPSS, Inc., Chicago, IL, USA). Normality of variable distribution was evaluated using the Kolmogorov-Smirnov test. Variables not normally distributed were analyzed using a non-parametric test. Qualitative and normally distributed quantitative variables were displayed as numbers (percentages) and means ± SD, respectively. Non-normally distributed quantitative variables were presented as median (interquartile range). Demographic variables were analyzed using a $\chi 2$ or independent sample t test. The differences within groups were compared by paired t test or Wilcoxon signed rank test. Between group comparisons at baseline were made by independent sample t test or Mann-Whitney U test. Analysis of covariance (ANCOVA) was used to identify any differences between the 2 groups at the end of the study, adjusting for baseline values and covariates (age, sex, disease duration, medications, and total energy intake). Comparison of variable changes between groups was performed using Mann-Whitney U test. P value < 0.05 was considered statistically significant.

Results

Participant demographics

From a total of 54 subjects who met the inclusion criteria and entered the study, 5 subjects in the CoQ10 group and 4 subjects in the placebo group were lost to follow-up (withdraw, $n = 3$; hospitalization and change in medications, $n = 3$; low compliance rate, $n = 2$; migration, $n = 1$). One patient in placebo group was excluded from analysis due to her low serum specimen. Therefore, data were reported for 44 patients (22 in the CoQ10 group and 22 in the placebo group). Participants did not report any adverse effects with the CoQ10 consumption or placebo during the study, which confirmed the safety of CoQ10 in the present study as well as previous trials. The

means ± SD age, disease duration, and BMI of participants were 49.6 ± 11.3 and 6.9 ± 6.1 years and 29.6 ± 5.2 kg/m^2, respectively. Baseline characteristics of participants are presented in Table 1 and there are no significant differences between the two groups. It should be alluded that the primary endpoints of this project have been published previously [25, 34].

Serum matrix metalloproteinases

According to Table 2, serum MMP-1 decreased significantly in both CoQ10 ($P < 0.001$) and placebo ($P = 0.001$) groups; however, there was no difference between two groups regarding variables and their changes after the experimental period. Serum MMP-3 decreased insignificantly in the CoQ10 ($P = 0.783$) and increased significantly in the placebo group ($P = 0.020$), so that the changes of MMP-3 at the end of the study was statistically significant between the two groups ($P = 0.027$).

Clinical status

As illustrated in Table 3, the independent sample *t* test results revealed no significant differences between the two groups in terms of ESR, VAS, and DAS-28 at baseline ($P > 0.05$). Moreover, no significant differences were observed between the two groups in terms of swollen and tender joint count at baseline. As shown in Table 2, after 2 months of supplementation, compared with baseline values, significant reductions in swollen joint count and DAS-28 were observed in both CoQ10 and placebo supplemented groups ($P < 0.001$ and $P = 0.009$, respectively). Furthermore, significant reductions were only observed in ESR, VAS score, and tender joint count in CoQ10 supplemented group compared with baseline ($P = 0.001$, $P < 0.001$, and $P < 0.001$, respectively). Results of ANCOVA showed statistically significant differences between the two studied groups in DAS-28, VAS score, and swollen and tender joint count at the end of the study ($P < 0.001$, $P < 0.001$, and $P = 0.012$ and $P < 0.001$, respectively), adjusted for baseline values and covariates (Table 3).

Table 1 Baseline characteristics of study subjects

Variables	CoQ10 group ($n = 22$)	Placebo group ($n = 22$)
Age (years)	48.8 ± 11.6	50.4 ± 11.3
Disease duration (years)	6.9 ± 5.8	7.0 ± 6.5
BMI (kg/m^2)	29.1 ± 5.8	30.0 ± 4.8
Energy intake (Kcal/day)	1953 ± 410	1867 ± 335
Sex		
Male	3 (13.6)	2 (9.0)
Female	19 (86.4)	20 (91.0)
Medications		
Methotrexate	21 (95.5)	21 (95.5)
Sulfasalazine	20 (90.9)	20 (90.9)
Hydroxychloroquine	14 (63.6)	15 (68.2)
Prednisolone	22 (100)	20 (90.9)
Folic acid	22 (100)	22 (100)
Calcium-D	20 (90.9)	19 (86.4)
Others[a]	11 (50)	14 (63.6)

BMI, body mass index

Data are presented as means ± SD and number (percentage)

[a] Losartan, omeprazole, alendronate

There were no significant differences between two groups

Discussion

This randomized placebo-controlled clinical trial assessed the effects of CoQ10 supplementation on serum MMPs and clinical status in patients with RA. After 2 months' supplementation, MMP-1 had no significant difference between groups. A non-significant decrease in MMP-3 in the CoQ10 and significant increase in the placebo group led to a significant difference between MMP-3 changes at the end of the study. In addition, a statistically significant difference was observed between the two groups in swollen and tender joint count, VAS score, and DAS-28 following supplementation with CoQ10.

There were limited studies about the effects of CoQ10 on serum MMP-1 or MMP-3, and were mostly carried out in vitro as well as in animal models. Lee et al. [35] demonstrated a therapeutic effect of CoQ10 in the osteoarthritis animal model including suppression of pain and cartilage degeneration by inhibiting inflammatory mediators such as MMP-13. In another study, Zhang et al. [36] reported that CoQ10 reduced UVR-induced MMP-1 level in embryonic and adult cells. Also, CoQ10 was shown to reduce UVA-induced MMP-1 in cultured human dermal fibroblasts [37]. CoQ10 supplementation decreased inflammatory markers including MMP-2 and MMP-9 in other studies [38, 39].

Given RA pathogenesis, the expressions of metalloproteinases, which are partially regulated by signaling through NF-κB and AP-1 (activating protein-1) pathways, increase in response to inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukine-1β (IL-1β), and interleukine-6 (IL-6) [40]. According to our previous study [25], CoQ10 supplementation suppressed TNF-α secretion in RA patients; therefore, it may lead to the MMP-3 inhibition in these patients. Moreover, ROS is considered as one of the major ways of MMP regulation through oxidation of the zinc-cysteine switch [41]. Alge-Priglinger et al. [42] showed that oxidative stress increased MMP-1 and MMP-3 in the retinal pigment epithelium. As we reported in our previous study [25], serum malondialdehyde (MDA) concentration decreased

Table 2 Effect of CoQ10 and placebo supplementation on serum matrix metalloproteinases in two study groups

Variables	Timing	CoQ10 group ($n = 22$)	Placebo group ($n = 22$)	P
MMP-1 (ng/ml)	Baseline	0.20 (0.17, 3.48)	0.18 (0.14, 0.64)	0.076[b]
	After 2 months	0.16 (0.14, 1.95)	0.15 (0.12, 0.21)	
	P[a]	< 0.001	0.001	0.557[c]
	Changes	− 0.04(− 1.63, − 0.02)	− 0.04 (− 0.48, − 0.01)	
MMP-3 (ng/ml)	Baseline	2.22 (1.91, 4.23)	2.26 (1.91, 5.95)	0.218[b]
	After 2 months	2.18 (2.06, 3.57)	2.57 (2.13, 6.81)	
	P[a]	0.783	0.020	0.027[c]
	Changes	− 0.02 (− 0.37, 0.27)	0.31 (− 0.07, 0.61)	

MMP, matrix metalloproteinase

Values are median (25th and 75th percentiles)

Comparison between groups at baseline using Mann-Whitney *U* test showed no significant difference. [a] Comparison within groups using Wilcoxon signed rank test. [b] Comparison between groups of variables using ANCOVA test (adjusted for baseline values and covariates (age, sex, disease duration, medications, and total energy intake). [c] Comparison between groups of variables changes using Mann-Whitney *U* test

significantly in RA patients following CoQ10 supplementation. Therefore, improvement in serum MMP-3 could be attributable to the decrease in oxidative stress.

In regard to clinical outcomes, CoQ10 exerted a significant reduction in DAS-28 compared with the placebo. Improvement of DAS-28 is related to significant decrease in components of DAS-28, since CoQ10 decreased swollen and tender joint count and VAS in comparison with placebo. ESR as another component of DAS-28 decreased significantly in CoQ10 group, though the difference between the two groups was near to significant ($P = 0.069$). It has been reported that baseline DAS-28 can affect supplement usefulness; the higher DAS-28 is, the more decrease will occur after supplementation [43]. Although in this study, the DAS-28 difference between two groups was not significant at baseline, it was partially greater in supplemented group compared with placebo. Therefore, a little more score of DAS can provide greater decrease following CoQ10 supplementation.

Based on the literature reviews, there was no published article about the effects of CoQ10 supplementation on clinical parameters in RA patients. In a study, Cordero et al. [22] showed the important clinical improvement including

Table 3 Effect of CoQ10 and placebo supplementation on clinical parameters in two study groups

Variables	Timing	CoQ10 group ($n = 22$)	Placebo group ($n = 22$)	P[a]
Swollen joint count	Baseline	2 (0, 5)	2 (0.75, 6.5)	0.012
	After 2 months	0 (0, 0)	0 (0, 3)	
	P[b]	< 0.001	0.009	
Tender joint count	Baseline	4.5 (1.75, 10.25)	3 (2, 8.5)	< 0.001
	After 2 months	0 (0, 0)	2 (0, 6)	
	P[b]	< 0.001	0.680	
ESR, mm/h	Baseline	39.64 ± 25.53	40.27 ± 25.75	0.069
	After 2 months	23.55 ± 14.53	36.27 ± 28.54	
	P[b]	0.001	0.395	
VAS (pain)	Baseline	63.18 ± 22.97	54.55 ± 20.81	< 0.001
	After 2 months	7.05 ± 10.54	48.86 ± 23.09	
	P[b]	< 0.001	0.169	
DAS-28	Baseline	5.01 ± 1.21	4.88 ± 0.96	< 0.001
	After 2 months	2.34 ± 0.68	4.04 ± 1.36	
	P[b]	< 0.001	0.009	

ESR erythrocyte sedimentation rate, *VAS* visual analogue scale, *DAS-28* disease activity score-28 joints

Mean ± SD and median (25th and 75th percentiles) are presented for normally and non-normally distributed variables

[a] Independent sample *t* test and/or Mann-Whitney *U* test for normally and non-normally distributed measures, respectively, at baseline showed no significant difference; or ANCOVA test adjusted for baseline values and covariates (age, sex, disease duration, medications, and total energy intake) after 2 months

[b] Paired *t* test and/or Wilcoxon signed rank test for normally and non-normally distributed measures, respectively

reduction in fatigue, morning tiredness, pain visual scale, and tender points in fibromyalgia patients. Also, a case report study indicated that CoQ10 led to a significant improvement in clinical symptoms in a woman with fibromyalgia [23]. Previous studies using animal models of RA [17, 18] also indicated that CoQ10 administration potentiated the anti-arthritic effects of methotrexate (MTX) and was effective in attenuating the severity of MTX-induced liver damage. Therefore, they concluded that CoQ10 could be served as a useful adjuvant therapy as well as in promoting the safe use of MTX in the management of arthritis. Furthermore, chronic use of standard DMARDs especially methotrexate often leads to cardiovascular problems [44]. Based on our previous study [34], CoQ10 led to a decrease in modifiable risk factors for cardiovascular diseases in RA. This was valuable though the decrease was non-significant, since patients with RA have strong high risk of cardiac death [45, 46].

It has been proposed that lipid peroxidation products, MDA levels, as an indicator of oxidative stress, increase significantly in RA patients who have high DAS-28 score [47]. According to Vugt et al. study, there was 27.5% reduction in DAS-28 after 10-week supplementation with antioxidant compound; however, disease activity increased after discontinuance of antioxidant taking. These authors indicated that antioxidants improved clinical symptoms in RA via decreasing oxidative stress [43]. Furthermore, Shrivastava et al. [48] showed that inflammatory cytokines such as high-sensitivity C-reactive protein (hs-CRP), TNF-α, IL-6, and MMPs especially MMP-3 had direct relationship with disease activity and joint destruction. According to our previous study [25], CoQ10 supplementation decreased MDA and suppressed TNF-α secretion in RA patients. Therefore, decrease in disease activity may be attributable not only to the decreased MMP-3 but also to the improved oxidative stress and inflammatory status.

To our knowledge, it is the first randomized placebo-controlled clinical trial that assesses the effects of CoQ10 supplementation in RA patients. However, the small number of participants and low dose of supplement are the main shortcomings.

In conclusion, CoQ10 decreased serum MMP-3 compared with placebo; also, the results of this study indicated both statistical and clinical benefits of CoQ10 in improving clinical parameters in patients with RA. The decrease in disease outcomes seems to be quite large over time and also the difference between the two groups seems spectacular, especially for VAS and to a lesser extent for DAS-28. MMP-3, MDA, and TNF-α attenuation following CoQ10 supplementation could to some extent justify these clinical outcomes; however, it must be kept in mind that in addition to them, CoQ10 may affect other biomarkers (including other MMPs, caspases, and a large number of inflammatory markers) that may have beneficial effects on clinical outcomes in RA patients. Therefore, it should be investigated in the future studies. Altogether, it seems that CoQ10 may provide a new complementary approach for patients with RA.

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Compliance with ethical standards

Disclosures None.

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