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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

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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

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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