BioFactors 25 (2005) 235–240
IOS Press

Coenzyme Q_{10} supplementation reduces corticosteroids dosage in patients with bronchial asthma

Anna Gvozdjáková[a,*], Jarmila Kucharská[a], Mária Bartkovjaková[a], Katarína Gazdíková[b] and František Gazdík[b]
[a]*Comenius University, Medical Faculty, Pharmacobiochemical Laboratory, Bratislava, Slovakia*
[b]*Research Base of Slovak Medical University, Institute of Preventive and Clinical Medicine, Bratislava, Slovakia*

Abstract. Bronchial asthma is a chronic inflammatory disease of respiratory system, with disturbances in the dynamic balance of oxidant-antioxidant capacity of the lungs. Long-term administration of corticosteroids has been shown to result in mitochondrial dysfunction and oxidative damage of mitochondrial and nuclear DNAs. We previously documented decreased coenzyme Q_{10} (CoQ_{10}) and α-tocopherol concentrations in plasma and blood in corticosteroid-dependent bronchial asthma patients. In the present study we demonstrate that CoQ_{10} supplementation reduces the dosage of corticosteroids in these patients.

Patients and methods: This was an open, cross-over, randomized clinical study with 41 bronchial asthma patients (13 males, 28 females), ages 25–50 years. All patients suffered from persistent mild to moderate asthma. The patients were divided into two groups, one group receiving standard antiasthmatic therapy and clinically stabilized, and the second group receiving, in addition, antioxidants consisting of CoQ_{10} as Q-Gel® (120 mg) + 400 mg α-tocopherol + 250 mg vitamin C a day. The groups were crossed over at 16 weeks for a total duration of 32 weeks.

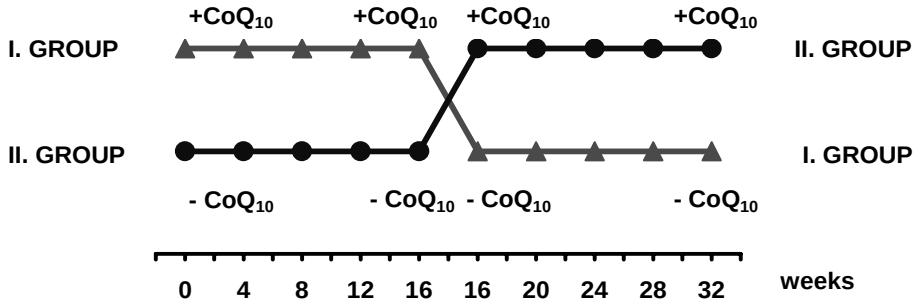
Results and conclusions: Data show that patients with corticosteroid-dependent bronchial asthma have low plasma CoQ_{10} concentrations that may contribute to their antioxidant imbalance and oxidative stress. A reduction in the dosage of corticosteroids required by the patients following antioxidant supplementation was observed, indicating lower incidence of potential adverse effects of the drugs, decreased oxidative stress. This study also demonstrates the significant uptake of CoQ_{10} by lung tissue in a rat model using hydrosoluble CoQ_{10} (Q-Gel®).

Keywords: Bronchial asthma, corticosteroids, coenzyme Q_{10}, oxidative stress, DNA

1. Introduction

Bronchial asthma is a chronic inflammatory disease of the respiratory system. It is estimated that there are about 150 million asthmatics in the world, with about 180.000 deaths a year due to asthma. Inflammatory process of asthma leads to serious disturbances in the dynamic balance of oxidant-antioxidant capacity of the lungs. Oxidative stress due to increased production of reactive oxygen species (ROS) and/or decreased antioxidant defenses contribute to the inflammatory process of bronchial asthma, which is mediated with cell injury [5]. Enhanced oxidant production during inflammatory process of lungs

*Address for correspondence: Anna Gvozdjáková, Comenius University, Medical Faculty, Pharmacobiochemical Laboratory, Hlboká 7, 811 05 Bratislava, Slovakia. Tel./Fax: +421 2 5249 1422; E-mail: physicus@netax.sk.



Scheme 1. Cross-over, open, randomized clinical study in asthmatics.

induce activity of oxidant enzymes, NADPH oxidase, myeloperoxidase, eosinophil peroxidase and nitric oxide synthases. ROS are released into the airways by activated inflammatory cells such as leukocytes [12]. The antioxidant defense mechanisms include both enzymatic systems such as superoxide dismutase, glutathione peroxidase and catalase, and nonenzymatic systems such as antioxidant vitamins, coenzyme Q_{10} (CoQ_{10}) and carotenoids. Low plasma antioxidants concentrations were documented in severe asthma [8]. Significant reduction of plasma vitamin C and vitamin E concentrations, reduced platelet glutathione peroxidase activity and serum selenium concentration have been reported in asthmatics [2,11]. Our previous study documented decreased plasma and blood concentration of CoQ_{10} and α-tocopherol in patients with corticosteroid-dependent bronchial asthma [2]. The purpose of the present study was to confirm and extend these findings to examine the baseline plasma levels of antioxidants CoQ_{10}, α-tocopherol, and β-carotene, and to examine the effect of CoQ_{10}, α-tocopherol, and vitamin C supplementation in bronchial asthma patients with reference to the dosage of corticosteroids required, measures of spirometric parameters and oxidative stress. The uptake of CoQ_{10} by lung tissue and incorporation into the mitochondria was also studied using hydrosoluble CoQ_{10} (Q-Gel®).

2. Material and methods

2.1. Clinical study

This was an open, cross-over, randomized clinical study on 41 bronchial asthma patients (13 male, 28 female) ranging in age from 25 to 50 years, suffering from persistant mild to moderate asthma. They were divided into two groups (Group I $n = 22$; group II $n = 19$). The total duration of the study was 32 weeks. All the patients were maintained on standard antiasthmatic therapy (inhaled corticosteroids, beta-agonists) and clinically stabilized with optimal dosages of corticosteroids. The total usage of corticosteroids was calculated every 4 weeks. The protocol for antioxidant supplementation is presented in Scheme 1. Before supplementation with antioxidants (baseline), and at 4 week intervals, the following spirometric parameters were monitored: FEV_1 (forced expiratory flow per second), FEV_1/FVC (ratio of forced expiratory flow per second to forced vital capacity), VCmax (maximal vital capacity), MEF50 (maximal expiratory flow in 50% of VC), MEF25 (maximal expiratory flow in 25% of VC), MEF 25–75 (maximal expiratory flow between 25–75 % of VC), and PEF (peak expiratory flow). Supplementation with antioxidants was done in the following cross-over manner: group I from 0 to 16 weeks, group II from 16 to 32 weeks. The antioxidant supplementation consisted of: CoQ_{10} as Q-Gel® (120 mg CoQ_{10}), 400 mg α-tocopherol and 250 mg vitamin C a day.

2.2. Animal study

An animal study using Wistar rats 19–22 months of age was carried out to examine the uptake of CoQ_{10} as Q-Gel® by lung tissue and its incorporation into lungs mitochondria. Q-Gel® was administered by oral gavage at a daily dose of 200 mg CoQ_{10}/kg bw for 4 weeks, the control group receiving the vehicle (6 animals per group).

The analyses of plasma CoQ_{10}, α-tocopherol and β-carotene, and lungs tissue CoQ_{10} were carried by HPLC methods [6]. Lipid peroxidation as malondialdehyde production in plasma was assessed spectrophotometrically [4]. Statistical evaluation in the clinical trial was made using paired Wilcoxon test, a value of $p < 0.05$ being significant (* = significant, ** = very significant, *** = extremly significant). Student's t-test was used for statistical comparisons in the rat study.

3. Results

3.1. Clinical study

Plasma MDA (malondialdehyde) values in the patients were in the high normal range. Supplementation with CoQ_{10}, vitamin E and vitamin C decreased MDA production significantly after 4 weeks ($p < 0.0068$) and after 32 weeks ($p < 0.0006$) in group I. However no significant changes in plasma MDA were observed in group II (Fig. 1). Baseline plasma levels of antioxidant nutrients in the patients were below the reference range for CoQ_{10}, α-tocopherol and β-carotene. There was a significant increase in the concentration of the antioxidant nutrients following 16 weeks of supplementation in both groups. The data for plasma CoQ_{10} are shown in Fig. 2, with very significant increases ($p < 0.0001$) following supplementation with hydrosoluble CoQ_{10} as Q-GEL® in group I (from 0.52 ± 0.05 to 1.96 ± 0.12 and 1.95 ± 0.21 mmol/l CoQ_{10}) and group II (from 0.57 ± 0.06 to 1.93 ± 0.33 and 1.69 ± 0.19 mmol/l CoQ_{10}). Furthermore, antioxidant supplementation resulted in a significant reduction in the dosage of corticosteroids in both groups; in group I from 23.74 ± 6.26 to 6.12 ± 4.38 mg corticosteroids/4 weeks, and in group II from 23.64 ± 6.86 to 4.74 ± 2.31 mg corticosteroids/4 weeks ($p = 0.0001$) (Fig. 3). Spirometric parameters did not change significantly during the study.

3.2. Animal study

CoQ_{10} supplementation in rats resulted in significant increases in both lung tissue ($p < 0.004$) and lung mitochondrial levels ($p < 0.0001$) of CoQ_{10} when compared with the control group (Table 1). There was also a significant incresae in CoQ_9 levels following CoQ_{10} supplementation in lungs mitochondria ($p < 0.0034$).

4. Discussion

Corticosteroids are the most effective drugs in the treatment of bronchial asthma. Therapeutic effects of corticosteroids involve inhibition of inflammatory cytokine production and induction of eosinophil apoptosis resulting from oxidant-mediated mitochondrial injury [1]. One of the effects of chronic corticosteroids ingestion is mitochondrial damage, increased oxidative stress and decreased antioxidant capacity. Long-term corticosteroids administration leads to mitochondrial dysfunction, and abnormal

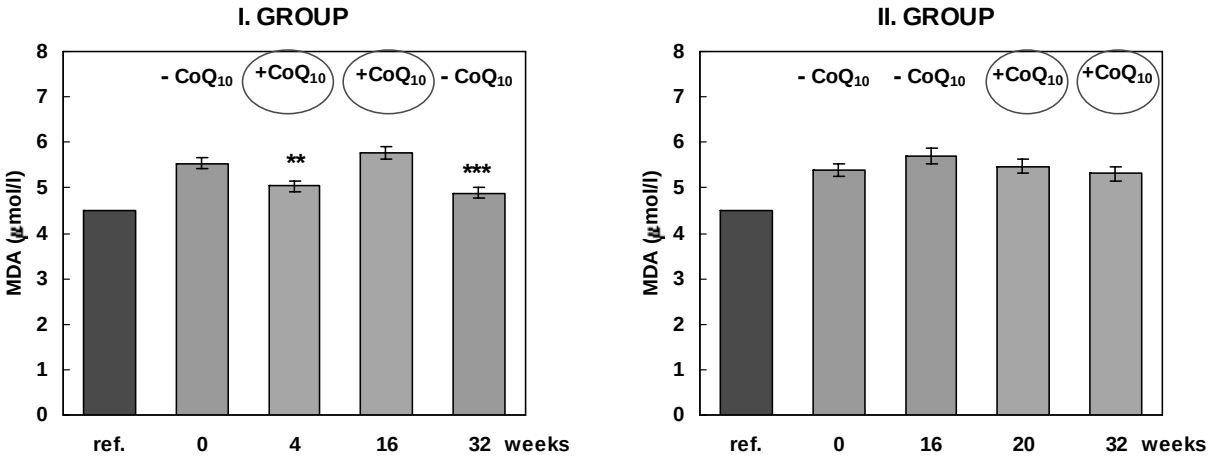


Fig. 1. Effect of antioxidant supplementation on plasma lipid peroxidation in asthmatics.

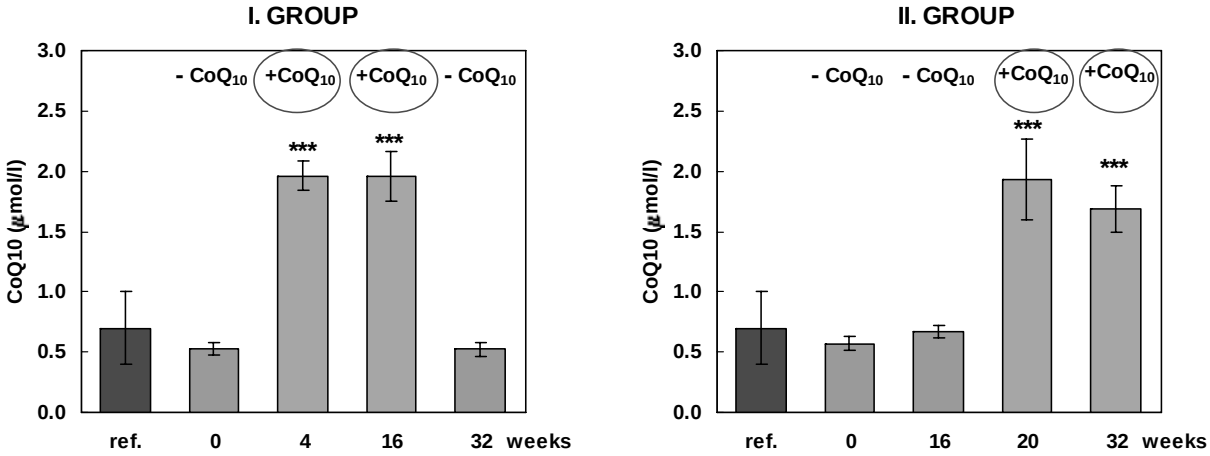


Fig. 2. Effect of antioxidant supplementation on plasma CoQ_{10} concentrations in asthmatics.

mitochondria of skeletal muscle in patients with presence of RRF fibers. Oxidative damage of biopsied skeletal muscle was evident in both mitochondrial and nuclear DNAs and also increased plasma 8-OH-dG arising from mitochondrial DNA [9,10].

Low plasma antioxidant status reported in severe asthma patients [8] was confirmed in this study. We have previously documented decreased circulating levels of CoQ_{10} and α-tocopherol in patients with corticosteroid-dependent bronchial asthma [2]. CoQ_{10}, a key component of mitochondrial respiratory chain plays a major role in energy production and is a potent anti-oxidant. According to Linnane and Eastwood [7] CoQ_{10} redox poise changes (in terms of ratio of reduced to oxidized form) determines its key metabolic control function in all subcellular membranes, resulting in a signaling process. The global functions of CoQ_{10} are in cellular bioenergetics, redox poise, metabolic flux modulation, gene regulation and oxygen radical production.

Baseline plasma levels of antioxidant nutrients in the asthma patients were below the reference range for CoQ_{10} (Fig. 2) and also for α-tocopherol (data not shown). Plasma CoQ_{10} showed a highly significant increase following supplementation with CoQ_{10} as Q-Gel® (Fig. 2). While a decrease in plasma MDA

Table 1
Uptake of CoQ_{10} by lung tissue and mitochondria of rats

Groups	Control	CoQ_{10}(Q-Gel®)
Lung tissue		
CoQ_{10-OX} (nmol/g ww)	2.92 ± 0.21	5.25 ± 0.97 $p < 0.004^{**}$
CoQ_{9-OX} (nmol/g ww)	15.12 ± 0.19	18.33 ± 4.00
Lung mitochondria		
CoQ_{10-OX} (nmol/mg prot.)	0.08 ± 0.02	0.38 ± 0.04 $p < 0.0001^{***}$
CoQ_{9-OX} (nmol/mg prot.)	0.54 ± 0.05	0.82 ± 0.05 $p < 0.0034^{**}$

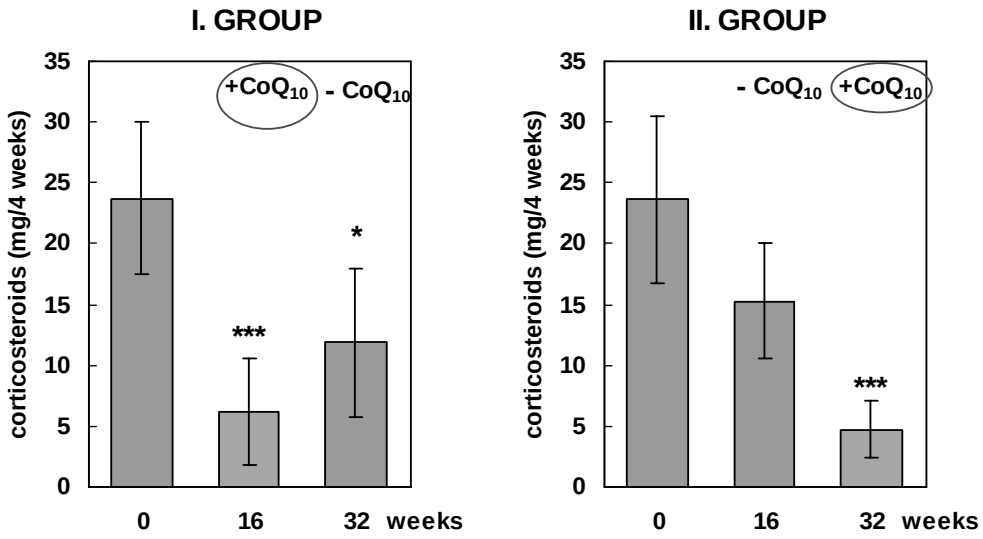


Fig. 3. Effect of antioxidant supplementation on consumption of inhaled corticosteroids in asthmatics.

levels was noted in group I, this was not evident in the case of group II and the reasons are not clear. The most important finding from this study is the highly significant reduction in the dosage of inhaled corticosteroids by the patients. On the basis of our experimental results with CoQ_{10} supplementation in rats leading to increased levels in lungs tissue and lungs mitochondria, the increased levels of CoQ_{10} along with the other antioxidants in lung tissue provide protection against oxidative damage and promote lung function. The data therefore indicate the potential clinical benefit of supplementation with CoQ_{10} and other antioxidant nutrients in patients with bronchial asthma [3].

5. Conclusions

This study shows that patients with corticosteroid-dependent bronchial asthma have low plasma CoQ_{10} concentrations that may contribute to their antioxidant imbalance and oxidative stress. The primary benefit of antioxidant nutrient supplementation is in the reduction of corticosteroid dosage resulting in the lowering of adverse effects due to corticosteroid therapy that is of clinical significance. This study also demonstrates the superiority of the hydrosoluble CoQ_{10} formulation (Q-Gel®) in promoting its absorption and tissue uptake.

Acknowledgements

This study was supported by Slovak Grant Agency for Science, No.1/7547/20 and 1/0564/03 and Tishcon Corp, USA. Technical assistance: Sumbalova Z. (figures), Štetkova A., Zauškova P.

References

[1] S.J. Gardai, R. Hoontrakoon, C.D. Goddard, B.J. Day, L.Y. Chang, P.M. Henson and D.L. Bratton, Oxidant-mediated mitochondrial injury in eosinophil apoptosis: Enhancement by glucocorticosteroids and inhibition by granulocyte-macrophage colony-stimulating factor, *J Immunol* **170** (2003), 556–566.

[2] F. Gazdík, A. Gvozdjáková, R. Nádvorníková, L. Repická, E. Jahnová, J. Kucharská, M.R. Pijak and K. Gazdíková, Decreased levels of coenzyme Q_{10} in patients with bronchial asthma, *Allergy* **57** (2002), 811–814.

[3] A. Gvozdjáková, J. Kucharská, M. Bartkovjaková, K. Gazdíková and F. Gazdík, *Coenzyme Q_{10} supplementation reduces corticosteroid dosage in patients with bronchial asthma*, Fourth Conference of the International Coenzyme Q_{10} Association, Abstract book, 2005, 108–109.

[4] D.R. Janero and B. Burghardt, Thiobarbituric acid-reactive malondialdehyde formation during superoxide-dependent iron-catalyzed lipid peroxidation: influence of peroxidation conditions, *Lipids* **24** (1989), 125–131.

[5] V.L. Kinnula, Production and degradation of oxygen metabolites during inflammatory states in the human lung, *Curr Drug Targets Inflamm Allergy* **4/4** (2005), 465–470.

[6] J.K. Lang, K. Gohil and L. Packer, Simultaneous determination of tocopherols, ubiquinols and ubiquinones in blood, plasma, tissue homogenates, and subcellular fractions, *Analytical Biochemistry* **157** (1986), 106–116.

[7] A.W. Linnane and H. Eastwood, Cellular redox poise modulation, the over arching role of coenzyme Q_{10}, gene expression and metabolic regulation, *Mitochondrion* **4/5-6** (2004), 779–789.

[8] N.L. Misso, J. Brooks-Wildhaber, S. Ray, H. Vally and P.J. Thompson, Plasma concentrations of dietary and nondietary antioxidants are low in severe asthma, *Eur Respir J.* **26/2** (2005), 257–264.

[9] T. Mitsui, H. Azuma, M. Nagasawa, T. Iuchi, M. Akaike, M. Odomi and T. Matsumoto, Chronic corticosteroid administration causes mitochondrial dysfunction in skeletal muscle, *J Neurol.* **249/8** (2002), 1004–1009.

[10] T. Mitsui, Z. Umaki, M. Nagasawa, M. Akaike, K. Aki, H. Azuma, S. Ozaki, M. Odomi and T. Matsumoto, Mitochondrial damage in patients with long-term corticosteroid therapy: development of oculoskeletal symptoms similar to mitochondrial disease, *Acta Neuropathol* **104/3** (2002), 260–266.

[11] K.R. Shanmugasundaram, S.S. Kumar and S. Rajajee, Excessive free radical generation in the blood of children suffering from asthma, *Clin Chim Acta* **305** (2001), 107–114.

[12] H. Vural, N. Aksoy, E. Ceylan, M. Gencer and F. Ozguner, Leukocyte oxidant and antioxidant status in asthmatic patients, *Arch Med Res* **36/5** (2005), 502–506.