PILOT STUDY

Levels of coenzyme Q_{10} in asthmatics

Gazdik F, Gvozdjakova A, Horvathova M, Weissova S, Kucharska J, Pijak MR, Gazdikova K

Department of Clinical Immunology, Institute of Preventive and Clinical Medicine, Bratislava, Slovakia. **gazdik@upkm.sk**

Abstract

Backround: **The contribution of free oxygen radicals in the pathogenesis of bronchial asthma is generally accepted. The modulation of antioxidative defence by supplementation with antioxidants represents additive approach in complex management of the disease.**
The aim **of the study was to assess the levels of coenzyme Q_{10}, α-tocopherol, ß-carotene and malondialdehyde (end-stage parameter of lipid peroxidation) in asthmatics (As).**
Methods: **Fifty six As (15 males and 41 females) aged from 19 to 72 yrs (mean age 46 yrs) were enrolled into the study. The control group comprised of 25 healthy volunteers (16 males, 9 females) aged 25–50 years.**
Results: **Concentrations of CoQ_{10} and α-tocopherol, decresed significantly both in plasma and whole blood, compared with healthy volunteers ($p<0.009$, $p<0.004$; $p<0.035$, $p<0.001$, respectively). The level of MDA was elevated, but not statisticaly significantly. No changes were seen in ß-carotene levels. Positive correlation was found between concentrations of CoQ_{10} and α-tocopherol.**
Conclusion: **Our results suggest possible contribution of suboptimal concentrations of CoQ_{10} on antioxidative dysbalance in As and provide rationale for its supplementation with clinical evaluation.** ***(Tab. 2, Fig. 1, Ref. 39.)***
Key words: bronchial asthma, antioxidants, coenzyme Q_{10}, α-tocopherol, ß-carotene, malondialdehyde.

Accumulating data indicate that bronchial asthma is a chronic inflammatory disease. Airway inflammation and it's control became a principal focus in asthma pathogenesis and treatment. The mechanisms underlying inflammation have not been fully clarified. Current understanding suggests that the dysbalance between increased production of free oxygen radicals, originated in the process of inflammation, and decrease of antioxidative potential seems to be of importance. In this respect, the dysbalance could be considered as the important triggering factor as well as the factor responsible for the maintenance of chronic inflammation (Rahman et al, 1996; Kelly et al, 1999; Dworski et al, 2001). Antioxidative protective system in humans is complex and comprises a number of substances possessing antioxidative effects e.g. vitamins A, C, E, some of trace elements, e.g. selenium and zinc, enzyme superoxid dismutase (SOD), glutathion peroxidase and etc. (Ďuračková, 1998).

In clinical trials disorder of antioxidative potential is well documented. Several authors reported decreased selenium levels in asthmatics (Stone et al, 1989; Flatt et al, 1990; Hasselmark et al, 1990; Pearson et al, 1991; Shaw et al, 1994; Kadrabová et al, 1996; Misso et al, 1996). Decreased levels of vitamin A, C, E or decreased enzyme activity of SOD in asthmatics have been published (Hatch, 1995; Smith et al, 1997; Kalayaci et al, 2000; Comhair et al, 2000).

Coenzyme Q_{10} (ubichinone), vitamin like substance, represents the important member of antioxidative potential in human. This substance plays crucial role in the production of cell energy and in the scavenger activity of free oxygen radicals. CoQ_{10} is localized in tissues and organs with high need of energy consumption (Hojerová, 2000).

The aim of the clinical pilot study was to assess both in plasma and whole blood, the baseline levels of CoQ_{10}, α-tocopherol and ß-carotene in patients suffering from bronchial asthma. The levels of malondialdehyde (MDA), marker of end-stage lipid peroxidation, was also determined in plasma.

Department of Clinical Immunology, Institute of Preventive and Clinical Medicine, Bratislava, and Pharmacobiochemical Laboratory of Medical Faculty, Comenius University, Bratislava

Address for correspondence: F. Gazdik, MD, PhD, Dept of Clinical Immunology, Institute of Preventive and Clinical Medicine, Limbova 14, SK-833 01 Bratislava 37, Slovakia.

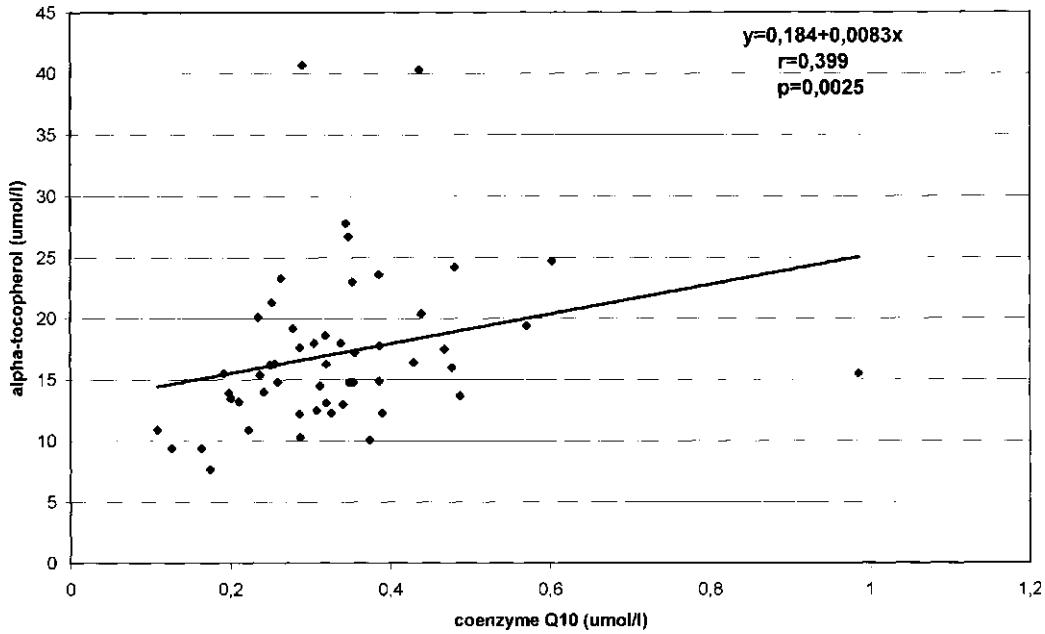

Fig. 1. Correlation between coenzyme Q_{10} and alpha-tocopherol.

Patients and methods

Fifty six asthmatics of both sexes (males 15, females 41) aged 19–72 years were enrolled into the study. They were non smokers, atopics by history and had positive skin test for allergy.

They suffered from mild to moderate form of persistent asthma (according to the criteria of GINA classification (Bousquet, 2000). All of them were regularly treated with inhaled corticosteroid (beclomethasone propionate) and clinical status was stabilized. Control group comprised of 25 healthy subjects (16 males, 9 females) aged 25–65 years. Informed consent was given by all subjects who have entered the study.

A venous blood sample was taken from each subject after 12 hours of fasting. Following parameters were assessed: both in plasma and whole blood, concentrations of CoQ_{10}, α-tocopherol and ß-carotene by using the HPLC method, as described previously (Takada et al, 1982; Lang et al, 1986), using HPLC LKB, device Sweden, with spectrophotometric detection. MDA was determined by method of spectrophotometry (Janero et Burghardt, 1989).

Baseline spirometric parameters before administration of medications (forced vital capacity – FVC, Tiffenau index: the ratio of forced expiratory volume per 1st second – FEV1 to FVC, peak expiratory flow – PEF and maximal expiratory flow in 25 % of FVC-MEF25, in 75 % of FVC, in 25–75 % of FVC, respectively) were examined using the spirometric machine Sanoscope (company Ganzhorn Medizine Electronic, Germany).

The statistics

The measured values were statistically evaluated by Wilcoxon test (non-paired test). P-value less than 0.05 was considered to be significant. The data analysis was done by using the program Statgraphics, version 5. Linear regression analysis was used for the determination of correlations.

Results

The concentration of CoQ_{10} both in plasma and whole blood were significantly decreased compared with healthy subjects ($p<0.009$, $p<0.004$, respectively) (Tab. 1). The concentration of alpha-tocopherol in plasma and whole blood was significantly decreased ($p<0.035$, $p<0.001$, respectively) (Tab. 1). The concentration of beta-carotene was in the reference range (Tab. 1). The level of MDA in plasma was over the reference range (r.r. 4.5 μmol/l) (Wagner, 1995), but did not significantly differ in comparison with control group (Tab. 1). We found positive correlation between the blood concentrations of CoQ_{10} and the α-tocopherol ($r=0.399$, $p=0.003$) (Fig. 1).

The results of spirometric parameters suggest clinical stabilization of asthmatics (Tab. 2).

Discussion

In a pilot clinical study we found significantly decreased levels of CoQ_{10} and α-tocopherol both in plasma and blood, compared with control group. The concentration of CoQ_{10} in blood correlated positively with α-tocopherol level. The levels of MDA were increased, but not significantly.

The contribution of free oxygen radicals in to the process of inflammation and the decrease of antioxidative defence in pathogenesis of bronchial asthma is well documented (Kelly et al, 1999;

Tab. 1. Levels of coenzyme Q_{10}, α-tocopherol, ß-carotene and MDA.

	As (n=56)		Controls (n=25)		p^*	p^{**}
	Plasma	Blood	Plasma	Blood		
coenzyme Q_{10} (mol/l)	0.34±0.02*	0.33±0.02	0.51±0.03	0.50±0.03	0.009	0.004
α-tocopherol (mol/l)	28.22±1.30	17.22±0.86	33.25±1.5	21.58±1.6	0.035	0.001
ß-carotene (mol/l)	2.07±0.0	1.63±0.22	3.04±0.8	2.10±0.5	NS	NS
MDA (mol/l)	5.20±0.08	–	4.87±0.1	–	NS	–

Notes: As — asthmatics, MDA — malondialdehyde, *±SEM, p^* — statistical significance between plasma levels, p^{**} — statistical significance between blood levels, NS — non significance

Tab. 2. Spirometric parameters (n=56).

Parameter	VCmax L	FEV1 L/s	FEV1/FVC %	MEF50 L/s	MEF25 L/s	MEF25-75 L/s	PEF m/s
Average	3.4	2.71	81.1	3.36	1.44	3.26	5.8
±SEM	0.12	0.10	1.1	0.17	0.1	0.15	0.26

Notes: No — number of patients, FEV1 — forced expiratory flow per 1. second, FEV1/FVC — ratio of forced expiratory flow per 1. 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, PEF — peak expiratory flow, SEM — standard error mean.

Beasley et al, 1991; Dworski et al, 2001). The thesis of contribution of oxidative stress in pathogenesis of bronchial asthma is generally accepted. Several authors reported benefit of selenium supplementation on reduction of systemic and inhaled corticosteroids (CS) consumption in asthmatics (Hasselmark et al, 1993; Gazdík et al, 2002). Currently combined antiinflammatory therapy is preffered in order to decrease the consumption of CS. The rationale of such therapeutic approach is to reduce the manifestations of adverse reactions, especially in long term CS therapy. Presented results demonstrate decrease levels of CoQ10 in asthmatics. We supposed that the suboptimal concentration of CoQ_{10} could participate in total decrease of antioxidative potential in asthmatic patients. In this respect no data have been yet published. These results provide rationale background for CoQ_{10} supplementation. In this respect clinical trial is necessary to perform. Limited information regarding the influence of CoQ_{10} on pulmonary functions has been reported. Protective effects of CoQ_{10} on pulmonary functions have been demonstrated in animal experiments (Hanagiri et al, 1994). The levels of CoQ_{10} have been decreased in patients with chronic obstructive pulmonary disease as well as in the patients with idiopathic pulmonary fibrosis (Karlsson et al, 1992; Fujimoto et al, 1993). Administration of CoQ_{10} reduces the pulmonary hypertension in humans (Munkholm et al, 1999).

In clinical practice supplementation of CoQ_{10} has been reported especially in patients with cardiovascular and neurodegenerative diseases (Rauchová et Lenaz, 2001; Gvozdjáková et al, 1991, 1993, 1999; Beal et Mattews, 1997).

Immunomodulating effects of CoQ_{10} have been reported also by several authors. In experimental animal model CoQ_{10} had protective effects against tumor expansion and enhanced anitiviral immunity (Tanner, 1992). The imunostimulating effects of CoQ_{10} on both, T cell mediated immunity, NK activity and antibody production have been documented (Folkers et al, 1993; Makabi-Panzu et al, 1998; Barbieri et al, 1999; Ravaglia et al, 2000).

We demonstrated significantly decreased concentrations of CoQ_{10} and α-tocopherol both in plasma and whole blood in patients with bronchial asthma as compared with healthy group. The contribution of CoQ_{10} on antioxidative dysbalance seems to be probable. Next studies are necessary to be performed in order to clarify the relevance of CoQ_{10} supplementation on clinical response in respect to its antiinflammatory potential.

References

Barbieri B, Lund B, Liundstrom B, Scaglione F. Coenzyme Q10 administration increases antibody titer in hepatitis B vaccinated volunteers — a single blind placebo-controlled and randomized clinical study. Biofactors 1999; 9: 351—357.

Beal MF, Mattews RT. Coenzyme Q10 in the central nervous system and the potential usefulness in the treatment of neurodegenerative disease. Mol Aspect Med 1997; 18: 169—179.

Beasley R, Thomson C, Pearce N. Selenium, glutathione peroxidase and asthma. Clin Exp Allergy 1991; 21: 157—159.

Bousquet J. Global initiative for asthma (GINA) and its objectives. Clin Exp Allergy 2000; 30 (Suppl 1): 2—5.

Comhair SA, Bhathena PR, Dweik RA, Kavuru M, Erzuru SC. Rapid loss od superoxide dismutase activity during antigen-induced asthmatics response. Lancet 2000; 355: 642.

Ďuračková Z. Free radicals and antioaxidants in medicine (I). Bratislava: SAP 1998: 285.

Dworski R, Roberts LJ 2nd, Murray JJ, Morrow JD, Hartert TV, Sheller JR. Assessment of oxidant stress in allergic asthma by measurement of the major urinary metabolite of F2-isoprostane, 15-F2t-IsoP (8-iso-PGF2alpha). Clin Exp Allergy 2001; 31: 387—390.

Flatt A, Pearce N, Thomson CD, Sears MR, Robinson MF, Beasley R. Reduced selenium in asthmatic subjects in New Zealand Thorax 1990; 45: 95—99.

Folkers K, Morita M, McRee J Jr. The activities of coenzyme Q10 and vitamin B6 for immune responses. Biochem Biophys Res Commun, 1993; 28 (193): 88—92.

Fujimoto S, Kurihara N, Hirata K, Takeda T. Effects of coenzyme Q10 administration on pulmonary function and exercise performance in patients with chronic lung disease. Clin Investig 1993; 71 (Suppl 8): S161—166.

Gazdík F, Kadrabová J, Gazdíková K. Decreased consumption of corticosteroids after selenium supplementation in corticoid-dependent asthmatics. Bratisl Lek Listy 2002; 1: 22—25..

Gvozdjáková A, Kucharská J, Gvozdják J. On the cardioprotective effect of Coenzyme Q10 in smoke cardiomypathy. J Mol Cell Cardiol 1991; 23: 101.

Gvozdjáková A, Kucharská J, Herichová I, Gvozdják J. On the protective effect of coenzyme Q10 on smoke mitochondrial cardiomyopathy. Cardiology 1999; 2: 14.

Gvozdjáková A, Kucharská J, Herichová I, Bada V, Gvozdják J. The relation of passive smoking to development of mitochondrial cardiomyopathy. In: Abstracts of 3rd Int. Conference on Preventive Cardiology in Oslo 1993: 213.

Gvozdjáková A, Kucharská J, Herichová I, Koprena I, Gvozdják J. On the benefical long-term effect of CoQ_{10} on the metabolic response of myocardial mitochondria. J Mol Cell Cardiol 1993; 25: 108.

Hanagiri T, Igisu H, Shiraishi T, Shirakusa T. Effects of coenzyme Q10 on lung preservation: a study with an isolated rat lung reperfusion model. J UOEH 1994; 1 (16): 85—89.

Hasselmark L, Malmgren R, Unge G, Zetterstrom O. Lowered platelet glutathione peroxidase activity patients with intrinsic asthma. Allergy 1990; 45: 523—527.

Hasselmark L, Malmgren R, Zetterstrom O, Unge G. Selenium supplementation in intrinsic asthma. Allergy 1993; 48: 30—36.

Hatch GE. Asthma, inhaled oxidants, and dietary antioxidants. Amer J Clin Nutr 1995; 61 (3): 625—630.

Hojerová J. Coenzyme Q10 — significance, properties and usade in nutrition and cosmetics. Čes a Slov Farm 2000; 69: 119—123.

Janero DR, Burghardt B. Thiobarbituric acid-reactive malondialdehyde formation during superoxide-dependent, iron-catalyzed lipid peroxidatiuon: influence of peroxidation conditions. Lipids 1989; 24: 125—131.

Kadrabová J, Maďarič A, Kováčiková Z, Podivinský F, Ginter E, Gazdík F. Selenium status is decreased in patients with intrinsic asthma. Biol Trace Elem Res 1996; 52: 241—248.

Kalayaci O, Besler T, Kilinc K, Sekerel BE, Saraclar Y. Serum levels of antioxidant vitamins (alpha tocopherol, beta carotene, and ascorbic acid) in children with bronchial asthma. Turk J Pediatr 2000; 42 (1): 17—21.

Karlsson J, Diamant B, Folkers K. Exercise-limiting factors in respiratory distress. Respiration 1992; 59 (Suppl 2): 18—23.

Kelly FJ, Meudway I, Blomberg A, Frew A, Sandstrom T. Altered lung antioxidants in patients with mild asthma. Lancet 1999; 354: 482—483.

Lang JK, Gohil K, Packer L. Simultaneous determination of tocopherols, ubiquinols and ubiquinons in blood, plasma, tissue homogenates, and subcellular fractions. Anal Biochem 1986; 157: 106—116.

Makabi-Panzu B, Sprott GD, Patl GB. Coenzyme Q10 in vesicles composed of archaeal ether lipids or conventional lipids enhances the immuno-adjuvanticity to encapsulated protein. Vaccine 1998; 16: 1504—1510.

Misso NL, Powers KA, Gillon RL, Stewart GA, Thompson PJ. Reduced platelet glutathione peroxidase astivity and serum selenium concentration in atopic asthmatic patients. Clin Exp Allergy 1996; 26: 838—847.

Munkholm H, Hansen HH, Rasmussen K. Coenzyme Q10 treatment in serious heart failure. Biofactors 1999; 9: 285—289.

Pearson DJ, Suarez-Mendez VJ, Day JP, Miller PF. Selenium status in relation to reduced glutathione peroxidase activity in aspirin-sensitive asthma. Clin Exp Allergy 1991; 21: 203—208.

Rahman I, Morrison D, Donaldson K, MacNee W. Systemic oxidative stress in asthma, COPD and smokers. Amer J Resp Crit Care Med 1996; 154: 1055—1060.

Rauchová H, Lenaz G. Coenzyme Q and its therapeutic aplication. Čes a Slov Farm 2001; 50: 78—82.

Ravaglia G, Forti P, Maioli F, Bastagli L, Facchini A, Mariani E, Savarino L, Sassi S, Cucinotta D, Lenaz G. Effect of micronutrient status on natural killer cell immune function in healthy free-living subjects aged /= 90y. Amer J Clin Nutr 2000; 71: 590—598.

Shaw R, Woodman K, Crane J, Moyes C, Kennedy J, Pearce N. Risk factor for asthma symptoms in Kawerau children. N Z Med J 1994; 107: 387—391.

Smith LJ, Shamsuddin M, Sporn PH, Denenberg M, Anderson J. Reduced superoxide dismutase in lung cells of patients with asthma. Free Radic Biol Med 1997; 22: 1301—1307.

Stone J, Hinks LJ, Beasley R, Holgate ST, Clayton BA. Reduced selenium status of patients with asthma. Clin Sci 1989; 77: 495—500.

Takada M, Ikenoya S, Yuzuriha T, Katayama K. Studies on reduced and oxidized coenzyme Q (Ubiquinone). The determination of oxidation-reduction levels of coenzyme Q in mitochondria, microsomes and plasma by high-performance liquid chromatography. Biochem Biophys Acta 1982; 679: 308—318.

Tanner HA. Energy transformation in the biosynthesis of the immune system: their relevance to the progression and treatment of AIDS. Med Hypotheses 1992; 38: 315—321.

Wagner P. Laboratory reference values. Praha: Triton 1995.

Received August 18, 2002.
Accepted September 20, 2002.