Beneficial effect of antioxidants and polarized light on selected metabolic and echocardiographic parameters in diabetics

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Background: Enhanced production of reactive oxygen species and decreased antioxidant function play a role in the development of chronic diabetic complications.
Objective: To determine whether supplementation with antioxidants (coenzyme Q_{10} (CoQ_{10}), α-lipoic acid (ALA), α-tocopherol) and simultaneous polarized light (PL) application can improve selected metabolic and echocardiographic parameters of the left ventricle (LV) in diabetics.
Patients and methods: Twenty patients with type 2 diabetes were enrolled in a prospective study. Antioxidants were taken in two daily doses (60 mg hydrosoluble CoQ_{10}, 100 mg ALA and 200 mg α-tocopherol) and PL was simultaneously applied on neuropathic diabetic ulcers (twice daily for 10 minutes in pulse regimen) for three months. Paired Student´s *t*-test was used for statistical analysis at the baseline and after the three-month treatment.
Results: Supplementation with CoQ_{10}, ALA and α-tocopherol with simultaneous PL application reduced plasma fibrinogen and lactate dehydrogenase activity, while plasma levels of CoQ_{10} and α-tocopherol were stimulated. An improvement was found in echocardiographic parameters.
Conclusions: Hydrosoluble CoQ_{10}, ALA and α-tocopherol supplementation with simultaneous polarized light application increased the plasma concentrations of antioxidants, decreased lactate dehydrogenase activity, and improved selected LV echocardiographic parameters.
Key words: Coenzyme Q_{10} – α-Lipoic acid – α-tocopherol – Polarized light – Left ventricle – Neuropathic diabetic ulcers

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Kontext: Na rozvoji chronických komplikací diabetu se podílejí zvýšená tvorba reaktivních druhů kyslíku a snížená funkce antioxidantů.
Cíl: Určit, zda suplementace antioxidantů [koenzym Q_{10} (CoQ_{10}), kyseliny α-lipoové (ALA), α-tokoferolu] a současná aplikace polarizovaného světla (polarized light, PL) může zlepšit hodnoty vybraných metabolických a echokardiografických parametrů levé komory srdeční u diabetiků.
Pacienti a metody: Do prospektivní studie bylo zařazeno 20 jedinců s diabetem 2. typu. Antioxidanty byly podávány ve dvou denních dávkách (60 mg ve vodě rozpustného CoQ_{10}, 100 mg ALA a 200 mg α-tokoferolu) a současně bylo na neuropatické vředy aplikováno PL (dvakrát denně po dobu 10 minut v pulsním režimu) po dobu tří měsíců. Ke statistické analýze výchozích údajů a hodnot po tříměsíční léčbě byl použit párový Studentův *t*-test.
Výsledky: Suplementace CoQ_{10}, ALA a α-tokoferolu spolu se současnou aplikací PL snížila koncentraci fibrinogenu v plazmě a aktivitu laktát dehydrogenázy, zatímco koncentrace CoQ_{10} a α-tokoferolu v plazmě se zvýšily. Bylo pozorováno zlepšení echokardiografických parametrů.
Závěry: Suplementace ve vodě rozpustného CoQ_{10}, ALA a α-tokoferolu se současnou aplikací polarizovaného světla zvýšila koncentrace antioxidantů v plazmě, snížila aktivitu laktát dehydrogenázy, a zlepšila vybrané echokardiografické parametry levé komory.
Klíčová slova: Koenzym Q_{10} – Kyselina α-lipoová – α-tokoferol – Polarizované světlo – Levá komora – Neuropatické vředy

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Introduction

Diabetes mellitus (DM) is a chronic disease caused by a disorder of insulin secretion in pancreatic β-cells, and its effect in tissues. Neuropathy, vasculopathy and cardiomyopathy are involved in chronic diabetic complications.

Coenzyme Q_{10} (CoQ_{10}) is a crucial component of the mitochondrial respiratory chain. The presence of high concentrations of ubiquinol in all membranes is necessary for antioxidant action either by direct reaction with radicals or by regeneration of tocopherol and ascorbate. Evidence for its function in redox control of cell signaling and gene expression was reported in a review.[1]

α-lipoic acid (thioctic acid, ALA) functions as an essential cofactor in oxidative decarboxylation of α-keto acids. Both ALA and its reduced form dihydrolipoic acid (DHLA) act as intra- and extracellular antioxidants that support the recycling of α-tocopherol. The antioxidant potency of ALA and DHLA lies in their capability to scavenge several reactive oxygen species (ROS) including those suspected to contribute to endothelial dysfunction in individuals with risk factors for cardiovascular disease.[2] ALA was shown to increase nitric oxide-mediated vasodilation in patients with diabetes, via a mechanism possibly linked to reduced oxidative stress.[3] Functions of ALA in diabetes were summed up in a review.[4]

The major role of *α-tocopherol* as an antioxidant is to protect polyunsaturated fatty acids in membranes and lipoproteins. Acting as a scavenger of free oxygen and lipid peroxyl radicals, α-tocopherol is oxidized to tocopheryl radical. Active α-tocopherol can be regenerated by ascorbic acid or by ubiquinol.[5]

Polarized light (PL) application belongs to the light therapy methods. Over the last years, biological effects of a single color from the visible spectrum were described. Red light (660-680 nm) was found to increase cell and mitochondrial energy metabolism.[6]

The *objective* was to determine the effect of antioxidant supplementation (CoQ_{10}, ALA, and α-tocopherol) with simultaneous PL application on selected metabolic and echocardiographic parameters of the left ventricle (LV) in diabetics.

Methods and patients

This randomized prospective study enrolled 20 patients (12 men), age 61.6 ± 9.0 years [expressed as mean ± standard deviation (SD)], with type 2 diabetes and neuropathic diabetic foot treated with insulin (14 pts, 70%) and/or with oral antidiabetics (9 pts, 45%). The study was conducted between January 2007 and May 2008. All patients diagnosed with the disease were examined in one center using the same methods. Randomization was compromised as we were restricted by the number of patients attending the clinic.

Baseline characteristics of the patients are summarized in *Table 1* as follows: body mass index (BMI) 29.4 ± 6.3 kg/m²; systolic blood pressure (sBP) 136.5 ± 16.5 mm Hg; diastolic blood pressure (dBP) 85.5 ± 14.1 mm Hg, pulse rate (PR) 77.0 ± 12.4 per minute; cardio-thoracic index (CTI) 0.46 ± 0.05; blood glucose 10.1 ± 3.7 mmol/l, and glycated hemoglobin (HbA_{1c}) 8.2 ± 2.5%. Beta-blockers were taken by four patients (20%), ACE (angiotensin-converting enzyme) inhibitors by 15 (75%), AT_1-receptor antagonists by five (25%), calcium-channel blockers by six (30%), and diuretics by six patients (30%). The study included patients whose treatment of hypertension had not changed during the last six months before randomization.

Table 1 **Baseline characteristics of diabetic patients**

Number of patients (%)	20 (100)
Men (%)	12 (60)
Age (years)	61.6 ± 9.0
Duration of type 2 diabetes (years)	8.2 ± 2.4
BMI (kg/m²)	29.4 ± 6.3
sBP (mmHg)	136.5 ± 16.5
dBP (mmHg)	85.5 ± 14.1
PR per minute	77.0 ± 12.4
CTI	0.46 ± 0.05
Blood glucose (mmol/l)	10.1 ± 3.7
HbA_{1c} (%)	8.2 ± 2.5

BMI – body mass index, sBP – systolic blood pressure, dBP – diastolic blood pressure, PR – pulse rate, CTI – cardio-thoracic index, HbA_{1c} – glycated hemoglobin

Antioxidants were taken in two daily doses (60 mg hydrosoluble CoQ_{10}, 100 mg ALA and 200 mg α-tocopherol) and PL (surface size 4 cm²) was simultaneously applied on neuropathic diabetic ulcers twice daily for ten minutes in pulse regimen during three months.

After 3 months, the following parameters were compared with their respective baseline values: C-reactive protein (CRP) determined by particle enhanced turbidimetric immunoassay (PETIA), fibrinogen by the method according to Clauss, and lactate dehydrogenase (LD) by the bichromatic rate technique (340, 383 nm). Concentrations of malondialdehyde (MDA) in plasma were determined by the reaction with thiobarbituric acid (TBA) spectrophotometrically at 532 nm,[7] and endogenous antioxidants (coenzyme Q_{10}, α-tocopherol, γ-tocopherol, β-carotene) by a modified method of high-performance liquid chromatography.[8] Selected echocardiographic parameters of left ventricular (LV) systolic and diastolic functions were measured by Doppler echocardiography: LV ejection fraction (LVEF), endsystolic and enddiastolic LV diameters (LVESD and LVEDD, respectively), interventricular septum thickness (IVS), LV posterior wall thickness (PW), deceleration time (DT) and ratio of early velocity and velocity during atrial systole (E/A).

Only patients with a negative ulcer culture were enrolled in the study. In the case of a positive culture, they first received antibiotic treatment. Patients entered the study voluntarily, the physician informed each patient about the nature of the study and received their written consent. This study is a non-intervention study, conforming to the principles outlined in the Declaration of Helsinki.

Statistical analysis

The normally distributed data (according to Shapiro--Wilk's test) are presented as means ± SD. Categorical variables are reported as a percentage of the total number of subjects. Paired Student´s *t*-test was used for intragroup comparisons of mean differences. All *P* values cited are two-sided alternatives; differences with *P* values less than 0.05 were judged as statistically significant. With the number of patients available for analysis, our study had a power of > 80% to discern treatment outcome differences as a function of baseline-parameter values in the patients.

Results

Supplementary treatment with CoQ_{10}, ALA, α-tocopherol, and PL application led to a significant increase in plasma CoQ_{10} and α-tocopherol levels. γ-tocopherol, β-carotene and the parameter of lipid peroxidation (malondialdehyde) in plasma were not changed *(Table 2)*. Supplementation with hydrosoluble CoQ_{10}, ALA and α-tocopherol with PL application during three months significantly reduced fibrinogen level and LD activity in plasma, while CRP, glycemia and glycated hemoglobin were not affected. Selected echocardiographic parameters of the left ventricle showed a significant improvement *(Table 3)*.

Table 3 **Effect of 3-month simultaneous antioxidant supplementation and polarized light application on selected metabolic parameters in diabetics**

Parameter	Before the study (mean ± SD)	After 3 months (mean ± SD)	Statistics (paired Student´s *t*-test)
LVEF (%)	59.60 ± 9.24	63.60 ± 8.38	< 0.0001
LVEDD (mm)	52.00 ± 3.69	49.50 ± 3.36	< 0.0001
LVESD (mm)	35.20 ± 4.19	32.90 ± 4.48	< 0.0001
IVS (mm)	11.20 ± 1.30	10.30 ± 1.16	< 0.0001
PW (mm)	10.50 ± 1.24	9.50 ± 1.23	< 0.0001
E/A	1.00 ± 0.06	1.03 ± 0.07	< 0.0001
DT (ms)	242.40 ± 25.50	227.80 ± 22.39	< 0.0001

LVEF – left ventricular ejection fraction, LVESD – endsystolic left ventricular diameter, LVEDD – enddiastolic left ventricular diameter, IVS – interventricular septum thickness, PW – left ventricular posterior wall thickness, E/A – ratio of early velocity (E) and velocity during atrial systole (A), DT – deceleration time, SD – standard deviation

Discussion

Selected metabolic parameters in diabetics

Hyperglycemia in diabetic patients leads to the generation of free oxygen radicals through glucose autooxidation and non-enzymatic glycation.[9] Increased levels of lipid peroxides have been implicated in the pathogenesis of diabetic complications.[10] Several antioxidant protective mechanisms reduce the deleterious effects of lipid peroxides. They constitute a primary defensive system that includes enzymatic defenses (glutathione peroxidase and superoxide dismutase) and naturally occurring antioxidants such as ubiquinol, α-tocopherol and β-carotene.

α-tocopherol participates in protecting polyunsaturated fatty acids in membranes and lipoproteins against peroxidation by scavenging lipid peroxyl radicals and thus breaking chain propagation steps.[11] Individuals with low blood levels of vitamin E were found to be more likely to develop type 2 diabetes.[12] Some previous studies have reported lower plasma α-tocopherol concentrations in patients with type 2 diabetes than in healthy control

Table 2 **Effect of 3-month simultaneous antioxidant supplementation and polarized light application on selected metabolic parameters in diabetics**

Parameter	Reference values	Before the study (mean ± SD)	After 3 months (mean ± SD)	Statistics (paired Student´s t test)
MDA (μmol/l)	< 4.5	4.43 ± 1.10	4.55 ± 1.03	NS
CoQ_{10} (μmol/l)	0.4–1.0	0.59 ± 0.19	1.11 ± 0.40	< 0.0001
α-tocopherol (μmol/l)	15–40	16.24 ± 3.44	23.44 ± 6.46	< 0.0001
γ-tocopherol (μmol/l)	2–7	1.08 ± 0.44	1.24 ± 1.33	NS
β-carotene (μmol/l)	0.3–3.0	0.47 ± 0.48	0.48 ± 0.35	NS
CRP (mg/l)	0–5.0	8.10 ± 3.67	5.90 ± 3.12	NS
Fibrinogen (g/l)	1.5–3.5	4.54 ± 1.40	3.74 ± 1.03	< 0.0001
LD (μkat/l)	1.67–4.0	3.58 ± 0.65	3.27 ± 0.53	< 0.0001
Blood glucose (mmol/l)	4.1–5.9	10.10 ± 3.74	10.10 ± 5.30	NS
HbA_{1c} (%)	< 4.5	8.19 ± 2.48	7.29 ± 1.88	NS
TAG (mmol/l)	0.1–2.28	1.26 ± 0.50	1.46 ± 0.75	NS
Total cholesterol (mmol/l)	4–5.2	4.76 ± 0.70	4.83 ± 0.81	NS
HDL-cholesterol (mmol/l)	0.83–2.49	1.22 ± 0.31	1.20 ± 0.31	NS
LDL-cholesterol (mmol/l)	3.3–4.32	2.96 ± 0.62	2.95 ± 0.73	NS

CRP – C-reactive protein, LD – lactate dehydrogenase, MDA – malondialdehyde, CoQ_{10} – coenzyme Q_{10}, HbA_{1c} – glycated hemoglobin, TAG – triacylglycerols, HDL – high-density lipoproteins, LDL – low-density lipoproteins, SD – standard deviation, NS – not significant subjects.[13,14] The antioxidant ability of α-tocopherol is continuously restored by other antioxidants (vitamin C, ubiquinols, thiols). DHLA protects against microsomal lipid peroxidation, but only in the presence of vitamin E.[15]

Patients with type 2 diabetes were found to have significantly lower blood levels of CoQ_{10} compared with healthy individuals.[16] A reduced CoQ_{10} level found in heart and liver mitochondria in diabetic rats can explain mitochondrial dysfunction and ATP production in diabetes.[17] Mutual connections of CoQ_{10}, ALA and α-tocopherol mechanisms under oxidative stress conditions could imply the benefit of combined antioxidant therapy in diabetics.

The mechanism of PL application through stimulation of Complex I of the mitochondrial respiratory chain was documented in experiment.[18] Simultaneous supplementation with CoQ_{10} and PL application improved also Complex II of the mitochondrial respiratory chain and energy production.[6]

In this study, plasma levels of CoQ_{10} and α-tocopherol were in the normal range at baseline, however, three-month antioxidant supplementation with PL application led to their significant stimulation.

C-reactive protein (CRP) is a plasma protein produced by hepatocytes and is a general marker of systemic inflammation. Its gene expression is regulated by tumor necrosis factor α and by interleukin 6, secreted by adipocytes.[19] Prospective studies showed CRP to be associated with the risk of diabetes,[20,21] and its increasing level is an independent predictor of cardiovascular events.[22] In an animal study, α-tocopherol at doses of 250, 500, or 1000 IU/kg diet reduced CRP by about 52% on average. Co-supplementation with CoQ_{10} further reduced CRP to about 30% of the baseline value, a total reduction of 70%.[23] Vitamin E supplementation in type 2 diabetic subjects with and without macrovascular complications significantly lowered the levels of CRP.[24] In this study, antioxidant supplementation alone with PL application decreased plasma CRP by 27% (NS), approaching the reference values.

Fibrinogen is an acute-phase soluble protein synthesized in the liver. It is a strong independent cardiovascular risk factor.[25] Patients with type 2 diabetes have a high prevalence of hyperfibrinogenemia,[26] suggesting that it contributes to the high cardiovascular morbidity and mortality in this disease. The fibrinogen level is associated with HbA_{1c} values.[27] In our study, three-month therapy with CoQ_{10}, ALA and α-tocopherol with simultaneous PL application on diabetic ulcers led to a significant decrease in plasma fibrinogen level, yet HbA_{1c} values were not changed. We suggest that an anti-inflammatory effect of the supplementary treatment may be involved.

There is a significant increase in the activity of lactate dehydrogenase in diabetes, which could be due to excessive accumulation of pyruvate. This excessive pyruvate is converted to lactate for which LD is needed and therefore the LD activity may be increased due to less insulin availability in diabetes.[28] *Table 2* shows plasma LD activity of the group under investigation at the basal level and its significant reduction by the three-month treatment, indicating control over gluconeogenesis.

Selected echocardiographic parameters in diabetic patients

Left ventricular function, both its systolic and diastolic components, is usually compromised in diabetic patients depending on the duration of diabetes. This may later develop into LV heart failure. Langsjoen et al.[29] published data on 109 patients with hypertensive heart disease and noted that treatment with CoQ_{10} improved in the NYHA functional classification and LV hypertrophy. They also observed significant improvement in diastolic function, as measured by Doppler echocardiography. Results of a long-term multicenter randomized study demonstrated that the addition of CoQ_{10} to conventional therapy significantly reduced hospitalization for worsening of heart failure and the incidence of serious complications in patients with chronic congestive heart failure.[30]

In our study, supplementary treatment with 60 mg CoQ_{10}, 100 mg ALA and 200 mg α-tocopherol led to an improvement in selected parameters of systolic and diastolic LV functions. Simultaneously, LV thickness, systolic and diastolic LV volumes were reduced. Ejection fraction of LV improved as did the E/A ratio and deceleration time *(Table 3)*. There was some improvement in sBP (136.5 ± 16.5 vs 135.7 ± 13.4 mmHg) and dBP (85.5 ± 14.1 vs 82.3 ± 10.3 mmHg) during the study, but it was not significant. Blood glucose and HbA_{1c} values before the study vs after three-month treatment were practically the same (10.1 ± 3.7 vs 10.1 ± 5.3 mmol/l, NS; 8.2 ± 2.5 vs 7.9 ± 1.9 %, NS). Conventional treatment of hypertension was not changed for six months before and during the study. The small number of patients and rather short duration of the study are its limitations. On the other hand, the study has some assets – it was conducted in one center where the same echocardiographic device and methodology of examination were used. We assume that long-term antioxidant supplementation could be useful in preventing the development of chronic heart failure in patients with type 2 diabetes.

In conclusion, supplementation with hydrosoluble coenzyme Q_{10}, α-lipoic acid, and α-tocopherol with simultaneous polarized light application decreased the inflammatory parameter fibrinogen, lactate dehydrogenase activity, increased plasma antioxidant (coenzyme Q_{10}, α-tocopherol) concentrations, and improved selected echocardiographic parameters in type 2 diabetics with disease duration of 8.2 ± 2.4 years. The described supplementary treatment appears to provide a useful therapeutic tool in diabetic patients with chronic complications.

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