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Effect of long-term treatment with antioxidants (vitamin C, vitamin E, coenzyme Q10 and selenium) on arterial compliance, humoral factors and inflammatory markers in patients with multiple cardiovascular risk factors

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Abstract

Background: Antioxidant supplementations have the potential to alleviate the atherosclerotic damage caused by excessive production of reactive oxygen species (ROS). The present study evaluated the effects of prolonged antioxidant treatment on arterial elasticity, inflammatory and metabolic measures in patients with multiple cardiovascular risk factors.

Methods: Study participants were randomly assigned to two groups. Group 1 received oral supplementation with 2 capsules per day of Mid Life Guard, SupHerb, Israel. In each capsule vitamin C (500 mg) vitamin E (200 iu), co-enzyme Q10 (60 mg) and selenium (100 mcg), Group 2 received matching placebo(SupHerb) for 6 months. Patients were evaluated for lipid profile, HbA1C, insulin, C-peptide, hs-CRP, endothelin, aldosterone, plasma renin activity and Homeostasis model assessment-insulin resistance (HOMA-IR). Arterial elasticity was evaluated using pulse wave contour analysis (HDI CR 2000, Eagan, Minnesota).

Results: Antioxidant-treated patients exhibited significant increases in large arterial elasticity index (LAEI) as well as small arterial elasticity index (SAEI). A significant decline HbA1C and a significant increase in HDL-cholesterol were also observed. In the placebo group, significant changes in LAEI, SAEI or metabolic measures were not observed.

Conclusions: Antioxidant supplementation significantly increased large and small artery elasticity in patients with multiple cardiovascular risk factors. This beneficial vascular effect was associated with an improvement in glucose and lipid metabolism as well as decrease in blood pressure.

Background

Oxidative stress has been considered as a potential pathogenic mechanism for initiation and progression of atherosclerotic disease [1]. Excessive production of reactive oxygen species, a mediator of the oxidative stress cascade, leads to release of inflammatory cytokines, oxidation of LDL and prothrombotic state, and finally results in endothelial dysfunction and atherosclerotic vascular lesions [2-4]. Adequate dietary, enzymatic and nonenzymatic

antioxidant supplementation may be effective in lowering oxidative stress. Although most trials with antioxidants in experimental models of atherosclerosis have demonstrated that this treatment is able to retard the progression of atherosclerosis, the results of clinical trials are equivocal [5]. Differences in the definition criteria of patients who are potential candidates for antioxidant treatment, type and dosage of antioxidant supplementation, as well as outcome measures may explain this variability. Since oxidative stress is activated by many cardiovascular risks factors such as hypertension, hyperglycemia, dyslipidemia and smoking, patients with multiple cardiovascular risk factors could obtain beneficial

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effect from antioxidant treatment [6-9]. Additionally, combinations of dietary antioxidants (vitamin C and vitamin E) with carrier in mitochondrial oxidative phosphorylation (coenzyme Q₁₀) and trace elements essential for adequate function of many antioxidant enzymes (selenium) may underlie the synergism between them and amplify the positive antioxidant effect. The present study was designed to determine the effect of antioxidant supplementation with vitamin C, vitamin E, coenzyme Q₁₀ and selenium on arterial compliance, inflammatory and metabolic parameters in patients with multiple cardiovascular risk factors.

Methods

In a randomized, placebo-controlled study 70 patients with at least two cardiovascular risk factors were recruited from the hypertension outpatient clinic at E.Wolfson Medical Center for study participation. Screening procedures included physical examination, complete blood chemistry; complete blood count, urinalysis and electrocardiogram.

Cardiovascular risk factors were defined using the National Cholesterol Education Program risk factors categories: hypertension (systolic blood pressure \geq 140 mm Hg and/or diastolic BP \geq 90 mm Hg and/or taking antihypertensive medication); diabetes (fasting plasma glucose level \geq 126 mg/dl on at least two blood samples and/or taking glucose lowering agents, hypertriglyceridemia (\geq 1.7 mmol/l); low HDL cholesterol level ($<$ 1.03 mmol/l in men and $<$ 1.3 mmol/l in women); or current cigarette smoking.

Patients with a history of unstable angina, MI, CVA or major surgery within the six months preceding entrance to the study were excluded. Patients with unbalanced endocrine disease or any disease that might affect absorption of medications were excluded, as were patients with plasma creatinine $>$ 2 mg/dl, elevation of liver enzymes to more than twice the upper normal limit, and electrolyte abnormalities. Patients included in the study were stabilized on their previous medical treatment in the outpatient clinic for up to three months, and an effort was made not to change treatment during the study. All concomitant medications were kept stable to prevent possible effects on the study parameters.

The study was approved by the Institutional Review Board and the patients signed a full informed consent.

Study participants were randomly assigned to two groups. Group 1 received oral supplementation with 2 capsules per day of Mid Life Guard, SupHerb, Israel. In each capsule vitamin C (500 mg) vitamin E (200 iu), coenzyme Q₁₀ (60 mg) and selenium (100 mcg), Group 2 received matching placebo(SupHerb) for 6 months.

Biochemical parameters

Blood sampling for full chemistry and metabolic parameters, including fasting glucose, lipid profile, HbA1C, hs-CRP, homocysteine, endothelin, aldosterone, plasma renin activity was performed at baseline and at the end of the study.

Arterial Elasticity Measurements

Arterial compliance measures were performed after an overnight fast and before blood sampling. Measures were performed between 8 and 10 AM, in a quiet, temperature-controlled laboratory. With the subject in a supine position, radial arterial waveforms were recorded for 30 sec. The pressure transducer amplifier system was connected to a specially designed device (Model CR-2000, Hypertension Diagnostics Inc. Eagan, MN). The passive transient response of the arterial vasculature to the initial loading conditions was determined by analyzing the diastolic portion of the pressure pulse-wave form. This technique, which has been validated for its reproducibility and used extensively [10-12], was performed with a simple noninvasive radial pulse wave recording and computer analysis of the diastolic decay. This provides separate assessment of the large artery or capacitive compliance (C1) and small artery reflective or oscillatory compliance (C2). Cardiac output and stroke volume were computed from the average waveforms. Systemic vascular resistance (SVR) is calculated as mean arterial pressure (MAP) divided by cardiac output (CO). Arterial elasticity was determined at the baseline visit and at the 3- and 6 -month on-treatment visits.

Sample size

The primary endpoint in the present study was the paired difference in small artery elasticity (SAEI) within each group. With a sample size of $n = 33$ in each group, the present study was designed to have not less than 80% power to detect a true, within group difference of at least 1.2 ± 2 mL/mm Hg \times 100 in SAEI in each of the two treatment groups assuming a two-tailed alpha of 0.025 (preserving to overall study alpha at 0.05).

Statistical analysis

Analysis of data was carried out using SPSS 10.0 statistical analysis software (SPSS Inc., Chicago, IL, USA, 1999). For continuous variables, such as arterial compliance parameters and biochemistry data, descriptive statistics were calculated and reported as mean \pm standard deviation. Normalcy of distribution of continuous variables was assessed using the Kolmogorov-Smirnov test (cut off at $p = 0.01$). Categorical variables such as sex and concomitant illnesses were described using frequency distributions and are presented as frequency (%). The t-test for independent samples was used to compare continuous

variables by treatment group. Categorical variables were compared by treatment group using the chi square test (exact as needed). General linear modeling was used to compare post-treatment continuous variables that differed by treatment group at baseline, including treatment group as the fixed factor and the baseline value of the modeled variable as a covariate. All tests are two-sided and considered significant at $p < 0.05$.

Results

Demographic and clinical characteristics of the 70 patients with multiple cardiovascular risk factors are presented in Table 1. Group 1 included 36 patients who received oral daily supplementation with vitamin C, vitamin E, coenzyme Q₁₀ and selenium. Group 2 included 34 patients who received placebo. As can be seen, both groups were similar with respect to age, sex, BMI, presence of cardiovascular risk factors, baseline blood pressure level and arterial elasticity parameters. Concomitant medications were similarly distributed in both groups at the start and end of the study.

Changes in hemodynamic and arterial elasticity parameters in patients treated with antioxidants

Table 2 shows six month follow-up of hemodynamic and arterial elasticity parameters in patients received antioxidants. Systolic blood pressure (SBP) decreased significantly from 145.2 \pm 25.4 at baseline to 136.1 \pm 22.3 mmHg after 6 months of treatment ($p < 0.001$). Diastolic blood pressure (DBP) decreased significantly during the treatment period from 78.4 \pm 11.7 to 75.0 \pm 12.3 mmHg ($p < 0.034$). Heart rate did not change during the study.

LAEI increased from 11.0 \pm 4.4 to 12.7 \pm 4.7 ml/mmHg \times 100 after 6 months of treatment ($p < 0.006$) (Figure 1). SAEI increased significantly during the study from 3.3 \pm 1.9 to 4.7 \pm 2.7 ml/mmHg \times 100 ($p < 0.0001$) (Figure 2). Although SVR decreased by 11% during the treatment period, this decrease did not reach statistical significance ($p = 0.102$) (Table 2).

Changes in hemodynamic and arterial elasticity parameters in the control group

As shown in Table 2, systolic blood pressure as well as diastolic blood pressure did not change significantly during the study ($p = 0.257$ and $p = 0.493$, respectively).

Neither LAEI nor SAEI improved significantly during the treatment period. LAEI was 12.9 \pm 6.2 ml/mmHg \times 100 at baseline and 11.3 \pm 4.3 ml/mmHg \times 100 after 6 months of follow-up ($p = 0.151$) (Figure 1). SAEI was 3.6 \pm 1.5 at baseline and 3.7 \pm 1.9 ml/mmHg \times 100 at the end of the study ($p = 0.732$) (Figure 2). SVR tended to increase during the study from 1594.7 \pm 351.3 to 1638.7 \pm 311.3 dyne \times sec \times cm, however this increase did not reach statistical significance ($p = 0.533$) (Table 2).

Changes in metabolic and inflammatory parameters during 6-month treatment period

As shown in Table 2, levels of HbA_{1c} decreased significantly from 7.08 \pm 1.69% to 6.33 \pm 2.3% ($p = 0.022$) in patients received antioxidants. Additionally, significant increase in HDL-cholesterol ($p = 0.022$) and marginal declines in triglycerides ($p = 0.058$) as well as total cholesterol levels ($p = 0.074$) were observed in antioxidant treated patients.

Metabolic parameters including HbA_{1c}, triglycerides, total cholesterol, HDL-cholesterol and CRP did not change in placebo group during the study.

Discussion

The present randomized, placebo controlled study demonstrates that antioxidant supplementation with vitamin C, vitamin E, coenzyme Q₁₀ and selenium significantly increased large and small artery elasticity in patients with multiple cardiovascular risk factors. This beneficial vascular effect was associated with an improvement in glucose and lipid metabolism as well as significant decrease in blood pressure.

Assessment of arterial function and structure can serve as a surrogate endpoint for prediction of morbid events and for estimation of success of treatment. Pulse wave contour analysis using the modified Windkessel model is one of several noninvasive methods for estimation of arterial properties. Numerous studies performed with the HDI CR-2000 equipment have shown good correlation to age, cardiovascular risk factors and markers of disease [13]. Therapeutic interventions with medications like statins, angiotensin II receptor blocking agents as well as weight loss, have also shown improvement in LAEI and SAEI which may suggest lowering of cardiovascular risk. Nevertheless, no major prospective study associating arterial elasticity with cardiovascular events has been performed. Although PWA using the modified Windkessel model has some limitations, this method provides complementary information about vascular health.

The favorable vascular effect of antioxidants has been observed *in vitro* and in animal models of atherosclerosis [14-16]. However, data on long-term vascular impact of antioxidant supplementation in humans are limited and controversial. The findings of the present study concur with those of previous study that has shown substantial reduction in the progression of common carotid atherosclerosis during three year treatment with combined supplementation of both vitamin E and vitamin C [17]. Additionally, the beneficial effect of antioxidant supplementation on LDL oxidation and endothelial flow has been demonstrated [18,19]. Moreover several prospective randomized controlled clinical trials such as Cambridge Heart Antioxidant Study, Secondary Prevention with Antioxidants of Cardiovascular Disease in End-stage

Table 1: Baseline demographic and clinical characteristics of study patient

| Variables | Patients received antioxidants n = 36 | Patients received placebo n = 34 | p value |
|------------------------------------|--|---|----------------|
| Age (y) | 62.17 ± 6.21 | 62.97 ± 5.09 | 0.559 |
| Male/Female | 21/13 | 15/21 | 0.678 |
| BMI | 30.10 ± 4.04 | 29.83 ± 5.06 | 0.968 |
| Current smokers, n (%) | 8 (23.53%) | 10 (27.8%) | 0.684 |
| Hypertension, n (%) | 25 (75.53%) | 26 (72.2%) | 0.902 |
| Diabetes mellitus, n (%) | 13 (38.23%) | 9 (25%) | 0.233 |
| Dyslipidemia, n (%) | 26 (76.47%) | 28 (77.8%) | 0.896 |
| Obesity, n (%) | 17 (50%) | 14 (38.9%) | 0.349 |
| Family history of IHD, n (%) | 26 (76.5%) | 27 (75%) | 0.886 |
| Concomitant medication: | | | |
| Statins (%) | 25 (73.53%) | 27 (75%) | 0.888 |
| ACEIs/ARBs (%) | 19(55.88%) | 12 (33.33%) | 0.150 |
| Diuretics (%) | 6 (17.64%) | 2 (5.56%) | 0.112 |
| B-blockers (%) | 19 (55.89%) | 16 (44.4%) | 0.338 |
| CCB-blockers (%) | 10 (29.41%) | 11 (30.56%) | 0.917 |
| Aspirin (%) | 13 (38.23%) | 16 (44.45%) | 0.598 |
| Baseline systolic BP (mm/Hg) | 125.2 ± 25.4 | 138.0 ± 20.8 | 0.203 |
| Baseline diastolic BP (mm/Hg) | 78.4 ± 11.7 | 75.9 ± 7.8 | 0.291 |
| Baseline fasting glucose (mg/dl) | 127.1 ± 52.8 | 118.9 ± 42.2 | 0.476 |
| Baseline HbA _{1c} (%) | 7.1 ± 1.7 | 6.8 ± 1.4 | 0.391 |
| Baseline total cholesterol (mg/dl) | 201.5 ± 53.1 | 198.8 ± 50.8 | 0.833 |
| Baseline LDL Cholesterol (mg/dl) | 117.5 ± 43.7 | 118.3 ± 47.1 | 0.945 |

Table 1: Baseline demographic and clinical characteristics of study patient (Continued)

| | | | |
|--|--------------|--------------|-------|
| Baseline HDL% | 22.1 ± 4.6 | 26.0 ± 5.4 | 0.004 |
| Baseline triglycerides (mg/dl) | 189.5 ± 95.0 | 122.8 ± 56.5 | 0.001 |
| Baseline hs-CRP (mg/dl) | 1.84 ± 2.9 | 1.35 ± 1.6 | 0.616 |
| Baseline endothelin(fmol/ml) | 0.7 ± 2.6 | 1.4 ± 4.8 | 0.293 |
| Baseline homocysteine (µmol/l) | 9.2 ± 2.8 | 8.8 ± 3.1 | 0.486 |
| Baseline renin (ng/ml/hr) | 1.8 ± 3.4 | 1.5 ± 1.8 | 0.695 |
| Baseline aldosteron (pg/ml) | 7.4 ± 5.6 | 6.7 ± 4.5 | 0.590 |
| Baseline urine cathacholamines (mg/24 h) | 24.74 ± 22.4 | 19.5 ± 12.1 | 0.278 |

Renal Disease study and Cholesterol Lowering Atherosclerosis Study reported that the administration of antioxidants reduced the risk of cardiovascular disease [20-22]. Nevertheless, subsequent large interventional studies do not support a benefit from antioxidant supplementation [23,24]. These clinical trials have demonstrated that vitamin E alone or in combination has no effect on the risk of death or prevention of cardiovascular disease. Moreover, a dose-response meta-analysis has shown that high-dosage vitamin E supplementation was associated with a small but statistically significant increased risk for mortality [25]. The lack of benefit seen in these clinical trials does not disprove the central role of oxidative stress in atherosclerosis and justify investigating the overall clinical impact of antioxidant treatment.

Although the anti-atherogenic effect of antioxidants has been assessed in several experimental studies, the mechanisms by which these agents inhibit atherosclerosis remain to be clarified. Combined supplementation of vitamin E and C have been shown to inhibit DNA oxidation by H₂O₂ in human lymphocytes, to enhance endogenous plasma and tissue antioxidant defenses and restore endothelium-dependent vasoactivity [18,26,27]. Coenzyme Q₁₀ which plays an essential role as an electron car-

rier in mitochondrial oxidative phosphorylation, improves endothelial dysfunction in diabetic patients [28]. Finally, selenium as a determinant of antioxidative glutathione peroxidase 1 expression and activity, provides significant protection of the coronary artery endothelium against damage by oxidative stress [29].

The findings of the present study concur with those of previous studies that have shown substantial reduction in blood pressure and improvement in long-term glycaemic control with oral CoQ supplementation, reduction in plasma glucose and insulin resistance with high doses of vitamin E supplementation and significant reduction in blood pressure levels with vitamin E as well as vitamin C in hypertensive patients [30-33]. Nevertheless, which particular antioxidant or combination of antioxidants is responsible for the favorable metabolic effect in the present study remains uncertain. Additionally, we cannot exclude the possibility that specific antioxidant combination which was used in the present study, has a contributory effect of on blood pressure, glucose and lipid homeostasis as well as on improvement of vascular elasticity.

In the present study, we did not observe significant changes in humoral factors such as homocystein, endothelin, aldosterone and renin in subjects received antioxidant supplementation. Levels of urine catecholamines also did not change during the treatment period. These findings emphasize a previously published data which have shown that pathophysiologic mechanism of antioxidants action is independent of the changes in plasma concentration of blood pressure modulators, such as renin, aldosterone, endothelin [34], although the precise mechanism for antioxidant action on the vasculature remains to be elucidated.

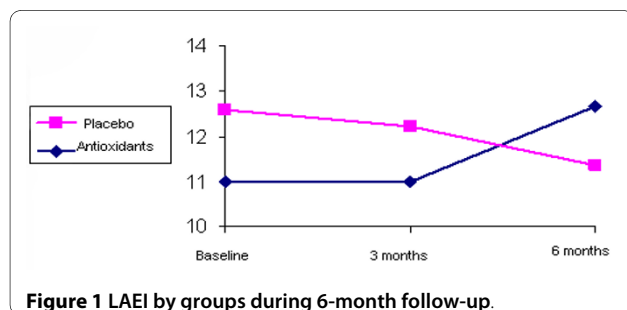


Figure 1 LAEI by groups during 6-month follow-up.

Table 2: Change from baseline in homodynamic, arterial stiffness and metabolic variables in each group

| Variables | Patients received antioxidants | | | Patients received placebo | | |
|-----------------------------|--------------------------------|----------------|---------|---------------------------|----------------|---------|
| | baseline | 6 month | p-value | baseline | 6 month | p-value |
| Systolic BP (mm/Hg) | 145.2 ± 25.4 | 136.1 ± 22.3 | 0.001 | 138.0 ± 20.8 | 135.0 ± 21.6 | 0.257 |
| Diastolic BP (mm/Hg) | 78.4 ± 11.7 | 75.0 ± 12.3 | 0.034 | 75.9 ± 7.8 | 75.0 ± 10.3 | 0.493 |
| LAEl(ml/mm Hg × 10) | 11.0 ± 4.4 | 12.7 ± 4.7 | 0.006 | 12.9 ± 6.2 | 11.3 ± 4.3 | 0.151 |
| SAEl(ml/mm Hg × 100) | 3.3 ± 1.9 | 4.7 ± 2.7 | 0.0001 | 3.6 ± 1.6 | 3.7 ± 1.9 | 0.732 |
| SVR(dynes·sec/cm5) | 1817.0 ± 751.5 | 1617.3 ± 305.2 | 0.102 | 1594.9 ± 351.3 | 1638.7 ± 311.3 | 0.533 |
| Glucose(mg/dl) | 127.0 ± 52 | 129 ± 62 | 0.535 | 118.9 ± 42 | 123.2 ± 55 | 0.496 |
| HbA _{1c} (%) | 7.08 ± 1.69 | 6.33 ± 2.3 | 0.022 | 6.82 ± 1.44 | 6.86 ± 1.66 | 0.767 |
| Total Cholesterol(mg/dl) | 201.5 ± 53.1 | 180.7 ± 58.3 | 0.074 | 197.12 ± 50 | 186.80 ± 37.78 | 0.125 |
| Triglycerides(mg/dl) | 189 ± 94 | 170.4 ± 72 | 0.058 | 124.5 ± 56.5 | 127.83 ± 46.7 | 0.645 |
| HDL% | 22.1 ± 4 | 26.2 ± 10 | 0.022 | 26 ± 5.4 | 27.11 ± 5.5 | 0.212 |
| LDL Cholesterol(mg/dl) | 116.8 ± 44.4 | 103.4 ± 47 | 0.13 | 117.91 ± 47.9 | 109.0 ± 33.1 | 0.135 |
| hs-CRP(mg/dl) | 1.94 ± 3 | 0.62 ± 0.77 | 0.222 | 1.44 ± 1.59 | 0.95 ± 0.90 | 0.271 |
| Renin (ng/ml/hr) | 1.79 ± 3.4 | 2.27 ± 2.6 | 0.494 | 1.36 ± 1.55 | 1.91 ± 1.87 | 0.149 |
| Aldosterone(pg/ml) | 7.38 ± 5.6 | 8.2 ± 5.06 | 0.354 | 6.70 ± 4.5 | 7.00 ± 3.84 | 0.638 |
| Homocysteine(μmol/l) | 9.24 ± 2.82 | 9.19 ± 2.83 | 0.911 | 8.75 ± 3.04 | 9.11 ± 3.3 | 0.139 |
| Ur cathacholamines(mg/24 h) | 24.74 ± 21 | 28.5 ± 19 | 0.118 | 19.54 ± 12 | 22 ± 20 | 0.283 |

Our study has several limitations. First, the present study contains relatively small number of participants and larger studies are required to establish the beneficial vascular effect of antioxidant supplementation. Second, we did not measure plasma levels of the antioxidants which would have added the information regarding treatment compliance and would have elucidated the pathophysiology for vascular action of antioxidants. Furthermore, since the present study has focused on patients with multiple cardiovascular risk factors, the application

of our findings to other patient populations remains uncertain.

Conclusion

We have demonstrated that combined antioxidant supplementation with vitamin C, vitamin E, coenzyme Q₁₀ and selenium has beneficial effect on glucose and lipid metabolism, blood pressure and arterial compliance in patients with multiple cardiovascular risk factors. The

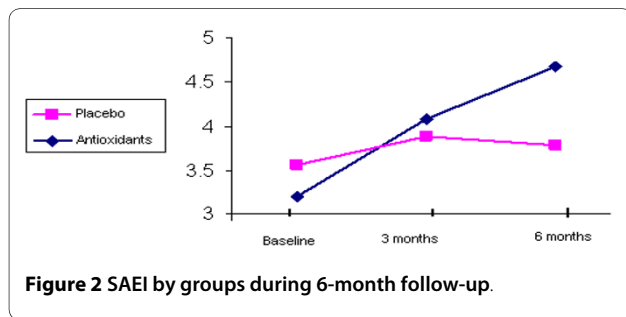


Figure 2 SAE by groups during 6-month follow-up.

findings of the present study justify investigating the overall clinical impact of antioxidant treatment in this population.

Abbreviations

CI: confidence interval; NSAIDs: non-steroidal anti-inflammatory drugs; SD: standard deviation.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MS, OD, ZM and RZ contributed to the study conception and design. MS, OD and RZ were responsible for the data acquisition. RZ and OD performed the analysis and interpretation of data. ZM carried out the immunoassays. MS were responsible for review the existing literature and for writing the first draft of the paper. All authors performed a critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

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