VITAMIN E SUPPLEMENT BLOCKS THE RESPONSE OF HDL TO LOVASTATIN THERAPY IN HYPERCHOLESTROLEMIC PATIENTS

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Abstract- HDL can prevent LDL-c oxidation. The low HDL-c State also may benefit clinically from supplemented antioxidant. This study was designed to evaluate the combination therapy of statin and vitamin E in hypercholesterolemic patients. The patients were randomized in a clinical trial aimed to avaluate the effect of vitamin E and/or statin.The life style of patients didn't alter during intervention. The subjects were randomized to two treatment groups A and B: (1) lovastatin 20mg daily at bedtime. (group A); (2) vitamin E 400 iu daily plus lovastatin 20mg daily (group B). The lipid values of each patients at baseline and after 8 weeks of treatment were compared by paired t test. The mean baseline lipid levels for 60 subjects were as follows: plasma cholesterol, triglyceride, LDL-c and HDL-c 285±68, 268±121, 158±32, 49±11 mg/dl respectively. Serum lipid levels changes in group A (statin only) and in group B (statin and vitamin E) were statistically significant. In comparison of lipid profiles changes between two groups we observed that HDL-c changes in group B were significantly lower than in group A. Vitamin E supplement blocks the respons of HDL-c to lovastatin therapy in hypercholestrolemic patients.

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INTRODUCTION

A large base of epidemiological evidence suggest that a 1 mg/dl increment in High Density Lioprotein-Cholestrol (HDL-c) would be associated with a significant decrement in cardiovascular discase risk. Also in several clinical trials aimed at lowering Low Density Lioprotein - Cholestrol (LDL-c), the HDL-c level was a significant inverse correlate with study outcome (1).

Antioxidants such as vitamin E have been shown to slow atherosclerosis. Observational studies have indicated that the persons who consume more than 100 IU of vitamin E a day for more than two years have lower rate of coronary events and lower rats of progression of coronary artery lesions (2,3). A variety of antioxidant defense systems in human body are able to detoxify prooxidants and scavenge oxygen free radicals. Among them vitamin E is the major chain-breaking lipophilic antioxidant in tissue and plasma, the most biologically active from is α-tocopherol. Several strategies for (CAD) Coronary Artery Disease patients with high cholesterol level have been proposed. They include 1- raising HDL-c with weight loss, exercise, diet and smoking cessation (life style modification; 2- increasing HDL-c to LDL-c ratio with statins; 3- Inhibiting LDL-c oxidation and atherogenesis with anti-oxidants; and 4- improving both the lipid profile and antioxidant status with a combination of a statin, and antioxidant therapy. We report here the effect of 8

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weeks treatment on plasma lipids in 2 therapy groups (statin only and statin plus vitamin E). HDL can prevent LDL-c oxidation. The low HDL-c state also may benefit clinically from supplemented antioxidant. This study was designed to evaluate combination therapy of statins and vitamin E in hypercholesterolemic patients.

MATERIAL AND METHODS

Sixty patients with serum cholesterol equal and over than 200 mg/dl and without drug history of lipid lowering during 4 weeks ago were enrolled in the study. The patients were enrolled in a clinical trial aimed to evaluate the effect of vitamin E and/or statin. The life style of patients didn't alter during intervention. The subjects were randomized to two treatment groups A and B: (1) lovastatin 20mg daily at bedtime. (group A); (2) vitamin E 400 Iu daily plus lovastatin 20mg daily. (group B)

Informed consent was obtained from all subject before entering the study.

Careful observation for potential drug adverse effect was performed.

Drugs administered for 8 weeks. Fasting Lipid profiles consist serum total cholesterol (Chol), serum Triglycerid (TG), serum HDL cholesterol was measured before and after 8 weeks of drugs administration by standard technique [6-7-8] and LDL cholesterol was calculated. Statistical analyses: the lipid values of each patient at baseline and after 8 weeks of treatment were Compared by paired T test, followed by 1-way ANOVA. Probability values < 0.05 are reported as significant changes. All analysis were performed with SPSS V.9 software.

RESULTS

Subjects

One hondred patients enrolled in this study, 40 patients of them dropped out. The remaining 60 subjects included 25 men and 35 women, ranging in age between 32 and 83 years (mean±SD, 56.95±14). There were 31 diabetic and 29 hypertensive and 22 smokers, disttributed among the 2 treatment groups as shown in table 1.

The mean baseline lipid levels for 60 subject were as follows: plasma cholesterol, 285 ± 68 mg/dl; Triglyceride, 268 ± 121; LDL-c, 158 ± 32; and HDL-c, 49 ± 11. There were no statistical significant differences in these baseline characteristics among the two treatment groups.

Lipids and lipoprotein response:

Serum lipid changes after 8 weeks treatment was observed. Lipid changes in both groups, A (statin only) and in group B (statin and vitamin E) were statistically significant. Table 2, shows lipid changes after 8 week treatment in both group A and group B. In comparison of lipid profile changes between two groups we observed that HDL-c changes in group B were significantly lower than in group A. (P<0.001)

Table 1. Baseline characteristic of patients in the 2 treatment groups.

Variable	(Group A) Lovastatin (n=30)	(Group B) Lovastatin + vitE (n=30)	*P* value
Age, y*	57	56.9	0.9
Sex, %male	36.7	46.7	0.4
Smoker, % †	33	40	0.5
Diabetes, %	56.7	46.7	0.4
Hypertention, %	43.3	53.3	0.4
Baseline Lipids, mg/dl *			
Plasma Chol	283 ± 65	288±73	0.7
Plasma TG	274 ± 127	262±117	0.7
LDL-C	158 ± 30	158±35	0.5
HDL-C	48 ± 11	50±11	0.9

* Values are mean ± SD
† Current smokers only

Table 2. Plasma lipid levels at Baseline and 8 weeks after Lovastatin therapy with or without vitamin E suplement

	Lovastatin (n=30)			Lovastatin + Vitamin E (n=30)			
Lipid	**Baseline**	**On therapy**	**Median change**	**Base line**	**On therapy**	**median change**	***P****
Chol	283±65	205±34	78±45	289± 73	214±36	74±47	0.7
TG	274±127	208±86	66.5±59	262±117	212±98	50±36	0.2
LDL-C	158±30	108±20	46±16	158±35	105±19	52±26	0.5
HDL-C	48.5±11	61.4±12	-12.8±12	50.4±11	59.2±13	-8.8±2.8	0.0001

Lipids Values are in mg/dl and represent meant ± SD
* *P* Values obtained by comparing the changes between the 2 treatment groups by one way annova test.

This difference was not due to any subgroup of individually in the subject, because this response was uniform between diabetics and nondiabetics, smokers and non smokers and hypertention and normotensive subjects in this treatment groups. Thus, when antioxidants were taken with lovastatin the favorable HDL-c responses of this drug regimen were blunted.

DISCUSSION

We evaluate combination therapy of statin and Antioxidant effect on plasma lipids. Treatment with statin therapy resulted in reduction of 27% in cholesterol; 24% in trigeglycerid; 31% in LDL-c; and increase 26% in HDL-c; and treatment with statin plus vitamin E resulted in reduction of 25% in cholesterol; 18% in trigelycerid; 32% in LDL-c and increase 17% in HDL-c. The significant difference between two groups was seen only in HDL-c changes.

To our surprise, when statin was taken with the antioxidant the potentially beneficial response of HDL-c to statin was markedly attenuated. This effect was also observed for TG but the difference wasn't significant ($P = 0.08$).

Reductions of LDL-c to HDL-c ratio have been associated either lesion improvement or slower lesion progression (1). In our trial we observed LDL-c to HDL-c ratio in both treatment groups significantly was reduced, (3.46 to 1.86 $P = 0.00$) in group A (3.29 to 1.87 $P = 0.00$) in group B. However the mean of reduction in both groups was not significantly difference. (-1.6 Vs - 1.4 $P = 0.3$).

Dr Marian *et al.* observed that statin and niacin reduce LDL-c - HDL-c ratio (1).

Recent clinical trials were showed that coadminstratior of antioxidants attenuated the long term effect vitamin E and vitamin C supplements on serum HDL-c. Although vitamin E had no effect on HDL-c levels vitamin C tended to elevate HDL-c in men but not in women.

On the other hand the results of the ASAP study concluded that supplementation with the combination of antioxidant vitamin C and E retard early progression of transplant- associated coronary arteriosclerosis. But in Hope trial and Dutch study vitamin alone could not change in lipid preoxidetion and reduce in carotid IMT (2). Dr salim yusuf in an experimental study evaluate the effect of vitamin E in 9541 patients at high risk for cardiovascular event suggest that treatment with vitamin E has no apparent effect on cardiovascular outcomes (4).

The 1999 AHA science advisory recommended that the general population, consume a balanced diet with emphasis on antioxidant-rich fruits, vegetable, and whole grains, advice that consistent with was the American Heart Association (AHA) dietary guidelines at the time. In the absence of data from randomized, controlled trials, no recommendations were made with regard to the use of antioxidant supplements (5).

Collectively, for the most part, clinical trials have failed to demonstrate a beneficial effect of oxidant supplements on Coronary Artery Diseases (CVD) morbidity and mortality. With regard to the meta-analysis the lack of efficacy was demonstrated consistently for different doses of various antioxidant in diverse population groups (9,10).

On the other hand evidence from some smaller studies documents a benefit of α-tocopherol (Cambridge heart antioxidant study, secondary prevention with antioxidants of cardiovascular disease in End-stage renal disease study) (11), α-tocopherol and slow-release vitamin C (antioxidant supplementation in Atherosclerosis prevention study)[12], and vitamin C plus vitamin E (Intravascular ultrasonography study) (13), on cardiovascular end points. In the women's angiographic vitamin and estrogen study (14), Post menopausal women with coronary disease on hormone replacement therapy given vitamin E plus vitamin C had an unexpected significantly higher all-cause mortality rate and a trend for on increased cardiovascular mortality rate compared with the vitamin placebo women.

AHA science advisory conclude that the existing scientific database dose not justify routine use of antioxidant supplements for prevention and treatment of CVD. Nonetheless AHA recommend that antioxidant research continue in order to resolve whether the oxidative modification hypothesis is relevant to human athrosclerosis (5). In conclusion, vitamin E as an antioxidant when taken with lovastatin, the favorable HDL-c responses of this drug was markedly altenuated. This effect should be consider in drug regimen for hyperlipidemic patients.

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Conflict of interests

The authors declare that they have no competing interests.

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