ORIGINAL ARTICLE

EFFECTS OF α-TOCOPHEROL ON LIPID PROFILE IN PRIMARY HYPERLIPIDEMIA

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ABSTRACT

Objective: To determine the antihyperlipidemic effects of α-tocopherol in primary hyperlipidemia.

Design: An analytical cohort study

Patients and Methods: This study was conducted in the Department of Pharmacology and Therapeutics, Basic Medical Sciences Institute of Jinnah Postgraduate Medical Center, Karachi, from February to April 2001. Newly diagnosed and un-treated primary hyperlipidemic persons of either gender between the ages 17 to 70 years were initially enrolled in the study for a 12 weeks (90 day) trial with fortnightly follow up visits. The selected patients were divided into 2 groups. The first group (Group-I) was treated with diet restriction and exercise only. The second group (Group-II) was treated with diet restriction, exercise and α-tocopherol. Results were compared using paired t-test.

Results: There were 35 patients in all. After treatment with α-tocopherol, cholesterol reduction was highly significant ($p<0.01$). Triglyceride reduction was significant ($p<0.05$). Increase in HDL-c level was highly significant ($p<0.001$). The LDL-c reduction was statistically highly significant ($p<0.001$). VLDL reduction was also significant ($p<0.01$).

When compared between the Groups I and II, the reduction in cholesterol was moderately significant ($p<0.01$), LDL-c reduction was found to be markedly significant ($p<0.01$). HDL and VLDL reduction was also found to be significant ($p<0.05$). In comparison there was no significant change in triglyceride level.

Conclusion: Diet restriction and exercise had significant beneficial effects on lipid profile. When supplemented with α-tocopherol, there was a highly significant beneficial effect on lipid profile.

Keywords: Lipid Profile, α-Tocopherol, exercise, diet

INTRODUCTION

It was in 1913 that Antischkoff (cited by Boyd, 1980), first succeeded in producing lesion in the rabbit aorta, which resembled those in humans by means of a cholesterol rich diet.[1]

Hyperlipidemia is the major cause of coronary heart disease (CHD) and atherosclerosis.[2, 3] More than 650,000 people die every year of coronary heart disease in the United States alone. In 1984 the link between serum cholesterol level and risk of CHD was demonstrated for the first time. A 1% drop in serum cholesterol reduces the risk for CHD by 2%.[4]

There exist many demographic and socio cultural differences between countries but one factor that relates most closely to CHD is the median cholesterol of middle-aged population. In a country such as Japan, where the average serum cholesterol level is low, other coronary risk factors do not seem to operate and hence CHD is relatively uncommon even in cigarette smokers and persons with Diabetes mellitus and hypertension.[5]

A major lipid soluble free radical scavenger α-tocopherol

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is transported in low-density lipoprotein and decreases the oxidation of LDL.[6-10] The biological membrane has poly-unsaturated fatty acids (PUFA) as a part of membrane phospholipids. Vitamin E is distributed in lipid phase of membrane contributing to the structure and stability of the membranes.Living cells have been vulnerable to be attacked by spontaneously formed free radicals either formed endogenously or exogenously, chemicals, toxins, radiation etc.The α-tocopherol as an anti-oxidant, breaks the free radical chain reaction.[11] Transportation of α-tocopherol , in circulation, is in clylomicrons (CMs). In blood, the α-tocopherol in CMs rapidly equilibrates with other plasma lipoproteins and the bulk is formed in the low density lipoproteins. Subsequently, it becomes associated with plasma B-lipoprotein.

Low-density lipoprotein (LDL) is a contributory factor. for oxidation of atherogenesis The oxidized LDL is taken up by the LDL macrophages affecting the vascular endothelial lining and producing vasoconstriction. Pharmacological doses of vitamin E appear to protect LDL from oxidation. Serum high-density lipoproteins (HDL) cholesterol is also increased via vitamin E supplementation.[7, 10, 12] Supplemental doses of vitamin E above the usual intake afford protection from various chemical toxicants. These include metals, such as silver, mercury, lead, selenium as well as hepatotoxic compounds such as carbon tetrachloride, Benzene, Cresol and several drugs.[13]

Though the antioxidant role of α-tocopherol is well established, there is sparse published data available regarding the lipid lowering effects of α-tocopherol. The objective of this study was to determine the antihyperlipidemic effects of α-tocopheral in primary hyperlipidemia.

PATIENTS AND METHODS

This study was conducted in the Department of Pharmacology and Therapeutics, Basic Medical Science Institute (BMSI), Jinnah Postgraduate Medical center (JPMC), Karachi from February to April 2001. Thirty five patients with primary hyperlipidaemia were enrolled in this study. Patients selected were newly diagnosed untreated primary hyperlipidemic of either gender between 17 to 70 years. Those with normal lipid profile were selected for control group.
After explaining the complete project, consent was obtained from all participants before they were enrolled in the study.
The study period consisted of 3 months with fortnightly follow up visits. The required information such as name, age, gender, occupation, address, previous medication, date of follow up visit laboratory investigation etc. of each patient were recorded on a performa especially designed for this study.

The selected patients were divided into 2 groups. Group- I (n=15) had fifteen primary hyperlipidemic patients according to the criteria mentioned above. They were advised an isocaloric weight maintaining diet (as percent calories) consisting of carbohydrates 50-60%, proteins 10-20%, total fats less than 30% and cholesterol less than 300 mg/ day. Diet was adjusted according to body weight and physical activity. This weight maintaining dietary programme was followed throughout the study period. This group was also advised exercise of 15-30 minutes daily (brisk walking). In group-II (n=20), hyperlipidemic patients with same criteria were given α-tocopherol acetate 400 mg once daily, alongwith diet control and exercise of same duration for 12 weeks.

Initially a detailed medical history and physical examination of all patients were carried out. All the baseline assessments took place on the day of inclusion (day 0) in the study and a similar assessment was done on day 45 and day 90 of research design. After the baseline measurement (day 0), patients were given α-tocopherol acetate as per schedule of the groups for 12 weeks. During this period patients were treated with individualized weight maintaining diets with caloric content adjusted to the patient's age, body weight and physical activity under supervision of a dietician. All patients were fully inquired about compliance and side effects of the treatment at each fortnightly visit.

Blood samples were drawn from each patient on the morning of day0, day45 and day 90, after an overnight fast of 12-14 hours.

All the laboratory tests were done in the National Institute of Cardiovascular Diseases and the reference values used were (cholesterol < 200 mg/dl, triglyceride < 159mg/dl, HDL > 40 mg/dl, LDL< 120mg/dl).
Serum total cholesterol, serum triglycerides and serum HDL-cholesterol were estimated by the enzymatic method, using Kit provided by Eli Tech Diagnostic, France. LDL-cholesterol was calculated according to formula given by Beamount et al.[14] VLDL cholesterol was calculated according to the formula, proposed by Wilson (cited by Delong et al).[15]

RESULTS

The observations of all the treatment groups were recorded on day 0, day 45 and day 90 on various parameters. The mean serum total cholesterol level of group I patients reduced gradually from 211.9 ± 3.7 mg/dl on day 0 to 199.9 ± 3.0 mg/dl on day 90. This reduction was not statistically significant when compared with day0 and day45 or day 45 and day 90, but was significant when evaluated between day 0 and day 90 ($p<0.05$). The average percentage changes being 5.6% . In group II patients, mean serum total cholesterol level decreased from 247.3 ± 6.4 mg / dl to 210.5 ± 8.0 mg/dl, on day-0 to183.8 ± 8.1 mg/dl on day 90. The reduction was statistically moderately significant, when it was compared between day0 and day 45 ($p<0.01$) and day 45 and day90 ($p<0.05$), but highly significant ($p<0.001$) when comparison was done between day 0 and day 90. The reduction was found to be 26.1% for this group as depicted in Table-1.

The mean serum total trigylcerides level of group I patients was reduced from 141.6 ± 7.1 mg/dl on day 0 to 138.3 ± 5.9 mg/dl on day 45 and 136.1 ± 5.7 mg/dl on day 90, however, the reduction when evaluated was not significant statistically. The average percentage change between day 0 and day 90 was 3%. (group II patients) for 90 days, the serum trigylcerides gradually reduced from 167.3 ± 7.1 mg/dl on day 0 to 150.5 ± 5.7 mg/dl on day 45 and 141.3 ± 6.0 mg/dl day 90. This reduction, when compared were not significant statistically as results of day 0 with day 45 and day 45 with day 90 were compared, but were significant ($p<0.05$) when comparison was done between day 0 and day 90. The average percentage change being 14.3% between day 0 with day 90 as depicted in Table- 1. Mean serum HDL-cholesterol level in 15 primary hyperlipidaemic patients kept only on diet restriction and exercise (Group-I) only increased gradually from 36.7 ± 2.5 mg/dl on day 0 to 41.4 ± 1.9 mg /dl on day 45 and then 45.1 ±1.6 mg/dl on day 90. This increase in HDL-c when evaluated statistically was found to be non-significant when results of day 0 with day 45 with day 45 and day 90 were compared, but were moderately significant ($p<0.01$) when HDL levels between day 0 and day 90 were compared. The average percentile increased was 19.5% between day0 and day 90. In 20 patients with primary hyperlipidaemia receiving α-tocopherol (Group-II) for 90 days, the mean HDL increased from 36.0 ± 2.1 mg/dl on day 0 to 41.5 ± 1.5 mg/dl on day 45 and then 46.5 ± 5.5 mg/dl on day 90. This increase was statistically significant ($p<0.05$), when compared with day 0 and day 45 with day 90 it was highly significant ($p<0.001$) and day 45 when comparison was made between HDL-c levels of day 0 and day90.The average increase was 32.8% after 90 days as shown in Table-1.

Mean serum LDL-c level in 15 primary hyperlipidaemic patients kept only on diet restriction and exercise (Group-I) reduced from 146.9 ± 4.7 mg/dl on day 0 to 137.9 ± 4.0 mg/dl on day 45 and 127.5 ± 3.9 mg/dl on day 90. This reduction was not statistically significant when compared between day 0 and day 45 or day 45 and day 90, However there was moderately significant ($p<0.01$) decrease when compared between day 0 and day 90. The decrease was 31.1% after 90 days. In 20 patients treated with α-tocopherol (Group-II) for 90 days, the mean serum LDL-c level decreased from 177.3 ± 6.8 mg/dl on day0, to 138.6 ± 7.9 mg/dl on day 45 and 109.1 ± 7.8 mg/dl on day 90. This reduction in serum LDL-c was significant ($p<0.05$) between day 45 to day 90, but statistically highly significant ($p<0.001$) between day 0 to day 45 and day 0 to day90. A 39.0% decrease as noted after 90 days as

TABLE1 : Changes in mean lipid profile level at day45 and day90 after treatment in primary hyperlipidaemic patients of group I and II

Lipid Profile	Groups	day 0 Mean ± standard error	Day 45	Day 90	P value		Percentage Change from days 0 to day 90	P Value
					day-0 vs. day-45	day-0 vs. day-90		
Serum cholesterol (mg / dL)	Group I (n = 15)	211.9± 3.7	206.9± 3.1	199.9 ±3.0	NS	<0.05	5.6% ↓	<0.01
	Group II (n = 20)	247.3 ± 6.4	210.5± 8.0	183.8±8.1	< 0.01	<0.001	26.1 % ↓	
Triglycerides (mg / dL)	Group I	141.6± 7.1	138.3± 5.9	136.1± 5.7	NS	NS	3.0 % ↓	NS
	Group II	167.3±7.1	150.5±5.7	141.3±6.0	NS	< 0.05	14.3 % ↓	
HDL (mg / dL)	Group I	36.7±2.5	41.4±1.9	45.1±1.6	NS	<0.01	19.5 % ↓	< 0.05
	Group II	36.0±2.1	41.5±1.5	46.5±5.5	<0.05	<0.001	32.8 % ↑	
LDL (mg / dL)	Group I	146.9±4.7	137.9±4.0	127.1±3.9	NS	<0.01	13.1 % ↑	< 0.01
	Group II	177.3 ± 6.8	138.6 ± 7.9	109.1 ± 7.8	<0.001	<0.001	39.0 % ↓	
VLDL (mg / dL)	Group I	28.3 ± 1.4	27.7 ± 1.2	27.2 ± 1.2	NS	NS	3.3% ↓	<0.05
	Group II	33.5 ± 1.4	30.1 ± 1.2	28.0 ± 1.2	<0.05	<0.01	15.3% ↓	

Figure in parentheses indicates number of patients. All observations were measured in mg/dl. NS = non- significant.

shown in Table-1.

Mean serum VLDL-c level of (Group-I patients) only decreased from 28.3 ± 1.4 mg/dl on day 0 to 27.7 ± 1.2 mg/dl on day 45 and 27.2 ± 1.2 mg/dl on day 90, however this reduction when evaluated was found statistically non-significant. A decrease of 3.3% was noted after 90 days. In Group-II patients, the mean serum VLDL-c level decreased from 33.5 ± 1.4 mg/dl on day0, 30.1 ± 1.2 mg/dl on day 45 and 28.0 ± 1.2 mg/dl on day-90. The reduction was significant ($p<0.05$) when level of day0 was compared with day 45 and moderately significant ($p<0.01$) when mean serum VLDL-c levels were compared to between day 0 and day 90, whereas no significant reduction was found between levels of day 90 and day 45. The average decrease was 15.3% as compared day0 with day 90 as shown in Table-1.

The percentage reduction of cholesterol, LDL & VLDL was statistically significant between the two groups ($p<0.5$). The Percentage increase of HDL was also significant ($p<0.05$) between the two groups (Table - I)

DISCUSSION

Diet has a strong impact on the level of cholesterol and triglycrides. There is a less incidence of coronary heart disease and thrombosis in population who take (or consume) large quantities of long chain polyunsaturated fatty acids. These acids are uncommon in normal diets, which typically contain mostly saturated and monounsaturated fatty acids. Since more than 20 years ago, polyunsaturated fat has been found to have a hypocholesterolemic effect when substituted for saturated fat in the diet.[16]

Patients on diet and exercise regime (Group-I), have reduction of serum triglycerides, VLDL serum cholesterol and LDL. It is evident by a report of NCEP expert panel, that exercise may lower the LDL –cholesterol level.[17] HDL-cholesterol increase was demonstrated by Wood et al.[18] In that study long distance runner have much higher HDL-cholesterol concentration than sedentary subjects. The rise in HDL concentration induced by physical training may be a consequence of enhanced catabolism of triglycerides rich lipoproteins.[19]

The present results did not corelate with the results of Levy et al.[20] He kept 12 young normal volunteers (aged 18 to 22 years) on both the average American diet and on type II therapeutic diet, which contained cholesterol less than 200 mg/day and a poly unsaturated to saturated fat ratio of 2.5. There was an average drop of 25% in total cholesterol, most of which was in LDL fraction. In the present study the serum cholesterol in 15 patients reduced to 5.6%, which is less than that reported by Levy et al.[20] The greater reduction in serum cholesterol is probably because levy included normal and younger patients where as in the present study the inclusion criteria for patients was primary hyperlipidaemia. The second reason is that levy used type II therapeutic diet while in this trial type I therapeutic diet was used.

Group II having 20 patients supplemented with vitamin E 400-mg/ day, showed highly significant fall in cholesterol levels. This fall in total cholesterol level is probably due to the fact that vitamin E is transported in lipoproteins mainly LDL. Vitamin E also enhances the clearance of cholesterol through liver and hence affects the total cholesterol level. The contributing factors influencing cholesterol level are diet restriction and exercise. The probable mechanism for LDL cholesterol reduction is again incorporation of vitamin E with LDL –c during its transport. Increased amount of vitamin E in LDL from other lipoproteins may lead to enhanced clearance of LDL.[13] Diet and exercise are other contributing factors in lowering the LDL levels.The increase in HDL-c is probably due to decrease in triglycerides levels. Hypertriglyceridemia is one of the factors decreasing the HDL-c.[17] In the present study triglyceride is also decreased, which may have a positive effect on HDL-c. Other contributing factors are diet restriction and exercise. The present results are compatible with the result of Herman et al.[21] He found that HDL level is increased with the supplementation of vitamin E. According to him the increase in HDL fraction occured due to redistribution of cholesterol Herman et al. also stated decrease in the total triglyceride levels after ingestion of large doses of vitamin E (600 IU/ day for 3 days).[21]

The mechanism for decreased triglyceride level as stated by Traber et al. relates with absorption of vitamin E from the intestine in chylomicrons while entering in circulation.[22] This incorporation of vitamin E with chylomicrons might result in increased hydrolysis of triglycerides by lipoprotein lipases leading to a less amount of triglycerides in chylomicron remnants, which is delivered to liver.[22] The other possibility regarding vitamin E action is that it may interfere in the synthesis of endogenous triglyceride in liver and the other contributing factors are diet restriction and exercise.[22]

Herman et al. in their clinical observation also found that there is decrease in VLDL after vitamin E supplementation.[21] The present findings relate with the result of herman et al. as VLDL levels were decreased,

although Herman et al. did not mention the mechanism.[21] However in another study the possible mechanism as stated by Traber et al is that VLDLs are the only lipoprotein involved in vitamin E secretion from liver, which is also distributed to other liproteins.Diet restriction and exercise are also influencing factors.[22]

This study also relates with the study of Prasad and Kalra, who studied the effects of vitamin E on serum cholesterol in rabbits.[10] They observed an increase in the HDL cholesterol and HDL: LDL ratio besides a decrease in the LDL cholesterol and triglycerides.

In another double blind clinical trials 35 diabetics were supplemented with vitamin E capsule , 100 IU/ day orally or placebo for 3 months . Their result showed that vitamin E supplementation significantly lowers lipoproteins and lipid levels in diabetic patients.[23] The study also favours the present study. The present results do not relate with finding of Kesaniemi and Grundy.[24] According to them vitamin E does not decrease plasma total cholesterol, VLDL and LDL-c or triglycerides concentration niether increase HDL-c level. They started the trial with vitamin E 400 mg/day and ended with 800 mg/day, which is a double dose used than the presently used dose, but they did not put patients on diet restriction and exercise, which may be an additional beneficial factor in the present study.

CONCLUSION

Diet restriction and exercise have beneficial significant effect on lipid profile; α-tocopherol have a pronounced beneficial effect on lipid profile.

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