Original article:

Vitamin E supplementation and risk of coronary artery disease in women

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Abstract

Introduction- Increase in prevalence of Coronary artery disease (CAD) in India warrants probing into the presence of various risk factors and their association with CAD. Traditional risk factors such as age, family history of CAD, hypertension, diabetes, dyslipidemia, smoking, and physical inactivity are predictors of risk in women. The recent risk factors with controversial status as individual risk factors are serum lp(a) and serum hsCRP which need to be addressed. Hence this study was designed to assess the response of traditional and recent risk factors to supplementation of vitamin E in women of reproductive age group.

Material and Methods- 106 women in reproductive age (18- 45 years) were screened from MIMER Medical College and Rural Health Training Centre for the parameters like serum lipid profile, MDA (malondialdehyde) ,Vitamin E, hsCRP and lipoprotein(Lp) (a). Vitamin E supplementation 400mg for 45 days was given to women in whom one or more parameters were found to be abnormal and the parameters were re-estimated.

Result- There was a significant fall in the serum total cholesterol and LDL levels after vitamin E supplementation in affected women. The levels of serum triacylglycerol , hsCRP, Lp(a) and MDA decreased and HDL, vitamin E levels increased insignificantly after supplementation in the affected females.

Conclusion-Screening of women in reproductive age group for lipid profile, Lp(a) and hsCRP would help to identify the risk factors for CAD. These women could be administered vitamin E so that the risk of developing CAD would be minimized in them.

Keywords- CAD, dyslipidemia, Lp(a), hsCRP, vitamin E, MDA

1. Introduction –

Coronary artery disease (CAD) is a leading cause of morbidity and mortality in most of the countries and is emerging as an epidemic in developing countries [1]. In India, increase in prevalence of CAD warrants probing into the presence of various risk factors and their association with CAD [2]. Traditionally CAD has been considered as a disease predominantly affecting men and for a long time women were not included in cardiovascular research programme [3]. More women than men die of CAD than of cancer (including breast cancer), chronic lower respiratory disease, Alzheimer disease, and accidents combined [4]. In the early 1990's attention was focussed on women with CAD especially postmenopausal women though recent studies reveal that women in reproductive age group are equally prone to CAD [3] . The lifetime risk of developing CAD at the age of 40 years is 50% for men and 33% for women. The consequences of CAD are worse in women than in men. Among individuals with premature MI (under age 50), women experience a 2-fold higher mortality rate after acute MI compared to men [5]. Although most risk factors contribute to CAD in both men and women, the impact of individual risk factors may be different [3]. It appears that the pathophysiology of CAD varies between women

and men. On cardiovascular computed tomography, women have been shown to have smaller coronary artery diameters than men do [6]. Recently, disorders of the coronary microvasculature and endothelial dysfunction have been implicated in the occurrence of non obstructive CAD in women. Han et al. [7] studied men and women with early CAD and found that men have higher degrees of atheroma and epicardial endothelial dysfunction, whereas women have more microvasculature affection. In Women's Ischemia Syndrome Evaluation (WISE) study, approximately one-half of women with chest pain without obstructive CAD had microvascular dysfunction [8]. Traditional risk factors such as age, family history of CAD, hypertension, diabetes, dyslipidemia, smoking, and physical inactivity are important predictors of risk in women. In contrast to the linear increase in CAD in men as they age, there is a more exponential increase in CAD in women after the age of 60 [9]. Elevated triglycerides have been shown to be of greater risk to women than to men [10].

The recent risk factors with controversial status as individual risk factors are serum lp(a) and serum hsCRP which need to be addressed [11].

The mainstay of development of CAD is oxidation of LDL which may occur due to various risk factors.

There has been a growing evidence suggesting that oxidation of low density lipoprotein (LDL) plays an important role in atherosclerosis. Oxidized LDL is taken up more readily by macrophages to create foam cells, it is chemotactic for circulating monocytes and inhibits motility of tissue macrophages [12]. Lipid peroxide concentration have been found to be higher in patients of atherosclerosis [13]. The susceptibility of LDL oxidation was correlated well with severity of atherosclerosis [14].

Under normal conditions, numerous cellular antioxidant systems exist to defend against oxidant stress and maintain the redox balance of the cell. ROS are cleared from the cell by enzymatic systems including superoxide dismutase, catalase, and glutathione peroxidase or the non – enzymatic system including vitamin E, ascorbic acid, and uric acid [15]. However, oxidative stress is developed when there is excessive production of ROS, outstripping endogenous antioxidant mechanisms. The major damage to cells results from the ROS induced alteration of macromolecules such as polyunsaturated fatty acids in membrane lipids, essential proteins and DNA [16].

Though it is unclear if high-sensitivity C-reactive protein (hsCRP) is an independent risk factor for CAD, it may improve risk detection in women [17,18]. The Reynolds risk score, a risk assessment tool, incorporates hsCRP and has been shown to improve risk prediction in women [19].

Many studies showed that CAD is mainly caused by genetic and environmental factors [20]. Lp(a) is produced in the liver and circulates in the plasma, which is an LDL-like particle that consists of an apolipoprotein (a) (apo(a)) moiety linked to one molecule of apolipoprotein B100 via a disulfide bond [21]. Elevated Lp(a) levels has been considered to be an independent risk factor for CAD [22].

Vitamin E is a potent lipid soluble antioxidant carried in LDL [23]. It inhibits the proliferation of smooth muscle cells in vitro[24] and when added to plasma, it increases the resistance of LDL to oxidation [25]. On supplementation of vitamin E to volunteers, they showed increased resistance of LDL to oxidation [26]. Several small trials of vitamin E in peripheral vascular disease have been reported, but the results have been inconclusive [27]. As vitamin E protects LDL from oxidation, many researchers have studied role of vitamin E in prevention and initiation of progression of CAD with varied results [28].

This study hence is an attempt to assess the response of traditional and recent risk factors to supplementation of vitamin E in women of reproductive age group.

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Aim and objectives-

The aim of this study is to evaluate the role of antioxidant vitamin E supplementation in women exposed to risk factors of CAD.

Objectives-

I. Estimation of risk factors for CAD – a. Serum lipid profile

b. Serum Lp(a)

c. serum hsCRP

II. Estimation of Index of oxidative stress - serum MDA-

III. Estimation of Antioxidant status - Vitamin E

2. Material and Methods-

a. Sample size- i. Screening of 106 women in reproductive age (18- 45 years) from M.I.M.E.R. Medical College and Rural Health Training Centre for the biochemical parameters. Sample size was determined by power calculation in consultation with the statistician.

ii. Selection of subjects for administration of vitamin E supplementation in whom one or more parameters were found to be abnormal.

b. Inclusion criteria- Clinically healthy women in age group 18-45 years with normal BMI.

c. Exclusion criteria – i. Postmenopausal women.

ii. Women on any medication and or Hormone replacement therapy,OC pills or supplementation like, vitamins or minerals.

iii. Women suffering from diabetes mellitus, hypertension or any other major illness.

d. Collection of sample – 5 ml of blood was collected under all aseptic precautions after a written and informed consent from all the subjects in plain bulb.

All the parameters were estimated on the sample.

e. Methods of assay-

1. Lipid profile-

i. Serum triacylglycerol- GPO – Trinder's method[29]

ii. Serum total cholesterol- Modified Roeschlau's method [30]

iii. Serum direct HDL cholesterol- Spectrophotometric method [31]

iv. Serum direct LDL cholesterol – Spectrophotometric method [32]

2. Serum hsCRP – Spectrophotometric method [33]

3, Serum Lp(a) – Turbidimetric immunoassay [34]

4. Serum vitamin E – Spectrophotometric method [35]

5. Serum MDA – Spectrophotometric method [36]

f. Statistical analysis- The results are expressed as mean +/- standard deviation and analysed using students paired t test and using EPI software 2017.

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3. Observation and Results-

Out of 106 women who were subjected to estimation of the biochemical parameters, 16 females had one or more abnormal parameters and were given supplementation of Tab. Evion (Vitamin E 400 mg) od for a period of 45 days.

Table 1 - Lipid profile –Before and after Vitamin E supplementation

N=16	Total cholesterol (Normal range <200mg/dl)	Triacylglycerol (Normal range <150mg/dl)	LDL (Normal range <130mg/dl)	HDL (Normal range 35-65mg/dl)
Before supplementation	191± 25	167 ± 60	107 ± 26	42 ± 8
After supplementation	161 ± 27	128 ± 51	91 ± 13	44 ± 7
P value	0.003	0.05	0.03	0.43

As seen in table 1 the means of all the lipid parameters except triacylglycerol are within the normal range in the affected women. There was a significant fall in the serum total cholesterol and LDL levels after vitamin E supplementation in those affected women. The levels of serum triacylglycerol decreased and HDL increased insignificantly.

Table 2- Effect of Vitamin E supplementation on Serum hsCRP, lipoprotein (a), vitamin E and MDA

	HsCRP (Normal range 3mg/l)	Lipoprotein (a) (Normal range 3.3-30mg/dl)	Vitamin E (Normal range 0.2-1.5mg/dl)	MDA (Normal range 2-4nmoles/ml)
Before supplementation	2.1 ± 1.3	8.6 ± 10.8	0.82 ± 0.2	2.6 ± 1.2
After supplementatio	1.7 ± 0.5	4.7 ± 3.1	1.23 ± 0.7	1.9 ± 0.9
P value	0.3	0.1	0.05	0.1

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Table 2 shows that the means of all the parameters are within the normal range but there is an insignificant decrease in serum hsCRP, Lp(a) and MDA and rise in serum vitamin E levels after vitamin E supplementation in the affected females.

Table 3- Percentage of women having abnormal parameters before and after vitamin e supplementation (N=16)

Parameter	% of women with abnormal parameter	% of women with **improvement** after vit E supplementation
Elevated triacylglycerol	10	30
Elevated total cholesterol	6	83
Elevated LDL	2	100
Decreased HDL	3	100
Elevated hs CRP	4	100
Elevated Lp(a)	1	100
Elevated MDA	2	100
Decreased vitamin E	0	100

Table 3 shows improvement in all the parameters to variable extent after vitamin E supplementation.

Vitamin E concentration was normal in all the 16 females before supplementation which showed an insignificant rise after supplementation with vitamin E.

Overall though the values of all the biochemical parameters were not in the normal range, there appears to be significant improvement in few abnormal parameters while in others the improvement was insignificant statistically after vitamin E supplementation inspite of the levels of vitamin E being in the normal range before supplementation in all 16 females.

4. Discussion-

Currently CAD is the leading cause of mortality in women.

Over the past 2 decades, considerable evidence has been gathered in support of the hypothesis that free-radical–mediated oxidative processes and specific products arising from there, play a key role in atherogenesis [2,3]. At the center of this hypothesis are low-density lipoproteins (LDLs), which undergo multiple changes on oxidation

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that are thought to be proatherogenic. Oxidation of LDL leads to the production of a diverse array of biologically active compounds, including some that influence the functional integrity of vascular cells [37]. One study showed that a deficiency of vitamin E was a major and most reliable indicator of heart disease risk [38]

The present study showed that the raised total cholesterol and LDL levels decreased to normal values significantly after supplementation of vitamin E . There was also a fall in the level of triacylglycerol and a rise in HDL level though not significant after vitamin E supplementation. The oxidation of LDL is a free radical driven lipid peroxidation process and the aldehyde products of lipid hydroperoxide breakdown are responsible for the modification of the LDL apoprotein. Aldehyde modified Apo B protein has altered receptor affinity, causing it to be scavenged by macrophages in an uncontrolled manner with the development of foam cells and the initiation of the atherosclerotic lesion [39]. Vitamin E also increases the expression of enzymes that suppress arachidonic acid metabolism thereby releasing prostacyclins from the endothelium which in turn dilates blood vessels and inhibits platelet aggregation [40]. The marker of lipid peroxidation – MDA was decreased after supplementation of vitamin E orally whereas the antioxidant capacity as shown by serum vitamin E levels increased though not significant in this study. An inverse association was observed by other workers between dietary vitamin E intake and coronary mortality in both men and women with relative risks of 0.68 (p for trend = 0.01) and 0.35 (p for trend >0.01) , respectively between the highest and lowest tertiles [41] There is an increased oxidative stress due to the excessive production of ROS, which may result in reduced antioxidant capacity. The mechanism behind the reduction in vitamin E levels is due to the ROS. This results in an imbalance between antioxidant power and prooxidants, which can facilitate and augment the atherosclerotic process [39]. Arterial stiffness is a precursor of heart disease [42]. Vitamin E has been shown to preserve arterial function and reduce arterial stiffness [43] .In context to the above findings,our study indicates that antioxidants exert their protective effect against CAD by two fundamental mechanisms. The first mechanism is LDL – specific anti-oxidant action i.e. the protection of LDL against oxidative modification by antioxidants present either in LDL or in the extracellular fluid of the sub endothelial space [39]. A low LDL vitamin E concentration might play a role in development of stenoses in coronary arteries and may contribute to clinically manifest CAD [44]. The second mechanism of antioxidant action is tissue or cell specific i.e. increased uptake of antioxidants by vascular cells and increased cellular antioxidant status. This increase in cellular antioxidants may result in decreased production or release of ROS and thus less cell-mediated LDL oxidation. In addition, the cellular antioxidants may increase the resistance of vascular cells to the damaging effects of modified LDL. Both the LDL-specific and cell-specific antioxidant actions may lead to decreased adhesion molecule and monocyte chemotactic protein- I (MCP -I) expression, decreased foam cell formation and thus improved vascular function and decreased atherogenesis [39].

HDL levels were found to be raised though not significant which may be due to the fact that vitamin E mainly prevents oxidation of the lipids in LDL and modifies the apoprotein component whereas it may be possible that this effect of vitamin E on HDL components is not that effective.

Triacylglycerols were insignificantly decreased after vitamin E supplementation in our study. This may be due to the presence of saturated fatty acids in triacylglycerol in contrast to unsaturated fatty acids in LDL which are more susceptible to oxidation may also have contributed. Secondly, shorter duration of vitamin E supplementation may also contribute to this.

The recent risk factors hsCRP and Lp(a) showed an insignificant fall after vitamin E supplementation. Lp(a) and LDL penetrate the inner layer of the arterial wall and accumulate together at sites for atherosclerotic plaque

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formation. Evidence suggests that Lp(a) may be more firmly retained in the arterial wall than LDL. Furthermore, Lp(a) transports oxidized phospholipids whose plasma levels are strongly correlated with the severity of coronary artery disease. Interestingly, these Lp(a) associated oxidized phospholipids possess pro-inflammatory activity. This might be one of the links between lipids and inflammation in atherosclerosis. This may be one of the mechanisms behind the involvement of Lp(a) in heart attack and stroke [45]. Increase in hsCRP concentrations might lead to binding to the LDL particle in atherosclerotic plaques leading to activation of complement, thus, being proinflammatory and contributing to atherogenesis, and it may also increase ischemic tissue damage by complement dependent mechanism and tissue factor production by macrophages [46]. The insignificant fall in Lp(a) and hsCRP in our study may be due to short duration of the vitamin E supplementation.

5. Conclusion-

The study concludes that vitamin E supplementation may reduce the risk of CAD in women by minimizing the effect of concerned risk factors.

6. Recommendations-

The above study suggests that the screening of women in reproductive age group for lipid profile, Lp(a) and hsCRP would help to identify the risk factors. These women could be administered vitamin E so that the risk of developing CAD would be minimized in them.

7.Limitations-

1. Smaller sample size. Larger sample size would help in endorsing the findings of the present study.
2. Shorter duration of vitamin E supplementation. The findings may be more emphatic if vitamin E is administered for a longer duration.

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