Review Article

Vitamin E in cardiovascular disease: has the die been cast?

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Cardiovascular disease, in particular coronary artery disease (CAD), remains the most important cause of morbidity and mortality in developed countries and, in the near future, more so in the developing world. Atherosclerotic plaque formation is the underlying basis for CAD. Growth of the plaque leads to coronary stenosis, causing a progressive decrease in blood flow that results in angina pectoris. Acute myocardial infarction and unstable angina were recently recognised as related to plaque rupture, not progressive coronary stenosis. Acute thrombus formation causes an abrupt coronary occlusion. The characteristics of the fibrin cap, contents of the plaque, rheological factors and active inflammation within the plaque contribute to plaque rupture. Oxidative processes are important in plaque formation. Oxidized low density lipoproteins (LDL) but not unoxidized LDL is engulfed by resident intimal macrophages, transforming them into foam cells which develop into fatty streaks, the precursors of the atherosclerotic plaque. Inflammation is important both in plaque formation and rupture. Animal studies have shown that antioxidants reduce plaque formation and lead to plaque stabilisation. In humans, high intakes of antioxidants are associated with lower incidence of CAD, despite high serum cholesterol levels. This observation suggests a role for inflammation in CAD and that reducing inflammation using antioxidants may ameliorate these processes. Men and women with high intakes of vitamin E were found to have less CAD. Vitamin E supplementation was associated with a significant reduction in myocardial infarction and cardiovascular events in the incidence of recurrent myocardial infarction. In the hierarchy of evidence in evidence-based medicine, data from large placebo-controlled clinical trials is considered necessary. Results from various mega-trials have not shown benefits (nor adverse effects) conferred by vitamin E supplementation, suggesting that vitamin E has no role in the treatment of CAD. These results do not seem to confirm, at the clinical level, the effect of antioxidants against active inflammation during plaque rupture. However, a closer examination of these studies showed a number of limitations, rendering them inconclusive in addressing the role of vitamin E in CAD prevention and treatment. Further studies that specifically address the issue of vitamin E in the pathogenesis of atherosclerosis and in the treatment of CAD need be performed. These studies should use the more potent antioxidant property of α-tocotrienol vitamin E.

Key words: Antioxidants, cardiovascular disease, vitamin E.

Introduction

Coronary artery disease (CAD) is an important disease for both developed and developing countries. Although CAD incidence has declined progressively in developed countries since its peak in the 1960s, it remains the number one cause of morbidity and mortality.[1] Further, perhaps due to increasing age in developed countries, the rate of decline has now decreased.[2] In many areas of the developing world, the incidence of CAD is still increasing. This is particularly seen in countries in rapid transition from an agro-based economy to an industrial economy.[3] Further, Murray and Lopez, in their study of burden of disease, estimated that developing countries will continue to be burdened with CAD over the next 20 years, and most CAD will be seen in developing countries.[4]

Coronary risk factors

The Framingham Heart Study has established the concept of risk factors, which are defined as conditions that predispose an individual to disease, but are not necessarily causative.[5] A number of coronary risk factors have been identified; some are well established (smoking, hypertension, diabetes mellitus), others are more recently identified (hyperhomocysteinaemia, elevated C-reactive proteins), some are modifiable (hyperlipidaemia, hypertension) and reversible (smoking, obesity), others are not (age, gender). Reversal or control of these risk factors have been shown to be associated with a reduction in the mortality and morbidity of CAD as well as its incidence and prevalence.[6]

Pathogenesis of CAD

The underlying pathogenesis of CAD is the formation of atherosclerotic plaque. The plaque is a collection of variable amounts of cholesterol, smooth muscle cells, fibrous tissue and inflammatory cells in the intima, separated by a fibrin cap from the flowing blood in the arterial lumen. The plaque

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often grows with time and thus progressively narrows down the coronary lumen. This leads to a corresponding reduction in blood supply to the myocardial tissues supplied by the artery. When a critical narrowing of the lumen is achieved (about 70% diameter reduction), myocardial ischaemia ensues, which is manifested clinically as angina pectoris. Angina occurs initially on exertion because it is only on exertion that the blood supply, restricted in a fixed manner, is not able to provide the increased demand for blood supply to nourish tissues requiring more energy. It is now well established that plaque begins as fatty streaks that are accumulations of foam cells. Foam cells are macrophages that have engulfed free radical-mediated, oxidised (ox)-low-density lipoprotein (LDL). Foam cell formation leads to endothelial injury and dysfunction, thus facilitating passage of LDL from the flowing blood into the intima. In the process, the LDL gets oxidised, thereby acting as a positive feedback to the process of fatty streak/plaque formation. Importantly, unoxidised LDL does not partake in the process of plaque formation.

Another manifestation of CAD is acute coronary syndrome (ACS), consisting of acute myocardial infarction (AMI) and unstable angina (UA). Davies and Thomas[7] and Falk[8] have independently observed that the pathogenesis of ACS is rupture of the fibrin cap, leading to an exposure of the highly thrombogenic contents of the plaque, thereby leading to the rapid formation of a platelet-rich thrombus on top of the ruptured plaque. This leads to rapid reduction in blood supply to the tissues, manifested as AMI or UA. Ross[9] has shown that within plaques that have ruptured, there is an intense inflammatory process with activation of macrophages and smooth muscle cells as well as accumulation of other inflammatory cells.

Inflammation and oxidation in plaque formation and plaque rupture

Both Steinberg[10] and Berliner *et al.*[11] have shown the role of free radicals in the oxidative process leading to atherosclerotic plaque formation. Oxidation of LDL cholesterol has a number of biological effects, including increased expression of endothelial cell surface adhesion molecules that facilitate the mobilisation and uptake of circulatory inflammatory cells,[12,13] modifications in the chemotactic functions of monocytes and monocyte-derived macrophages[14,15] and alteration in LDL receptor recognition characteristics resulting in increased internalisation of LDL by macrophages through scavenger receptors.[16,17] These processes are important in the formation of macrophage-derived foam cells, which are precursors of atherosclerotic plaques. Oxidative processes are also involved in the maturation of these plaques and in triggering various clinical events through intimal proliferation, fibrosis, calcification, endothelial dysfunction, plaque rupture and thrombus formation.

Anti-inflammation and antioxidation ameliorate plaque formation and rupture

Evidence has shown that antioxidation may inhibit specific steps in atherogenesis.[18] Further, increased LDL oxidative resistance is observed when its α-tocopherol component is enriched.[19,20] Observations such as these lead to suggestions that intervention with antioxidant therapy may have a role in treating CAD.[21]

Early observations on the effect of vitamin E on CAD

The Mediterranean diet, rich in green vegetables, nuts and olives, has been shown to accord a 46% risk reduction of death or acute myocardial infarction after a follow up of 46 months.[22] The Mediterranean diet is rich in antioxidants, especially vitamin E.

The Nurses' Health Study, involving over 85 000 subjects followed for about 8 years, showed a 34% relative risk reduction (95% CI, 0.50–0.87) of major coronary disease after adjustment for smoking and age among women with the highest compared to the lowest quintile of reported vitamin E intake.[23] The higher quintile was achievable only by supplementation of vitamin E. It was also shown that there was a 43% reduction among those who had vitamin E supplementation compared with those who did not. The Health Professionals Follow-up Study, involving 39 000 men followed up for 4 years, also showed similar benefits from vitamin E.[24] Another study looked at the effect of dietary and vitamin E supplementation in 34 486 postmenopausal women without CAD who completed a questionnaire in 1986 enquiring into their intake of vitamins A, C and E.[25] The subjects were followed up for 7 years during which time 242 had died of CAD. Table 1 shows the estimated effects of vitamin E intake and supplementation on deaths from CAD in this cohort of women.

Table 1. Effect of vitamin E intake and supplementation on CAD deaths in postmenopausal women

	Vitamin E intake or supplementation					
	1st Quintile	2nd Quintile	3rd Quintile	4th Quintile	5th Quintile	*P*-value
Vitamin E intake (IU/day)	<4.91	4.92–6.24	6.25–7.62	7.63–9.63	>9.64	
No. deaths from CAD	36	30	36	25	35	
Relative risk (95% CI)	1.0	0.70 (0.41–1.18)	0.76 (0.44–1.29)	0.32 (0.17–0.63)	0.38 (0.18–0.80)	0.004
Vitamin E supplement (IU/day)	<5.68	5.69–7.82	7.83–12.18	12.19–35.58	>35.59	
No. deaths from CAD	52	58	38	43	51	
Relative risk (95% CI)	1.0	1.05 (0.69–1.69)	0.52 (0.31–0.87)	0.68 (0.41–1.10)	0.96 (0.62–1.51)	0.27

CAD, coronary artery disease.

That study showed that there was a clear benefit of vitamin intake among these postmenopausal women but curiously, such a relationship was not seen between high and low supplementation of vitamin E. Estimation of vitamin E intake from the questionnaire was difficult; validation was carried out in only 44 women with a correlation coefficient of 0.55 for vitamin E intake and 0.79 for vitamin E supplementation. Further, deaths due to CAD were obtained from the National Death Index and were not validated. Given these shortcomings, the inconsistent effect of vitamin E intake and vitamin E supplementation on CAD deaths could be because the amount of supplementation was not large enough to show such a relationship. Therefore, these observations could not, in total, be taken as proof of the benefit of vitamin E on CAD.

Early experimental studies on vitamin E and CAD

Experimental studies by way of clinical trials were required to confirm or refute the results of the large observational studies. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study[26] was performed on 29 133 male smokers who were randomised to daily doses of 50 mg α-tocopherol vitamin E, 20 mg β-carotene, both or placebo and followed up for 5–8 years. The major end-point was incidence and deaths from lung cancer but CAD incidence and deaths were also recorded. Among those on α-tocopherol, there were 602 deaths from CAD (rate 71.0/10 000 person-years) compared to 637 deaths (rate 75.0/10 000 person-years) among those not on α-tocopherol. There was no reduction in any of the end-points. Unexpectedly, there was an increased incidence of haemorrhagic stroke with vitamin E supplementation (66 *vs* 44 deaths from haemorrhagic stroke) and increased mortality from lung cancer and CAD with β-carotene supplementation. In this study, low-dose (50 mg/day) α-tocopherol was used.

Clinical trials therefore failed to confirm the beneficial effects of vitamin E supplementation on CAD. There are a number of plausible reasons. Confounding factors may have been present and were not corrected for in the observational studies, which may strongly influence the results of these observational studies. For instance, it was found that among the nurses who participated in the Nurses' Health Study those with high vitamin E intake were more conscious of their health status and were more likely to undertake regular exercise than those who had a lower intake of vitamin E. Foods rich in vitamin E and other antioxidants are lower in saturated fat and cholesterol and higher in fibre and rich in other potentially important micronutrients such as minerals and flavonoids.[27] On the other hand, the lack of benefit of vitamin E in the clinical trials may be due to the study design (CAD end-point was not the designated primary end-point) and that the dose of vitamin E used may not be adequate to prevent or ameliorate CAD.

Large clinical trials on vitamin E and CAD

The Cambridge Heart Antioxidant Study (CHAOS) showed a reduction of 77% for myocardial infarction and a reduction of 47% for all cardiovascular events in 2002 angiographically proven CAD patients given 400 IU/day and 800 IU/day α-tocopherol.[28] There was a non-significant increase in cardiovascular deaths in the α-tocopherol group (27 *vs* 23; 1.18 (0.62–2.27); $P = 0.61$). Secondary analysis of the ATBC study involving 1862 patients with previous myocardial infarction given vitamin E showed a 38% reduction of recurrent non-fatal myocardial infarction, although the risk for fatal coronary events was not reduced.[29] It has also been shown that high vitamin E intake could inhibit atherosclerotic plaque progression.[30,31] Vitamin E was also shown to be beneficial in patients who underwent angioplasty.[32,33]

For a number of reasons, the results from these clinical trials were, however, considered not definitive in addressing the question of whether vitamin E is or is not beneficial in preventing CAD. For instance, the pooling of data between a two doses regimen (400 mg/day and 800 mg/day) of vitamin E in the CHAOS study imposed a methodological problem for this study. Secondary analysis (as in the ATBC trial) is always open to potential confounding factors that may contribute to the conclusions reached. Large clinical trials designed specifically to address this question were required.

GISSI-3 randomised patients ($n = 11\,324$) who survived a recent myocardial infarction into groups and supplemented with n-3 polyunsaturated fatty acids (1 g daily, $n = 2836$), vitamin E (300 mg daily of synthetic α-tocopherol, $n = 2830$), both ($n = 2830$) or none ($n = 2828$) and followed up for 3.5 years.[34] In each of the supplemented groups, about one-third of patients discontinued their assigned supplementation. Analysis of data was performed on the basis of intention-to-treat. GISSI-3 showed that n-3 polyunsaturated fatty acids, but not vitamin E, significantly lowered the risk of the primary end-point of death, non-fatal myocardial infarction and stroke. The Heart Outcomes Prevention Evaluation (HOPE) study enrolled 10 576 patients at high risk of cardiovascular events.[35] The patients were randomised to 10 mg ramipril or placebo daily and 400 IU vitamin E or placebo daily. The study was terminated 6 months early (after 4.5 years follow-up) because of the clear beneficial effects of ramipril on a wide spectrum of cardiovascular outcomes. Vitamin E provided no benefit (and no adverse effect) compared with the placebo. Thus, two well-conducted large clinical trials showed a neutral effect of vitamin E supplementation on cardiovascular outcomes. These two large studies were taken as proof that vitamin E supplementation confers no benefit to cardiovascular outcomes either in patients who had had an acute myocardial infarction (GISSI-3) or in patients at high risk of cardiovascular events (HOPE).

Overview of the role of vitamin E in CAD

The observations from GISSI-3 and HOPE concerning the role of vitamin E in the treatment of CAD do not seem to confirm the pathogenetic role of free radicals in atherosclerosis, at least at the clinical level, and diverged from observations from other dietary studies and population

observations. There might be a few reasons why this was so. In these high risk groups of patients, vitamin E supplementation does not provide any further benefit over and above the standard therapy provided to these patients. However, alternative views could also be offered. First, both studies were not mechanistic studies but rather, clinical outcomes studies, and therefore do not provide the mechanistic reasons for the observations seen. Second, both studies were not primary prevention studies but rather, studies in subjects who already had atherosclerosis (postinfarction patients in GISSI-3 and patients who already had or were at high risk of having CAD). It may be that once atherosclerosis has taken place, antioxidants and vitamin E are not effective in the prevention of plaque rupture, which leads to the clinical events measured in these studies. However, these two studies did not address the issue of primary prevention, that is, preventing subjects from developing CAD in the first place. Third, the doses used were less than the doses (at least 400 mg/day) used in earlier studies that showed benefit. Fourth, almost all studies used α-tocopherol as the vitamin E and none used the more potent antioxidant α-tocotrienol vitamin E. Inadequate antioxidant activity provided by α-tocopherol may contribute to the observations seen in these studies. Fifth, the HOPE study was terminated early because of the positive outcomes from ramipril. HOPE was not a study comparing ramipril and vitamin E, rather a study of the effect of either (compared to placebo on patients on optimal then standard therapy) on cardiovascular outcomes in high risk subjects. As such, it is possible that the effect of ramipril was more potent than vitamin E on cardiovascular outcomes. Whatever it is, in this high risk group of patients, ramipril showed benefit and its use should be encouraged. Therefore, despite these seemingly persuasive studies, the controversy concerning the effects of vitamin E on CAD is still not settled.

Conclusions and recommendations

Basic science has consistently shown the essential activity of lipid oxidation and inflammation in the pathogenesis of atherosclerotic plaques and plaque rupture. Observational studies, dietary studies and animal studies have supported this hypothesis. However, clinical trials thus far have not shown the benefits of vitamin E supplementation, especially in patients already with CAD. These studies, though, had a number of limitations, in particular concerning the dose and type of vitamin E used (α-tocopherol rather than α-tocotrienol). As such, despite suggestions to the contrary, the role of vitamin E in CAD remains inconclusive. It is therefore essential that proper studies of vitamin E in CAD be conducted. It is proposed that α-tocotrienol vitamin E, being the more potent antioxidant vitamin E, be used in basic science research and clinical trials to address the issue of antioxidant utility in CAD.

Acknowledgement. This work was supported by IRPA grant numbers 06-02-05-7009 and 03-07-03-077 from the Ministry of Science, Technology and Environment, Malaysia.

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