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Coronary heart disease (CHD) (also known as atherosclerotic coronary artery disease or ischemic heart disease) is by far the most common cause of death of both men and women in the United States when all age groups are considered. The clinical symptoms of CHD can be angina pectoris, myocardial infarction, or simply, sudden death. By far the most common cause of CHD is coronary artery atherosclerosis, a patchy nodular type of arteriosclerosis (a general term for hardening and thickening of the artery wall), which causes reduced perfusion and increased susceptibility to occlusion (1). The initial lesion in atherosclerosis, the fatty streak, is usually asymptomatic and consists mostly of accumulated foam cells. Foam cells develop from monocyte/ macrophages and contain large quantities of cholesterol ester and free cholesterol in cytoplasmic lipid droplets. The fatty streak can develop into a fibrous plaque, which consists of a fibrous cap of smooth muscle cells and dense connective tissue, a cellular layer, and a core of dead tissue. A complex lesion involving calcification, necrosis, ulceration, hemorrhage, and thrombosis of the fibrous plaque can also occur and cause the clinical symptoms of CHD (2).

LDL is considered to be the major atherogenic lipoprotein in the blood; serum concentration of LDL has been shown to be directly related to risk for CHD (serum concentration of HDL, on the other hand, has been shown to be inversely related to risk for CHD) (3). The complete pathological process of atherogenesis and the role of LDL in the process is unknown, but one generally accepted theory, the reaction to injury hypothesis, describes atherogenesis as a reaction of endothelial cells to injury: mechanical, immunologic, or metabolic (1). Chronic high cholesterol, in the form of LDL, could be considered a form of metabolic stress; however, much evidence suggests that it is oxidized LDL and not unmodified LDL that plays a key role in the formation of at least the initial atherosclerotic plaque. This theory is known as the oxidative modification hypothesis (4). It is based on knowledge that the classic LDL receptor is downregulated with an increased intracellular concentration of cholesterol and, therefore, not likely to be involved in the unregulated uptake of LDL-cholesterol by macrophages developing into foam cells. Another receptor, however, the macrophage scavenger receptor, recognizes modified LDL (oxidized or acetylated), is not downregulated, and could be the mechanism by which macrophages are loaded with cholesterol in the fatty streak. Oxidation seems to be the most likely modification of LDL in vivo, because endothelial cells, smooth muscle cells, and macrophages in vitro are able to oxidize LDL. In addition to being a ligand for the scavenger receptor, oxidized LDL also seems to have other biological effects: cytotoxicity, stimulation of endothelial-leukocyte adhesion, chemoattraction of monocytes, inhibition of macrophage migration, inhibition of NO (endothelium derived relaxation factor), and increased tissue factor expression (2). All of which may be involved in the formation of the initial lesion. If the oxidative modification hypothesis is true, preventing oxidation of LDL could lead to a reduction in fatty streak formation and possibly prevention of the more advanced lesions involved in CHD.

Antioxidants

Simply stated, an antioxidant is "any substance that, when present at low concentrations compared to those of an oxidizable substrate, significantly delays or prevents oxidation of that substrate." This is a general definition and includes substances that may act in biological systems by inducing genes whose products act as antioxidants (5). More often the term is used to refer to compounds that serve to quench damaging free radicals in biological systems (6).

Free radicals are molecules with an unpaired electron, which enables them to initiate damaging free radical chain reactions. Normal metabolism produces a small amount of these free radicals. Oxidative phosphorylation, for example involves reduction of molecular oxygen by stepwise addition of electrons. Under normal conditions, ninety-eight percent of the oxygen is reduced to water, but two to five percent of the reduced oxygen enters the univalent pathway which produces by-products called reactive oxygen species (ROS). Most of the ROS are taken care of by superoxide dismutase, catalase, and glutathione peroxidase. The hydroxyl radical is the most dangerous of the ROS. Polyunsaturated fatty acids (PUFAs), due to their carbon-carbon double bonds, are particularly prone to peroxidation by ROS (6).

A significant part of LDL is made up of cholesterol esterified to linoleate, a PUFA (7). This is another reason to suspect that LDL may be prone to the oxidation that, in keeping with the oxidative modification hypothesis, would be necessary to induce atherogenesis. There is a natural line of defense against

oxidation, however. Vitamin E is proposed to be the main chain-breaking antioxidant in the lipid membrane of tissues and in LDL.

Vitamin E as an antioxidant

Vitamin E is the name given to alpha-tocopherol and tocotrienol derivatives that show biological properties similar to alpha-tocopherol. Tocopherols are generally found in oil seeds and the green parts of plants, while tocotrienols are generally found in the germ of certain cereals and seeds (8).

Vitamin E works as an electron receptor in the breaking of radical chain reactions; however, it is present in very low concentrations in the plasma membranes and lipoproteins. One hypothesis is that vitamin E acts as a temporary store for the electron until other species can accept the electron and reduce vitamin E back to its original form. The species that oxidize the reacted vitamin E may fluctuate in concentration and only when all the vitamin E is used up will oxidation damage occur. Figure 1 shows a simplified schema of how this might work (9).

What evidence suggests that vitamin E might help prevent cardiovascular disease?

It fits with the oxidative modification hypothesis.

From the oxidative modification hypothesis, it would seem that if the amount of vitamin E in the plasma, membrane, and LDL were increased, the amount of protection from oxidation would also increase. With reduced oxidation, less oxidized LDL would form and less damage would be done. There is little doubt that a vitamin E deficiency could cause problems, but the question remains of whether higher dietary intake would lead to more vitamin E in the right place and whether more is needed anyway since it is not an end electron receptor itself but eventually gets oxidized back to its original form.

An in vitro model

Evidence that vitamin E can confer some amount of protection, at least in vitro, was shown in a recent study on cultured human aortic endothelial cells. The cells were preincubated with several different concentrations of alpha-tocopherol and then exposed to free radicals. It was found that the higher levels of vitamin E reduced cell damage as compared to the control. It was also found that there was lower production of PGI₂ and IL-1-beta. PGI₂ is released when endothelial cells are under mechanical or oxidative stress, and IL-1-beta, which is released by endothelial cells in response to oxidative stress, may have an important role in the initiation of a plaque because it stimulates the release of chemotactic factors and increases the expression of cell surface adhesion molecules to neutrophils, monocytes, and lymphocytes (10).

Observational studies

One of the earliest studies in which evidence that vitamin E might be involved in the prevention of heart disease was a cross sectional study of twelve different European populations in which an inverse relation was found between plasma vitamin E levels and ischemic heart disease. Vitamin E, after adjustments for cholesterol were made, was found to be a better indicator of risk for ischemic heart disease than blood pressure or cholesterol (11). A few years after the large cross-sectional study was reported, two large prospective cohort studies, the Nurse's Health Study with 87,245 subjects (12) and the Health Professionals Follow-up study with 39,910 subjects (13), were reported in which the relative risk for coronary heart disease of the people who took high amounts of vitamin E was found to be significantly lower than the relative risk for people who took low amounts of vitamin E.

The Nurse's Health Study was carried out on a group of female nurses, aged 34 to 59, who were participants in a study that began in 1976. Initially the participants filled out a questionnaire on lifestyles and medical histories. Follow-up questionnaires were sent every two years to update information and identify new health problems. In 1980, questions on vitamin intake were added and the group was followed until 1988. For this study the endpoint was major coronary disease (MI, fatal or nonfatal). The results of the

study showed that participants in the highest quintile for vitamin E intake had a risk of 0.66 (95% CI 0.50-0.87) compared to participants in the lowest quintile even after compensation for slight differences in other risks.

The other prospective cohort study, which was a follow up to the Nurse's Health Study, was carried out on male health professionals who were age 40 to 75 at the beginning of the study in 1986. As with the Nurses Health study, questionnaires were filled out by the participants every two years over the course of the study and major coronary heart disease was used as an endpoint. The group was divided into quintiles with respect to intake of vitamin E, and a statistical analysis was carried out which found a relative risk of 0.64 (95 CI 0.49-0.83) compared to the lowest quintile.

Although these studies both showed a statistically significant as well as a clinically significant reduction in risk of heart disease for the groups who had high intake of vitamin E, both authors acknowledged that a clear cause and effect relationship could not be drawn from observational data alone. Perhaps the most health conscious of the sample self selected for the vitamin E treatment. Although, as Stamfer pointed out, no correlation was found for people that took other vitamins such as vitamin C. A well run randomized trial would be needed to strengthen the case.

Another observational study reported on recently was a subgroup analysis of a study, the Cholesterol Lowering Atherosclerosis Study (CLAS) (14) (15), in which 156 men, aged 40 to 59 years, who had a history of coronary bypass surgery were followed with serial angiography to see if there was a difference in vessel lumen diameter progression between those who took vitamin E supplements greater than 100 IU/day and those who did not. The original study involved the randomized controlled study of colestipol-niacin versus a placebo. Over four years, it was found that there was a benefit from taking vitamin E for those who did not take the colestipol-niacin while there was no benefit for those who were taking the colestipol-niacin. Another interesting finding was that there was very little benefit from vitamin E, regardless of treatment group, for men with severe lesions. This finding would also fit in with the oxidative modification hypothesis since the prevention of oxidation of LDL would help prevent early lesions and not the progression to advanced lesions.

This problem of detecting early lesions was addressed in another substudy of a study, a four year longitudinal study that was looking at the cognitive and vascular aspects of aging (the EVA study) (16). In this study, ultrasound was used to assess intima-media thickness of the common carotid arteries. The authors argued that intima-media thickness was a better indicator of early atherosclerosis than lumen diameter because lumen diameter is subject to remodeling of the vasculature. After analysis, it was found that erythrocyte vitamin E was "significantly and negatively associated with common carotid intima-media thickness. While this still doesn't give conclusive evidence that vitamin E can prevent early atherosclerosis it at least tried to look at an endpoint that would be consistent with the hypothesis.

Randomized, double blind, controlled, experimental studies

While the observational and cross-sectional studies might hint at an association of vitamin E levels with decreased risk for heart disease, compelling evidence would need to come from an experimental, randomized, double blind trial in which a clear and clinically significant reduction in risk could be causally associated with vitamin E intake. Unfortunately, there is conflicting data in some of the recent attempts to do just this.

One interesting study in which the goal was simply to find out the minimum dose of vitamin E required to give some oxidative protection to LDL was reported recently (17). In this randomized, double blind, controlled study, different doses of vitamin E (placebo, 500, 1000, or 1500 IU/day) were given to a group of individuals (43 men and women). The outcomes were simply lag time to copper induced LDL oxidation in the plasma, and changes in plasma vitamin E levels. It was found that a dose of 500 IU/day significantly reduced the lag time to oxidation in vitro and also that the percent change in plasma vitamin E was highly correlated with increase in lag time. The study also found a "threshold effect"; higher doses did not confer much added protection. The author is quick to point out that these results may have nothing to do with decreasing the risk of coronary heart disease. But if the oxidative modification hypothesis were valid, the

findings would be consistent with reducing risk. This conclusion, however, depends on the assumption that in vitro oxidation by copper is a valid model for in vivo oxidation, which may or may not be the case.

Recently two studies have been reported that tackle the question of whether vitamin E intake significantly reduces the risk of heart disease head on. They are randomized, double blind, controlled trials. But they give conflicting verdicts on the question. One study is part of an eight year cancer study, the Finnish Alpha Tocopherol, Beta Carotene Cancer Prevention (ATBC) Study, in which men, aged 50-59 years, who smoked five or more cigarettes per day, and who lived in south-western Finland were randomized to groups given 50 mg/day vitamin E, 20 mg/day beta carotene, both vitamin E and beta carotene, or placebo (18). The endpoint was angina pectoris symptoms. The rationale for this was that, since angina pectoris is the first symptom of coronary heart disease, this would increase the sensitivity of the study. The end result was that the vitamin E group did show a statistically significant decrease in risk for angina pectoris (0.91 95% CI 0.83-0.99) but this decrease in risk was so small that it has very little clinical relevance. The beta carotene group was found to have a statistically insignificant increase in risk.

The other recent study, the Cambridge Heart Antioxidant Study (CHAOS) (19), was another randomized, double blind, controlled study which was specifically designed to test if treatment with vitamin E would reduce risk of MI in patients who already have atherosclerosis. 1035 patients were followed for an average of 510 days. The dosage of vitamin E in this study was 400 IU/day and the results showed a significant decrease in non-fatal MI, 0.53 95% CI 0.34-0.83. While on the surface this result might look like proof that vitamin E is beneficial, there were some problems with the study. First of all, the study also showed a non-significant increase in MI death. Another problem that was raised in some of the articles written on the study, was that the study was not very careful in measuring endpoints, there was no scheduled follow up, there was lack of compliance in the treatment groups, and in the only hard endpoint that the study did measure (death from MI) there was no significant difference between treatment and placebo (20).

Conclusion

So where does all of this leave us if we need to advise someone about whether to take vitamin E or not and, if so, what dose? On the one hand we have the theory that vitamin E should help prevent oxidation of LDL and, therefore, slow down the formation of early lesions. So you wouldn't expect to see short term benefit. The CHAOS study, even with its flaws, may have given some evidence in favor of vitamin E. The deaths in the study occurred early on and the patients may not have had time to benefit from treatment. On the other hand, maybe some caution should be exercised because of this finding. The ATBC study after all found no significant benefit from vitamin E; although they did use a very small dose of the vitamin. Unfortunately, the best advice we may be able to offer at this point is that if the person wants to take about 500 IU of vitamin E a day (remember Simons et. al.), it most likely will not hurt, and it may help.

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