Lycopene, Tomatoes, and the Prevention of Coronary Heart Disease

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Coronary heart disease (CHD) is one of the primary causes of death in the Western world. The emphasis so far has been on the relationship between serum cholesterol levels and the risk of CHD. More recently, oxidative stress induced by reactive oxygen species (ROS) is also considered to play an important part in the etiology of this disease. Oxidation of the circulating low-density lipoprotein (LDL_{ox}) is thought to play a key role in the pathogenesis of atherosclerosis and CHD. According to this hypothesis, macrophages inside the arterial wall take up the LDL_{ox} and initiate the process of plaque formation. Dietary antioxidants such as vitamin E and β-carotene have been shown in *in vitro* studies to prevent the formation of LDL_{ox} and their uptake by microphages. In a recent study, healthy human subjects ingesting lycopene, a carotenoid antioxidant, in the form of tomato juice, tomato sauce, and oleoresin soft gel capsules for 1 week had significantly lower levels of LDL_{ox} compared with controls. The antioxidant effects of lycopene have also been shown in four other human trials, including one where lycopene consumption reduced the levels of breath pentane. However, in one recent study, dietary supplementation with β-carotene but not with lycopene was shown to inhibit LDL oxidation. The sources of lycopene used in most of these studies were either tomato products or lycopene extracted from tomatoes containing other carotenoids in various proportions. Therefore, it is not possible to attribute the effects solely to lycopene. Mechanisms other than the antioxidant properties of lycopene have also been shown to reduce the risk of CHD. Lycopene was shown to inhibit the activity of an essential enzyme involved in cholesterol synthesis in an *in vitro* and a small clinical study suggesting a hypocholesterolemic effect. Other possible mechanisms include enhanced LDL degradation, LDL particle size and composition, plaque rupture, and altered endothelial functions. Recent epidemiological studies have also shown an inverse relationship between tissue and serum levels of lycopene and mortality from CHD, cerebrovascular disease, and myocardial infraction. However, the most impressive population-based evidence comes from a multicenter case-control study where subjects from 10 European countries were evaluated for relationship between antioxidant status and acute myocardial infarctions. After adjusting for a range of dietary variables, only lycopene levels but not β-carotene were found to be protective. At present, the role of lycopene in the prevention of CHD is strongly suggestive. Although the antioxidant property of lycopene may be one of the principal mechanism for its effect, other mechanisms may also be responsible. Controlled clinical and dietary intervention studies using well-defined subject populations and disease end points must be undertaken in the future to provide definitive evidence for the role of lycopene in the prevention of CHD. Mechanistic studies must also be initiated to understand the mode of lycopene action. Exp Biol Med 227:908–913, 2002

Key words: lycopene; carotenoids; coronary heart disease; oxidative stress; antioxidants

Coronary heart disease (CHD) is the major cause of deaths in North America and the rest of the Western world. It is also being recognized as an important contributor of morbidity and mortality in the developing countries of the world. Although genetic factors and age are important in determining the risk, other factors, including hypertension, hypercholesterolemia, insulin resistance, and lifestyle factors such as smoking and diet are also major risk factors associated with the disease (1). The emphasis so far has been on the relationship between serum cholesterol levels and the risk of CHD. Recently, oxidative stress induced by reactive oxygen species (ROS) is also considered to play an important part in the etiology of several chronic diseases, including CHD (2–8). Oxidation of the circulating low-density lipoprotein (LDL) that carry cholesterol into the blood stream to oxidized LDL (LDL_{ox}) is thought to play a key role in the pathogenesis of atherosclerosis, which is the underlying disorder leading to heart attack and ischemic strokes (5, 9–10). Antioxidant nutrients are believed to slow the progression of atherosclerosis because of their ability to inhibit the damaging oxidative processes (10–12). Lycopene is one such dietary antioxidant that has received much attention recently. It is a naturally present carotenoid in tomatoes and tomato products. It is an open-chain hydrocarbon containing 11 conjugated and two nonconjugated double bonds arranged in a linear array (13). Lycopene, because of its high number of conjugated dienes, is the most potent singlet oxygen quencher among the natural carotenoids (14). Recent epidemiological studies have shown an

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inverse relationship between the intake of tomatoes and lycopene and serum and adipose tissue lycopene levels and the incidence of CHD. These observations have generated scientific interest in lycopene as a preventative agent for CHD.

Oxidative Stress and the Risk of CHD

There is convincing evidence to indicate that ROS generated both endogenously and also in response to diet and lifestyle factors may play a significant role in the etiology of atherosclerosis and CHD (2–8). Central to this oxidative hypothesis is the oxidation of LDL as the primary initial step leading to its uptake by the macrophages inside the arterial wall and the formation of foam cells and atherosclerotic plaque (5) (Fig. 1). LDL, which is the major carrier of cholesterol in the body, consists of a large molecular weight-protein, the apolipoprotein B, neutral and polar lipids, and a mixture of lipophilic antioxidants including β-carotene and vitamin E. Oxidation of the LDL is known to take place is several stages starting with the native LDL and progressing to seeded LDL, minimally modified LDL (mm-LDL), and finally, the fully oxidized LDL (11). The characteristics of these LDL forms is shown in Table I. The polyunsaturated fatty acids in the LDL-surface phospholipids may be the first to be oxidized, followed by the core lipids. These oxidative modifications reflect not only the polyunsaturated fatty acids, but also oxidation of the cholesterol, phospholipids, and oxidative degradation of the apolipoprotein B itself (15, 16). As a result of these oxidative modifications of the native LDL molecule, several biologically active molecules can be formed, including protein adduct products with the breakdown products of oxidized fatty acids that facilitate the recognition of the modified LDL by the macrophage's scavenger receptors.

In addition to influencing the formation of foam cells and plaque in the arterial walls, components of the LDL_{ox} can also influence other events that are related to increased risk of CHD. These include their ability to increase cholesterol accumulation by macrophages, their ability to produce proteins that are chemotactic to monocytes and cytotoxic to a variety of cells causing endothelial injury; alter the gene expression in arterial cells leading to increased expression of colony-stimulating factors; increase expression of adhesion molecules at the endothelial cell surface; inhibit the endothelium-dependent relaxation factor and promote vasospasm; inhibit vasodilatation; increase binding to type 1 collagen; enhance coagulation pathways and platelet aggregation; stimulate the synthesis of autoantibodies, and their ability to promote migration and proliferation of smooth muscle cells and the formation of foam cells and fatty streaks in the arterial intima and cause eventual rupture of the plaque (17, 19–21). In this respect, LDL_{od} can represent many different biological functions depending upon the extent of its oxidation.

Antioxidants and the Risk of CHD

Several epidemiological and prospective studies have shown that consumption of antioxidant vitamins such as vitamin E and β-carotene may reduce the risk of CHD (17, 18). Randomized clinical trials also suggest a reduced risk of CHD with vitamin E supplementation (22–24). The protective effect of vitamin E observed in these studies has been ascribed to its antioxidant properties. Support for the protective effect of antioxidants also comes from the observations that men and women with CHD exhibit lower levels of circulating antioxidants (11). However, some large-scale human trials have failed to confirm the protective effect of β-carotene and have produced inconclusive results with vitamin E . In the recently completed Heart Outcomes Prevention Evaluation (HOPE) Study, supplementation with 400 IU/day vitamin E for 4.5 years did not result in any beneficial effects on cardiovascular events in patients at high risk (25).

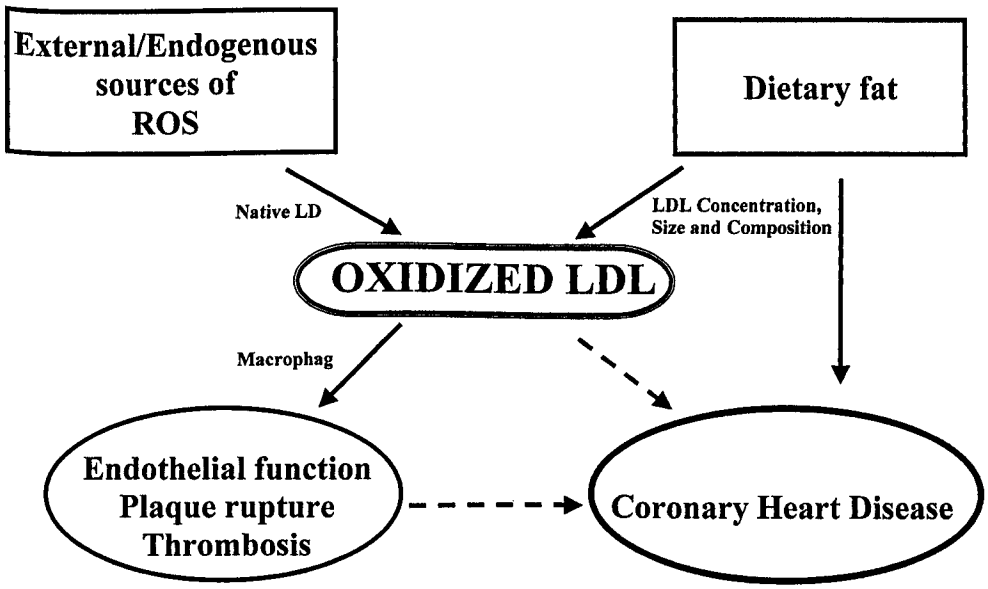

Figure 1. LDL oxidation hypothesis in the etiology of coronary heart

Table I. Characteristics of Different Stages of LDL Oxidation[a]

Stage of LDL oxidation	Characteristics
Native LDL	Degrades via the LDL receptor
	Foam cells are not generated from macrophases
	Contains lipid soluble antioxidants
Seeded LDL	Contains lipid peroxides (generated by cells)
	Degraded via LDL receptor
	Contains lipid soluble antioxidants
	More readily oxidized
Minimally oxidized LDL	Contains lipid peroxides (oxidation of LDL lipids)
	Contains intact apoprotein B (degraded via LDL receptor)
	Contains lower amounts of fat-soluble antioxidants
	Oxidized further and is biologically active
Oxidized LDL	Contains lipid peroxides and degradation products
	Contains modified apoprotein B (degraded via scavenger receptor)
	Causes lipid accumulation in the macrophages
	Contain very low levels of lipid-soluble antioxidants
	Immunogenic and biologically active

[a] Modified from S. Parthasarathy, 1998 (11).

Lycopene and the Risk of CHD

Several epidemiological studies as well as experimental studies using *in vitro* systems, animals, and human intervention trials have been carried out to investigate the role of vitamin E and β-carotene in the prevention of CHD. Very few similar studies have been performed with lycopene (26–29).

A number of *in vitro* studies have shown that lycopene can protect native LDL from oxidation and can suppress cholesterol synthesis (30, 31). In J-774 A.1 macrophage-like cell line, lycopene at a concentration of 10 μ*M* induced 73% inhibition in cholesterol synthesis from [^{3}H]acetate. A slightly lower inhibition was also observed with β-carotene (31). In this study, both the carotenoids augmented the activity of the macrophage LDL receptor. However, in another study, dietary enrichment of endothelial cells with β-carotene but not lycopene inhibited the oxidation of LDL (32). The predictability of *in vitro* LDL oxidation as a marker of atherosclerosis or CHD has been questioned in recent years (22). Similarly, animal intervention studies where the resistance of extracted LDL *in vitro* to oxidation is shown to increase do not necessarily correlate to reduced risk of atherosclerosis (33).

The evidence in support of the role of lycopene in the prevention of CHD stems primarily from the epidemiological observations on normal and at-risk populations. The present knowledge largely relies on the data obtained from dietary estimates or plasma values in relation to the risk of CHD. A number of epidemiological studies have suggested that a diet rich in a variety of fruits and vegetables results in lower risk of CHD. Fruits and vegetables are in general good sources of dietary carotenoids, including lycopene. The antioxidant properties of lycopene have been suggested as being responsible for the beneficial effects of these food products. A Mediterranean diet rich in tomatoes, tomato products, lycopene, and other carotenoids is associated with the lower incidence of atherosclerosis and CHD. One of the earlier studies that investigated the relationship between serum antioxidant status, including lycopene and myocardial infarctions (34), reported an odds ratio of 0.75. However, in this study, other variables were not controlled. The strongest population-based evidence comes from a recently reported multicenter case-control study (EURAMIC) that evaluated the relationship between adipose tissue antioxidant status and acute myocardial infarction (17). Subjects (662 cases and 717 controls) from 10 European countries were recruited to maximize the variability in exposure within the study. Needle aspiration biopsy samples of the adipose tissue were taken shortly after the infarction, and the levels of α- and β-carotenes, lycopene, and α-tocopherol were measured. Adipose lycopene levels expressed as milligrams per gram of fatty acids varied from the lowest at 0.21 to the highest at 0.36. After adjusting for age, body mass index, socioeconomic status, smoking, hypertension, and maternal and paternal history of the disease, only lycopene, and not β-carotene, levels were found to be protective with an odds ratio of 0.52 for the contrast of the 10th and 90th percentiles with a *P* value of 0.005. Results also showed a dose-response relationship between each quintile of adipose tissue lycopene and the risk of myocardial infarction. The protective potential of lycopene was maximal among individuals with the highest polyunsaturated fat stores. Interestingly, the odds ratios for lycopene of subjects who never smoked, exsmokers, and smokers were 0.33, 0.41, and 0.63, respectively. These findings seem to support the antioxidant hypothesis. A component of this larger EUREMIC study representing the Malaga region was analyzed further (35). In this case-control study consisting of 100 cases and 102 controls, adipose tissue lycopene levels showed an odds ratio of 0.39 with 95% CI of 0.13 and 1.19. The *P* value for the trend was 0.04. In another Atherosclerosis Risk in Communities (ARIC) case-control study, fasting serum antioxidant levels of 231 cases and an equal number of control

subjects were assessed in relationship to the intima-media thickness as an indicator of asymptotic early atherosclerosis (36). After controlling for other variables, an odds ratio of 0.81 was observed, but the *P* value for the association was not significant. Statistical significance was observed only for β-cryptoxanthin, lutein, and zeaxanthin. In a cross-sectional study comparing Lithuanian and Swedish populations showing diverging mortality rates from CHD, lower blood lycopene levels were found to be associated with increased risk and mortality from CHD (37). In the Austrian stroke prevention study, lower levels of serum lycopene and α-tocopherol were reported in individuals from an elderly population at high risk for microangiopathy-related cerebral damage, which is considered as a risk factor for cerebrovascular disease (38).

Although the epidemiological studies conducted so far provide convincing evidence for the role of lycopene in CHD prevention, it is at best only suggestive and not proof of a causal relationship between lycopene intake and the risk of CHD. Such a proof can be obtained only by performing controlled clinical dietary intervention studies where both the biomarkers of the status of oxidative stress and the disease are measured. To date, very few such intervention studies have been reported in the literature. In one study, when healthy human subjects consumed a lycopene-free diet for a period of 2 weeks, their serum lycopene levels decreased by 50% by the end of Week 2 and, at the same time, an increase of 25% in the *in vivo* lipid oxidation was observed (39). In a small dietary supplementation study, six healthy male subjects consumed 60 mg/day lycopene for 3 months. At the end of the treatment period, a significant 14% reduction in their plasma LDL cholesterol levels was observed (31). As part of the same study, the authors investigated the effect of lycopene *in vitro* on the activity of macrophage 3-hydroxy-3-methyl glutaryl coenzyme A (HMGCoA) reductase, a rate-limiting enzyme in cholesterol synthesis *in vitro*. Based on these observations, they concluded that dietary supplementation of carotenoids may act as moderate hypocholesterolemic agents (31). In a randomized, crossover dietary intervention study, 19 healthy human subjects (10 male and 9 female), nonsmokers, and not on any medication and vitamin supplements, consumed lycopene from traditional tomato products and nutritional supplement for 1 week. The levels of lycopene consumption ranged from 20 to 150 mg per day. Lycopene was observed to be absorbed readily from all dietary sources, resulting in significant increase in serum lycopene levels and lower levels of lipid, protein, and DNA oxidation (40). In the same study, serum lipoproteins and LDL oxidation were also evaluated. LDL oxidation was estimated by measuring the levels of thiobarbituric acid-reactive substances (TBARS) and conjugated dienes (CD). Although there were no changes in serum total cholesterol and LDL and HDL cholesterols, serum lipid peroxidation and LDL cholesterol oxidation were significantly decreased as the serum lycopene levels increased (Fig. 2) (41).

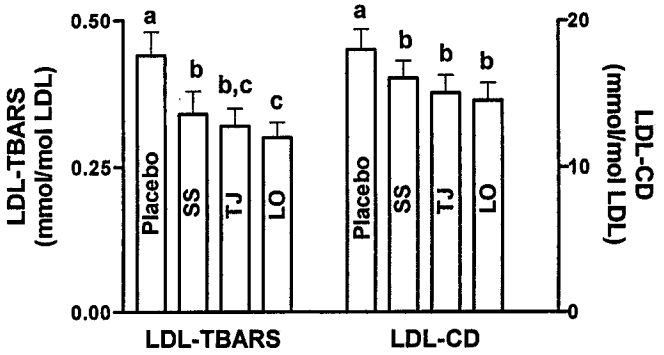

Figure 2. Effect of dietary lycopene supplementation on serum low density lipoprotein (LDL) oxidation. Dietary lycopene was provided to healthy human subjects in the form of spaghatti sauce (SS), tomato juice (TJ) or lycopene oleoresin (LO) with a standard breakfast for a period of 1 mk in a random order. Fasting blood samples were collected at the end of each treatment. Serum LDL was seperated and oxidation measured. Results are mean ± SEM. Bars with different letters are statistically significant ($P < 0.05$) (Agarwal S, Rao AV. 1988)

Concluding Remarks and Future Directions

There is convincing epidemiological evidence in support of the role of antioxidants, in particular vitamin E and β-carotene, in the prevention of CHD. Only a few studies have looked at lycopene specifically. Serum and adipose tissue lycopene levels were shown to be lower in population groups either at risk of CHD or those with the disease. To date, only two dietary intervention studies have appeared in the literature. One study showed a mild but significant hypocholesterolemic effect of dietary lycopene supplementation and the other showed a significant reduction in LDL oxidation with the consumption of dietary lycopene sources. Although the evidence for a relationship between *in vitro* LDL oxidation and the risk of ischemic heart disease and CHD is not fully established, LDL oxidation is now recognized as representing an important early event in the development of cardiovascular diseases. There is data to indicate the presence of oxidized LDL *in vivo*. Mechanisms other than oxidative stress have also been proposed in recent years, including inhibiting the activity of the key HMGCoA reductase activity in cholesterol synthesis, LDL degradation, alterations in the size and composition of LDL particles, plaque rupture, and altered endothelial functions (5, 11, 17, 26).

CHD is a progressively degenerative disease consisting of early, middle, and late events that eventually lead to death (Fig. 3). Review of the literature shows that most of the population-based epidemiological studies use deaths due to CHD as the end point. On the other hand, most of the *in vitro* investigations study the early events in the progression of the disease. The link between early events of the disease such as LDL oxidation and the terminal outcome of death is an important area of future research. This is an area where well-controlled clinical and dietary intervention studies will provide information that will be helpful in the management of CHD. The use of well-defined subject populations, standardized outcome measures of oxidative stress and the dis-

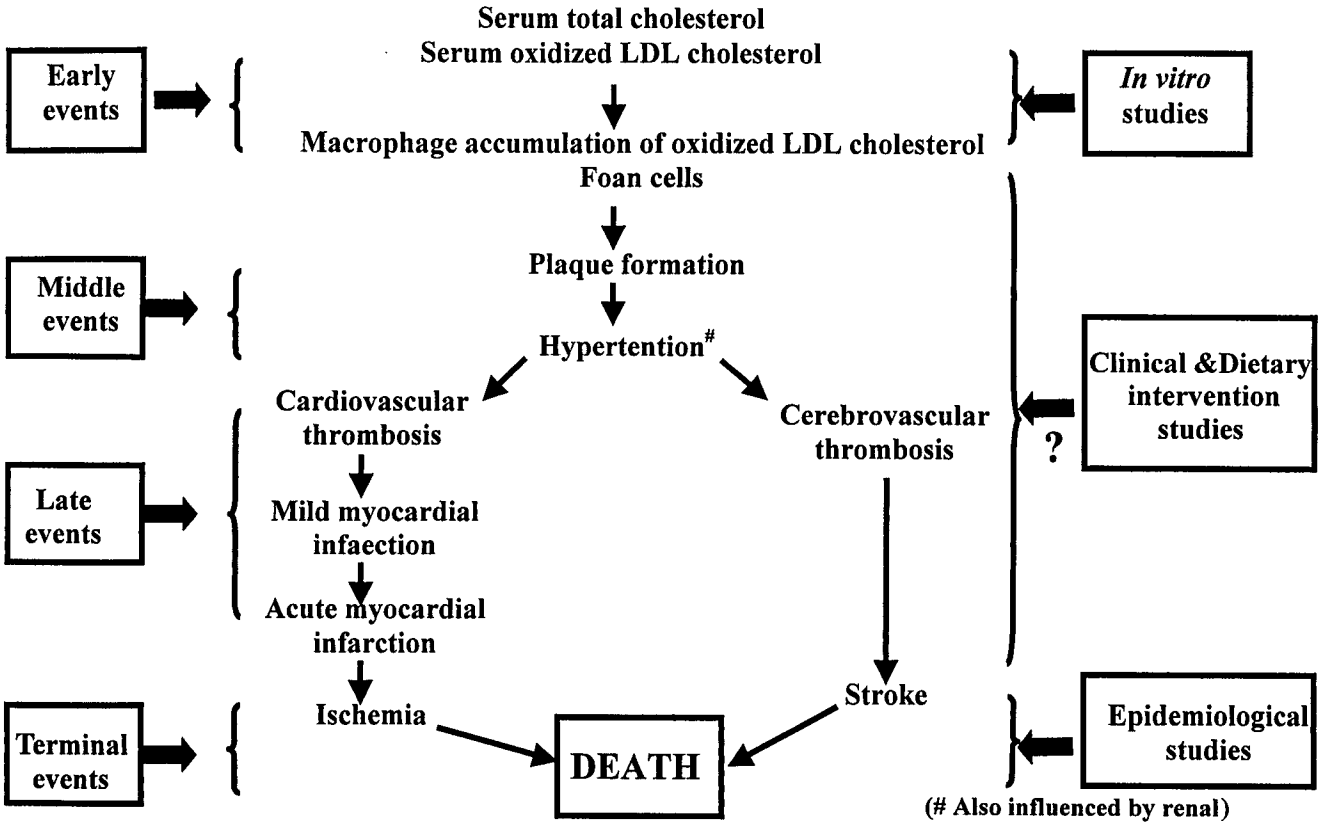

Figure 3. Cardiovascular and cerebrovascular events leading to death

ease, and lycopene ingestion that is representative of normal healthy dietary intakes are essential for a meaningful interpretation of the results in terms of therapeutic applications. There is also the need for long-term studies. Another important consideration in studying lycopene is its absorption. Lycopene must be absorbed first from dietary sources for it to be beneficial. A number of questions are now being raised regarding the bioavailability of dietary lycopene. Factors such as heat induced *cis*-isomerization of the all *trans* lycopene, the predominant form in which it is present in fresh tomatoes, presence of dietary lipids, and the presence of other antioxidants are being shown to influence the absorption of lycopene. Some of the conflicting epidemiological observations being reported in the literature may be related to this issue. In general, circulating and adipose tissue levels of lycopene seem to be better indicators of disease prevention than dietary intake data. Lycopene has been shown to be better absorbed from processed tomato products than from fresh tomatoes. Close to 50% of tomato consumption was shown in a recent survey conducted in Canada to be fresh. Therefore, calculation of total lycopene intake based on dietary surveys may not reflect the true picture *in vivo*. Careful consideration must be given to all these factors in designing future studies to evaluate the role of lycopene in the prevention of CHD.

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