Protective effect of lycopene in cardiovascular disease

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Abstract. – Coronary artery disease (CAD) represents the primary cause of death in Western Countries with an high incidence on human health and community social costs. Oxidative stress induced by reactive oxygen species (ROS) plays an important role in the aetiology of this disease. In particular, the LDL-oxidization has a key role in the pathogenesis of atherosclerosis and cardiovascular heart diseases through the initiation of plaque formation process. Dietary phytochemical products such antioxidant vitamins (A,C,E) and bioactive food components (alpha- and beta-carotene) have shown an antioxidant effect in reducing both oxidative markers stress and LDL-oxidization process. Scientifical evidences support the beneficial roles of phytochemicals in the prevention of some chronic diseases. Lycopene, an oxygenated carotenoid with great antioxidant properties, has shown both in epidemiological studies and supplementation human trials a reduction of cardiovascular risk. However, controlled clinical trials and dietary intervention studies using well-defined subjects population haven’t been provided a clear evidence of lycopene in the prevention of cardiovascular diseases. The present short review aims to evaluate the beneficial effect of lycopene in the prevention of cardiovascular disease.

Key Words: Lycopene, Atherosclerosis, Cardiovascular risk, Vitamins, Oxidized LDL.

Abbreviations

CVD: Cardiovascular diseases
CHD: Coronary heart disease
TIA: Transient ischemic attack
CHF: Congestive heart failure
LDL: Low density lipoprotein
HDL: High density lipoprotein
Lyc: Lycopene
NO: Nitric oxide
ROS: Reactive oxygen species
SOD: Superoxide dismutase
GSHpx: Glutathione peroxidase
MI: Myocardial infarction
LDL-C: Low density lipoprotein cholesterol
HDL-C: High cholesterol density cholesterol
PVD: Peripheral vascular disease
CRP: C-reactive protein

Introduction

Heart diseases and stroke represent an epidemic cause of death and disability in developed countries1, responsible for about 30 percent of all deaths worldwide each year. The term cardiovascular diseases (CVD) include coronary heart disease (CHD) (myocardial infarction [MI], angina pectoris, coronary insufficiency, and coronary death), cerebrovascular diseases (stroke and transient ischemic attacks [TIA], peripheral vascular disease (PVD), congestive heart failure (CHF), hypertension, valvular and congenital heart disease2.

Numerous epidemiological investigations have characterized the risk pattern for CHD. In particular, male sex, elevated low density lipoprotein cholesterol (LDL-C) levels, low high density lipoprotein cholesterol (HDL-C) levels, diabetes mellitus, and cigarette smoking are key risk factors for CHD3.

Along with genetic factors and age, lifestyle and diet are also considered important risk factors. In particular carotenoids, a group of phytochemicals substances responsible for different colors of the foods, play an important role in the prevention of human diseases and maintaining good health4.
It is estimated that nearly one-third of all cancer deaths in the occidental developed countries could be prevented through an appropriate dietary modification. Various dietary antioxidants have shown considerable promise as effective agents for cancer prevention by reducing oxidative stress which has been implicated in the development of many diseases, including cancer. Therefore, for reducing the incidence of tumour formation, modifications in dietary habits, especially by increasing consumption of fruits and vegetables rich in antioxidants, are increasingly advocated. Accumulating research evidence suggests that many dietary factors may be used alone or in combination with traditional chemotherapeutic agents to prevent the occurrence of neoplasms, their metastatic spread, or even to treat cancer. The reduced cancer risk and lack of toxicity associated with high intake of fruits and vegetables suggest that specific concentrations of antioxidant agents from these dietary sources may produce cancer chemopreventive effects without causing significant levels of toxicity.

Epidemiological studies regarding intake of tomatoes and tomato-based products and blood lycopene reported an inverse associations between tomato intake or blood lycopene level and the risk of cancer. The evidence for a benefit was strongest for tumours of the prostate, lung, and stomach. Because the data are from observational studies, a cause-effect relationship cannot be established definitively. However, the consistency of the results across numerous studies in diverse populations, for case-control and prospective studies, and for dietary-based and blood-based investigations argues against bias or confounding as the explanation for these findings. Lycopene may account for or contribute to these benefits, but this possibility is not yet proven and requires further studies. Numerous other potentially beneficial compounds are present in tomatoes, and, conceivably, complex interactions among multiple components may contribute to the anticancer properties of tomatoes. The consistently lower risk of cancer for a variety of anatomic sites that is associated with higher consumption of tomatoes and tomato-based products adds further support for current dietary recommendations to increase fruit and vegetable consumption.

Antioxidant nutrients are believed to slow the progression of atherosclerosis because of their ability to inhibit the tissue damage deriving to oxidative process. Lycopene (Lyc) is one of such dietary antioxidant naturally present in tomatoes and tomato products, which has received much attention recently.

**Oxidative Stress**

Advances in pathophysiological research suggested that CVD represent a continuum pathophysiological process that includes oxidative stress, endothelial dysfunction, inflammatory process, and vascular remodeling. Normal endothelial function appears to depend greatly on the homeostatic balance between nitric oxide (NO) and reactive oxygen species (ROS), such as superoxide anion and hydrogen peroxide. ROS are highly reactive oxidant molecules generated endogenously through regular metabolic, lifestyle activity, and diet. They react with cellular components, causing oxidative damage to such critical cellular biomolecules as lipids, proteins and DNA. This damage may play a significant role in the pathogenesis of several chronic diseases.

Oxidative stress induced by ROS is characterized by production of oxidized-LDL (LDL_{ox}), that play a key role in the pathogenesis of atherosclerosis and represent a underlying disorder leading to heart attack and ischemic stroke.

In particular, the endothelial cells actively participate to the development of inflammatory reactions. The recruitment of leukocytes to sites of inflammation is initiated by endothelial secretion of chemotactic molecules and enhanced expression of adhesion molecules that interact with surface proteins and leukocytes. Cytokynes and arachidonic acid metabolites of the leukocyte pathway derived from cells of vessels wall stimulates endothelial secretion of many of these molecules.

Inflammation characterizes all phases of atherothrombosis and provides a critical pathophysiological link between plaque formation and acute rupture, leading the occlusion and infarction. An inflammation complex novel risk factors including high sensitivity C-reactive protein (hsCRP), lipoprotein(a), homocysteine, and markers of fibrinolytic and hemostatic function such as fibrinogen, D-dimer, tissue plasminogen activator (t-PA), and plasminogen activator inhibitor (PAI-1) antigens characterize the several phases of atherothrombosis. In particular, hsPCR, a circulating member of pentraxin family, plays a major role in the human immune response. Although it is a primarily derived from the liver, recent data indicate that cells within human coronary arteries, particularly in the athero-
sclerotic intima, can elaborate CRP\textsuperscript{20,21}. More than a simply marker of inflammation, CRP may influence directly vascular vulnerability through several mechanisms, including enhanced expression of local adhesion molecules, increased expression of endothelial PAI-1, reduced endothelial nitric oxide bioactivity, altered LDL uptake by macrophages, and colocalization with complement within atherosclerotic lesions\textsuperscript{22}.

Large series of prospective epidemiological studies has demonstrated that CRP, when measured with high-sensitivity assays (hsCRP), strongly and independently predicts risk of myocardial infarction, stroke, peripheral arterial disease, and sudden cardiac death even among apparently healthy individuals\textsuperscript{23,24}. The hsCRP levels correlate only modestly with underlying atherosclerotic disease as measured by carotid intima-media thickness or by coronary calcification. This observation suggests that hsCRP does not simply reflect the presence of subclinical diseases but rather indicates an increased propensity for plaque disruption and/or thrombosis\textsuperscript{25}.

**Antioxidants**

Antioxidants are protective agents that inactivate ROS and therefore significantly delay or prevent oxidative damage. In particular, superoxide dismutase (SOD), catalase and glutathione peroxidase (GSH\textsubscript{p}) are endogenous naturally antioxidants present within human cells. In addition, antioxidants such as vitamin E, vitamin C, polyphenols and carotenoids are available from foods. Current dietary guidelines to combat chronic diseases, including cancer and CHD, recommend increased intake of plant foods, including fruits and vegetables, which are rich sources of antioxidants\textsuperscript{26,27}. The role of dietary antioxidants, including vitamin C, vitamin E, carotenoids and polyphenols, in disease prevention has received much attention recently and appears to have a wide range of antiatherogenic properties\textsuperscript{28-31}. These observations may explain the epidemiological data indicating that diets rich in fruits and vegetables are associated with a reduced risk of numerous chronic diseases\textsuperscript{32,33}.

**Lycopene (Lyc)**

**Chemical Structure**

Lyc, the most predominant carotenoid in human plasma, a natural pigment synthesized by plants and microorganisms, is an acyclic isomer of beta-carotene\textsuperscript{34,35} containing 11 conjugated and two non-conjugated double bonds arranged in a linear array\textsuperscript{36}. Lyc from natural plant sources exists predominantly in an all-trans configuration, the most thermodynamically stable form, and in human plasma is present as an isomeric mixture, with 50% as cis isomers\textsuperscript{37}.

Because of its high number of conjugated dienes, lyc is one of the most potent antioxidants, with a singlet-oxygen-quenching ability twice as high as that of beta-carotene and 10 times higher than that of alpha-tocopherol\textsuperscript{38-41}. Owing to their lipophilic nature, lyc and other carotenoids are found to concentrate in serum low-density and very-low-density lipoprotein fractions\textsuperscript{35}. Lyc is also found to concentrate in the adrenal gland, testes, liver and prostate gland, where it is the most prominent carotenoid\textsuperscript{42-45}. Tissue-specific lyc distribution may be important in the antioxidant role. However, unlike other carotenoids, lyc levels in serum or tissues do not correlate well with overall intake of fruits and vegetables\textsuperscript{46,47}.

Red fruits and vegetables, including tomatoes, watermelons, pink grapefruits, apricots and pink guavas, contain lyc\textsuperscript{48}. Processed tomato products, such as juice, ketchup, paste, sauce and soup, all are good dietary sources of lyc\textsuperscript{49}.

**Mechanisms of Action**

Two major hypotheses have been proposed to explain the antiatherogenic activities of lyc: non-oxidative and oxidative mechanisms. The non-oxidative mechanisms has been suggested to be due to regulation of gap-junction communication in mouse embryo fibroblast cells\textsuperscript{50,51}. The oxidative hypothesis include 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\textsuperscript{52}. The oxidative modifications reflect not only the polyunsaturated fatty acids (PUFA), but also oxidation of the cholesterol, phospholipids, and oxidative degradation of the apolipoprotein B itself\textsuperscript{53}. In addition to the formation of foam cells and plaque in the arterial wall, components of LDL\textsubscript{ox} can also influence other events that related to the increased risk of CHD\textsuperscript{54}. These include their ability to increase cholesterol accumulation by macrophages, their ability to produce proteins with chemiotactic activity to monocytes and cytotoxic activity to a variety of cells causing endothelial injuries\textsuperscript{55}.  

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Lyc also has been shown to act as a hypocholesterolemic agent by inhibiting HMG-CoA (3-hydroxy-methylglutaryl-coenzyme A-reductase)\textsuperscript{56}, and has been hypothesized to prevent atherogenesis by protecting critical cellular molecules, including lipids, lipoproteins, proteins and DNA\textsuperscript{57-59}. In healthy human subjects, lyc- or tomato-free diets resulted in loss of lyc and increased lipid oxidation\textsuperscript{60}, whereas dietary supplementation with lyc for 1 week increased serum lyc levels and reduced endogenous levels of oxidation of lipids, proteins, lipoproteins and DNA\textsuperscript{57,58}.

**Lycopene and Cardiovascular Disease**

**Risk of Cardiovascular Disease**

Several epidemiological and prospective studies have shown that the consumption of antioxidant vitamins such as vitamin E and beta-carotene may reduce the risk of CHD\textsuperscript{61,62}. However, if some large-scale human trials have failed to confirm the protective effect of antioxidant supplementation (vitamin E and beta-carotene) observed in previously\textsuperscript{9,10}.

Few similar studies, in vitro and in vivo, have been performed with lyc. A number of studies in vitro have shown that lyc can protect native LDL from oxidation and can suppress cholesterol synthesis\textsuperscript{54,55}. However, the predictability of in vitro LDL-oxidation as a marker of atherosclerosis has been questioned in recent years\textsuperscript{63}.

**Epidemiological Studies**

Several 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 lyc, the major responsible for the beneficial effects of these food products. In particular mediterranean diet is rich in tomatoes, tomato products, lyc, and other carotenoids, and is associated with lower risk of CHD\textsuperscript{56,57,59}.

In the Physicians’ Health Study, Sesso et al\textsuperscript{64} have found in 499 patients with CVD (MI, stroke, CVD death, or revascularization procedures) an association between higher plasma lyc concentration and low risk of CVD.

In the CARDIA/YALTA study, Hozawa et al\textsuperscript{85} have demonstrated that circulating serum carotenoids (alpha-carotene, beta-carotene, zeaxanthin/lutein, beta-cryptoxanthin, and lyc) were associated in apparently beneficial directions with markers of inflammations (leucocyte counts, fibrinogen, CRP), oxidative stress, and endothelial dysfunction (F2 isoprostane, serum ICAM-1, and P-selectin).

Lidebjer et al\textsuperscript{66} in a case-control study on 139 subjects (39 with acute coronary syndrome, 50 with stable CAD, and 50 healthy controls) have demonstrated a significantly lower plasma levels of oxygenated carotenoids (lutein, zeaxanthin, lyc, beta-cryptoxanthin, alpha- and beta-carotene) in both patient groups.

The EURAMIC multicentre case-control study, has evaluated the relation between antioxidant status and acute MI. 1,389 subjects (662 cases and 717 controls) were recruited from 10 European countries to maximize the variability in exposure within the study. Adipose tissue antioxidant levels, which are better indicators of long-term exposure than blood antioxidant levels, were used as markers of antioxidant status. Biopsy specimens of adipose tissue, taken directly after the MI, were analysed for various carotenoids. After adjustment for a range of dietary variables (age, BMI, socioeconomic status, smoking, hypertension, and maternal-paternal history of the disease), only lyc levels, and not beta-carotene levels, were found to be protective (odds ratio 0.52 for the contrast of the 10\textsuperscript{th} and 90\textsuperscript{th} percentile with a 0.005 \textit{p} value). In particular this study have showed a various odds ratio in subjects never smokers (0.33), ex-smokers (0.41), and smokers (0.63) supporting the antioxidant hypothesis\textsuperscript{66}. Similarly, Handelman et al\textsuperscript{57} in a study from John Hopkins University showed that smokers with low levels of circulating carotenoids have an higher risk for subsequent MI.

Lower blood lyc levels were also found to be associated with increased risk for death in a population study comparing Lithuanian and Swedish cohorts with different rates of death from CAD\textsuperscript{68}. Even in a Japanese population-based study (11.9 year follow-up) Ito et al\textsuperscript{69} have found in 3,061 subjects (1,190 males and 1,871 females) an association between low hazard ratio for cardiovascular disease mortality and high serum values of carotenoids (alpha- and beta-carotene, lyc, total carotene values).

Only in the Atherosclerosis Risk in Communities (ARIC) case-control study, the fasting serum antioxidant levels of 231 cases and an equal number of control subjects were assessed in rela-
tionship to the intima-media thickness (IMT) as an indicator of asymptomatic early atherosclerosis. After controlling for other variables, an odds ratio of 0.81 was observed, but the $p$ value for the association for lyc was not significant\textsuperscript{70}.

**Supplementation Clinical Trials**

Although epidemiological studies conducted so far provide convincing evidence for the role of lyc in CHD prevention, there is a good suggestion but not the proof of a causal relationship between lyc intake and risk of CHD. However, very such supplementation studies have been reported in literature.

Bose et al\textsuperscript{71}, recently, in a clinical case-control study on subjects with CHD have demonstrated a significant improvement in the level of serum enzymes involved in antioxidant activities (lipid peroxidation rate, SOD, GSH\textsubscript{px}) after 60 days of tomato supplementation in the CHD group respect to control group suggesting that the tomato lyc may have a considerable therapeutic potential as an antioxidant.

Visioli et al\textsuperscript{72} in three-weeks supplementation study of tomato products (raw, sauce, and paste) on twelve females have found an increased significant lyc concentrations after tomato consumption and a reduced LDL-oxidizability suggesting an important role for tomato products in the prevention of lipid proxidation.

In a small dietary supplemention study\textsuperscript{73}, six healthy male subjects consumed 60 mg/day lyc for three months. At the end of treatment period, a significant 14\% reduction in their plasma LDL-C level was observed.

In a randomized, crossover dietary intervention study\textsuperscript{74}, 19 non smokers healthy human subjects (10 male, 9 females) consumed lyc from traditional tomato products and nutritional supplement for one week (from 20 to 150 mg/day). Lyc was observed to be absorbed readily from all dietary sources, resulting in significantly increase in serum lyc levels and lower lipid levels, protein, and DNA oxidation. In the same study\textsuperscript{75} although there were no changes in serum total cholesterol and LDL-C and HDL-C, serum lipid peroxidation were significantly decreased and serum lyc levels increased.

Conversely, Peterson et al\textsuperscript{76} have designed a single-blind, randomized, controlled, crossover dietary intervention study aimed to determine wheter an increase of five portions of fruits and vegetables in the form of soups and beverages have beneficial effects on markers of oxidative stress and CVD risk factors. After 4 weeks consumed carotenoid-rich or control vegetable soups and beverages they have found an increase of dietary carotenoids (alpha- and beta-carotene, lyc), vitamin C, alpha-tocopherol, potassium, and folate, but not alterations of oxidative stress markers or cardiovascular risk factors.

**Conclusion**

The current dietary recommendation to increase the consumption of fruits and vegetables rich in antioxidants has generated interest in the role of lyc in disease prevention. However, the evidence thus far is mainly suggestive, and the underlying mechanisms are not clearly understood\textsuperscript{77,78}.

Nutrition has a significant role in the prevention of many chronic disease as CVD\textsuperscript{79,80}. A great intake of fruit and vegetables can help prevent heart disease and mortality by preventing the oxidation of cholesterol in arteries. Even epidemiological studies yielded conflicting results, carotenoids, in particular lyc, has an important role and play a key effect in the prevention of CVD.

Only few lyc dietary supplementation small studies have shown a mild significative both hypcholesterolemic effect than reduction of LDL oxidation. However, a clearly relationship between lyc intake supplementation and reduction risk of CHD is not fully established. For this reason long-term study are need for to evaluate a clear and significative link between lyc and risk of CVD.

Another important aspect regard the bioavailability of dietary lyc which is influenced in absorption by other antioxidants. Lyc has been shown to be better adsorbed from processed tomato products than from fresh tomatoes. Many factors (bioavailability, metabolism, isomerization, interaction with other carotenoids, and mechanism) are important in establishing long-term and well-designed future studies to evaluate the role of lyc in prevention of CHD.

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