Review

Role of Antioxidant Lycopene in Cancer and Heart Disease

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Lycopene, a carotenoid without provitamin-A activity, is present in many fruits and vegetables; however, tomatoes and processed tomato products constitute the major source of lycopene in North American diet. Among the carotenoids, lycopene is a major component found in the serum and other tissues. Dietary intakes of tomatoes and tomato products containing lycopene have been shown to be associated with decreased risk of chronic diseases such as cancer and cardiovascular diseases in several recent studies. Serum and tissue lycopene levels have also been inversely related with the chronic disease risk. Although the antioxidant properties of lycopene are thought to be primarily responsible for its beneficial properties, evidence is accumulating to suggest other mechanisms such as modulation of intercellular gap junction communication, hormonal and immune system and metabolic pathways may also be involved. This review summarizes the background information about lycopene and presents the most current knowledge with respect to its role in human health and disease.

Key teaching points:

- Oxidative stress is causally related to the incidence of chronic diseases such as cancer and heart disease.
- Lycopene may be a key component responsible for the protective effects of fruits and vegetables.
- Tomatoes and tomato products are the main dietary sources of lycopene.
- Lycopene is a major carotenoid of plasma and other body tissue.
- Dietary intake and/or serum levels of lycopene have been reported to be inversely related to the risk of cancer and heart diseases.
- Recommended daily intake of lycopene is 35 mg which can be obtained by ingesting two glasses of tomato juice or through a combination of tomato products.

BIOCHEMISTRY AND PHYSIOLOGY

Lycopene is a natural pigment synthesized by plants and microorganisms but not by animals. It is a carotenoid, an acyclic isomer of β-carotene, and has no vitamin A activity [1,2]. It is a highly unsaturated, straight chain hydrocarbon containing 11 conjugated and two non-conjugated double bonds. Recent interest in lycopene has focused on its antioxidant properties [1–3]. However, other mechanisms such as modulation of intercellular gap junction communication [4,5], hormonal and immune system [6–8] and metabolic pathways [9,10] are also beginning to be investigated.

As a polyene it undergoes *cis-trans* isomerization induced by light, thermal energy or chemical reactions [3,11]. Lycopene from natural plant sources exists predominantly in *trans* configuration, the most thermodynamically stable form [3,11]. In human plasma, lycopene is an isomeric mixture containing 50% of the total lycopene as *cis* isomers. All *trans*, 5-*cis*, 9-*cis*, 13-*cis* and 15-*cis* are most commonly identified isomeric forms of lycopene [12]. The biological significance of these isomers of lycopene is unclear.

Lycopene, ingested in its natural *trans* form found in tomatoes, is poorly absorbed. Recent studies have shown that heat processing of tomatoes and tomato products induces isomerization of lycopene to the *cis* form which in turn increases its bioavailability [13]. However, there is some indication that

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isomerization reactions may be taking place in the body. High concentration of *cis* isomers were also observed in human serum and prostate tissue [12], suggesting that tissue isomerases might be involved in *in vivo* isomerization of lycopene from all *trans* to *cis* form.

In a recently completed study [14] we demonstrated that serum and prostate levels of lycopene in prostate cancer patients were significantly lower than their age matched controls. It is hypothesized that prostate cancer patients perhaps lack the ability to isomerize dietary lycopene and therefore do not absorb it efficiently.

AVAILABILITY IN DIFFERENT FOOD PRODUCTS

Lycopene is mainly available from a very limited list of fruits and vegetables, in contrast to other dietary carotenoids. Red fruits and vegetables, including tomatoes, watermelons, pink-grapefruits, apricots and pink-guavas, are the most common sources of lycopene [1,3]. Tomatoes and processed tomato products such as juice, ketchup, paste, sauce and soup all are good sources of lycopene and may account for over 85% of dietary lycopene in the North American diet. The lycopene content of tomatoes varies with the variety and increases with fruit ripening.

In a recent study [15], we assessed the average daily dietary lycopene intake levels by administering a food frequency questionnaire and estimated it to be 25 mg/day, with processed tomato products accounting for 50% of the total intake. Based on these findings it was concluded that the recommended daily intake of lycopene of 35 mg was not being met. Lycopene from processed tomato products appears to be more bioavailable than from raw tomatoes [13]. Comparative bioavailabilities of lycopene from different tomato products such as paste, juice, ketchup, sauce and soup are not known. However, lycopene from tomato paste was shown to be more bioavailable than from fresh tomatoes [16]. Release of lycopene from the food matrix due to processing, presence of dietary lipids and heat-induced isomerization from all *trans* to *cis* conformation enhance lycopene bioavailability [1,17]. It is however not clear if *cis*-isomers are biologically more effective than *trans*-isomers. Bioavailability of lycopene is also affected by the dose and presence of other carotenoids such as β-carotene [18].

CELLULAR AND MOLECULAR STUDIES ON THE POTENTIAL PREVENTIVE ACTION IN HEART DISEASE AND CARCINOGENESIS

Reactive oxygen species (ROS) and the related oxidative damage have been implicated in the pathogenesis of various human chronic diseases [19–22]. Lycopene is one of the most potent antioxidants [23] and has been suggested to prevent carcinogenesis and atherogenesis by protecting critical biomolecules including lipids, low-density lipoproteins (LDL), proteins and DNA [24–26]. Several studies have indicated that lycopene is an effective antioxidant and free radical scavenger. Lycopene, because of its high number of conjugated double bonds, exhibits higher singlet oxygen quenching ability compared to β-carotene or α-tocopherol [27]. In *in vitro* systems, lycopene was found to inactivate hydrogen peroxide and nitrogen dioxide [28,29]. Using pulse radiolysis techniques, Mortesen *et al.* [30] demonstrated its ability to scavenge nitrogen dioxide ($NO_2^{\cdot}$), thiyl ($RS^{\cdot}$) and sulphonyl ($RSO_2^{\cdot}$) radicals. Lycopene is highly lipophilic and is most commonly located within cell membranes and other lipid components. It is therefore expected that in the lipophylic environment lycopene will have maximum ROS scavenging effects. Lycopene was shown to be the most effective antioxidant in protecting the 2,2′-azobis(2,4-dimethylvaleronitrile) (AMVN)-induced lipid peroxidation of the liposomal membrane [31]. Oxidative modification of LDL is hypothesized to be the key step in the atherogenic process, and LDL associated antioxidants provide protection against this oxidation [32]. *In vitro* lycopene and other carotenoids are able to inhibit oxidation of LDL [33]. Lycopene was also found to protect lymphocytes against $NO_2^{\cdot}$-induced membrane damage and cell death twice as efficiently as β-carotene [28,34]. *In vivo* antioxidant effects of lycopene and its interaction with the host and other dietary antioxidants are now being investigated.

A number of studies have used tissue culture and *in vitro* systems to demonstrate potential disease preventive action of lycopene and provided a mechanistic hypothesis. Levy *et al.* [6] showed that lycopene inhibited the growth of human endometrial, mammary and lung cancer cells grown in cultures and was more effective than α- or β-carotene. Lycopene along with vitamin D3 synergistically inhibited cell cycle progression and induced differentiation of the HL60 promyelocytic leukemia cell line [35]. In mouse embryo fibroblast cells, lycopene enrichment upregulated gap-junction-communication by enhancing the expression of the connexin43 gene, which encodes a major gap junction protein, and thereby acted as an anticarcinogenic agent [4,5]. Lycopene was also shown to protect against microcystinCR-induced mouse hepatocarcinoma by suppressing the phosphorylation of regulatory proteins and arresting cells in the G0/G1 phase of the cell cycle [36]. Preliminary *in vitro* evidence indicates that lycopene reduces cellular proliferation induced by IGF-1 in various cancer cell lines [6]. In a recent investigation, lycopene, together with α-tocopherol at physiological concentrations, synergistically inhibited cell proliferation of an androgen insensitive prostate carcinoma cell line [37]. In the J774A.1 macrophage cell line, lycopene was shown to act as a hypocholesterolemic agent by inhibiting the HMG-CoA reductase pathway [10].

RELEVANT ANIMAL DATA

Lycopene may play an important protective role in several human cancers. Animal models have been used to measure lycopene's absorption and tissue distribution. Jain *et al.* [38] have recently demonstrated that 10 ppm dietary lycopene in rat diet was absorbed and distributed to various tissues. Liver, spleen and prostate showed the highest levels of lycopene, whereas brain had the lowest level. The varying levels of lycopene in different tissues suggest its selective uptake involving tissue-specific mechanism(s) [38]. Use of animal models to investigate *in vivo* biochemical functions of lycopene has allowed undertaking studies under well-defined, controlled environmental conditions where the confounding variables are minimum. Although several animal models of experimental cancer are available, very little is known about the absorption, metabolism and distribution of dietary lycopene and the possible mechanism of its effects on carcinogenesis. As early as 1959, dietary lycopene or intraperitonial injections of lycopene were demonstrated to provide protection against ionizing radiation, resistance towards bacterial infections and inhibition of ascites-producing tumors in mice [39,40].

In rats, growth and development of C-6 glioma cell xenographs were inhibited by intraperitonial injections of lycopene [41]. Growth-inhibitory effects were more pronounced when lycopene was given before the glioma cell inoculation. Chronic dietary intake of lycopene markedly delayed the onset and reduced growth and development of spontaneous mammary tumors in a mouse strain with high incidence [7]. This effect was associated with reduced activity of mammary gland thymidylate synthetase and lowered levels of serum free fatty acids and prolactin, a hormone known to be involved in breast cancer development that stimulates cell division. Lycopene was also shown to enhance the immune response by increasing helper T cells and normalizing intrathymic T cell differentiation caused by tumorigenesis in mice [8]. Lycopene in small doses reduced the N-methylnitrosourea (MNU)-induced development of aberrant crypt foci (ACF) in the colon of Sprague-Dawley rats [42]. In a dimethylbenzanthracene (DMBA)-induced mammary tumor model of rats, intraperitoneal injections of lycopene-enriched tomato oleoresin, but not of β-carotene, suppressed tumor growth as quantified by size and tumor numbers [43].

Diethylnitrosamine (DEN)-induced liver preneoplastic foci in rats were significantly reduced by dietary lycopene and not by any other carotenoid tested [9]. It was hypothesized that lycopene provided protection through its modulating effect on the liver enzymes activating diethylnitrosamine, cytochrome P-450 2E1, and not through an antioxidative mechanism [9]. Ingestion of tomato juice inhibited the development of N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN)-induced development of urinary bladder transitional cell carcinomas in male Fischer 344 rats [44]. Recent investigations in our laboratory indicated that dietary lycopene (10 ppm) significantly reduced lipid and protein oxidation and demonstrated an apparent protective effect against azoxymethane (AOM)-induced colonic preneoplastic lesions [38]. Dietary lycopene in the form of vegetable juice was also found to be protective against AOM-induced aberrant crypt foci in the rat colon model [45].

Dietary lycopene dissolved in drinking water at a 50 ppm dose significantly decreased diethylnitrosamine (DEH)-, methylnitrosourea (MNU)- and dimethylhydrazine (DMD)-induced lung adenomas along with carcinomas in male mice [46]. The protective effects of lycopene against lung cancer were, however, not observed in female mice. Similarly, dietary lycopene did not alter colon or kidney tumors in the same study [46]. In another study, treatment with dietary lycopene had no effect on tobacco-smoke carcinogens benzo[a]pyrene and 4-[methyl]nitrosamino]-1-[3-pyridyl]-1-butanone induced-lung tumor multiplicity in A/J mice [47]. Lack of protection against benzopyrene-induced lung tumors was probably due to the lack of involvement of DNA oxidation in this model. Lycopene also had no effects on 2-nitropropane-induced hepatocarcinogenesis or dimethylhydrazine (DMH)-induced colon carcinogenesis in mice, as indicated by proliferation of colonic crypt epithelial cells as measured by BrdU incorporation assay [48]. Similarly, aflatoxin B1-induced liver preneoplastic foci in the rat were not affected by dietary lycopene, whereas β-carotene provided significant protection [49].

IMPORTANT CLINICAL STUDIES

The interest in lycopene and its potential protective role in prevention of chronic diseases stems largely from 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 chronic diseases. Epidemiological investigations to study the role of lycopene in relation to chronic diseases has focused primarily on cancers. The Mediterranean diet, which is rich in fruits and vegetables, including tomatoes, has been suggested to be responsible for the lower cancer incidences in that region [50]. Dietary intake of tomatoes and tomato products has been found to be associated with a lower risk of a variety of cancers in a number of epidemiological studies [51]. In a prospective cohort study, Colditz *et al.* [52] investigated the frequency of intake of different types of vegetables and cancer deaths in 1271 elderly persons from Massachusetts. High intake of tomatoes was linked to a 50% reduction in mortality from cancers at all sites. Carrots and other carotenoid-rich vegetables had no effect [52].

The most impressive results came from U S Health Professionals Follow-up Study evaluating the intake of various carotenoids and retinol, from a food frequency questionnaire, in relation to risk of prostate cancer [53]. The estimated intake of lycopene from various tomato products, and not any other

carotenoid, was inversely related to the risk of prostate cancer. A risk reduction of almost 35% was observed for a consumption frequency of 10 or more servings of tomato products per week, and the protective effects were even stronger for more advanced or aggressive prostate cancer [53]. Similarly serum and tissue levels of lycopene were inversely associated with prostate cancer risk in recent case-control and cohort studies [14,54]. It is noteworthy that no significant association with other major carotenoids including β-carotene was observed in these studies [14,54].

High intake of tomatoes was consistently associated with reduced risk of digestive tract (especially stomach, colon and rectal) cancers in a case control study from Italy, where cases were patients with histologically confirmed cancers of oral cavity, pharynx, esophagus, stomach, colon and rectum and controls were patients with unrelated conditions [55]. Similarly, an inverse association between lycopene (estimated intakes or serum levels) and breast cancer risk was reported by some investigators in epidemiological investigations. However, these observations were not confirmed by other investigators [56–58]. In a recent case-control study from the Breast Cancer Serum Bank in Columbia, Missouri, only serum lycopene and none of the other antioxidants showed a significant inverse relationship with breast cancer risk [59]. Dietary intake of lycopene as well as serum lycopene levels showed an inverse association with the risk of cervical intraepithelial neoplasia in another case-control study [60]. In a cohort study, serum lycopene levels were found to be inversely related to the risk of bladder cancer [61]. It appears that cancer risk is inversely associated with lycopene status, which can be improved by dietary sources rich in this carotenoid as well as through supplements.

Giovannucci [51] recently reviewed 72 epidemiological studies including ecological, case-control, dietary studies and blood specime-based investigations on tomatoes, tomato-based products, lycopene and cancer. A significant number of studies analyzed demonstrated an inverse relationship between intakes of tomatoes or plasma lycopene levels and cancer. The strongest associations were observed for cancers of the prostate, lung and stomach. However, for cancers of pancreas, colon and rectum, esophagus, oral mucosa, breast and cervix the associations were only suggestive. These results were consistent across numerous diverse populations and with the use of several different study designs. None of the studies analyzed indicated increased risk of cancer [51].

Oxidation of LDL which carries cholesterol into the blood stream has been hypothesized to play an important role in the causation of atherosclerosis, the underlying disorder leading to heart attack and ischemic strokes [21,62]. Antioxidant nutrients are believed to slow the progression of atherosclerosis because of their ability to inhibit damaging oxidative processes [32,62,63]. Several epidemiological studies have provided evidence for the protective effect of vitamin E, which has been ascribed to its antioxidant properties [63–66]. However many dietary intervention trials involving α-tocopherol or β-carotene have yielded inconclusive results. Similar studies have not been performed with lycopene.

A recent multicenter case-control study (EURAMIC) evaluated the relationship between adipose tissue antioxidant status (α- and β-carotene and lycopene) and acute myocardial infarction [67]. Subjects were recruited from 10 European countries to maximize the variability in exposure within the study. After adjusting for a range of dietary variables, only lycopene, and not β-carotene, levels were found to be protective [67]. The protective potential of lycopene was maximal among individuals with highest polyunsaturated fat stores, supporting the antioxidant theory [67]. Similarly lower blood lycopene levels were also found to be associated with increased risk and mortality from coronary heart disease in a concomitant cross-sectional study comparing Lithuanian and Swedish populations showing diverging mortality rates from coronary heart disease [68]. Limitations of the epidemiological studies undertaken to date include heterogeneous population, levels of serum carotenoids, duration of the study and biomarkers of the disease. Further studies should address these study variables to provide a more precise role of lycopene in disease prevention.

Although there is compelling epidemiological evidence in support of the role of lycopene in cancer and heart disease prevention, it only provides suggestive evidence rather than experimental proof. To date a very limited number of human intervention trials have been performed investigating the effectiveness of lycopene intake on lowering cancer and heart disease risk. Oxidative damage to lipids, proteins and DNA has been suggested to be involved in the causation and progression of cancer and heart disease [19,22]. A 50% loss of serum lycopene with an 25% increase in lipid oxidation (TBARS) was observed in human subjects ingesting a lycopene-free diet for two weeks [69]. Consumption of vegetable juices and tomato juice containing lycopene has been shown to reduce DNA strand breaks in healthy subjects [26]. Studies involving healthy human subjects in our laboratory indicated that lycopene from traditional tomato products is absorbed readily, increases serum levels and lowers oxidative damage to lipids, lipoproteins, proteins and DNA [24,25]. The level of consumption of tomato products used in this study was one to two servings/day (126 g spaghetti sauce or 500 mL tomato juice per day); that was easily achievable and in keeping with the current dietary recommendations pertaining to healthy eating. There are suggestions that tomato extract supplementation in the form of capsules lowered the PSA levels in prostate cancer patients [70]. In a small clinical trial involving six male subjects, dietary supplementation of lycopene (60 mg/d for three months) resulted in 14% reduction of plasma LDL levels and thus acted as a moderate hypocholesterolemic agent [10].

SUMMARY OF AVAILABLE INFORMATION

Lycopene is a naturally present carotenoid in tomatoes and other fruits and vegetables. Unlike β-carotene, it does not have provitamin A activity. It is one of the most potent antioxidants among the dietary carotenoids. It is readily absorbed from different food sources, distributes to different tissues and maintains its antioxidant properties in the body. It is suggested to have anti-cell-proliferative, anticarcinogenic and antiatherogenic activities. Epidemiological and a small number of animal and experimental studies have provided evidence in support for its protective role in heart disease and cancer. Recent meta-analysis of the epidemiological literature indicated that higher intake or serum levels of lycopene are related to reduced risk for several human cancers. Although antioxidant properties of lycopene are thought to be responsible primarily for its biological effects, other mechanisms are also being identified. However, several questions, such as absorption and utilization of lycopene (alone or in combination with other antioxidants) in patients with chronic diseases, isomerization and metabolism of lycopene, biological significance of different isomers and metabolites of lycopene and the fate of lycopene in tumor cells, are still unanswered. More mechanistic studies, as well as controlled clinical intervention trials involving healthy subjects, subjects at high risk for cancer and heart disease and patients with chronic diseases, are needed to understand fully its health-promoting effects and establish clear dietary guidelines.

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