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ROLE OF LYCOPENE AS ANTIOXIDANT CAROTENOID IN THE PREVENTION OF CHRONIC DISEASES: A REVIEW

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ABSTRACT

Lycopene is a naturally present carotenoid in tomatoes. Among the carotenoids, lycopene is a major component found in the serum. High levels of lycopene have also been found in the testes, adrenal glands, prostate. Several recent studies including cell culture, animal and epidemiological investigations have indicated the effect of dietary lycopene in reducing the risk of chronic diseases such as cancer and coronary heart disease. 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 intercellular gap junction communication, hormonal and immune system modulation 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.

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KEY WORDS: Lycopene, Carotenoids, Oxidative stress, Antioxidant, Chronic Diseases

INTRODUCTION

Cancer and cardiovascular diseases are the major causes of deaths in North America. Although genetic factors and age are important in determining the risk, dietary component is also a major risk factor associated with the diseases (1). Approximately 70% of all cancers are attributable to diet. Role of reactive oxygen species (ROS) and oxidative damage to biomolecules is one of the main foci of recent research related to cancer and cardiovascular diseases. Oxidative stress has been widely postulated to be involved in the causation and progression of several chronic diseases (2-8). Dietary antioxidants, which inactivate ROS and provide protection from oxidative damage (2-8), are being considered as important preventive strategic molecules.

Recent dietary guidelines to combat chronic diseases including cancer and coronary heart diseases

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recommend increased consumption of plant foods including fruits, vegetables, cereals and legumes. This is in part due to epidemiological studies (international comparisons and cohort studies) indicating a strong relationship between high calorie, high fat/meat diet, low fiber and increased risk for many cancers (1,9). Plant foods are also rich sources of flavonoids, lignans and carotenoids which in laboratory animal, cell culture, case control or cohort studies appear to protect against the development of cancer (10,11). Micronutrient phytochemical components of plant foods have been suggested to have chemopreventive activity possibly through their effect on hormonal metabolism and oxidative damage (1).

Recent epidemiological studies have recommended that high consumption of fruits and vegetables reduces the risk of cancer. Carotenoids are plant pigments commonly found in fruits and vegetables and are considered to be the important micronutrients responsible for the protective effects. Two competing hypotheses have been proposed to explain the anticarcinogenic carotenoid activity: their ability as precursors of vitamin A or their intrinsic property as antioxidant. Non-provitamin A carotenoids such as lycopene or canthaxanthin also exhibit biological activity related to their cancer preventing effects. This review will focus on the role of lycopene in human health and disease.

CHEMISTRY

Carotenoids, in general, are made up of two tetraterpenes units joined by tail-to-tail bond. Most carotenoids have one or two ring structures (5 or 6 membered) formed by the cyclization of the end groups. In addition to carbon and hydrogen, they may also contain oxygen atoms. Lycopene is a 40 carbon atom, open chain hydrocarbon containing 11 conjugated and 2 non-conjugated double bonds arranged in a linear array (12) (**figure 1**).

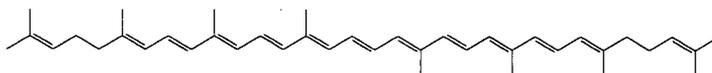


FIG. 1. Structure of Lycopene

These bonds can undergo isomerization from *trans* to mono or poly-*cis* isomers by light or thermoenergy or during chemical reactions. All *trans*, *5-cis*, *9-cis*, *13-cis* and *15-cis* are the most commonly identified isomeric forms of lycopene. Since lycopene lacks β -ionone ring structure it lacks provitamin-A activity. Molecular formula is $(C_{40}H_{56})$ and the molecular weight is 536.85 daltons. Lycopene is a lipophilic compound and is insoluble in water. It is a red pigment, absorbs light in the visible range and petroleum ether solution of lycopene has λ_{max} 472 nm and $\epsilon^{%}$ 3450.

DIETARY SOURCES

Lycopene, like other carotenoids, is a natural pigment synthesized by plants and microorganisms to absorb light during photosynthesis and to protect them against photosensitization. Red fruits and

vegetables are the most common sources of lycopene. Tomatoes and tomato based products account for more than 85% of the dietary lycopene in North America. Watermelon, pink grapefruit, apricots, pink guava and papaya are also rich sources of lycopene (13-17) (**Table 1**). The lycopene contents in tomatoes differs with tomato varieties and increase with fruit ripening (17). All-*trans* is the predominant isomeric form of lycopene in raw tomatoes but *trans* to *cis* isomerization occurs during cooking/food processing and storage (18). Loss of lycopene contents appears to be minimal during cooking or food processing (15-18). Tomato juice, ketchup, soup and tomato based pizza and spaghetti sauce are the major contributor of lycopene in diet (13-19) (**Table 2**).

Table 1. Lycopene contents of common fruits and vegetables (13-17).

Fruits / Vegetables	Lycopene ($\mu\text{g/g}$ wet weight)
Tomatoes	8.8 - 42.0
Water melon	23.0 - 72.0
Pink Guava	54.0
Pink Grapefruit	33.6
Papaya	20.0 - 53.0
Apricot	< 0.1

Table 2. Lycopene contents of common tomato based foods (13-19).

Tomato Products	Lycopene ($\mu\text{g/g}$ weight)
Fresh Tomatoes	8.8 - 42.0
Cooked Tomatoes	37.0
Tomato Sauce	62.0
Tomato Paste	54.0 - 1500.0
Tomato Soup (condensed)	79.9
Tomato Powder	1126.3 - 1264.9
Tomato Juice	50.0 - 116.0
Pizza Sauce	127.1
Ketchup	99.0 - 134.4

UPTAKE, METABOLISM AND TISSUE DISTRIBUTION

Carotenoids detectable in different human tissues are of dietary origin. In a recent study, when subjects consumed tomato free diet for two weeks, their lycopene levels dropped significantly (20). Ingested carotenoids including lycopene are incorporated into dietary lipid micelles, absorbed into the intestinal mucosal lining via passive diffusion. They are incorporated into chylomicrons and released into lymphatic system for transport to the liver. Carotenoids are transported by the lipoproteins into the plasma for distribution to the different organs (21). Many factors influence absorption and hence bioavailability of dietary lycopene. Release of lycopene from the food matrix due to processing, presence of dietary lipids, heat induced isomerization from all *trans* to *cis* conformation enhance the bioavailability (22). Ingestion of cooked tomato juice in oil medium increased serum lycopene levels by three fold whereas consumption of an equivalent amount of

unprocessed juice did not have any effect (22). In a recent study, lycopene from tomato paste was shown to be more bioavailable than from fresh tomatoes (23). There are indications that *cis* isomeric form is more bioavailable than *trans* (22). Absorption of lycopene seem to be more efficient at lower dosages. Also, lycopene when ingested with β -carotene was absorbed more than when ingested alone (24). Information regarding the relationship between dietary lycopene (calculated or estimated) and serum or tissue lycopene levels is lacking.

Serum lycopene levels are affected by several biological and lifestyle factors. Fasting serum lycopene levels were found to be higher and more reproducible than post prandial levels indicating the diet induced metabolic stress (20). Lycopene levels in blood do not differ significantly between men and women (25,26). In women, blood lycopene levels were found to be affected by the phases of menstrual cycle with a peak during mid-lute phase (27). Controversial results were reported on the effects of smoking on serum lycopene levels (25,28,29). In a recent study (20), it was found that there were no significant differences in serum lycopene levels between smokers and non-smokers. However, the serum lycopene levels fell by 40% with a 40% increase in lipid peroxidation in smokers immediately following smoking three cigarettes (20). Similarly in-vitro exposure of fresh plasma to cigarette smoke depleted lycopene and several other lipophilic antioxidants (30). Alcohol consumption has also been found to alter serum lycopene levels (25).

Lycopene is the most predominant carotenoid in human plasma and has a half life of about 2-3 days (31). In human plasma, lycopene is an isomeric mixture containing 50% of the total lycopene as *cis* isomers. The most prominent geometric isomers from plant sources are *all trans*. There are some indications of *in-vivo trans* to *cis* isomerization reactions (32). Very little is known about *in-vivo* metabolism of lycopene. Only a few metabolites, such as 5,6-dihydroxy-5,6-dihydro lycopene, have been detected recently in human plasma (33,34). It was suggested that lycopene may undergo *in-vivo* oxidation to form epoxides which then may be converted to 5,6-dihydroxy-5,6-dihydro lycopene through metabolic reduction (33,34). Owing to its lipophilic nature lycopene was found to concentrate in LDL and VLDL fractions and not in HDL fraction of the serum (31).

Table 3. Lycopene levels in human tissues (36-42).

Tissue	Lycopene (nmol/g wet wt)
Testes	4.34 - 21.36
Adrenal	1.9 - 21.60
Prostate	0.8
Liver	1.28 - 5.72
Breast	0.78
Pancreas	0.7
Lung	0.22 - 0.57
Kidney	0.15 - 0.62
Colon	0.31
Skin	0.42
Ovary	0.3
Stomach	0.2
Brainstem	not detectable

Lycopene is known to accumulate in human tissues. Prolonged and excessive consumption of tomato juice increased serum lycopene levels and resulted in coloration of skin and liver, a condition identified as lycopenemia (35). Tissue distribution of dietary carotenoids including lycopene is not uniform. Tissue specific carotenoid distribution suggest that certain carotenoids may exert a unique biological effect in some tissues but not in the others. **Table 3** shows the lycopene levels in human tissues reported by different investigators (36-42).

However, inter-individual variations in reported tissue-lycopene levels are about 100 fold. Adipose tissues may serve as a marker for the assessment of body lycopene status since they are a potential source of easily available biological material. Lycopene was found to concentrate and be the most prominent carotenoid in adrenal glands, testes, liver and prostate (36-42). The exact biochemical mechanism for the high concentration in these tissues is not clear. One hypothesis is that these tissues have large number of lipoprotein receptors and lycopene is mainly transported through lipoprotein (37). Lycopene and other carotenoids have been recently identified in several body fluids. 34 carotenoids including 13 geometric isomers and 2 lycopene oxidation products were recently reported in human milk (33). Lycopene and β -carotene were also found in human seminal plasma and their levels were lower in immunoinfertile men compared to normal individual (43).

BIOCHEMICAL EFFECTS

Although, the effect of lycopene on the reactivity of ROS has been studied extensively its effects on metabolic processes have also been reported.

Oxidative Effects:

Endogenous or exogenously generated ROS have been implicated in the pathogenesis of various human diseases (2-8). Consumption of carotenoid rich food is often associated with several health benefits. Most of the important health benefits are hypothesized to occur through their ability to protect against oxidative damage. In-vitro studies have indicated that lycopene is an effective antioxidant and radical scavenger (44-46). Lycopene, because of its high number of conjugated dienes, is the most potent singlet oxygen quencher among natural carotenoids (46). Lycopene was also reported to inactivate hydrogen peroxide and nitrogen dioxide (47,48). Mortensen et al (49) using pulse radiolysis technique demonstrated carotenoids' ability to scavenge nitrogen dioxide (NO_2^*), thiyl (RS^*), and sulphonyl (RSO_2^*) radicals. In recent studies, lycopene was found to be at least twice as active as β -carotene in protecting lymphocytes against NO_2^* radical induced membrane damage and cell death (48,50). There are indications that lycopene is the most potent scavenger of ROS among other major dietary carotenoids (46,49). In-vivo antioxidant effects of lycopene and its interaction with host and other dietary antioxidant defenses are beginning to be investigated. Lycopene is extremely hydrophobic and is most commonly located within cell membranes and other lipoprotein components. Interactions of lycopene with ROS is therefore expected to be more profound in a lipophilic environment. Lycopene protected human LDL against photosensitized oxidative damage (51). Skin lycopene was destroyed preferentially over β -carotene during ultraviolet light exposure in humans suggesting a superior role of lycopene over β -carotene in mitigating oxidative damage in tissues (52).

Non-oxidative:

Carotenoids ability to induce gap junctional communication between cells has also been suggested to be a potential basis for their protective effects towards cancer development. Lycopene is shown to be capable of improving cell to cell communication, but its effects are less pronounced than β -carotene or canthaxanthin (53). A recent study reported differential dose related effects of β -carotene and lycopene on gap junctional communication in rat liver. Very low doses (0.5 mg/kg b.w.) had no effect where as medium dose (5 mg/kg b.w.) was enhancing and very high dose (50 mg/kg b.w.) was inhibiting gap junctional communication in rat liver *in vivo* (54). It appears that the gap junctional communication ability of carotenoids and their singlet oxygen quenching abilities or antioxidant properties are independent of each other (55). Lycopene has been found to act as a moderate hypocholesteremic agent and this effect is related to the inhibition of 3-hydroxy-3-methyl glutaryl coenzyme A (HMGCoA) reductase, the rate limiting enzyme in cholesterol synthesis (56). Lycopene has also been suggested to have modulating effects on liver drug metabolizing enzyme cytochrome P-450 2E1 (57).

ROLE OF LYCOPENE IN HUMAN HEALTH

Lycopene, a predominant carotenoid in tomatoes, exhibits highest antioxidant activity among all dietary carotenoids. Its potential role in human health is beginning to be recognized (31,58,59). The main supporting evidences come from three different research directions: (a) tissue culture studies using different cell lines to investigate anti cell proliferative activities, (b) use of animal models to study anti tumorigenic properties of lycopene and (c) epidemiological studies done with control and at risk population.

Tissue culture studies:

Tissue culture systems have provided unique evidence for molecular and biochemical effects of lycopene in normal and malignant cell lines. So far the work has mainly concentrated on antitumorigenic activity of lycopene. **Table 4** provides an updated list of the cell culture studies on the role of lycopene.

Lycopene caused about 40% inhibition in cell growth in human leukemia cell lines (60), more over when added with retinoic acid, which causes cellular differentiation, it potentiated the effects (61). In C3H/10T1/2 mouse embryo fibroblast cell line, lycopene inhibited the methylcholanthrene induced malignant transformation (62). Lycopene was also shown to enhance the expression of connexin43, a gene encoding major gap junction protein, and thereby upregulated gap junction communication and acted as anticarcinogen (53,63). Improved survival and suppression of lipid peroxidation in CCl_4 exposed rat hepatocytes was observed by lycopene treatment (64). Lycopene also protected the mouse hepatocytes microcystin-LR, a liver tumor promoter (65). The retinoids and α -tocopherol showed none to very little effects in the same system. It was hypothesized that lycopene might have arrested G_0/G_1 cell cycle phase by suppressing carcinogen induced phosphorylation of regulatory proteins such as p^{53} or Rb antioncogene by non-oxidative mechanism (65). In an in-vitro study using Raji cells (Epstein-Barr virus genome carrying lymphoblastoid cells) lycopene inhibited 12-*O*-tetradecanoylphorbol-13-acetate induced Epstein-Barr virus activation almost as much as β -carotene (66). Lycopene was a powerful inhibitor of

endometrial (Ishikawa), mammary (MCF-7) and lung (NCI-H226) human cancer cells proliferation and suppressed insulin-like growth factor-I-stimulated growth. α - and β -carotene were far less effective inhibitors, however, normal fibroblast were far less sensitive to lycopene (67). In a recent study, using J-774 A.1 macrophage cell line lycopene as well as β -carotene suppressed 60-70% of cholesterol synthesis by acetate and were implicated as moderate hypocholesteremic agent (56).

Table 4. Anticarcinogenic and other effects of lycopene in cell culture

Investigators	Cell type	Major Findings
Countryman et al. (60)	HL-60 human leukemia cell line	Lycopene (10 μ mol/L) caused 40% reduction in cell growth.
Bankson et al. (61)	HL-60 human leukemia cell line	Lycopene enhanced the differentiating effects of retinoic acid.
Bertram et al. (62)	C3H/10T1/2 mouse embryo fibroblast cell line	Inhibition of malignant transformation.
Zhang et al. (53,63)	C3H/10T1/2 mouse embryo fibroblast cell line	Enhancement of connexin43 gene expression.
Kim (64)	Rat hepatocytes	Reduced the CCl ₄ poisoning.
Matushima et al. (65)	Mouse hepatocytes	Protected against microcystin-LR induced liver tumors.
Tsushima et al. (66)	Raji cells	Inhibited the activation of genes.
Levy et al. (67)	Human cancer cell lines endometrial (Ishikawa) mammary (MCF-7) lung (NCI-H226) normal fibroblast	Lycopene suppressed the growth of cancer cells but not of normal fibroblast.
Fuhrman et al. (56)	J774A.1 macrophage cell line	Lowered cholesterol synthesis by inhibiting HMGCoA reductase

Animal studies:

Animal models have provided excellent system to investigate in-vivo biochemical functions of lycopene in a well defined, controlled environment where the confounding variables are minimum. Radioprotective as well as antibacterial activities of lycopene were established almost 40 years ago using laboratory mice (68,69). Dietary lycopene increased the survival rate of mice exposed to whole body x-irradiation (68). Intraperitoneal injections of lycopene also protected the mice from bacterial infections and inhibited the development of ascites tumors (69). **Table 5** provides a list of studies done using animal model systems.

Lycopene inhibited the growth and development of C-6 glioma cell (malignant brain cells) transplanted into rats (70). Growth inhibitory effects were more pronounced when lycopene was given before the glioma cells inoculation. Chronic intake of lycopene markedly delayed onset and reduced spontaneous mammary tumor growth and development in SHN virgin mice (71). 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 by stimulating cell division. Lycopene was also shown to enhance the immunoresponse by increasing helper T cells and normalizing the intraathymic T cell differentiation caused by tumorigenesis in SHN retired mice (72). Lycopene and lutein at small doses reduced the N-methylnitrosourea (MNU) induced development of aberrant crypt foci (ACF) in Sprague-Dawley rats (73). In a dimethyl benzanthracene (DMBA) induced mammary tumor model of rats, intraperitoneal injections of lycopene enriched tomato oleoresin but not of β -carotene suppressed tumor growth in size and tumor numbers (74). Dietary lycopene dissolved in drinking water at 50 ppm dose significantly decreased the diethylnitrosamine, methylnitrosourea and dimethylhydrazine (DMD) induced incidences and multiplicities of lung adenomas plus carcinomas in male mice (75). The protective effects were however, not observed in female mice or in the colon or kidney in the same study (75). Diethylnitrosamine (DEN) induced liver

Table 5. Protective effects of lycopene demonstrated in animal studies

Investigators	Animal Model	Major Findings
Forssberg et al. (68)	Mice	improved survival
Lingen et al. (69)	Mice	increased resistance towards bacterial infections
Wang et al. (70)	Wistar rats inoculated with rat brain tumor cells (Glioma cells)	inhibited growth and development of tumor cells
Nagasawa et al. (71)	High mammary tumor strain of SHN virgin mice	delayed onset and reduced tumor growth
Narisawa et al. (73)	Sprague-Dowley Rats	reduced the MNU induced colonic ACF
Sharoni et al. (74)	Sprague-Dowley Rats	reduced DMBA induced mammary tumors
Kim et al. (75)	B6C3F ₁ Mice	decreased DMD induced lung adenomas in male mice
Astrog et al. (57)	SPF Wistar Rats	reduced DEN induced liver preneoplastic foci
Kim et al. (76)	B6C3F ₁ Mice	no effect on DMH induced colonic carcinogenesis
Okajima et al. (77)	Fischer 344 Rats	tomato juice inhibited BBN induced urinary bladder carcinogenesis
Gradelet et al. (78)	male weanling rats	no effect on aflatoxin B1 induced liver preneoplastic foci
Rao et al. (unpublished)	Fischer 344 Rats	apparent protective effect on AOM induced colonic ACF

preneoplastic foci in rats were significantly reduced by dietary lycopene and not by any other carotenoid tested (57). Lycopene however had no effects on 2-nitropropane induced hepatocarcinogenesis. It was hypothesized that lycopene provided protection through its modulating effect on the liver enzymes activating diethylnitrosamine, cytochrom P-450 2E1, and not through antioxidative mechanism (57). Lycopene had no protective effect on dimethylhydrazine (DMH) induced colon carcinogenesis in mice as indicated by proliferation of colonic crypt epithelial cells as well as BrdU incorporation assay (76). Lutein and fucoxanthin had

significant protection in the same carcinogenesis model (76). 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 (77). Aflatoxin B1-induced liver preneoplastic foci in rat were not affected by dietary lycopene whereas β -carotene provided significant protection (78). Recent investigations in our lab indicated that dietary lycopene (10 ppm) significantly reduced the lipid and protein oxidation and demonstrated an apparent protective effect against azoxymethane induced colonic preneoplastic lesions in rats (Rao et al. unpublished).

Epidemiological studies:

The interest in lycopene and its potential protective role in prevention of chronic diseases stems largely 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 chronic diseases. Various epidemiological studies have suggested that a diet rich in a variety of fruits and vegetables results in a lower risk of cancer and other chronic diseases (79,80). An early epidemiological study on elderly Americans indicated that high intake of tomatoes was associated with a significant reduction of mortality from cancers at all sites (81). Epidemiological investigations to study the role of lycopene in relation to chronic diseases has focused primarily on cancers. Epidemiological studies showing a relationship between lycopene and chronic diseases are listed in **Table 6**.

Table 6. Lycopene and chronic diseases in epidemiological studies.

Investigators	Type of Study	Major Findings
Giovannucci et al. (82)	Prospective Cohort Prostate cancer	Dietary intake of tomato products inversely associated with prostate cancer risk
Franceschi et al. (83)	Case control study Digestive tract cancer	high intake tomato was associated to reduced risk of all types of digestive tract cancer
VanEewyck et al. (84)	Case control study Cervical cancer	only lycopene showed an inverse association with cervical cancer risk
Helzlsour et al. (85)	Case control study Bladder cancer	serum lycopene associated with decreased risk
Dorgan et al. (89)	Case control study Breast cancer	inverse association between serum lycopene and breast cancer risk
Kohlmeier et al. (93)	Case control study Myocardial Infraction risk	adipose tissue lycopene associated with lowered risk
Kristenson et al. (95)	Cross sectional population Mortality from chronic heart disease	low serum lycopene associated with increased mortality from heart disease
Coodley et al. (96) Periquet et al. (97)	HIV positive women and infected children	lower serum lycopene levels in cases
Schmidt et al. (98)	Elderly population cerebrovascular disease risk	lower serum lycopene in high risk individuals

An inverse association between high intake of tomato products (based on food frequency questionnaire) and prostate cancer risk was confirmed in US Health Professionals Follow-up Study (82). The estimated intakes of total carotenoid, β -carotene, α -carotene, lutein and β -cryptoxanthin were not associated with the risk factor. Higher estimated lycopene intake was inversely related to risk of prostate cancer. Almost 35% risk reduction was observed based on consumption frequency of more than 10 servings of tomato products per week and the protective effects was even stronger when the analysis was focused on more advanced or aggressive prostate cancer (82). In a case-control study (cases were the patients with histologically confirmed cancers of oral cavity, pharynx, esophagus, stomach, colon and rectum and controls were the patients with unrelated conditions) in Italy, high lycopene intake was consistently associated with reduced cancer risk of all sites, and especially of stomach, colon and rectum (83). A case-control study comparing women with cervical interepithelial neoplasia with normal controls, reported that among all dietary carotenoid intake and serum carotenoid concentrations, only lycopene showed an inverse association with the risk (84). Serum lycopene levels were also found to be inversely related to the risk of bladder cancer (85). An inverse association to no association between lycopene (estimated intakes or serum levels) and breast cancer risk were reported by several investigators (86-88). In a recent case control study nested a cohort from the Breast Cancer Serum Bank in Columbia MO, only serum lycopene and non of the other carotenoids or α -tocopherol showed a significant inverse relationship with breast cancer risk (89).

Coronary heart disease has also been shown to be the major cause of morbidity and mortality in Western world. There is extensive evidence that oxidatively modified low-density lipoproteins are involved in the initiation and promotion of atherosclerosis (5). It has been suggested that dietary antioxidant vitamins and carotenoids may protect low-density lipoproteins from oxidative damage and may thus contribute to reducing the risk of atherosclerotic vascular disease (7,8). However, many dietary intervention trials involving α -tocopherol or β -carotene have yielded inconclusive results (90-92). Very little work has been done on lycopene. In a multicenter case-control study conducted in 10 European countries (EURAMIC study) to evaluate the relations between antioxidant status assessed in adipose tissue biopsies and acute myocardial infraction, it was concluded that lycopene and not β -carotene, contribute to the protective effect of vegetable consumption (93,94). The protective potential of lycopene was maximum among individuals with highest polyunsaturated fat stores, supporting the antioxidant theory (93). Similarly, lower serum lycopene levels were found associated with increased risk and mortality from coronary heart disease in a cross sectional study comparing Lithuanian and Swedish populations showing diverging mortality rates from coronary heart disease (95). Lower serum lycopene levels were also reported in human immunodeficiency virus (HIV) positive women and also in children infected with HIV (96,97). Lower levels of serum lycopene and α -tocopherol were also reported in individuals from an elderly population at high risk for microangiopathy-related cerebral damage (a risk factor for cerebrovascular disease) in Austrian stroke prevention study (98).

Dietary supplementation studies:

Since lycopene is available in very limited number of food sources, a precise and accurate intake calculations from food frequency questionnaire can be performed. However, the vast epidemiological data provides only a suggestive evidence rather than a proof of a causal relationship of lycopene intake and risk of chronic diseases. To date, practically no intervention

trials have been performed investigating the effectiveness of lycopene intake on lowering the risk of chronic diseases. Ingestion of lycopene free diet for two weeks resulted in 50% loss of serum lycopene with a 25% increase in *in-vivo* lipid oxidation in healthy human subjects (20). In a small clinical trial, lycopene was found to act as a moderate hypocholesterimic agent (56). Studies involving healthy human subjects in our laboratory indicated that lycopene from traditional tomato products is absorbed readily, increases serum levels and lowers the oxidative damage to lipids, lipoproteins, proteins and DNA (Agarwal & Rao, submitted for publication) (Figure 2). The level of consumption of tomato products used in this study were about one or two servings/day, were easily achievable and were in keeping with the current dietary recommendations pertaining to healthy eating.



FIG. 2. Effect of lycopene supplementation on serum lycopene and the levels of lipid, protein and DNA oxidation. Dietary lycopene was provided to healthy human subjects in the form of spaghetti sauce (Sauce), tomato juice (Juice) or tomato oleoresin (Oleoresin) with a standardized breakfast for a period of one week in a random order. Fasting blood was collected at the end of each treatment. Serum lycopene was extracted by hexane and analyzed by HPLC. Serum lipid oxidation was estimated by measuring total serum TBARS (Serum-TBARS), isolated serum LDL TBARS (LDL-TBARS) and isolated LDL conjugated dienes (LDL-CD). Serum protein oxidation was estimated by measuring reduced thiol groups in serum proteins (Thiols). Lymphocytes DNA oxidation was estimated by HPLC measurement of 8-hydroxydeoxyguanosine (8-OHdG).

CONCLUSION

Dietary guidelines for the prevention of cancer and coronary heart disease recommend increased consumption of plant foods that include fruits, vegetables, cereals and legumes. Presence of micronutrient phytochemical compounds are now being recognized as playing an important role in the disease prevention properties of the plant foods, possibly through their effect on hormonal

metabolism and oxidative damage. Lycopene, a carotenoid antioxidant, has been shown in recent epidemiological and experimental studies to protect against oxidative damage and contribute towards reducing the risk of cancer and coronary heart disease. In addition to its antioxidant mediated activity, other metabolic effects of lycopene have also been demonstrated. Based on current knowledge the role of lycopene in human health is summarized in **Figure 3**.

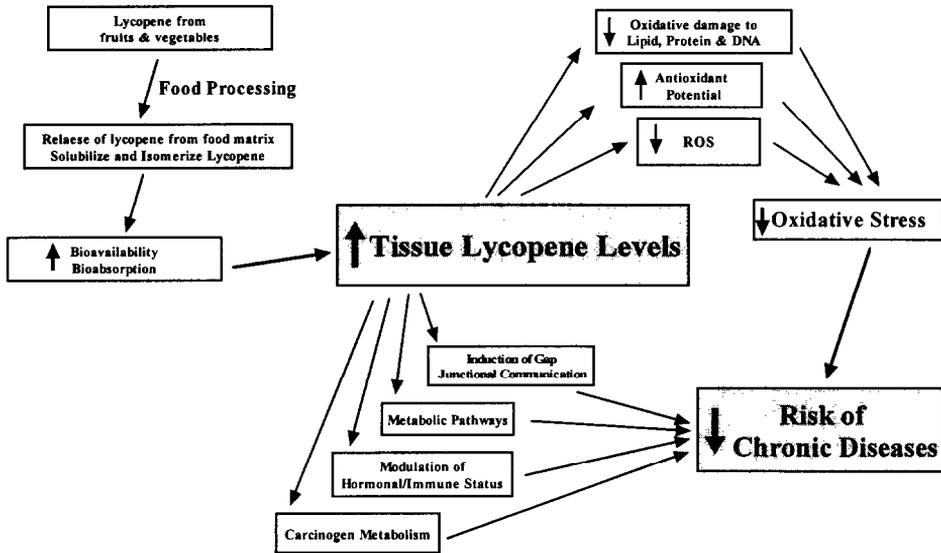


FIG. 3. Role of lycopene in human health

Further studies are required to gain a better understanding of the role of lycopene in human health. Processing has traditionally been considered as contributing towards the loss of nutritional quality of foods. There is, however, indication that in the case of lycopene processing might actually enhance its bioavailability and nutritional quality. Although it is generally recognized that heat treatment of tomatoes induces the formation of cis-isomers from the all trans form present in raw tomatoes, specific types of isomers formed and their biological significance is not fully understood. Bioavailability of lycopene is influenced not only by its isomeric form but also the presence of other dietary components including dietary fat, other carotenoids, vitamins and minerals. These factors should be evaluated in an attempt to maximize lycopene absorption from the diet. Another area of future research should include elucidation of mechanisms other than antioxidant properties of lycopene in the prevention of chronic diseases. Preliminary data suggests the possibilities of these alternate pathways of lycopene activity. Finally, long term human intervention studies should be carried out with populations at risk for cancer and coronary heart disease. Based on the results from these studies an effective dietary strategy can be developed for the management of chronic diseases in humans that will be based on increased consumption of lycopene containing foods.

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