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Cardiovascular benefits of lycopene: fantasy or reality?

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Epidemiological evidence indicates that high consumption of tomatoes and tomato-based products reduces the risk of chronic diseases such as CVD and cancer. Such potential benefits are often ascribed to high concentrations of lycopene present in tomato products. Mainly from the results of *in vitro* studies, potential biological mechanisms by which carotenoids could protect against heart disease and cancer have been suggested. These include cholesterol reduction, inhibition of oxidation processes, modulation of inflammatory markers, enhanced intercellular communication, inhibition of tumourigenesis and induction of apoptosis, metabolism to retinoids and antiangiogenic effects. However, with regard to CVD, results from intervention studies gave mixed results. Over fifty human intervention trials with lycopene supplements or tomato-based products have been conducted to date, the majority being underpowered. Many showed some beneficial effects but mostly on non-established cardiovascular risk markers such as lipid peroxidation, DNA oxidative damage, platelet activation and inflammatory markers. Only a few studies showed improvement in lipid profiles, C reactive protein and blood pressure. However, recent findings indicate that lycopene could exert cardiovascular protection by lowering HDL-associated inflammation, as well as by modulating HDL functionality towards an antiatherogenic phenotype. Furthermore, *in vitro* studies indicate that lycopene could modulate T lymphocyte activity, which would also inhibit atherogenic processes and confer cardiovascular protection. These findings also suggest that HDL functionality deserves further consideration as a potential early marker for CVD risk, modifiable by dietary factors such as lycopene.

Lycopene: Cardiovascular health: Intervention trials: Mechanisms

Results from observational studies suggest that high consumption of fruit and vegetables reduces the risk of chronic diseases such as CVD and cancer[1–3]. A recent meta-analysis of sixteen prospective cohort studies including over 800 000 participants concluded that a higher consumption of fruit and vegetables is associated with a lower risk of mortality, particularly from CVD[4]. The results indicated that, for the consumption of up to five servings/d, the risk of cardiovascular mortality was decreased by 4 % for each additional daily serving of fruit and vegetables, and by 5 and 4 % for each additional daily serving of fruit and vegetables, respectively. However, the actual components of these foods that confer the protective effect and the mechanisms by which they act have yet to be firmly identified. Potential candidate chemical compounds include carotenoids, which represent a large family of over 700 hydrophobic red, orange and yellow pigments abundant in fruit and vegetables. However, only six of them (lycopene, α- and β-carotenes, β-cryptoxanthin, zeaxanthin and lutein) are found predominantly in human serum and constitute over 95 % of total circulating carotenoids[5].

Much interest in recent years has focused on tomato-rich diets and lycopene, since observational studies associated high lycopene intake with reduced risk of

Abbreviation: CRP, C-reactive protein.

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prostate cancer[6–8]. High consumption of tomato-rich diets (seven or more servings/week) has also been associated with a 30 % reduction in relative risk of CVD[9]. Such potential benefits to vascular health from a tomato-rich diet are often ascribed to high concentrations of lycopene present in the fruit, as tomato products usually account for the majority of the dietary intake of this carotenoid[10,11]. Blood lycopene concentrations are strongly associated with tomato intake[12–14]. Lycopene is the most abundant carotenoid present in serum in the American population[15] and the second contributor to total serum carotenoids in Europeans[16]. Nevertheless, serum concentrations are usually low and below 0·3 mg/ml[15]. Based on the results mainly obtained from *in vitro* studies and animal models, potential biological mechanisms by which lycopene could protect against heart disease and cancer have been suggested. These include cholesterol reduction, inhibition of oxidation processes, modulation of inflammatory markers, enhanced intercellular communication, inhibition of tumourigenesis and induction of apoptosis, metabolism to retinoids and antiangiogenic effects[17]. However, with regard to CVD, the results from intervention studies have given mixed results. The present paper reviews the evidence for the health benefits of high lycopene intake, and proposes the integration of novel mechanisms by which lycopene could confer cardiovascular protection.

Lycopene sources, structure, intake and bioavailability

Lycopene is a symmetrical tetraterpene comprising eight isoprene units. It is non-provitamin A carotenoid with very potent antioxidant properties due to its ability to efficiently quench singlet oxygen species[18] and hypochlorous acid[19]. Tomato and tomato-based products are the main dietary source of lycopene and account for over 80 % of lycopene intake in western countries, but watermelon, pink grapefruit, apricot, pink guava and papaya also significantly contribute to lycopene intake[5]. Dietary intake of lycopene varies greatly depending on the populations considered. Median intake in the UK is about 1 mg/d[20,21], while estimated intakes in American and Italian populations are over 7 mg/d[22,23].

Lycopene occurs naturally mainly as all-*trans* isomer[24], whereas *cis* isomers are the most abundant form in plasma and tissues[13,25]. Isomerisation occurs during food preparation and processing, as well as physiologically during digestion and absorption, which could impact on bioavailability[26]. However, many uncertainties remain with regard to lycopene metabolism. The process of *trans*-to-*cis* isomerisation can occur in the stomach[27], enterocytes[28] and liver[29]. Intestinal absorption of lycopene is facilitated by scavenger receptor B1[30] and CD36[31]. Partial metabolisation can occur in the enterocyte via the action of two enzymes, β-carotene 15,15′-oxygenase-1, which has been associated with blood lycopene status[32] and β-carotene-9,10′ oxygenase-2[33].

Due to the difficulty of producing labelled lycopene molecules, few tracer studies have been carried out to date. An accelerator MS study using ^{14}C-labelled lycopene (92 % *trans* lycopene) showed that all *trans* lycopene was extensively isomerised (5-, 9-, 13- and 15-*cis* lycopene isomers) after dosing and rapidly metabolised into polar metabolites excreted into urine[34]. The rapid excretion of $^{14}CO_2$ found in that study also suggested that part of the lycopene ingested was quickly fully oxidised. A recent compartmental modelling study using ^{13}C-labelled lycopene found no differences between the bioavailability of *cis*- and all-*trans* lycopenes (24·5 *v.* 23·2 %, respectively). However, the study revealed that postabsorptive *trans*-to-*cis* isomerisation influences tissue and plasma isomeric profiles[35]. The half-life of plasma lycopene was originally estimated to range between 12 and 33 d[36]. However, the latest tracer study showed half-lives of 5·3 and 8·8 d for all-*trans* and *cis* isomers, respectively[35].

Interindividual variability in lycopene bioavailability is at least partly genetically controlled and has been linked to a combination of twenty-eight SNP in sixteen genes involved in lycopene and lipid metabolism[37]. Another recent study examined the association between variation across the genome (over seven million SNP included) and serum concentrations of lycopene in a multiethnic population involving 2581 post-menopausal women[38]. The study identified three novel loci (SCARB1, DHRS2 and SLIT3) associated with serum lycopene concentrations, the last two being specific to African Americans. These findings could perhaps explain the interindividual variability in physiological responses to increased lycopene intake frequently observed in human subjects.

Observational studies

The majority of epidemiological evidence suggests that serum lycopene concentration is inversely associated with CVD risk[39–41]. More recently, high serum concentrations of carotenoids, including lycopene, have been inversely associated in middle-aged men with lower intima-media thickness, suggesting that high serum lycopene concentrations could protect against early atherosclerosis[42]. Results from the same study showed that in men within the highest quartile of serum lycopene concentration, the risk of ischaemic stroke and any stroke was reduced by 59 and 55 % respectively compared with the lowest quartile[43]. Results from the 2003–2006 National Health and Nutrition Examination Survey showed similar associations with biomarkers of CVD risk such as LDL-cholesterol, homocysteine and C-reactive protein (CRP) concentration[44]. However, studies assessing dietary intake of lycopene usually showed no association between dietary intake and CVD risk[9,45–48]. These findings are supported by the results of a recent meta-analysis of prospective studies on lycopene intake and serum concentrations and the risk of stroke, which showed that circulating concentrations of lycopene, but not dietary lycopene, was associated with a significant decrease in the risk of stroke[49]. Such discrepancy between dietary intakes and serum concentrations could be linked to genetic variability

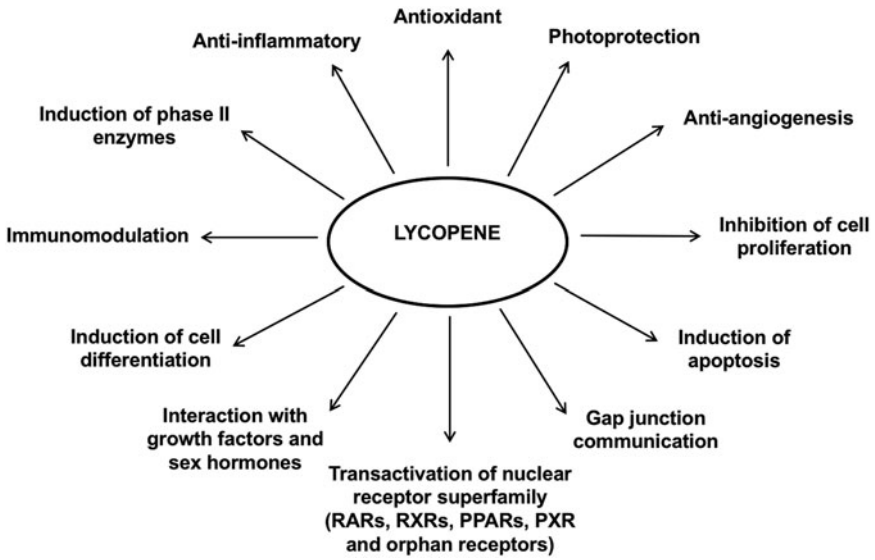

Fig. 1. Potential mechanisms by which lycopene can modulate cellular activity.

modifying lycopene absorption. However, it has also been attributed at least partly to misclassification of lycopene intakes[22]. When compensating for this potential issue by using repeated measures of intake obtained over a 10-year period, lycopene intake was found to be significantly inversely associated with CHD incidence[22].

Mechanistic studies

The discovery of mechanisms (Fig. 1) by which lycopene and derivatives can modulate cellular activity mainly originated from the extensive work carried out in cancer cells, and can be partially related to the antioxidant properties of lycopene[50]. These mechanisms have been recently reviewed[17,51], and include induction of apoptosis[52,53] and inhibition of cell proliferation involving the modulation of the expression of genes involved in the phosphatidylinositol-4,5-bisphosphate 3-kinase/protein kinase B and mitogen-activated protein kinases signalling pathways as well as genes involved in the regulation of the cell cycle[54–56]. The induction of cell differentiation[52] via the restoration of gap junctions[57] has also been suggested. Other mechanisms include prevention of oxidative damage[58,59], inhibition of angiogenesis[59,60], induction of phase II enzymes[61–63], interaction with growth factors and sex hormones[64] and the induction of nuclear receptors activation[65–67]. Lycopene has also been found to confer photoprotection[68]. Interestingly, it has been recently shown that lycopene, via bioactive metabolites, possesses partial pro-vitamin A activity transmitted via retinoic acid receptor-mediated signalling in mice[69].

Many studies using cellular models relevant to atherosclerosis have also been used in recent years, and a scheme integrating the potential cellular mechanisms by which lycopene could modulate atherosclerotic processes has been proposed[70]. Vascular endothelial dysfunction is commonly regarded as a key event in atherogenesis. Lycopene, at physiological concentrations, can protect endothelial cells from oxidative damage induced by hydrogen peroxide[71]. Lycopene also inhibits cytokine-induced adhesion molecule expression and monocyte–endothelium interactions[72]. Inhibition of agonist-stimulated platelet aggregation have also been observed at physiologically relevant concentrations[73,74]. Experiments carried out in THP-1 (a human monocytic leukemia cell line) macrophages showed that lycopene can inhibit cholesterol synthesis as well as scavenger receptor expression, which suggests that it could potentially modulate foam cell formation[75,76].

Lycopene has potent antioxidant chemical properties, and therefore much interest has focused on its potential ability to inhibit LDL oxidation, which is central to the initiation of atherosclerosis. The outcomes of such studies largely depend on the conditions used to oxidise the LDL particles. However, considering the very central position of lycopene within the core of LDL particles, it is unlikely that lycopene under normal physiological conditions can effectively protect LDL from oxidation[77].

Atherosclerosis has a strong inflammatory component. The anti-inflammatory properties of lycopene have been tested using various relevant cell culture models, including macrophages, foam cells and smooth muscle cells and the outcomes of such studies have been previously reviewed[70]. Overall, results suggest that lycopene can neutralise reactive oxygen species, as well as reduce the secretion of pro-inflammatory cytokines and metalloproteinases by macrophages[78,79], inhibit smooth muscle cell proliferation[80] and decrease monocyte proliferation[81]. More recently, work in our group showed that low, physiological concentrations of lycopene can significantly inhibit mitogen-activated T lymphocyte activation by modulating mechanisms involved in early activation[82]. Lycopene significantly inhibited mitogen-activated lymphocyte proliferation by up to 40 % and also significantly inhibited the expression of an early marker of activation, CD69, as well as IL-2 secretion. However, IL-2

receptor expression and cell-cycle profile were unaffected by lycopene. T lymphocytes are an active component of the chronic inflammatory process during atherogenesis. A reduction in T-cell activation would reduce the inflammatory responses involved in atherosclerotic plaque formation and development.

Whether lycopene acts directly, or indirectly via oxidised metabolites, still remains to be determined. Food processing-induced or metabolic oxidation of lycopene can lead to the formation of apo-lycopenoids, a family of compounds containing a ketone or an aldehyde function. Particular interest has focused on apo-lycopenals, which can modulate cellular function via the antioxidant response element transcription system[64] and inhibit tumourigenesis[83]. Apo-10′-lycopenoic acid can also modulate adipocyte activity via the retinoic acid receptors[84].

Interestingly, lycopene has recently been found to reduce the formation of advanced glycation end products in HK-2 cells and in rat kidneys, which led to a concomitant decrease in the expression of their receptors and NF-κB and matrix metalloproteinase 2[85]. Advanced glycation end products and the activation of their receptors lead to oxidative stress and inflammation, and enhanced generation and accumulation of advanced glycation end products have been associated with increased risk for cardiovascular complications associated with atherosclerosis and diabetes[86]. The inhibition of these processes by lycopene could therefore represent additional mechanisms by which lycopene can protect against CVD and related disorders.

Intervention trials

Human intervention studies related to the cardioprotective effects of lycopene have given mixed results. The majority (thirty-five) of fifty-four intervention trials using lycopene supplements or tomato-based products carried out between 1998 and 2010 found beneficial effects on CVD risk markers[87]. However, only thirteen studies included conventional markers of CVD (such as blood pressure, CRP and serum cholesterol concentrations) of which only five showed beneficial effects. The majority of studies (thirty-one out of forty-nine), which included non-established markers for CVD risk, such as lipid peroxidation, DNA damage, LDL oxidation, platelet activation and inflammatory markers other than CRP, showed some benefits of increasing lycopene intake. Unfortunately, the search strategy was not provided and the quality of the study design was not assessed in that review. Most of the studies lacked statistical power as they usually included a relatively low number of volunteers (below 100). The majority of the trials (forty-three out of forty-nine) were also of short duration (up to 30 d) and some were poorly controlled. The sources of lycopene (supplements, tomato juice, soup, puree or tomato extract) as well as the daily dose provided (from 5 to 80 mg) also varied considerably between studies, making comparison between trials difficult.

Comparison of efficacy between tomato intake and lycopene supplementation in modifying CVD risk factors was also recently reviewed[26]. The authors included studies reporting effects on LDL oxidation, various markers of oxidative stress and damage, inflammatory markers, endothelial function, blood pressure and serum lipid concentrations. Overall, and despite the heterogeneity of results, growing evidence suggests that increasing lycopene intake from tomato products would be more effective compared with supplements for improving serum lipids, protein and DNA damage and some inflammatory markers including CRP, whereas lycopene supplementation seems to be more effective in reducing blood pressure compared with tomato-based foods. The reason behind this disparity is unclear. Tomatoes contain other components such as ascorbic acid, potassium and a range of bioactive phytochemicals such as tomatine, a steroidal glycoalkaloid and its metabolite, tomatidine, which could also provide health benefits[17]. However, it is possible that some of these compounds interfere with the hypotensive effect of lycopene. Only a few trials reported on blood pressure (five supplementation trials and three tomato studies), which is insufficient to draw any substantial conclusion. The mechanisms by which lycopene could modulate blood pressure remain also to be elucidated.

A recent pilot study carried out in forty heart failure patients (twenty-three men, seventeen women) showed that the daily consumption of 29·4 mg lycopene (one can daily of V8 juice) for 30 d significantly reduced serum CRP concentrations in women only, while compliance to the intervention seemed similar between men and women[88]. The effect of lycopene supplementation (7 mg daily over 2 months) on vascular function was recently assessed in healthy volunteers and statin-treated CVD patients in a randomised, placebo-controlled, double-blind intervention trial[89]. Lycopene supplementation significantly improved endothelial-dependant arterial vasodilation by 53 % in patients under optimal secondary prevention treatment, but had no effect in healthy volunteers. These results suggest that lycopene supplementation could positively modify cardiovascular outcomes in high-risk populations and could increase the efficacy of secondary prevention pharmacological treatment for heart disease.

In 144 patients with sub-clinical atherosclerosis, as assessed by the measurement of carotid artery intima-media thickness, lycopene supplementation (20 mg/d) for 12 months significantly improved the efficacy of lutein supplementation (20 mg/d) to decrease carotid artery intima-media thickness (0·035 mm decrease with lutein supplementation alone *v.* 0·073 mm decrease with both lutein and lycopene supplementation[90]). These results suggest a synergistic effect between lutein and lycopene. However, this trial should have ideally also included a group receiving lycopene only to confirm whether the larger decrease was due to the combination of lutein and lycopene or lycopene alone. Whether the magnitude of reduction of carotid artery intima-media thickness observed is clinically relevant needs to be evaluated with the inclusion of other risk factors, as meta-analyses suggest that carotid artery intima-media thickness alone only minimally improves disease-risk predictive power beyond traditional risk factors[91].

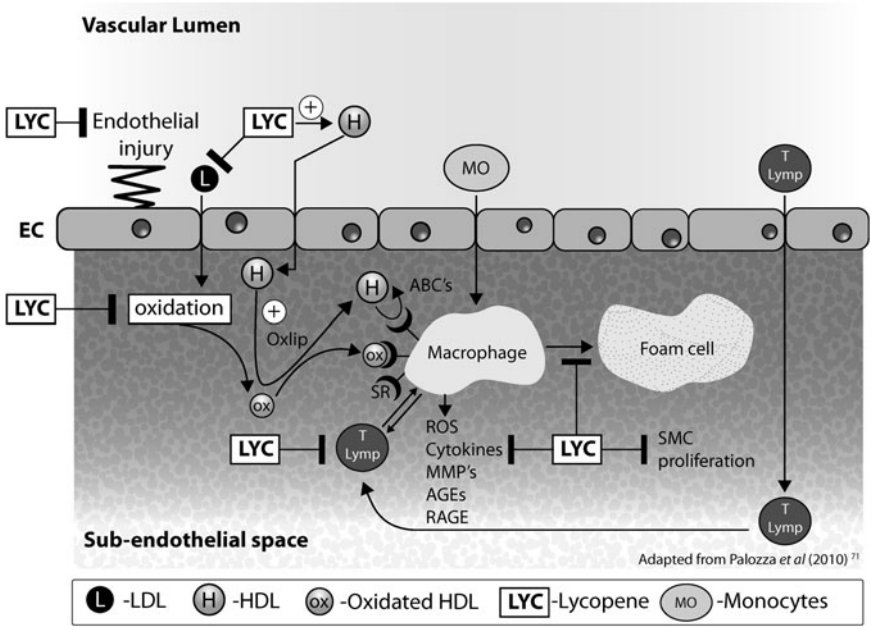

Fig. 2. Integrated mechanisms potentially responsible for the antiatherogenic effects of lycopene: Lycopene may inhibit endothelial injury, inhibit cholesterol synthesis, inhibit LDL oxidation, restore HDL functionality, inhibit proinflammatory activity driven by macrophages and T lymphocytes, inhibit foam cell formation and inhibit smooth muscle cell proliferation. ABC's, ATP-binding cassette transporters; AGE, advanced glycation end products; MMP, metalloproteinases; RAGE, receptor for advanced glycation end products; SMC, smooth muscle cells.

The first worldwide comprehensive, well-controlled, randomised trial aiming to determine whether increased lycopene consumption, from supplement or high tomato diet, can modulate markers of CVD risk was carried out in the UK a few years ago[21]. After a 4-week run-in period with a low-tomato diet, 225 volunteers (ninety-four men and 131 women) aged 40–65 years were randomly assigned into one of three dietary intervention groups and asked to consume a control diet (low in tomato-based foods), a high-tomato-based diet (35–50 mg lycopene/d), or a control diet supplemented with lycopene capsules (10 mg/d) for 12 weeks. Despite excellent compliance in all treatment groups, none of the systemic markers (inflammatory markers, markers of insulin resistance and sensitivity, lipid concentrations) significantly changed after the dietary intervention. Blood pressure and arterial stiffness were also unaffected by the treatments, indicating that increased lycopene intake, from supplement or from a tomato based-rich diet, is ineffective at reducing conventional CVD risk markers in the population considered. However, in order to identify novel potential markers for cardiovascular risk modifiable by lycopene, the authors examined the effect of the intervention on HDL-functionality and HDL-associated inflammation in a subgroup of participants (eighteen per treatment group). The results showed that increased lycopene intake using supplements or by dietary means over 12 weeks reduced serum amyloid A content in serum and HDL_3[92]. These changes were associated with a concomitant improvement in HDL functionality, as measured by the activity of HDL-associated enzymes such as paraoxonase 1, lecithin cholesterol acyl transferase and cholesterol ester transfer protein, potentially enhancing HDL-antiatherogenic properties.

Conclusion

The integrated potential mechanisms involved in the antiatherogenic effects of lycopene are summarised in Fig. 2. Despite some discrepancies between observational and intervention studies, the evidence for cardioprotective effects of lycopene is increasing. The recent discovery of novel mechanisms by which lycopene could exert its beneficial effects also warrant further research, and also suggest novel biomarkers for cardiovascular risk such as HDL functionality, susceptible to modification by dietary intervention. The identification of specific genetic patterns linked to interindividual variability in lycopene bioavailability also highlights the requirement for further research to understand how genotype modifies the cardiovascular benefits of lycopene.

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Conflict of Interest

None.

Authorship

F. T. presented the work and drafted the manuscript. F. T., L. M. M., S. M. and L. F. M. researched and contributed to sections for the manuscript. All authors reviewed the manuscript prior to submission.

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