Carotenoids and cardiovascular health

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Cardiovascular diseases (CVD) are the main cause of death in the Western countries. Nutrition has a significant role in the prevention of chronic diseases like CVD, cancers and degenerative brain diseases. The major risk and protective factors in the diet are known, but also new candidates are still being intensively studied. It is well known that a higher intake of fruits and vegetables can help to prevent heart diseases and mortality. Since fruits, berries and vegetables are chemically complex foods, it is difficult to pinpoint any one single nutrient contributing most to the cardioprotective effects. There are probably several potential components and multiple mechanisms in fruits, berries and vegetables that may have protective effects against CVD. The proposed beneficial substances include antioxidant vitamins, folate, fiber and potassium. The antioxidant compounds in fruits and vegetables, such as vitamin C, carotenoids and flavonoids may influence on the risk of CVD by preventing the oxidation of cholesterol in the arteries. In this review the role of main dietary carotenoids, lycopene, β-carotene, α-carotene, β-cryptoxanthin, lutein and zeaxanthin in the prevention of heart disease are discussed.

INTRODUCTION

Cardiovascular diseases (CVD) are the main cause of death in the Western countries. However, even though CVD mortality has decreased during the last decades in many countries these diseases still account for over 40% of the total mortality. The CVD prevalence rate varies greatly between national populations. In the Seven Countries Study[1], low coronary heart disease (CHD) -related mortality rates have been found in Southern European countries and Japan in contrast to the high mortality rates that have been found in USA, the Netherlands and Finland. Diets also vary extensively between different populations. In the eastern part of Finland, the mortality rate was 10-times higher than that in Crete, where the population consume a Mediterranean diet which is rich in plant foods year-round and relatively poor in animal foods[1]. There are likely to be multiple nutrients and mechanisms through which a plant dominated diet can promote health. Some of the proposed beneficial substances are carotenoids, which are pigments responsible for the yellow to red color of fruits and vegetables. More than 600 carotenoid compounds have been characterized and approximately 50 are consumed in the human diet[2,3]. About a dozen carotenoids account for the majority of dietary intake and are found in measurable concentrations in human blood and tissues[3,4], with the most common being lycopene, lutein, α-carotene, β-carotene, β-cryptoxanthin and zeaxanthin[4]. To a lesser extent, carotenoids can also be ingested in eggs, poultry and fish, which are typically fed with plant and algal products, e.g. zeaxanthin in chicken originates from maize in the poultry feed.
Various biological effects have been attributed to carotenoids. One possible mechanism of action of carotenoids is via their antioxidant activity but other mechanisms may also contribute to their beneficial effects[5]. The plasma concentrations of carotenoids are considered useful as biomarkers of total dietary intake of vegetables and fruit[6].

Chemistry, metabolism and bioavailability of main carotenoids

Most carotenoids have provitamin A activity. In addition to their provitamin A activity, carotenoids have been suggested to have many other biological functions[7,8]. They are proposed to be efficient scavengers of free radicals[7] and they have also been shown to protect low density lipoproteins (LDL) against oxidation in vitro. Some[9,10], but not all[11] dietary intervention studies with either lycopene-containing foods or lycopene supplementation have shown potential short-term improvements in LDL oxidation. However, the results are inconsistent and some recent experiments using cells in culture have shown not only a loss of antioxidant effectiveness but also pro-oxidant effects of carotenoids at high concentration[12]. To date, the provitamin A function is the only well proven physiological function of carotenoids in humans.
The bioavailability of carotenoids appears to be dependent upon several factors. In general, the absorption of carotenoids depends on their bioavailability from the food matrix and their solubility in micelles[13,14]. Many carotenoids are absorbed better in the presence of dietary fats and from heat processed foods than from unprocessed sources[15,16]. The nature of the isoforms of carotenoids also affects their bioavailability and absorption, i.e. trans isomers of lycopene are absorbed more poorly than the cis-isomers[16]. Other factors that influence the absorption of carotenoids include the presence of dietary fiber, the health status of the individual and the physical form of the carotenoid[17]. The blood concentration of carotenoid varies between individuals. In an American study with 400 male and female participants, low serum concentrations of α-carotene, β-carotene, β-cryptoxanthin, and lutein plus zeaxanthin were generally associated with male gender, smoking, young age, low non-HDL cholesterol, high alcohol consumption and high body mass index[18]. There are no recommended dietary allowances for carotenoids in the USA or in Europe. The amount of carotenoids in the diet is difficult to estimate, partly because methods used for the establishment of food composition tables are not sufficiently specific or sensitive. The main sources of selected carotenoids are presented in table.

CAROTENOIDS IN HUMAN HEALTH

Epidemiological studies about carotenoids and CVD health

Many epidemiological studies have detected an association between carotenoids and the risk of heart diseases or atherosclerosis. In the Basel Prospective Study after 12-year of follow-up, CVD and stroke mortalities were significantly increased in subjects with initially low plasma levels of carotene and/or vitamin C, independently of vitamin E and of the classical cardiovascular risk factors[19]. In 1994 Morris and colleagues examined the relationship between total serum carotenoid levels and the risk of subsequent CHD events in analysis of a cohort from the Lipid Research Clinics Coronary Primary Prevention Trial and Follow-up Study[20]. They found that those men in the highest quartile of serum carotenoids had an adjusted relative risk (RR) of 0.64 (95% confidence interval [CI], 0.44 to 0.92) compared

with the lowest quartile. For men who never smoked, this RR was 0.28. In 1994, Knekt and colleagues published results of their longitudinal cohort study of 5,133 Finnish men and women aged 30-69 years and found an inverse non-significant association between dietary intake of carotenoids with provitamin A activity with the risk of coronary mortality in women[21]. Similar findings were published in 1997 for β-carotenoid intake and the risk of stroke in the Chicago Western Electric Study which evaluated 1,843 middle-aged men[22].

A number of prospective and case-control studies have shown an association between low β-carotene and the risk of CVD, although the results of the studies are inconsistent. In a European multicentre case-control, European Study of Antioxidants, Myocardial Infarction and Cancer of the Breast (EURAMIC), α-tocopherol and β-carotene concentrations were measured in adipose-tissue samples collected in 1991-92 from 683 people with acute myocardial infarction (AMI) and 727 controls[23]. The age-adjusted and centre-adjusted odds ratio for risk of myocardial infarction (MI) in the lowest fifth of β-carotene as compared with the highest was 2.62 (95% CI 1.79-3.83). The increased risk was mainly confined to current smokers: the multivariate odds ratio in the lowest β-carotene fifth in smokers was 2.39 (95% CI 1.35-4.25), whereas it was 1.07 for people who had never smoked. In the Bruneck study high plasma levels of α- and β-carotene were also associated with a lower risk of atherosclerosis[24].

Iribarren and co-workers observed in their study of 231 asymptomatic age-, sex-, race- and field center-matched case-control pairs from the Atherosclerosis Risks in Communities (ARIC) Study an association of serum β-cryptoxanthin, lutein plus zeaxanthin, lycopene, α- and β- carotene levels with carotid atherosclerosis[25]. They noted that serum beta-cryptoxanthin and lutein plus zeaxanthin levels were inversely related to the extent of atherosclerosis. Increases in α-carotene and lycopene were associated with nonsignificantly lower odds of being a case.

In 1998 Kritchevsky and co-workers published a cross-sectional study between intake of carotenoids with provitamin A activity and carotid artery plaques in 12,773 participants of the ARIC cohort[26]. They noted that in both women and men, those in the highest fifth of carotenoid consumption had a lower prevalence of plaques compared to those in the lowest fifth of carotenoid consumption. In women, this inverse association was particularly strong for current smokers, in men no such effect modification by smoking was seen.

The Dutch Rotterdam Study provided evidence for a modest inverse association between levels of serum lycopene and presence of atherosclerosis, with the association being most pronounced in current and former smokers[27]. They did not found any association between other carotenoids and atherosclerosis.

Recently Osganian and colleagues studied prospectively the relation between dietary intake of carotenoids and risk of coronary artery disease (CAD) in 73,286 female nurses using a semiquantitative food-frequency questionnaire[28]. During the 12 years of follow-up, (803,590 person-years), they identified 998 incident cases of CAD. After adjustment for age, smoking, and other CAD risk factors, they observed modest but significant inverse associations between the highest fifths of intake of β-carotene and α-carotene and risk of CAD but no significant relation with intakes of lutein plus zeaxanthin, lycopene, or β-cryptoxanthin. The association between the specific carotenoids and CAD risk did not vary significantly according to current smoking status. In the Italian case-control study with 433 cases and 869 paired controls, the risk of nonfatal AMI in women was inversely related to intake of β-carotene containing foods[29]. In the Rotterdam Study after a four year of follow-up, there was significantly reduced risk of MI in those subjects in the highest β-carotene intake third as compared to subjects in the lowest third[30].

The large prospective Physicians' Health Study did not find any evidence for a protective effect against MI for higher baseline plasma levels of α- and β-carotene, β-cryptoxanthin, lutein, or lycopene[31]. Among current and former smokers, but not among never-smokers, higher baseline plasma levels of β-carotene tended to be associated with lower risk of MI. In the same study baseline plasma levels of α-carotene and β-carotene and lycopene tended to be inversely related to risk of ischemic stroke[32]. In the prospective Health Professionals Study[33], a high dietary intake of lutein had a modest association with reduced risk for ischemic stroke, whereas the dietary intake of lycopene or α- or β-carotene measured by food-frequency questionnaire had no association with the stroke risk. In the α-Tocopherol, β-Carotene Cancer Prevention (ATBC) Study in Finland, the dietary intake of β-carotene was inversely associated with the risk for cerebral infarction (RR of highest versus lowest quartile 0.74, 95% CI 0.60 to 0.91), lutein plus zeaxanthin with the risk for subarachnoid hemorrhage (0.47, 0.24 to 0.93), and lycopene with risks of cerebral infarction (0.74, 0.59 to 0.92) and intracerebral hemorrhage (0.45, 0.24 to 0.86)[34]. This Finnish study cohort consisted of 26,593 male smokers, aged 50 to 69 years, without any previous history of stroke.

Clearer associations of carotenoids have been found between higher tissue or circulating levels of lycopene and lower risk of heart diseases, although this has not been noted in all studies. The multicenter case-control study EURAMIC examined the association between the lycopene concentration in fat tissue and the risk of MI in ten countries[35]. The study found that men with the highest concentrations of lycopene in their adipose tissue had a 48% reduction in the risk for developing CVD when compared with men with the lowest lycopene levels. In a part of the EURAMIC study from the Malaga center[36], there was a 60% lower risk of MI among those participants in the highest fifth of adipose tissue lycopene concentration as compared with the participants in the lowest fifth. In a nested case-control study from Washington County[37], low serum levels of β-carotene, lycopene, lutein and zeaxanthin were associated with an increased risk of subsequent MI in smokers, but not in nonsmokers.

There are also two Finnish studies which have examined the role of blood levels of lycopene with regard to cardiovascular health in women and men living in the eastern part of Finland. The first study examined the association between the plasma concentration of lycopene and the intima-media thickness of the common carotid artery wall (CCA-IMT) in a cross-sectional analysis of Antioxidant Supplementation in the Atherosclerosis Prevention (ASAP) Study in 520 high risk men and women[38]. Low plasma levels (lower than the median) of lycopene were associated with an 18% increased IMT in men, compared with men whose plasma levels of lycopene were higher. In women, the difference was not significant. The second Finnish study examined the association between serum levels of lycopene and CCA-IMT in 1,028 middle-aged men in the Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study[39]. In men with low serum levels of lycopene (lowest quarter) the adjusted CCA-IMT had a significant increment in both mean CCA-IMT and maximal CCA-IMT as compared with the other subjects. The KIHD study also examined the role of serum levels of lycopene with regard to the risk of acute coronary events and ischemic strokes[40]. Men with a low serum level of lycopene (the lowest quarter) had an over three-fold risk of suffering an acute coronary event or stroke as compared with the others. Sesso and co-workers recently described an association between plasma lycopene and the risk of CVD in middle-aged and elderly women in their prospective, nested, case-control Women's Health Study conducted in 39,876 women initially free of CVD at study baseline[41]. For CVD, the women in the upper three quartiles had a significant 50% risk reduction compared with those in the lowest quartile.

Clinical trials about carotenoids and CVD health

Although a higher plasma beta-carotene concentration has been associated with a reduced risk of heart diseases in several cross-sectional and prospective studies, four large randomized trials did not reveal any reduction in cardiovascular events with β-carotene use, and, in fact, there may even be an increase in heart disease and total mortality in male smokers[42,45].

In the ATBC Study, 29,133 male smokers aged 50 to 69 years received α-tocopherol (50 mg), β-carotene (20 mg), both, or placebo daily for 5 to 8 years[42]. Total mortality was 8 % higher (95% CI 1 to 16%) among the participants who received β-carotene than among those who did not, primarily because there were more deaths from lung cancer and IHD. The beneficial and adverse effects of supplemental α-tocopherol and β-carotene disappeared during postintervention follow-up[43]. The authors concluded that smokers should avoid β-carotene supplementation.

In a randomized, double-blind, placebo-controlled trial of beta carotene (50 mg on alternate days), Hennekens and co-workers enrolled 22,071 male physicians, 40 to 84 years of age, in the United States[44]. They concluded that 12 years of supplementation with β-carotene produced neither benefit nor harm in terms of the incidence of CVD, or death from all causes.

The effects of a combination of β-carotene and vitamin A on lung cancer and heart disease were studied in a multicenter, randomized, double-blind, placebo-controlled primary prevention trial, the β-Carotene and Retinol Efficacy Trial (CARET), involving a total of 18,314 smokers, former smokers, and workers exposed to asbestos[45]. The authors found that in the active-treatment group, the risk of death from any cause was 1.17 (95% CI 1.03 to 1.33); of death from lung cancer 1.46 (1.07 to 2.00); and of death from CVD 1.26 (0.99 to 1.61). On the basis of these findings, the randomized trial was stopped 21 months earlier than planned.

Greenberg and colleagues examined the relationship between β-carotene supplementation and risk of death from major disease causes in the randomized, placebo controlled Skin Cancer Prevention Study of supplementation of β-carotene, 50 mg per day for a median of 4.3 years[46]. During a median follow-up period of 8.2 years, there were 285 all cause deaths. There was no evidence of lower mortality following supplementation among patients with initial β-carotene concentrations below the median for the study group. The subjects randomly assigned to β-carotene supplementation showed no reduction in relative mortality rates from all causes (adjusted RR 1.03; 95% CI 0.82 to 1.30) or from CVD (1.16; 0.82 to 1.64).

In the secondary prevention trial, Heart Protection Study, 20,536 UK adults with CHD, other occlusive arterial disease, or diabetes were randomly allocated to receive antioxidant vitamin supplementation (600 mg vitamin E, 250 mg vitamin C, and 20 mg β-carotene daily) or matching placebo[47]. Although this regimen increased blood vitamin concentrations substantially, it did not produce any significant reductions in the 5-year mortality or incidence of any type of vascular disease, cancer, or any other major outcome. However, in the ATBC Study (smokers aged between 50 and 69 years), in 1,862 men who had had a previous MI, the risk of fatal CHD increased in the groups that received either β-carotene or the combination of α-tocopherol and β-carotene[48].

In the supplementation studies, synthetic β-carotene has been used, which may have different effects than the natural form of β-carotene. On the other hand, β-carotene and other carotenoids are often found in the same foods, and it is possible that serum or adipose tissue β-carotene is only an indicator for the consumption of other carotenoids or vitamins. Thus, β-carotene could be a marker for favourable dietary or lifestyle factors associated with a reduced risk of CVD. As mentioned before, it is also possible that high doses of carotenoids could have a pro-oxidant effect[12]. Thus, it is possible that at physiological levels, carotenoids could prevent cellular damage, but at the higher doses used in supplementation studies, the ability to protect against cell damage becomes lost.

FUTURE DIRECTIONS AND CONCLUSIONS

In conclusion, it is now recognized that a higher intake of fruit and vegetable can help to prevent CHD and mortality. More information is needed to clarify the association between the intake of single nutrients and the risk of heart diseases. In addition, clinical trials are warranted to evaluate the antioxidative effects and other possible benefits of carotenoids. Despite a plausible theory that antioxidants can prevent diseases caused by oxidative damage, trials thus far have not substantiated this. At the moment, there is no reason to recommend carotenoids in pill forms for the treatment or prevention of CHD. When studying associations between nutrients and diseases, it is important to include not only the traditional risk factors into the statistical models, but also other factors which are a part of a healthy lifestyle, such as exercise or nonsmoking.

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Table. Main dietary carotenoids

CAROTENOID				
Lycopene	**Beta-carotene**	**Alpha-carotene**	**Lutein + Zeaxanthin**	**Beta-cryptoxanthin**
Tomato and tomato products Watermelon Pink grapefruit Papaya Guava Rosehip	Carrots Apricots Mangoes (Red) Pepper Kale Spinach Broccoli	Carrots Collard Pumpkin Corn (Yellow) Pepper Cloudberry	Kale Spinach Broccoli Peas Brussels sprout Collard Lettuce Corn Egg yolk	Avocado Oranges Papayas Passion fruit Paprika Persimon
No provitamin A activity	Bioavailability from green leafy vegetables is low		No provitamin A activity	
Processing increases bioavailability of most carotenoids				

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