

Carotenoids as Potential Antioxidant Agents in Stroke Prevention: A Systematic Review

Abstract

Stroke and other cerebrovascular diseases are among the most common causes of death worldwide. Prevention of modifiable risk factors is a cost-effective approach to decrease the risk of stroke. Oxidative stress is regarded as the major flexible operative agent in ischemic brain damage. This review presents recent scientific advances in understanding the role of carotenoids as antioxidants in lowering stroke risk based on observational studies. We searched Medline using the following terms: (Carotenoids [MeSH] OR Carotenes [tiab] OR Carotene [tiab] OR “lycopene [Supplementary Concept]” [MeSH] OR lycopene [tiab] OR beta-Carotene [tiab]) AND (stroke [MeSH] OR stroke [tiab] OR “Cerebrovascular Accident” [tiab] OR “Cerebrovascular Apoplexy” [tiab] OR “Brain Vascular Accident” [tiab] OR “Cerebrovascular Stroke” [tiab]) AND (“oxidative stress” [MeSH] OR “oxidative stress” [tiab]). This search considered papers that had been published between 2000 and 2017. Recent studies indicated that high dietary intake of six main carotenoids (i.e., lycopene, (- and @-carotene, lutein, zeaxanthin, and astaxanthin) was associated with reduced risk of stroke and other cardiovascular outcomes. However, the main mechanism of the action of these nutrients was not identified, and multiple mechanisms except antioxidant activity were suggested to be involved in the observed beneficial effects. The dietary intake of six major carotenoids should be promoted as this may have a substantial positive effect on stroke prevention and stroke mortality reduction.

Keywords: Carotenoids, oxidative stress, stroke

Introduction

Stroke and other cerebrovascular diseases are the second common leading cause of death in many, especially developing, countries.^[1,2] The burden of stroke is likely to increase as a result of population growth and aging.^[3,4] Despite the high prevalence of stroke, there are limited effective preventive approaches for reducing its burden.^[4,5] The guidelines of the American Heart Association Stroke Council categorises the risk factors for a first stroke as nonmodifiable and modifiable factors.^[6,7] Among the modifiable risk factors, lifestyle modification, such as dietary intake of antioxidants, has long been investigated as a way to decrease the extent of injury caused by an ischemic stroke.^[8] A simple and practical approach to healthy food choice might facilitate the primary prevention of stroke by improving nutrition status. Guidelines generally advise a well-balanced diet low in saturated fat and salt, rich in fiber, and high in fruits and vegetables to reduce the incidence of stroke.^[9] Oxidative stress, defined as an

imbalance between oxygen-free radicals or oxidants and antioxidants, can potentially cause damage to cellular compounds and is thus regarded as the major contributing factor in ischemic brain injury.^[10,11] Therefore, several free-radical scavengers have been proposed as antioxidants to reduce radical loads in cells and the consequent alteration of the redox balance occurring in some pathological conditions such as stroke.^[12-14] The development and implementation of efficient strategies for the reduction of the global burden of stroke require a comprehensive understanding of the relationship between dietary antioxidants and the risk of stroke.^[15,16] Since the biochemical pathways triggered by oxidative stress can induce neuronal damage, numerous targets have been recommended for stroke therapy^[17] and modulating the effects of oxidative stress.^[18] As a result, the role of carotenoids has attracted growing attention following recommendations to increase the consumption of fruits and vegetables rich in antioxidants.^[19]

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Methods

Search strategy and eligibility criteria

We conducted a comprehensive literature search of the epidemiological studies in Medline (PubMed), Scopus, and Google Scholar databases to identify relevant studies. The electronic search was performed in May 2017. Papers were evaluated if they were published from 2000 up to the present. All titles and abstracts containing the search terms were examined, and full texts were reviewed when necessary. We searched Medline using the following terms: (Carotenoids [MeSH] OR Carotenes [tiab] OR Carotene [tiab] OR “lycopene [Supplementary Concept]” [MeSH] OR lycopene [tiab] OR beta-Carotene [tiab]) AND (stroke [MeSH] OR stroke [tiab] OR “Cerebrovascular Accident” [tiab] OR “Cerebrovascular Apoplexy” [tiab] OR “Brain Vascular Accident” [tiab] OR “Cerebrovascular Stroke” [tiab]) AND (“oxidative stress” [MeSH] OR “oxidative stress” [tiab]).

The identified studies were only included in this review if they offered new insights or opinions and investigated responses to the consumption of different types of carotenoids or clearly assessed the effects of dietary carotenoids, i.e., lutein, zeaxanthin, β -cryptoxanthin, and astaxanthin, and their serum concentrations on stroke prevention or stroke mortality. Only English articles were evaluated. The studies were only reviewed if their full text or abstract was available. The studies were excluded if they (1) were not related to the carotenoids-stroke association; (2) did not clearly explain the effects of carotenoids on each type of stroke; (3) were case reports, case series, communication letters, posters of conferences, and protocols; and (4) were conducted on animals or *in vitro*. Figure 1 shows the flowchart of the study selection phase.

Data extraction

For each paper, two researchers independently extracted the required information including the first author's name, sample size, participants' age, study design, duration of follow-up (for prospective studies), study objectives, context of the study, and the effects of carotenoids on the outcomes. We did not exclude any low-quality papers because we wanted to help our readers to get a complete understanding of all research in this field.

Study quality assessment

The Newcastle-Ottawa scale was used to assess the quality of cohort and case-control studies. The results of quality assessments and the characteristics of the selected studies are listed in Table 1.

Discussion

Carotenoids and stroke

Carotenoids are some of the most vital colored phytochemicals responsible for the yellow to red color

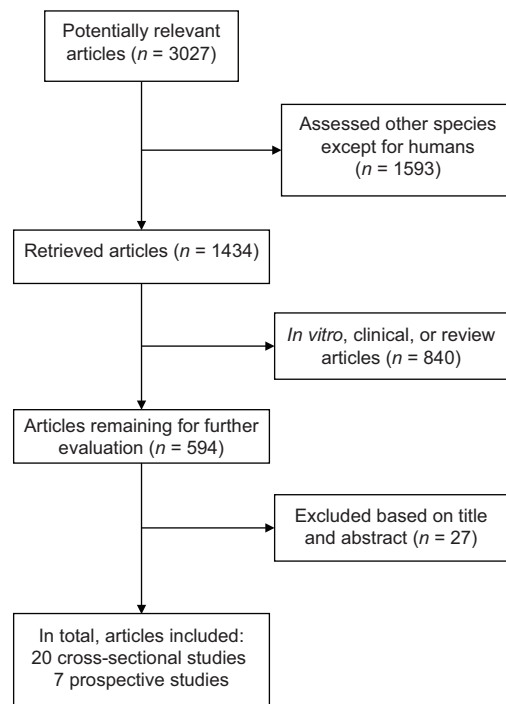


Figure 1: The study selection process

of some fruits and vegetables. Known as lipophilic antioxidant vitamins,^[20] carotenoids are found in the human diet, particularly in fruits and vegetables.^[21] Owing to their nutritional benefits, carotenoids and their isomers play an important role in protecting cells from oxidation and cellular damages and maintaining good health.^[22,23] Recent research on carotenoids has focused on their potent antioxidant properties and their role in preventing the incidence of human diseases such as cancer, cardiovascular diseases, osteoporosis, and diabetes.^[24]

Many cross-sectional and case-control studies investigated the relationship between the concentrations of plasma carotenoids and the incidence of stroke.^[25-27] According to some studies, most plasma carotenoids are lowered immediately after an ischemic stroke. Moreover, total antioxidant activity of the plasma is associated with the volume of ischemic cerebral infarction and the degree of the subsequent neurological impairment.^[28,29]

Some cohort studies also attempted to establish associations between lower plasma carotenoid concentrations or carotenoids intake and higher risk of stroke. Many studies have documented inverse associations between all types of stroke and plasma values or carotenoids intake.^[30-32] However, one study on postmenopausal women did not find substantial reductions in the risk of stroke.^[33] Iversen *et al.* detected a relationship between serum concentrations of total carotenoids and survival of ischemic stroke.^[34] This cohort included 165 patients aged above 65 years admitted to hospital for acute stroke. The authors found that plasma levels above the median for total carotenoids

Table 1: Summary of the reviewed studies

Author	Year	Design	Participants	Aim	Results	Quality
Iversen ^[34]	2015	Cohort	165 patients >65 years	Examining the survival of stroke patients with the highest baseline antioxidant capacity	Plasma levels above the median for total carotenoids were associated with reduced risk of death in the intervention group (adjusted HR: 0.29; 95% CI: 0.12-0.71)	4
Sen ^[45]	2011	Cross-sectional	786 individuals with a mean age of 66±7 years	Assessing association between higher plasma carotenoid concentrations and longer LTL	Higher plasma concentrations of lutein, zeaxanthin, and Vitamin C were associated with longer LTL in normal elderly persons (β' =0.0009; 95% CI: -0.0110-0.0288)	10
Karppi ^[49]	2012	Cohort	1031 Finnish men aged 46-65 years	Whether serum concentrations of major carotenoids, i.e., α -tocopherol and retinol, are related to any stroke and ischemic stroke in men	The highest quartile of serum lycopene concentrations had 59% and 55% lower risks of ischemic stroke and any stroke compared with men in the lowest quartile (HR=0.45; 95% CI: 0.25-0.95; P =0.036 for any stroke and HR=0.41; 95% CI: 0.17-0.97 for ischemic stroke)	8
Larsson ^[35]	2013	Cohort	34,670 women and 40,291 men	Examining the relationship between specific consumption of fruit and vegetable subgroups and stroke risk	Inverse associations with total stroke were observed for apples/pears (RR=0.89; 95% CI: 0.80-0.98 for green leafy vegetables and RR=0.92; 95% CI: 0.81-1.04 for Stroke)	8
Oude Griep ^[36]	2011	Cohort	20,069 men and women aged 20-65 years	Evaluating the associations between consumption of fruit and vegetable color groups with 10-year stroke incidence	Each 25-g/d increase in white fruit and vegetable consumption was associated with a 9% lower risk of stroke. HR, 0.91; 95% CI, 0.85-0.97. Apples and pears were the most commonly consumed white fruit and vegetables (55%)	8
Ito ^[58]	2006	Cohort	1260 males and 1,994 females aged 39-85 years	serum carotenoids and cardiovascular disease mortality	High serum values of β -carotene, total carotene, Pro-Vitamin A, and total carotenoid for colorectal cancer or stroke also appeared to be related to low HR	8
Hak ^[31]	2004	Nested case-control	297 physicians with ischemic stroke	Fruit and vegetable consumption and ischemic stroke	In the lowest plasma levels quartile, OR of ischemic stroke among men with the highest levels were 0.59 (95% CI: 0.36-0.98) for α -carotene, 0.62 (95% CI: 0.38-1.01) for β -carotene, and 0.61 (95% CI: 0.37-1.00) for lycopene	8
Chia-Yu Chang ^[59]	2005	Case-control	68 patients with acute ischemic stroke	Examining the associations of antioxidants, inflammation markers, and neurologic deficits among patients with stroke 48 h after the stroke onset	Plasma concentrations of α - and β -carotene were lower in patients with acute ischemic stroke than in healthy controls. This difference remained significant after adjustment for age and sex (P =0.04)	5
Polidori ^[28]	2002	Cross-sectional	28 participants aged 76.9±8.7 years	Determining the associations between ischemic stroke and oxidative stress and plasma carotenoids in patients with an acute ischemic stroke of recent onset (<24 h)	The majority of plasma carotenoids were lowered immediately after an ischemic stroke	5
Rissanen ^[50]	2001	Cohort	725 men aged 46-64 years	Assessing the relations between serum levels of lycopene and increased risk of acute coronary events and stroke in middle-aged men	Low serum level of lycopene was associated with an increased risk of atherosclerotic vascular events and stroke in middle-aged men previously free of coronary heart disease and stroke	8

Contd...

Table 1: Contd...

Author	Year	Design	Participants	Aim	Results	Quality
Yochum ^[33]	2000	Cohort	34,492 postmenopausal women	Evaluating the association between antioxidant vitamin intakes and death from stroke	Antioxidant intake did not seem to substantially reduce the risk of stroke in this cohort	8
Hirvonen ^[60]	2000	Cohort	26,593 male smokers aged 50-69 years	Examining the association between dietary antioxidants and subtypes of stroke	Dietary intake of β -carotene was inversely associated with the risk of cerebral infarction (RR: 0.77; 95% CI: 0.61-0.99)	8

OR=Odds ratios, HR=Hazard ratio, CI=Confidence interval, RR=Relative risk, LTL=Leukocyte telomere length

were associated with reduced risk of death with adjusted hazard ratio of 0.29 (95% confidence interval [CI]: 0.12–0.71). Other research regarding fruit and vegetables intake identified inverse associations between high apples/pears intake and total stroke (relative risk [RR]: 0.89; 95% CI: 0.80–0.98; *P* for trend = 0.02). Each 25 g/day increase in white fruit and vegetables, for example, apples/pears, consumption was associated with 9% reduction in the risk of stroke.^[35,36] Therefore, recommendations to consume apples or Pears are consistent with the mentioned research. The various carotenoids in these foods are believed to be responsible for their antioxidant properties and may be involved in the prevention of chronic diseases.^[37-39] These findings suggest that the majority of plasma carotenoids are lowered immediately after an ischemic stroke, perhaps as a result of increased oxidative stress, as indicated by a concomitant rise in malondialdehyde concentrations.^[28]

In fact, antioxidant activity of plasma may be an important factor in protection from neurological damage caused by stroke-associated oxidative stress. The antioxidants are consumed or oxidized during the cerebral process before the stroke so their levels of antioxidants are lower before the stroke. Therefore, considering conjugated double bonds, combined therapy using antioxidants might be effective in the acute and convalescent stages of stroke.^[40] Table 1 provides a summary of the selected studies.

β -carotene

β -carotene is an efficient quencher of singlet oxygen and comprises several isomers (i.e., all trans and 9-cis β -carotene) capable of inhibiting the oxidative stress and decreasing neuronal damage. Some research on stroke-prone spontaneously hypertensive rats (SHRs) demonstrated that β -carotene significantly enhanced the expression levels of genes related to cholesterol regulation, including apo E, and promoted neuronal repair after brain injuries.^[41]

Sansawa *et al.* focused on the beneficial effects of serum values of β -carotene on mortality rates in a population-based follow-up study of 3254 participants. During the 11.7 years of follow-up, high serum values of β -carotene and total carotene appeared to be

related with low hazard ratios for colorectal cancer or stroke.^[42] Another study conducted a prospective, nested case–control analysis on male physicians with and without diagnosed cardiovascular diseases. It found that plasma levels of α - and β -carotenes were inversely related to the stroke risk.^[31] Despite these positive results, a prospective observational study reported that Vitamins C and E and β -carotene did not have protective effects on stroke risk^[43] Similarly, Leppälä *et al.* investigated the effects of β -carotene supplementation on the risk of stroke in 28,519 male cigarette smokers aged 50–69 years without a history of stroke who participated in the Alpha-tocopherol, beta carotene cancer prevention (ATBC) study. The participants were supplemented with 20 mg/day β -carotene or placebo and followed up for a median duration of 6 years. The results showed that β -carotene supplementation increased the risk of intracerebral hemorrhage by 62% (95% CI: 10%–136%; *P* = 0.01). However, no obvious mechanism was detected. Meanwhile, the 6-year postintervention evaluations indicated that β -carotene supplementation had no effects on stroke and its subtypes (RR: 0.97; 95% CI: 0.86–1.09).^[44] These conflicting results may be due to differences in the conduct of trials as human trials were performed by administering a synthetic all-trans β -carotene whose dose was higher than the β -carotene content of fruits and vegetables. Only a few studies systematically examined the impact of other subtypes of carotenoids on the incidence of stroke. Thus, a specific reduction in stroke risk for single subgroups of carotenoids still needs to be interpreted with caution.

α -carotene

In a prospective, nested case–control study, called the Physicians' Health Study, 297 male physicians were followed up for up to 13 years. Levels of five major carotenoids (α - and β -carotene, β -cryptoxanthin, lutein, and lycopene), retinol, and α - and γ -tocopherol were measured in participants with ischemic stroke and paired controls. The multivariate adjusted odds ratios of ischemic stroke among men with the highest levels were 0.59 (95% CI: 0.36–0.98) for α -carotene, 0.62 (95% CI: 0.38–1.01) for β -carotene, and 0.61 (95% CI: 0.37–1.00) for lycopene.^[31]

β-cryptoxanthin

A prospective study of the relations between baseline plasma levels of β -cryptoxanthin and tocopherols and the risk of ischemic stroke indicated the absence of an inverse association between β -cryptoxanthin and ischemic stroke.^[31] A cross-sectional cohort study confirmed these findings.^[45]

Lycopene

Dietary lycopene is mainly obtained from tomatoes and tomato-based products. Lycopene is the most potent antioxidant among plasma carotenoids.^[25] Although the antioxidant properties of lycopene are thought to be primarily responsible for its beneficial effects, other mechanisms such as hormonal and immune system modulations are also suggested.^[46,47] Many studies have highlighted associations between serum concentrations of lycopene and decreased risk of all types of stroke and ischemic stroke.^[48] Furthermore, in a prospective, nested case-control study performed on 297 physicians suffering from ischemic stroke, baseline plasma levels of α - and β -carotene and lycopene tended to be inversely related with the risk of ischemic stroke and had an apparent threshold effect compared to controls. A study on the association of major carotenoids, i.e., α -tocopherol, retinol, and lycopene, with ischemic stroke in 1031 Finnish men aged 46–65 years found that the highest quartile of serum lycopene concentrations had 59% and 55% lower risks of ischemic stroke and any stroke, respectively.^[49] These results support the results previously reported by Rissanen *et al.* who conducted a cohort study on 725 middle-aged men.^[50]

Similarly, the meta-analyses with 116,127 and 1989 cases supported the benefits of circulating lycopene, not dietary lycopene, on stroke risk. Further studies are hence required to evaluate the mechanism of action of this nutrient in the reduction of stroke risk. Overall, lycopene has been confirmed to prevent cardiovascular events such as stroke.^[25,51]

Lutein and zeaxanthin

Lutein and zeaxanthin are xanthophyll carotenoids found particularly in dark-green leafy vegetables and egg yolk. They are widely distributed in tissues and are the principal carotenoids in the eye lens and macular region of the retina.

Recent studies have suggested that lutein and zeaxanthin contribute to the prevention of heart disease and stroke. In a cross-sectional cohort study, Sen *et al.* demonstrated that higher plasma concentrations of lutein, zeaxanthin, and Vitamin C were associated with longer leukocyte telomere length in normal elderly persons. They concluded that these antioxidants had a protective role in telomere maintenance in elderly adults with a mean age of 66 ± 7 years.^[45] Another study investigated the protective role of lutein

in cerebral ischemic/reperfusional (I/R) injury in a mouse model of ischemic stroke. The results indicated higher survival rate, better neurological scores, smaller infarct area, and smaller infarct volume in the lutein-treated group after lutein (0.2 mg/kg) intake.^[52] Therefore, lutein could diminish the deleterious outcomes of cerebral I/R and may be used as a potential treatment for stroke patients. Moreover, due to their extra conjugated double bond, some types of carotenoids such as zeaxanthin are believed to be potent antioxidants and facilitate the protection of brain tissue from oxidative damages.^[53] As the evidence for the role of lutein and zeaxanthin in disease prevention continues to evolve, particularly from human studies directed to their bioavailability, metabolism, and dose-response relationships with intermediary biomarkers and clinical outcomes, it is noteworthy that recommendations to consume foods rich in xanthophylls are consistent with current dietary guidelines.^[54]

Astaxanthin

The ketocarotenoid astaxanthin is the main carotenoid present in aquatic animals (salmon, trout, red sea bream, shrimp, and lobster) and contributes to the pinkish-red color of their flesh. It is also present in some birds (particularly flamingoes and quails). Astaxanthin is biosynthesized by microalgae and phytoplankton. The highest levels of this carotenoid in nature were found in Chlorophyte alga *Haematococcus phuvialis*.^[26,27] A previous study hypothesized that astaxanthin had antithrombotic and antihypertensive effects and exhibited noticeable neuroprotection against brain damage induced by I/R which could partly be attributed to its antioxidant activity.^[55]

An experimental study by Lu *et al.* investigated the neuroprotective effects of astaxanthin on oxidative stress-induced toxicity in primary culture of cortical neurons and on focal cerebral I/R-induced brain damage in rats.^[56] They found that pretreatment with intragastric astaxanthin 5 and 1 h before ischemia dramatically decreased the infarct volume and improved neurological deficit in a dose-dependent manner. In another study, oral administration of astaxanthin-O (50 mg/kg) for 5 weeks induced a significant reduction in arterial blood pressure and delayed the incidence of stroke in SHR. These antihypertensive effects of astaxanthin-O might have been caused by an NO-related mechanism.^[57]

Conclusions

While many epidemiological studies have reported the promising effects of the five major carotenoids (i.e., lycopene, α - and β -carotene, lutein, and zeaxanthin) on the reduction of stroke risk, we did not find any clinical trials of carotenoid administration either among healthy people for the reduction of stroke risk or among stroke survivors for the reduction of stroke mortality and

morbidity. Moreover, there are still many unanswered questions about the contribution of individual carotenoids to the risk of stroke. Likewise, the main mechanism of stroke risk reduction by carotenoids and the effects of carotenoids on stroke-related complications are still unknown.

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Conflicts of interest

There are no conflicts of interest.

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