

Astaxanthin, oxidative stress, inflammation and cardiovascular disease

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It is accepted that oxidative stress and inflammation play an integral role in the pathophysiology of many chronic diseases including atherosclerotic cardiovascular disease. The xanthophyll carotenoid dietary supplement astaxanthin has demonstrated potential as an antioxidant and anti-inflammatory therapeutic agent in models of cardiovascular disease. There have been at least eight clinical studies conducted in over 180 humans using astaxanthin to assess its safety, bioavailability and clinical aspects relevant to oxidative stress, inflammation or the cardiovascular system. There have been no adverse outcomes reported. Studies have demonstrated reduced markers of oxidative stress and inflammation and improved blood rheology. A larger number of experimental studies have been performed using astaxanthin. In particular, studies in a variety of animals using a model of myocardial ischemia and reperfusion have demonstrated protective effects from prior administration of astaxanthin both intravenously and orally. Future clinical studies and trials will help determine the efficacy of antioxidants such as astaxanthin on vascular structure, function, oxidative stress and inflammation in a variety of patients at risk of, or with, established cardiovascular disease. These may lead to large intervention trials assessing cardiovascular morbidity and mortality.

Oxidative stress and inflammation have been accepted as important contributors to the development of atherosclerosis and hence, cardiovascular morbidity and mortality [1]. Nutritional antioxidants can decrease lipid and protein oxidation, potentially protecting against atherosclerosis and arterial stiffening [2–4]. Cross sectional studies [5,6] and observational prospective cohort studies have supported the premise that oxidative stress is involved in vascular damage by demonstrating an association between nutritional antioxidant intake and/or their plasma levels and reduced adverse cardiovascular disease outcomes [5–10]. In addition, a lower dietary intake of antioxidants has been associated with increased inflammation and oxidative stress [11]. Carotenoids, such as β -carotene have been assessed in such studies, but other antioxidant supplements such as astaxanthin, have not yet been investigated in this way. Many studies assessing β -carotene intake or β -carotene supplementation in the diet have demonstrated reduced cardiovascular disease associated with higher β -carotene intake [8,12–17]. Other antioxidants used in clinical trials so far have included vitamin E, vitamin C, α -lipoic acid and *N*-acetyl cysteine. Studies using vitamin E and vitamin C have been reviewed elsewhere [18]. Except for a few studies [19–21], antioxidant intervention trials

have failed to demonstrate cardiovascular benefits [22–24], perhaps because of an inappropriate choice and dose of antioxidant given to undifferentiated participants. Thus, more research is required either using previously studied antioxidants in different populations or at different doses for longer duration or alternatively, investigating new, more potent antioxidants with different biological actions. Astaxanthin, a xanthophyll carotenoid, is one such compound and this review will summarize the available evidence supporting further investigation of this agent as an intervention in oxidative stress, inflammation and cardiovascular disease.

Carotenoids

Carotenoids are ubiquitous in nature and present in plants, algae and microorganisms. However, humans and other animals are unable to manufacture carotenoids and hence require these in their diet [25]. There are two types of carotenoids based on their chemical composition; carotenes and xanthopylls. Carotenes include β -carotene and lycopene and, xanthopyll carotenoids include lutein, canthaxanthin, zeaxanthin, violaxanthin, capsorubin and astaxanthin [26,27].

McNulty *et al.* have proposed that carotenoids exert differing effects based on their interactions with membranes [26]. This group assessed

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the effects of astaxanthin, zeaxanthin, lutein, β -carotene and lycopene on lipid peroxidation using a polyunsaturated fatty-acid-enriched membrane model [26,28]. Nonpolar carotene carotenoids such as lycopene and β -carotene actually caused disorder of model membranes and resulted in lipid peroxidation, unlike the polar xanthophyll carotenoid astaxanthin, which preserved the structure of the model membrane [28]. These differing effects of the carotenoids may account for the different biological effects seen with these agents in clinical trials. In some studies, the nonpolar carotenoid, β -carotene has been demonstrated to be associated with no benefit in cardiovascular disease [29–33]. Furthermore, at high doses, β -carotene may be pro-oxidant [34]. By contrast, the polar carotenoid astaxanthin has been shown to have protective effects on the cardiovascular system although this was demonstrated in animal studies and has not been investigated in human trials [35–37].

Astaxanthin

Astaxanthin is a xanthophyll carotenoid, and unlike other carotenoids it contains two additional oxygenated groups on each ring structure, as seen in FIGURE 1, resulting in enhanced antioxidant properties [38]. The compound occurs naturally in a wide variety of living organisms including microalgae, fungi, complex plants, seafood and some birds such as flamingos and quail [39]. It is reddish-colored, and gives salmon, shrimp and lobster their distinctive coloration [39]. The US FDA approved astaxanthin in 1987 as a feed additive for the aquaculture industry and in 1999 approved its use as a dietary supplement (nutraceutical) [38]. The main astaxanthin isomer (3S, 3S') produced by the microalgae *Hematococcus pluvialis* is identical to that present in wild salmon. Astaxanthin cannot be manufactured in animals or converted to vitamin A and therefore must be consumed in the diet [40,41]. Xanthophyll carotenoids such as astaxanthin and canthaxanthin have antioxidant activity, are free radical scavengers, potent quenchers of reactive oxygen and nitrogen species including singlet oxygen single and two electron oxidants, and are chain-breaking antioxidants [42–44]. These molecules have terminal carbonyl groups conjugated to a polyene backbone [27]. They are superior antioxidants and scavengers of free radicals compared with the carotene carotenoids such as β -carotene [44,45]. It has been suggested that astaxanthin may play a valuable role in antioxidant protection of cells and in

protection against cardiovascular disease [46]. In addition, carotenoids may also alter immune response and transcription [47,48].

Available forms of astaxanthin

Natural astaxanthin

The most common source of natural astaxanthin used in dietary supplements is a mixture of configurational isomers obtained from the unicellular microalgae *Hematococcus pluvialis* [49]. Astaxanthin is produced in its natural form on an industrial scale [50].

Synthetic astaxanthin

The manufacture of astaxanthin to the standard required for the pharmaceutical industry is more complex [27]. However, synthesis of enantiopure astaxanthin (3S, 3'S) has been achieved and this enables further derivations to be developed for assessing in clinical trials [27].

Disodium disuccinate astaxanthin

Disodium disuccinate astaxanthin (DDA) is manufactured by Cardax Pharmaceuticals and is the compound used in all of the ischemia-reperfusion studies in animals. This synthetic form of astaxanthin overcame the limitations of carotenoids related to their poor aqueous solubility and enabled investigation of this agent in the animal models of myocardial ischemia and reperfusion using both intravenous and oral routes of administration [51].

It is controversial to consider whether the natural form of astaxanthin from the microalgae source should be used in clinical studies compared with a pure synthesized compound such as DDA. With differing quantities of stereoisomers, these alternative forms of astaxanthin therapy would not necessarily be equivalent [52]. The development of a compound such as an improved derivative of astaxanthin could result in different outcomes once tested clinically [53]. Certainly DDA has been demonstrated to be effective in animal cardiovascular studies administered both intravenously and orally [36,37,51,54].

Experimental studies using astaxanthin

Astaxanthin has undergone investigation in a large number of experimental studies. Those specifically relevant to the cardiovascular and cerebrovascular systems are summarized in TABLE 1. There are many other studies where astaxanthin has been demonstrated to have beneficial effects when used in noncardiovascular models of disease and at the same time attenuated mediators of oxidative stress and

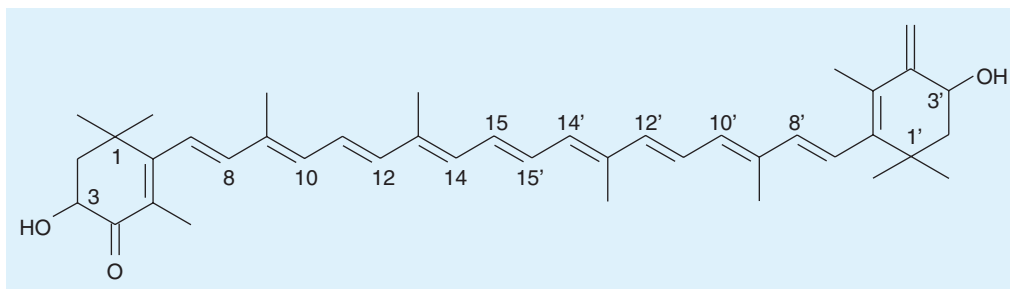


Figure 1. Astaxanthin molecular structure.

inflammation [55–66]. In addition, there have been studies that have specifically demonstrated the beneficial effects of astaxanthin on oxidative stress with a reduction in lipid peroxidation [67] and inflammation [58,59,64,65].

Cardiovascular

Lockwood and other investigators have conducted a series of experiments in rats, rabbits and dogs assessing the potential efficacy of DDA in ischemia-reperfusion models [36,37,51,68]. In the myocardium of Sprague-Dawley rats it has been demonstrated that prior treatment for 4 days with intravenous DDA at doses of 25, 50 and 75 mg/kg bodyweight, significantly reduced the subsequent myocardial infarct size and hence improved myocardial salvage [36]. There was a correlation between this effect and the dose administered. The same group of investigators used prior treatment for 4 days with 50 mg/kg/day of intravenous DDA in a rabbit myocardial ischemia–reperfusion model [54]. Again, there was a significant reduction in myocardial infarct size and improved myocardial salvage in the DDA-treated animals. In addition, as an assessment of inflammatory activity, complement activation was measured. This marker was found to be attenuated in DDA-treated animals suggesting a reduction in tissue inflammation associated with DDA administration [54]. Gross *et al.* extended their rat studies [36,37] to the dog model using intravenous DDA at 2 h, prior to coronary artery occlusion or daily for 4 days prior to occlusion of the left anterior descending coronary artery [68]. After 1 h of occlusion and 3 h of reperfusion there was a significant reduction in myocardial infarct size in astaxanthin treated dogs after both 2 h and 4 days of astaxanthin administration prior to induction of ischemia. Two out of three dogs in the 4-day treatment group had 100% cardiac protection [68]. In a further study in rats, this same group of investigators used 7 days of oral pretreatment with DDA at two doses, 125 and 500 mg/kg/day [37]. Myocardial tissue

was assessed for free astaxanthin concentrations. After 7 days of 125 mg/kg/day of oral DDA the myocardial-free astaxanthin concentration was 400 nM and after 500 mg/kg/day it was 1634 nM. Multiple lipid peroxidation products were also reduced. The authors noted that similar studies in humans with prior treatment with statins had produced similar outcomes [69], which raises the possibility that perhaps astaxanthin might have therapeutic potential in humans. It should be noted that, the doses used in these experiments were high in comparison with oral dosing in humans and it may not be safe to use these doses clinically. Confirmation of these results from an independent group is important.

Hussein *et al.* assessed the effects of astaxanthin on blood pressure in spontaneously hypertensive rats (SHR) [70]. There was a significant blood pressure reduction with 14 days of oral astaxanthin administration that did not occur when given to normotensive Wistar-Kyoto rats. In another experiment, the same investigators administered oral astaxanthin for 5 weeks to stroke-prone SHR [70]. There was also a significant reduction in blood pressure in astaxanthin-treated animals. *In vitro* experiments on the rat aortas revealed astaxanthin enhanced nitric oxide-induced vascular relaxation. In separate experiments, Hussein *et al.* assessed oxidative parameters in SHR [71]. Oral astaxanthin significantly decreased nitric oxide end products further supporting the effect of astaxanthin on this pathway. *In vitro* studies of the rat aorta and coronary arteries have also demonstrated astaxanthin decreased elastin bands in the aorta and reduced the wall:lumen ratio in the coronary arteries indicating a further mechanism of action [71].

Cardiac & skeletal muscle

Aoi *et al.* investigated the effects of astaxanthin supplementation in 7-week-old C57BL/6 mice [60]. Astaxanthin-treated mice had reduced exercise-induced increases in markers of oxidative

Table 1. Animal studies investigating the cardiovascular and cerebrovascular effects of astaxanthin.

Study	Model	Dosage	Duration of supplementation	Effects of astaxanthin	Ref.
Lauver <i>et al.</i> (2008)	Dog with occlusive carotid artery thrombus	DDA 10, 30, or 50 mg/kg/body weight iv.	30 min after occlusion	Reduced incidence of secondary thrombosis	[35]
Aoi <i>et al.</i> (2003)	C57BL/6 mice	Diet supplemented with astaxanthin 0.02% weight/weight and food intake recorded	3 weeks	Attenuation of exercise increased 4-hydroxy-2-nonenal-modified protein and 8-hydroxy-2'-deoxyguanosine in cardiac and gastrocnemius muscle Attenuation of exercise increases in creatine kinase and myeloperoxidase activity in cardiac and gastrocnemius muscle Astaxanthin accumulated in cardiac and gastrocnemius muscle	[60]
Gross and Lockwood (2004)	Myocardial infarct model Sprague-Dawley rats	DDA 25/50/75 mg/kg iv. daily	4 days prior to myocardial infarction	Myocardial infarct size significantly reduced	[36]
Hussein <i>et al.</i> (2005)	Stroke prone Spontaneously hypertensive rats	50 mg/kg bodyweight/day	5 weeks	Significant blood pressure reduction Delayed incidence of stroke	[70]
Lauver <i>et al.</i> (2005)	Rabbit model of myocardial ischemia-reperfusion	DDA 50 mg/kg/day iv.	5 days	Significant reduction in complement activation Significant reduction in myocardial infarct size	[54]
Gross <i>et al.</i> (2005)	Canine model of myocardial ischemia-reperfusion	DDA 50 mg/kg/day iv.	2 h or daily for 4 days	Significant reduction in myocardial infarct size Two of three dogs treated for 4 days had 100% cardiac protection	[68]
Gross <i>et al.</i> (2006)	Sprague-Dawley rats Left anterior descending coronary artery occlusion/reperfusion	DDA 125 or 500 mg/kg/day orally	7 days	Astaxanthin loading of myocardium indicating good bioavailability Trends in lowering of lipid peroxidation products Significant reduction in myocardial infarct size	[37]
Hussein <i>et al.</i> (2006)	Spontaneously hypertensive rats	5 mg/kg bodyweight/day	7 days	Significant reduction in nitric oxide end products Significant reduction in elastin bands in aorta Significant reduction in wall:lumen arterial ratio in coronary arteries	[71]
Shen <i>et al.</i> (2009)	Middle cerebral artery occlusion in the rat	Injected intracerebroventricularly	Single injection	Reduced ischemic cerebral injury Reduced lipid peroxidation	[72]

DDA: Disodium disuccinate astaxanthin; iv.: Intravenous.

stress; 4-hydroxy-2-nonenal-modified protein and 8-hydroxy-2'-deoxyguanosine in cardiac and gastrocnemius muscle. In addition, astaxanthin attenuated the increases in creatinine kinase and myeloperoxidase activity in cardiac and gastrocnemius muscle. There was also evidence of astaxanthin accumulation in cardiac and gastrocnemius muscle after the 3 weeks of supplementation.

Vasculature

The effects of DDA were studied in a canine model of carotid artery thrombosis [35]. There was a dose-dependent decrease in carotid artery

rethrombosis in DDA-treated animals with no effect on hemostasis and a reduction of rethrombosis after thrombolysis [35].

Ischemic brain injury

Shen *et al.* assessed the effect of prior intracerebroventricular injection of astaxanthin on a cerebral ischemic model in rats [72]. Astaxanthin-treated animals had reduced cerebral infarction and improved locomotor activity compared with controls. In addition these investigators assessed brain tissue for free radical damage and the presence of apoptosis. Astaxanthin decreased lipid peroxidation in the ischemic cerebral cortex. The

authors concluded that astaxanthin decreased cerebral cortex ischemic injury by decreasing oxidative stress and apoptosis [72].

Kidney

Chronic kidney disease and in particular diabetic nephropathy is associated with premature atherosclerotic vascular disease [73]. In an experimental model using diabetic db/db mice, astaxanthin administration resulted in lower blood glucose levels [57]. The relative mesangial area was reduced significantly in the astaxanthin-treated group. Furthermore, the urinary protein excretion and 8-OHdG increases were attenuated in the astaxanthin treated group. The astaxanthin-treated mice had less 8-OHdG immunoreactive cells in the glomeruli [57]. Astaxanthin significantly suppressed hyperglycemia induced reactive oxygen species production, activation of transcription factors, and cytokine expression and production by normal human mesangial cells [63]. The authors concluded astaxanthin might be useful in the prevention of diabetic nephropathy. This may indirectly impact on cardiovascular outcomes that are closely linked to diabetic nephropathy.

In summary, astaxanthin has shown promise as a therapeutically effective antioxidant in a variety of animals with a range of disease models.

Astaxanthin studies in humans relevant to the cardiovascular system

Only a few studies have investigated the potential benefits of astaxanthin in human health and disease (TABLE 2). Most of these have been performed in healthy volunteers to assess dosing, bioavailability, safety and oxidative stress. Studies have also been conducted in noncardiac conditions such as reflux oesophagitis and these have often included assessments of measures of oxidative stress or inflammation. No studies have yet been published, specifically assessing cardiovascular parameters in humans.

Dosing

The studies in humans have used oral doses of astaxanthin from 4–100 mg, for durations from a single dose to 1-year (TABLE 2). Wild or aquacultured salmon has 5 µg of astaxanthin per gram of salmon [74]. Therefore, consumption of 500 g of salmon per week would provide around 350 µg of astaxanthin per day.

Bioavailability

The bioavailability of astaxanthin after ingestion of 250 g of wild or aquacultured salmon was assessed in a randomized double blind

trial using 28 volunteers [74]. Wild salmon acquire astaxanthin from zooplankton (e.g., krill) and other crustaceans, whereas aquacultured salmon acquire it from fish-feed fortified with astaxanthin. Initial plasma astaxanthin levels were higher at 3, 6, 10 and 14 days during ingestion of aquacultured compared with wild salmon, but not at 14 days. Stereoisomer bioavailability differed in plasma distribution compared with the ingested source. The astaxanthin (3S, 3'S) isomer appeared at higher levels in the plasma than its proportionate level in the salmon flesh suggesting that astaxanthin isomers may have different bioavailability and/or metabolism. Coral-Hinojosa *et al.* studied the plasma isomers of astaxanthin after ingestion of both 10 mg as a single dose and 100 mg over 4 weeks. The plasma elimination half-life of astaxanthin was $52 \pm$ standard deviation (SD) 40 h. In addition, there was a non-linear dose–response and selective absorption of Z-isomers of astaxanthin [75].

Safety

A randomized, double blind, placebo-controlled trial was conducted in 35 healthy adults to investigate the safety of astaxanthin supplementation [76]. Participants were required to consume 6 mg/day of astaxanthin or placebo for 8 weeks. Measures of blood pressure and blood chemistry conducted at 4- and 8-weeks revealed no significant differences between the treatment and placebo groups and they also did not differ from baseline. The authors concluded that healthy adults could safely consume 6 mg/day of astaxanthin from a *Hematococcus pluvialis* algal extract. So far there have been no reported side effects noted in any of the Medline-published human studies.

Oxidative stress & inflammation

Studies conducted in healthy human volunteers and patients with reflux oesophagitis have found significant reductions in oxidative stress, hyperlipidemia and inflammatory markers after oral supplementation with astaxanthin [67,77,78]. In particular, Iwamoto *et al.* investigated 24 healthy volunteers who took four doses of astaxanthin from a low dose (for a supplement) of 1.8 up to 21.6 mg/day for 2 weeks [67]. LDL lag time as a measure of LDL oxidation was significantly greater in the four astaxanthin groups after 2 weeks compared with baseline indicating an inhibition of LDL oxidation [67]. In a study conducted in 40 healthy nonsmoking Finnish males the investigators assessed

Table 2. Clinical studies investigating the safety, bioavailability and effects of astaxanthin on oxidative stress.

Study	Study population (n = subjects)	Dosage	Study design	Duration of supplementation	Effects of astaxanthin	Ref.
Iwamoto <i>et al.</i> (2000)	Volunteers (24)	Different doses: 1.8, 3.6, 14.4 and 21.6 mg/day	Open labeled	2 weeks	Reduction of lipid (LDL) peroxidation	[67]
Osterlie <i>et al.</i> (2000)	Middle aged male volunteers (3)	100 mg	Open labeled	Single dose	Astaxanthin taken up by VLDL chylomicrons	[82]
Mercke Odeberg <i>et al.</i> (2003)	Healthy male volunteers (32)	40 mg	Open labeled parallel	Single dose	Enhanced bioavailability with lipid-based formulation	[83]
Spiller <i>et al.</i> (2003)	Healthy adults (35)	6 mg/day (three-times 2 mg tablets/day)	Randomized, double blind, placebo controlled	8 weeks	Demonstrated safety assessed by measures of blood pressure and biochemistry	[76]
Coral-Hinostroza <i>et al.</i> (2005)	Healthy adult males (3)	10 and 100 mg	Open labeled	Single dose or 4 weeks	C_{max} 0.28 mg/l at 11.5 h at high dose and 0.08 mg/l at low dose Elimination half-life 52 ± 40 h Z-isomer selectively absorbed	[75]
Karppi <i>et al.</i> (2007)	Healthy nonsmoking Finnish males (40)	8 mg/day	Randomized, double blind, placebo controlled	12 weeks	Intestinal absorption adequate with capsules Reduced levels of plasma 12 and 15 hydroxy fatty acids Decreased oxidation of fatty acids	[77]
Parisi <i>et al.</i> (2008)	Nonadvanced age-related macular degeneration (27)	4 mg/day	Randomized controlled trial open labeled no placebo	12 months	Improved central retinal dysfunction in age-related macular degeneration when administered with other antioxidants	[79]
Miyawaki <i>et al.</i> (2008)	Healthy males (20)	6 mg/day	Single blind, placebo controlled	10 days	Decreased whole blood transit time (improved blood rheology)	[80]
Rufer <i>et al.</i> (2008)	Healthy males (28)	5 µg/g salmon flesh (wild vs aquacultured)	Randomized, doubleblind, placebo controlled	4 weeks	Bioavailability initially better with ingestion of aquacultured salmon but equivalent at day 28. Isomer (3 <i>S</i> , 3' <i>S</i>) greater in plasma compared with isomer proportion in salmon flesh	[74]

C_{max} : Maximum concentrations.

plasma levels of 12- and 15-hydroxy fatty acids, which were significantly reduced in those taking astaxanthin [77]. This suggested astaxanthin reduced fatty acid oxidation [77]. Andersen *et al.*, in a study conducted in 44 patients with functional dyspepsia, found astaxanthin administration at a dose of 40 mg/day orally upregulated CD4 and down regulated CD8 and significantly reduced gastric inflammation in *Helicobacter pylori*-positive patients [78].

Macular degeneration

Parisi *et al.* performed a randomized, open labeled, controlled (with no placebo) trial in 27 patients with nonadvanced age-related

macular degeneration. The active treatment group took astaxanthin 4 mg along with vitamin C, vitamin E, zeaxanthin, zinc, copper and lutein for 12 months. There was an improvement in the selective dysfunction in the central but not peripheral retina [79]. As there were many antioxidants given to the treated group it is not possible to know whether astaxanthin specifically contributed to the improvement.

Blood rheology

Miyawaki *et al.* studied the effects of astaxanthin on human blood rheology assessed by whole blood transit time in 20 healthy males.

Oral astaxanthin at 6 mg daily for 10 days improved blood rheology demonstrated by decreased whole blood transit time [80].

In summary, astaxanthin has been demonstrated to be safe, have adequate bioavailability and has potential as a therapeutic antioxidant and anti-inflammatory agent for further testing in human disease. Additional studies that improve our understanding of antioxidant efficacy may lead to important clinical benefits in the prevention of atherosclerosis and vascular disease. It will also be important to investigate whether astaxanthin has any additional anti-inflammatory mechanisms of action.

Human clinical study in progress

A study is being conducted assessing the effects of astaxanthin 8 mg/day orally on measures of oxidative stress, inflammation and vascular function in kidney transplant recipients [81]. This study will measure surrogate markers of cardiovascular disease such as aortic pulse-wave velocity, augmentation index, brachial forearm reactivity and carotid artery intimal medial thickness. Results from this pilot study may lead to a large randomized, controlled trial assessing cardiovascular outcomes such as myocardial infarction and death. A search of clinical trial registries failed to detect any other registered clinical trials using astaxanthin in humans.

Conclusion

The oxidative stress theory of progressive arterial disease is supported by observational studies connecting antioxidant intake with

oxidative stress and cardiovascular outcomes. Surprisingly and disappointingly clinical intervention studies using antioxidants, such as those assessed in the observational studies, including vitamin E, β -carotene and vitamin C, have been mainly negative [23,24]. There are many potential reasons for this discrepancy that need to be considered prior to abandoning the oxidative stress theory. It may be that the intervention studies failed because they recruited patients that did not actually have elevated oxidative stress, or that administering the antioxidant did not adequately correct the oxidative stress. It is also possible the agents used such as vitamin E, β -carotene and vitamin C may have been ineffective because they were given in insufficient doses or not in the right form or for adequate duration to correct elevated oxidative stress. Astaxanthin has potential as a potent antioxidant to test in human clinical trials based on theoretical grounds related to its physicochemical properties and on the basis of preliminary experimental studies in cardiovascular models. Although its use in human clinical studies has been limited so far there have been no safety concerns that have arisen. We predict that because of its greater antioxidant potency and membrane preservation, astaxanthin will reduce measures of oxidative stress and inflammation and potentially provide vascular benefits. The availability of new antioxidants and new measures of oxidative stress provide the opportunities for establishing the potential benefits of these agents in cardiovascular disease. Perhaps the conundrum of the

Executive summary

Oxidative stress

- Oxidative stress and inflammation are major factors contributing to the pathophysiology of atherosclerotic cardiovascular disease.

Antioxidants

- Observational studies have supported the notion that increased antioxidant intake is associated with reduced cardiovascular disease
- Antioxidant therapies, such as vitamin E, β -carotene and vitamin C, tested in clinical trials have generally failed to produce measurable hard outcome benefits. These trials may have failed because the antioxidant and/or dose used, patient group studied and the duration followed may, not have been ideal.
- Prior to enrollment and inclusion in a clinical trial using an antioxidant, the presence of oxidative stress should be established using a valid, sensitive and reliable marker.
- Novel and more potent antioxidants may support better studies assessing the effects of antioxidants on cardiovascular outcomes as well as assessing whether the therapy actually impacts on measures of oxidative stress and inflammation.

Astaxanthin

- Astaxanthin, a xanthophyll carotenoid is a potent antioxidant with potential cardiovascular benefits.

Experimental studies using astaxanthin

- A series of studies conducted using a myocardial ischemia–reperfusion model in a range of animal types has demonstrated that astaxanthin in the disodium disuccinate astaxanthin formulation is effective in limiting myocardial infarct size and improving myocardial salvage.

Current clinical trial using astaxanthin

- A clinical trial is in progress with astaxanthin in kidney transplant recipients, a group at high risk of cardiovascular disease.

unexplained paradox of the known pathophysiology of oxidative stress contrasted with the failure of antioxidants as therapy will be answered.

Future perspective

Many proof-of-concept studies and randomized, controlled trials are required to establish the safety and efficacy of astaxanthin and other xanthophyll carotenoids in cardiovascular disease. A clinical trial is in progress, investigating the effects of astaxanthin on oxidative stress and inflammation and surrogate vascular outcomes measures in kidney transplant recipients who are at high risk of cardiovascular disease. In the future it is quite possible antioxidant supplements such as astaxanthin could take a role as significant as statins in the treatment and perhaps prevention of cardiovascular disease.

Financial & competing interests disclosure

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