

The antioxidant advantage of the Mediterranean diet in cardiovascular disease

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Abstract: To date, discrepancy exists among scientific data in regard to the benefit of administering antioxidant vitamin supplementation to cardiovascular disease (CVD) patients or toward protecting those who are at risk. Data of conducted randomized-controlled clinical trials so far did not produce solid evidence for the benefit of supplementing such antioxidant vitamins. Several meta-analyses confirmed that there was no effect of such supplementation, and adverse effects resulted when vitamin E was given in high doses. Thus, there is no scientific or medical basis to recommend the use of antioxidant vitamin supplements for CVD risk reduction at present. Currently, recommendations focus more on the naturally-occurring vitamins and other phytochemical antioxidants found in common dietary items. With emphasis being directed to the adequacy of the diet to provide needed antioxidants, this article explores the aspect of adequacy of the Mediterranean-type diet and dietary habits of inhabitants of this region. Collectively, the Mediterranean diet consists of food items that contain a number of antioxidants, and thus is likely to be adequate in providing a dietary level of antioxidants. Such dietary patterns should be preserved and promoted for the derived benefits to reduce the risk of CVD in the long run.

Keywords: antioxidants, health, lifestyle, nutrition, phytochemicals, vitamins

Introduction

Cardiovascular diseases (CVDs) are leading causes of death in many developed and developing countries, including the Middle East Region.^{1,2} Several studies revealed a role of low-density lipoprotein oxidation in the development of atherosclerosis. This has led to the thought that antioxidants can be helpful in protecting against and treating a number of CVDs.³ Dietary recommendations to reduce the risk of CVD have been directed toward reducing intake of saturated fat, trans fat, and cholesterol as well as to increase dietary fiber consumption. Such recommendations have promoted a dietary pattern that focuses on the consumption of diets rich in fruits, vegetables, whole grains, low-fat or nonfat dairy products, fish, legumes, poultry, and lean meats.⁴ Many epidemiological and population studies reported that antioxidant vitamins such as vitamin E, vitamin C, and beta-carotene may be beneficial to reduce the risk for CVD.⁵ Currently, there is an interest in assessing the value of many plant-based phytochemicals, such as carotenoids, catechins, and flavonoids, that exert an antioxidant effect to reduce the risk of CVD. A number of clinical studies reported the effects of antioxidant vitamin and mineral supplements on CVD risk.^{3,6-11} Data on the use of antioxidant supplements to reduce the risk of CVD showed inconsistent results. Thus, the question of whether or not supplemental antioxidant vitamins are effective still remains. Lack

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of solid evidence of beneficial effects of supplementation of antioxidant vitamins to reduce the risk of CVD would logically lead to reliance on naturally-occurring antioxidants of dietary sources. The purpose of this article is to provide a present-day stand on the issue of supplementing antioxidants in CVD and to explore the antioxidant compounds contained in the Mediterranean-type diet that form the basis of benefits to reduce the risk of CVD.

Results of clinical trials

Few clinical trials on antioxidant vitamin supplementation have been conducted. Data of these studies involved supplementation with vitamin E, beta-carotene, or vitamin C, either separately or in selected combinations of two or all three. The duration of these trials varied and involved patients with many CVDs and conditions. Outcomes under study included myocardial infarction, fatal and non-fatal coronary disease, changes in thickness of the intima-media of arterial wall, overall mortality due to ischemic heart disease, hemorrhagic and ischemic stroke, and all-cause mortality. Table 1 shows

that obtained results of conducted trials were varied; some studies showed beneficial effects,^{12–16} others did not prove to be beneficial,^{17–25} while others yielded adverse effects.^{26–28}

Critical appraisal and consensus

Recent articles and meta-analyses provided confirmation that antioxidant vitamin supplementation proved noneffective in CVD.^{29–31} A meta-analysis of 15 studies (seven studies of vitamin E, 50–800 IU; eight studies of beta-carotene, 15–50 mg) with 1,000 or more subjects per trial has been conducted to ascertain the effects of antioxidant vitamins on cardiovascular morbidity and mortality.³² This meta-analysis revealed the lack of efficacy for the different doses of the administered antioxidants in varied population groups. A computerized search and analysis of relevant studies on treatment with vitamin E showed no statistically significant or clinical importance to such supplementation.³³ Thus, it seems that clinical trials have failed to demonstrate a beneficial effect of antioxidant supplements on CVD morbidity and mortality. Another meta-analysis revealed that high doses of

Table 1 Summary of clinical trials showing beneficial, nonbeneficial, and adverse effects of antioxidant vitamin supplementation to female and male patients

Category	Subjects	Antioxidant(s)	Duration (years)	Outcome	Reference
Beneficial	F and M with coronary disease	Vitamin E, 400 or 800 mg	1.4	Decrease in MI	12
	M smokers with MI	Vitamin E, 50 IU	5.3	Reduction in MI	13
	F and M hemodialysis patients	Vitamin E, 800 IU	2	Decreases in MI, stroke and angina	14
	F and M with high cholesterol	Vitamin E, 182 mg + vitamin C, 500 mg	3	Reduced intimal progression in men	15
	F and M cardiac transplant patients	Vitamin E, 400 IU + vitamin C, 500 mg	1	No increase in intimal index	16
	F and M post-MI patients	Vitamin E, 300 mg (synthetic)	3.5	No effect on MI	17
Non-beneficial	F and M at risk of CVD	Vitamin E, 300 mg (synthetic)	3.6	No effect on MI, CVD death or stroke	18
	F and M with high risk of CVD	Vitamin E, 400 IU (natural)	4.5	No effect on CVD or mortality	19
	F and M diabetic patients	Vitamin E, 400 IU (natural)	4.5	No effect on CVD or mortality	20
	F and M patients	Vitamin E, 400 IU	3	No effect on intimal thickness	21
	Healthy males	Beta-carotene, 50 mg	12	No effect on MI, CVD or mortality	22
	F and M skin cancer patients	Beta-carotene, 50 mg	8.2	No effect on CVD mortality	23
	M smokers	Beta-carotene, 20 mg	6.1	No effect on all coronary cases	24
	M smokers	Beta-carotene, 20 mg + vitamin E, 50 mg	6.1	No effect on all coronary cases	24
	F and M with high risk of CVD	Vitamin E, 600 mg + vitamin C, 250 mg + beta-carotene, 20 mg	~5	No effect on CVD mortality	25
	M smokers	Vitamin E, 50 mg or beta-carotene, 20 g	6.1	Increase in stroke and CVD mortality	26
	M asbestos workers	Beta-carotene, 30 mg + retinol, 2,500 IU	5.5	Increase in all-cause mortality	27
Adverse	Postmenopausal women with CVD	Vitamin E, 800 IU + vitamin C, 1,000 mg	2.8	Higher all-cause mortality	28

Abbreviations: CVD, cardiovascular disease; F, female(s); M, male(s); MI, myocardial infarction.

vitamin E supplementation (greater than 150 IU/day) may progressively increase all-cause mortality.³⁴ Conclusions of this analysis created a stir among specialists in the field.³⁵ Thus, it seems likely that the debate over this subject will continue until concrete scientific evidence is found.

Many factors may have contributed to the lack of benefits of such supplementation so far. Conducted clinical studies (trials) differed in many respects with regard to subject populations studied (including those who are healthy), type and dose of antioxidant, single vitamin supplementation or cocktail, length of study, and study outcomes. Additionally, only known antioxidant vitamins were used, and their synthetic forms were used in some of the trials while their natural forms were used in others.³⁶ Also, subjects of these trials were followed-up for varied durations ranging from 1–12 years. Therefore, these factors make it difficult to fully assess the real value of supplementing antioxidants to reduce the risk of CVD. However, while these particular trials failed to provide evidence of beneficial effects, this would not nullify the role of oxidative mechanisms in the development of atherosclerosis.³⁶ More in vitro and in vivo investigations as well as sound experimentally controlled studies are needed. Future clinical trials ought to be conducted with a few, but known, variables to secure more reliable data. As antioxidant compounds differ quantitatively and qualitatively from one another, they should not be used in combination. For the purpose of medical practice, it is clear that existing data do not support prescribing the routine use of antioxidant supplements for the prevention and treatment of CVD.^{9,10,32,37,38} Thus, there is presently no scientific or medical basis to recommend individuals to take antioxidant vitamin supplements to reduce their risk of CVD.

Meanwhile, scientific evidence supports recommending consumption of a diet that is high in sources of antioxidants and other cardioprotective nutrients such as fruits, vegetables, whole grains, and nuts instead of antioxidant supplements to reduce the risk for CVD.^{39,40} Results of a meta-analysis suggested that increase in dietary intake of antioxidant vitamins has encouraging prospects for possible coronary heart disease prevention.⁴¹ In support of this view, it has been recently expressed that it may be misleading to focus on a single element of the diet, as if searching for a “magic bullet” for preventing a myriad of chronic diseases.⁴² Current recommendations included the intake of natural food sources of antioxidant nutrients, principally from a variety of plant-derived foods such as fruits, vegetables, whole grain products, and vegetable oils.⁴³ These recommendations were also among several that emphasized an active and healthy lifestyle for an

overall health benefit. With this being the prevailing view, future clinical trials should also consider the dietary antioxidant content in the overall scope of their design.

Antioxidants and the Mediterranean diet

With the lack of a solid recommendation for supplementing antioxidant vitamins to those who suffer from CVD or are at high risk for it, as well as to healthy individuals, emphasis is presently directed toward following a healthy diet and securing needed antioxidants from their natural sources.⁴⁴ Vitamins known for their antioxidant property are found in commonly consumed food items such as vitamin A, found in liver, dairy products, and fish; vitamin C, found in green peppers and citrus fruits; vitamin E, found in oils, sunflower seeds, and nuts. Selenium, a trace mineral that is believed to help in protecting cells from free radical damage, is found in Brazil nuts, meats, and tuna. Antioxidants are not just limited to known vitamins but also include a number of compounds that are capable of protecting against oxidative damage. Some of these compounds, known as phytochemicals, are currently being recognized, and it seems others are still to be discovered. Among the known phytochemicals are sulfur allyls, cysteine, and allicin (found in garlic, onions, chives, leeks, and scallions); sulforane, brassin, indoles, glucosinolates, isothiocyanate (found in broccoli, kale, brussel sprouts, cabbage, and cauliflower); terpenes and flavones (found in citrus fruits); flavonoids, ellagic, and quercetin (found in grapes, wine, and cranberries); flavonoids, polyphenols, and catechins (found in green and black teas); oleuropein and hydroxytyrosol (found in extra virgin olive oil); and lycopene (found in tomatoes and watermelon).^{45–47} Epidemiological studies have shown that diets rich in fruits, herbs, and spices are associated with a low risk for CVD.⁴⁸ Garlic, for example, contains a number of compounds, among which are antioxidants that can be beneficial to reduce the risk of atherosclerosis and with antiplatelet aggregation action.^{49–51} Dual-derived benefits of olive oil consumption include its content of a number of antioxidants and of monounsaturated fatty acids.⁵² Virgin olive oil is also rich in micronutrients,⁵³ and regular consumption of olive oil has been found to be conducive to longevity.⁵⁴ Individuals who commonly consume a diet that is high in monounsaturated fatty acids and high intake of garlic, onions, fresh fruits, and vegetables can benefit from the phytochemicals contained in such food items.⁵⁵ Realizing the beneficial roles of antioxidants in scavenging free radicals has recently led to the idea of establishing a database for their contents in food items.⁵⁶

The Mediterranean diet is a modern nutritional recommendation based on the traditional dietary patterns of Greece, Spain, and Southern Italy. It is characterized by proportionally high consumption of olive oil, legumes, unrefined cereals, fruits, and vegetables, with moderate to high consumption of fish. It also includes moderate consumption of dairy products (mostly cheese and yogurt), wine, and low consumption of meat and meat products.⁵⁷ The Mediterranean diet has been recognized by the United Nations Educational, Scientific and Cultural Organization (UNESCO) as being an intangible cultural heritage of many of the Mediterranean Sea basin countries, namely Spain, Portugal, Morocco, Italy, Greece, Cyprus, and Croatia, in December 2013.^{57,58} However, the diet is being followed by many people worldwide as a part of a healthy lifestyle.

The protective effects of antioxidants to reduce the risk of major diseases such as cancer and CVD have been the focus of many studies. As for breast cancer, oxidative stress was associated with its incidence, and antioxidants can combat such adverse effect.^{59,60} Dietary antioxidants were found effective to reduce the risk of breast cancer.^{61–64} Antioxidants of the Mediterranean diet were described as the choice for cancer prevention in Europe.⁶⁵ Benefits of the Mediterranean-type diet were reported in a study that compared many of the risks of CVD and mortality between railroad workers in the US and Italy, for 25 years. Dietary patterns in Italy were implicated in reduced risks for CVD and mortality.⁶⁶ Ever since then, the Mediterranean diet has been viewed as the most consistently beneficial measure with respect to risks of CVD^{67–69} and as a model to provide protection against coronary heart disease.⁷⁰ An energy-unrestricted Mediterranean diet that was supplemented with extra virgin olive oil was efficient in the primary prevention of CVD.⁷¹ Thus, this dietary pattern has been characterized as being cardioprotective.⁵⁵

Concluding remarks

Collective data of all types of studies are inconsistent and do not provide solid evidence to recommend supplementation with one or more antioxidant vitamin as being beneficial in protection against CVD or reducing its risk factors. Until more clinical trials are conducted and become sufficient in number for evidence-based analysis to indicate a solid benefit for supplementation with antioxidants, the current view is not to administer supplements in medical practice. This means that emphasis would be directed toward aspects of healthy diet and lifestyle. With our current scientific knowledge about antioxidants and their food sources, increased consumption of such food items would make a practical recommendation for

improving health. While well-controlled scientific research continues to elucidate mechanisms of action for particular antioxidant compounds, individually or in combinations, it is also important and practical to view dietary habits and patterns as a “whole package” and assess their real combined value. As far as food-based antioxidants are concerned, the Mediterranean dietary patterns can be viewed as mostly adequate. However, future studies on dietary antioxidants can utilize the new concept of “total antioxidant capacity”^{72–74} for attaining reliable and quantifiable data for consumed food items. This approach would prove valuable nutritionally and in relation to aspects of public health. Based on what has been explored herein, the Mediterranean diet has many food items that furnish adequate amounts of a variety of antioxidants, whether known vitamins or phytochemicals. A multicountry effort has been launched toward devising a Mediterranean diet pyramid and in promoting this diet type.⁷⁵ In this context, it should be mentioned that the wide spread of fast food restaurants all over the world and the menus they offer can be viewed as a danger to the prevalent Mediterranean-type dietary pattern, as they are high in calories and fat and do not provide significant plant-derived antioxidants. Thus, it is of significance to inhabitants of the Mediterranean Sea basin countries in the Middle East as well as those who follow their diet worldwide to preserve this dietary pattern. In this respect, this diet type should also be promoted for best benefits to reduce the risk of CVD and for an overall healthy existence.

Disclosure

The author reports no conflicts of interest in this work.

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