

Preventing disease with antioxidants

SBU Summary and Conclusions

Introduction

The oxygen which people need to survive can also harm cells. This occurs when certain chemical processes in the body lead to the formation of so-called oxygen free radicals. Research results have shown that these oxygen free radicals contribute toward aging in humans and are involved in the onset of many diseases, eg, arteriosclerosis and cancer.

Numerous substances are found in nature and in the body which function as protective agents against oxygen free radicals. These substances are commonly referred to as antioxidants.

Some of the more well-known and researched antioxidants include vitamins C and E and beta-carotene, a preliminary stage of vitamin A. Along with many other antioxidants, these natural components are found in food and beverages. Vitamin C and beta-carotene are found mainly in vegetables, roots, fruits, and berries. Vitamin E is one of many so-called tocopherols and is found in, eg, vegetables and fruits, bread, wheat germ, vegetable oils, and fish.

Selenium and ubiquinone, or Q10, and flavonoids are noteworthy substances in antioxidant research. Selenium is part of an enzyme that helps defend against free radicals. This element appears in soil and is taken up by plants and animals, and is found in, eg, fish, meat, milk products, and eggs. Q10 is a substance formed mainly in the body and has antioxidative characteristics. Flavonoids are growth substances, several of which are antioxidants. They are found in apples, onions, red wine, and tea.

Some research findings suggest that people having diets rich in fruit and vegetables are at lower risk for cancer and myocardial infarction. This may be a result of the high level of antioxidants in such food, but has not been confirmed scientifically. Other beneficial substances in fruits and vegetables may also be a reason. Another explanation may be that individuals who attempt to maintain a well balanced diet are also health conscious in other ways, and may exercise regularly, avoid smoking, and may not abuse alcohol.

Given the observed association between diet and health, one may be inclined to presume that it is possible to reduce the risk for disease through a diet rich in antioxidants or by complementing one's diet with antioxidant tablets, eg, particular vitamins, beta-carotene, selenium, and Q10. There is widespread belief that extra intake of antioxidants is beneficial. This, in turn, has led to the widespread use of antioxidative products. The annual sale of vitamin and mineral supplements is estimated to exceed 600 million Swedish kronor (SEK) in Sweden.

The scientific literature on antioxidants is extensive and not easily reviewed and interpreted by the public or by researchers, physicians, and other health professionals.

The following review was initiated jointly by SBU and Sweden's National Institute of Public Health to present the known facts about the opportunities for using antioxidants to help prevent serious disease.

Methodology

The potential association between diet/dietary supplements and illness is based largely on hypotheses and basic research concerning cells, but also, to a very limited extent, on clinical studies.

It is difficult to develop reliable knowledge on the association between health status and diet, including supplementary antioxidants. During a followup period that is sufficient in length to study the differences in the incidence of various diseases, dietary patterns and other lifestyle factors may change substantially among the subjects included in a study.

Numerous epidemiological studies have been conducted on the potential association between the intake of antioxidants and the prevalence of various diseases. In most of these studies, researchers have used questionnaire surveys to determine the dietary habits of certain population groups. The dietary habits reported by different individuals, and their dietary intake, has then been related to the extent to which they are affected by various diseases much later in life. In this way, it may be possible to identify certain associations between diet and health, but the estimates concerning antioxidant intake may be uncertain for many reasons, eg, the design of the questionnaire survey. These studies are much less certain when the results are based on official statistics of dietary intake among a particular population and the prevalence of various diseases in that population. Hence, the different methods used to analyze statistical associations and methods used to study dietary composition and how it influences the onset of disease have been given particular attention in this report.

In many other types of studies, researchers have directly measured the antioxidant levels in subjects by analyzing blood or tissue, eg, in nails or fatty tissue. These test results can then be used for theoretical estimates of expected disease rates and for later comparisons with actual disease rates. Studies of this type may also be affected by sources of error and are therefore of limited scientific value. For example, the subjects may change their dietary intake over time, and sporadic testing does not necessarily reflect continual levels of antioxidants. Some types of studies also require samples to be preserved for an extended period without a change in sensitive substances.

Some studies have examined the association between antioxidants and risk factors for a particular disease, but not the association between antioxidants and actual disease. Such studies attempt to estimate the theoretical risk for a particular group of individuals to be affected by a particular disease in relation to their intake of antioxidants. This indirect methodology yields evidence which is weaker than that gained from studies which register the actual rates of disease or death.

The randomized controlled trial (RCT) is the type of study which yields the most valuable scientific evidence. In these studies, a large number of individuals are

randomly distributed to two different groups, where one group receives a high, constant dose of antioxidants and the other group receives placebo, ie, an inactive substance. Only a few such studies published in recent years have analyzed the disease prevention capacity of antioxidants. None of these studies have analyzed the importance of antioxidants in food, but all examined the effects of synthetically produced antioxidants as dietary supplements. A criticism of these studies is that they address specific groups of individuals, eg, smokers and asbestos workers, but not the general population.

Scope of the review

Numerous substances have antioxidative characteristics. This review is limited to certain substances, namely vitamin C (ascorbic acid), vitamin E (tocopherol), beta-carotene (a carotenoid which is a precursor to vitamin A), and selenium, a basic element.

The project group distinguished between studies which analyzed the importance of antioxidants that occur naturally in food, and the studies which specifically examine one or more of these substances as a supplement to the daily diet.

The review is based on all scientific studies published from 1989 through 1996. Over 5 000 studies appear in the scientific literature, whereof approximately 1 300 were found to be relevant to the hypothesis. Approximately half of these consisted of reviews of previously published studies in the field. The remaining 550 (approx.) studies were thoroughly reviewed according to a predetermined protocol. A three-level scale (high, moderate, or poor scientific quality) was used to judge the scientific quality of the various studies. Only a few studies were found to be of high scientific quality, mainly because the methods used to collect data on dietary habits contained major sources of error.

In addition to the antioxidants mentioned above, the report also reviews the more limited scientific facts available concerning growth substances, eg, flavonoids and carotenoids other than beta-carotene, and Q10 (ubiquinone).

Q10 is formed in the body and is necessary for metabolism. The ability of the body to produce this substance appears to decline as people age. This also appears to happen when the body is subjected to extra stress. Hence, Q10 has received attention as an antioxidant, which theoretically should be able to prevent disease and increase physical capacity, mainly in individuals who are active in sports. The limited scientific literature in this field has not shown that Q10, as a dietary supplement, prevents the onset of disease.

Carotenoids are a large group of growth substances and include carotenes, lycopene, and xanthophyll. The findings on beta-carotene are presented in greater detail below. No studies have demonstrated the possible association between disease prevention and the intake of extra supplements of other carotenoids. However, several studies have related the progress of disease to the estimated intake of carotenoids in the diet, or their concentration in blood plasma. Some observations suggest a preventive effect. In the

absence of a sufficient number of studies in the field, the results must be judged as uncertain.

Like the carotenoids, the flavonoids are a large group of substances widely present in the plant world. People consume flavonoids via, eg, fruits, vegetables, red wine, and tea. The dietary habits in the Mediterranean countries, with a higher daily intake of flavonoids than in Northern Europe, have been suggested as an explanation why mortality from cardiovascular disease is less common in Southern Europe than in Northern Europe. Numerous epidemiological studies have attempted to relate the estimated intake of flavonoids to cardiovascular disease or cancer rates. The results are contradictory, hence the conclusions cannot be confirmed.

The report

This report consists of two volumes. Volume 1 presents background information and facts from scientific studies on the role of antioxidants in preventing cardiovascular diseases, diabetes, eye diseases, neurological diseases, infectious diseases, and rheumatoid arthritis. Volume 2 presents current scientific facts about the possible role which antioxidants play in preventing cancer.

It should be observed that this report addresses scientific information about the role of antioxidants in preventing diseases in humans. It addresses only briefly the effect of antioxidants on the course of disease. It should also be noted the absence of scientific studies does not necessarily mean the absence of effects, but only that no effects have been confirmed.

Summary of results

Cardiovascular Diseases

Blood lipids

The administration of high doses of vitamin C can reduce the level of total cholesterol in individuals with elevated cholesterol values and with low concentrations of vitamins in blood plasma. In other cases, the effects of vitamin C have not been confirmed. An increased intake of vitamin E has no effect, and the data on beta-carotenes and selenium is too limited to provide evidence for definite conclusions.

Blood pressure

There is a relationship between higher intake of vitamin C and lower blood pressure in healthy individuals. Studies of the relationship between blood pressure and vitamin E, and selenium respectively show contradictory results. There are no studies on beta-carotene and prevention of elevated blood pressure.

Blood clots

A few studies address the potential which antioxidants have to limit the body's ability to form blood clots. Results from one study where subjects were given high doses of

antioxidant supplements with food suggest that the tendency for blood cells to clot is reduced.

Myocardial infarction

Large ecological studies, ie, studies which compare large population groups, have shown that the risk for morbidity and mortality is lower among people with a higher intake of fruits and vegetables, including dietary supplements. These studies have also shown that low intake and low blood levels of vitamin C, vitamin E, and beta-carotene are associated with an increased risk for myocardial infarction. Interpreting these associations is complicated by the fact that other known factors in food, such as the saturated fat content, influence the risk for myocardial infarction, and that fruit and vegetables may have beneficial characteristics along with antioxidants. These studies have not shown an association between myocardial infarction and the intake of selenium.

Other epidemiological studies, with fewer participants but with somewhat more reliable methodology, so-called case control studies, have yielded varying and somewhat contradictory results. Many of these studies do not show that a higher intake of antioxidants would reduce the risk for myocardial infarction. A meta-analysis based on 15 cohort studies suggests that there is an association between a high intake of beta-carotene or other carotenoids, vitamin C, and vitamin E and a low risk for cardiovascular disease. When the results of all cohort studies are jointly analyzed, the results show that each of these three antioxidants may potentially offer some protection against cardiovascular disease. All of these studies are, however, affected by the uncertainty that is associated with studies where participants are recruited voluntarily. Furthermore, meta-analyses have certain methodological deficiencies, which means that they may not be representative of the population in general. This, and the fact that these studies relate disease onset to data collected many years ago, and that many studies have not yielded unequivocal results, makes it difficult to draw definitive conclusions concerning the role of antioxidants in preventing cardiovascular disease.

In regard to antioxidants as a dietary supplement, the associations observed above cannot be confirmed based on the results of several randomized studies. Six different interview studies have been conducted and published. The substances given as dietary supplements mainly included beta-carotene and vitamin E. Four of these studies come from the United States, one comes from Finland, and one from China. One of the studies from the United States included only persons at high risk for cancer, namely smokers, early smokers, and asbestos workers. The Finnish study also addressed smokers. None of these studies, which included a total of 100 000 persons, were able to show a reduction in the risk for myocardial infarction. The Finnish study, which investigated beta-carotene and vitamin E, reported more cases of fatal cerebral hemorrhage in the group receiving vitamin E.

Some studies of myocardial infarction also reported on stroke cases. Overall, the results do not suggest that antioxidants as a dietary supplement impact on the risk for stroke. An exception is the Finnish study mentioned above, where vitamin E increased the risk for fatal cerebral hemorrhages in smokers.

Conclusions

The studies are based on various methods which attempt to determine the association between antioxidants and cardiovascular disease, and have shown that a low intake of beta-carotene, vitamin C, and vitamin E are associated with an increased risk for cardiovascular disease, mainly myocardial infarction. However, several randomized studies show that beta-carotene and vitamin E, as dietary supplements, do not have this effect. To the contrary, negative effects of dietary supplements have been noted. Regarding selenium and cardiovascular disease, the data are insufficient to enable reliable conclusions. The scientific literature does not support the hypothesis that antioxidant supplements to a well-balanced diet prevent cardiovascular disease.

Diabetes

A Finnish study has shown that people with low levels of vitamin E in blood plasma are at increased risk for diabetes. However, there are no controlled studies to show that vitamin E supplements or other antioxidants can prevent diabetes.

Conclusions

There is no scientific evidence to show that diabetes can be prevented by antioxidant supplements.

Eye Diseases

Cataracts

Data from experimental studies suggest that oxidative tissue injuries, ie, injury from oxygen free radicals, can play a role in the onset of cataracts. Hence, it is theoretically possible that disease could be prevented by antioxidants. Studies to date have shown contradictory results or no preventive effects. The only published randomized study shows that supplements of vitamin C alone or a combination of beta-carotene, vitamin E, and selenium have no preventive effects.

Macular degeneration

This disease is the most common cause of blindness after the age of 65 years. In experimental studies, researchers have observed an association between the disease and antioxidants. However, no studies show that antioxidants can prevent disease. The results from some studies suggest that a high intake of vegetables rich in the carotenoids lutein and zeaxanthin (which are found in the macula) can reduce the risk for developing a serious form of the disease.

Conclusion

The scientific studies conducted to date in this field are insufficient for drawing conclusions on how cataracts or macular degeneration can be prevented by antioxidants.

Neurological Diseases

Parkinson's disease

Epidemiological studies published to date do not show that antioxidants prevent Parkinson's disease, even though one study demonstrated that a high consumption of

vegetables was associated with a lower incidence of the disease. There are no clinical studies addressing the ability of antioxidants to prevent or delay the onset of Parkinson's disease. However, one randomized study has shown that vitamin E has no effect on the deterioration of the patient's condition in early stages of the disease.

Multiple sclerosis

Biochemical analyses of blood plasma, blood cells, and spinal fluid suggest that oxygen free radicals may influence this disease. The scientific literature addressing antioxidants and the prevention of multiple sclerosis is limited and of poor quality, and does not permit conclusions concerning the potential preventive effects of antioxidants.

Alzheimer's disease

Analyses of various areas in the brain among individuals with Alzheimer's disease have shown signs of increased oxidative stress, ie, increased presence of oxygen free radicals.

A few studies have also shown that antioxidant levels in blood plasma are lower in individuals with Alzheimer's disease compared to healthy individuals. This may be a result of poorer dietary habits in patients with the disease rather than a factor which influences the onset of the disease. Two published studies on dietary habits attempted to analyze the association between antioxidants and Alzheimer's disease. In both of these studies, the authors rely on weak scientific methodology, making it impossible to draw conclusions.

In the only intervention study reported in the field, the authors found that supplements of vitamin E may possibly delay the progression of the disease.

Conclusions

Concerning the three neurological diseases reviewed, the scientific literature to date is too limited to determine the potential role which antioxidants play in preventing disease.

Infectious Diseases

In experimental basic research, antioxidants have been shown to play a role in the immune defense, and that the inflammation caused by infection increases oxidative stress. Given this background, antioxidants can be thought to have preventive effects against infections or the symptoms which they generate. Two studies address vitamin supplements and trace elements in healthy older people. One of the studies reported signs of improved immunological defense and a lower number of infection days among those who received antioxidant supplements. The second study was unable to demonstrate such effects. Studies in which supplements of single antioxidants were given suggest a preventive role for beta-carotene and vitamin E. Vitamin C is the most studied antioxidant. Several studies have shown that persons who regularly take vitamin C supplements in high doses do not reduce their risk for colds, but symptoms may be somewhat milder and subside somewhat earlier. Preliminary data also suggest that the risk for infection from *Helicobacter pylori* in the mucous membrane of the stomach is lower with a high intake of vitamin C.

Conclusions

With one exception, there is weak scientific evidence for determining whether infectious disease can be prevented by one or more antioxidants in the diet, or by dietary supplements. The exception is vitamin C, which in large daily doses appears to ameliorate, but not prevent, colds.

Rheumatoid Arthritis

Experimental studies have shown that in rheumatoid arthritis the inflammatory process in the joints is accompanied by increased oxidative stress in the tissues. This suggests a potential role for antioxidant protection. Earlier studies have also shown lower levels of selenium in blood plasma in patients with rheumatoid arthritis compared to healthy individuals. A Finnish epidemiological study was, however, unable to demonstrate an association between plasma levels of selenium and the risk for developing rheumatoid arthritis. Other studies in the area have addressed antioxidant levels during ongoing disease and treatment with antioxidants. These studies have not provided convincing evidence concerning the role of antioxidants.

Conclusions

Due to a lack of factual evidence, no conclusions can be drawn concerning the potential preventive role of antioxidants in rheumatoid arthritis.

Cancer

The scientific literature on antioxidants and various cancers is extensive. Nearly 3500 scientific articles published from 1989 through 1996 were identified in various databases. Approximately 3100 of these studies contained mainly experimental data or were overview articles without original data. The remaining 400 studies were reviewed in detail. Volume 2 of this report presents these studies, grouped in 16 chapters, with an assessment of their scientific quality. Some of the studies are limited to one type of cancer while others investigate several types concurrently.

Only a small number of all reviewed studies were found to be of high scientific quality. Nearly half of all studies were of such low scientific quality that it was not possible to use the results in an overall assessment of the role of antioxidants. The literature is too limited and/or of insufficient quality to be able to draw conclusions concerning the possible association between antioxidants and tumors in the brain, liver, biliary tract, pancreas, pituitary, kidneys, urinary tract, bladder, and skin. Concerning several other tumors, general conclusions can be drawn, and in some cases an association appears to exist between a lower incidence of cancer and high consumption of fruits and vegetables, and specific antioxidants in food.

Cancers Having Some Association With Fruits/Vegetables/Antioxidants

Head and Neck Cancer

Sixteen of 40 articles were found to be of sufficient scientific value to draw conclusions on the association between antioxidants and cancer in the head and neck. The assessed literature offers no convincing support for the hypothesis that a high intake of beta-carotene, vitamin C, or selenium would result in a reduced risk for cancer in the head and neck. The studies that investigated vitamin E supplements are more difficult to

interpret, and provide insufficient support for positive effects. The studies which investigated the effects of fruits and vegetables have demonstrated some protective effects. In the early stages of cancer in the mouth (leucoplakia), there is some indication that supplements of beta-carotene, and possibly vitamin E, may have beneficial effects.

Esophageal cancer

Ten of 26 articles were found to be of sufficient scientific value for drawing conclusions on this type of cancer. These studies do not lend support to extra supplements of single antioxidants as a means to reduce the risk for cancer of the esophagus. However, high consumption of fresh fruits, and possibly vegetables, may protect against the onset of this type of cancer.

Stomach cancer

Twenty-eight of 42 studies were found to be of moderate to high scientific quality. Overall, they offer some support that abundant antioxidants in diet, and high consumption of fresh fruits and vegetables, can reduce the risk for stomach cancer. There are no confirmed findings demonstrating the protective effects of a particular antioxidant.

Colon cancer

Twenty-six of 42 articles were found to be of moderate scientific quality. They provide no reliable evidence that the risk for developing cancer in the colon can be prevented by abundant intake of antioxidants in the diet. However, they provide some support that a high intake of vegetables, but not fruit, has some protective effects. It may possibly be the quantity of fiber and not the antioxidants in vegetables which has protective effects. There are no confirmed findings demonstrating the protective effects of a particular antioxidant.

Cancers Having no Association With Fruits/Vegetables/Antioxidants

Lung Cancer

Thirty-one of 49 articles addressing this form of cancer were found to be of high or moderate scientific quality. They provide little support that an abundant dietary intake of vitamin C or vitamin E would reduce the risk for lung cancer. There are no confirmed findings demonstrating the protective effects of high consumption of fresh fruits and vegetables against this form of cancer. Dietary supplements of beta-carotene may carry the risk for increased mortality in smokers. The results from studies concerning selenium supplements in the prevention of lung cancer are difficult to fully assess.

Breast cancer

Twenty-nine of 47 articles in this field are of high or moderate scientific quality. These studies do not provide a clear understanding of the potential preventive effects of antioxidants or of fruits and vegetables as regards breast cancer. The four studies that were found to be of high scientific quality do not support previous assumptions that an abundant intake of fruits and vegetables in the diet would protect against breast cancer.

Gynecological cancers

Fifteen of 32 published studies addressing antioxidants and cancer in the ovaries, uterus, and cervix were found to be of moderate scientific quality. These studies do not provide

sufficient grounds for reliable conclusions concerning the preventive effects of fruit and vegetables or antioxidants in other forms. However, there is some indication that beta-carotene in the diet offers some protection against gynecological cancers.

Prostate cancer

Twenty-one of 31 studies form the basis for conclusions on the relationship between antioxidants and cancer in the prostate gland. Four of these studies are intervention studies of moderate scientific quality. Predominantly, the documentation suggests that neither fruits, vegetables nor antioxidant supplements can prevent prostate cancer.

General conclusions regarding cancer

It is probable that a high intake of fruit and vegetables and other antioxidants in food can prevent certain cancers, primarily those which originate in the gastrointestinal tract. Whether this effect depends on antioxidants in food, or if fruits and vegetables contain a harmonious combination of active substances, or if there are other biological effects from these food substances, cannot be determined from these studies.

There is no unequivocal support that antioxidants as dietary supplements prevent cancer. Evidence from randomized trials have the greatest scientific value. A favorable effect of antioxidants on cancer mortality (particularly from stomach cancer) was noted in only one randomized study. This study was conducted in an area in China where malnutrition was widespread. However, no positive effects on cancer incidence have been reported in the randomized studies conducted in the United States and Finland. While alphanatocopherol supplements have no impact on the risk for cancer, beta-carotene supplements were clearly associated with an increased risk for lung cancer in two of the high quality studies.

- Assessment of the scientific literature shows that a dietary intake which includes an ample supply of antioxidants, mainly fruits and vegetables, may help prevent a variety of serious diseases.
- However, there is no scientific evidence to show that supplemental antioxidants, beyond those found in a balanced diet including fruits and vegetables, would prevent disease. Hypotheses presented in this field have yet to be scientifically verified.
- Controlled, scientific studies have shown that high doses of beta-carotene and vitamin E supplements have caused serious negative effects in smokers.
- Methods used to measure dietary habits and the content of antioxidants in food are often unreliable. Hence, these methods must be improved before conclusions can be drawn from studies relating antioxidants to disease.