

What Are the Effects of Taking Vitamin C and E Supplements on Patients with Risk Factors for Atherosclerosis and Associated Hypertension?

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Citation

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Abstract

INTRODUCTION

Atherosclerosis and associated hypertension is the number one cause of death facing developed societies today. Numerous treatment plans and lifestyle modifications have been suggested in order to combat the disease, but the number of deaths due to cardiovascular events continues to rise. It is the job of the healthcare provider to continue to explore treatment options for patients in order to prevent premature disability and ultimately, premature death due to this disease.

There has been significant evidence suggesting that antioxidants can play a role in the prevention of aging and its inevitable associated health problems. Vitamins C and E have been a particular focus of interest due to the mechanisms of action that each have in the body. "Mechanistic studies have demonstrated a role of vitamin C in maintaining the normal production and biological activity of endothelium-derived nitric oxide which plays a role in vascular tone and reactivity (1)." These studies stemmed from analysis of the Dietary Approaches to Stop Hypertension (DASH) trial. The DASH diet is rich in vegetables, fruits, low fat dairy foods and reduced saturated and total fat intake. "Vitamin E has been proposed to have a role in preventing or reversing atherosclerosis by inhibiting oxidation of low-density lipoprotein (2)." Therefore, could vitamin C and E supplementation lead to a decrease in the incidence and/or prevention of atherosclerosis and hypertension?

BACKGROUND

Atherosclerosis is a process that occurs in humans over a period of many years. Patients may have clinical evidence of the disease in the form of hypertension or hyperlipidemia.

While this may be the initial presentation of the disease, it sometimes manifests itself in the form of an acute cardiovascular event such as a myocardial infarction, stroke, angina, claudication, gangrene, mesenteric ischemia, or sudden cardiac death. Other patients may never have clinical manifestations of the disease.

Initiation of atherosclerosis begins with a "fatty streak" as the initial lesion. This is a collection of lipoproteins that form in the intima of blood vessels throughout the body. This occurs more readily in those patients with hypercholesterolemia and consists mostly of low density lipoprotein (LDL) particles. This collection of lipoproteins leads to a local inflammatory response which signals leukocytes to accumulate at the site. This signals early formation of atherosclerotic lesions. These lesions are most likely to form in areas of high laminar shear forces, such as branch points of arteries. Leukocytes then embed themselves into the lesion, triggering cytokines such as interleukin 1 and tumor necrosis factor α .

Once the leukocytes are present, the formation of foam cells begins. Foam cells are essentially cytoplasm filled with lipid droplets. Foam cell formation indicates the fully formed "fatty streak" which can then lead to formation of an atheroma. Smooth muscle cells from the media migrate and accumulate into the expanding intima where extracellular matrix is laid down. This forms the bulk of advanced lesions. As these lesions continue to advance, breaks in endothelial integrity occur, causing injury to the site of the vessel. At this point, platelets are activated and begin to adhere to the site of injury causing a fibrotic response. Microvascular networks then begin to develop at the site, possibly leading to rupture and focal hemorrhage. This can

lead to thrombosis, thus blocking the vessels and disturbing blood flow to downstream organs. Thus, the occurrence of adverse cardiovascular events as mentioned.

Major risk factors for atherosclerosis include hypertension, cigarette smoking, low HDL cholesterol, diabetes mellitus, family history of CHD, age >45 years in men, age >55 years in women, obesity ($>30\text{kg/m}^2$), physical inactivity, atherogenic diet, and other emerging risk factors. "A wealth of epidemiologic data support a relationship between hypertension and atherosclerotic risk, and extensive clinical trial evidence has established that pharmacologic treatment of hypertension can reduce the risk of stroke, heart failure, and CHD events (3)." Therefore, avoiding these risks is the best information to give to patients regarding prevention of these associated sequelae.

Hypertension, like atherosclerosis, is a process that occurs in humans due to a variety of causes. Various factors are involved in the regulation of arterial pressure. The first factor involved is intravascular volume. As intravascular volume expands, this causes resistance from the walls of the arteries. Arteries are expandable in order to correct for this increase in pressure. However, with age, hardening of the artery walls occurs due to various causes and this auto-correction diminishes to increase the pressure.

The second factor involved is the autonomic nervous system. This system maintains cardiovascular homeostasis. Actions include adrenergic reflexes to modulate blood pressure over the short term, hormonal and volume-related factors, circulating catecholamine concentrations, and baroreflexes. The three endogenous catecholamines are norepinephrine, epinephrine, and dopamine. Release of these chemicals is triggered by neuron stimulation during adrenal stimulation (stress on the body). Response of baroreflexes occurs in response to stretch-sensitive receptors in the carotid sinuses and aortic arch. Increased firing occurs with increases in arterial pressure, resulting in a decrease in sympathetic outflow and subsequent decrease in arterial pressure. This allows for pressure regulation on a minute-to-minute basis.

The third factor controlling blood pressure is the renin-angiotensin-aldosterone system. This contributes to the regulation of blood pressure via the vasoconstrictor properties of angiotensin II and the sodium retaining properties of aldosterone. Renin secretion is stimulated by three variables; decreased NaCl transport in the ascending limb of the loop of Henle, decreased pressure or stretch

within the renal afferent arteriole, and sympathetic nervous system stimulation of renin-secreting cells. Renin cleaves angiotensinogen to produce angiotensin I. Angiotensin I is then converted to angiotensin II via angiotensin-converting enzyme (ACE). Blockage of ACE is a common pharmacologic mechanism used to decrease blood pressure.

Vascular resistance and compliance of resistance arteries are also important in determining arterial pressure. As the lumen size of the blood vessels decreases, either due to vasoconstriction or a build up of plaque on the walls of the arteries, resistance to the flow of blood increases. Vessels that are highly elastic can accommodate the increase in resistance. However, buildup of plaque in the vessels makes them stiff and less compliant to increased pressures. As mentioned before, baroreceptors are found at the carotid sinuses and at the aortic arch. Thickening of the vessel walls decreases the baroreceptor's sensitivity to stretch. Therefore, blood pressure regulation by this mechanism is greatly impaired and the patient becomes hypertensive.

A number have studies have demonstrated significant inverse relationships between vitamin C and blood pressure. Vitamin C plays a large role in antioxidant activity, promotion of non-heme iron absorption, carnitine biosynthesis, conversion of dopamine to norepinephrine, and the synthesis of peptide hormones (3). It also plays a role in maintaining the normal production and biological activity of endothelium derived nitric oxide. Nitric oxide plays a role in vascular tone and reactivity which ultimately affects blood pressure. This mechanism is the basis for the proposed hypothesis that supplementation of vitamin C can decrease blood pressure.

Vitamin E has also been shown to have anti-hypertensive and lipid-lowering properties. Vitamin E is an antioxidant and plays a role in inhibiting oxidation of low-density lipoproteins (LDL) and polyunsaturated fats in membranes. Oxidation of LDL increases atherogenesis, which induces the accumulation of lipids and cells in the vessel wall. Therefore, inhibition of this process may inhibit atherosclerosis. Furthermore, vitamin E inhibits smooth muscle cell proliferation and platelet aggregation, two crucial steps in the development of plaques. Improvement in arterial compliance has also been shown to be an effect of vitamin E (4). It also inhibits prostaglandin synthesis and the activities of protein kinase C and phospholipase A₂ (3). These mechanisms are the basis for the proposed hypothesis that supplementation of vitamin E can decrease blood

pressure and reduce atherogenesis.

Based on the physiology described above, studies have been done to determine this correlation. Can supplementation of vitamin C and E have an effect on the prevention and/or treatment of atherosclerosis and hypertension?

METHODS

In choosing research articles, a search was done in the Google search engine for the word “antioxidants” and “atherosclerosis.” This brought up a number of results, one of which was an article from Nutrition Journal called “Vitamin C in Plasma is Inversely Related to Blood Pressure and Change in Blood Pressure During the Previous Year in Young Black and White Women.” The level of evidence in this article is level 2 since it is a cross-sectional analysis that follows a group of women over a period of time, comparing multiple variables. The article is from 2008 and is up to date.

The second article, “Six Year Effect of Combined Vitamin C and E Supplementation on Atherosclerotic Progression: The Antioxidant Supplementation in Atherosclerosis Prevention Study,” was found in a section at the bottom of the first article entitled “related articles.” It is from the journal, Circulation, and is a randomized controlled clinical trial analyzing the effect of vitamin C and E supplementation on progression of atherosclerosis. This article is level 1 evidence supporting the question. It was written in 2003.

Both of these articles were found by searching on the Google search engine. The first search was done by searching for the words “vitamin C” and “hypertension.” The second search was done by searching for the words “vitamin E” and “hypertension.” Inclusion criteria that were used in choosing the articles included straightforward language, appropriate level of evidence, and recent date. The language of each of these articles is straightforward and easy to understand. The question being asked is a question of therapy and so is answered adequately by a level 1 randomized controlled clinical trial. The two articles chosen are fairly recent. Both articles are English-written articles, owing to their accuracy.

DISCUSSION

The article, “Vitamin C in Plasma is Inversely Related to Blood Pressure and Change in Blood Pressure During the Previous Year in Young Black and White Women” asked the question: Does plasma ascorbic acid level have any relation to blood pressure and/or change in blood pressure of 18-21 year old female patients (1)? A cross-sectional analysis was performed on 18-21 year old female patients

involved in a larger longitudinal multi-center study.

This study was performed on a group of patients who were part of a larger study by the National Heart, Lung, and Blood Institute. This larger Growth and Health study was being done to investigate the development of obesity in adolescent females and the correlating environmental, psychosocial, and cardiovascular disease risk factors. Patients were recruited from Richmond, CA, Cincinnati, OH, and Washington, DC areas. By the time adequate analysis was done at the end of the study 242 participants, 155 black females and 87 white females were still eligible. Those that were not included in the study were left out due to refusal to participate, pregnancy, or refusal to have an additional procedure.

The study was done to find a correlation between plasma ascorbic acid levels and blood pressure. Blood pressure readings and plasma ascorbic acid levels were taken at the beginning of the longitudinal study when the participants were 8-11 years of age. Each participant’s blood pressure was taken seated after the patient was in that position for 5 minutes. Three consecutive readings were taken on the same arm with at least 30 seconds between each reading. The second and third readings were averaged and this value was used. This protocol was used to measure the blood pressure at the initial visit and at the 9th and 10th annual visits. These visits were separated by one year.

The second factor, plasma ascorbic acid, was also measured at the initial reading and at the 10th annual visit. Each patient fasted for 12 hours prior to the blood draw. This measurement was done using the 2, 4-dinitrophenylhydrazine method. Blood samples were stabilized with 10% metaphosphoric acid and frozen within 4 hours of collection. Analysis of collections was done within 6 months of the blood draw.

Other factors were incorporated into this study in order to take into account anthropometry, socioeconomic and lifestyle variables, and dietary variables. At the 10th visit, each patient was weighed without shoes while wearing just a gown. Height was also assessed. Both height and weight were measured twice and BMI in kg/m² was calculated. Information on socioeconomic and lifestyle factors was assessed at the 10th visit as well using a standard questionnaire administered by the researchers. This questionnaire included information on smoking, alcohol consumption, physical inactivity, pregnancy history, and oral contraceptive use. Smoking was measured as number of

cigarettes smoked per month and alcohol consumption was measured as number of 12 oz. beers and/or 6 oz. glasses of wine per month. Physical inactivity was assessed by the number of hours per week of television watched. An assumption was made that the more hours per week of television watched, the less physical activity the patient participated in. Dietary variables were also taken into account and were determined at the 10th visit by using 3 day dietary records for two consecutive weekdays, and one weekend day. These records were then reviewed by a dietitian and analyzed for nutrient composition.

Statistical analysis of the data was done using unpaired two-tailed t-tests. Mean systolic and diastolic blood pressure was analyzed and adjusted for race, BMI, education, and intake of fat and sodium. Other covariates were taken into account and considered as possible confounders such as intake of total energy, potassium, calcium, dietary antioxidants and fiber, pregnancy history, use of birth control pills, smoking, alcohol intake, and number of hours of television watched per week. None of these variables proved to have any significant impact on the outcome of the results.

When analyzing the results of this study, it was found that there was a significant inverse linear trend in both systolic and diastolic blood pressure compared to plasma ascorbic acid concentration. These linear trends remained significant even after adjusting for BMI, race, education, and dietary fat and sodium intake. Patients with the highest plasma ascorbic acid concentration had a 4.66 mmHg lower systolic blood pressure and a 6.04 mmHg lower diastolic blood pressure than the patients found to have the lowest plasma ascorbic acid concentration. This is a statistically significant difference. When analyzed cross-sectionally, systolic blood pressure decreased by 4.1 mmHg and diastolic blood pressure decreased by 4.0 mmHg with each incremental increase of plasma ascorbic acid concentration of 1 mg/dL. This also is a clinically significant finding assuming that these effects may be multiplied over a longer period of study.

It was also found that change in systolic and diastolic blood pressure between the 9th and 10th annual visits was also inversely related to plasma ascorbic acid concentration after adjustment for BMI, race, education, and dietary fat and sodium intake. Patients with the lowest plasma ascorbic acid concentration had an increase in systolic blood pressure of 1.40 mmHg between the 9th and 10th annual visits while the patients with the highest concentrations had a decrease in

systolic blood pressure. Diastolic blood pressure increase was 5.97 mmHg in patients with the lowest concentrations, while the increase in patients with the highest concentrations was only 0.23 mmHg. This measurement was done to demonstrate a yearly effect.

In conclusion, the results of this study suggest that higher plasma ascorbic acid concentrations have a statistically significant effect on systolic and diastolic blood pressure and on the change in blood pressure over time in women 18-21 years of age. Therefore, increasing vitamin C intake as an adolescent may have a positive effect on preventing the development of hypertension. The effects of vitamin C levels on blood pressure were also compared to the effects that the DASH diet has on blood pressure. One may suggest the possibility that if patients with the lowest plasma ascorbic acid concentration increased levels to those in patients with the highest concentrations, effects comparable to those of the DASH diet may be achieved. This possibility may warrant further follow up studies.

The first article was from a reliable source and is up to date and accurate. The hypothesis was tested appropriately using a cross-sectional study. Possible confounding factors were taken into account and variables associated with altered outcome such as BMI, diet, etc. were corrected for. Accuracy of dietary records and questionnaires may be a source of error since those aspects were reliant on patient responses. Each patient was treated equally throughout the study. The sample size of patients was large enough to gather statistically significant data. The conclusions made in this study were clearly beneficial to the patients involved and the results may improve health care costs to them in the future. It was an ethical study as none of the intervention was detrimental to the patients' health. Each of the girls in the study was being treated and followed in the same manner. There was no room for bias in this study because the researchers at the intervals of the study were analyzing definitive measurements of blood pressure and plasma ascorbic acid level. This article was written in 2008 in Nutrition Journal and so is up to date. It is an American article and was not translated, also owing to its accuracy. One drawback of this study is that it was only done on women. It may be beneficial in further studies to include men in order to make conclusions with a broader base of analysis. Men weren't included in this study because of the fact that the sample population was taken from a larger study on female obesity. Problems with long term studies such as

this are that many subjects are lost to follow up problems and compliance issues can affect data analysis. It would be beneficial to prolong this study to determine even longer term effects of taking vitamin C on the sample population.

The second article, "Six-Year Effect of Combined Vitamin C and E Supplementation on Atherosclerotic Progression" asks the question: Does antioxidant supplementation have an effect on intima-media thickness of the common carotid artery (5)? The article is from the journal, *Circulation*, and is a commonly referenced article used to explain the effects of vitamin C and E on the progression of atherosclerosis.

Based on previous studies it was hypothesized that the combined effect of vitamin C and E had the greatest effect on atherosclerotic progression. This study was a 6 year study on 520 subjects; 212 of which were men and 228 of which were women. Each of the participants had hypercholesterolemia at the beginning of the study. This was defined as a serum cholesterol level of $>193\text{mg/dL}$. The true definition of hypercholesterolemia in both men and women is a cholesterol level $>200\text{mg/dL}$. A range of $200\text{--}239\text{mg/dL}$ is considered borderline hypercholesterolemia. Participants were excluded if they had a regular intake of antioxidants or any drug with antioxidant properties, a regular intake of Aspirin, severe obesity ($\text{BMI} >32\text{kg/m}^2$), type 1 diabetes, uncontrolled hypertension (sitting diastolic blood pressure of $>105\text{ mmHg}$), limited mobility due to disability, shortened life expectancy due to life-threatening disease, were premenopausal, or had a regular intake of oral estrogen therapy.

Subjects were separated into four groups. Each subject was randomly selected to receive one of four treatments twice daily with meals. The first group was to take a supplement of 91 mg of d- α -tocopherol (vitamin E) twice daily with meals. The second group was to take a supplement of 250 mg of slow release ascorbic acid (vitamin C). The third group was to take a single tablet of combined d- α -tocopherol and slow release ascorbic acid. The fourth group was to take a placebo only. Each of the tablets received were identical in appearance, color, and size. This occurred during the first three years of the study. During the last three years of the study, an open treatment period was established. All supplemented subjects during the first three years were then given the combination tablet, while the placebo subjects continued taking the placebos.

During the 6 year study, patients were asked to attend follow

up visits at 6, 12, 18, 24, 30, 36, and 72 months. At each visit, patients returned any unused tablets which were then counted. Each subject also underwent an ultrasonographic assessment of common carotid artery intima-media thickness. Ultrasonographic scanning included the common carotid artery, the carotid bulbs, and the proximal internal carotid artery. The area of greatest intimal media thickness was determined and scanned at three different angles. The technician performing the ultrasonography was blind to the supplement status of the participants. Mean intimal media thickness was calculated from the right and left sides of each participant and plotted on a linear regression slope. At each of the follow up visits, levels of plasma ascorbic acid, α -tocopherol, and F2 isoprostane were assessed as well.

When analyzing the results of atherosclerotic progression, it was shown that the mean annual increase of mean common carotid artery intimal media thickness was 0.0156 mm/year in the 105 non-supplemented patients, and 0.0118 mm/year in the 335 supplemented patients. This first mean estimate was the linear slope across all time points. When estimated as the simple difference between the last and first assessments, the mean annual increase was 0.0134 mm/year in the non-supplemented patients, and 0.0095 mm/year in the supplemented patients.

In covariance analysis, a 26% treatment effect was observed in both men and women combined. The treatment effect was 33% in men, a statistically significant effect. The treatment effect in women was 14% in women, an insignificant effect based on the statistical analysis. It was also shown that the treatment effect was greater in patients who already had plaques in the common carotid arteries at baseline (at least one plaque obstructing $>20\%$ of the arterial lumen). These patients had a 54% treatment effect overall.

The 6 year change of common carotid artery intimal media thickness correlated inversely with plasma α -tocopherol levels in men only. Plasma vitamin C and E concentrations were similar in men and women in years 1 and 3 of supplementation. In men, the F2-isoprostane levels were significantly reduced in the vitamin E group, but were increased in the placebo and vitamin C groups. In women, the F2-isoprostane levels were decreased more in the placebo group than in the vitamin C or E groups. Serum HDL cholesterol was also measured throughout the study. Mean HDL cholesterol in men who were supplemented with vitamin C increased significantly whereas vitamin E had no effect on HDL levels.

In conclusion, this study confirms that the combination of supplemented doses of combined vitamin E and C may slow down the progression of carotid atherosclerosis. The study also suggests that this benefit may be limited to men. This modification in sex should undergo further testing in the future. Because men had considerably lower baseline levels of both vitamins, this benefit may be due to the greater increase in plasma levels of the two vitamins. The overall treatment effect in this study is comparable to the effects of some lipid-lowering medications. The study is greatly cost effective as supplements of vitamins E and C are much cheaper in comparison to most lipid-lowering medications and side effects were minimal. Adherence to treatment by all subjects participating was good with minimal drop out rates. Average annual dropout rates were only 2.6%.

This article was clearly focused on the question being asked. The study design was appropriate for the parameters being studied at each point in time. All clinically important outcomes were considered and the results were reported without any source of bias. However, certain factors were not taken into account, such as dietary variances and physical activity. This study was done on both men and women which was important since treatment effects were different between the sexes. The sample size of patients was large enough to gather statistically significant data. The conclusions made in this study were clearly beneficial to the patients involved and the results may improve health care costs to them in the future. It was an ethical study as none of the intervention was detrimental to the patients' health. This article was written in 2003 and is fairly up to date. As with the first article, problems occur with studies that go on this long such as compliance of the sample population. Longer studies with increased accuracy would provide better, more precise data.

CONCLUSION

What is the effect of vitamin C and E supplementation on patients with atherosclerosis and hypertension? Based on the results of these studies, it can be concluded that supplementation with both vitamin C and E has a significant favorable effect on both blood pressure and the progression of atherosclerosis. Therefore, it would be advisable for patients at risk for these two conditions to consider incorporating this into his/her treatment regimen as a lifelong therapy. Regular checkups should also be recommended and encouraged in order to keep track of changes and to measure other risk factors for increases in blood pressure and lipid levels. Based on the reliability of the results of these studies, recommendations for this type of treatment may be supplemented into teaching for health care providers to their patients. Minimal side effects are involved with supplementation and safe measures should be taken to avoid overdose. This is also an excellent way to treat patients who refuse to take prescribed medications and only want to take natural supplements.

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