Effects of Vitamin C and E Against Oxidative Stress: Is Antioxidant Supplementation Efficient?

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Abstract: Objective: Numerous epidemiological studies show an increased prevalence of metabolic diseases related to oxidation stress causing cell damage. Antioxidant supplementation is therefore useful to protect against the oxidative stress mediated disease development and has become an increasingly popular practice. In this review, a selection of clinical and in vitro studies on vitamin C and E supplementation and the evaluation of their beneficial or negative effects have been analyzed.

Results: Clinical studies and supplementation trials show a correlation between antioxidants and metabolic improvement in different diseases such as cancer, cardiovascular disease, diabetes, obesity. Vitamin C (ascorbic acid) and E (α-tocopherol) appear to be among the most commonly used antioxidants. However, taking antioxidant supplements in high doses can be harmful. In some studies, little supportive evidence has been provided on substantial protection against chronic diseases by antioxidants. In addition, previous studies have revealed negative effects of antioxidant supplements such as pro-oxidant activities in particular conditions including their dosage and the body oxidant/antioxidant status.

Conclusion: Antioxidant supplements should be used with caution.

Keywords: Diseases, health, negative effect, supplementation, vitamin C, vitamin E.

1. INTRODUCTION

Highlighting a link between the occurrence of diseases and diet is an area of study that attracts the attention of many researchers. Particularly, the usefulness of some antioxidants is now recognized [1-5], including vitamins with antioxidant activity, to fight against free radicals and oxidative stress. In fact, because of the great reactivity and deleterious action of free radicals on biological systems, they are incriminated in the mechanisms of aging and intervene in the physiopathology of several types of diseases [6, 7]. Strengthening the body’s antioxidant defenses, therefore, seems a major issue to fight oxidative stress and preserve health [8]. Antioxidants may prevent the damage caused by free radicals to the body’s cells, prevent and/or improve different diseased states, thereby promoting longevity and warding off diseases. This field of study is booming, and considerable data on the potential benefits of antioxidant supplementation have been reported in recent years [1-5].

Several antioxidants have been introduced to protect the cells; vitamin E (α-tocopherol) and C (ascorbic acid) appear to be among the most commonly used antioxidants.

Epidemiological studies have shown an inverse correlation between antioxidants (vitamin E and C) levels in the body and the risk of metabolic diseases [9]. However, taking antioxidant supplements in high doses can be harmful. In some studies, little supportive evidence has been provided on substantial protection against chronic diseases by antioxidants [10, 11]. Besides, the negative effects of antioxidants, when used as supplements, have been revealed by some investigations. These investigations show that antioxidants may exhibit pro-oxidant activity depending on the dose and the oxidant/antioxidant status of the body [12].

So it will be pertinent to examine the beneficial role of antioxidant vitamins in stress oxidative prevention, but also their potentially detrimental effects, in this review.
2. PHYSIOLOGICAL ACTIONS OF VITAMIN C AND E

Vitamin C, or ascorbic acid, is an essential component of human nutrition. Vitamin C is a water-soluble vitamin found particularly in fruits and vegetables. In the body, it is present in the cytosol and extracellular fluid; it can directly capture O₂⁻ and OH⁻. Vitamin C prevents LDL oxidation by various oxygen reactive species generating systems. It plays an essential role in the regeneration of oxidized vitamin E. Vitamin C is involved in many physiological reactions (Fig. 1). It acts mainly as an “electron donor”, useful for enzymes functions involved in the hydroxylation of collagen, in the synthesis of catecholamines, carnitine and peptide hormones [13]. Through oxidation, it contributes to cholesterol metabolism with increased high density lipoprotein (HDL) -cholesterol and decreased low-density lipoproteins (LDL) -cholesterol and triglycerides, facilitates iron absorption and calcium incorporation in bones, and stimulates immune defense mechanisms and the elimination of carcinogens [14]. It stimulates B and T lymphocyte proliferation, antibody and cytokine production [15]. Besides, vitamin C accelerates histamine degradation by reducing their inflammatory reactions and preventing cold symptoms [16].

Vitamin E is found in oil-rich products such as grains, nuts, and seeds. Being fat-soluble, vitamin E binds to cell membranes and can sequester free radicals that prevent the spread of lipid peroxidation reactions. By its antioxidant action, it prevents or reduces oxidation of LDL associated with atherosclerosis and cardiovascular disease [17]. It has anti-inflammatory, anti-platelet and vasodilator properties. Other physiological roles are attributed to vitamin E as a role in immunity, phagocytosis, and a cofactor in RNA/DNA metabolism and hormone production (Fig. 2) [18]. Also, it predicts the risk of cancer, reduces the damage caused by toxic substances, protects against lipid peroxidation, reduces the markers of inflammation TNFα (tumor necrosis factor-alpha), modulates cell signaling, helps to increase exercise resistance, and protects the skin against oxidative stress.
induced by exposure to ultraviolet rays and pollutants [19-23]. Vitamin E regulates the expression of specific genes associated with oxidative stress, and also those of cholesterol homeostasis, inflammatory pathways, cell traffic, including synaptic vesicular transport and neurotransmitter secretion, those coding for apoptosis, cell cycle, cell growth, lipoprotein receptors and metabolism [24]. Moreover, vitamin E reduces the production of pro-inflammatory cytokines by macrophages and their precursors. It also influences T-lymphocytes (auxiliaries) and thus weakens inflammations [25].

3. CLINICAL STUDIES ON VITAMIN C AND E SUPPLEMENTATION

Nowadays, numerous epidemiological studies show an increased prevalence of metabolic diseases. The general consensus indicates that the mechanism involves an inflammation-related cascade and oxidative stress causing cell damage. Antioxidant supplementation is then useful to protect against the oxidative stress-mediated disease development, and has become an increasingly popular practice. Clinical studies and supplementation trials in humans and animals show a correlation between antioxidants and metabolic improvement in different diseases such as cancer, cardiovascular disease, diabetes, obesity… [5, 26]. In addition, vitamin supplements enhance the effectiveness of the immune system, fight infections and oxidative stress [27].

Several previous studies have shown the effectiveness of antioxidants in reducing the risk of cardiovascular disease and plasma cholesterol concentrations, in reducing the risk and prevalence of cancers, in vision improvement and eye protection, in the treatment of neurodegenerative diseases such as Alzheimer’s and Parkinson’s disease and even in reducing complications associated with many pathologies [22, 28-30].

The SU.VI.MAX study followed individuals who were taking an antioxidant supplement (vitamin C, vitamin E) in capsule form daily for seven years. The results showed that low-doses of antioxidants significantly reduce the incidence of cancers and mortality from all causes in men [31]. The absence of a protective effect in women was explained by a threshold effect, indicating that in women having adequate levels of dietary antioxidant intake, an additional dosage did not bring benefits.

A combined daily supplement of vitamin C, vitamin E and β-carotene in men significantly reduced the oxidative damage of lymphocytic DNA and prevented cancer [32]. In the study by Baskin et al. [33], supplementation with lutein, β-carotene, and vitamin E was associated with decreased DNA oxidative damage and increased resistance of low-density lipoproteins (LDL) and very low density (VLDL) to oxidation.

Johnston et al. [34] showed that regular consumption of orange juice, as well as vitamin C supplements, reduced plasma markers of lipid peroxidation in adult women. Bryer and Goldfarb [35] noted that vitamin C supplementation (3g/day) reduced muscle pain and oxidative stress from intense exercise in sportsmen. Block et al. [19] indicated that vitamin C supplementation reduced inflammation markers, the reactive C protein, in patients at risk for cardiovascular disease. In patients with type 2 diabetes, vitamin C supplementation (1 g/day) was associated with a reduction in oxidative stress and long-term diabetes complications [36]. Besides, vitamin C and E supplementation significantly reduced depression and anxiety in these diabetics [37]. A recent study indicated that vitamin C is involved in glycemic control in type 2 diabetics [38]. Vitamin C and E supplements improved endothelial function and oxidative stress markers in hypertensive patients [39]. Vitamin C reduced blood pressure in hypertensive individuals [40]. Numerous supplementation studies showed that vitamin C improved sperm quality, sperm mobility and morphology [41]. Some studies indicated that vitamin C could decrease the duration and severity of upper respiratory tract infections [42]. Similarly, studies on infertile humans reported a beneficial effect of vitamin E supplementation on sperm quality with decreased markers of sperm lipid peroxidation [43].

Vitamin E supplementation in pregnant women reduced pregnancy complications, particularly in cases of gestational diabetes [44]. A study by Lu et al. [45] showed that vitamin E supplementation increased growth performance and antioxidant status, improved innate immunity and protected against bacterial infections.

Protection of cardiovascular risk was observed after vitamin E supplementation in women at high risk for this disease, but no effect on the risk of developing type 2 diabetes were observed [46].

In addition, a beneficial effect on coronary disease progression in patients with cardiovascular disease was achieved with vitamin E supplements [47]. Vitamin E intake reduces platelet aggregation, and thus the risk of thrombosis [48].

Vitamin E supplements reduced the risk of male prostate cancer and female colon cancer [49, 50]. They prevented the risk of cataracts and neurodegenerative diseases in the elderly [51, 52]. Vitamin C and E supplementation played a role in reducing muscle damage markers of aerobic exercises in female athletes [53], and also in male athletes [54]. Vitamin C and E supplementation have shown to decrease lipid peroxidation after endurance exercise [55]. Antioxidant supplementation including vitamins C and E has been shown to improve insulin sensitivity in women with the polycystic ovarian syndrome and may improve their chances of achieving pregnancy or correcting the endocrinopathies associated with this syndrome [56, 57]. Previous studies showed that the administration of vitamin E to hemodialysis patients resulted in a significant decrease in lipid peroxidation status and improvement of anemia [4]. This beneficial effect was attributed to the reduction in erythrocyte osmotic fragility resulting in stable cell membranes. In addition, the combined therapy with daily vitamins E and C improved microcirculation in hemodialysis patients [4]. It has been shown that the use of vitamins E and C may be beneficial in reducing oxidative stress and cardiovascular risk induced by oral contraceptives in women [58]. Previous studies demonstrated that the administration of vitamin C and E improved endothelium function and arterial stiffness indices [59, 60]. Proposed mechanisms for the effects of vitamins on endothelium function include...
increasing NO bioavailability and reducing NO inactivation by free radicals.

Antioxidant supplementation appears to be a key component to promote healthy aging [5]. The elderly receiving vitamin C and vitamin E supplements have a reduced risk of osteoporosis associated with reduced oxidative stress [61].

4. IN VITRO STUDIES ON VITAMIN C AND E SUPPLEMENTATION

Cells produce different free radicals, by-products of cellular oxidation-reduction reactions, involved in thousands of chemical reactions during metabolic activity. It is accepted that free radicals are second messengers involved in gene expression and regulation of proliferation and cell death. Also, the controlled production of free radicals appears as an essential mechanism of cellular signaling that contributes to cell homeostasis. However, in excess, they produced cellular oxidative stress [62]. This oxidative stress induced alterations in cell function, including peroxidation of polyunsaturated fatty acids, decreased fluidity and resistance of cell membranes, or ruptures leading to cell death, denaturation of specific proteins with decreased enzyme activity, DNA damage, and alteration of ion transport systems [63]. Several researchers around the world have therefore focused their work on the effects of antioxidants on cell cultures.

Numerous in vitro studies prove the antioxidant effect of vitamin C and its protective effect on immune cells (Fig. 3). The addition of vitamin C to cell cultures increases the proliferative response of lymphocytes in vitro while improving the intracellular antioxidant profile [64, 65]. Moreover, vitamin C supplementation increases the production of cytokines by peripheral blood mononuclear cells [66]. Vitamin C stimulates lymphocyte proliferation by inducing NADPH formation and subsequently the regeneration of lymphocyte glutathione by promoting the pathway of phosphate pentoses and the activity of G6PDH enzyme [67]. Vitamin C is actively involved in the repair of oxidized proteins in cells [68]. Previous studies have shown that vitamin C can affect gene expression by serving as a co-factor for DNA and histone demethylase enzymes. These demethylases of DNA remove a methyl group from the thymine residues and induce the activation of several genes [69]. This may explain the differentiation of stem cells induced by vitamin C [70]. Vitamin C prevents apoptosis of endothelial cells in the culture [71].

The cellular antioxidant properties of vitamin E have been the subject of several previous studies. These studies confirm the powerful effect of vitamin E in stimulating cell proliferation, reducing apoptosis, improving membrane fluidity, and protecting cells [64, 66, 72]. The hydrophobic character of vitamin E allows it to be inserted into biological membranes rich in polyunsaturated fatty acids and it plays an effective protective role in preventing the spread of lipid peroxidation induced by reactive species of oxygen. Vitamin E has been shown to modulate cytokine production by its effect on transcription factors that are regulated by redox status, and by influencing prostaglandin PGE2 synthesis, which plays a key role in the Th1 response and the regulation of pro-inflammatory cytokines [73]. Other studies confirm the modulation of cytokine secretion by vitamin E through the stimulating effect of vitamin E on the production of IL-2 and IFN-γ [74]. In addition to these effects, in lymphocytes cultivated in the presence of vitamin E, a decrease in markers of oxidative stress such as MDA, carbonylated proteins and superoxide anion was observed along with an increase in antioxidant defense such as GSH and catalase [66].

Vitamin E is capable of modulating gene expression through several signaling and nuclear receptor pathways [75]. Indeed, it has been described that vitamin E is a ligand of the PXR receptor, a nuclear receptor involved in the metabolism of xenobiotics as well as in the catabolism of vitamin E [76]. Vitamin E is capable of regulating the expression of genes whose expression is dependent on the
nuclear receptor activated by peroxisome γ proliferators (PPARγ) and appears to have a stimulating effect on the expression of PPARγ and lipid accumulation during cell differentiation especially of fat cells [75].

Other findings demonstrated the modulation of cytokine secretion by vitamins C and E following a reduction in inflammation and improvement of T-cell capacity by IL-2 secretion [64-66]. Other in vitro studies have reported that vitamin C and vitamin E protect immune cell membranes from oxidation, stimulate their proliferation, differentiation and maturation while improving their redox status [16, 77, 78]. Incubation of lymphocytes with vitamin C decreased the pro-inflammatory cytokines TNF-α and IFN-γ production and increased anti-inflammatory IL-10 production [65].

Other authors showed that vitamins C and E protected liver cells from oxidative stress caused by several toxic substances and metals such as arsenic [79, 80]. In this case, vitamins influenced cellular signaling pathways leading to increased hepatic antioxidant defenses. Jaiswal et al. [81] noted that the pre-treatment of hepatocytes with vitamin C induced the protection of these cells from oxidative stress induced by toxic substances.

Long-term use of vitamin supplements has been shown to increase telomere length [82]. This was explained by the higher activity of an enzyme that synthesizes telomeres called telomerase. A scientific study of cultured cells has shown that shortening of telomeres is slowed down by intracellular vitamin C enrichment and by suppression of oxidative stress [83]. Another study highlighted the protection of telomeres and telomerase activity in the presence of vitamin E [84]. These studies indicated that the reduction of cellular oxidative stress by vitamins protects the DNA against free radicals, maintains the activity of the telomerase enzyme and preserves the length of telomeres, accompanied by a significant lengthening of the life of the cells. Vitamin C has been shown to inhibit the activity of the enzyme glycerol phosphate dehydrogenase (GPDH) and reduce the accumulation of triglycerides in adipocytes [85].

A previous study has shown that vitamin C can increase collagen gene expression in fibroblasts [86]. A reduction in oxidant generation and NFkB activation, the pro-inflammatory transcription factor nuclear factor κB, has been noted in dendritic cells incubated with vitamin C [87].

5. HARMFUL EFFECTS OF VITAMIN C AND E SUPPLEMENTATION

Some negative effects of antioxidant supplements have emerged in the last decades. Previous studies have raised the possibility that antioxidant supplements could interfere with health.

An analysis of several randomized controlled trials of vitamin C and E supplementation showed that none of these supplements improved fasting blood glucose or insulin levels in diabetic patients [88].

SUVIMAX intervention trial observed an adverse serum lipid profile in the antioxidant supplementation group with high triglyceride concentrations [89]. In the Women’s Health Study, vitamin E supplementation did not lower the rates of major cardiovascular events and cancer [10]. Vitamin E supplementation was associated with higher all-cause mortality [90]. No benefits of vitamin C and E supplementation in oxidative stress markers and muscle damage in trained weightlifters were reported [91]. In a review, the results did not prove that there was a clinically positive effect of vitamin C supplementation in cancer patients [92].

The lack of an evident beneficial effect of vitamin E supplementation on the incidence of cardiovascular events was previously reported [93]. Randomized clinical trials have not proven to be beneficial on the use of vitamin E to reduce atherosclerotic risk in humans [94]. Another study confirmed that the administration of vitamin E had no evident impact either on cancer risk or on major cardiovascular events and death [95]. The “Women’s antioxidant Cardiovascular Study (WACS)” failed to find any preventive effects of vitamin C and E on cardiovascular diseases [96]. Previous studies have demonstrated that antioxidant supplementation may interfere with exercise-induced cell signaling in muscle [97] and may block adaptations to training [98].

In randomized controlled trials, vitamin E or vitamin E and C supplements did not have beneficial effects in patients with mild cognitive impairment [99, 100]. Supplementation with vitamins C and E failed to slow cognitive decline in aged women [101]. Randomized trials did not support routine vitamin C supplementation alone or in combination with vitamin E in pregnancy, for normal or at high risk of pregnancy [102].

CONCLUSION

A large number of studies investigating the effectiveness of vitamin C and E supplementation in humans raised contrasting results depending on the dose and the bioavailability of the molecules used and on the population genetics. Even if vitamins C and E are protective as part of a healthy diet, supplements do not appear as promising. It is worth to underline that excessive vitamin C and E supplementation may not be healthy. We suggest then that antioxidant supplements should be used with caution. In the end, a balanced diet that includes antioxidant-rich foods is considered healthier than taking antioxidant supplements.

LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>GSH</td>
<td>Reduced Glutathione</td>
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<tr>
<td>GPDH</td>
<td>Glycerol Phosphate Dehydrogenase</td>
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<td>G6PDH</td>
<td>Glucose 6 Phosphate Dehydrogenase</td>
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<td>HDL</td>
<td>High Density Lipoprotein</td>
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<td>IFN-γ</td>
<td>Interferon γ</td>
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<td>IL-2</td>
<td>Interleukin 2</td>
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<td>LDL</td>
<td>Low Density Lipoprotein</td>
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<tr>
<td>MDA</td>
<td>Malondialdehyde</td>
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<tr>
<td>NADPH</td>
<td>Nicotinamide-adenine Dinucleotide Phosphate</td>
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<tr>
<td>NFkB</td>
<td>Nuclear Factor-Kappa B</td>
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<tr>
<td>NADPH</td>
<td>Nicotinamide-adenine Dinucleotide Phosphate</td>
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NOTES

PGE2 = Prostaglandin E2
PPAR γ = Peroxisome Proliferator-Activated Receptor Gamma
Th1 = type 1 T Helper Cells
TNFa = Tumor Necrosis Factor α
VLDL = Very Low Density Lipoprotein

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