VITAMIN E AND METABOLIC DISORDERS

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Abstract

Introduction. Antioxidant properties of vitamin E are implicated in the prevention of chronic diseases associated with oxidative stress.

Material and methods. We evaluated the published studies, using the data basis MEDLINE and EMBASE.

Results. High circulating levels of vitamin E fractions, α- and γ-tocopherol, reduce the risk of prostate cancer and protect against genetic-predisposed breast cancer. Administration of vitamin E daily reduced the risk of heart attack in diabetic patients. Vitamin E supplementation showed a lower incidence of tract infections in patients aged at least 65 years. Supplementing with vitamin E may improve liver function in obese children and also in treatment of nonalcoholic fatty liver disease. Vitamin E can prevent the adverse effects associated with salt intake, such as salt-dependent hypertension and nephropathy. In patients with moderately severe Alzheimer's disease, treatment with selegiline, α-tocopherol or both slows the progression of disease. Humans who took vitamin E supplements for at least 10 years had a risk of death from amyotrophic lateralsclerosis less than half of those who did not use it.

Conclusions. Antioxidants such as vitamin E act to protect cells against effects of free radicals, which are potentially damaging products of energy metabolism.

Keywords: vitamin E, antioxidants, metabolic disorders, diabetes, cancer.

Introduction

Vitamin E is a term that encompasses a group of potent, lipid-soluble, chain-breaking antioxidants. One form, α-tocopherol, is the most abundant in nature, has the highest biological activity and reverses vitamin E deficiency symptoms in humans. Due to the potent antioxidant properties of tocopherols, the impact of α-tocopherol in the prevention of chronic diseases believed to be associated with oxidative stress has often been studied, and beneficial effects have been demonstrated. Tocopherols and tocotrienols (vitamin E) as well as the carotenoids and ascorbic acid (vitamin C) react with free radicals, notably peroxyl radicals, and with singlet molecular oxygen, this being the basis of their function as antioxidants. α-tocopherol is the major peroxyl radical scavenger in biological lipid phases such as membranes or low-density lipoproteins (LDL). Many studies used F2-isoprostanes, isomers of prostaglandin F2, as index for free radical generation and oxidative lipid damage. 8-iso-PGF2 is one of the most abundant F2-isoprostanes produced in vivo in

humans and its excretion is depressed in humans by antioxidant vitamins, vitamin E supplementation resulting in a dose-dependent reduction in 8-iso-PGF2 excretion and decreased sensitivity of LDL to in vitro oxidation[22]. Non-radical oxidation products are formed from the reaction between α-tocopheryl radical and other free radicals, which are conjugated to glucuronic acid and excreted through the bile or urine.

Antioxidant functions are associated with lowering DNA damage, malignant transformation, and other parameters of cell damage in vitro as well as lowered incidence of certain types of cancer and degenerative diseases, such as ischemic heart disease. They are also important in the process of aging. Reactive oxygen species occur in tissues and cells and can damage DNA, proteins, carbohydrates, and lipids[10]. These reactions are controlled in part by antioxidants that eliminate prooxidants and scavenge free radicals.

Vitamin E and metabolic disorders

Oxidative stress is increased in both diabetes mellitus and insulin resistance syndrome and may contribute to the development of microvascular and cardiovascular diseases associated with both of these syndromes. The increases in oxidative stress is probably due to hyperglycemia, dyslipidemia and elevated free fatty acids which commonly occur in patients who have diabetes and poor glycemic control and also, in metabolic syndrome.

Hyperglycemia results in the generation of reactive oxygen species, leading to increased oxidative stress in a variety of tissues.[1] In the absence of an antioxidant response, stress-sensitive intracellular signaling pathways are activated. One major consequence is the production of gene products that cause cellular damage and are ultimately responsible for the late complications of diabetes. Some theories have proposed that most oxidants induced by hyperglycemia derive from glycolysis and mitochondrial oxidative phosphorylation with production of superoxide. This process causes activation of protein kinase C and aldose reductase, production of hexosamine and glycated products.[8,11] Other researches showed an increased NADPH oxidase activity that leads to alteration of NADPH/NADP ratios [5].

Elevation of free fatty acids that appears in diabetes and metabolic syndrome, even in the absence of hyperglycemia, can also increase oxidants production because their metabolism is dependent on β-hydroxylation, acetyl-CoA, and mitochondrial oxidative phosphorylation[7]. The role of antioxidant treatment in the prevention or delay of diabetic complications and metabolic disorders was studied in cultured vascular cells, animal models and humans.

Some prospective clinical trials testing vitamin E demonstrated beneficial cardiovascular effects: vitamin E supplementation (800 IU/day) showed a reduction in acute myocardial infarct and alpha-tocopherol (400-800 IU/day) determined a reduction in nonfatal myocardial infarct in patients with diabetes [20]. Higher doses of vitamin E (1000 UI/day) administrated for three months in patients with type 1 diabetes mellitus caused a significant improvement in endothelium-dependent vasorelaxation [16]. The same effect was observed using a combination of vitamin E (800 UI/day) and vitamin C (1000 mg/day) for

six months. In another study, vitamin E (680 mg/day) and C (1250 mg/day) improved renal function in patients with type 2 diabetes mellitus.[9]

Vitamin E supplementation with or without vitamin C, slowed the progression of coronary lesions and atherogenesis, by inhibiting LDL oxidation and decreasing the release of reactive oxygen species. It was also observed the reduction in pro-inflammatory cytokines release and inhibition of monocyte endothelial cell adhesion [6].

Most studies reported that oxidative stress markers in plasma, urine and circulating cells, such as, lipid peroxidation, increasing isoprostanes and plasma malondialdehyde, improved after vitamin E therapy [19].

Even if in animal models, early markers of diabetic retinopathy, nephropathy, neuropathy, and even cardiovascular disease were prevented or delayed, including blood flow, nerve conduction velocity, permeability, endothelial dysfunctions, albuminuria, and vascular contractility [19], there is a lack of evidence in clinical trials.

The mixed results obtained from a variety of clinical studies involving vitamin E suggests the need for future researches on the potential protective role of vitamin E against chronic diseases.

Vitamin E and cardiovascular diseases

Concerning the etiology of cardiovascular disease, 2 theories related to antioxidant defense have been tried to explain the initiation of the atherogenic process: the oxidation theory and the response-to-injury theory. In both theories the oxidative modification of LDL is considered to be a key step in the initiation and progression of the disease. Based on the demonstrated role of α-tocopherol in the inhibition of LDL oxidation in vitro, many studies concentrated on vitamin E capacity to prevent atherosclerosis. Inhibition of LDL oxidation by antioxidants should also determine an inhibition of early atherogenic events.

Several epidemiological studies have revealed an inverse relationship between vitamin E intake and the progression of chronic diseases. It is believed that vitamin E's various actions, including its role as an antioxidant, have both antiatherogenic effects and chemoprotective action.

In the Cambridge Heart Antioxidant Study (CHAOS)[17], researchers observed that high doses of vitamin E treatment significantly reduced the risk of nonfatal myocardial infarction (MI) and cardiovascular death in patients with established ischemic heart disease.

Other studies concentrated on the protective effect of vitamin E against cardiovascular disease endpoints and myocardial infarction in hemodialysis patients with prevalent cardiovascular disease. High mortality rate that appears in these patients might be associated with the increased oxidative stress in hemodialysis patients compared with non-hemodialysis. The results showed a significant decrease in cardiovascular disease endpoints and myocardial infarction in the patients assigned to vitamin E *versus* placebo [6].

In another study it was found that a combined supplementation of both vitamin E and slow-release vitamin C can reduce the progression of atherosclerosis in men. Atherosclerotic progression was defined by

common carotid artery mean intima-media thickness (IMT), using ultrasonography. The proportion of men with disease progression was reduced by 74% in the group with both vitamins E and C, compared to the placebo group. But, no significant reduction in mean IMT was reported in women[15].

Contrary to the these studies demonstrating the beneficial effects of vitamin E supplementation against coronary artery disease, several papers have revealed potential pro-oxidant and pro-atherogenic effects of α-tocopherol when administered in certain populations[23]. In smokers consuming a high polyunsaturated diet, vitamin E may function as a pro-oxidant. These findings suggest that caution should be taken in the administration of vitamin E as a therapeutic agent for reducing the risk of coronary artery disease in smokers. Also, lifestyle of the patients, dietary habits, type and dose of vitamin E supplementation must be taken into account.

Vitamin E and cancer

There have been several reports on the potential anticancer properties of α-tocopherol. It is believed that many types of cancer develop as a result of cellular oxidative stress and that antioxidants may be beneficial in suppressing this process. Attempts to prevent cancer by vitamin E are based on the rationale that carcinogenesis results from free radicals attacking DNA. As an antioxidant, vitamin E may inhibit cancer formation by scavenging reactive oxygen or nitrogen species.

A 32% reduction in prostate cancer incidence and a 41% reduction in prostate cancer mortality were observed in men who received supplementary vitamin E and β-carotene. High circulating levels of vitamin E fractions, α- and γ-tocopherol, reduce the risk of prostate cancer by 50 % each, in some studies. The link between high tocopherol levels and low cancer risk is stronger among subjects using supplements than among non-users [3].

In other studies[18], vitamin supplements, particularly vitamin E plus β-carotene and selenium, had a significant decrease in the incidence of gastric cancer versus individuals that didn't receive vitamin supplementation.

Vitamin E appears to protect against genetic-predisposed breast cancer better than environmental-induced breast cancer. Based on comparative studies, forms of vitamin E found in food (such as gamma tocopherol and tocotrienols) may be responsible for the protective effect against breast cancer[12].

Vitamin E supplementation in patients treated with cisplatin chemotherapy decreased the incidence and severity of peripheral neurotoxicity[1]. Despite these promising data, additional human studies question the benefits of vitamin E supplementation in the prevention of carcinogenesis.

REFERENCES

1. Argyriou AA, Chroni E, Koutras A, Iconomou G, Papapetropoulos S, Polychronopoulos P, Kalofonos HP. A randomized controlled trial evaluating the efficacy and safety of vitamin E supplementation for protection against cisplatin-

induced peripheral neuropathy: final results. Support Care Cancer. 2006 Nov;14(11):1134-40.

2. Ascherio A, Weisskopf MG, O'reilly EJ, Jacobs EJ, McCullough ML, Calle EE, Cudkowicz M, Thun MJ. Vitamin E intake and risk of amyotrophic lateral sclerosis. Ann Neurol. 2005 Jan;57(1):104-10.

3. Brawley OW, Parnes H. Prostate cancer prevention trials in the USA. Eur J Cancer 2000;36:1312-5).

4. Cankurtaran M, Kav T, Yavuz B, Shorbagi A, Halil M, Coskun T, Arslan S. Serum vitamin-E levels and its relation to clinical features in nonalcoholic fatty liver disease with elevated ALT levels. Acta Gastroenterol Belg. 2006 Jan-Mar;69(1):5-11.

5. Ceriello A. New Insights on Oxidative Stress and Diabetic Complications May Lead to a "Causal" Antioxidant Therapy. Diabetes Care, 2003, 26:1589–1596.

6. Dutta A., Dutta S.K. Vitamin E and its Role in the Prevention of Atherosclerosis and Carcinogenesis: A Review. Journal of the American College of Nutrition.2003; vol 22, No. 4, 258–268

7. Evans JL, Goldfine ID, Maddux BA, Grodsky GM: Oxidative stress and stress-activated signaling pathways: A unifying hypothesis of type 2 diabetes. Endocr Rev. 2002; 23: 599–622.

8. Evans JL, Goldfine ID, Maddux BA, Grodsky GM: Are oxidative stress-activated signaling pathways mediators of insulin resistance and beta-cell dysfunction? Diabetes. 2003;52: 1–8.

9. Gaede P, Poulsen HE, Parving HH, Pedersen O. Double-blind, randomised study of the effect of combined treatment with vitamin C and E on albuminuria in Type 2 diabetic patients. Diabet Med. 2001;18:756–760.

10. Herrera E, Barbas C. Vitamin E: action, metabolism and perspectives. J Physiol Biochem. 2001 Mar;57(2):43-56.

11. Itani SI, Ruderman NB, Schmieder F, Boden G: Lipid-induced insulin resistance in human muscle is associated with changes in diacylglycerol, protein kinase C, and I_B-alpha. Diabetes. 2002;51:2005–2011.

12. Kolonel LN, Altshuler D, Henderson E. The multiethnic cohort study exploring genes, lifestyle and cancer risk. Nature Rev 2004;4:1-9.

13. Meydani SN, Han SN, Hamer DH.Vitamin E and respiratory infection in the elderly. Ann N Y Acad Sci. 2004 Dec;1031:214-22.

14. Nunomura A, Castellani RJ, Zhu X, Moreira PI, Perry G, Smith MA. Involvement of oxidative stress in Alzheimer disease. J Neuropathol Exp Neurol. 2006 Jul;65(7):631-41.

15. Radulian G, Dragomir A. Vitamin E and the prevention of metabolic disorders. International Journal of Metabolisn by Fax. 2008 ian; vol XI: nr. 2.

16. Salonen J, Nyyssonen K, Salonen R, Lakka H, Kaikkonen J, Porkkala-Sarataho E, Voutilainen S, Lakka TA, Rissanen T, Leskinen L, Tuomainen TP, Valkonen VP, Ristonmaa U, Poulsen HE: Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) study: a randomized trial of the effect of vitamins E and C on 3-year progression of carotid atherosclerosis. J Int Med. 2000;248:377–386.

17. Salonen RM, Nyyssonen K, Kaikkonen J, et al. Six-year effect of combined vitamin C and E supplementation on atherosclerotic progression: the Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) Study. Circulation. 2003;107:947-953.

18. Stephens N, Parsons A, Schofield P, Kelly F, Cheeseman K, Mitchinson M, Brown M: Randomized controlled trial of vitamin supplementation in patients with congestive heart failure. Am J Clin Nutr. 2001; 73:219–224.

19. Sugimura T. Nutrition and dietary carcinogens. Carcinogenesis 2000;21:387_/95.

20. Tatsuya K., Keiji I., George L. Oxidative Stress: The Lead or Supporting Actor in the Pathogenesis of Diabetic Complications. King J Am Soc Nephrol. 2003;14: S216–S220.

21. Terentis A, Thomas S, Burr J, Liebler D, Stocker R: Vitamin E oxidation in human atherosclerotic lesions. Circ Res. 2002;90:333–339.

22. Vajro P, Mandato C, Franzese A, Ciccimarra E, Lucariello S, Savoia M, Capuano G, Migliaro F. Vitamin E treatment in pediatric obesity-related liver disease: a randomized study. J Pediatr Gastroenterol Nutr. 2004 Jan;38(1):48-55.

23. Wang X, Quinn PJ. Vitamin E and its function in membranes. Prog Lipid Res. 1999 Jul;38(4):309-36.

24. Weinberg R, VanderWerken B, Anderson R, Stegner J, Thomas M: Pro-oxidant effect of Vitamin E in cigarette smokers consuming a high polyunsaturated fat diet. Arterioscler Thromb Vasc Biol. 2001;21: 1029–1033.