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Health Aspects of Antioxidant Nutrients: A Consice Update

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Abstract

Oxidative stress (OR) reflects an imbalance between the systemic manifestation of reactive oxygen species and a biological system's ability to readily detoxify the reactive intermediates or to repair the resulting damage. Disturbances in the normal redox state of cells can cause toxic effects through the production of peroxides and free radicals that damage all components of the cell, including proteins, lipids, and DNA. Further, some reactive oxidative species act as cellular messengers in redox signalling. Thus, oxidative stress can cause disruptions in normal mechanisms of cellular signalling. In humans, oxidative stress is thought to be involved in the development of cancer, Parkinson's disease, Alzheimer's disease, atherosclerosis, heart failure, myocardial infarction, fragile X syndrome, Sickle Cell Disease, lichen planus, vitiligo, autism, infection and chronic fatigue syndrome. Dietary active agents are good sources of antioxidants and phytonutrients that provide a protective effect against the OR-mediated DNA and lipids cell membrane structures damage. Nutrition must benefit for human health by providing nutrients and chemical components (proteins, carbohydrates, fats, vitamins, polyphenols, minerals and water), which are needed for energy production, growth, body tissue maintenance, organ function and health. There has been great interest in the health benefits of antioxidants that are important constituents of most foods of plant origin. Many naturally occurring antioxidants in fruits, vegetables, herbal plants, cereal grains, nuts, seeds and spices have significant protective activity against ROS-induced oxidative stress in organs of biological systems.

Introduction

Oxidative stress and cancer

Among the mechanisms related to the pathogenesis of non-communicable chronic diseases, including cancer, we have changes caused by oxidative metabolism [1,2]. The generation of free radicals is a continuous and physiological cell process [3]. In adequate proportions, its production will enable the generation of energy through adenosine triphosphate (ATP), phagocytosis, cell growth regulation and the participation in defense mechanisms during the infectious process. However, their excessive production shows harmful effects [4]. Nonetheless, an imbalance between reactive species concentrations and antioxidant defense mechanisms in the body, favouring the first, will result in oxidative stress. The harmful effects of this process are membrane lipid peroxidation and damage caused to tissue and membrane proteins, to enzymes, to carbohydrates, in addition to oxidative damage to deoxyribonucleic acid (DNA) [5,6]. The metabolism of cancer patients changes gradually, affecting all metabolic pathways. As for carbohydrate metabolism, tumors show an excessive glucose consumption, causing glucose intolerance, with peripheral insulin resistance [7,8]. Protein catabolism is present, while most of the times there is a massive loss of musculoskeletal tissue in those patients. This event is

related to a sulphated glycoprotein called proteolysis-inducing factor (PIF). This entire scenario contributes to the cachectic state very often encountered in cancer patients [9]. As for lipid metabolism, inhibition of plasma lipoprotein lipase activity leads to hyperlipidemia [9]. Increase of lipolysis associated with lowered lipogenesis; and increased turnover of glycerol, free fatty acids, and triacylglycerols (which are depleted from the adipose tissue) are all metabolic changes induced by advanced tumours, and they may be related to an increase of hormone-sensitive lipase (HSL) and to the release of lipolytic tumour factors [10].Lipolytic activity can also be mediated by the lipid mobilization factor (LMF).

Oxidative stress and diabetes

Increasing evidence in both experimental and clinical studies suggests that oxidative stress plays a major role in the pathogenesis of both types of diabetes mellitus. Free radicals are formed disproportionately in diabetes by glucose oxidation, nonenzymatic glycation of proteins, and the subsequent oxidative degradation of glycated proteins. Abnormally high levels of free radicals and the simultaneous decline of antioxidant defense mechanisms can lead to damage of cellular organelles and enzymes, increased lipid peroxidation, and development of insulin resistance. These consequences of oxidative stress can promote the development of complications of diabetes mellitus. Changes in oxidative stress biomarkers, including superoxide dismutase, catalase, glutathione reductase, glutathione peroxidase, glutathione levels, vitamins, lipid peroxidation, nitrite concentration, nonenzymatic glycosylated proteins, and hyperglycemia in diabetes, and their consequences, are discussed in this review. In vivo studies of the effects of various conventional and alternative drugs on these biomarkers are surveyed. There is a need to continue to explore the relationship between free radicals, diabetes, and its complications, and to elucidate the mechanisms by which increased oxidative stress accelerates the development of diabetic complications, in an effort to expand treatment options [11].

Oxidative stress and cardiovascular disease

Oxidative stress occurs when there is an imbalance between free radical production and antioxidant capacity. This may be due to increased free radical formation in the body and/or loss of normal antioxidant defenses. Oxidative stress has been associated with the development of cardiovascular disease. The role of antioxidants in the primary and secondary prevention of coronary heart disease is currently under study. Although epidemiologic evidence indicates that antioxidants may decrease cardiovascular risk, clinical trial data are not conclusive. Information regarding the use and benefits of antioxidants in persons with diabetes is limited. Persons with diabetes may be more prone to oxidative stress because hyperglycemia depletes natural antioxidants and facilitates the production of free radicals. In addition, other factors such as homocysteine, insulin resistance, and aging may be contributory. This article highlights landmark clinical trials that have examined the cardioprotective effect of antioxidants. Because these trials have not been designed to study persons with diabetes, and clinical trial data for this group are not available, correlational studies are also presented. Finally, the concept of oxidative stress, the antioxidant and pro-oxidant factors that may contribute to oxidative stress, and the consequences of oxidative stress in persons with type 2 diabetes [12].

Antioxidants and Oxidative stress

An imbalance between oxidants and antioxidants in favour of the oxidants, potentially leading to damage, is termed 'oxidative stress'. Oxidants are formed as a normal product of aerobic metabolism but can be produced at elevated rates under pathophysiological conditions. Antioxidant defense involves several strategies, both enzymatic and non-enzymatic. In the lipid phase, tocopherols and carotenes as well as oxy-carotenoids are of interest, as are vitamin A and ubiquinols. In the aqueous phase, there are ascorbate, glutathione and other compounds. In addition to the cytosol, the nuclear and mitochondrial matrices and extracellular fluids are protected. Overall, these low molecular mass antioxidant molecules add significantly to the defense provided by the enzymes superoxide dismutase, catalase and glutathione peroxidases [13].

Antioxidant enzymes (Glutathione peroxidase, Glutathione transferase, SOD, CAT, Mono Amine Oxidase)

An antioxidant is a molecule that inhibits the oxidation of other molecules. Oxidation is a chemical reaction involving the loss of electrons or an increase in oxidation state. Oxidation reactions can produce free radicals. In turn, these radicals can start chain reactions. When the chain reaction occurs in a cell, it can cause damage or death to the cell. Antioxidants terminate these chain reactions by removing free radical intermediates, and inhibit other oxidation reactions. They do this by being oxidized themselves, so antioxidants are often reducing agents such as thiols, ascorbic acid, or polyphenols [14].

Substituted phenols and derivatives of phenylenediamine are common antioxidants used to inhibit gum formation in gasoline (petrol). Although oxidation reactions are crucial for life, they can also be damaging; plants and animals maintain complex systems of multiple types of antioxidants, such as glutathione, vitamin C, vitamin A, and vitamin E as well as enzymes such as catalase, superoxide dismutase and various peroxidases. Insufficient levels of antioxidants, or inhibition of the antioxidant enzymes, cause oxidative stress and may damage or kill cells. Oxidative stress is damage to cell structure and cell function by overly reactive oxygen-containing molecules and chronic excessive inflammation. Oxidative stress seems to play a significant role in many human diseases, including cancers. The use of antioxidants in pharmacology is intensively studied, particularly as treatments for stroke and neurodegenerative diseases. For these reasons, oxidative stress can be considered to be both the cause and the consequence of some diseases [15].

Antioxidant nutrients (Vitamin C, E, β-carotene, Vitamin A and Selenium)

Antioxidants are intimately involved in the prevention of cellular damage -- the common pathway for cancer, aging, and a variety of diseases. The scientific community has begun to unveil some of the mysteries surrounding this topic, and the media has begun whetting our thirst for knowledge. Athletes have a keen interest because of health concerns and the prospect of enhanced performance and/or recovery from exercise. The purpose of this article is to serve as a beginners guide to what antioxidants are and to briefly review their role in exercise and general health. What follows is only the tip of the iceberg in this dynamic and interesting subject.

Free radicals are atoms or groups of atoms with an odd (unpaired) number of electrons and can be formed when oxygen interacts with certain molecules. Once formed these highly reactive radicals can start a chain reaction, like dominoes. Their chief danger comes from the damage they can do when they react with important cellular components such as DNA, or the cell membrane. Cells may function poorly or die if this occurs. To prevent free radical damage the body has a defense system of antioxidants [16].

Antioxidants are molecules which can safely interact with free radicals and terminate the chain reaction before vital molecules are damaged. Although there are several enzyme systems within the body that scavenge free radicals, the principle micronutrient (vitamin) antioxidants are vitamin E, beta-carotene, and vitamin C. Additionally, selenium, a trace metal that is required for proper function of one of the body's antioxidant enzyme systems, is sometimes included in this category. The body cannot manufacture these micronutrients so they must be supplied in the diet [16].

Vitamin E: d-alpha tocopherol. A fat soluble vitamin present in nuts, seeds, vegetable and fish oils, whole grains (esp. wheat germ), fortified cereals, and apricots. Current recommended daily allowance (RDA) is 15 IU per day for men and 12 IU per day for women. Vitamin C: Ascorbic acid is a water soluble vitamin present in citrus fruits and juices, green peppers, cabbage, spinach, broccoli, kale, cantaloupe, kiwi, and strawberries. The RDA is 60 mg per day. Intake above 2000 mg may be associated with adverse side effects in some individuals.

Beta-carotene is a precursor to vitamin A (retinol) and is present in liver, egg yolk, milk, butter, spinach, carrots, squash, broccoli, yams, tomato, cantaloupe, peaches, and grains. Because beta-carotene is converted to vitamin A by the body there is no set requirement. Instead the RDA is expressed as retinol equivalents (RE), to clarify the relationship [17].

Intracellular Antioxidant Metabolites

The concept of “total antioxidant capacity” (TAC), which originated from chemistry and then was applied to biology and medicine, and further to nutrition and epidemiology, needs critical appraisal, because there are serious limitations that preclude meaningful application to in vivo conditions. This article briefly describes 1) strategies of antioxidant defense, 2) development of assay systems, 3) applications in vitro vs. in vivo-all of which lead to 4) the problem of “comparing apples with oranges” in applying in vitro dietary composition data to in vivo plasma and tissue status. Cells, tissues, and body fluids are equipped with powerful defense systems that help counteract oxidative challenge. To maintain a steady-state of metabolites and functional integrity in the aerobic environment, antioxidant defense is organized at 3 principal levels of protection: prevention, interception, and repair (Sies, 1993). Matching the diversity of prooxidants, the antioxidant armamentarium comprises a widespread array of systems (antioxidant network).

Glutathione is a cysteine-containing peptide found in most forms of aerobic life [18]. It is not required in the diet and is instead synthesized in cells from its constituent amino acids [18]. Glutathione has antioxidant

properties since the thiol group in itscysteine moiety is a reducing agent and can be reversibly oxidized and reduced. In cells, glutathione is maintained in the reduced form by the enzyme glutathione reductase and in turn reduces other metabolites and enzyme systems, such as ascorbate in the glutathione-ascorbate cycle, peroxidases well as reacting directly with oxidants. Due to its high concentration and its central role in maintaining the cell's redox state, glutathione is one of the most important cellular antioxidants. In some organisms glutathione is replaced by other thiols, such as by mycothiol in the Actinomycetes, bacillithiol in some Gram-positive bacteria [19], or by trypanothione in the Kinetoplastids [19].

Antioxidants are an important area of nutrition that is in depth and complex, due to the nature of the chemicals involved and the numerous mechanisms through which they effect human cells and the greater human body. Cells can be damaged by oxidative stress which occurs when there are not enough natural antioxidants in the body [20]. Two molecules, bound weakly, may be separated in the presence of oxygen which is a powerful oxidizing agent and removes electrons from other molecules. The molecules which are now un-bound become free radicals. Free radicals are unstable molecules with a single unpaired electron in the outer orbital. This molecule will take an electron from another molecule and separating another bond. Without enough antioxidants to bind the free radicals, they will continue to break existing bonds and create more free radicals .This process is called oxidative stress. Antioxidants stabilize the free radicals without becoming oxidized themselves [21].

Oxidants and oxidative stress have been found to have an effect on the development of cardiovascular disease. In particular, low-density lipoproteins (LDL), when oxidized are implicated in the development of atherosclerosis. Atherosclerosis occurs when plaques build up in arteries and blood vessels and is an important risk factor in the development of cardiovascular disease. The process of plaque formation begins with a fatty streak which then leads to a fibrous then complex plaque. These plaques become clinical events when the complex plaque ruptures and causes thrombosis which can lead to a stroke or ischaemic event [22].

Fatty plaques are formed when LDL is retained into the artery wall [23]. The LDL in the subendothelial space becomes oxidized [24], and this space does not provide access to the antioxidants present in the blood plasma. Therefore, these oxidized lipids become trapped in the subendothelial space of the artery. The LDL protein receptors are modified and no longer recognized, leading into cellular uptake of LDL which results in an accumulation of cholesterol. These cells are known as 'foamy' cells due to the appearance of their cytoplasm which is affected by the high intake of cholesterol [20-22]. High-density lipoprotein (HDL) prevents the oxidation of LDL resulting in fatty streaks [23].

Free-radicals have also been implicated in the damage to tissues done by diabetes. It has been found that in those with diabetes, there are high levels of free-radicals and reduced internal antioxidant defense [24]. Glucose oxidation is one of the main sources of free radicals, as the oxidation of glucose can result in the formation of the highly reactive hydroxyl radical [24] There are many other pathways which may lead to the production of free-radicals in diabetes including the hyperglyceamic promotion of lipid peroxidation, as well as the formation of nitric oxide from the Amadori product [10,11]. In those with diabetes, it has been observed that there are decreased levels of glutathione and increased levels of thiobarbituric acid reactants, nitric oxide and glycated proteins [21].

It has been found that an intake of antioxidants can have an effect on reducing the risk of developing type 2 diabetes, it has been found that vitamin E was significantly associated with a reduced risk, and intake of alpha-tocopherol, y-tocopherol, delta-tocopherol and b-tocotrienol were inversely related. B-cryptoxanthin was associated with a reduced risk of type 2 diabetes [22].

Low levels of antioxidants have been found in many different types of cancers. An increase in DNA lesions suggests an increase in free radical activity and is associated with decreased antioxidant activity in lung cancer [22-24]. Hydroxyl, hydrogen peroxide (H2O2) and Malondialdehyde(MDA) were found to be higher in people with breast cancer than in controls [24]. In gastric cancer, the risk of developing either cardia and distal gastric cancers was significantly decreased with an increasing intake of antioxidants, in a dose-dependent manner [25]. Those with colorectal cancer also have lower intake of fruit and vegetables in their diet [26]. However, use of antioxidants to help treat those who have been diagnosed with cancer is an unclear issue and it is unclear whether there are positive or negative effects of antioxidants on cancer.

Low levels of antioxidants also implicated in chronic obstructive pulmonary disease (COPD). It has been found that oxidants, such as lipid peroxidation measured as thiobarbituric acid-malondialdehyde adducts was present in a level significantly higher in those with COPD. Trolox

Equivalent Antioxidant Capacity (TEAC) was measured in this study as the antioxidant capacity and was found to be lower in those with COPD than in healthy controls [27]. In those with stable COPD, exhaled breath condensate has increased levels of H2O2 which indicates an increase of ROS in these patients. In those patients with exacerbated COPD, the levels of H2O2 were even higher. This suggests that antioxidant and oxidants are imbalanced in those with COPD [28].

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