Review

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The Double-edged Sword of Antioxidant Supplements on Metabolic Diseases, A Necessity for Quantification of Oxidative Status

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The Double-Edged Sword of Antioxidant Supplements on Metabolic Diseases, a Necessity for Quantification of Oxidative Status

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Abstract: Cells produce reactive oxygen species (ROS) as by-products of metabolism, which can give rise to a two-sided effect on the body under balanced and imbalanced oxidant homeostasis conditions. Antioxidant supplements exert their beneficial efficacy in the treatment of metabolic diseases only when the oxidant homeostasis is imbalanced with the over-production of ROS. Over-supplementation of antioxidant(s) can also cause an imbalanced oxidant homeostasis to exert detriments to the induction of metabolic diseases. This commentary raises a concern that prior to precise supplementation of antioxidants, an establishment of oxidant homeostasis status is required in avoiding an imbalanced oxidant homeostasis in vivo. In searching for valid oxidant stress makers, 3-Nitrotyrosine seems to fit in with the selection criteria and its quantification can be correlated with the degree of oxidative stress in vivo.

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Introduction

Consumption of antioxidant supplements has become popular since the1990's, forming a multi-billion-dollar market capacity. They are a group of substances including vitamins, minerals and plant extracts or synthetic chemicals that enable to erase or inhibit or regulate the production of reactive oxygen species (ROS) and derivatives. Following the discovery that overproduced-oxygen free radicals play a pivotal role in the pathogenesis of many metabolic diseases [1,2], a widely spread marketing of antioxidants as vital health-giving nutrients has begun and still is continuing. Since they are available without medical prescription and professional guidance, the detrimental effects have appeared clinically and could become a public health disaster if they are not regulated or misused by the general population. The current commentary aims to explore the clinical evidence of the benefits and detriments of antioxidant supplements with possible mechanisms and to recommend the oxidative status to be quantified for corrective consumption.

Benefits of Administration of Antioxidant Supplements

Cell metabolisms produce harmful compounds of free oxidative radicals or ROS, which can be destroyed or neutralized by the existing anti-free-radical compounds of the antioxidant system under physiological conditions. However, over-produced such radicals under some pathophysiological conditions and our body cannot be able to eliminate them in vivo can cause oxidative stress and trigger a series of reactions with cell membranes, proteins/enzymes, carbohydrates and DNA. Those reactions interfere with cell metabolisms and survival, resulting in disturbance of cellular normal division and functions, block of energy generation, damage of DNA and interruption of biochemical signalling. Despite free oxidative radicals within a normal range or under certain conditions playing a defensive role in protecting from microbiological infections and in maintaining normal cell metabolism and function, oxidative stress becomes a key factor in the development of the metabolic syndrome and other metabolic disorders, cardiovascular diseases, neurodegenerative disorders, cancers, and acceleration of aging [3]. Antioxidants play a pivotal role in fighting against oxidative

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stress [4]; supplements of nutritional antioxidants attempt to protect against the detrimental effects of ROS, assuming a normal diet only could not achieve a correct balance between oxidants and antioxidants; exogenous antioxidants could accomplish the protection against those diseases in addition to exogenous antioxidants [5]. Enormous literature and press have frequently publicized the benefits of antioxidant consumption, including its efficacy in many "incurable" disease treatments and in prolonging the life span of a healthy individual.

Antioxidants of vitamins D and C as immune boosters have been applied in enhancing the immune system, protecting from viral infection and reducing inflammatory reactions to promote an improvement of immunity in fighting COVID-19 [6,7]. Vitamin C supplementation improves endothelial function and creatinine clearance in kidney transplant recipients despite it is prone to kidney stones and interacts with its essential medicine of cyclosporine [8]. Supplementation of vitamins E and C combination can decelerate atherosclerotic progression [26]. A healthy pregnancy and optimal fetal development could be beneficial from an adequate supply of selenium [9] and patients with obstructive sleep apnea [10]. The mixtures of selenium and antioxidant could reduce CVD and all-cause mortality risk [20]. Some antioxidant supplements on the market demonstrate cardioprotective effects attributed to antioxidant and anti-inflammatory properties [11] in the management of cardiovascular disease prevention [12]. It may be attainable to use antioxidant supplementals in reducing the damage of traumatic brain injury [16]. The plant-antioxidant supplements have been suggested as adjuvant strategies in chemotherapy with platinum drugs [13]. Antioxidant supplementation may improve an antioxidant-oxidant balance in patients with liver disease displayed by modestly improved liver function test results [14]. Curative cancer therapies implement antioxidant supplementation to reduce the treatment side effects in achieving a better tolerance for the treatment and in improving quality of life, despite the antioxidants may interfere with the cytotoxic effects of chemotherapy if used improperly [15]. Although the effectiveness of antioxidant supplements could differ by type of antioxidants [16] with no firmed evidence on the improvement of lifespan, beneficial effects of antioxidant supplements seem undoubtful in anticipation of antioxidant deficiencies [17].

Detriments of Administration of Antioxidant Supplements

Over the last decades of administration of antioxidant supplements, many detriments have been clinically discovered in individual users. Those detrimental effects can offset the purposed benefits, and become a concern of the complications caused by unrestricted administration of the supplements in addition to many uncertainties of the effectiveness. Whether antioxidant supplements could be beneficial for patients with liver diseases [18] or justify usefulness in critically ill patients [19] or reduce risks of pancreatic cancer incidence and mortality in a nonlinear dose-response pattern [20] or mitigate adverse health effects associated with traffic-related air pollution [21] are still uncertain. In comparison with an optimal antioxidant-rich diet in a healthy population [22], the intake of individual antioxidants scarcely achieves health benefits even at high doses in patients during cancer treatment despite the possible side effects induced by oversupplied antioxidants [23,24] and the association with risks of pancreatic cancer incidence and mortality in a nonlinear dose-response pattern [20]. Vitamin E supplement has shown an inverse association with CVD in interventional trials [25]. Large-scale trials could not support the continued use of antioxidants to mitigate free-radical-induced changes in the cardiovascular system [27]. The randomized trials on vitamin A, vitamin E or selenium treatments have shown no significant effect or even increased mortality of several diseases [26]. Supplementation of antioxidants to patients with metabolic syndrome is still contradictory due to the counterproductive effects of excessive blocking on ROS production [27].

The detrimental effects of antioxidants may exert disturbances of redox homeostasis. Normal and stable redox homeostasis is a prerequisite for normal cell metabolism, differentiation, growth, DNA repair and survival, absorption of certain minerals, immunity and defence against pathogens since cell biochemical signalling and integrity require normal levels of free radicals to maintain. Clinical studies have revealed that an optimal source of antioxidants can be obtained from our diet but may not be sufficient from the supplements of pills or tablets [28]. Due to the detrimental effects

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of antioxidant supplements and the extensive marketing of such products continued, a compelling proposal has been raised to register them as medicinal products and to undergo sufficient evaluation prior to promotion [29]. Antioxidant supplements may not possess preventive effects and may be harmful with unwanted consequences for our health, especially in well-nourished populations. Therefore, further study should be focused on the limited efficacy or even harmful effects of antioxidant supplementation and the effective dose, supplement formulation, timing of administration, or various populations [21].

Determination of Redox Homeostasis Status is a Key to Accurate Dosing

In general, a "correction" of an imbalanced redox homeostasis undertakes those benefits achieved by antioxidant supplements in vivo; but an "oversupply" of antioxidants may cause those detriments. An imbalance of the redox species between ROS and antioxidants could cause cell dysfunction and death, and the efficacy of antioxidant supplementation relies on the capability of correction to ROS over-production. The ROS status in redox homeostasis becomes a necessity for antioxidant selection or supplemental quantity, given that more antioxidant(s) is not better or even worse. It could be plausible that over-dosing of the supplement(s) could eliminate the potential benefit(s) of antioxidant administration, which actually may induce an unjustified clinical side effect(s) [30]. Analysis of oxidative stress quantitative levels individually, therefore, becomes a necessity prior to the administration of most antioxidant supplements in gaining the proposed benefits without harmfulness. A quantitative baseline level as an index, once established, could be beneficial in overcoming the discrepancy in the different efficiencies among individuals caused by absorbance or the efficacy of the possible derivatives, in the establishment of individual dose recommendations, or in monitoring the prognosis of metabolic and other disorders in vivo.

Accurate and direct quantification of ROS is a challenging task, due to ROS having a very short half-life. The practicable approach is to indirectly measure the stable by-product which is modified under oxidative stress induced proportionally by ROS and exists in circulation as a biomarker. The recognized oxidative stress markers of ROS vary consisting of small molecules, enzymes, and proteins or derivatives. Due to many practical difficulties in obtaining clinical specimen(s), analyte stability, accessibility of instrumentation, and analytical specificity, sensitivity and reproducibility [31], reliable markers are scarce. In spite of the challenge for the selection of reliable oxidative stress biomarkers, 3-Nitrotyrosine (3NT) has become an outstanding candidate, fitting in with these criteria. 3NT is one of the promising biomarkers that is formed by oxidative stress through nitration of protein-bound and free tyrosine residues by the reactive peroxynitrite molecules involving ROS generation, well-established being a stable molecule in circulation. A simplified and commonly accessible analytical method has been developed and validated for the quantitative determination of blood 3NT to assess oxidative stress clinically [32]. Selection of an integrative panel of multi-markers is also recommended for the quantification of oxidative stress in humans [33] and 3NT should be one of them.

Conclusion

Oxidative stress involves in the pathogenesis of many metabolic diseases. Supplementation of antioxidants can confront ROS over-produced under pathophysiological conditions to achieve a profound treatment for the disease. Due to a variety of oxidative homeostasis exists among individuals and over-supplementation of antioxidant(s) could be inefficacy or harmful, accurate dosing individually becomes a great issue for treatment of the metabolic diseases. Marketing for those supplements must be aware of the adverse effects. In avoiding any potential detriments of the supplements, the oxidative status of individuals should be determined for accurate dosing. A reliable biomarker for oxidative stress status should be established and to be analyzed individually prior to supplementation. Among the potential biomarkers of oxidative stress, 3-NT seems promising to act as a reliable biomarker with its close correlation to the degree of oxidative stress and is ready for clinical applications.

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