Supplemental Antioxidants: A Hype in Disease Prevention

Bhupinder Singh Kalra

Abstract
Supplemental antioxidants are being prescribed by medical practitioners without considering its ill effects at higher doses. Antioxidants dosing has not been standardized and optimum or recommended daily dose is inconsistent too. Literature and Cochrane database search for review and meta analysis for efficacy of preventing and treating chronic disorders like cardiovascular diseases, diabetes, cancer, infertility etc shows inconclusive or negative results. Despite lack of evidence these drugs are rampantely being prescribed without any specific indication. Antioxidants are extensively being marketed too and their over the counter availability is again is the reason for its inappropriate use by consumers. Need is to practice evidence based medicine, define recommended daily doses with upper intake levels and antioxidants should be prescribed only in profound deficiency states.

Antioxidants or free radical scavengers are believe to neutralize products of oxidation reaction happening in the body. Excess of free radical production is considered as deleterious for cells as it can damage DNA, protein components and membranes. Our body naturally possess some of these antioxidants(endogenous) and we also get them from diet. These dietary antioxidants are mainly betacarotene, lycopene, and vitamins A, C, and E (alpha-tocopherol). Fruits, vegetables and grains have numerous antioxidants.

Do we require supplemental antioxidants in the form of commercial vitamins, what for and how much? The answer to this question till date is not clear. As a result, hype is being created by pharmaceutical industry to cash upon this opportunity to promote sales of supplemental antioxidants. It has been observed that antioxidants are two edge sword, at high concentration it has destructive role and may also lead to cancer. Although, various animal studies have established role of antioxidants in prevention of certain disease conditions like cardiovascular disorders, diabetes, cancer prevention etc. but clinical evidence has been either inconclusive or negative.

The global antioxidants market is estimated at $377.1 million as of 2016 and is forecast to reach $485.17 million by 2021. Antioxidants are mainly categorized as natural or synthetic. Natural antioxidants are generally used for disease prevention and synthetic antioxidants are used as preservative in food and beverage industry to prolong shelf life. Natural antioxidants market has been categorized into four types-rosemary extract, vitamin A, vitamin C, and vitamin E; while synthetic antioxidants comprise three types-butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), and others. Our concern is growing natural antioxidant market wherein supplemental antioxidants are being marketed rampantly.

Consumers have been misguided by overemphasized advantages of consuming supplemental antioxidants by Pharmaceutical industry. Effect of antioxidants on ageing, cancer prevention, chronic disorders like Diabetes, Hypertension, congestive heart failure etc has not been substantiated by clinical evidence (Table 1). Unnecessary, hundreds of animals especially rodents are being killed to see the effect of antioxidants (herbal or synthetic) as a part of animal research. Is this research justified in lieu of lack of clinical evidence? Animal efficacy data with antioxidants is not being translated into human benefit.

Are medical practitioners aware of this fact? Since, patients will consume as they are being asked to take antioxidants by treating doctor. Role of treating physician is vital in this process. They should be made aware and practice of prescribing antioxidants without any indication or deficiency state should be curbed down. Evidence based medicine should be inculcated in routine practice. The other important flaw is lack of awareness on the part of consumer and availability of these antioxidants over the counter.

Large scale cohort studies or national surveys are needed to establish total antioxidant intake from diet and the percentage that comes from supplements. This holds the key in establishing a relationship between antioxidants and disease. Both inadequate and excess intakes of antioxidants impact vital body functions and are associated with increased morbidity and mortality. To begin with, need is to establish Recommended dietary allowance (RDA), average requirement (AR)/ adequacy intake (AI) and upper intake levels (UIL) of antioxidants in different geographic population. United States antioxidant intake data might not be relevant in Asian subcontinent.

In a study conducted in India, it was found that majority of the supplements contained vitamins and antioxidants in higher than recommended intakes RDA, but many contained lower amounts or nutrients or other compounds that do not have recommended intakes. Since, retinol is the primary form of vitamin A in supplements, it is likely that the risk of excessive intakes is undesirably high for multivitamin users. In another study involving a multiethnic cohort in US, 10-15% of the participants had higher intakes of vitamin A. In a national survey in US,
it was observed that the labels of most preparations listed nutrients below the UIL. Amounts of vitamin B6, vitamin C and vitamin A were at or above the UIL.7

Antioxidants generally are not considered as drug rather they are regarded as dietary supplements. As a result the approval from Regulatory agencies for marketing is relatively easier process. Efficacy data is not mandatory or required for approval of antioxidants as they are considered as food supplement or nutraceuticals. This is again a flaw in the system leading to bulk manufacturing and marketing. The only beneficiary in this vicious cycle of supply and demand is the manufacturer of antioxidants.

The reason for failure of antioxidants in clinical studies despite positive findings in invitro and invivo studies could be pharmacokinetic, optimal dose not known, negative results of "ADDITIONAL TEXT"

Table 1: Evidence for effect of supplemental antioxidants

<table>
<thead>
<tr>
<th>Title of study</th>
<th>Type of study</th>
<th>Number of patients/studies</th>
<th>Outcome</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Antioxidant supplements for preventing gastrointestinal cancers</td>
<td>Meta analysis</td>
<td>20 randomised trials (211,818 participants), assessing beta-carotene (12 trials), vitamin A (4 trials), vitamin C (8 trials), vitamin E (10 trials), and selenium (9 trials)</td>
<td>1. Antioxidant supplements were without significant effects on gastrointestinal cancers (RR 0.94, 95% CI 0.83 to 1.06)</td>
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<tr>
<td>Antioxidant supplements for liver diseases</td>
<td>Meta analysis</td>
<td>Twenty randomised trials with 1225 participants. The trials assessed beta-carotene (3 trials), vitamin A (2 trials), vitamin C (9 trials), vitamin E (15 trials), and selenium (8 trials)</td>
<td>2. Beta-carotene in combination with vitamin A (RR 1.16, 95% CI 1.09 to 1.23) and vitamin E (RR 1.06, 95% CI 1.02 to 1.11) significantly increased mortality</td>
<td>10</td>
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<td>A randomized factorial trial of vitamins C and E and beta carotene in the secondary prevention of cardiovascular events in women: results from the Women’s Antioxidant Cardiovascular Study</td>
<td>Randomized Controlled Trial</td>
<td>1450 women experienced 1 or more CVD outcomes</td>
<td>No overall effect of ascorbic acid (relative risk [RR], 1.02; 95% CI, 0.99-1.05) and vitamin E (RR, 0.94; 95% CI, 0.85-1.04 [P = .23]), or beta carotene (RR, 1.02; 95% CI, 0.92-1.13 [P = .71]) on the primary combined end point</td>
<td>11</td>
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<td>Vitamins E and C in the prevention of prostate and total cancer in men</td>
<td>Randomized Controlled Trial</td>
<td>Total of 14,641 male physicians in the United States initially aged 50 years or older, including 1307 men with a history of prior cancer at randomization, were enrolled</td>
<td>Vitamin E had no effect on the incidence of prostate cancer [HR], 0.97; 95% [CI], 0.85-1.09; P = .58 or total cancer (active and placebo vitamin E groups [HR], 1.04; 95% CI, 0.95-1.13; P = .41). There was also no significant effect of vitamin C on total cancer [HR], 1.01; 95% CI, 0.92-1.10; P = .36)</td>
<td>12</td>
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<tr>
<td>Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT)</td>
<td>Randomized Controlled Trial</td>
<td>Total of 35,533 men from 427 study sites. Primary analysis included 34,887 men who were randomly assigned to 1 of 4 treatment groups: selenium; vitamin E; both agents, and placebo.</td>
<td>Compared with placebo, the absolute increase in risk of prostate cancer per 1000 person-years was 1.6 for vitamin E, 0.8 for selenium, and 0.4 for the combination.</td>
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| Effects of vitamins C and E and beta-carotene on the risk of type 2 diabetes in women at high risk of cardiovascular disease | Randomized Controlled Trial  | 8171 female health professionals aged > or =40 y randomly assigned to receive vitamin C (ascorbic acid, 500 mg every day), vitamin E (RRR-alpha-tocopherol acetate, 600 IU every other day), beta-carotene (20 mg every other day), or their respective placebos. | Median follow-up of 9.2 y | 14
| The Effect of Vitamin E and Beta Carotene on the Incidence of Lung Cancer and Other Cancers in Male Smokers | Randomized Controlled Trial  | Total of 29,133 male smokers randomly assigned to one of four regimens: alpha-tocopherol (50 mg per day) alone, beta carotene (20 mg per day) alone, both alpha-tocopherol and beta carotene, or placebo. Follow-up continued for five to eight years. | No reduction in incidence was observed among the men who received alpha-tocopherol (change in incidence as compared with those who did not, -2 percent; 95 percent confidence interval, -14 to 12 percent) | 15
| Efficacy of vitamin and antioxidant supplements in prevention of cardiovascular disease | Meta analysis               | 50 randomised controlled trials with 294478 participants (156663 in intervention groups and 137815 in control groups) | Supplementation with vitamins and antioxidants was not associated with reductions in the risk of major cardiovascular events (relative risk 1.00, 95% confidence interval 0.98 to 1.02; 12 to 42%) | 16

Need of the hour is to come up with guidelines or recommendations for optimal consumption of antioxidants.
Regulatory authorities, academia and pharmaceuticals should jointly work upon this process to draft recommendations to enlighten and benefit consumers.

References


