CORRESPONDENCE

Good Stress, Bad Stress—The Delicate Balance in the Vasculature

by Dr. rer. nat. Kirstin Wingler, Prof. Dr. med. Harald H. W. Schmidt
in volume 42/2009

Nature as the Optimal Organizer

In their article, the authors (1) say that antioxidants don't work—but that is not true. The specialist literature contains many descriptions of different enzymatic and non-enzymatic antioxidants that work synergistically in a network very effectively and are available exactly where they are required—optimally organized by nature (2). Interestingly, Wingler et Schmidt confirm elsewhere in the article the effectiveness of antioxidant enzymes and non-enzymatic antioxidants from among the secondary plant substances in tea, dark chocolate, and red grapes.

With regard to vitamins C and E, the authors cite a negative selection of studies whose quality is very much doubted by experts: neither study design nor the results are consistent with today's requirements (for example, Bjelakovic [reference e16 in the article] and Ristow [reference 10 in the article]).

It is not the case that most studies into antioxidants have yielded mostly negative results. The authors did not mention many studies with positive outcomes that were conducted according to the criteria of evidence based medicine and that confirmed significant and physiologically based benefits of antioxidants for a wide range of disorders (3, 4).

Further, we wish to draw attention to the fact that there are indeed different markers for oxidative stress—for example, hydroperoxide, malondialdehyde, and desoxyguanosine—and that these can be easily measured in clinical practice or in the laboratory.

DOI: 10.3238/arztebl.2010.0224a

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Conflict of interest statement

During his time as a specialist physician in private practice, the author provided advice on lifestyle medicine and adequate nutrition (including optimiz-

ation of micronutrient supplies and therapy with individually prescribed, high dose micronutrients, including antioxidants) as a private service with a preventive orientation.

Disputed Meta-Analyses

This is not an attempt to forcefully rehabilitate studies with the “old” antioxidants. However, two of the meta-analyses that Wingler and Schmidt cited in their very readable article (1) have come under strong criticism. The main result of the study reported by Bjelakovic et al (2007) was that in the total analysis of all 68 studies, intake of the 5 implicated micronutrients (vitamin E, vitamin C, vitamin A, beta-carotene, and selenium) had no significant effect on mortality (relative risk 1.02). Only when the authors subcategorized the 68 studies according to their own criteria into 47 with low bias and 21 with high bias, they found that mortality was slightly raised (RR 1.05) for the studies with low bias and reduced for those of “low” quality (RR 0.91).

Bjelakovic et al have ignored further fundamental principles of meta-analysis by categorizing 4 physiologically entirely different molecules and a trace element as “antioxidants” and by including studies with observational periods of between 1 day and 12 years. For 2 studies they used incorrect mortality data and were forced to publish a comprehensive correction in JAMA when prompted by the author of this commentary (2).

The allegedly raised total mortality in the subgroup of “methodically sound” studies went down by another percentage point. The results were also driven by the negative results of known studies of beta-carotene and vitamin A in male smokers who consumed vast amounts of alcohol. The cited Miller study into vitamin E was examined in detail and almost discredited (3).

The question that remains to be asked is why the important links between γ -tocopherol and the NO metabolism were not explained—the substitution of γ -tocopherol (by α -tocopherol) would even offer an explanation for the failure of the decades of α -tocopherol monomania (4).

DOI: 10.3238/arztebl.2010.0224b

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Lucid Scientific Analysis

This lucid scientific analysis (1) confirms that antioxidants do not have the effects that are often attributed to them. Because of possible negative effects, the current study situation should be considered before initiating regular intake of antioxidant supplements. The multivitamin study of the Association of Retired People on prostate cancer is an example for harmful effects: of the 295 344 men who underwent regular examinations for a mean period of 5 years, 10 241 developed prostate cancer; 1476 developed advanced stage cancers. If more than 7 multivitamin tablets were taken per week, the relative risk of advanced prostate cancer rose by 32%, but no relation was found for local prostate cancer. An intake of >7 multivitamin tablets per week increased the incidence of prostate cancer compared with abstinence from multivitamin preparations from 113.4 to 143.8 per 100 000 person years.

If 200 µg selenium was taken in addition to more than 7 multivitamin tablets per week then the RR of prostate cancer rose in a linear fashion: 1.01 for 1–6 days', 1.23 for 7 days', and 1.39 for >7 days' intake.. It is possible that one of the functions of reactive oxygen species (ROS) is to reduce damaged—even precancerous—cells. Prevention of prostate cancer is possible neither by using selenium (200 µg/day) nor in combination with vitamin D (400 IU/d). This was shown in the prospective, randomized SELECT study in 35 533 men (3).

What is remarkable is the health effect of red wine—beyond the “French paradox.” One of its bioactive substances is the stilbene resveratrol (red wine contains about 30 times the concentration of peanuts), which stimulates NO production, which in turn inhibits NADPH oxidase and the important transcription factor NF-kappa B. The result is a down-regulation of prostate specific antigen (PSA) (4). Accordingly, a case-control study has shown that red wine itself is suitable for primary prevention.

DOI: 10.3238/arztebl.2010.0225a

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Conflict of interest statement

The author declares that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

In Reply:

The three letters to the editor show how difficult it is to discuss this topic in an evidence-based manner, even amongst physicians. The belief in antioxidants is deeply rooted. It does indeed sound plausible: radicals and oxidative stress—they must be harmful; antioxidants—these must be beneficial. Scientific studies have shown, however, that supplementation with antioxidants is ineffective in the general population; in some cases it is even harmful (e.g. vitamin E or beta-carotene in smokers). As Dr Altwein points out, this risk also exists for multivitamin preparations in association with prostate cancer. Nevertheless, some redox-active compounds—for example those present in red wine, as discussed by Dr Altwein and in our article (resveratrol)—can have health promoting effects, albeit not by their antioxidant actions, but rather, for example, by influencing gene expression.

We were aware of the criticisms on the meta-analyses of vitamin E. Therefore, we had cited a more recent analysis (Dotan et al, 2009, reference 8 in our article[1]). This analysis used a different, more robust statistical model and still came to the same result: general supplementation with vitamin E is harmful rather than beneficial.

There are no commercial diagnostic assays that can measure “oxidative stress” in a reproducible manner and with acceptable variability. Values obtained with these assays (for example, plasma lipidperoxide and malondialdehyde) often do not correlate with each other (2). Oxidative stress is not a uniform phenomenon that affects the entire body. It seems naive to assume that taking antioxidants will result in detoxification of free radicals in the entire body and therefore reduce the redox potential of all cells within the organism. Moreover, radicals and other reactive oxygen species also mediate essential body functions.

We agree with the term “alpha-tocopherol monomania” and with the statement that nature has optimally organized itself. Therefore, we believe that the resulting natural balance should not be disturbed by administering antioxidant supplements.

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Conflict of interest statement

Dr Winkler was employed by vasopharm GmbH, which develops inhibitors for NADPH oxidases. Professor Schmidt has received research funding from Bayer Schering und Servier. He also acts as an adviser to Bayer Schering.