Oxidative Stress, Dietary Antioxidant Supplements and Health:

Is the Glass Half Full or Half Empty?

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Oxidative stress, defined as an imbalance between reactive oxygen species and the antioxidant defense system, the latter of which relies heavily on nutrients, has been associated with the risk of many different chronic diseases, including cancer. Historically, researchers studied oxidative stress and disease with the use of animal models, wherein dietary depletion of selected antioxidant nutrients induced disease, and repletion reversed the process. My own introduction into the research world of antioxidant nutrients and disease involved one such model, wherein chicks that were fed diets deficient in vitamin E and selenium developed a disorder characterized by subcutaneous edema (exudative diathesis)—a consequence of altered permeability of capillaries due to uncontrolled oxidation of lipid-rich cell membranes lining the capillary walls (1). The disorder could be readily reversed by the provision of vitamin E and/or selenium. The sheer simplicity was extremely appealing; visible disease could be induced or prevented by manipulation of antioxidant nutrients in the diet.

Over the past three decades, this paradigm of a direct relationship between nutrients and disease has been widely applied in human studies of chronic disease prevention, with many studies involving nutrients whose biochemical actions are thought to involve antioxidant activity (e.g., vitamin E, selenium, beta-carotene, vitamin C). However, several assumptions were made in attempting to extend the paradigm to human chronic disease, in particular: (i) that humans had an antioxidant nutrient insufficiency (i.e., absolute insufficiency or relative to some optimal, possibly supraphysiological status), which could be intervened upon; (ii) that oxidative stress played a central role in the pathogenesis of human chronic disease; and (iii) that systemically reducing oxidation was an end goal which would ultimately lead to disease prevention.
Based on evidence from epidemiologic research over the past several decades, we now recognize the naiveté of these assumptions as we have seen that antioxidant nutrient interventions in humans have produced benefits, harms, and null effects (reviewed in (2)). Thus, a pause for reflection as to what we have and have not learned is warranted.

The first assumption made in human intervention trials involving antioxidant nutrients was that of human insufficiency of antioxidant nutrients that needed to be rectified. Despite having a very limited understanding of dose-response relationships between nutrients and human chronic disease, intervention trials in numerous populations were undertaken, often using pharmacological rather than physiological doses of the antioxidant nutrient. The trial results indicated that interventions in nutrient deficient populations produced some clear benefits (3, 4), while interventions in more well-nourished populations produced some clear harm (2, 5-7). This raises the question, could other observational research have identified these non-linear responses before mounting intervention trials?

The article by Goyal et al. in this issue of the journal (8) tackles this problem, with an evaluation of vitamins A, C, E and selenium, modeling the dose-response relationship between quintiles of serum concentrations of these nutrients and various endpoints (overall mortality, cancer mortality, cardiovascular disease mortality) using data from the Third National Health and Nutrition Examination Survey (NHANES III). For all cause-mortality, results showed that people in the lowest quintile of the selected nutrients had the highest risk, and risk appeared to decline as status improved from the first to the second quintile, but after that results were inconsistent. The study design used by Goyal et al. is observational, and characteristics that track with either low or high nutrient status could explain some of the non-linearity in response, but arguing against confounding as an explanation are the findings emerging from subgroups of
numerous intervention trials, wherein people with the lowest status of a nutrient appear to be the most likely to benefit from the intervention. So, while the current findings provide some reassuring congruence between results from observational studies and trials, it is perhaps worth repeating that since low serum concentrations of nutrients are associated with factors such as smoking, obesity and inflammation (9-14), causality cannot be inferred from observational data alone. The authors suggest that intervention trials could be “personalized” based upon individual nutrient concentrations, which seems reasonable as long as the goal is treating “insufficiency” with modest doses of the nutrient of interest, to achieve physiological rather than pharmacological nutritional status. The authors also suggest intervening based upon biomarkers of oxidative stress, which holds more potential pitfalls, as discussed below.

Considering the issue of biomarkers of oxidative stress, Kantor et al. in this issue of the journal (15) examine the cross-sectional associations between self-reported specialty supplement use and biomarkers of oxidative stress and DNA damage in the VITamins And Lifestyle (VITAL) biomarker study. While there are numerous biomarkers of oxidative stress available (16), these authors used urinary 8-isoprostane and PGF2α to assess lipid peroxidation, and the well-known Comet assay, which reflects both DNA damage and repair. For the biomarkers of lipid peroxidation, they observed lower urinary PGF2α levels with use of glucosamine, chondroitin, and fiber supplements (none of which are particularly known for “antioxidant” activity). For the biomarker of unrepaired DNA damage, lower biomarker levels were observed in coenzyme Q10 supplement users.

The results are intriguing on several fronts, including which supplements were associated with lower biomarker levels, as well as which supplements were not (e.g., vitamins C, E, selenium). The glucosamine and chondroitin data add to previously published findings from this
group showing an inverse association between use of these two, but not other, dietary supplements and all-cause mortality (17). Because these are not truly nutrients, the dose-response considerations in relation to “insufficiency” are less relevant, but there is likely some insurmountable confounding in observational studies of glucosamine/chondroitin supplement use. Glucosamine is taken primarily to minimize symptoms of or prevent osteoarthritis, and users tend to be female, non-smokers, have higher-incomes and private health insurance, be more physically active and generally health-conscious than non-users and use has been reported to be lower in individuals with either cardiovascular disease or cancer (18). In contrast, coenzyme Q10, an endogenous antioxidant in the body, is marketed as a supplement for wellness (e.g., increase energy, aid recovery from exercise), as well as for possible therapeutic benefit in patients with disease (e.g., heart failure, cancer), so the direction of potential confounding is less clear.

Even if the associations between these specialty supplements and biomarkers are causal, the public health relevance of the findings is unclear as is well appreciated by the authors. That is, the predictive value of biomarkers of oxidative stress for chronic disease prevention is quite uncertain, and even for those biomarkers that have been associated with chronic disease, alteration of the biomarker by a supplement cannot be assumed to translate into disease risk alteration by that same agent. The best example here is the oxidation of low-density lipoprotein (LDL), which is recognized as part of the pathophysiological process of atherogenesis (19). Many biomarker studies demonstrated that vitamin E supplementation inhibited LDL oxidation \textit{ex vivo} (20) (vitamin E is carried by LDL in circulation), and along with the oxidative modification hypothesis involving LDL, supported the hypothesis that vitamin E supplementation held potential for reducing coronary heart disease (19). Unfortunately,
modulation of this relevant biomarker of oxidative stress by vitamin E did not translate into modulation of the chronic disease endpoint (21), even in the setting where the biomarker is seemingly located within the disease pathogenic process (albeit early in the disease process).

So how do we move forward with the complex relationships between oxidative stress and stress biomarkers, and dietary supplements and human health? Returning to our assumptions, it is now clear that interventions involving nutrients that target populations with clear insufficiency have a greater chance of success than interventions that target unselected populations (2). It is also clear that while oxidative stress may play a role in chronic disease, the mechanisms are likely much more complex than previously anticipated. While we have known for some time that reactive oxygen species play an important physiological role in host defense against infection, basic science research over the past decade paints an even more complex picture, wherein we now recognize that reactive oxygen species, such as hydrogen peroxide, can act as important physiological regulators of intracellular signaling pathways (22, 23), and may also play key roles in inflammation by altering the activation and duration of inflammatory processes (24). Inflammasome activation, for example, is sensitive to cellular perturbations in reactive oxygen species (25). This newer evidence suggests that dysregulated signaling involving reactive oxygen species may underlie many chronic diseases (23); that is, the role of oxidative stress and reactive oxygen species in human disease is much more nuanced than we originally hypothesized.

From the glass half empty perspective, the complexity of these relationships is daunting, and reminds us that over-simplification of complex disease processes has led to many detours in our path to translate science into disease prevention. But from the glass half full perspective, we now have new avenues to pursue by partnering with basic scientists studying tumors and their
microenvironment whose research promises to identify new and better biomarkers/genetic factors for future epidemiologic inquiry.

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