Use of Biomarkers of Oxidative Stress in Research Studies\textsuperscript{1,2}

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EXPANDED ABSTRACT

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In research studies, biomarkers can be employed to reflect environmental prooxidant exposures and dietary antioxidant intake or to serve as a surrogate measure of a disease process (1,2). To be truly useful, the biomarker must have some degree of predictive validity, but full substantiation of this relation still is lacking (3–5). A number of challenges must be overcome to obtain not only a better understanding of the contributions of reactive species to carcinogenesis but a rational application of biomarkers of oxidative stress to observational studies and clinical trials of antioxidants and cancer (6). Nonetheless, without measuring parameters relevant to the status of antioxidant defenses and oxidative stress, it is not possible to determine whether the selection, dose, and duration of an antioxidant intervention achieves its intended biochemical or physiologic endpoint or whether the enrolled subjects even present with oxidative stress (7–9).

Exposure to endogenous and environmental carcinogens causes DNA damage indicative of oxidative stress, with consequences for cytotoxic and mutagenic activity as well as aberrant changes to cell cycle progression and replication (10–12). Moreover, oxidation of cellular lipids and proteins can adversely affect several steps of the carcinogenic process through changes in a variety of cell regulatory functions, including signal transduction and gene expression (13). Thus, biomarkers of oxidative stress have the potential to help establish pathogenic stages of and risk for disease and should be employed to inform the design and outcome measures of clinical trials (14–16). Identification and application of suitable biomarkers should shorten the time it takes to demonstrate that an agent has a beneficial, untoward, or null effect on health promotion and disease prevention or a therapeutic value in disease treatment. However, some proposed biomarkers of oxidative stress might simply prove to be general markers of oxidative damage and relate poorly to disease process and outcome.

New research studies must address whether and how biomarkers adequately measure relevant physiologic functions or relate to established pathological signs, particularly with regard to their accuracy, precision, and reliability (17–19). Such efforts must consider the potential for artifacts produced during sample collection, processing, storage, and instrumental analyses, as well as confounding by the presence of related factors such as the status of facets of the antioxidant defense network that are not under direct study. The validation of biomarkers must include an assessment of the degree of bias in their measurement, especially the characterization of their prevalence and variability within large-scale population studies. An important issue for study is to determine whether specific biomarkers reflect short- or long-term exposure to an antioxidant status or oxidative stress.

When establishing the Dietary Reference Intakes, the Institute of Medicine (IOM) used biomarkers of oxidative stress to define dietary antioxidants (20). The IOM definition of dietary antioxidants includes their ability to substantially decrease the adverse effects of reactive species, such as reactive oxygen and nitrogen species, on normal physiologic function in humans. However, it is not clear whether a sufficient scientific agreement yet exists regarding the validity of these biomarkers as a reflection of the action and efficacy of dietary antioxidants. This issue is confused by the apparent difficulty, in many studies, of demonstrating an antioxidant effect unless oxidative stress is first markedly elevated, as found, for example, in smokers or patients with marked inflammatory conditions.

One common working definition of oxidative stress is the disturbance in the prooxidant–antioxidant balance in favor of the former, which leads to potential cellular damage. However, measuring oxidative stress can be difficult due to the presence of complex endogenous systems for correction and repair (e.g., as may occur when a brief elevation in oxidative stress rapidly induces various antioxidant defenses, particularly...
antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase) that quickly reduce the stress and limit the ability of testing methods to detect a change. Oxidative stress can result from diminished antioxidant protection as well as increased free radical production. Therefore, investigating antioxidant depletion as a biomarker of oxidative stress may involve assessment of decreases in antioxidant concentrations or increases in their metabolites. However, such changes may not reflect a clinically significant or pathogenic event but merely indicate that the antioxidant defense system is functioning.

DNA, lipid, and protein oxidation products provide an extensive and growing array of potential biomarkers, although our understanding of the relation between their status in cells and tissues, including plasma and urine, remains to be elucidated (1). Development of a broader panel of biomarkers to examine both pro- and antioxidant reactions should be pursued. This might include the capacity of a biological sample to resist oxidation in vitro or ex vivo and modulation of redox-sensitive transcription factors or related alterations in signal transduction pathways.

In practice, single elements or combined parameters from these approaches currently are employed, although, not infrequently, only one analyte is measured. The incorrect conclusion may then be drawn that it satisfactorily reflects oxidative stress. Although the capability to adequately assess genomic factors relevant to antioxidant defenses and oxidative stress is limited, this facet of new research approaches will become increasingly important in determining which individuals are most likely to respond to antioxidant interventions. Further elucidation of the relation between antioxidants and cancer risk will require validation of existing biomarkers of oxidative stress as well as the creation of new indices.

**LITERATURE CITED**


