

In response to an acute inflammatory response, neutrophils are elevated whereas in chronic inflammation, affected tissues and the systemic circulation contain an excess of macrophages, lymphocytes and plasma cells. During the inflammatory process, activated free radicals are generated by these cells as a result of the "respiratory burst" that include superoxide and hydroxyl radicals, hydrogen peroxide, nitric oxide and peroxynitrite. The clinical signs of inflammation are pain, edema and fever, all attributed to oxidative stress. To date, over 8,000 reports have appeared in the literature that have attempted to link inflammation with TBARS measurements, reactive oxidative species, antioxidant deficiency, or synthesis of inflammatory cytokines. Prominent clinical disorders discussed in this newsletter are associated with sepsis, liver, digestive system, lungs, joints, uterus, kidney and periodontal disease. All-risk mortality is greater in the elderly where individuals with high TBARS and low antioxidant status are more susceptible to oxidative damage than those with low levels of TBARS and protection by high antioxidants (1).

**HEPATITIS:** Hepatic oxidative stress can lead to hepatitis in patients who require treatment consisting of partial hepatectomy, or common bile duct ligation. In these studies, TBARS and its main lipid peroxide metabolite 4-HNE were significantly elevated relative to sham-surgical controls (2). Levels for both biomarkers were found to be higher in females. This is the first report on the effect of hepatitis core protein on oxidative stress during hepatic inflammation due to biliary tract obstruction and was measured using the ZeptoMetrix TBARS kit. One possible cause for the elevated levels could be impaired antioxidant protection resulting in reduced glutathione and inhibition of gamma glutamylcysteine transferase and methionine adenosyl transferase activity which cause a decrease in biliary glutathione output.

**SEPSIS:** Patients in the Intensive Care Units have high mortality (3). Such patients also have elevated levels of lipid peroxidation and inflammatory biomarkers as well as reduced levels of antioxidants. For example, in early-onset neonatal sepsis TBARS was increased from 4.2 in controls to 10.1 in sepsis, while inflammatory cytokines were elevated from 2.5 to 2.9 times above normal (4). TBARS was also shown to be a better independent predictor than IL-6; odds ratios were 2.16 for TBARS vs. 1.2 for IL-6. When CRP and TNF-alpha were also measured, over a 3 year period, increases were associated with an unfavorable outcome (5). These authors state that TBARS and inflammatory biomarkers are closely linked in the development of sepsis. Interestingly, resistin, a hormone derived from macrophages was also increased and speculated to be a prognostic indicator that represents a link to inflammation.

**ARTHRITIS:** It is projected that by the year 2030, more than 60 million patients will suffer from arthritis at an annual cost of \$ 10,000 / person. TBARS is increased in patients with either osteoarthritis, or rheumatoid arthritis. Arthritis is characterized by high levels of arachidonic acid metabolites such as prostaglandin E2 / thromboxanes and leukotriene B4 which are generated from COX-2 and 5-LOX reactions respectively. Elevated matrix metalloproteinases (MMP) are pro-inflammatory enzymes that are activated by inflammatory cytokines such as TNF-alpha and IL-6. Consequently they are also elevated. IL-10 is important because it acts faster than the other interleukins. Some investigators consider MMPs and cytokines mentioned above to be the most important factors in promoting inflammation. In the osteo-form, there is a significant increase in the level of lipid peroxidation as detected by the TBARS assay with a corresponding decrease in antioxidant activity (6). In the rheumatoid form, antioxidant biomarkers like catalase, superoxide dismutase, and glutathione peroxidase were decreased, while TBARS, oxidized carbonyls and oxidized DNA were increased (7). During oxidative stress, synovial and blood-borne cells in arthritic joints are known to produce nuclear factors kappa B that activate secretion of proinflammatory cytokines especially IL-6 leading to a variety of lipid peroxides and their TBARS positive metabolites. Of interest is the finding that C-reactive protein (CRP) was also elevated in conjunction with TBARS (8). Clear evidence is still lacking regarding whether TBARS or CRP appears first in the blood, but if either is present it is an unequivocal sign of inflammation. Experimental models of oxidative stress-induced inflammation using the pro-inflammatory mediator LPS (MD Biosciences) are available to possibly answer this question. Anti-inflammatory nutrients that are important include curcumin, fish oil, gamma-linolenic acid, vitamin C, soluble fiber, isoflavones and coenzyme Q10 (for further reading see Life Extension magazine September 2010, vol. 16, no. 9, page 20, reference numbers 44, 52, 54, 58, 59, 63, 75, 77, 87, 88, 153, 162, 164 and page 79, reference 16).

**INFLAMMATORY BOWEL DISEASE:** This term includes ulcerative colitis and Crohn's disease. The former is a diffuse, superficial, acute inflammation with intermittent clinical symptomatology and is limited to the colon. Crohn's disease is a chronic inflammatory disorder that penetrates all layers of the bowel. Patients with Crohn's disease have 3-fold higher risk of developing intestinal cancer. TBARS is elevated in these disorders (10.3 and 11.3 mmol / ml respectively compared to 8.7 in controls.)  $p < 0.05$  (9). The antioxidant profile including vitamins A, E, C, beta-carotene, reduced glutathione and CuZn SOD were markedly reduced.

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Although contradictory results have been reported, a recent review publication links initiation and progression of oxidative stress to the pathophysiology of IBD (10). Paraoxonase-1, another antioxidant enzyme is also reduced in Crohn's disease, but is not a powerful indicator compared to CRP which is elevated in inflammatory bowel disease (11). However, in that study, TBARS using the ZeptoMetrix kit was within the normal range and the authors speculate this might be due to a more effective hydrolysis of lipid peroxides, thus reducing TBARS levels. On the other hand, TBARS was increased (2.5 mol/ ml vs. 1.1 in controls) and PON-1 was decreased (158 UI vs. 233 in controls) in a separate study (12).

In summary, there is a broad spectrum of changes documented for inflammatory biomarkers of oxidative stress. These are linked to most, if not all inflammatory disorders with a uniform elevation of TBARS, activation of nuclear factors, increased inflammatory cytokine activity and reduced antioxidant capacity being the general trend. Lin and Thomas conclude that free radicals initiate inflammatory responses, followed by symptomatology (34). The most widely applied assay is TBARS because of its simplicity, disease associated specificity, early detection in oxidative-induced disorders and cost effectiveness. Most authors suggest that as a single biomarker, TBARS is superior to any of the other assays for measuring oxidative stress. Appropriate studies comparing TBARS and CRP, or inflammatory cytokines have not been conducted as yet.

Such studies have to measure responses at extremely short time intervals to detect differences in developing and interpreting the relationship of TBARS to inflammatory patterns.

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