Measuring Oxidative Stress

Joseph Pizzorno, ND, Editor in Chief

I assume every healthcare professional in integrative medicine is highly aware of oxidative stress and its key role in virtually all chronic disease. But while we all recognize many factors that increase and decrease oxidative stress, I suspect most of us do not know how to actually measure it. Trying to figure this out led me on an interesting journey with a surprising conclusion. As I am sure most readers have found, there are few tests for oxidative stress and those that do exist are expensive and available only from specialty labs. Many of these are quite useful, but I was looking for tests that are less expensive and more readily accessible.

Surprisingly, Ryan Bradley, ND, recommended I consider gamma glutamyltransferase (GGT) and sent me a copy of the lecture he had presented at last year's annual convention of the American Association of Naturopathic Physicians. After looking at his presentation, I realized that this readily available, very inexpensive test included in the standard liver enzyme panel might be what I was looking for. Following are my findings.

GGT

GGT is found on the membranes of all cells and at particularly high concentrations in the liver, bile ducts, and kidneys. Normally, we think of elevated serum GGT as a sensitive indicator of liver damage. High levels are found in severe alcoholics as well as in patients with cholestatis, hepatic fibrosis, and hepatitis and those taking some drugs such as erythromycin, flucloxacillin, phenobarbitone, steroids (including oral contraceptives), and trimethoprim/sulfamethoxazole .

Of interest to this article is that elevation of GGT within the supposedly normal range has now been shown to correlate with oxidative stress. How so? The primary role of GGT is to metabolize and transport extracellular reduced glutathione (GSH), allowing for precursor amino acids to be assimilated and reutilized for intracellular GSH synthesis. As the need for glutathione production increases, for example as a protective response to oxidative stress or heavy metal exposure, so does the production of GGT to facilitate GSH production. Serum GGT correlates with F2-isoprostanes (an oxidative product of arachidonic acid), fibrinogen, and C-reactive protein—all markers of inflammation. While oxidative stress and inflammation are not the same, they are highly correlated: The proinflammatory cytokine tumor necrosis factor alpha induces GGT promoter transactivation, messenger ribonucleic acid, protein synthesis, and enzymatic activity.[1]

Some clues as to the importance of GGT in oxidative stress can be found when considering that elevated levels still within the "normal" range are now known to be risk indicators for diabetes and cardiovascular disease. Also of interest is the recent finding that GGT appears to help transport vitamin C into cells.[2] As might be expected, serum levels of GGT correlate with lifestyle and other factors known to be associated with oxidative stress. Among the more notable are that body mass index and obesity correlate with serum GGT, and there is a strong inverse correlation between dietary carotenoids and GGT.[3]

GGT and Disease Risk

A long-term, 18-year study looked at the predictive value of GGT for a cardiovascular event. The results were remarkable: Those with the highest quartile GGT (>35 U/L) had more than 3 times the risk of those in the lowest (<13 U/L). A prospective analysis of data from the British Women's Heart and Health study (n=2961) found that each 1 U/L elevation of GGT was associated with a health risk (HR) of 1.20 for coronary heart disease and a HR=1.54 for stroke.[4] Analysis of a subgroup of nondrinkers yielded the same results: GGT's predictive value for cardiovascular disease has been shown to be independent of alcohol consumption, extent of coronary atherosclerotic disease, left ventricular ejection fraction, age, serum glucose, cholesterol subfractions, and C-reactive protein. At a 3-year follow-up, cardiac mortality was 9% in patients with serum GGT activity >25 U/L vs 3.5% in those with serum GGT<25 U/L.[5]

A large study of 9621 patients with Type 2 diabetes found elevated GGT in 23.1%.[6] Another large study, this one of 4844 black and white men and women 18 to 30 years of age in 1985 to 1986 followed at 2, 5, 7, 10, and 15 years found a strong predictive value of GGT for diabetes and hypertension—with those above the mean having 3 to 4 times the risk as those below the mean GGT levels.[7]

Ways to Therapeutically Affect Serum GGT

Both lifestyle and dietary factors (especially decreasing alcohol consumption) as well as several nutritional supplements decrease serum GGT. As might be expected, most of the supplements are either antioxidants or stimulate the production of glutathione. Among the most important are the following, which are also included as part of Table 1.

Qigong: A small, controlled study of qigong found that 1 month of practice lowered the serum levels of several liver enzymes including GGT in healthy individuals.[8]

Milk thistle (*Silybum marianum*): A pregnant rat study showed that milk thistle protected both mother and fetuses from alcohol toxicity as measured by a normalization of their GGT compared to the untreated group.[9]

Fenugreek (*Trigonella foenum-graecum*): In another rat alcohol study, fenugreek was found to restore to normal the serum enzyme markers of liver injury including GGT.[10]

N-Acetylcysteine (NAC): At 600mg/day for 4 weeks,

Table 1. Factors Affecting Serum GGT Levels[17-20]	
Factors That Increase Serum GGT	**Factors That Decrease Serum GGT**
Acetaminophen (which aggravates the effects of alcohol by also depleting glutathione in the liver)	Dietary and supplemental vitamins C and E, carotenoids, and fiber
Drugs: dilantin, erythromycin, flucloxacillin, phenobarbitone, steroids (including oral contraceptives), and trimethoprim/sulfamethoxazole	Foods: beans, coffee, fruits, lentils, nuts, vegetables, whole-grains
Elevated blood sugar	Herbs: milk thistle (*Silybum marianum*), fenugreek (*Trigonella foenum-graecum*)
Excessive alcohol consumption	Homeopathy: *Arsenicum album* 30x
Food: meat and fried foods	Nutrients: N-Acetyl-Cysteine, probiotics
Herbs: Kava kava (*Piper methysticum*)	Physical activity
Obesity	Qigong
Smoking	

NAC reduced GGT from 62.7 to 46.3 U/L in patients with non-alcoholic steatohepatitis—most likely as a result of increased GSH production.[11]

Vitamin E: A study of vitamin E in patients with polymorphous light eruption (PMLE), a photo-induced disease resulting from high oxidative stress that clinically manifests in the form of pruritic eruptions on sun/light exposed parts, used GGT as one of the measures of efficacy. Researchers found that 400 mg/day of alpha tocopherol acetate resulted in a highly significant reduction of GGT from 64.0 to 28.50 U/L in just 7 days.[12]

Vitamin C: A number of studies have shown that supplementation with the antioxidant vitamin C protects the liver from many oxidative toxins as measured by decreases in GGT.[13]

Probiotics: Probiotics appear surprisingly effective in reducing the elevated GGT seen in excessive alcohol consumption. Since heavy alcohol use appears to cause a reduction in colon counts of healthy bowel bacteria, perhaps part of the liver damage from alcohol is an increased load of intestinal toxins due to a suboptimal microbial balance. An interesting study found that 5 days of *Bifidobacterium bifidum* and *Lactobacillus plantarum* 8PA3 resulted in a 14% drop in serum GGT versus standard therapy after only 1 week.[14]

Homeopathy: A placebo-controlled, double-blind study of 39 residents of 2 villages in India with arsenic-contaminated water found that administration of homeopathic *Arsenicum album* 30x once per day resulted in the lowering of both clinical and laboratory measures of arsenic toxicity. Interestingly, after 2 months, GGT also dropped from 40 to 10 U/L in men and 30 to 6 U/L in women.[15] As homeopathy is a controversial philosophy and therapy, seeing such an objective measure of efficacy is quite fascinating!

Kava kava (*Piper methysticum*): On the other hand, chronic kava consumption appears to significantly raise GGT levels. A study of 31 healthy adult kava drinkers were compared against a control group of 31 healthy adult non-kava drinkers in Hawaii. Turns out that 65% of chronic consumers had an elevation of GGT compared to 23% of controls.[16]

Conclusion

After looking at a lot of studies on GGT, I am quite impressed by its usefulness in an integrative medicine practice. Its low expense, good predictive power, and direct correlation with health behaviors can be quite valuable for patient motivation and monitoring of progress. While the optimal health range has not yet been fully determined, at this time my recommendation is 11-20 U/L for men and 7-20 U/L for women.

In This Issue

With the election of a new president and a Congress with strong democratic majorities, all are watching with great interest to see what changes may come to healthcare. Hence, in a special report, *IMCJ* Associate Editor William Benda, MD, covers The Institute of Medicine's Summit on Integrative Medicine and the Health of the Public (held February 25-27, 2009, in Washington, DC). The Institute of Medicine (IOM) and the Bravewell Collaborative partnered to convene a conference that explored the science and practice of integrative medicine (IM). The meeting reviewed the state of the science, assessed IM's potential and priorities, and began to identify elements to improve understanding, training, practice, and other actions that might help improve future healthcare. Prevention, research, education, and clinical care were also addressed.

Unfortunately, as Bill so aptly comments, "the majority of panels were populated by representatives of academic medicine, the insurance industry, research centers, think tanks, and consumer groups. No in-the-trenches practitioners. No membership organizations. (No journalists.)"

A chiropractor who attended the meetings reported to me, "It was MDs talking to MDs as usual."

Also in our special report, John Weeks adds his insights on the IOM summit in News and Analysis: "'Integrative Healthcare Week'": Can 5 Days Crack the Status Quo of Medicine?" A 25-year veteran of integrative medicine publishing, John gives voice to where this all may be going.

Our original research is a randomized, prospective, double-blind, comparative study by Nandhakumar Jothivel, PhD, et al, comparing efficacy, tolerability, and safety of glucosamine hydrochloride or glucosamine sulfate to a non-steroidal antiinflammatory drug (NSAID) in the treatment of knee osteoarthritis. I think the key take-away message from this study is that, while NSAIDs reduce symptoms more quickly, the cartilage regeneration effect of glucosamine has better long-term efficacy.

We all know that psychological stress is a contributing factor to most chronic diseases. Donielle Wilson, ND, CPM, presents on the disruption of neurotransmitter balance and how this causes anxiety and depression. She then shows how supplements such as 5-hydroxy-tryptophan, amino acids, γ-aminobutyric acid, glutamine, taurine, and theanine can

help restore neurotransmitter balance.

In this issue's Quality Assurance column, Rick Liva, ND, RPh, explains the difference between quality assurance and quality control—a concept that demands the attention of every practicing clinician. The information presented gives the clinician a working knowledge of how easily to ensure they get high-quality products from dietary supplement manufacturers.

I would like to emphasize the concern of product claims using what is called "borrowed science." If all the research on a product, such as pomegranate juice mentioned in Rick's article, is done on a specific product, then the onus is on other manufacturers to prove that their product has equivalent constituents if they are to assert the same clinical benefits as the researched product. Different manufacturing processes can produce very different results and, as Rick so aptly demonstrates, spiking a product with a known active constituent does not mean the products are the same.

Many readers have found great value in the "Manufacturer Quality Assurance Self-Audit Form" written by Rick. Important additions in this issue are the inclusion of an updated version of the form plus guidelines to help interpret results when they are returned. I cannot stress enough how important it is for clinicians to take the time to send this form out to their vendors. With the way laws are now set up, clinicians are the gatekeepers of quality. The responsibility should not be taken lightly.

As usual, Bill Benda, MD's, BackTalk does not need any comment: Vested interests want more of the same, just with different labels.

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Correction: On the Table of Contents for the Apr/May 2008 issue of *IMCJ*, for the article "Modulation of Neurogenic Inflammation in Osteoarthrosis Patients Undergoing a Combined Treatment of Mud Packs, Thermal Baths, and Acetaminophen: A Preliminary Study," *IMCJ* incorrectly listed Francesco Grossi as an author and omitted Mattia Zaccarin. (The authors were correctly listed on the article itself.) We apologize for this error and any confusion it may have caused.