Metabolic Detoxification: A Review of the Scientific Literature on its Application to Clinical Practice

Research Review

EXECUTIVE SUMMARY

The sheer volume to which humans are exposed to environmental toxicants and biological toxins on a daily basis can overburden the body's natural metabolic detoxification capacity. Mounting evidence has suggested that the accumulation of toxins is associated with a number of chronic conditions, and lifestyle and nutrition have critical roles in minimizing toxicant and toxin exposure and optimizing the functioning of the detoxification system.

In this review, we will focus on examining the evidence in the scientific literature connecting toxin and toxicant exposure to various chronic health conditions (**Table 1**), supporting the role of proper nutrition for effective metabolic detoxification (**Figure 1**), and providing insight into the clinical practice of detoxification support. We will provide basic concepts of physiology and biochemistry required to better understand the need to support biotransformation and elimination in a clinical setting.

DETOXIFICATION

While the body has sophisticated processes for detoxification, it is constantly being challenged by the ever-increasing burden of toxins and toxicants in the environment. It has been estimated that 80,000 novel chemicals have been registered with the United States Environmental Protection Agency since World War II, yet the majority have not been evaluated for their effects on human and environmental health.[1] Approximately 700 new industrial chemicals are introduced into the marketplace each year without due testing of their reproductive or chronic toxicities.[2] There are concerns about the interactions of these chemicals leading to a synergistic effect, perhaps more detrimental than each chemical taken in isolation. Further, toxins and toxicants may be stored in the body.[1,3] Persistent organic pollutants biomagnify up the food chain, eventually accumulating in human fatty tissues,[3-5] such as the brain and adipose tissue.

How this toxic burden manifests clinically depends on the exposures, genetics, and the function of a person's detoxification systems. Toxicant exposures and compromised clearance may play a role in obesity,[6] cardiovascular disease,[1] cancer,[1,6,7] neurocognitive disorders,[1] immune dysfunction,[8] chemical intolerance,[7] and reproductive and developmental disorders.[6,9,10] Overall, a comprehensive strategy to reduce a patient's toxic burden includes: identify exposures, counsel the patient in avoidance and alternatives, and optimize all 3 phases of detoxification, as well as balance activity of Phase I and Phase II, using nutrition and phytonutrients.

The National Cancer Institute defines the word "toxin" as a poisonous compound made by biological organisms such as bacteria, plants or animals, and the word "toxicant" as a poison made by humans or that is put into the environment by human activities.[11] Toxicants include heavy metals, pesticides, or herbicides.

LINKS TO CHRONIC HEALTH CONDITIONS

Cardiometabolic Disease. Mounting evidence suggests the role of a range of toxins and toxicants in the pathogenesis of cardiovascular disease. Obesity, diabetes, and metabolic syndrome have been linked to pesticides,[6] polychlorinated biphenyls (PCBs), dioxins, and flame retardants.[1] Bisphenol A, found in hard plastics and considered an endocrine disruptor, has been implicated in obesity,[12] diabetes, and cardiovascular disease.[13] Toxic metals are also believed to interfere with cardiovascular function.[1]

Cancer. High exposures to occupational carcinogens has been extensively studied as a cause of cancer.[1] A number of cancers have been linked to compromised detoxification ability, although research is inconclusive.[7] Higher levels of fat-soluble pesticides and PCBs were found in breast adipose tissue of women with breast cancer. Higher blood levels of these chemicals increased the risk of breast cancer by four-fold.[4] In a study of childhood brain cancers, a significant positive association was found between cancer and those who used pesticides, insecticides, and herbicides at home.[4]

Table 1. Common Clinical Symptoms & Conditions Associated with Environmental Toxicity[14-23]

Abnormal pregnancy outcomes
Atherosclerosis
Broad mood swings
Cancer
Chronic fatigue syndrome
Chronic immune system depression
Contact dermatitis
Fatigue
Fertility problems
Fibromyalgia
Headaches
History of increasing sensitivity to exogenous exposures, odors, or medications
Joint pain
Kidney dysfunction
Learning disorders
Memory loss
Mineral imbalances (particularly zinc and calcium)
Multiple chemical sensitivities
Muscle pain and weakness
Nonresponsive or recurrent yeast infections
Panic attacks
Parkinson's disease
Tinnitus
Unusual responses to medications
Worsening of symptoms after anesthesia or pregnancy

Prenatal & Childhood. One of the most startling ramifications of the high toxicant concentration in the environment is that expectant mothers can transmit toxicants to the unborn baby. Persistent organic pollutants can cross the placental barrier and even low levels of these toxicants present a danger to the developing brain.[9] A study from the National Health and Nutrition Examination Survey (NHANES) showed that there were measurable levels of toxicants thought to be harmful to human reproduction and development in *all* of the pregnant women tested: lead, mercury, BPA, phthalates, pesticides, toluene, perchlorate, perfluorochemicals, PCBs, and polybrominated diphenol ethers (PBDEs).[2]

The possible synergistic interaction of multiple toxicants has not been adequately explored. Prenatal tobacco exposures *together* with lead act synergistically and increase the risk for attention deficit hyperactivity disorder (ADHD) in children, more so than the simple additive effects of the toxins.[9] This underscores the potentially damaging impact of toxicant combinations on the developing brain. Since cord blood has been shown to contain upwards of 200 chemicals,[24] multiple toxicant exposures in utero is the rule, rather than the exception.

Numerous studies show an association between chemical exposures and impaired neurodevelopment.[25] For instance, lead causes cognitive deficits, anxiety, decreases IQ, and interferes with attention.[9] According to the Centers for Disease Control and Prevention (CDC), even the lowest detectable amount of lead may pose risks (blood lead <10 ug/dL).[9] BPA and pesticide exposures can increase the risk for reproductive disorders and birth defects,[6,10] and pesticides can increase the risk of pervasive developmental disorder, ADHD, inattention, and hyperactivity in children.[9]

Neurological Disorders. Heavy metals and pesticides can lead to neurocognitive dysfunction. Most common pesticides are neurotoxic by design.[4] Clinical manifestations may include learning disorders, attention problems, aggression, increased susceptibility to amyotrophic lateral sclerosis (ALS),[6] Parkinson's disease, or Alzheimer's disease.[1] In particular, pesticides have been linked to higher rates of Parkinson's, Alzheimer's, and ALS.[6] This may be the result of compromised detoxification, genetic susceptibility, and increasing toxicant body burden.[26]

Immune Dysfunction. Toxicant stress may alter immune function and possibly initiate autoimmunity. Environmental chemicals can decrease cell-mediated immunity as well as increase sensitivity (allergy).[4] Benzene exposure altered immunological markers in gasoline workers.[15] Authors observed that the innate immune system was activated while the adaptive immune system was suppressed.[15] Exposures to BPA and other xenoestrogens may increase a person's risk for developing autoimmune diseases[8] and poor

detoxification capability has been linked to systemic lupus erythematosus and rheumatoid arthritis.[26]

Chemical Sensitivity & Idiopathic Conditions. Inability to properly transform toxicants and their metabolites may be one explanation for idiopathic conditions such as chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivity.[7] The milder form of multiple chemical sensitivity, chemical intolerance, is thought to affect 10% to 30% of the US population.[25] Low-level exposure to a wide variety of chemicals, foods, drugs, caffeine, or alcohol may initiate multisystem symptoms that often involve the central nervous system.[25] In such patients, a triggering event may be a home remodeling project or chemical pest treatment at the home or office.[25]

DETOXIFICATION FUNCTION

The body is incredibly well equipped to biotransform and eliminate toxins and toxicants. An overview of the 3 phases of metabolic detoxification can be found in the related research review, "The Role of Detoxification in the Maintenance of Health" (MET2221). Briefly, Phase I is dominated by cytochrome P450 enzymes that biotransform the mainly lipophilic toxin or toxicant into a more water-soluble molecule. Phase II includes a variety of different conjugation reactions whereby the toxic compound is bound to a chemical group (such as a methyl group or amino acid) that renders the toxin even more water soluble so that it can be excreted. Phase III is the elimination of the biotransformed or conjugated toxins from the cell.

These pathways are tremendously energy intensive, requiring healthy mitochondria and adequate ATP production. Excess activity of Phase I, without coordinated Phase II activity, such as in the case of fasting or poor nutrition, can generate an overload of potentially harmful reactive toxic intermediates. This can lead to oxidative stress, inflammation, and disease.

There is a deficit of research investigating the clinical effects of different detoxification protocols.[1,7] The principal strategies are:[1,7]

- Identify and avoid exposures
- Support physiological detoxification with nutrients

Because some patients might have a negative response to detoxification programs, medical supervision is advised.[27]

IDENTIFY & AVOID EXPOSURES

Exposures must be dramatically reduced with lifestyle and behavioral changes in the home and work environment for long-term clinical results. Clinicians practicing environmental medicine recommend taking a thorough history to identify past and present toxic exposures[1] and testing for exposures when possible (**Table 2**).[2,28] Once identified, clinicians should counsel patients on how to avoid the toxins in question and offer alternatives.[4,5,29,30] There are a number of resources available to clinicians to help identify toxic exposures in patients, including:

- The Quick Environmental Exposure and Sensitivity Inventory (QEESI, available at: http://familymed.uthscsa.edu/qeesi.pdf), which is a validated survey for detecting chemical intolerance
- Environmental Exposure Assessment for prenatal health (available at http://prhe.ucsf.edu/prhe/pdfs/Huffling%20prenatal-preconception%20assessment.pdf)

Table 2. Clinical Considerations for Programs to Support Biotransformation

- Identify exposures
- Decrease exposure to toxins
- Provide nutritional support for biotransformation and conjugation reactions
- Provide nutritional support for energy production during detoxification programs
- Support endogenous antioxidant mechanisms for biotransformation and heavy metal detoxification
- Provide methyl donors to promote methylation pathways
- Support healthy digestion and excretion

Table 3. Alternatives for Reducing Toxicant Exposures

Instead of Using These Items	Try Using These Items
Indoor or outdoor pesticides; mothballs	Baits or traps to control bugs indoors; tightly seal foods so as not to attract bugs
Paints, varnishes, glues, polishes	Low solvent paints, water-based finishes and glues (apply away from home)
Bleach, ammonia, strong cleaning products, disinfectants	"Elbow grease," soap and water, vinegar and baking soda
Scented products, perfumes, incense, and air fresheners	"Free and clear" laundry detergent, fabric softeners, unscented cleansers, unscented cosmetics, organic essential oils
Hair coloring, permanents, hair spray, or aerosol products	New haircut, unscented hair gel or styling gels or creams (no spray)
Dry cleaning, odorous soft plastic toys, or mattress covers	Washable toys, bedding, and clothes; all natural toys
Odorous flooring material (vinyl, pressed wood, particle board) or carpeting	Ceramic or stone tile or hardwood floors
Conventional foods or beverages that may contain pesticides, additives, or other manmade chemicals	Organic foods and whole foods without additives or artificial colors
Plastic food containers	Glass, stainless steel containers, parchment or wax paper, BPA-free plastics

Table adapted from Heilbrun et al.[25]

Lead exposures can be reduced by investigating levels in cosmetics, occupational exposures, and home renovations.[28] Hand washing can also reduce lead exposure.[31] Indoor air quality can be improved by evaluating indoor building materials and avoiding renovations.[32]

Choosing organic food sources is desirable, as it has been shown to decrease levels of circulating pesticides.[2] To reduce BPA levels, patients should avoid canned food packed in epoxy and bottled water with the number "7" on the bottom.[28] This was an effective intervention to reduce BPA levels in a study of children and adults.[2] Another study showed that a 5-day vegetarian diet reduced levels of phthalates.[2,33] Patients with high levels of PCBs may need to avoid dietary fish for a time period.[34] Other recommendations can be found in **Table 3** (adapted from Heilbrun et al).[25] Long-term lifestyle interventions may be necessary to reduce the total body burden of toxicants.

Allergenic foods may add to the toxic burden in certain patients. Diets that help eliminate common food allergens, in combination with nutritional detoxification support, have been shown to improve chronic fatigue symptoms, fibromyalgia symptoms, and improve markers of detoxification.[7,35,36]

SUPPORT PHYSIOLOGICAL DETOXIFICATION WITH NUTRIENTS

Nutritional status influences the absorption of toxicants and their physiological impacts on the body. The impacts of toxic exposures on the body can be exaggerated or mitigated by nutritional status.[2] For example, vitamin C intake,[37] calcium, and iron supplementation have significantly reduced maternal and infant blood lead levels.[31] A summary of the 3 phases of detoxification and the nutrients that are known to support each phase can be found in **Figure 1**.

It is important to promote the endogenous mechanisms of detoxification. The function of these processes in the individual patient depends entirely on his/her physiological functioning and biochemical status. Nutritional testing can be used to determine a patient's nutritional status and monitor treatment.

Nutritional Support for Phase I. Phase I detoxification calls for antioxidant support and some key nutrients (such as niacin, riboflavin, and iron) while Phase II calls for significant specific nutritional support.[7] Phase I detoxification is not dependent on high nutritional requirements and can remain active under fasting or poor nutritional status. Therefore, traditional methods of detoxification that utilize fasting may be detrimental. In this case, Phase I detoxification can accelerate while Phase II activity may slow down due to nutritional deficiencies leading to accumulation of harmful intermediate molecules produced by Phase I reactions.[7] In addition, fasting can liberate toxins stored in fat tissues, leading to additional toxicant stress. Proper nutritional support for Phase II detoxification is essential.

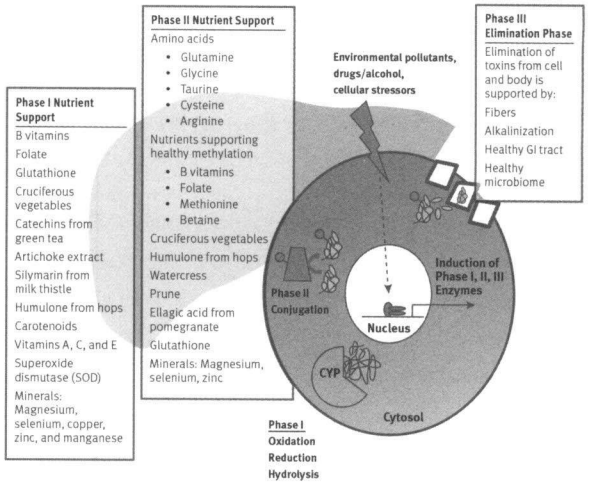
Nutritional Support for Phase II. Phase II reactions involve glutathione conjugation, methylation, sulfation, and glucuronidation. Glutathione is recommended in detoxification protocols.[1] Supplementing with sulfur-containing foods, N-acetylcysteine (NAC), taurine, or methylsulfonylmethane when used in the clinical setting increase glutathione and metallothionein synthesis.[1] Folate and methyl donors assist in Phase II methylation, especially arsenic biotransformation and excretion.[1] In humans, glucosinolates in the form of Brussels sprouts (300 g/d) were able to increase glutathione-S-transferase 1.5-fold in men[38] and curcumin was able to increase human glutathione levels.[7]

An elimination diet and nutritional support for detoxification improved chronic fatigue symptoms and improved measures of Phase I and Phase II clearance.[7,35] More recently, an elimination diet and a rice protein and botanical formula decreased symptoms of fibromyalgia (pain, stiffness, and tender points) without adverse effects.[36]

Nutritional protocols for detoxification in humans are lacking and therefore animal research is a useful reference. An excellent, comprehensive review of dietary ingredients and their biological effects on detoxification pathways, mainly in animal and cell studies, is available.[39] d-Limonene from lemon can promote detoxification ability and can prevent glutathione depletion with chronic acetaminophen administration.[26] Indole-3-carbinol (I3C) has been shown to enhance Phase II glutathione pathways in rats.[7,40] Curcumin, alliums, quercetin, selenium, *Parachlorella*, *Chlorella*, fiber, and antioxidants have been shown to facilitate excretion and reduce the toxic effects of chemicals on the organism.[1]

Nutritional Support for Phase III. After biotrans-formation and conjugation, toxins and toxicants should be eliminated from the body. Specific nutritional approaches can help to remove accrued toxicants from the body, although high level evidence is lacking. The liver, kidneys, skin, and lungs are the major routes of elimination and most clinicians optimize clearance via these organs.[1]

Figure 1. Liver Cell Detoxification Mechanisms



Detoxification occurs primarily in the liver, but also throughout the GI tract, kidneys, lungs, and brain. Nutrient support is vital for optimal functioning of cellular detoxification pathways.

Table 4. Metabolic Detoxification Support

Phase I: Bioactivation	Phase II: Conjugation	Phase III: Excretion
Niacin	Protein	Fiber
Iron	Amino acids • Glutamine • Glycine • Taurine • Cysteine, N-acetylcysteine (NAC), methyl-sulfonyl-methane	DMSA or other heavy metal chelators
Riboflavin		NAC
Carotenoids		Sweating
Vitamin E		Olestra
Vitamin C		Cholestyramine
Antioxidants • Silymarin • Green tea catechins • Humulone from hops • Artichoke	Vitamin B_{12}, folate, choline, and methionine	Hubbard protocol
	Indole-3-carbinol	
	Phytochemicals • Watercress glucosinolates • Prune • Ellagic acid • Curcumin • d-Limonene	

Sweating, or depuration, is an age-old tradition that effectively eliminates heavy metals, PCBs, and BPA.[1,41,42] The mode of sweating–whether exercise, dry sauna, wet sauna, or infrared sauna–are equally effective for toxicant excretion.[1] The inclusion of fiber in the diet is important as fiber may act like a sponge, mopping up toxicants and improving elimination.[1]

Chelators, such as dimercaptosuccinic acid (DMSA), are well-known agents to remove heavy metals from the body in cases of metal toxicity.[1,43] NAC has been used to chelate arsenic, chromium, mercury, and platinum in experimental studies.[43]

Other interventions have been proposed for removing toxins stored in fat deposits. Olestra blocks absorption of pesticides and hastens elimination and has even been proposed as a treatment for cloracne from dioxin exposure.[44] Cholestyramine has been used to remove perfluorinated compounds from storage, which are resistant to removal by sweating.[3]

The Hubbard protocol was developed for eliminating body burdens of psychoactive chemicals. It is a 3-week regimen of polyunsaturated oils, sauna, exercise, niacin, and vitamin and mineral supplementation designed to mobilize fat-stored toxicants. It has been used in treatment of workers at the 9/11 World Trade Center site,[45] electrical workers,[46] capacitor workers,[47] and firefighters.[48] It has been shown to reduce PCBs, PBBs, chlorinated pesticides, and hexachlorobenzene; reverse the clinical symptoms of toxicity; and improve neurobiological function.[47-49]

Toxicant testing for pesticides, PCBs, heavy metals, phthalates, and BPA are available to clinicians. Testing can pinpoint which toxicants are elevated and customize an appropriate treatment. Organic acid biomarkers of detoxification capacity and whole blood glutathione may be useful. The length of detoxification treatment depends on the patient's laboratory results, symptoms, and the practitioner's judgment.

There is a dearth of research on the efficacy and safety of detoxification protocols. Given the ever-increasing quantity of toxicants released into the environment and the burgeoning evidence of their deleterious effects on human health, further research is needed so that safe clinical interventions can be implemented in patient care.

IDENTIFYING CANDIDATE PATIENTS

Identifying patients that will have a positive response to detoxification therapy is difficult because complaints may span multiple systems. Candidates for assessment and treatment include those with chemical intolerance, cardiometabolic conditions (including obesity), neurological disorders, developmental and reproductive disorders, endocrine disruption, cancers, and immune system suppression, particularly if they are non-responsive to typical treatments.[1,4] The best intervention for pregnant women is to minimize exposure to toxins (see "Identify and Avoid Exposures") and optimize nutritional status. Patients who are fragile or nutritionally depleted may react poorly to detoxification treatments designed to enhance toxicant excretion.

Symptoms and warning signs that may point to a toxic etiology of disease are:[7]

- History of multiple medications
- Increasing sensitivity to toxicant exposures
- Regular use of toxic agents in the home, outdoor, or work environment
- Sensitivity to odors
- Musculoskeletal symptoms (such as fibromyalgia)
- Poor cognitive function
- Unilateral paresthesia
- Worsening of symptoms after anesthesia or pregnancy
- Paradoxical responses or sensitivities to medications or supplements
- Autonomic dysfunction and patterns of edema that are recurring
- Patients taking medications, vitamins, pain killers, or hormones
- Signs of endocrine disruption: sleep disturbance; fatigue; alterations in weight, appetite, and bowel function; changes to the menstrual cycle, sexual interest, temperature, sweating, or flushing; and alteration of hair growth or skin texture[4]

CONCLUSIONS

Toxic exposures are ubiquitous, however they don't affect everyone equally. Genetic susceptibility, diet, medications, chemical exposures, and the sensitivity of tissues to secondary metabolites of detoxification determine if and how a person may react.[7] There may be synergistic activities between chemicals or toxicants that are yet unknown.

The goal of the integrative and functional medicine practitioner is to identify exposures and counsel the patient about alternatives and lifestyle changes. In addition, nutritional support is vital to reinforce the physiological functioning of the 3 phases of metabolic detoxification.

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