Detoxification and Biotransformation

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D. Noland et al. (eds.), *Integrative and Functional Medical Nutrition Therapy*,
https://doi.org/10.1007/978-3-030-30730-1_14

14.1 Introduction

Detoxification is the process by which the body breaks down and removes substances that are undesirable and have potential for harm. These can be endogenous waste products or such exogenous substances as medications, environmental toxins or any substances that we ingest, inhale or absorb. Detoxification is a natural process of the body carried out continuously by the liver, the kidneys, the skin, and the lungs [1].

"Detox" is a popular topic and there is a lot of disagreement about what it is and how to do it. While many companies sell detoxification products, the claims that these products are essential to cleanse the body are often exaggerated. The body is designed to effectively eliminate toxins in the majority of cases. Using a radical detoxification product and then returning to the same poor dietary and lifestyle habits is like going on an extreme diet for weight loss and then returning to the prior way of eating. The approach of using an aggressive detoxification product is not necessarily effective to help the body function properly and may even result in harm. Better approaches to detoxification are discussed below.

The critical role of detoxification is handled primarily by the liver [2]. Rich blood flow is seen throughout the liver, bathing its columns of orderly arranged cells separated by spaces. As the blood is transported through the spaces between the liver cell units, it is filtered and chemicals, dead cells, drugs, microorganisms, and other debris are removed from the bloodstream. Important in this process, Kupffer cells are specialized macrophages found in the liver sinusoids and make up more than 80% of macrophages found in the entire body. Kupffer cells are especially important for elimination of infectious agents circulating in the blood filtered through the liver, but also important for other debris and toxin degradation [3]. A significant elaborate system of breakdown of the removed debris is handled by several step processes, beginning with the inherited cytochrome P450 enzymes that require important cofactors for function in the form of nutrients such as B vitamins [2]. (Please see ▶ Chap. 13). This critical first phase of the detoxification addresses fat-soluble toxins that are chemically converted into intermediate metabolites that become more water-soluble. The second phase completes the chemical transformation into water-soluble compounds on their way to excretion into bile and subsequently into the gastrointestinal tract for removal from the body. Amino acids, vitamins, and other cofactors are important for this second phase. More in-depth understanding can be gained from ▶ Chap. 13.

The kidney's filtering system is comprised of glomeruli that remove waste products and toxins from the blood with subsequent excretion into the urine [4]. Urinary excretion is one of the primary ways that toxins are eliminated. Kidneys not only eliminate wastes but also maintain levels of water and minerals, produce renin to manage blood pressure, synthesize erythropoietin to make red blood cells, and synthesize the active form of Vitamin D for strong bones and a variety of other functions. We want to do everything we can to keep these important organs healthy.

Encountering a patient immediately following an alcoholic binge, one notes a distinctive odor emanating from the skin; this is the body's way to eliminate alcohol metabolites. We often don't think of the skin as an organ of elimination, but waste products and toxins, such as heavy metals, phthalates, and other environmental toxins do diffuse into the sweat glands for elimination in the sweat [5, 6]. Saunas are often promoted for their detoxification effects due to the benefits of sweating. Vigorous exercise with sweating has similar outcomes.

The lungs are primarily designed to remove carbon dioxide in exhaled breath, but the lungs are also able to filter and remove other waste products [7]. A well-known example is a diabetic patient in ketosis exhaling ketones in the breath, with its characteristic odor. While this is often described as a fruity odor, the actual chemical odor being eliminated is acetone. Other metabolites are also eliminated by the lungs when in abundance, which brings up images of a breathalyzer in the hands of a police officer. However, exhaled breath has the potential to surpass blood and urine for toxicity testing because breath gives unlimited supply, does not require trained medical personnel, is noninvasive, and does not produce potentially infectious waste such as needles.

14.2 Primary Approach – Avoidance

The primary approach to detoxification is avoidance of the exposure when possible. Unfortunately, the majority of populations around the world are exposed to chemicals and foreign substances that were not present until the early twentieth century. Estimates suggest there are almost 100,000 chemicals in current use with only a fraction of them rigorously tested for safety in humans [8]. A further concern is that tested chemicals are evaluated based on a single exposure without interaction with other chemicals, unlike the daily experience where humans are exposed to a chemical soup from personal care products, food contaminants, drugs, pesticides, etc. Since exposure to multiple chemicals occurs daily, the risk of toxicity is actually much higher and taxes the detoxification system. This makes the concept of avoidance even more critical, and patients need to be educated about the potential sources of exposures. The more patients are aware of exposures, the better equipped they will be to reduce them. Ultimately this leads to reduced burden on the normal biological processes [9].

What we now call "organic food" was simply called "food" 100 years ago. People had relatively small plots of land where they usually had a combination of animals and crops. The manure from the animals and other organic waste were composted to provide fertilizer for the garden and field plantings. Currently, the majority of crops are farmed large in monoculture plots using chemical fertilizers, pesticides, herbicides, and fungicides. Monoculture farming and use of chemicals on the land have led to nutrient depletion of the soil [10, 11]. Some crops are "Roundup

Ready," meaning that they are genetically modified to withstand large amounts of herbicide (glyphosate). Besides being a risk for cancer, kidney disease and other health problems, glyphosate can bind with minerals in the soil including copper, iron, magnesium, manganese, nickel cobalt and zinc, making them less available in our food [12]. Roundup is also sprayed on other crops, such as wheat, as a desiccant prior to harvest [13, 14].

It is not only plant food that is modified with chemicals. Animals are factory farmed in crowded warehouses or pens, making them more susceptible to distress and disease [15]. They are fed food containing genetically modified (GMO) corn and soy and are given antibiotics and hormones to hasten weight gain. When cattle are crowded into pens full of urine and feces, is it any surprise that *E.coli,* a fecal-borne bacteria, can end up in the meat [16]? It is not a healthy situation for the animals or those who consume them.

Cattle are intended to eat grass and similar plant materials as they have four stomachs designed to break down the cellulose. Feeding cattle grain is not a healthful alternative. Nor is crowding the animals in pens without exercise options or giving them chemicals and antibiotics to produce rapid weight gain. These procedures produce a marbling appearance in meat that many people desire and create a milder flavor; but these practices do not contribute to animal health and well-being or health benefits for those who consume the meat produced in this manner.

When large amounts of urine and feces are produced in small contained areas by animal factory farming, there is often contamination of nearby groundwater [17]. When cattle, poultry or hogs are rotated on pastures in traditional farming techniques, their wastes fertilize the ground without overwhelming the area. Just as with human detoxification, nature has the means to handle the waste products in small quantities.

Our water supply can be contaminated by other sources of toxins. Herbicides such as Roundup, pesticides, lawn chemicals, factory farm waste, heavy metals, and prescription drugs can all be found in tap water [9]. If the water is from a metropolitan water supply (as opposed to a private well), it may also contain fluoride (a neurotoxin) and will have chlorine or chlorinated by-products that have been used to kill microorganisms. The list of possible contaminants is too long to include here, but the recommendation is to use filtered tap water [9]. Reverse osmosis systems are the most effective at removing these, but other filters are also helpful. Bottled water may be no different than tap water, plus there is the risk of leaching endocrine-disrupting contaminants like bisphenol-A (BPA) from the plastic bottle, especially if exposed to sunlight [18].

Common everyday sources of toxic chemicals are in personal care and cleaning products. We have become obsessed with cleanliness and with killing germs to a degree that is unhealthy. Our bodies are hosts to around 100 trillion microorganisms that live in the gastrointestinal tract and on the skin, and these are necessary for health [19]. Anything that disturbs the balance of these microorganisms can create problems. Therefore, any chemical-containing products, particularly antibacterial-containing products for everyday use, should be discouraged [9].

The Food and Drug Administration does not approve cosmetics or personal care product ingredients but is, by law, charged with regulating these ingredients [20]. For example, the FDA has banned the use of triclosan in soaps, but triclosan may still be found in other products such as toothpaste [21]. Otherwise, unless there is evidence of obvious harm, ingredients are not premarket-approved. Because we apply these products directly to the skin, any toxins contained in them can be absorbed. The European Union has banned more than 1100 chemicals that are allowed in the United States [22]. One way to avoid the most toxic products is to use the Environmental Working Group website (► ewg.org), which lists products and rates them according to ingredients.

Cleaning products are even more likely to contain toxic ingredients when compared to cosmetics and personal care products. Most cleaning products do not list their ingredients on the label, and many consumers are unaware of what their exposure may be. There are green products that do list ingredients and are less toxic, and can be found easily locally. Once again, the Environmental Working Group is a source of information that can guide buying decisions. Another option is to make products from safe ingredients and recipes are found on the internet for this purpose.

Are you aware that the "new car smell," the smell of fresh paint, the smell of new carpet and similar smells include chemical fragrances? These are volatile organic compounds (VOCs) and should be avoided as they can be toxic [23]. Air fresheners, fabric softeners, oven cleaners, flame retardants, and plastic food containers should also be avoided for similar reasons [9]. Unscented products and low VOC products are preferred. If fragrance is desired, essential oils provide a better alternative than artificial fragrances which contain multiple chemicals and phthalates (hormone-disrupting chemicals).

Now that we have discussed the first step, avoidance of toxins, let us look at ways that we can support the detoxification process by care of organs of detoxification and aiding excretion through liver and kidneys.

14.3 Secondary Approach – Caring for Organs of Detoxification

14.3.1 Liver Considerations

Because of poor dietary intake high in sugars and damaged fats, people may have impaired liver function. One very common problem is what is commonly called "fatty liver" or hepatic steatosis. Fatty liver may occur in those with excessive alcohol intake, but a more common problem is non-alcoholic fatty liver (NAFLD). This can be either isolated fatty liver, nonalcoholic steatohepatitis (NASH), or

NAFLD, which is more severe and associated with inflammation, obesity, and metabolic syndrome [24]. Patients often have no symptoms but will probably have abdominal obesity. It can be found via imaging (ultrasound, CT or MRI), or if more severe, via elevated liver enzymes. NASH and NAFLD can progress to cirrhosis as scarring accumulates in the liver tissue. The treatment for fatty liver is primarily lifestyle changes, including abstinence from alcohol, weight loss, and controlling blood sugar. High fructose corn syrup is especially detrimental to the liver and should be eliminated from the diet [25]. Coffee appears to reduce the build-up of scarring in NASH, so it is beneficial [26]. The first-line treatment for non-diabetic NASH is Vitamin E [27]. Other things that may be beneficial include omega-3 fatty acids, N-acetylcysteine (NAC), glycyrrhizin (from licorice root) and whey protein [28–33]. Both NAC and whey protein have high levels of cysteine which can increase glutathione, an antioxidant that is liver-protective. Whey protein may also aid in weight loss.

Other liver diseases include viral hepatitis, chemical hepatitis (such as results from acetaminophen overdose), cirrhosis, and cancer. The presence of any of these can affect the liver's ability to break down toxins by deficiencies in Phase I and Phase II nutrients and by generally overwhelming the detoxification pathways [2].

14.3.2 Kidney Considerations

Chronic kidney impairment can result from diabetes and/or hypertension [34]. The kidneys may also be damaged by direct injury, such as a severe blow or something that decreases blood flow such as an acute hemorrhagic injury that results in significant blood loss. A backup of urine may also damage the kidneys, such as with prostate enlargement, with certain medications or with kidney stones that block the urine outflow. Infections may start in the bladder and ascend into the kidneys which, if not treated promptly, can result in problems such as scarring. Infections from hepatitis, HIV, and strep also may affect the kidneys. Autoimmune diseases, like lupus, that attack body tissues can also damage kidneys. Long-term use of NSAIDS and lead poisoning are other risks.

Kidney impairment can be diagnosed by increased microalbumin in the urine and elevated creatinine in the blood [35]. The estimated glomerular filtration rate (eGFR) is calculated from the creatinine level and considers age, gender, and race. These should be monitored regularly in patients with diabetes and/or hypertension and other chronic medical conditions; keeping blood pressure and blood glucose under good control is paramount. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are commonly used to control blood pressure and reduce proteinuria and are often prescribed for normotensive diabetics for their kidney protective effects.

14.4 Tertiary Approach – Detoxification Support

14.4.1 Start with Food

After protecting the organs of detoxification, the next step is aiding in support of the body's inherent detoxification pathways [36–38]. The baseline issues for patients to enhance detoxification are a clean, good diet and adequate hydration, with clean water providing the best source for fluid intake [36, 37]. Liquids containing caffeine with a diuretic action, such as coffee, soda and, to a lesser extent, tea, result in the body losing more water than is ingested. Caffeinated drinks should not be the primary source of dietary liquid intake. Alcohol also has a diuretic function and inhibits organs of detoxification. Fruit juices are generally high in sugars and not likely healthy choices for detoxification purposes. If patients prefer juice and do not want to eat adequate amounts of vegetables and whole fruit, a blender can be used to make a smoothie with predominantly vegetables and minimal fruit. A juicer that extracts the juice and leaves the fiber behind is not recommended. Fiber is a very important part of the diet in maintaining gastrointestinal health and slowing the absorption of sugars. Vegetables and fruit provide antioxidants and phytonutrients essential for good health [39, 40]. Vegetables should be the mainstay of the diet, especially colorful vegetables such as dark leafy greens, dark yellow, orange, and purple varieties. Fruit also provides important nutrients and fiber, but if used predominantly may provide too much sugar.

Sugar has an inflammatory effect and should be avoided as much as possible [41]. Artificial sweeteners, such as aspartame, have controversial yet concerning effects on human health and should be avoided during detoxification [42]. If added sugar is used, it should be organic cane sugar. Concerns are also raised regarding genetically modified foods (GMO), although this area also remains controversial [43, 44]. We just don't know enough about the safety of GMO foods, but there is emerging research to show there are differences that may be detrimental to health [44]. Sugar beets are a common GMO crop and most of the commercially available sugar uses GMO sugar beets. Corn sweeteners, such as high-fructose corn syrup, are also produced using GMO corn. Because many healthcare practitioners now advise against high-fructose corn syrup and many patients seek to avoid it, manufacturers may refer to it by a different name on food labels [45].

Stevia and monk fruit are safe sweeteners derived from plants [29]. Stevia comes in liquid and powder forms and is a safe sweetener but may have an aftertaste if too much is used. Other sweeteners considered low-glycemic are the GMO or Non-GMO birch or corn derived polyols (examples are xylitol, erythritol, malitol). They contain about 40% fewer calories than sugar and do not cause a rapid increase of blood sugar. They are partially absorbed in the gastrointestinal tract which can produce a laxative or loosening of the stool for some people.

In the 1950s, the role of sugar as an etiology of heart disease began to come to light. However, in 1965, the Sugar Research Foundation paid scientists to do a literature review that downplayed the role of sugar and laid the blame on fat and cholesterol [41]. This led to decades of poor nutritional advice and patients still follow low-fat, low-cholesterol diets to this day. Recommendations to follow a low-fat diet resulted in higher carbohydrate consumption, obesity, metabolic dysfunction, and NAFLD [24]. Rather than low-fat diets, food sources should be rich in beneficial fats. Healthy fats are an important part of the diet (See ▶ Chaps. 10 and 11). Healthy fat ratios should be higher in omega-3 fatty acids rather than omega-6 fatty acids and other fats, like medium-chain fats and omega-9 fats, are to be recommended. Unfortunately, healthy omega-6 fats are not consumed as often as the highly processed damaged vegetable oils which are high in inflammatory omega-6 fatty acids. Processed foods tend to contain fats that are the damaged omega-6 fatty acids and may even contain trans-fats and should be avoided, especially during detoxification. It is important to strike a balance between omega-3 fatty acids and unprocessed omega-6 fatty acids obtained from natural sources. We also now know that saturated fat and cholesterol are not the demons they have been made out to be, but have roles in healthy diets and normal metabolism. Recommended dietary sources of fats include, but are not limited to, coconut oil, olive oil, avocados, grass-fed butter, and fatty fish (wild-caught).

Wheat and gluten have been a subject of much interest in recent years with books like *Wheat Belly* and *Grain Brain* becoming best sellers [46, 47]. Gluten-free products are now found ubiquitously because of the popularity of gluten-free diets. Certainly, the wheat we are using today has been bred to contain more gluten, which is advantageous for bakers wanting to create light, fluffy bakery products. Unfortunately, the gluten, gliadin, and agglutinin found in wheat, especially the modern hybrids, are irritating to the digestive tract and can lead to intestinal permeability, AKA "leaky gut" [46]. The use of glyphosate as a desiccating agent prior to harvest has also been implicated in the rise of gluten intolerance [13, 14]. Intestinal permeability associated with gluten intolerance has been linked to the rise in autoimmune conditions, obesity, and other chronic health problems. Therefore, many detoxification programs recommend eliminating the use of grains, especially wheat.

While some people find that they must completely eliminate grains from their diet, others can tolerate limited amounts without any problems. One of the best ways to determine sensitivity is to try an elimination diet for a period of several weeks. When wheat or gluten is added back to the diet as a challenge, the subsequent reaction – or lack of one – can be evaluated and assessed (See ▶ Chap. 24 for guide to elimination diet). This author has found that, in many patients, eliminating sugars and grains result in a remission of some symptoms, such as gastrointestinal problems, allergic symptoms, and a reduction in chronic pain.

A recent study on long-term gluten-free diets and heart disease indicated that a gluten-free diet increases the risk of coronary heart disease [48]. They concluded that gluten-free diets should not be recommended for people without celiac disease. The answer to this dilemma may reside in the types of food used in substitution of wheat/gluten. Many gluten-free products available to consumers are processed and high in carbohydrates and simple sugars, but not high in fiber and nutrients. This dietary substitution is not particularly conducive to good health. The fiber content of whole grain is a big reason why it is routinely recommended, but it is possible to get high-quality fiber by eating plenty of high-fiber vegetables and fruit. Otherwise, the addition of such high-fiber substances as psyllium husk is an alternative dietary fiber source.

Dairy consumption is another concern during detoxification. In the case of lactose intolerance, dairy sensitivity may be easy to recognize. Casein, the protein in dairy, may also cause intolerance but is more difficult to assess. Regardless, most detoxification programs recommend eliminating dairy. Again, an elimination diet with subsequent challenge is a good way for the patient to see if dairy is contributing to their health problems. If dairy is used, it should be organic.

The diet should contain adequate protein with sources from meat, poultry, fish, eggs, dairy, nuts and seeds, and legumes [49]. The recommended daily allowance (RDA) for protein is 0.80 g/kg per day. This is a minimum amount and a higher intake of protein may be indicated in active individuals to maintain and promote muscle growth. However, most Americans eating a standard diet are easily exceeding the RDA for their protein requirement. Most can obtain adequate good quality protein while reducing the quantity of meat by choosing a predominantly plant-based diet [49]. Protein is essential to support enzymatic detoxification processes because of the amino acids supplied. Patients who might be at risk for not getting enough good quality protein include vegans or those who are severely restricting calories.

14.4.2 Supplementation Use

It is imperative that nutritional counseling be sought to ensure those preparing for detoxification are getting all the necessary nutrients in their diets to support the detoxification process. Because our food may not provide an optimal level of nutrients, a good multivitamin/mineral supplement provides a back-up for what is not received in the diet. Of importance for detoxification are the B vitamins, which are co-factors in many enzymatic reactions. One concern for restricted diets is vitamin B12. Since Vitamin B12 is only found in animal products, those who do not eat animal products will need to use a supplement. As people age, their absorption of Vitamin B12 is lower so older people may also need to take this as a supplement. Magnesium, selenium and zinc are minerals that are frequently deficient and critical for enzymatic conversion of endogenous and exogenous toxins.

Other critical yet deficient nutrients include vitamins D and C. Since a multivitamin/mineral supplement may not provide enough of these critical nutrients, additional supplementation may be needed and can be guided by diet history assessment and laboratory testing.

There are many supplements that are often recommended for detoxification. One common medicinal plant recommended is milk thistle, *Silybum marianum* [29, 50]. This herb has been used for detoxification because of its hepatoprotective properties. It acts as an antioxidant and inhibits the binding of toxins to the hepatic cell membranes and reduces fibrosis. It has been used to treat viral hepatitis as well as to reduce the injury caused by acetaminophen, alcohol, iron overload, and carbon tetrachloride [50].

Another popular medicinal plant, dandelion extract, has also been used for many years for its antioxidant properties and its usefulness in treating liver disorders. Research in rats has confirmed its ability to prevent fibrosis from chemical damage and to promote regeneration [51, 52]. This, in part, is related to its effects on Phase I detoxification pathways, particularly cytochrome P450 2E1. Ginger (*Zingiber officinale*) is another substance that is helpful to prevent fibrosis through its antioxidant capabilities [53–55].

Garlic and vitamin C are useful for many detoxification purposes, but also for reducing lead levels [56–61]. This is especially important for children whose neurodevelopment is damaged by lead toxicity [59]. Garlic has been found to be more effective than d-penicillamine in treating lead poisoning [60].

Glutathione (glutathione S-transferase or GSH) functions as an antioxidant and chelator of metals, including aluminum and mercury, so substances that increase glutathione help with detoxification [62–65]. Spices such as black pepper, curcumin or turmeric, rosemary, and ginger have many beneficial effects, including the potential to increase glutathione levels. Other natural products that may increase glutathione include alpha lipoic acid, chlorella, dark roast coffee, methylsulfonylmethane (MSM), N-acetyl cysteine (NAC), phosphotidylcholine and phosphotidylethanolamine, probiotics with soluble fiber, selenium, sulforaphane (found in cruciferous vegetables), whey protein, and zinc [66–77].

In summary, the approach to detoxification involves three steps: the primary approach – avoidance; the secondary approach – caring for organs of detoxification; and the tertiary approach – detoxification or metabolic biotransformation support. All of these steps promote the health of the detoxification organs and encourage the breakdown and excretion of toxins that will do much to transform the health of your patients and prevent chronic disease.

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