



## Advanced Clinical Focus: Detoxification and Biotransformation Transcript – Class 3 Part 3

0:00

Phase II liver detoxification, the conjugation pathways. Now I remember back in high school when I was learning French, and we learned how to conjugate verbs. It was all about taking the root and adding a piece to it, in order to make it a word that worked in the sentence. So we're talking about conjugation, we're talking about binding two things together. One of the effects of this is neutralization, and it takes a toxin, remember, that might be an intermediate, that might be more harmful to the body, and it neutralizes it. At this point that toxin is no longer harmful. It's almost like taking a toxin and putting handcuffs on it with a conjugate and making it unharmed that way. You can think about a toxin as this renegade person maybe robbing banks with a gun and everything around your body; we catch it in the liver, we handcuff it with handcuffs, and then we put it in the police wagon, which is our inner small intestine, and we transport it outside of the city, which is into the toilet. So neutralization, we make these conjugates bile ready, so we can dump them into the bile and then excrete them or eliminate them. And we can make them water-soluble, which would just end up back into the bloodstream, filtered by the kidneys and then eliminated via our urine.

1:36

There are six pathways to consider, which are called the conjugation pathways. We're going to go through each one of these in detail. But just to give you a bit of a preview, number one is the glutathione conjugation pathway. Number two is the amino acid conjugation pathway. Number three is methylation. Number four, sulfation. Number five is acetylation. And number six is glucuronidation. So we're now focusing on the Phase II liver detoxification pathways.

2:08

Now, these are very nutrient dependent and these are the nutrients needed for Phase II enzymes. You can see a breakdown of the pathways on the left hand column. So for the glutathione conjugation pathway, we need, of course glutathione, and specifically vitamin B6. For amino acid conjugation, we need the lysine, specifically that amino acid. For methylation, we need S-adenosyl-L-methionine. For sulfation, we need cysteine, methionine, and molybdenum. For acetylation we need Acetyl-CoA, and for glucuronidation, we need glucuronic acid. Now you'll also notice as we go through these slides, there's a lot of information on each slide. These are going to be great references for you when you start working with a client or yourself and want to go back to the detoxification pathways and dive a little bit deeper into the specific ones and what might induce them, inhibit them, how to tell if they're out of balance, etc.



3:10

Inducers of the Phase II enzymes, we've got cruciferous vegetables, limonene, which is found in citrus peel, dill, and caraway, upregulating glutathione conjugation. Now, what's really cool about limonene is it's found in the peel of citrus. We don't really normally eat citrus peel, but a cool thing you can do and actually part of certain herbal formulas, you can find orange peel, but if you're consuming an organic lemon, lime, or orange, you can use that peel in a soup or in a tea. I like to use it as a tea and you get some of the benefits, because a lot of the key anticancer phytonutrients are found in the pith and in the skin, interestingly enough. Not as many in the actual juicy part that we like to eat. Amino Acid conjugation glycine is critical. Methylation, we need choline, methionine, betaine, folic acid and vitamin B12. Many of those are lipotropic factors. Sulfation we need cysteine, methionine, and taurine to induce it. For acetylation, there's nothing that really will induce it per se. And for glucuronidation, fish oils, cigarette smoking as a negative inducer, birth control pill, phenobarbital, and limonene. So you can see that here we see some things that are good and some things that are bad that can still induce. One of the reasons why that happens as well is because if something bad is inducing a detox pathway, it's actually telling the body 'hey, you need to process this toxin quicker speed up that activity

4:56

Then inhibition of Phase II enzymes we see so selenium deficiency, B2 deficiency, glutathione deficiency, and zinc deficiency really affecting glutathione conjugation. A low protein diet really affecting amino acid conjugation and we saw that glycine was really important and of course other amino acids, hence the name. So if we're not getting enough protein and amino acids, we can't carry out that activity. Methylation, a deficiency in folic acid and B12 will inhibit methylation. For sulfation pathway, non-steroidal anti-inflammatory drugs will inhibit it. Tartrazine, which is the yellow dye found in a lot of processed foods and molybdenum deficiency. For acetylation, vitamin B2, B6, and vitamin C deficiency all inhibit, and for glucuronidation, aspirin and probenecid will inhibit it.

5:55

We're going to dive a little bit deeper now into each specific detoxification pathway in Phase II. Starting with glutathione, glutathione is the primary route for Phase II detoxification. Remember, we talked about how if I wanted to travel from Toronto to Vancouver, I could take many different routes? There's redundancy in the detoxification pathways. Well, if I wanted to get there the fastest, I take the primary route, I take the best route from here to there, and that's what the glutathione conjugation pathway is like for us. You can see that the glutathione molecule is made up of glutamate, cysteine, and glycine, three amino acid, which make up this tripeptide molecule glutathione. So you might be thinking, well, why don't they just take glutamine, cysteine, and glycine to get more glutathione? And if you're thinking that you're quite correct, that's actually a really great way to increase glutathione levels, specifically cysteine. We'll look



at that in a moment. But glutathione is also critical for detoxifying, active detoxification, and as an antioxidant. As you age glutathione levels go down, it's actually somewhat of a marker of how quickly you're aging, depending on where your glutathione levels are; there's quite a bit of research on that. So we really want to maintain and preserve our glutathione levels to the best of our ability.

7:33

Now, because it's part of a conjugation pathway and Phase II, it's an active detoxifier; it helps to detoxify chemicals. If we have chemicals coming through that are using up glutathione in the conjugation pathway too quickly, well, guess what? We have less glutathione to act as an antioxidant. And where is it really important as an antioxidant? It's important as an antioxidant for the intermediates that might be up to five times more harmful that we see after Phase I detoxification. So I left a little bit hanging back there when we were talking about Phase I showing you that we have those intermediate metabolites that could be possibly more harmful, like shards of glass, but we have mechanisms in our body to protect us from those and they're called antioxidants. Think for a moment, where do antioxidants come from in our diet? They don't come from the Jell-O that says fortified with antioxidants. They come from fruits and vegetables and all those bright vibrant colours, and we'll talk about that more in the last class. But we need lots of those to protect us in that phase. But getting back to glutathione it's a key antioxidant to protect us from free radicals.

9:03

Now, glutathione detoxifies some specific drugs like acetaminophen, nicotine, it even detoxifies insecticides, if you remember all the way back to our example with Sandra in the first class, how her family was exposed to fumigation for the ants. It helps to detoxify carcinogens, and heavy metals; very important for heavy metal detoxification. In a lot of heavy metal detoxification formulas we find precursors to glutathione because of that. Nutrients needed for glutathione conjugation are glutathione, of course, vitamin B6, which actually will help to regenerate some glutathione, methionine, an amino acid and cysteine. So cysteine by far is probably the most important nutrient for glutathione conjugation and in the form N-acetyl cysteine, or NAC, that is a really great way to increase glutathione levels in the body. So cysteine is the rate limiting amino acid to increase glutathione levels. We also have various inducers of glutathione. Again, cruciferous vegetables, you going to love the cruciferous vegetables. If you don't remember anything from this course, remember one thing; eat more cruciferous vegetables. We also have limonene, which is found in citrus peel, dill, and caraway inducing this. Inhibitors are deficiency in B2, glutathione, selenium, and zinc, which are all important. And clinical indications of dysfunctions of glutathione conjugation are, one, chronic exposure to toxins and also alcohol can greatly deplete glutathione stores. For laboratory assessment of glutathione levels, we can check acetaminophen clearance and see how much actually ends up in the urine. Obviously something that most of us cannot do, unless we're doing those types of tests.



11:16

Now, Acetaminophen is detoxified through the glutathione pathway and glutathione helps. So I want to just hone in on that for a moment because I believe it's about 100,000 people have some sort of adverse drug reaction to Tylenol per year, and there are many actual deaths from Tylenol every year and many people end up in hospital from even taking properly prescribed amounts of Tylenol. Although this is something that's abused quite a bit because of its availability, it's an over the counter drug. People think oh, if it's over the counter might not be that harmful, but yes, it does give us some risk. Another thing to appreciate is that one Tylenol will not kill you or harm you, two Tylenol's probably won't kill you, and probably a week of taking Tylenol won't hurt you. But as we take Tylenol, more and more, and this is not just for Tylenol, this is for other drugs as well, if we take it day after day, week after week, month after month, year after year, we use up the substances that help to detoxify these chemicals, until one day, we take that Tylenol and it's the straw that breaks the camel's back. It's the one that puts us into a toxic overload. And in the case with acetaminophen, we see that glutathione is really critical for decreasing Tylenol toxicity. So in this chart here, you can see that acetaminophen has a number of pathways it could go down. It gets conjugated to become a glucuronide, it gets conjugated to become a sulfate, but it's also processed through the cytochrome P450 2E1 pathway and ends up into an intermediate called NAPQI. Now NAPQI is very toxic to the body and this is where people run into issues, because if you don't have enough glutathione to continue this process, it builds up and that's where the toxicity happens. So as you can see here, there's a very simple solution to help us with that. And that's called N-acetyl cysteine or NAC, and NAC is a great precursor to glutathione and is very effective at increasing glutathione. In fact, it's so good at helping to increase glutathione and to help us with acetaminophen poisoning, that if someone shows up in the hospital with acetaminophen poisoning, the one and only treatment to this is IV N-acetyl cysteine; a natural supplement and natural nutrient that can be found in any health food store. How cool is that? So this just gives us a little bit of insight. If you're dealing with a client that has to take it long term or has taken it long term at any point, we might want to think about replenishing their glutathione levels with N-acetyl cysteine. I have a client who has chronic migraine headaches and he's been taking various anti-inflammatories for years and still continues as we're trying to figure out the right formula for him, the right foods, and the right supplements to get him off these things. In the meantime, we have in mind N-acetyl cysteine to protect his liver and to prevent liver failure later on in life. Very important thing to consider.

14:52

Moving on to amino acid conjugation. Now just like the name describes, it's the process of amino acid combining with a toxin to neutralize them. Basically we're cuffing the toxin, like aspirin in this case, you can see in the picture, we're cuffing it to glycine for it to be transferred out of the body. Now it doesn't just use glycine, it uses taurine, glutamine, arginine, and ornithine, as well. But glycine is



definitely the most common conjugate in this pathway and the most important. This is where we see that a low protein diet could be detrimental to this pathway. Proteins, of course, are made up of many amino acids and those amino acids specifically are used for detoxification here as we can see. So we want to make sure that if someone is going through the detoxification process, that they're getting adequate levels of protein if they want the amino acid conjugation pathway to work appropriately. I hope you're getting some ideas as to whether juice fasts are good or bad, or even how to implement them appropriately (hint, hint).

16:09

Amino acid conjugation detoxifies benzoates and aspirin, nutrients needed are glycine. Glycine is also an inducer. An inhibitor is a low protein diet. Remember, we need those amino acids for the conjugates. Clinical indications of dysfunction are intestinal toxicity and toxemia of pregnancy. And laboratory assessment that can be done is using aspirin, taking it orally, and seeing what the clearance is and checking the urine.

16:46

Methylation; methylation is a pathway where it uses methyl groups to combine those with toxins to clear them out of the body. Most of the methyl groups are going to come from something known as SAME or S-adenosyl-methionine, which is a byproduct of methionine, uses choline, B12, and folic acid as key cofactors to get the SAME, and of course choline, B12, and folic acid are methyl donors; they give up their methyl group for a greater cause for the production of SAME, which is key for methylation and detoxification in the liver. It detoxifies dopamine, epinephrine, histamine, and thiouracil. Thiouracil is used for hyperthyroidism, it blocks thyroid peroxidase enzyme. What's interesting is, if you look at some of these things like dopamine, let's look at epinephrine for example, which is a stress hormone and an excitatory neurotransmitter. What if someone is releasing these chemicals, and they can't detoxify them appropriately? They have a much longer prolonged response to some sort of stimulus. So say I'm driving my car, and someone nearly cuts me off and I release epinephrine, norepinephrine. Well, it's good for the moment, but I'm definitely going to want to detoxify those neurotransmitters after the event. And it sort of shows the difference between someone who might be able to recover quickly and someone where that affects them for a long period of time. We also do histamine, so, that has implications with allergies. Dopamine, which has implications with mental health as well. And thiouracil, which has to do with the thyroid.

18:39

Nutrients needed are SAME. Inducers are lipotropics like Choline, methionine, betaine, folic acid, and B12. Very important methyl donors, which can help increase methylation. Inhibitors are folic acid and B 12 deficiency; very detrimental to methylation. Clinical indications of dysfunction are PMS, estrogen dominance, cholestasis, and birth control pill usage. So what's interesting is that



birth control pill is just hormones, it's extra estrogen, it's extra progesterone, and with a lot of drugs, we have nutrient depletions. Well birth control pill depletes B2 B6 B12, folic acid, vitamin C, magnesium, and zinc. Why do you think the birth control pill depletes these? The answer is because it uses a lot of these nutrients to detoxify it when it's going through the body. So, birth control pill depletes all these nutrients; we need to replete them if someone is on it, at least to mitigate some of the damages, and definitely once they've come off of it.

Laboratory assessment is genetic testing. There are genetic tests you can get to see how well you're methylating. There's a certain polymorphism or a genetic mutation known as MTHFR mutation, which shows how well you're methylated. And you can even look at homocysteine, which tells us a little bit about where our B6, B12, and folic acid levels are at because we need those nutrients to convert homocysteine back into methionine, or to bring homocysteine into cysteine. If there's high levels of homocysteine, that's an indicator that methylation is probably being compromised.

20:40

Sulfation; sulfation is the conjugation of toxins with sulfur containing compounds. The main way to detox steroid and thyroid hormones and neurotransmitters is through sulfation. Dysfunction in this process can result in nervous system disorders. So, as I alluded to before, many neurotransmitters need to be detoxified too. Hormones, neurotransmitters, they're all just messengers, and we make them when we need them, but they're used and then they have to be detoxified and cleared. And these are the mechanisms by which we clear them. If we can't clear them appropriately, those chemicals continue to exude their effect on the body. It detoxifies aniline dyes, coumarin, and acetaminophen. We also saw acetaminophen being detoxified through glutathione conjugation. This shows us another example of redundancy here. Methyl dopa, estrogen, testosterone, and thyroid hormone. Nutrients needed are cysteine, methionine, and molybdenum. Inducers are cysteine, methionine, and taurine. Inhibitors or tartrazine, so you know that yellow dye that's in a lot of processed foods? It can actually inhibit sulfation conjugation pathway. How about that? Non-steroid anti-inflammatory drugs and molybdenum deficiency. Clinical indications of dysfunction would be internal toxicity, Parkinson's disease, Alzheimer's disease, and even rheumatoid arthritis. And a laboratory assessment would involve acetaminophen clearance, and showing low urine acetaminophen sulfates.

22:35

Moving on to acetylation. Conjugation with toxins with Acetyl Co-A. It's the primary route for sulfa drugs and sulfa drugs are often used as antibiotics for urinary tract infections. It detoxifies sulfonamides, sulfa drugs and antibiotics as well as mescaline. And nutrients needed are Acetyl Co-A. And inhibitors are vitamin B2, B6, and vitamin C deficiencies.



23:11

Moving on to glucuronidation. Glucuronidation, of course, binds things up to glucuronic acid, and it requires an enzyme known as UDP-glucuronosyltransferase. Most people have no issue with this enzyme, but there is a specific group of the population that does have quite a bit of an issue with this enzyme. And they end up with something called Gilbert's syndrome, which is fairly benign and doesn't really create many problems. But it's important to know about because there's a lot of wiggle room with how we can affect this person's liver detoxification and improve it for the better. So we're going to hone in a little bit on Gilbert's syndrome because it does happen in about 3% to 7% of the population; something to keep on your radar. I have had a couple clients come through where they have symptoms of Gilbert's syndrome where they get access to levels of bilirubin in their blood, or they get jaundice easily, or even some other factors that have pointed us in this direction. It results from a UGT1A polymorphism. So this is a SNP, a single nucleotide polymorphism in the gene, which causes a mutation, which then affects the enzyme, and particularly this enzyme works in the glucuronidation pathway in the liver. These people get the inability to conjugate bilirubin. Bilirubin is a blood byproduct and that can cause jaundice. I remember I was at a retreat centre a while ago, it was a detoxification retreat centre, and they did pretty intense detoxes with these people. One morning we all woke up and just one individual came down. He was a little heavyset, probably somewhat overweight, and he came down and he was yellow all over. His eyes were like yellow and his skin was a pigment I've never seen before. And I was wondering at the time if he had Gilbert's syndrome, and maybe started to process some toxins through that pathway and couldn't deal with the overload. Or I thought maybe his bile duct was completely blocked, and we'd have to rush him to the hospital. I checked in with the retreat centre later on, and he was fine. But he was going through some serious detoxification and buildup of the toxins, which again, is what why it's necessary to make sure these detoxification pathways are working appropriately, and that the channels of elimination are open.

25:53

So let's look at a study looking at the UGT polymorphism and cruciferous vegetables, because if someone has Gilbert's syndrome, I don't want them to just be sent home and say, oh, there's nothing we can do for you. So is there something we can do for them and of course, there is. Cruciferous vegetables coming back for the save! Individuals with a 7/7 genotype had reduced bilirubin concentration, so 7/7 referring to a homozygous mutation, meaning both base pairs are mutated for that gene, with increased dietary cruciferous vegetables. So bilirubin is decreased with increased cruciferous vegetables in individuals who don't have the polymorphism or are heterozygous, so only one mutation, didn't really make a difference. They went on to say with regard to detoxifying carcinogens individuals with decreased UGT activity due to 7/7 genotype may be at greater risk for carcinogenesis. So this pathway that's affected with Gilbert's syndrome is slowed down. And that actually increases the risk of carcinogenesis to these individuals; increase the risk of cancer, because certain chemicals are



detoxed through glucuronidation. But results imply that they also have a greater opportunity to decrease the risk through dietary intervention. So how cool is that? Those without the polymorphism can't really change the way it works that much through dietary intervention, but they're good anyway. Whereas those with the mutation can see quite a benefit from changing their diet and from eating cruciferous vegetables for example. So there is quite a bit of wiggle room if you have a mutation, if you have a slowed activity or sped up activity. I love that study.

27:54

It detoxifies acetaminophen, there we see acetaminophen again, morphine, diazepam, digitalis, aspirin, vanillin, which is a fake vanilla flavour they use in a lot of processed foods, benzoates, and some hormones. Nutrients needed are glucuronic acid, which is the conjugate that binds up, and inducers are fish oils, cigarette smoking, birth control pill, phenobarbital, and limonene. Inhibitors are aspirin and probenecid. Clinical indications of dysfunction are, as we just talked about, Gilbert's disease, yellow discolouration not due to hepatitis, so that bilirubin not being detoxified properly and ending up in the in the skin and even in the whites of the eyes. Laboratory assessment; acetaminophen clearance shows low urine acetaminophen glucuronide. So if you recall back to one of the things that can happen, if a toxin goes through the liver and then into the bile and then into the small intestine, we can create an enzyme called glucuronidase, which cleaves off glucuronic acid from one of these toxins that we see here in the top right corner, estrogen being one of them.

29:24

So you can see the names, glucuronidase, glucuronic acid, glucuronidation; it's all referring to the same thing. So say estrogen comes into the liver, it's processed, it goes to Phase II detoxification, it goes through glucuronidation, we bind up glucuronic acid with the estrogen, it's dumped into the gallbladder, the gallbladder squeezes and releases its contents into the small intestine, it makes its way down the small intestine into the large intestine, and then someone has dysbiosis, they have too many of the bad bacteria. Well the bad bacteria create an enzyme called beta glucuronic days that cleaves off the glucuronic acid and estrogen goes back into circulation. So would you think that digestion, probiotics, prebiotics, and making sure we have good microbiome is important for detoxification and for estrogen detoxification specifically? I sure hope you would agree that the answer is yes.

30:37

And then we have another process that goes on in the liver, also dealing with sulfur containing drugs and foods called sulfoxidation. Now, just a little question for you. We have two types of apricots here, which ones would you choose to eat if you didn't know any better? Now some of you might know that these two apricots are the exact same taste. The only difference is that the ones that are nice, bright and orange actually have sulfites in them to preserve them. That's the only difference. So you're getting more stuff for you to detoxify if you eat those ones.



It's used a lot in dried fruit. Sulfites are used in salad bars; they're used as preservatives, in lemon juice in those little containers. If you've ever consumed or seen Sriracha sauce, sulfates are used in that. They're used a lot of time to preserve really bright colours. It detoxifies sulfites, garlic compounds, chlorine, and chlorpromazine. Nutrients needed or molybdenum. Inducers are molybdenum. Clinical indications of dysfunction are adverse reactions to sulfites. So, one of the things that can happen to people when they have an adverse reaction to sulfites as they get asthma or have trouble breathing. Dr. Jonathan Wright, who's a pretty well known alternative doctor, discovered many years ago that when he used molybdenum with people who were asthmatics, it actually quelled or decreased their asthmatic reactions, interestingly enough, probably because they were detoxifying and clearing sulfites a lot easier through the body. We also find sulfites in wine. As a side note that some people have reactions to wine, so that's something to try as well, to almost use it as a somewhat of a diagnostic tool on how they're doing with sulfoxidation. And other clinical indication is garlic sensitivity, strong smelling urine after eating asparagus, interestingly enough. Some people have it some people don't, it's indication about sulfoxidation. Laboratory assessment would be elevated sulfate:sulfate ratio in the urine.

33:12

So those are the full detoxification pathways. One final note here is just with elderly, detoxification is slowed down, they usually have decreased blood flow to the liver, there's usually a lack of physical exercise and also poor nutrition. So in regards to liver detoxification, it's also the elderly that are more prone to be prescribed a drug, and they are the ones that are at higher risk for adverse drug reactions because of these factors, and because their liver detoxification are somewhat compromised.

33:51

So just to summarize, we talked about Phase I liver detoxification, and the cytochrome P450 enzymes, 50 isozymes. We talked about Phase II liver detoxification, the six conjugation pathways, binding up the toxins to make them more water-soluble and allow for their excretion. We talked about how we can have too high of a Phase I liver detoxification, which would increase the intermediate metabolites and create more free radicals. And if we have a slow Phase II, that creates a real imbalance, or we can have the opposite, where liver detoxification just isn't happening fast enough. What we want is to raise both, support both pathways with all those great nutrients. And just to reflect back to my question about water fasts, fasting and juice fasts, are those really the best way to detoxify? Well, they sure do give the body a break. They have really great effects on our immune system and there is a place for them. When it comes to detoxification, I'm afraid that you probably are not getting the nutrients you need. If you just do a juice fast, we saw that protein was super important. We saw that the amino acids are necessary for amino acid conjugation, for glutathione conjugation. We need the glycine for amino acid conjugation and without those, we can't bind things up and get them out of the body. We need



those amino acids. So it might be wise if you're doing a juice fast to maybe do one protein shake a day, give your digestive system a little break, get the juices in, load up on nutrients and get a little protein in with that. So that's the liver detoxification pathways. Thanks again for joining me.