

Functional Medicine for the Brain and Thyroid

A Clinical Conversation with Datis Kharrazian, PhD, DHSc, DC, MS, MMSc, FACN, and Robert Rountree, MD

Dr. Kharrazian obtained his Doctor of Chiropractic degree from Southern California University of Health Sciences. He has an MS in Human Nutrition from the University of Bridgeport and a PhD and Doctor of Health Science from Nova Southeastern University. His PhD was in Health Science with concentrations in immunology and toxicology. Dr. Kharrazian completed his postdoctoral training at Harvard Medical School and Massachusetts General Hospital. At the same time, he completed a Master of Medical Sciences degree in Clinical Investigation from Harvard Medical School. Dr. Kharrazian is now a professor, research scientist, and functional medicine healthcare provider. In healthcare, he develops evidence-based models using diet, nutrition, lifestyle, and neurological exercises for various chronic diseases. He is an Associate Clinical Professor at Loma Linda University School of Medicine, a Research Fellow at Harvard Medical School, and a Research Fellow at the Department of Neurology at Massachusetts General Hospital.

Robert Rountree: Can you start by telling us a little bit about your early motivators, and a bit about yourself?

Datis Kharrazian: I grew up in San Diego, California. When I was growing up, a family member was very sick. She was going from doctor to doctor, just trying to get better. The only person who really made a difference in her life was a chiropractor who practiced nutrition. At that point, functional medicine was not a concept. The chiropractor recommended a few things and, in his opinion, immediately knew what was going on. For the first time in 20 years, she actually started to feel better. After seeing many experts, it was shocking for our whole family. This person made a huge difference in my family member's life.

This experience got me interested in being a chiropractor, and then also a nutritionist. Years later, I had several shoulder dislocations, and I went to see the same man. He made some changes to my diet. In the end, I did not need to go in for surgery anymore. My shoulder stopped dislocating, and

I thought about how powerful this all was. I really wanted to learn how to do this. This was the motivating event for me to go into chiropractic, not really so much for spinal adjusting but more for a lifestyle and nutritional approach.

I eventually went to the Los Angeles College of Chiropractic, which is now Southern California University of Health Sciences. Soon after, I got to meet Dr. Aristo Vojdani, PhD. I got to know him pretty well, and I eventually told him about my family member. He suggested that we check her blood. We checked everything, even things that were not commercially available. She had antibodies to different neurotransmitters, such as serotonin and dopamine. There is no published information on individuals with antibodies to their own serotonin. She had significant adverse reactions to many different antidepressant medications.

So, 20 years later, I decided I really wanted to get my PhD in immunology. I got into a PhD program at Nova Southeastern University in Fort Lauderdale, Florida. Dr. Vojdani became my mentor in that program. He was one of my PhD advisors for the university. We worked with the department of health science there, and we come up with a proposal of trying to look at how chemicals can become new triggers if they bind to proteins. Under his mentorship and guidance, I was looking at how chemicals bind to proteins and become new antigens, developing new epitope sites for binding called neoepitopes.

When I look back, I realize how much the experience with my family member had to do with where my career went. These experiences as a child really guided me in my adulthood. I was not aware of all these things as I was going through the process. I was just thinking that I should learn about this.

Once I finished my PhD, I got an opportunity to do a postdoctoral fellowship at Harvard Medical School. I started in 2015 in the Department of Neurology at Massachusetts General Hospital with another great mentor, Dr. Martha Herbert, MD, PhD, at the TRANSCEND lab. She has done some great work with autism and is really one of the main leaders around how the environment can impact the development and progression of autism. While I was doing my postdoc, I was also enrolled in a Master of Medical Science and Clinical Investigation program at Harvard Medical School. I was in a class with 12 people, all studying how to do clinical research. We trained with some of the best researchers, clinical trialists, statisticians, and epidemiologists in the field of medical research. I was picked for this program because they wanted diversity and different perspectives. They wanted

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people in the program who had some background in science, who had published but had also come in from a completely different point of view. So, I was their alternative medicine person. They wanted all of us to work on projects together and think together while working with these brilliant researchers.

It was interesting coming into a program like that. I was able to point out the alternative medicine approach to many things. What I found at Harvard Medical School was that they were so open-minded. Over the years, I have taught at various medical, naturopathic, and chiropractic schools. My experience at Harvard Medical School made me realize that the reason they have major breakthroughs is because they want to have completely different perspectives coming in and analyzing everything. At the end of the day, data are data, and they realize that their own biases can get in the way of seeing real data and real treatment.

In the program I was in, Clinical Investigation, we had some of the major statisticians and researchers sharing publications and research, and showing everything we are all doing wrong with data analysis in the field of medical research. We had a gentleman named Dr. Miguel Hernan, MD, DrPH, at the Harvard T.H. Chan School of Public Health, who I would say is one of the major game-changers in the world of medical research. He has published about how clinical trials are being done incorrectly, and the limitations in the way we are looking at endpoints. Harvard Medical School was very aware of the limitations of medical research and how it is being done. So, even though they are very proud that they have been the number one medical research university for the past 80 years in a row, they also realize how they are doing research incorrectly and where research and data analysis models need to evolve.

Dr. Rountree: One of the things that Dr. Vojdani talked about in our last interview for *Alternative and Complementary Therapies*¹ was that when he first started doing antibody testing to environmental toxins, he could not get his data published because no one believed his findings. Has that been your experience as well?

Dr. Kharrazian: Absolutely. That is a real thing. And I think that is a big problem. Dr. Vojdani is so far ahead of everyone, they do not even comprehend what he is doing. When you submit a paper to a journal, you are sending it to some random reviewers. The random reviewer may not have the capacity to understand the next level of research or breakthrough research concepts. So, what gets published is essentially what reviewers all decide makes sense, the information that follows the paradigm shift. What I found, with having great publications with Dr. Vojdani, is that many different reviewers would just immediately reject the paper without any useful commentary other than they did not believe the outcomes or concept of the study. Our data or analyses were never scrutinized. Our laboratory methods were never scrutinized. It was just that they did not understand the possibility of novel concepts, so they rejected it.

That is real bias. It is unfortunate. Many times, especially in some of the medical journals, you have good data and laboratory science submitted, but then you have a physician or

other reviewer who does not have a background in data analysis or laboratory methods. They just reject the paper because they were the reviewer on the print journal.

So, we have that frustration with trying to get some of those studies published. However, many of them have been published, and many more manuscripts are in the process. It is just that with every new submission, three reviewers have to approve, and one rejection means starting all over again.

Dr. Rountree: When you were doing your clinical research fellowship at Harvard, did you feel like you were able to move the needle a little bit with regards to acceptance?

Dr. Kharrazian: Many people at Harvard were already doing breakthrough research. They were breaking paradigms in their own way. There were different groups of people. There were people who were working with established clinical trial methods, with the drug companies, and publishing major studies. Then there were other researchers, such as Dr. Herbert, who was doing phenomenal breakthrough research with autism and the environment and other factors.

But overall, there was just a general attitude of openness that I had never been involved with before in my entire career. When I first went there, I thought it was going to be the most conservative, strict, and anti-alternative medicine environment that I had ever been in. However, it was just the opposite. I found out that they were studying the microbiome, the gut-brain axis, intestinal permeability, and many of the topics so important to us in a functional medicine model. The School of Public Health is also doing great research in various fields of nutrition. There is an entire department at the School of Public Health looking at how environmental compounds in our buildings are making people sick. What I realized was that they were conducting some of the most important functional medicine research of our time and that was very exciting. The focus of research was not just on large pharmaceutical clinical trials.

In fact, the people who were in charge of the School of Public Health made sure that there was a diverse list of healthy foods in the cafeteria that everyone could eat. I was expecting regular hospital and cafeteria food. These people understand the importance of diet, nutrition, and lifestyle. And of course, they are leaders in nutritional medicine as well.

Dr. Rountree: What new insights did you come up with after working with Dr. Herbert? Did you have your own sense of what you think autism is about?

Dr. Kharrazian: I think the problem with autism research is that there are so many variables that are involved with the disorder, the development of any type of clinical trial is very difficult. So, what we were really looking at was the role of “N of 1” clinical trials. With these trials, we can do Bayesian statistical methods, where you look at what is called a posterior probability test. You look at how multiple variables are used to treat a person and then look at different biomarkers throughout their treatment. Then those biomarkers are analyzed to see if a personalized multi-treatment protocol has an impact on the patient’s outcomes.

This type of research allows us to collect all the data on each patient. After looking at the same biomarkers in a group of patients, we can combine the results, and do a type of meta-analysis. It is really the only way that we can look at personalized lifestyle medicine. This was one of the key things I learned while working with Dr. Herbert.

As an example, let us say we are looking at hemoglobin A1c and other endpoints. We look at different treatment variables, and we see which endpoints change for them. Then, we can statistically calculate these and compare them while on treatment or without treatment. Then we can come up with a very accurate treatment model that is personalized to one individual.

N of 1 clinical trials are getting a lot more support in research publications. With a clinical trial, the focus is on generalizability to the entire population and not on individuality. Also, there is a limitation to only one treatment approach. In a real clinical setting, we do multiple treatment approaches because we are trying to do many different things to make the patient feel better. We get patients to change their lifestyle, maybe try to sleep more, as well as change their diet, and take a few supplements. We are not doing these one at a time for 12 weeks and then measuring a primary outcome. There is a lot of difficulty in establishing a clinically realistic model with a standard clinical trial for complicated conditions that have a lot of diversity in their pathophysiology. For example, we really cannot design an accurate clinical trial with so much variability with each patient who suffers from autism. Each patient has a unique set of physiological parameters that makes the standard clinical trial approach an ineffective model because of the wide range of uniqueness that cannot be accounted for in a group study despite the power of randomization.

Dr. Rountree: Can you discuss how you use this in your clinical practice? When people come to see you, don't you typically spend several hours with them?

Dr. Kharrazian: I have patients send me their medical history and all of their laboratory tests before they come in for their first visit. I might spend a couple of hours reading their file and their past history. I spend some time on PubMed doing some research. Then, when the patient comes in, I can organize my exam in the best order for them. I might need the day just to examine them. Then I will probably need another few hours to put all my notes together, and maybe another day or two to put together a treatment plan.

For me, it is one patient at a time, trying to figure it out. I work as long as it takes to get it done. Going back to my own personal experience of having a chronically sick person in my family and seeing what it really took to turn them around was really a motivating factor for me. I think there are only going to be a few people who really have the motivation to do this. This allows me to figure out a few insights into something that might be new.

Dr. Rountree: One thing I have noticed from your lectures is that you are doing some pretty elaborate testing to try to determine the problem. If someone has cognitive impairment, for example, you do functional neurological testing in order to really try to understand where his or her

problem is originating in the brain. Can you describe the discipline of functional neurology and how you use it to make recommendations?

Dr. Kharrazian: Functional neurology is a clinical model that incorporates a standard neurological exam. However, the idea is to look for all the subtleties in their exam. We are looking for neurological function, not just obvious hard neurological signs found with progressed disease.

For example, while doing the Romberg's test for neurological function related to balance, when patients close their eyes, they might not fall to the ground, but they might have significant sway to one side. That tells us something about what is going on with their brain and the vestibular integrity on that side. So, in our case, we are looking for the subtleties. We then try to triangulate the area of the brain that is involved. In order to do that, we have to know the examination findings and exactly which pathways are being checked. We can add up all the different exam findings to come up with a potential conclusion. If we think a certain area of the brain is being affected, we can try to do some stimulation to that area. Maybe it could be eye movements because we are trying to activate the frontal eye fields with saccades. Or it could be doing some rotations in the chair to activate the vestibular ocular reflex and cerebellum. Then, if we see some of the exam findings change immediately after stimulation, this becomes our therapy. The goal is to try to develop plasticity in regions of the brain that are not functioning ideally.

The field of functional neurology is really growing. We organized the International Association of Functional Neurology 10 years ago. There are about 1000 members right now in approximately 40 countries. We have developed several 150-hour programs, everything from childhood development to neurological rehab for the brain and vestibular dizziness programs for practitioners to learn about. It is a growing field, and it is becoming more and more multidisciplinary. Although it was initially started with mostly chiropractors, we are now getting functional medicine practitioners, physicians, physical therapists, optometrists, and all types of healthcare professionals who are working with patients suffering from various neurological and developmental disorders.

Dr. Rountree: Based on your experiences, you wrote a book about problems that affect the brain. What was the main focus of the book?

Dr. Kharrazian: Yes, the book, *Why Isn't My Brain Working*, is really a functional medicine approach for the brain.² I wrote it to try and share an approach of how to support the brain from a nutritional model. We look at circulation, neurotransmitter pathways, brain barrier access. We present clinical symptoms and patterns to walk through it.

I had 3000 peer-reviewed references in the book when I first wrote it. The reference section was bigger than the whole book. I cut out a lot of the references to reduce the bulk of the book. However, there are still 1000 scientific citations because I wanted to make sure that I referenced everything, so that everyone would have some confidence recommending that book to their patients,

and I could help them connect the latest research with the clinical approaches I was recommending in my book.

Dr. Rountree: Do you have a sense from your research and clinical experience as to how a neuro-cognitive disorder develops?

Dr. Kharrazian: I will give you a great example. Last week, I had a patient with some cognitive decline and focus and concentration issues. She was in her late 30s, and she had suffered with this all the way through high school and college. She scores off the charts with IQ testing. So, she is very intelligent; she just does not have the ability to focus and concentrate. On top of that, her brain function goes down throughout the day, meaning that she cannot perform. She was not able to finish a master's program because of her impairment and brain function, despite her intelligence.

She came in to see me. From the exam, every finding was normal, even in the functional perspective. We essentially checked the function from the front of the brain to the back, and from the top of the brain down. We spent about two hours doing a detailed neurological exam with her. It really came down to the fact that she was suffering from more of a brain endurance issue. She was not getting fuel to her brain. During the examination, we found that she had a history of mitral valve prolapse. She had thrombocytopenia, and her hemoglobin and hematocrit were really low. She had poor circulation with white nail beds. Her tissue saturation was off. She was just not getting oxygen to her brain.

We realized that we had to improve her hemoglobin and hematocrit, so that she could carry oxygen to her brain. There are many publications on thrombocytopenia, and how antioxidants can dampen the inflammatory reaction that impacts red blood cell function.³ So, we put her on a cocktail of antioxidants for support. We gave her things to improve her endothelial and nitric oxide pathways, such as vinpocetine. We got her to do some quick five-minute burst exercises while she was breathing oxygen. There was a huge difference in her function. So, here was an example of a patient who had focus/concentration issues and cognitive decline, but it was really related to a mechanism of improper oxygen getting to her brain from genetic issues. She had been on a cocktail of pretty much every supplement for the brain, but until you do an exam and find the mechanism, you do not know what the appropriate treatment is for the patient. General supplementation might work for many people. But then you get the patients who are frustrated because they need more specific direction, specific to their own unique physiology.

Dr. Rountree: I heard you once say something to the effect of the earliest sign of brain degeneration is brain fatigue. Can you tell us a little more about what that means? How do you know the difference between brain fatigue and body fatigue?

Dr. Kharrazian: For me, one of the most useful clinical tools to distinguish between the two is just to ask the patient when they notice their fatigue kicking in. If they notice their fatigue kick in after they do a task that involves the brain, such as reading or

driving or being on a computer, it strongly suggests that it is brain fatigue. On the other hand, if they wake up every day and they are exhausted and cannot do anything, that is really suggestive of a metabolic fatigue. Of course, some people have both.

Often, patients come in with a chief complaint of fatigue or a diagnosis of chronic fatigue syndrome. While working with them, I find that their fatigue happens toward the second hour of the day, when they are actually engaged in cerebral tasks. They wake up okay. Then during an examination, some areas of the brain are not functioning well. In some cases, there are patterns of early neurodegeneration, such as early Parkinsonism or dementia, or perhaps they had an earlier brain injury that has caught up with them over time. They may have done many different things to treat their fatigue from a metabolic point of view, such as supporting their adrenal glands or trying to detox, but there was no effect, and no one really spent any time trying to improve their brain function.

We will do some brain exercises to improve plasticity for the brain. We will also develop a specific protocol to address their brain needs nutritionally. In many cases, we have some good clinical outcomes that may have been overlooked if there was not an understanding that sometimes fatigue is really an early sign of a neurodegenerative process taking place. One of the key things is to activate the brain so we can develop mitochondrial biogenesis and plasticity. A functional neurology approach involves activating the brain, meaning we have to fire specific neurons for the specific regions of the brain that are impaired. We use various exercises that fire receptors and induce post-synaptic changes in the necessary regions of the cortex, such as balance therapy, eye movement exercises, sensory exercises, and so on. When you activate specific neurons through receptor stimulation, that is when you actually have neurons connect with each other. There is a lot of research on mitochondrial biogenesis and plasticity using nutrients, but it is not actually showing the change in mitochondria quantity or axon branching. This research is only showing various nutrients can turn on the cellular messengers to activate mitochondria and neurogenesis.⁴⁻⁷ I think we have to be careful when we look at the available research related to mitochondrial biogenesis because transcriptional factors can turn on all the time for various things. But does that mean these supplements are actually increasing the mitochondria in humans? We know that direct stimulation of a neurological pathway can increase the actual quantity of mitochondria.⁸ Brain activation is similar. If we activate the brain, neurons can connect to each other and also increase the mitochondria within the healthy cells. For many patients with brain impairment, they need the nutritional support their brains, and they need to activate their neurological pathways directly. They need to dampen the mechanisms that promote neurodegeneration, such as inflammatory reactions in the brain and so forth. That is where the functional neurology approach comes in and addresses these mechanisms. As an example, if someone has a weak and atrophied muscle from being in a cast, you can't just give them supplements to have them regain their arm function. You actually have to have the person move their arm and activate their ascending and

descending motor pathways in their brain in order to promote both peripheral and central mitochondria biogenesis. The brain responds in the same manner; it has to be activated so it can connect and branch and have mitochondrial biogenesis.

Practicing functional neurology in a functional medicine community, we see a lot of patients with brain-based fatigue who have not responded to a functional medicine model. We isolate the areas of the brain involved, and try to activate them and develop plasticity in those areas through activation with various types of exercises. The exercises might involve color therapy or vestibular therapy. They might involve focus and attention, concentration exercises, or various other things. We can sometimes see dramatic changes in their chronic fatigue syndrome. In the end, their chronic fatigue syndrome is an early sign of neurodegeneration related to brain impairment.

Dr. Rountree: There is a general agreement that exercise is generally a good thing—that everyone should engage in physical exercise on a regular basis. We know that will help with Alzheimer’s, heart disease, and so on. You are saying that we need to go beyond that general recommendation—that we need to get very precise in what areas of the neuromuscular system we are activating. Can you elaborate on that?

Dr. Kharrazian: Exactly. General physical exercise such as jogging or riding a bicycle increases growth factors and brain-derived neurotrophic factor.⁹ These are essential for us to have neurons connect to each other. The specific brain exercises that we suggest for our patient might be to turn their head to the left, close their eyes, and touch their finger to their nose 10 times. This may seem trivial to most of us. However, for people who have a parietal lobe injury, it is the most difficult thing in the world. After 5–10 of those, the heart rate jumps up because the brain is fatiguing. Then we have to stop, wait a minute or two, and try again. It really depends on the region of the brain that is involved. Most of the brain therapies we do can appear trivial, but they are very specific to the neurons and functions that they are involved with.

A lot of people have been approaching the concepts of brain plasticity and mitochondrial biogenesis through activation with different models. The brain responds to stimulation; however you find it and get it there is critical to recovery.

Dr. Rountree: Can we jump to functional endocrinology? This is also an area that you are deeply involved in. Are endocrinologists treating Hashimoto’s hypothyroidism correctly? I ask because I have many patients who feel better with a consistently low or high thyrotropin (TSH)—even when those levels are outside of the “normal” range according to thyroid specialists.

Dr. Kharrazian: I would say endocrinologists are treating Hashimoto’s hypothyroidism correctly for their scope of practice. Their scope of practice is to identify and diagnose the condition and then to make sure that the patient is receiving adequate hormones for their physiological needs. They put the

patient on thyroid replacement and make sure they are not in a thyroid deficient state by monitoring TSH.

However, the issue with the condition itself is that most hypothyroidism is really due to an autoimmune pathophysiology involving Hashimoto’s. This is where diet and nutrition, lifestyle, and other factors can have an impact on it.

So, most patients with hypothyroidism should definitely be working with a conventional physician or endocrinologist to make sure that they are not in a hypothyroid state. But diet, nutrition, and lifestyle changes to modulate the expression of their autoimmunity are also really important for them. I can understand the hesitation with the traditional endocrinology model because there is not a lot of published information of this personalized, individualized approach to a thyroid condition.

Ultimately, I think the patient makes the final choice as to who they work with and what works best for them. The thing with TSH is that it fluctuates all over the place. It can change with the amount of thyroid hormone replacement someone has, but there is also a thyroid receptor sensitivity that has to be taken into account. When thyroid replacement is prescribed, it should be noted that thyroid replacement also suppresses both TSH and TSH releasing hormone (TRH). TRH is a major stimulator of autonomic pathways in the brain stem.¹⁰ So, if you completely suppress TRH release, you get autonomic dysfunctions and impairments in gut function, enzyme release, and so forth.

There are patients who are not feeling well because they are fatigued and their metabolism is slow. They are working with someone who only knows to keep increasing the dose of replacement as a treatment option. Then at some point, they are suppressing TRH function, and their TSH is so low, they are feeling worse. During an examination, there is hyperreflexia, borderline tachycardia, and some insomnia. They are being overstimulated.

On top of that, there is the autoimmune disease that may flare up and destroy some of the thyroid gland. Then those tissues break down, and now there is a huge surge of thyroid hormones, and they are going between a mixed hyper and hypo state. They are not in a thyroid storm. They do not know what to do. The practitioner doesn’t understand why they aren’t getting better. The problem is that there is some fine-tuning or evaluation that often does not take place in a conventional model, where they just fixate on the specific number for TSH.

Dr. Rountree: Is this what you mean when you say that Hashimoto’s hypothyroidism is a disease of the brain, not just an endocrine disease?

Dr. Kharrazian: Absolutely, and there are several other examples of this. In the field of immunology, we have always thought of antibodies as binding to one specific target protein. So, we think that the thyroid peroxidase (TPO) antibody only binds to TPO. However, TPO binds to cerebellum tissue proteins. So, in the condition thyroid encephalopathy, patients have a TPO antibody count that goes up.¹¹ All of a sudden, they start to get neurological symptoms. This happens in a person who has an impaired blood–brain barrier, but many patients end up with

impaired blood–brain barriers because of various things. We know that TPO antibodies can bind to cerebellum proteins, specifically Purkinje cells, and astrocytes in the cerebellum.¹² Also, we have done some research that we have not published yet suggesting that thyroid antibodies bind to more than just cerebellum tissues; they bind to different myelin proteins as well.

So, if someone has Hashimoto’s disease, traditionally thought of as just a thyroid disease, it really is not. The antibodies they are making can bind to different protein sites. This is why a lot of Hashimoto’s patients also have brain impairment issues. Thus, it is more than just taking a replacement. Now their brain is inflamed, and they have some degenerative changes. They need to develop plasticity there. Also, we need to deal with the leaky blood–brain barrier because these antibodies can only bind to the cerebellum if the blood–brain barrier is permeable enough.

There is research coming out that is showing that when zonulin is released, like in leaky gut mechanisms with celiac disease, it opens up the blood–brain barrier as well. So many individuals with Hashimoto’s have the HLA-DQ genotype, where they are also gluten sensitive or have celiac disease.¹³ This genotype increases intestinal permeability because of celiac disease. Then they start to release zonulin, which opens the blood–brain barrier. Because they also have thyroid antibodies, now they have TPO binding to their cerebellum target proteins. Now they have a subtle neuroinflammatory response in their cerebellum. They start to get changes in the brain. The brain starts to degenerate; they lose their focus, attention, and concentration. Their brain endurance goes down. They go on replacement and are wondering why they are not feeling better. That is because there is this other underlying autoimmune response that is there.

A very interesting thing about antibodies is that they can bind to so many different target proteins. That is one of the things we are studying right now. What is basically showing up is that thyroid TPO antibodies are also binding to different brain target proteins. I think there are a lot of direct connections between autoimmunity of Hashimoto’s and some subtle brain neuroinflammation taking place.

We know that there are some publications on GAD65 antibodies.¹⁴ There is one publication that suggests that 5% of Hashimoto’s patients also have GAD65 antibodies. Not only does this specific antibody bind to different tissues, once people develop an autoimmune response, they have multiple autoimmunity in different regions. Then there are different food proteins and chemical proteins that can trigger each of these binding sites, which is what we spend a lot of our research on.

In a recent publication, we looked at food proteins, such as the specific cross-reactive nature of various food proteins to thyroid autoimmunity.¹⁵ This was published in the *Journal of Thyroid Research*. We took 204 purified foods and used monoclonal antibodies with different thyroid target sites. I wanted to do this because since I wrote a book on Hashimoto’s, I see a lot of Hashimoto’s patients just because of the referrals. When I do a panel looking at their immune reaction to food proteins, almost every food protein shows up. There is cross-reactivity between food proteins. However, some of it is just that they have lost their tolerance. One of things that I need to understand is which ones

really matter. Which ones are the ones that can have the biggest impact on the thyroid? When we find food proteins that directly bind to TPO or thyroxine or triiodothyronine, these are on the higher list of things for me to consider removal.

I was just in Dr. Vojdani’s lab recently. We put out a blueprint of what we think autoimmune disease evaluation should include. The first thing it should include is the binding at the target protein antibody to which other tissues in the body. For example, the TPO antibody. Where does TPO also bind to? Is it just the thyroid or is it other tissue proteins too? So now, we can take TPO and do a cross-reactivity examination with monoclonal antibodies with direct proteins. We find out that TPO can also bind to myelin, for example. Now we can understand the condition more generally than just the destruction of the thyroid. The next question is which food protein reactions can actually bind to the target, to the thyroid. We make that list. Then which chemicals bind to albumin, the most abundant circulating blood protein. Then we ask how they trigger the autoimmune response.

Now, we may be narrowing down our list of foods to 10 things or a few chemicals that are more critical than other food proteins. If we check for every chemical and every food, and try to remove all of them, it becomes impossible. But if we can find out which ones have specific immune cross-reactivity with the target site of the autoimmune response, then we can blueprint it out.

So, we are trying to blueprint out Hashimoto’s and type 1 diabetes. We have made a list of about six other autoimmune diseases that we are trying to put our efforts into, and we are scheduling time in the lab to do the research. That is our ultimate goal, but it will take a few years to complete.

Dr. Rountree: I know that you have published a paper on bisphenol A (BPA). It seems like there is a lot of cross-reactivity between antibodies to BPA and a lot of other proteins. Can you tell us about that?

Dr. Kharrazian: We know that BPA has toxic effects. We also know that BPA can bind to albumin. As it binds to albumin, albumin becomes a new antigen. Now we have a foreign trigger for the immune system. We published a paper recently where we took 100 blood samples of patients who had antibodies to or not to BPA.¹⁶ We found that there was a significant correlation, suggesting that there was a strong correlation between making antibodies to BPA and making antibodies to myelin.¹⁶ This could result in illnesses such as multiple sclerosis (MS), or result in subtle neuroinflammatory responses that may have not progressed to the point of diagnosis with MS, an MS-like syndrome.

A neuroradiologist friend told me that white matter lesions are expected with age. He says they have seen so much of it, and they do not know what to call it. He says it is injury against the myelin, but because it is so common, they just consider it a normal variant now. I think this is very interesting. I think a lot of people have subtle neuroinflammation in the brain. We definitely see high levels of antibodies for target proteins of the brain with many people who have chronic illnesses.

BPA exposure can be a factor in all of this. Our current understanding regarding BPA is that everyone has BPA exposure.

Biomonitoring studies have shown that > 96% of people tested have high levels of BPA in the blood. We showed previously that if we take 400 random blood samples, we find BPA antibodies in about 15% of the population. If we take those blood samples and check them for neurological antibodies, there is a very high correlation with neurological antibodies.¹⁷ Our understanding is that it is not just exposure, but exposure that then leads to binding of proteins and immune triggering responses. Also, the integrity of our barrier systems totally dictate how we respond to chemical exposures, unrelated to just liver biotransformation pathways. What we are learning is that this tolerance game is a big issue. Dendritic cell function, permeability of the blood–brain barrier, gut barrier, lung barrier, Treg function in the gut, different polarizations between, for example, T helper cell subdivisions—I think that is where functional medicine has to go.

We are breaking down all the different profiles and then figuring out the models. In my practice, I am breaking down T helper cell profiles and doing cluster differentials and trying to work through different protocols to try to find a relationship.

Dr. Rountree: Are you actually measuring T helper subsets or are you measuring cytokines?

Dr. Kharrazian: We are measuring all of the above. We can do the cytokine-stimulated tests. It is in the laboratory setting, but not in the commercial setting. It is really the only way to find the subtle cytokine shifts because you do not see these levels elevated in serum unless they are really progressed to a severe autoimmune disease such as lupus. With a stimulated-cytokine test, we stimulate the T cells with an antigen, such as pokeweed mitogen, and we see what kinds of cytokines are released. Then we try an intervention and see how to change it.

I am trying to do as much of that as possible within my clinical practice. There are lots of publications in the immunology literature of these things being done in various laboratories throughout the world. I try to hint to Dr. Vojdani to create a commercial test for this, since he is in the commercial side of things. I think he is trying, but he has so much research that he wants to publish and so many other things that he wants to do.

Dr. Rountree: You have talked a lot about being able to measure antibody responses to food, and if you see these antibody responses, it suggests an inflammatory response. Is this also true for lectins? Is it necessary to induce an antibody response to have a problem with lectins, or is it more of a biochemical inflammatory response?

Dr. Kharrazian: Lectins cross-react with everything based on an analysis that we just did in thyroid autoimmune target sites. I think there is some cross-reactive binding with lectins, specifically antigen antibody reactions of lectin to different target food and human tissue proteins in susceptible individuals. This makes it really scary.

For most of us, our first understanding of lectins came from the patients we saw who had changed their diet and found that they really felt better not eating certain foods. We realized that those

were high-lectin foods. Since then, there has been research that has come out of that.¹⁸ In my experience, and based on some of the research we are doing, high-lectin foods are a major concern for patients who have autoimmune disease. Remember, the key thing with autoimmune disease is that patients lose their immune tolerance. So, at some point, they have lost their barrier function. Their Tregs are dysfunctional. Their T cells are polarized and in an inflammatory state. They are responding abnormally to immune reactions. If they have a heightened state of immune reactivity and then have proteins that can bind to target proteins, it becomes a very dangerous combination. A lectin-free diet may be something that is critical because of the high affinity of lectin to binding to tissue proteins when someone loses their tolerance.

Dr. Rountree: How do you convince people, without being able to test for specific reactivity, that certain foods are bad for them? No one in our sphere is questioning the pro-inflammatory effects of gluten. But when you get to a really expanded list of foods to avoid, it becomes much more difficult. How do you work with that?

Dr. Kharrazian: Many patients are upset. They have already cut out so many things. So, when you start adding lectin-containing foods to the list, it really adds so many more foods they have to restrict. I start off by suggesting a trial period to see how they feel—maybe a month. Ultimately, elimination provocation is still the gold standard because lab tests all have their flaws. This does not mean that everyone needs to avoid lectins. With any extreme position, there is lots of room for bias. Ultimately, each patient is unique to themselves. When I work with patients, I work through their individual case. I tell them that we do not have all the answers. We have to try things, go through the process. It is an exercise of endurance for psychology and emotional well-being. It will be exhausting, but there is no other way to do it. We have to try different things and figure it out. Then, as time goes by, we will figure out what works best for each patient.

That is really the goal I have with working with autoimmune disease patients. It is trying to take them through that journey to help them develop their own individualized diet and lifestyle program that calms down their autoimmune reactions.

Dr. Rountree: You are saying ultimately that it really does come down to trial and error. And this gets back to what you were saying earlier, that it is an N of 1. You start with an idea that lectins might be a trigger, but you do not think that everyone with an autoimmune disease needs to avoid lectins.

Dr. Kharrazian: Exactly. I personally am flexible with that. I have seen many patients who have Hashimoto's or an autoimmune disease and also have significant blood sugar issues. Sometimes, the only way they can keep up their blood sugar is by having some nut or seed butter. Then they can manage their significant drops in blood sugar. On the other hand, in other people, lectins can devastate them. If they get any exposure, they completely fall apart.

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Classifying all lectins is kind of tough. However, it is common to see many autoimmune patients with adverse reactions to lectins. There always needs to be caution whenever you see a patient being able to consume some type of lectin. We need to make sure that they are feeling okay. We need to look at markers. But some people are okay.

Dr. Rountree: Is there a general marker you might look at besides an antibody test in order to determine if lectins could be a problem?

Dr. Kharrazian: The antibody test is the way to figure out which food proteins are there. But at the end of the day, we can see inflammatory markers that they are expressing. It could be complement markers, T-cell shifts, or cytokine shifts, for example. I try to get as many baseline inflammatory markers as possible before we try anything with the patient. Then we use those as their baseline from that point on. Everyone is different. For example, some people might have a very high C-reactive protein (CRP), but most autoimmune patients do not. That means CRP can't be used as a tool in those people. In those cases, we might have to use a cytokine-stimulated test. Or sometimes we can only look at the patient's inflammatory reactions, their swelling, pain, or other chief complaints to see if things are working.

Dr. Rountree: Thank you so much for this conversation. Clearly, we could talk much longer! Your ideas are things that we can all do—trying certain diets, rebuilding tolerance, working on leaky barriers. Some of them are more sophisticated, such as functional neurology or the antibody tests that are really not available to regular practitioners. What do you recommend for people who want to understand this more, especially functional neurology? Is there an “easy” beginner’s book—“Functional Neurology for Dummies”—available? Or is there a way people can get in touch with you to find out more?

Dr. Kharrazian: An easy resource is a good idea. Unfortunately, right now, all that is available is the research. It is very complex. The brain has so many pathways and so many presynaptic and postsynaptic projections. If someone does not know that, they cannot even play the game. It makes it hard. But I think it could be simplified a bit so that if a few tests are done, a few things could be tried. Maybe that is something that we should develop as an organization.

All of the information I have is on DrKNews.com. That is a way that people can find out more. We write articles and post publications that we have just completed. I have papers in submission right now, and research ready to be published, some with Dr. Vojdani who is brilliant in this field. We are on a roll. ■

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