The Gut Microbiome and Autoimmune Disease (Part 1)

presented by AIP Certified Coaches

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Dr. Sarah Ballantyne: I'm Dr. Sarah Ballantyne, and in this presentation I'm going to talk about how the gut microbiome is linked to autoimmune disease. And with that information, how we can refine the focus of the autoimmune protocol in order to best support that health so that we can best mitigate autoimmune disease. And it helps to start with defining what gut health is.

The four main functions of the gut that are really relevant to our overall health; the first is digestion and absorption of nutrients. If our guts aren't doing that; we aren't healthy. We can't use all of those important nutrients for biological functions. There's also 80% of our immune system housed within the tissues surrounding the gut. So a huge part of gut health is immune regulation.

Another aspect is hormone and neurotransmitter regulation. The gut is a producer of a huge collection of both hormones and hormones that double as neurotransmitters. And if those aren't properly regulated, that affects the signaling between the gut and the rest of the body. And the last is detoxification pathways. So, there are a variety of detoxification pathways that occur in the gastrointestinal tract as well as the broader digestive system, which includes the liver. So if those detoxification pathways aren't occurring properly; again, the whole body can't be healthy.

So the gut has these four main functions that if any one of those functions are not up to snuff, the entire body suffers. And what's really fascinating is the gut microbiome actually influences all four, and contributes to all four of those functions.

So what is the gut microbiome? It is a biological niche. It's an entire ecosystem. And it includes a tremendous array of not just bacteria, but archaea, yeast, and other eukaryotes, as well as viruses. And they're really just a community of microbes. And like any ecosystem, one of the most important hallmarks of a healthy ecosystem is diversity. So any ecosystem on the planet, one of the things we look for is biodiversity. The more different species are, typically the healthier that ecosystem is. The same is absolutely true of the gut microbiome.

Within our guts there is approximately, give or take, about 100 trillion microbes. Our microbes actually outnumber our own human cells by anywhere between 3 to 1 and 10 to 1 depending on the estimate

that we're looking at. And collectively, they outnumber human genes by about 150 times. And that's really important, because genes are the map for making proteins. And proteins have a function. So what that actually translates to is that our gut microbes collectively can do 150 times more functions than we can do. And that's going to become really apparently when we talk about how our gut microbes contribute to digestion.

But it helps to sort of talk a little bit about what are the hallmarks of a healthy gut microbiome beyond just the diversity aspect. So there are certain what are called keystone species or foundational species of genera of bacteria in the gut that we know are so important for that entire ecosystem and for our health, that we can say the absence of them is a problem. It's a form of dysbiosis; which means an imbalance that is problematic in the gut microbe ecosystem. And this slide shows you some of the best studied of those sorts of foundational, keystone type species. So without their presence, we just end up with a skewed ecosystem that is no longer benefiting the human body.

So certain strains of bacteria you're going to hear me talk about again and again. Among them, the two most important probiotic species we have in our gut, or their genera. There are multiple species of them. Bifidobacterium and Lactobacillus. But there are also really important ones; we're going to talk about Faecalibacterium, Akkermansia. We're going to talk about Roseburia, Clostridium, Bacillus species. These all have a really important contribution in the niche.

You can think of them as; if you thought of our gut ecosystem as a city, different bacterial species fulfill different roles of different jobs. So some are like the policemen, and some are like the doctor, and some are like the teacher, and some are like the garbage person. So without any one of those really important jobs being filled, then you start to have a breakdown of the entire society; of the entire ecosystem.

So let's talk about how our gut microbiomes actually contribute to these really important functions that our gut performs as a whole. Let's start with digestion. We actually can consider this ecosystem of gut microbes in our digestive tracts as a virtual organ. They are so fundamental to our digestion, that we actually have somewhere in the neighborhood of 800 different compounds in foods that are considered non-nutritious that our gut bacteria are able to transform into thousands of biologically active molecules that are absorbed into our bodies that have a variety of really important health benefits. So without our gut bacteria, not only would those thousands of important molecules not be produced, but those 800 plus non-nutritious compounds in foods would go to waste.

So what our gut bacteria do is they actually expand our digestive capacity. And that is really apparent when we talk about their ability to digest carbohydrates. So there's a whole class of enzymes call CAZymes that are enzymes that break apart carbohydrates. And in our digestive tracts, us humans, we make 17 of them. There are 17 different types of molecular bonds within a carbohydrate that we have enzymes that specialize in breaking those apart.

Our gut microbes, on the other hand, collectively have about 10,000 different CAZymes. So they have, collectively, about 10,000 different types of molecular bonds that they can break apart within a carbohydrate molecule. And carbohydrates can be these incredibly complex long strings and sheets of carbohydrates that otherwise we wouldn't be able to access the energy within them. But also because most types of fiber are not digestible by us, because they're incompatible with our CAZymes, form the foundational food for our gut microbes.

And it's the fermentation, or the eating of those types of carbohydrates, that are incompatible with our digestive enzymes, by our gut microbes that produce some of the most foundational health benefiting biologically active molecules that our gut bacteria produce. Most notably short-chain fatty acids. Short-

chain fatty acids include acetate, propionate, and butyrate. And these are absolutely fundamental for our health. So the cells that form our gut barrier, or enterocytes, actually use, especially butyrate, as a direct fuel source. And they basically cannot be healthy unless they get sufficient butyrate to use as a fuel source. But short chain fatty acids have a variety of roles within the human body. They are especially involved in metabolism in general. But also in glycemic control and in immune regulating pathways, reducing inflammation.

But, our gut bacteria don't just help us digest carbohydrates. So it's very easy with the type of education we see, either from the USDA dietary guidelines or online to get very focused on fiber, fiber, fiber for the gut microbiome. And fiber is incredibly important; both the quantity and quality of fiber that we're consuming. But our gut bacteria actually have other essential nutrients. And especially amino acids.

So just like we use amino acids for the building blocks for proteins in our body, so do our gut microbes. And they have a collection of essentially amino acids just the same way we do; it's just that they aren't quite the same amino acids. And actually our ability to digest protein decreases the farther down the digestive tract you go. So we produce a bunch of protein digesting enzymes in the stomach. And then the pancreas produces additional protein digesting enzymes that are secreted into the first section of the small intestine, when we're digesting foods. Those enzymes basically get tired as they go through the digestive tract. And their ability to digest protein diminishes.

As we get further down the small intestine, especially to the large intestine, the protein degrading capacity of our gut microbes take over. So they are able to then digest any protein that doesn't get fully digested down in our small intestines. And that actually creates a range of metabolites, depending on the balance of the diet, some of these are potentially problematic. Linked to cancer. And some of them are very beneficial. So this is where balance between fiber and protein becomes really important and also the types of proteins that we're consuming.

But our gut bacteria are also able to synthesize amino acids. They're able to make amino acids that are then absorbed into our body and also contribute to our amino acid pool; lysine being the most important amino acid that our gut bacteria produce that we then directly use.

Our gut bacteria also regulate fat metabolism. This is a very recent discovery. It used to be thought that fat was entirely absorbed before it got to the large intestine, and therefore our gut microbes had very little role in fat metabolism. We now know that the gut bacteria that live in the small intestine, even though there's far fewer of them, they still perform very vital functions and they are contributing to not just the digestion of fat, but they're actually regulating how fat and cholesterol are absorbed. And there actually have been studies now that showed the composition of the gut microbiome itself is directly responsible for about 4.5% of the variation in BMI, as well as variation in cardiovascular disease risk factors; namely the bad form of cholesterol, LDL, as well as triglycerides.

They also metabolize bile salts before they are reabsorbed. This can, again, lead to beneficial regulation of what's called enterohepatic recirculation. So this is a recycling pathway between the liver and the gut. But it can also, again, when our diets don't have the right balance between plant foods and animal foods; between proteins, carbohydrates, and fats, can lead to the production of potentially harmful metabolites.

Our gut bacteria also directly control how minerals are absorbed into the body. The most important way that they do this is actually by helping to solubilize minerals by producing acids. So the short chain fatty acids that I already mentioned are part of the broader collection of organic acids that our gut bacteria

makes, so there's not just short-chain fatty acids, but there are also things like lactic acid. And this lowers the pH of the gut environment completely.

And this has a couple of really important downstream effects. One, it actually helps to make a more hostile environment for most pathogens. So most pathogens that will take residence in our gut or undesirable strains of bacteria prefer a more neutral to even basic pH. The more acidic the pH is in our guts, which is something that our beneficial bacteria do by creating all of these organic acids, typically that supports a healthy ecosystem because it supports the more beneficial strains that we know make metabolites that are absorbed into our body benefit us.

That, in terms of mineral metabolism, has the benefit of helping minerals basically dissolve. They become more soluble in a lower pH. And no matter how those minerals are absorbed; so minerals can be absorbed via passive transport. They just kind of dissolve across the gut barrier. Or various forms of active transport, where the absorption is being regulated by transporter molecules and active transport requires energy in order to; typically this is when you're transporting something that would, if you were just going to have it transfuse across a gradient, would go the other way. So active transport helps it go from an area of low concentration to high concentration, when it would normally want to go the other way. So solubilizing minerals is basically a prerequisite for all of those different ways that minerals are absorbed into the body.

Finally, vitamins. Our gut bacteria are able to synthesize a wide array of vitamins. Basically, all of the B vitamins as well as vitamin K2. And studies have now shown that the amount of vitamins that they produce is such a dramatic contributor to our vitamin pool that we could be vitamin deficient even if we're consuming lots of vitamin rich foods, without our gut bacteria.

So for example, they're producing up to 86% of our vitamin B6. 27% of our vitamin B3. 37% of our folate. 31% of our vitamin B12. And while 90% of the vitamin K that we consume is K1, 50% of the vitamin K in our bodies is K1. The other 50% is K2. That difference, from 90/10 to 50/50, is the vitamin K2 that's being synthesize by our gut bacteria.

They also are really important for phytonutrients. So phytonutrients include this class of over 10,000 different compounds, almost all of which are very potent antioxidants. Many of which are anti-inflammatory. They have other benefits like anticancer. Heart protective. Liver protective. They can prevent UV damage from the sun. These are really the beneficial antioxidants in plant foods that make plant foods such a uniquely beneficial food.

So we consume; we know from a variety of studies, that the more of these phytonutrients we consume, the healthier we are. Especially the polyphenol class, which is the majority of the phytonutrients. But also we only directly absorb about 5% of them from our food. The other 95% are modified by our gut bacteria to actually create a more diverse array of phytonutrients than what's inherent to the food that then gets absorbed.

So phytonutrients are interesting, because they directly influence the composition of our gut microbiome. And we're going to be talking about other things that directly influence gut microbiome composition at length in this presentation. But they're also something that our gut bacteria transform in order to be more beneficial for our health. So it's another way that our gut bacteria contributes to digestion and nutrient absorption.

As I mentioned, there's other functions of our gut that our gut bacteria contributes to. So they produce a variety of neuroactive compounds. So these are neurotransmitters. They also produce a variety of

chemical mediators that then can bind with receptors in the body and signal a variety of; when you have a healthy gut microbiome, beneficial effects. When you have an unhealthy gut microbiome; detrimental effects. So for example, one of the things our gut bacteria can do is control how leaky the blood-brain barrier is. And this can be a really big problem; because a leaky blood-brain barrier means toxins are getting inside the brain, that's turning on inflammation. When the brain is inflamed, that affects nervous signaling. That then has a whole pile of downstream effects on hormone regulation, organ function. It's a bad situation to have an inflamed brain. And that is something that is directly controlled by our gut bacteria.

They also directly influence how our gut barriers are functioning. Our gut barrier is basically made of a single layer of cells. These are the enterocytes that I mentioned earlier. And they are sort of glued together by a few different junction structures; the most important of which is called a tight junction. Tight junctions serve two main purposes. They help glue cells together. They're also a communication point between cells. But most importantly, the cell uses it as it's way of delineating the different aspects of its membrane.

So the top part of the membrane that faces inside the gut is called the apical membrane. It has a different structure and different function than the rest of the membranes. So the sides and bottom of the membrane is called the basolateral membrane. And the tight junction is the structure that basically separates the apical membrane from the basolateral membrane, and helps the cell determine what proteins are going to go where. Basically, it lets the cell know which side of it is the top and which side is the bottom.

And those tight junctions are basically formed by this tangled web of proteins that span from the inside of the cell to the outside of the cell. And you can kind of think of it as throwing a bunch of loose balls of yarn together and then mixing them up. That's how these proteins sort of tangle. They can loosen and pull apart a little bit. That actually helps nutrient absorption; so some nutrients actually go between our cells and other nutrients go through our cells. And then they can tighten back up when there's something you don't want to let into the body. When cells lose the ability to control that tight junction structure, that's when you get intestinal permeability. Or more colloquially referred to as leaky gut.

Those different proteins that form that tight junction structure are regulated by our gut bacteria. And this has a really, really important implication for autoimmune disease. Because we know that autoimmune disease and leaky gut tend to go hand in hand. And the autoimmune protocol, of course, eliminates a whole pile of different foods that we know directly influence tight junction function, the health of the gut barrier. So we're eliminating all of these foods that we know are problematic from a gut barrier perspective. But we cannot heal a leaky gut without first fixing a dysbiotic gut microbiome. So that is part of this equation. It's not just about eliminating foods that are directly influencing gut barrier health. It's also about restoring a healthy gut microbiome, so that they can also regulate the gut barrier.

Our gut bacteria are also really important for immune function. They actually regulate nearly aspect of our immune systems. They control the gene expression for a whole variety of cytokines; including interleukins, interferons, tissue transforming factors. All of these different cytokines that are really important signaling molecules are regulated by our gut bacteria. They regulate different populations of cells. They help balance regulatory cells versus effector cells. So the TH1 and TH2 cells are effector cells; TH3 and regulatory T-cells are regulatory cells. They actually modulate, for example, the activity of cytotoxic T-cells and natural killer cells. They even can intersect the immune system at the point of antigen presentation. So when an immune cell detects something it thinks is foreign, and presents that to the immune system, that entire process is called antigen presentation. And it is also regulated by our gut bacteria.

So regulating an immune system that is imbalanced. That is overstimulated. Also requires, again, nurturing a healthy gut microbiome. That is a prerequisite. So everything that we're doing on the autoimmune protocol is targeting gut health, hormone health, and immune regulation. And all three of those things require a healthy gut microbiome in order to be achieved.

So gut dysbiosis is the thing we're trying to avoid. And it really is a very general term for any imbalance that's problematic in that ecosystem. So that could mean missing beneficial species. That could mean the present of pathogens or potentially particularly problematic species. That could mean too many bacteria. That could mean lack of diversity. That could mean bacteria growing in the wrong spot. It really refers to a whole variety of different abnormalities in that ecosystem.

And the impact is things like; inflammation. Leaky gut. Hormones and neurotransmitters being imbalanced. It impacts our metabolism. How our liver is functioning. It impacts our detoxification pathways. So all of these things are impacted when there's some kind of imbalance in our gut.

And we actually know that at least 90% of disease now can be traced back to the health of the gut; and in particular, the health of the gut microbiome. And this includes a huge variety of autoimmune disease. There is enough data that we can speculate that all autoimmune diseases are linked to gut dysbiosis. In those best studied, most common autoimmune diseases, we now are even starting to get some data, at least in animal models, where manipulation of the gut microbiome is able to reverse symptoms.

So far in that research that even though we don't have a; here's the multiple sclerosis probiotic, and here's the Hashimoto's thyroiditis probiotic; we don't have that yet. And that may be too simplistic of a way of thinking about manipulating the gut microbiome to benefit autoimmune disease. But we do have some really direct lines that we can draw between individual bacterial species; either lack of good ones or the presence of bad ones, that we can now make some really specific statements about a dysbiotic gut microbiome and autoimmune disease. And I'll actually go through some of that research for; again, these sort of most common/best studied autoimmune diseases.

Let's start with multiple sclerosis. We're going to see a very common theme here. In multiple sclerosis, in patients, we have measured a pretty dramatic reduction in microbial diversity in the gut. We see an increase in certain species; ones that we know are either overtly problematic, or what are considered opportunistic. So an opportunistic bacteria is one that, in small amounts in a normal healthy gut microbiome, it fills a biological niche. And it's a fine normal thing to be there; in a small amount.

But when it has the opportunity to overgrow, it creates an imbalance. This could be in some metabolites that it produces, that can then drive dysbiosis and problems. So some of these species are; again, these are genera. Some of these genera are known to include species that are opportunistic. There is also a decrease in multiple sclerosis in some key beneficial strains. And what's really interesting is mouse experiments have been able to show that the disease severity; symptom severity; is directly related to the absence of beneficial strains. So we can actually draw almost a straight like. So as beneficial species are reduced in the gut microbiome, symptoms of multiple sclerosis increase.

For Sjogren's symptoms; again, we see this reduction in microbial diversity. We see an increase in, in this case, overtly problematic specie of bacteria. And we see a decrease in; again, ones that we know are very beneficial that fulfill a biological niche. So we're seeing a measurable imbalance where we can see the pattern.

In lupus, again, we see this drop in microbial diversity. We also see a change in firmicutes to Bacteroides ratio, which is quite problematic because it drives inflammation. We, again, see an increase in problematic spices, including some overt pathogens. We see a decrease in beneficial species. And actually we've even seen some really interesting lab studies. These are done where they take feces from lupus patients; they enrich them with certain strains of bacteria, like Bifidobacterium bifidum, and then they apply them to blood samples. So it's all done outside of the human body.

We need to, obviously, these types of studies can be very challenging inside a human to get regulation and permission for. But in, again, sort of in isolated white blood cells from the same patient; enriching the microbiomes with these beneficial species ends up helping regulate the immune system. So they're very cool studies, but again, they're sort of very pre-clinical.

In autoimmune thyroid disease, which includes both Hashimoto's thyroiditis and Graves disease, we see that SIBO; which stands for small intestine bacterial overgrowth, is incredibly common. So there's one study that actually measured SIBO in 54% in their Hashimoto's thyroiditis patients compared to 2% of controls. We also see H. pylori infection is much more common in autoimmune thyroid disorders compared to healthy individuals. And studies have looked at how the gut dysbiosis is contributing. So we see an increase in a huge variety of species; that's not a surprise with SIBO. But also a decrease in really key beneficial ones, including both Bifidobacterium and lactobacillus.

In inflammatory bowel disease, which includes both Crohn's disease and ulcerative colitis; again, reduced bacterial diversity in the gut. It is very, very thematic. Increase in; in this case, overt pathogens. There are actually some studies that think that inflammatory bowel disease is purely triggered by an infection. This enterotoxigenic Bacteroides fragilis is one of the species of bacteria that is one of the most suspected culprits behind inflammatory bowel disease completely. But we also see this decrease in very important beneficial; again, Bifidobacterium and lactobacillus are on this list. Faecalibacterium prausnitzii is a really, really important beneficial species. It's also on this list.

And there have been a variety of studies where they have been able to improve the maintenance of remission in ulcerative colitis patients with the addition of probiotics. And some of this is done in VSL3; some of this is done with individual probiotics. So there is a fairly broad collection of studies showing that probiotics is a really important adjunct to management of ulcerative colitis.

Now; I think this is a really good point to pause and say; the goal is not overt manipulation of the gut microbiome through probiotics. The goal here is to understand how food and lifestyle choices support a healthy and diverse gut microbiome. One of the problems with probiotic is; it doesn't create that balance. It doesn't create that diversity, in general. There are some exceptions. But in general, you are adding a probiotic species to the mix without addressing the problem with the ecosystem as a whole.

You can think of it as bringing in FEMA after a natural disaster to serve a very narrow role, but it's not the same as looking at all of the damage and fixing all of the damage to that city we were talking about before.

With celiac disease; again, we see this reduction in microbial diversity and increase in, again, opportunistic and pathogenic species. Decrease in those really important; again, Bifidobacterium, lactobacillus; Faecalibacterium prausnitzii. It's the same types of beneficial species that we're seeing missing over and over again, as well.

And what's really fascinating with some of the research in celiac disease is that the depleted species are actually known to be able to degrade toxic and inflammatory gliadin peptides. So, we see that there's

actually a fairly impressive gluten digesting capacity in our gut microbiomes. And there are some researchers who believe that celiac and non-celiac gluten sensitivity are actually symptoms of gut dysbiosis. That's kind of a really interesting way to think about; again, sort of the importance of our gut bacteria in regulating gut barrier health. Because of course; the loss of the villi in the small intestinal structure in celiac disease is a hallmark of that disease. So it's really interesting to think of that being regulated by our gut bacteria, and the lack of important species driving all of these problems.

Last slide of specific autoimmune disease; rheumatoid arthritis. There are these different models for studying the gut microbiome. And in rodents there's something called the germ-free rodent. Generally, it's rats or mice. And they are microbially sterile. They have no microbes growing inside or n their bodies. And these have been used for decades now to help understand the gut microbiome. So you can understand what missing gut microbes are. You can do fecal microbiota transplants, or you can introduce a handful of species. So you have a lot of control when you start with a germ-free animal.

And 100% of germ-free rats develop rheumatoid arthritis compared to 20% of wild-type rats in old age. Which is kind of amazing. And what's really interest ins; in rheumatoid arthritis, while there are some species that are decreased, it seems to be; again, much more driven by the presence of overt pathogens. And finding the exact pathogen that might be driving that is, again, one of the challenges of rheumatoid arthritis research.

Now, chronic fatigue syndrome, which is becoming much more relevant now due to COVID-19 potentially triggering chronic fatigue syndrome in a fairly large percentage of survivors, has sort of long been linked to, again, reduced microbial diversity. It also is potentially linked to the production of D-lactic acid. So a lactic acid that our bodies can't actually degrade very well. And the specific microbial imbalance in chronic fatigue syndrome is one where D-lactic acid is being overproduced. And the species that degrade lactic acid are also decreased.

So that metabolite of a dysfunctional gut microbiome is specifically implicated in the chronic fatigue syndrome symptom collection. But here's where we have finally some really neat studies, where they have actually taken people and given them probiotics as the only intervention, and shown significant improvements in symptoms. In particular, in this study, chronic fatigue symptom patients were given one very specific strain of lactobacillus casei, and they experienced a significant decrease, especially in their anxiety symptoms.

But also; one of the things I mentioned is, sometimes when we're overtly manipulating the gut microbiome with a probiotic, we are again; we're bringing in FEMA, but we're not necessarily addressing all of the underlying damage. There are certain keystone species that when you introduce them into the gut, you actually create an environment that's more favorable for other probiotic strains to thrive. And you can actually manipulate the gut ecosystem as a whole.

This is a fairly new area of research, and it's one that I would like to see a lot more science on these individual strains before getting to the point where we're like; aha! We're a long way away from precision editing of the gut microbiome where we're like; you have this particular imbalance. We throw this strain in you and everything gets fixed.

