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### Imbalance of Bacteria: How the Gut Microbiome Can Impact Systemic Sclerosis

Dr. Caudle:

The gut microbiome has been the topic of extensive research as of late. Our evolving knowledge has established its own involvement across multiple functions including metabolism, physiology, and even the immune system; but what about its impact on autoimmune rheumatic diseases like scleroderma?

Welcome to the Clinician's Roundtable on ReachMD, and I'm your host, Dr. Jennifer Caudle. Joining me today to share her insights on this topic is Dr. Elizabeth Volkmann, founder and co-director of the UCLA Connective Tissue Disease-related Interstitial Lung Disease Program.

Dr. Volkmann, welcome to the program.

Dr. Volkmann:

Thank you, and thank you for that kind introduction.

Dr. Caudle:

Absolutely. Well, we're excited that you're with us. And really, to start us off, I'd really love to know what initially drove you to study the microbiome as a rheumatologist. You know, I think that some people may not put those two things together, so how did this get on the radar for you while you were focusing on connective tissue diseases?

Dr. Volkmann:

So my interest in the microbiome actually initially developed during my fellowship in rheumatology. I was seeing patients at that time who suffered from systemic sclerosis, and I observed that many of these patients experienced disabling gastrointestinal symptoms, symptoms you're probably familiar with, like diarrhea, severe distension and bloating, and even fecal incontinence, and these symptoms had a major impact on their quality of life.

Dr. Caudle:

Absolutely. I mean, I think a lot of us physicians who encounter patients with connective tissue diseases certainly experience those symptoms as well, and you're right, they can absolutely be disabling.

Dr. Volkmann:

Yes. And another thing was that there were not many treatment options for these patients to manage their symptoms, and there certainly were not any curative options, but a lot of the patients would tell me that if they altered their diet or took probiotics or even a course of antibiotics, that many times their symptoms would improve.

Dr. Caudle:

That's interesting, so it's almost like they were doing things on their own to try to fix their symptoms; almost they were kind of trying to think through this problem on their own.

Dr. Volkmann:

Exactly, and a lot of things they were doing were interventions that would ultimately alter the bacteria in their gut, and so this got me wondering whether there was a potential imbalance in the bacteria in their gut that was contributing to their symptoms. So at that time we designed the first study to look at the gut microbiome in systemic sclerosis, and this initial study was published in 2015, and we did confirm that there were alterations in gut microbial composition in these patients. And since this initial study, several other groups have

published reports affirming these findings as well.

Dr. Caudle:

I think that's actually really exciting. And I noted that you mentioned you published the first study connecting the microbiome with systemic sclerosis, so I'm sure that must be a very exciting thing for you; but also, for the rest of us physicians, it sounds like it's really opened up a gateway to learning more about this potential connection.

Dr. Volkmann:

Yes, absolutely, and it's inspired a lot of interesting collaborations too where I now work with other scleroderma researchers throughout the world that are doing similar research. And one thing that's interesting is that we do find that there are subtle differences in the microbial composition looking at patients with scleroderma from different countries, and some of this may be related to genetic differences. It could be related to dietary differences too.

Dr. Caudle:

So, moving on, like many autoimmune diseases, scleroderma often goes undetected. So I'm a family physician. There are so many of our physician and healthcare provider colleagues out in communities all over the country. What really should we be looking for besides the vague initial symptoms?

Dr. Volkmann:

So this is an excellent question, and you're absolutely right in that many patients suffer for years and visit several physicians before diagnosis of systemic sclerosis is made. A family practice physician like yourself may be the first person that the patient is seeing to evaluate them, and there's really 3 hallmark features of systemic sclerosis that are present in virtually all patients.

Dr. Caudle:

That's actually really good to know. And I think you're right. As a family physician, I can speak about myself—and I know some of my other generalist colleagues—we are often the first people that patients come to see, and you're right, that sometimes symptoms can be particularly vague and it can sometimes be difficult to kind of narrow down that differential diagnosis.

Dr. Volkmann:

Exactly, but these 3 hallmark features are some things that could really help the first providers seeing these patients in terms of generating a proper referral to a rheumatologist. So the first feature is Raynaud's phenomenon. This, as you know, is when your hands and feet turn different colors when exposed to cold or stress. The second feature is sclerodactyly, so when the skin of the fingers becomes initially puffy and then thickened; the patient feels that the hand is getting tighter. And then the third is a positive antinuclear antibody test, or the ANA test. This test is actually positive in over 95% of patients with systemic sclerosis.

Dr. Caudle:

I think those are really good sort of touch points for us to kind of keep in mind as we're approaching patients that may have what seem like vague symptoms, or at least things that we should ask about, symptoms we should ask about in labs to test for if we're suspicious.

Dr. Volkmann:

Exactly. And alone these features are not necessarily specific for systemic sclerosis. The ANA test can be positive in other diseases, such as lupus or autoimmune thyroid disease, but if it happens at the same time as in a patient who has Raynaud's and sclerodactyly, then this should definitely raise a suspicion for systemic sclerosis. And even if just 2 of the features are present, Raynaud's and a positive ANA, the patient still should be referred to a rheumatologist for evaluation for systemic sclerosis, because early on they may be the only 2 features present.

Dr. Caudle:

I think that's actually a really important point for everyone who's listening, actually, to keep that in mind and not to delay referral, especially if we see even those 2 signs.

Dr. Volkmann:

Yes, I think it's always good to err on the side of caution. I don't think you can ever go wrong in generating a referral because most rheumatologists are adept at just getting a referral for a positive ANA and working that up, so it's always good to just err on the side of caution and generate a referral if there's any suspicion there.

Dr. Caudle:

You know, I'm sure that the diagnostic uncertainties around this and other connective tissue diseases cause a lot of frustration for physicians, but it must also take a huge toll on patients as well. So, what can physicians do to help these patients through that journey to diagnosis?

Dr. Volkmann:

I definitely agree with you. Both patients and physicians can often experience frustration when the diagnosis is unclear, especially early on. However, I always think it's much worse for the patient because they are the ones who are experiencing the symptoms that they cannot even attribute to a specific disease. Also, sometimes family members or friends will question the legitimacy of a patient's symptoms since no one knows what to call it and the patient may look fine to them.

Dr. Caudle:

You know, I'm actually really glad that you brought that up, because I think that sometimes with autoimmune diseases in general, but specifically with this particular condition and others, I do agree with you. I do think that sometimes patients face persecution and uncertainty, and sometimes they feel like people actually don't believe them, so I'm really glad that you mentioned that.

Dr. Volkmann:

Exactly. Though, to help patients with this process, I think there are a lot of things that physicians can do, but I think the most important thing is to just listen. Diagnosing autoimmune diseases is really like putting together pieces of a puzzle. Physicians need to not only ask about the symptoms the patient is experiencing now but also the timing of the symptom development and other symptoms that may have been present in the past. This not only helps get to the bottom of what's going on, but it also helps to ensure that the patients feel heard and that their thoughts and feelings are validated.

Dr. Caudle:

Very good points there. I think we can always be reminded to try to listen and be good listeners as best as we can. It's always a good reminder.

Dr. Volkmann:

Yes, absolutely. I can't tell you the number of times where patients come to me almost traumatized by seeing providers who dismissed them because they looked well. And you have to keep in mind that most autoimmune diseases occur in young women who otherwise do look fine, and so you really have to just get into the details of how they're feeling, and this can really help too in making the diagnosis.

Dr. Caudle:

Right. No, I think that's a good point too. I mean, you're not just talking about listening and the importance of being a good listener as physicians, but you're also really touching on making sure that as physicians that we don't judge inappropriately or prematurely, right?—that we're looking at the whole picture and looking at the whole patient and being thorough, so I think that's also a really good point and a good reminder.

Dr. Volkmann:

Exactly. Yes, I couldn't agree more that you really have to get sort of underneath. And a lot of, for example, young women will come to the doctors and they'll present themselves in a really nice way with makeup and getting their hair done, but it doesn't mean that they're not suffering inside with disabling fatigue or arthritis, and so it's really important to just get down into the details and not be caught up in just sort of the outer appearance of a patient.

Dr. Caudle:

So, for those of you who are just joining us, this is the Clinician's Roundtable on ReachMD. I'm your host, Dr. Jennifer Caudle, and today I'm speaking with Dr. Elizabeth Volkmann from the UCLA Connective Tissue Disease-related Interstitial Lung Disease Program. So, Dr. Volkmann, this has been a really great conversation about not just connective tissue diseases but microbiome and also the doctor-patient relationship. And earlier you talked about the challenges in recognizing scleroderma, but now I really want to shift over to the study that you're currently involved in. As I understand it, this study is looking to characterize the GI tract in patients with scleroderma. So, can you describe what you found so far and really what you hope to learn more about throughout this study?

Dr. Volkmann:

Absolutely. So, as you mentioned, I'm currently involved in several studies to help characterize the gut microbiome in systemic sclerosis so that we can ultimately develop better treatments to target these imbalances that we have discovered. So far we have found that patients with systemic sclerosis have decreased abundance of beneficial commensal bacteria. These are bacteria that are thought to protect against inflammation. And at the same time we found an increase abundance of what we call pathobiont bacteria. These are bacteria which we think promote more inflammation.

Dr. Caudle:

Interesting, so there's almost an imbalance in the type of bacteria that you're finding—that that sort of reduces inflammation, that that promotes it.

Dr. Volkmann:

Exactly. And we found sort of commonalities across studies. I mentioned to you earlier that I have some collaborators in other countries, and even in these other countries they are finding the same type of imbalances with higher levels of some bacteria that cause inflammation and lower levels of bacteria that are thought to be protective against inflammation.

Dr. Caudle:

Very interesting.

Dr. Volkmann:

Yes, and we've even done some research linking these specific bacteria with the severity of symptoms, so some patients we've found that have higher levels of these potentially proinflammatory bacteria, they have more gastrointestinal tract symptoms, so more diarrhea or more distension and bloating. So I think a lot more research, though, is needed to further characterize the gastrointestinal microbiome in systemic sclerosis and specifically understand how these alterations can affect things like inflammation in other parts of the body and fibrosis, and then just clinical outcomes in general. Some of the research I'm doing now is looking at the microbiome in patients who have very early systemic sclerosis, so patients who haven't even started therapy, who haven't really developed any signs of organ failure. When we do this study, we're aiming to see whether these microbiome changes are present very early in the disease. This will help us to determine if these are really things that cause the disease to evolve. And also, it could be ultimately a target that we could intervene to prevent the development of symptoms.

Dr. Caudle:

If I can just interrupt you for just a second, it actually sounds quite groundbreaking and like a whole new direction. You mentioned earlier that some of the work that you've done and are doing is some of the first work in its sort of class and category, and it definitely feels that way and sounds that way. I mean, it sounds like there is maybe some hope for alternative treatments and therapies potentially down the line.

Dr. Volkmann:

I would hope so, because at this point in time, we still don't have a lot to offer these patients. There's a lot more interest from industry in terms of clinical trials, but the microbiome is still one area in terms of research where it's relatively in its infancy and there's just so much more to do, but I think targeting these patients who have very early disease may be one way to get at the question of do these changes we see—are they really the cause of many symptoms.

Dr. Caudle:

And, finally, Dr. Volkmann, as you look ahead—and we touched on this a little bit before—do you think this study could ultimately update or change the treatment paradigm for scleroderma?—which honestly, right now the disease is incurable. So, what do you think that your research or where do you hope that your research will fit into the future treatment paradigm for scleroderma?

Dr. Volkmann:

Yes, absolutely. I'm really hopeful that the results of the research that we're doing and others around the world could help uncover specific bacteria that could be the link to the development of particular features of systemic sclerosis. So, for example, if we find that a specific type of bacteria is lower in patients that go on to develop lung disease, perhaps we could intervene early on and replete this deficiency through a tailored probiotic regimen and this may help prevent the development of lung disease.

Dr. Caudle:

That's really interesting. I mean, that would be amazing, actually.

Dr. Volkmann:

It would be, but it's probably not going to be that simple. We may need to replete a number of bacteria. We may need to ask patients to make alterations in their diet, as dietary modifications can really shift the microbiome.

Dr. Caudle:

Right, right, and that makes a lot of sense as well.

Dr. Volkmann:

So I'm hoping that with our research and the research of others there is a tremendous shift in the way we treat this disease. I hope that we can one day offer patients a more personalized treatment approach that doesn't just involve giving them this broad-spectrum immunosuppression, that we really have a more personalized and tailored approach to what we give them.

Dr. Caudle:

I completely agree, and I think that's a really great description, I think, for those of us who are listening. I mean, the potential changes

that we're maybe hoping for through some of your work, right, is that instead of only being able to give people, as you mentioned, broad-spectrum medications, perhaps we can start to tailor treatment more individually based on gut microbiome, etc. So I really appreciate you saying that and really putting that into context for all of those of us who are listening.

Dr. Volkmann:

Yes, you're welcome, because I think that while these existing therapies, the immunosuppression, can be effective in some patients, they also come with a plethora of side effects that many of your listeners may be familiar with, and these alone can cause problems for patients and limit their ability to function, so shifting the microbiome could be potentially even a more safe option for intervening that wouldn't generate so many side effects for patients like a lot of these other toxic drugs do that we give them.

Dr. Caudle:

Right. No, I mean, certainly that would be the hope, agreed.

Dr. Volkmann:

Yes, so I thank you for this opportunity because it's been really exciting to share some of the research that I'm doing and others, because I think that for the future, a lot of autoimmune diseases is going to involve really looking at the microbiome and how this relates to the disease features and also how we can use what we learn to develop new treatments for these patients.

Dr. Caudle:

Absolutely. I mean, again—once again, you couldn't have said it better, because I really do appreciate you coming on the program, and I think that even that statement is a really great way to round out this discussion on scleroderma and really the potential influences of the gut microbiome. I'd really love to thank you, Dr. Volkmann, for joining me today. It was wonderful having you on this program.

Dr. Volkmann:

Thank you so much.

Dr. Caudle:

Thank you. I'm Dr. Jennifer Caudle, and to access this episode and others in the series, please visit us at [ReachMD.com](https://ReachMD.com) where you can Be Part of the Knowledge. Thank you for listening.