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Inflammatory Origins of Chronic Disease: Novel Clinical Insights for Effective Management

Narrator:

You are listening to **Integrative and Functional Medicine In Practice** on ReachMD, sponsored by the Metagenics Healthcare institute for Clinical Nutrition, Seeking to Optimize Patient Outcomes with Support from Clinical Nutrition and Lifestyle Medicine.

Dr. Bhatia:

Welcome to ReachMD. I'm your host, Dr. Taz Bhatia, and joining me today we have Dr. Joan Claria. Dr. Claria is the faculty member at the Department of Biochemistry and Molecular Genetics at the Hospital Clinic of Barcelona and an associate professor at the Barcelona University School of Medicine.

We are excited to have you on, and we are talking about inflammation. Most of us have heard about inflammation but, believe it or not, there are some new clinical insights on inflammation that Dr. Claria is going to share with us today. So, welcome to the show.

Dr. Claria:

Thank you.

Dr. Bhatia:

Thank you. Well, we appreciate you coming here all the way from Spain, so let's just jump right in. So inflammation, for many of us physicians, is something we're now accustomed to hearing about and working with. It's widely considered to be the underlying cause of chronic disease. There are some new clinical work that suggests that there's a new active pathway that will help manage more effective control and response of inflammation. Can you spend maybe just a few minutes talking to us about that and what that means for us as physicians?

Dr. Claria:

The concept of inflammation involves two completely different parts. One is the initiation of inflammation, which is the kind of inflammation that has been addressed by most pharmaceutical companies, and I'm talking about the mediators that promote inflammation. We're talking about the Omega 6 derived mediators such as prostaglandins. Everybody knows about the anti-inflammatory drugs, about the aspirin, ibuprofen. These kind of anti-inflammatory drugs block the formation of these mediators, but there's a second part of the inflammatory response that has been mostly ignored in the last 15 years. This is the resolution of inflammation. So, when you have an inflamed tissue or you have an inflammation going on, it's not enough to reduce the number of pro-inflammatory mediators but to clean up the mess, so to remove all the inflammatory cells and to remove all the inflammatory factors from the inflamed site, and this is called the resolution of inflammation.

Dr. Bhatia:

And this in itself, for many of us that work with patients all the time, is groundbreaking information, because we're used to thinking about

inflammation as just a static, linear process, but as you're saying, there are two phases. There's an initiation phase and there's a resolution phase. How did you even discover that? How did that even come about? I'm curious.

Dr. Claria:

We have been working for many years with compounds that are not inflammatory but they are anti-inflammatory and pro-resolution, so we had some initial evidence that they would play a role in the resolution of inflammation. I'm referring, for example, to my initial work with Professor Serhan 15 years ago when we discovered the 15 epi-lipoxins, novel compounds that were anti-inflammatory and promote the resolution of inflammation. So, after all these years, we have been discovering more and more pro-resolution mediators, and now we are in the position to place resolution as a very active program in the control of inflammation.

Dr. Bhatia:

And that's fascinating. So now we need to think about two phases. We need to think about resolution of inflammation. Applying this now to practice, to clinical practice, as we're seeing patients, how do you see this playing a role when you're dealing with metabolic syndrome, for example, or obesity, which so many of us in practice have to see day in and day out?

Dr. Claria:

The important point here in these decisions is that the inflammation is of low intensity. It's called low-grade inflammation, and this is chronic. You can have inflammation for 10, 15 years before the complications appears and, of course, you cannot take an anti-inflammatory compound for so many years because you are exposed to unwanted side effects. These **cases* 4:32** are the perfect scenario for testing the new resolution mediators because they don't have unwanted side effects. So by promoting the resolution, especially by nutritional compounds, you will be able to return the inflamed tissue to homeostasis without side effects.

Dr. Bhatia:

Fantastic. And for the practitioners listening to us, how would they know when they're dealing with metabolic syndrome? Would they need to measure something, look for something in lab work to know that they're dealing with chronic low-grade inflammation, or is just metabolic syndrome in itself enough to know that this is chronic low-grade inflammation, move on to resolution, stop working with initiation?

Dr. Claria:

The lab data indicates that any obese patient has a low-grade inflammation, and there are a number of good markers, for example, C-reactive protein, the secretion of inflammatory adipokines by the inflamed adipose tissue, that can guide us to classify these patients having a low-grade inflammatory response. This is also true for patients with diabetes, type 2 diabetes, and also for patients with obesity-related hepatic complications. And we are now collecting data that this is also true for patients with atherosclerosis because atherosclerosis is a kind of low-grade inflammation in the vessel that at the end initiates the cardiovascular disease.

Dr. Bhatia:

So we, as practitioners, should be thinking about metabolic syndrome, obesity, diabetes, atherosclerosis as all low-grade inflammatory states where we need to be thinking about the resolution of inflammation. Are there any other conditions where we should be thinking about this as well?

Dr. Claria:

Well, you have some, for example, skin diseases, eczema. We have, for example, dry eye for ophthalmologists. We have some kind of **(inaudible) arthritis* 6:41,** lung diseases like asthma; although, they have exacerbation of the inflammatory response, and then the inflammatory response is very evident. So, let's say the core of the low-grade inflammatory response are those diseases related to obesity and metabolic complications.

Dr. Bhatia:

Once we tackle that resolution of inflammation with any of these conditions that you've mentioned, what can we expect to see? What kind of results do you usually see? What can we expect first, and then what may be further down the line?

Dr. Claria:

Well, basically, this has not been confirmed empirically, so we haven't tested yet, but the prospects are that appearance of complications will be delayed, and they will result in a lower number of complications in these patients.

Dr. Bhatia:

And then for the providers as well or for physicians, are there algorithms we can use? Is there a chart of what to do first, what to do second, as we're working with this patient population? And then also to follow up, we learned about the conditions. Is there a further demographic? Is there an age where we should be looking at this more closely or a certain type of patient beyond the condition itself that we should be thinking about the second phase of inflammation?

Dr. Claria:

What we're seeing at the clinical practice with the samples that we are analyzing at the lab is that this unresolved inflammation is very evident in young people.

Dr. Bhatia:

In young people, wow.

Dr. Claria:

Yes, so at least stages of overweight or obesity, I think we should target this population of people. Then when the obese is morbid obese, the inflammatory response is so exacerbated that it's very difficult to tackle the resolution of inflammation.

Dr. Bhatia:

So, it's easier to tackle the resolution of inflammation earlier in the course of disease. Is that what you're thinking?

Dr. Claria:

Yes, that's what I'm saying.

Dr. Bhatia:

So, we should be thinking about tackling this in our younger patient population.

Dr. Claria:

Yes.

Dr. Bhatia:

Even children or not necessarily?

Dr. Claria:

Not children because, unfortunately, there's some reason there are not many clinical studies with children, but I can tell that, at least from our clinical obesity unit, the patients that may benefit for this resolution of inflammation are people between 20 to 30, 40 years old.

Dr. Bhatia:

Finally, is there a way for physicians to measure the success? Do you actually see, once we deal with the resolution of inflammation, do you see some of these biomarkers that you mentioned go down? What have you seen maybe in your research and in practice?

Dr. Claria:

Well, there are now some markers that are commercially available. You can buy the license. You can buy some **reagents* 9:41** to measure these biomarkers of inflammation. Even in the clinical practice, for example, in obese patients, it's not difficult to ask for a measurement of the leptin or adiponectin or interleukin-6. Also, there's a very **routinary* (9:59)** factor that is the C-reactive protein that gives you an idea of the overall inflammatory status of the individual. So, we should use these markers, not just adipometric parameters like body weight, BMI. We have now also this controversial group of obese people that are healthy and healthy people that have phenotype like obese. So, it's not just a matter of the body mass index. It's a matter of, too, properly determine the inflammatory markers in these patients.

Dr. Bhatia:

So, we should be, as physicians and providers, in this group of patients starting early in their 20s, which you say is a good place to start, measuring, sounds like a CRP. Would you do a homocysteine as well, measuring a CRP, you said interleukin-6?

Dr. Claria:

I would say, if possible, adipokines because adipokines are good markers of the adipose tissue inflammation, which is the first tissue that becomes inflamed in the obese individuals, so I would say at least measure leptin, adiponectin, and you can add IL-6 and even MCP-1.

Dr. Bhatia:

Okay, fantastic, that's great information. And as a physician working on -- now that I understand the resolution of inflammation and I understand this and I have my biomarkers now that help me to realize that this is what I'm dealing with, how do you approach that patient? What do you do? What are, maybe, two or three things you would do to begin to work that second phase of inflammation?

Dr. Claria:

Okay, basically, seeing this from behind the patient, because I receive and I process all the samples, the blood samples, but I know that the obesity unit is approaching this in the right direction to isolate a group of patients that may benefit from resolution. They are trying, for example, with novel drugs. They have been initiating trials with Omega 3s. They have been initiating trials with changing the nutritional needs for these patients and also with new drugs like, for example, glitazones that target the PPAR gamma system. However, the drugs have these…they are controversial because most of them have unwanted side effects. So, my idea is that obesity, the bottom is a nutritional problem. It's caused because you are using or consuming more nutrients than needed, and I think the solution is probably not that; it's probably in the nutrition by itself.

Dr. Bhatia:

So, beginning really with the nutritional work...

Dr. Claria:

With nutritional work.

Dr. Bhatia:

… is the foundation of trying to beat the second phase of inflammation.

Dr. Claria:

Exactly.

Dr. Bhatia:

And then fish oils may play a role as well it sounds like, correct?

Dr. Claria:

Well, there's a controversy about fish oil because the problem that you have, you have not a precise control on what are you taking. For example, in the market there are, like, 100 different fish oils, and some of them carry less than 200 mg of Omega 3. Others have a mixture of EPA and DHA. So, I would recommend, for example, going to more precise compositions like EPAs or DHA with 90, 100% purity. And, of course, if you want to be more precise, use, for example, new SPM that are currently available because you exactly know the amount of these nutrients that you are ingesting.

Dr. Bhatia:

So, SPMs as well may be something for all of us to be thinking about.

Dr. Claria:

Yes, definitely. I think it's one of the priorities.

Dr. Bhatia:

So, Dr. Claria, we were talking about SPMs and their potential role in shutting down that second phase of inflammation or the resolution of inflammation. Can you tell me a little bit more about SPMs and the patients for whom they work and what maybe the obstacles might be in using them?

Dr. Claria:

SPM are the end products of polyunsaturated fatty acids, basically of the Omega 3 origin, and they are really important because they can exert biological activities at very low concentrations. For the biosynthesis of SPM, the cells need specific enzymes called lipoxygenases, and what we have found recently in our lab and also in other labs with many colleagues is that in metabolic diseases there is an impairment in the enzymatic mechanisms that process Omega 3s into conversion into SPM. So, what I'm referring to is that it is not enough by providing Omega 3 precursor to these patients because they lack the proper activity of the enzymes to convert them to SPM. If we can override this problem by giving SPM (inaudible 15:33), I think these will be the proper solution.

Recently has appeared an article that reports that healthy subjects compared to obese subjects with metabolic diseases taking the same

amount of Omega 3s, the healthy subjects have proper levels of SPM circulating in the body, whereas the patients with metabolic syndrome, they cannot efficiently convert Omega 3s to SPM. The solution here is not giving more Omega 3 because you have an intrinsic impairment in the conversion of these Omega 3s to SPM. So the solution here is to replace the Omega 3s by the SPM and then get the wanted biological activities that will reduce inflammation and promote the resolution of inflammation in these patients.

Dr. Bhatia:

So, this patient population, basically, cannot use the Omega 3s that we're all thinking is going to be helpful and reverse inflammation. They really need to be given SPMs. Is that the way of thinking?

Dr. Claria:

That idea is that if you measure Omega 3s in healthy and these kind of patients with metabolic syndrome, you will find the similar Omega 3 levels in the blood, but they are not converting these efficiently to SPM, so the SPM levels are reduced, and this won't change increasing the amount of Omega 3s.

Dr. Bhatia:

What fascinating information and research. I think it's really going to turn things around for how a lot of us practice. I'm sure the listeners feel the same way.

Thank you for listening to ReachMD. I'm Dr. Taz Bhatia joined by Dr. Joan Claria. I hope you've learned a lot from this session.

Narrator:

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