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Dr. Cheeley:

Welcome to *Heart Matters* on ReachMD. I'm your host, Dr. Mary Katherine Cheeley, and joining us today to discuss his study about artificial sweeteners and its link to cardiometabolic disease risks, which was published in *Nature Medicine* in February 2023, is Dr. Wilson Tang. Not only is Dr. Tang a co-author of this research, but he's also a Professor of Medicine at the Cleveland Clinic Lerner College of Medicine of Case Western Reserve University. Dr. Tang, welcome.

Dr. Tang:

Nice to see you.

Dr. Cheeley:

I want to start off with a little disclaimer. So I enjoy a diet soda every now and again, so I am very excited to hear your research and try to think through my own lifestyle patterns as it results to cardiometabolic disease. So let's get started with some background. What prompted you to conduct this study, and why do you think artificial sweeteners are so popular?

Dr. Tang:

Thank you for the opportunity. And we started looking into this line of research mainly from metabolomic analysis, which been looking at metabolites in biospecimens—in this case, blood samples in patients, particularly, those who subsequently developed adverse cardiac events like heart attack and stroke—and compared to those who doesn't. And so we have previously done many different types of studies looking at different biomarkers and different metabolites, but I think it's not just the association that we are interested in. We certainly are very interested in why that association occurs. So one line of metabolites that we've looked into are these sugar alcohols. We call them polyols. And these have been used in the food industry as artificial sweeteners.

Now there are many types of artificial sweeteners, and this is just some of it, but one that did catch our eye was a compound called erythritol, and this is a sugar alcohol that actually has been used in the food industry for a long time. And in fact, it is also a bulking agent, so it also allows people to feel a little full and maybe even a little bloated, and that actually makes people eat less, so people actually use this quite often for weight loss. And in fact, this is touted by many individuals to use that as a substitute for sugar in terms of their weight loss regimens, and particularly in food that has the word keto in that. There's a lot of keto foods that you see in the supermarket and all that. So this is not usually reported, and usually, when you report it, you see in your can and your drinks or whatnot, it just say erythritol, but they don't really tell us how much they are in terms of content concentration or the amount, and so it has been used in different combinations as well.

So the reason why it perked our interest was because when we looked at our large cohort of patients, we did see both in a US cohort and a European cohort that patients with cardiac problems, they had the highest level of erythritol levels in the blood. And these are fasting samples. These are patients coming in for cardiac evaluation with fasting erythritol levels. They seem to have the highest amount of adverse cardiac outcomes over time. So clearly, there is an association between bad cardiac outcomes and high levels, which actually prompted our interest because here we are having our ingestion of these compounds to our body, and would that be a problem as it accumulates? And so how much does it accumulate of any physiologic effects? And that's where we bring this question from the bedside to the bench.

We started to actually look at human samples, as well as animal models that we actually have the ability to induce clotting. And we found that if the animal models that had the higher levels when they ingest erythritol, and this compound is in the body, they actually have a faster time of clotting, which means that they have a higher susceptibility of thrombosis, which is clotting in the blood vessels.

And that could explain why there is also a higher chance that they may have downstream events. We see the same thing in the human samples that we do in a dish. We are trying to see how likely they are to clot, and we saw the same thing.

Finally, we did want to understand whether this erythritol ingestion would stay in the body for what period of time and how that would affect the blood samples. We did see that it does raise up to the level that we see in the dish that would actually cause clotting, and it may even stay up there for at least a day or so. So this actually gave us some concern because for the longest time, erythritol is widely used and is FDA and the European Agency has approved this. But of course, many of the approval does not look at cardiovascular outcomes and events. And truly, it's very possible that some of it is not related to ingestion. It could be the patients' own levels are high, but the fact that if there is some questions about some individuals being susceptible of having adverse consequences, we certainly need to be cautious in terms of the amount that we ingest, or also, to understand what is in the food that we are taking that may have this compound. So I think all in all it is an objective way of looking at what we are eating on a day-to-day basis, and particularly, with a food group that is supposed to be substituting what we thought that was bad, which is sugar.

Dr. Cheeley:

So I want to clarify a little bit about the patient population that you were looking at. Are these patients who previously had cardiovascular disease and you checked their levels at that point, or are these primary prevention patients who then went on after to have cardio—

Dr. Tang:

These are patients coming and getting cardiac evaluation and all that. They're getting a cardiac catheterization and all that, so there is certainly, a level of underlying susceptibility, but the truth of the matter is we start to realize that that is an association. Now so that's step number one. Step number two is that, well, we are ingesting this substance, which doesn't really get metabolized that much. Certainly, it's absorbed very easily, and so now we have this question about if higher levels in the body, does it actually alter the physiology that we are concerned about?

Dr. Cheeley:

Well, I think that's really interesting because you have these patients who are clearly at high risk already, have been counseled about their diet and lifestyle, and told to "eat healthier" or choose healthier options, which erythritol is marketed, for lack of a better word, as a healthier substance; but insult to injury, especially if you're increasing or decreasing clotting time, making it more likely for someone to clot. Are we being counterproductive in that? And I think that's what you were looking at.

Dr. Tang:

Yeah. And again, we have to caution the findings, of course. Just like anything that we look in the associations, it's not always causation, but the fact that we did have the subsequent bench experiments to show that in the presence and absence of this, we actually could demonstrate the physiologic changes. That being said, again, anything that we reduce it into an experiment, may or may not occur in everyday, in vivo we call it, which is in the body and whatnot, but still, the assumption that this is a better alternative need to be challenged. And also, we need to understand who is susceptible and who will be higher risk, and is it the ones who intake a lot of it? Is it individuals who are already susceptible? So we still have a lot to know, but right now there is a public health message here. Since we actually don't know what is in the different foods that we eat, buy in the supermarket or eat, we actually have very little understanding of how much we are consuming. And so in some ways it is something that we are starting to look into. What are the ways to identify and also to really need further studies to confirm whether this is a risk that we need to be concerned about.

Dr. Cheeley:

For those just tuning in, you're listening to *Heart Matters* on ReachMD. I'm Dr. Mary Katherine Cheeley, and I'm speaking with Dr. Wilson Tang about his research on the impacts of artificial sweeteners on cardiovascular health.

Dr. Tang, I want to jump right back in. So you've given me so many things to think about, and especially, about when it comes to erythritol and our patients who probably are at higher risk already of cardiovascular disease, trying to make healthier swaps, but really, your point is very well made in terms of, we don't know how much of this is in our food. Did you find a level where it wasn't as concerning? Was there a cutpoint? How did that work?

Dr. Tang:

Yeah, and that's always the question out there, how many experiments have you have to do, particularly in humans. So we did pick one that a lot of studies have used, and obviously, that is one of the things that people may push back and say 30 grams of erythritol as a drink. It is a sweet drink, but it's really the average amount that people take in in a day or so, so it's not completely outrageous. So it is a physiologic amount. Now is there a dose dependent? Is it different if you space it out? That's actually some of the things we wanted to learn. And in fact, that is also the reason why we actually do this concentration curve. So we actually have almost like a

pharmacokinetic, which means that we actually measure the levels in the blood at different points in time, and we look at those thresholds.

So we know that about 45 micrograms is the thrombin calcium release, which is how angry the platelets are actually trying to make a clotting occurs. So that's about 45. The levels that actually was elevated about 45 took a good day or day and a half, actually a little bit at 24 hours, so that means that for a 30-gram drink, you actually see the level stay up. And so we actually don't know the accumulation of that, how does it work if you go throughout the day. One can argue that maybe we are not taking in that much at one time or whatnot. But those are the questions that we have to ask further, particularly when we don't know what is in the content of different types of food.

Dr. Cheeley:

I think that's such an important message is that right now there's not a ton of guidance as to what is in there. It's just listed as an ingredient. It's not on your nutrition label. So you talked about it a little bit, but I'd like to just put a fine point on it. What do you think are some of the public health recommendations that are needed about either just the consumption of artificial sweeteners in general, or an amount, or awareness? What do you think we need to do as a society?

Dr. Tang:

Well, I think that the next phase is certainly to confirm whether some of this is seen in regular consumption with erythritol or not, and it's still a question at large. We found this association. We need to actually better understand do consumption of erythritol actually lead to, even in epidemiologic studies or whatnot. The issue here though is many of the dietary studies, diet studies, are largely based on diet recall, and many times it's not the easiest to know if you actually don't even know what is in the food, so that's where there's still a missing link.

So there's another concept that comes along in this precision nutrition area is that what if the mechanism of understanding risk is to really measure the metabolites. And that is actually what some of the studies have been doing, but whether those metabolites are measured in response to changes in diet, changes in food choices, those are difficult studies. We are what we eat, and we like to pick on what we like to eat. And again, that comes back down to the challenge of doing nutritional studies. We assume that that's accurate, but many times it may not be.

So we basically need more experience and more controlled studies to better understand are there physiologic effects. We just demonstrated some. That has to be replicated. That has to be also expanded to different patient populations and different ways that we ingest. There could be a seed in the soil. It could be something that is already inherited on how our body metabolized, and that's why the levels are up there associated with bad outcomes, but also, there is the component of the ingestion.

Dr. Cheeley:

This is a great first step, but you're exactly right. We need to think about it. We need to get a little bit more data around it before we can really draw conclusions. So in the last little bit of our conversation, as clinicians, what strategies can we use to help our patients better understand the effects of artificial sweeteners? How can we educate our patients?

Dr. Tang:

Yeah. So the first is to learn what they are and what are the artificial sweeteners that we are using. Now it is not one-size-fit-all, but different artificial sweeteners have been associated with different health effects. So I think in general at large, I think humans have tried to substitute what we considered bad with something artificial, and many times we have not actually done the best job. I mean, trans fat is a great example, and so it took us some time to learn what is the unintended consequences. So I think most nutritionists and dieticians do recommend whole foods. And in cardiovascular literature, of course the Mediterranean Diet is still the one that has the randomized control trial that showed benefits, which many of these dietary interventions have really focused on less red meat and much broader legumes, beans, and leafy vegetables, and a balanced diet. And it's really more of a habit, part of a behavioral approach rather than what is good and bad food. Anything in moderation.

Dr. Cheeley:

Yeah. I think that's fantastic and a great way to end our discussion. I want to thank my guest, Dr. Wilson Tang, for sharing his insights on consuming artificial sweeteners and the risks associated with heart disease. Dr. Tang, it has been lovely to speak with you.

Dr. Tang:

Thank you very much. You too.

Dr. Cheeley:

For ReachMD, I'm Dr. Mary Katherine Cheeley. To access this and other episodes in this series, visit *Heart Matters* on ReachMD.com,

where you can Be Part of the Knowledge. Thanks for listening.