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Finding the Answer to How & Why Arteries Age

Dr. Sorrentino:
Why and how do arteries age? It's a question that's baffled scientists for quite some time now, but now we finally may have the answer and a solution that could be as simple as modifying our diet.
For ReachMD, this is Heart Matters, and I'm Dr. Matthew Sorrentino. Joining me today is Dr. Vienna Brunt, a Post-Doctorate Fellow in the Department of Integrated Physiology of Aging Lab, at the University of Colorado in Boulder. Dr. Brunt is the first author of a recent study in the journal Hypertension, that explored how a compound produced in the gut, called "trimethylamine N-oxide," can harm the endothelial lining of our arteries and increase the risk of heart disease with aging. Dr. Brunt, welcome to the program.

Dr. Brunt:
Thank you so much for having me.

Dr. Sorrentino:
So Dr. Brunt, let's begin by taking a look at what we already know about trimethylamine N-oxide, or TMAO, and its effect on our bodies. What can you tell us about this compound?

Dr. Brunt:
So TMAO or like you said, trimethylamine N-oxide, is a metabolite that is produced by certain bacteria that reside in the gut microbiome, and with our work, and work by others, we found that the abundance of these bacteria can change with aging, so we have more bacteria producing TMA, which is the precursor, that's then converted to TMAO. As you get older, compared to in young adults eating things like red meat more and then certain other clinical conditions can also increase the prevalence of these bacteria. So TMAO was first studied and discovered by a group at the Cleveland Clinic, led by Stanley Hazen, and they found that higher levels of TMAO could directly induce the development of atherosclerotic plaques in mice that are prone to develop atherosclerosis. They also found that if you prevented the production of TMAO in the gut by this compound33 dimethyl 1 butanol, you could prevent TMAO production and then you could also prevent a production of plaques in these mice. And so that was the initial work that was done to identify TMAO as an important metabolite. They later did work where they also measured it in humans and found that it was correlated with risk of developing cardiovascular disease later in life as well as five-year mortality risk and other markers related to atherosclerosis. So that's kind of the main work that was done prior to when we came in. And then we've been interested in seeing not only if it associated with the clinical development of cardiovascular diseases, but whether it contributes to changes that occur with arterial function that precedes cardiovascular disease.

Dr. Sorrentino:
You mentioned that TMAO is produced by bacteria in the gut. Does everybody have these bacteria, or is it highly variable from person to person?

Dr. Brunt:
At least based on what we've measured and what others have measured, it seems that they are bacteria that naturally reside in the gut, so everyone does have some level of them. However, the abundance of these bacteria will increase under certain conditions, and we've shown that they increase with aging.

Dr. Sorrentino:
So let's go to some of the methods of your study. How can you determine the effects of TMAO on the vascular endothelium? What type of procedures did you do to determine how it affects our arteries?

Dr. Brunt:
So, the initial studies that we did were in humans, and as you know, it's hard to do mechanistic studies in humans. So those initially were correlative. So we showed that individuals who have higher levels of TMAO in their blood had lower levels of endothelial function, which we measure using flow mediated dilation of the brachial artery. And so that was the initial findings that we did, and then we moved into a mouse model to be able to isolate things better. So, in young mice,— we supplemented TMAO in their diet, so that we could look at the direct effects of supplementing it, independent of what might be going on in the gut microbiome, and we found that the supplementation for six months induced oxidative stress and impaired endothelial function in these mice. And then, to kind of confirm that, this relevant within the context of aging, we did the reverse, where we took old mice next, who had higher levels of TMAO and who had impaired endothelial function, and then in those mice, we gave them that compound, 33 dimethyl 1 butanol, or DMB, which blocks the ability the gut microbes to produce TMA, which then gets converted into TMAO so we could suppress TMAO production. And in these mice, we were able to reverse the endothelial dysfunction that they had.

Dr. Sorrentino:
So, let's move back to the human endothelial function. You said that you used flow-mediated dilatation studies. Just so that our audience knows what that means, tell us a little bit about how this mechanism is done, and what TMAO does to show that it's impairing endothelial function.

Dr. Brunt:
Sure, so flow-mediated dilation is a commonly used test to measure the endothelium-dependent dilation of the brachial artery. We essentially put a blood pressure cuff just distal to the elbow that's inflated to occlude blood flow for five minutes. Then when we release the cuff, blood rushes back into the forearm, which creates a sheer stress, or a blockage from the higher velocity to the blood flow creates a frictional stress on the brachial artery and stimulates nitric oxide dependent dilation. And nitric oxide's a major vasodilator that is reduced as we get older, and which contributes to the development of cardiovascular diseases. So this test, we can use to look at how well the artery dilates. It's been used in a huge number of clinical studies and has been closely correlated with future risk of developing cardiovascular disease as well as risk of cardiovascular-related morbidity. And it's a predictive test, to show if someone's at higher risk later on. And we use ultrasound to look at the brachial artery there. So at our first initial experiments we just correlated plasma levels of TMAO with how well the brachial artery dilated on this test. And then, mechanistically later on, we could also do a test where we give Vitamin C, which is an antioxidant and so scavenges superoxide and other reactive oxygen species, which all work in concert to impair the ability of the arteries to dilate. And when we give the Vitamin C in older adults, it makes it so that their artery will dilate more on this test, which is indicative that they had greater oxidative stress to begin with. So the older adults that had more TMAO circulating in their blood on this test had greater suppression of dilation by oxidative stress. So it's a way to mechanistically show that TMAO, in the human subject is driving greater oxidative stress and causing greater impairment in their endothelium-dependent dilation.

Dr. Sorrentino:
For those just tuning in, this is Heart Matters on ReachMD. I'm Dr. Matthew Sorrentino, and today I'm speaking with Dr. Vienna Brunt, who's the first author of a recent study that explored the link between gut bacteria and the aging of our arteries. So if we can go back to what you found in your study – the higher doses of TMAO in older patients caused more endothelial dysfunction, and you said that by giving Vitamin C you were able to blunt that effect. So, I guess the question is, can I just have a big glass of orange juice every day and prevent aging of my arteries?

Dr. Brunt:
Haha, good question. This comes up a lot in the aging literature, because we know that oxidative stress is a major mechanism that contributes to decline in vascular health. However, the current literature looking at Vitamin C supplementation is actually quite mixed. There have been clinical trials that have given Vitamin C to older adults to try to improve artery function as well as other outcomes, and it does not seem to be as effective as one would think, and we believe that the main reason for this is that those reactive oxygen species that cause the oxidative stress —they're actually important signaling molecules but they're also doing a whole bunch of other beneficial things in your body, so you might not want to block those at all times. We're trying to look what might be causing passive physiological levels of oxidative stress and so can we try to push that scale back to a more healthy balance of oxidants and antioxidants. And then in this case we're looking towards the gut microbiome for a place to intervene.

Dr. Sorrentino:
You mentioned that diet may influence the gut microbiome and influence the amount of TMAO that is produced by the gut bacteria. Are there certain things in our diets that have been linked to higher levels of TMAO and if we just reduce those, or eliminate those from the diet, could that help?

Dr. Brunt:

Yeah, so TMAO the precursors to it are choline and L-carnitine. L-carnitine is found predominantly in red meats, and then choline is found in meat, poultry, eggs, and dairy. And so, it is possible that a diet that limits those things might lead to lower production of TMAO, and there have been studies that have shown that people who eat red meat for their entire lives have higher risk of atherosclerosis than vegetarians, and they think part of that is because they're producing more TMAO. However, you do want to be careful here, because everything's in moderation, right? So you need to have choline in your diet in order for other processes to be maintained as you get older. The key is to keep it in moderation, so don't have such excessive choline that you're causing your gut microbes to produce excessive amounts of TMA and then TMAO. I think that's the key.

Dr. Sorrentino:
So what are your next steps? You now know that there is a link between TMAO and endothelial dysfunction. Are there any ways that we can target the microbe biome to impact production of TMAO, and what type of studies are you thinking of doing next on that?

Dr. Brunt:
Yeah, so 33 dimethyl 1 butanol, or DMB is a really, promising compound, or at least compounds that do similar things may be promising because it's nonlethal to the gut microbes, so all it does is it blocks the enzyme that converts the food precursors, choline and carnitine, into TMA. It doesn't kill the bacteria, they just go digest something else instead. So you're able to very selectively just prevent that TMAO production. DMB currently has not been developed for use in humans, and we are not personally doing that development, but I am sure that others elsewhere in the world are, or at least developing compounds that can do similar things. So I think in the coming years, we'll be watching out for the development of those types of compounds and then those could ideally be given as a dietary supplement that hopefully down the road, someone could just take in addition to their healthy lifestyle and prevent some of these adverse effects with their arteries as they get older.

Dr. Sorrentino:
As a final question, we know that antibiotics can certainly disrupt the microbiome in the gut. Are there any studies of antibiotics worsening or helping endothelial function due to TMAO?

Dr. Brunt:
Yeah, so we actually did a study prior to this where we gave antibiotics short-term to old mice, and premise behind this was that the old mice have a change in the composition of the microbiome as they get older, same as humans do. The idea was that by giving them the antibiotics, we could suppress those bacteria that are maybe more pro-inflammatory and may be driving more of the adverse effects on the cardiovascular system. So when we gave antibiotics for three weeks, this actually reversed their vascular dysfunction as well, back to levels that we see in young mice. So, using antibiotics at least as proof of concept, shows that we can manipulate the gut microbiome, and it can have beneficial effects on the host's physiology. That said, we obviously don't want to give antibiotics long-term in humans. So we kind of see that as the proof of concept that manipulating certain communities of bacteria may be beneficial. There is obviously still a lot to do in terms of figuring out what types of compounds are going to affect certain communities of bacteria in a favorable way, without adversely affecting other bacteria. That's the key that this field is gonna need to focus on as we move forward and design these types of intervention.

Dr. Sorrentino:
So I guess at this point, the best way to prevent aging of our arteries is all become vegetarians.

Well, I want to thank Dr. Vienna Brunt for joining me today, to share the results of her groundbreaking work, on the gut microbiome and how it ages our arteries. Dr. Brunt, it was a pleasure speaking with you today.

Dr. Brunt:
Thank you so much for having me.

Dr. Sorrentino:
For ReachMD, I'm Dr. Matthew Sorrentino. To access this episode, and others from Heart Matters, visit www.reachmd.com/heartmatters, where you can Be Part of the Knowledge. Thanks for listening.