TMAO: Why You Must Know Your Blood Level

Joel Kahn, MD, FACC
with Stanley Hazen, MD, PhD

Joel Kahn, MD, FACC
Alright everybody, we are turning to big time academic interview. This is very exciting for me. First time I've had a chance to speak with Dr. Stanley Hazen, Professor Stanley Hazen, thank you Dr. Hazen.

Stanley Hazen, MD, PhD
Thank you.

Joel Kahn, MD, FACC
And this is the reversing your heart disease naturally summit. Of course I could spend the entire interview reading Dr. Haze's biography but I want to give you his fair share. Both an MD and a PhD Barnes, Jewish hospital St. Louis, Missouri. One of the best places to train now at the Cleveland clinic. He's got so many positions. It's crazy. But chair the department of cardiovascular and metabolic services coast section had at the Lerner Research Institute, preventive cardiology and rehab. Director of center for Microbiome and Human Health. That's a lot of hats, he's not wearing one today. But this is a very busy man with hundreds and hundreds of academic publications that are really very, very translatable to what we're talking about in this summit, which is enhancing your health, making intelligent decisions.

Being up to date on the science, he's involved in many, many patents. Maybe we'll share some of that. And we're gonna get going. So the first thing is I will say I learned about a molecule, a compound in the body. We're gonna talk about T. M. A. O. Tri methyl amine an oxide in 2011 when you and your co workers started to publish widely visible articles. So we're only talking a dozen years. And I will probably say I've ordered 56, 7000 T. M. A. Levels in patients I think pretty hard to find too many more orders in that. It's an incredibly interesting tests but it wasn't really well known. This isn't a brand new compound. So why don't you tell us what's TMAO and prior to Dr. Stanley Hazen, what kind of people were studying it? Because I don't think it was endocrinologist and cardiovascular specialists.

Stanley Hazen, MD, PhD
We began our search not thinking we were going to get into the gut microbiome world. But we were looking for chemical signatures and blood and patients who did not have disease but had been followed over time. And we knew who went on and developed a heart attack stroke or death and the ensuing three year period. And so we asked are there chemical compounds in the blood that predict the future development of disease independent of risk factors. And this compound rose to the top of the list. We didn't know what it was when it was first discovered. And when looking and reading about it, the only two areas where literature existed were either papers about deep sea fish where a subset of fish will use it as an antifreeze method to prevent you know like in arctic waters, you know fish have to not free solid but remain alive even though there's icebergs in the water and and T. M. A. O. Is a small molecule that raises to very very high levels in certain fish as an antifreeze.

That was the one example. And then the other place where we were reading about it is the precursor of the molecule which we figured out is something called T. M. A. Tri methyl amine. We found papers describing how during rotting of things putrefied cation bacteria would generate that as a product. And that's what gives rotting fish that horrible odor. And the last piece of the puzzle was there is a very rare genetic disorder where the gene for converting T. M. A. into TMAO makes people smell like rotting fish. And so it's called fish smell odor syndrome. And they have very high levels of T. M. A. and so putting the whole piece together this compound that's elevated in the blood would predict future risk of disease. And it was coming from gut microbes and after absorption into the bloodstream, the portal system to the liver, it gets converted into T. M. A. O. And in the absence of that rare genetic, you know, in the rare genetic disorder that the liver won't convert it. They have the... those poor sufferers have elevated levels of T. M. A. And smell like rotting fish. That's how this all began essentially.

Joel Kahn, MD, FACC
So if you and I as both people interested in cardiac disease and prevention, we're talking in 2010, we'd say diabetes is associated smoking high blood pressure, high cholesterol, maybe lipoprotein and we could add in 345 others. We would never say in 2010 there's a compound you can get a blood test for called T. M. A. Oh that might actually predict heart disease. And I think you'd probably go so far as to say may actually cause atherosclerosis. So we wouldn't say that in 2010.

Stanley Hazen, MD, PhD
Absolutely.

Joel Kahn, MD, FACC
Are you ready to see all of that now, 12 years later that I think no, it's associated with. Are you ready to say causes an

Stanley Hazen, MD, PhD
I would say it's one of the many causes or contributors to. And so I think there's a substantial body of evidence now, particularly in the animal model world that where you can show that providing the compound and elevating the level will foster afros Croesus. It will enhance thrombosis and platelet function. You can transplant microbes into animals that have the capacity to make this product and transmit from a donor to the recipient. The capacity to have enhanced atherosclerosis, enhanced thrombosis. You can essentially fulfill Koch's postulate, which is what we, you know read about for cholera or diphtheria. Now, those same type of experiments are being done in the gut microbiome world as a proof of concept that microbes in your intestine can actually confer a phenotype to the host.

And you can literally transplant that from a donor into a recipient and show that it lowers or you can change the susceptibility in the recipient for expression of a disease phenotype in this case a heart attack or stroke or a four sclerosis and we think the same thing is happening in humans simply because there's now so many clinical studies that show that changing levels of T. M. O. or a very strong and independent predictor of future development of disease and even in healthy subjects, if you place them on certain supplements that make TML levels rise, you can show that if you take blood from them and measure the function of how quickly it will clot and how the platelets react as the TML levels go up the so to the susceptibility for clotting goes up not only the ability to transplant microbes or to give the drug one other thing, the compound we have now developed drugs that will target the pathway and block formation of TM. AO and in animal models those will block the development of atherosclerosis or thrombosis in various diseases.

Joel Kahn, MD, FACC
Fantastic. A new therapeutic category. But we're speaking to an audience that is at least interested or practicing largely a plant forward. Plant based may be completely plant diet. We've interviewed Dr. Dean Ornish and Dr. Joel Fuhrman as my co host. We're allowed to say words other than potato and carrot but you know speaking and you found fairly quickly that you can drive the production and measure in the blood in the human every day in my clinic TMAO if your diet is rich in l carnitine in your diet is rich in choline. So tell us where those food substances are most likely concentrated.

Stanley Hazen, MD, PhD
So animal source foods and in particular red meat are a major source of the nutrient precursors that give rise to forming T. M. A. O. So being on a vegetarian or a vegan type of diet we have shown will help lower TMAO levels. It won't bring them down to zero. You know there are but it will substantially reduce the levels. Part of the way we digest food and is by taking bile and a large component of bile includes less thin or choline. And so even the most ardent of vegetarian or vegans can still have a high level of T. M. AO. it's a mixture of what you eat as well as the microbes in your intestine. And right now we don't really have a good way to manipulate the microbes in our intestine.

Other than a chronic and sustained dietary effort, we do see that will shift the community to one that is much less likely to produce TM A and TMAO. And so from a practical standpoint, what can be done is and I mentioned this all the time with my patients is is to try cutting back first and foremost on the red meat and also to look and read the labels and make sure that nothing that they're taking, especially anything that's in a powder form or as a supplement has less if in in it or carnitine in it. A lot of energy drinks and a lot of protein supplements will have less thin and this can really substantially drive TML levels up and people are trying to do something helpful for themselves by taking a supplement and yet maybe in it inadvertently doing something that might be adversely impacting them. So I say go to the produce section rather than the powder or capsules.

Joel Kahn, MD, FACC
Love that and very well received. And if you transition your diet from a meat heavy red meat heavy because it's you raise your TML, correct me if among largely with red meat processed unprocessed less so with white meat. So to some degree there's an enriched l carnitine content and white meat choices.

Stanley Hazen, MD, PhD
No. Okay you mentioned both Colin and carnitine. Those are the two major families of nutrient precursors that give rise to TMAO carnitine the whole that whole family of those carnitine and carnitine, those are much more abundant in red meat, not white meat or plant or non meat sources like egg white for example has very little if any either choline or carnitine in it. It's a very good protein source. However you can't get away from the choline source. It's an essential amino are essential vitamin and,

Joel Kahn, MD, FACC
And soybeans. It's very rich in soybeans which a lot based eaters you know enjoys a protein source.

Stanley Hazen, MD, PhD
Yeah so I mean we need to have protein in our diet. There are certain essential amino acids we can't avoid. And so and many of the foods that have those will also have full lean in them, they won't necessarily have carnitine in them. So but reducing the red meat content will help to suppress the TMAO levels from the carnitine side, not the coal inside.

Joel Kahn, MD, FACC
You know and anybody listening if you're dragging your rear end in the morning on your way to work, stopping at the gas station and getting a monster energy drink, turn it around. You'll see L carnitine is one of the nutritional supplements. And you, Dr. Hazen has studied how you know it's not just food based but supplement based, concentrated sources of colon and l carnitine can

both raise T. M. I. O. And as you said potentially cause the blood to clot. That's not a good consequence of being tired on your way to work. So go for bottled filtered water if you have a choice please audience or black coffee or green tea or something. A little healthier.

There's a big debate online as you know, you've changed our understanding of gut heart physiology. Not everybody likes that. You bring up that there are some downsides to red meat. So there's been the big push back on the official university sites called twitter and Instagram you know what about fish because as you already said there are some deep water fish. I think gar is an example. But my people in my clinic never tell me They had, you know, roasted gar for dinner last night. They're having salmon and whitefish and perch or they're vegan, but they're having none of that. What about that debate? If fish can raise your blood T. M. A. O. Level, it can't be bad for you because population studies suggest fish is a potentially healthy choice. Which fish and what are your thoughts? And it's preformed TMAO and some of these fish, right?

Stanley Hazen, MD, PhD
Correct. First of all, not our fish are created equal and you know, the same arguments I'm using for TME are also true for omega three fatty acids. You know, they're not found in all fish also. And it turns out that the fish that have high T. M. A levels tend to be, you mentioned gar, but that's not really eaten a cod. The kind of fish that are made into fish sticks. That's what I tell my patients, that's the fish you want to avoid. The type of fish that you can eat are like freshwater fish, Tuna is fine. That's not, but in terms of non freshwater fish, tuna and salmon have relatively low levels comparatively. So the best fish are any of the freshwater fish, like and trout and bass and walleye and steelhead, those are all perfectly fine. Catfish is fine. And then tuna, salmon, the levels the fish that have high levels, they only have high levels during certain seasons. So it's also complex, you know the weather changes the temperature of the water changes. And so when they don't need an antifreeze the fish that have high TMAO if they're swimming into the gulf waters they get rid of it. And so it's not such a a whitewash thing where you can say off fish or even even the subset of fish that occasionally have high TMAO it's only during part of their life cycle.

Joel Kahn, MD, FACC
Interesting. Thank you for sharing that. I know you're published a paper about a molecule and maybe many papers called D. M. B. Dimethylbutane that potentially may block the production of T. M. A. O. And I don't know if that's the springboard for some of these pharmacologic agents. You mentioned that that is something you could find balsamic vinegar if I remember.

Stanley Hazen, MD, PhD
So dimethylbutanol is a small fermented molecule, it's like alcohol but only a little bit bigger and it looks like killeen. But it's not quite the same structure and we were able to show that it inhibited got microbial production of TMA and therefore in animal models it did lower TMA levels. It is not something that I would suggest in any way that a patient should have and you

know, even though it so because but it was a proof of concept tool, but what's interesting is that we are able to find that certain fermented products like balsamic vinegar Guinness lager stout and extra virgin olive oil. Cold pressed extra virgin olive oil. Some forms can have a high level of D. M. B. In them. But many of the olive oils don't. And that's because they're like steam and heat extracted. And it will just you know it has a low vapor pressure and it will cook off. So that's another thing if you use cold pressed extra virgin olive oil. It's not just D. M. V. There are other small molecules that are in that that you lose when you heat and cook with the oil. So if you think about how a real Mediterranean diet uses extra virgin olive oil. It's not usually with cooking it's after the cooking it's drizzled on top. And you know that's the suggestion of how we recommend to use it.

Joel Kahn, MD, FACC
And you've actually studied that the Mediterranean diet and as you said a diet without egg yolk and red meat or whether it be completely vegan or close to vegan will lower TME. Oh you've published that data. I wasn't aware the extra virgin olive oil could be an additional reason why the Mediterranean diet may lower TMAO talk a little bit I wanna hear I'm gonna I pulled up you published very recently along with Dario movies are and I believe about a very well known nutritional researcher dietary meat TMAO an incident cardiovascular disease. The cardiovascular health study in a prominent journal in thousands of people where you had blood samples and were able to follow to see if they develop heart disease. You know, it's one of many studies. So you have a certainly associated if not proven that a diet that raises TMAO, can be related to having more heart attacks, strokes deaths, bypass stents. That was sort of the observation in that study.

Stanley Hazen, MD, PhD
Yeah. What there are two questions that were asked and one was the question that many have asked before is does a red meat or an animal product rich diet contribute to heightened risk of atherosclerosis and if so, how or cardiovascular disease. And what's that dose response relationship. And what was seen is that for each one portion per day of an animal product source product or red meat, there was about a 20% increase. And the development of atherosclerotic cardiovascular disease over the period of follow up, which averaged about 12 years. And this was, as you mentioned, like over 6000 subjects.

On the other hand, then the type of analysis was done to say, what is mediating this increase in risk associated with or due to the animal source food or the red meat component. And what was really informative in this analysis was cholesterol was not the case blood pressure was not the case. There were really three things that were driving the increased risk. The first was related to diabetes and glucose and insulin. The second was related to inflammation. And the third major thing was TMAO pathway related metabolites. TMAO and some other metabolites in that pathway were contributing to the heightened risk associated with a red meat rich diet about 10%,

Joel Kahn, MD, FACC
10%, 10%. It's worth just shouting about 10% in that study of the risk of developing heart disease. Was this single compound you brought to the world's attention a dozen years ago and all the other things we have known for decades like smoking and blood sugar and blood pressure contributed to 90% but 10% is a big piece of a pumpkin pie.

Stanley Hazen, MD, PhD
I try to describe TMAO is it's like the rheostat on the light switch. You know, it's still 120 volts. That's the cholesterol. You need to have cholesterol to have atherosclerosis. But how bright the light is and how susceptible to the cholesterol you are is impacted by many other factors. And if you have a high TMAO the real status turned up the light shines bright your low TMAO then you know you're not as susceptible to the cholesterol. It just low, it makes you more prone to develop plaque and also have a clot a heart attack or a stroke.

Joel Kahn, MD, FACC
I want to emphasize something you said quickly because people listening to this not on this summit but in other locations will hear people say cholesterol is necessary for health cholesterol is not the cause of atherosclerosis, inflammation is or insulin resistance is or you can make a list but you just said the necessary component for atherosclerosis. And what you meant necessary to cause a disease is you have to have circulating LDL cholesterol or oxidized LDL cholesterol. I mean you and I are 100% in agreement. Of course we work hard to lower cholesterol total and LDL cholesterol and lipoprotein in people with atherosclerosis. But I just wanted to point out, I mean we're talking to a professor at the Cleveland clinic and one of the top brains in this field and you know the L. D. L. It's not a hypothesis but the fact that LDL causes LDL cholesterol causes atherosclerosis is something that people should be excited about because it's so many ways to lower it between lifestyle and now. And I would say supplements. Although Steve Nissen from your institution might say don't you dare say supplements after his recent contribution and of course pharmacologic agents. I mean a low LDL is a happy patient if you have heart disease. Right?

Stanley Hazen, MD, PhD
Correct. And in fact one of the questions always asked is okay beyond an intensive diet and like recommending less red meat and more vegetarian, what do you do if you have an elevated TMAO What can you do? Because time and time again it is a very strong and powerful predictor of heightened risk for future development of a heart attack or stroke or mortality rate. So what we do and it's being used in our clinical practice as well. We will move the goalposts for how aggressive we are in many many different established preventive efforts. So one thing we'll do is we will aim for lower LDL goals in subjects with high TMAO rather than using the established let's say a target of less than 100. Which you would in a primary prevention patient. Someone without known heart disease. If you have a high TMAO we shoot, we aim can you go for less than 70. Because just that rheostat analogy, even if you lower the cholesterol enough you start to

make some of the effects of TMAO less relevant. We see the same thing with elevated LPLA. You have a high L. P. L. A. We aim for lower LDL goals. In addition we're more likely to give an anti platelet agents like Low dose aspirin. Now the pendulum on use of aspirin has been swinging back and forth. You know over the years we used to say if you went back five years or 10 years ago, if you were over the age of even 35 we would put someone on low dose aspirin for lower heart attack and stroke risk.

But then now we see that as long as you treat cholesterol to the recommended goals in randomized trials, like you don't see the benefit if you've lowered the LDL enough. And you do see with low dose aspirin a heightened risk for G. I distress or even bleeding. If someone has a high TMAO and a heightened thrombosis risk, I think that there is now this is arguable, this needs to be someday shown in randomized clinical trials, but as long as there's not a high bleeding risk in the patient and there's no clear contra indication one of the recommendations were using is to go ahead and give a low dose baby aspirin. And along with the more aggressive global preventive efforts.

Joel Kahn, MD, FACC
Really, I agree and I am very liberal in my use of coronary calcium scoring and you know, if you're over 100 based on UT Southwestern data, you're getting a baby aspirin. Now you're right, throw in an elevated TMAO , that's not easily coming down with supplement and diet changes and you absolutely should consider a baby aspirin. This is a reverse your heart disease naturally summit. But your team in a worldwide series of scientists have now associated a high TML with a range of other medical conditions probably audience wants to avoid. So just took off, you know, half a dozen of the other diseases that are at minimum associated with a chronically elevated TMAO

Stanley Hazen, MD, PhD
Well I'll start with the ones that have not only association but also causal data in the animal model world. The foremost is chronic kidney disease. An impairment and renal function. What you see is a chronic elevation in TMAO will lead to a reduction in G fr globally or filtration rate and it will promote chronically fibrosis in the kidney and chronic kidney disease. And animal models and in parallel human studies show that a chronic elevation of T. M. A. O. Is associated with the future development of chronic kidney disease. Heart failure is another one. We see chronic elevation and TMAO associated with the development of heart failure and adverse outcomes in heart failure.

And similarly in animal models TMAO both fosters heart failure phenotype is and lowering TMAO treats heart failure phenotype. And I would say one of the more up and coming interesting aspects that will be in the news soon because of some collaborative studies that are about to be published high TMAO is linked to aneurysm development. So abdominal aortic aneurysm risk and expansion of abdominal aortic aneurysms are linked to a high TMAO level probably because T. M. A. O. Is like a small molecule like urea it kind of gets into the nooks and crannies of a protein

and it changes the protein unfolding response and it changes protein confirmation and it's thought that interaction there's a receptor for TMAO called Perk which is involved in protein folding and the response to unfolded proteins. And that pathway is thought to be involved in mediating the TMAO interaction with abdominal aortic aneurysm.

Joel Kahn, MD, FACC
Everybody listen. There's smoke coming out of here because we went deep into science which is wonderful. We're talking to an eminent you know, you do see patients or clinicians but you're a scientist but I wanna just draw it back because I mean I think that relationship to abdominal aortic aneurysm is going to be very practical to know that we have another pathway to attempt to slow down the progression. And we look forward to that publication. Before we went on I was asking the question. There's a couple of molecules in the body that we wonder why they're even made PCS canine lipoprotein. Is there anything good to say about them? I was always taught trying to find to say something good about everybody. What can you say good about TMAO. Is there even a theory that the human body and our microbiome can produce it because there's a rare benefit or there might be no unknown.

Stanley Hazen, MD, PhD
Well there's none proven. But for speculation standpoint. One of the strongest physiologic effects that tm oh elicits is enhancement in the potential to form a clot and for the platelet to that's the first soldier in the army to block you know bleeding bleeding. And so what is interesting is it has been shown that during pregnancy in the very end of the third trimester TMAO levels shoot up and it's thought that maybe the hormonal changes in the late stages of pregnancy might give rise to an environment that causes a bloom in the microbes that are more prone to generate TMAO So you know one of the biggest risks to a woman is hemorrhage during delivery in peri partum hemorrhage. And if you think back you know what are the major drivers of evolution and survival you have to be able to survive infection and survive hemorrhage. And so that is you know but that's a very hard thing to prove you know other than discuss it in terms of association.

Joel Kahn, MD, FACC
And give us, since we have a world expert, you mentioned your lab probably others are working on. It sounds like pharmacologic pathways. Are you gonna have to do the whole phase one? Phase two phase three F. D. A. Are we talking half a dozen years 3 to 5 years off to see something tested?

Stanley Hazen, MD, PhD
Well you know the development of a pharmacologic agent is going to have to no matter what follow all the same pages phases as any other FDA approved or Eu approved drug beyond what you method you mentioned dimethylbutanol all we actually came out later with a subsequent follow up study where we had second generation inhibitors that were 10,000 fold more potent

and showed that in animal models those would actually attenuate clotting risk in thrombosis potential. But unlike other anti platelet agents, what they do is they just make the platelet not hyper responsive and move it back to normal function. So bleeding is not an adverse consequence of those inhibitors. We are moving some of those drugs and analogs of those into human clinical studies now and actually have already had interactions with the FDA and but you are right, all of the same types of safety studies still need to be done.

And one day though I tell this all the time too, when I give talks our medicine cabinets are going to be filled not just with drugs that block enzymes and homo SAPIEN, but drugs that target microbial pathways. And I'm not talking about antibiotics. I'm talking about something that actually just inhibits the formation of a metabolite by your microbial community in your intestine and has a beneficial effect in the host. And there are many, many exciting advantages to giving a drug to the gut microbiome because you don't have to have a drug that enters the human body then. So from a safety standpoint, there's a lot more safety built into it if the molecule that you develop has built into it, you know, the targeting of just the microbes in your intestine and don't even have to have systemic absorption and so it's a very interesting and alternative way to do you know pharmacology and medicinal chemistry. Try to develop a compound that is not absorbable in the host but is still functioning at the level of the microbe.

Joel Kahn, MD, FACC
Excellent. Excellent. The next ground flaxseeds something that stays in the gut and does good things. So the last point I just want to make for everybody listening because I want to respect your time and we learned so much is this is not theoretical, anybody can ask their health care practitioner. I want to know my TMAO Level and I shared with you I think it was about 2015, maybe early 16. Cleveland heart lab developed with you the essay and I was an early adopter and thousands of people And now I know quest will do it. I'm not sure if there's other labs that have contracted to measure T. M. A. O.

But you can find out audience, you can work hard with your dietary changes and read those labels like Dr. Hazen shared with us and we can wait and follow the science while he's developing these very gut based molecules and compounds which is very exciting. I don't think the goal is to make a safer monster energy drink. I don't think anybody should gravitate to that. But I could see the day that there's even such a commercially available way to you know, enjoy some of the benefits of some of those amino acids and without, you know, blood clotting and atherosclerosis. So wouldn't it be great to eliminate 10% of cardiovascular risk by being able to mediate, you know, T. M. AO pathways? I guess that's what you're chasing. Sounds like a big, big, wonderful goal, right?

Stanley Hazen, MD, PhD
Not just the cardiovascular disease. I think the chronic kidney disease is, I mean that affects up to a third of middle aged and elderly adults. You know, we're becoming an older population and

our kidney function just always naturally declines as we age. And what we are seeing is if you're TMAO level is high, that rate of age related decline is substantially accelerated.

Joel Kahn, MD, FACC
Well, thank you for sharing. I think everybody learned a lot and I really think the majority of listeners came away with 1000 new points of light as a former president used to say. And it translates for now and to be very careful and mindful about your diet while you're pursuing, you know, other pathways that will just augment dietary changes. So, I personally want to thank you for just stellar research and for the few patients we share. Thank you for your excellent notes and feedback and I hope to see you soon.

Stanley Hazen, MD, PhD
Thank you very much.