Key Strategies to Upregulate NAD Production for Optimal Health
A Special Interview With Nichola Conlon, Ph.D.
By Dr. Joseph Mercola

Dr. Joseph Mercola:

Welcome everyone. Dr. Mercola helping you take control of your health. Today we're going to go into some fundamental biology that will help you understand some powerful, and I do mean powerful, strategies to improve your health at the most fundamental level and provide resilience, extraordinary resilience to just about any disease, including infectious diseases like we've been struggling with. I'm going to have this dialogue with a molecular biologist, which is my favorite discipline. Her name is Nichola Conlon. She comes to us from the U.K. She basically vectored out of the bad guys, Big Pharma and did her own company to provide a strategy to improve one of the most important biomolecules in your body, which we're going to talk about. You may have heard me talk about it before, which is NAD (nicotinamide adenine dinucleotide), specifically NAD+. Welcome and thank you for joining us today.

Nichola Conlon:

Hello, Dr. Mercola. Thank you so much for the wonderful introduction and for of course having me on.

Dr. Joseph Mercola:

I'm excited to have this dialogue. We've talked before on the phone and it's good to connect with you on Zoom. Basically, one of your passions is NAD. You actually formed a company to provide an NAD, not really a precursor, but an NAD augmenter, I guess would be my way to describe it. Because there are a lot of precursor products out there. I've been disenchanted with them for a while. When I heard you, your presentation, it really resonated with me because I thought they were better strategies and the strategies evolved from understanding of the basic science, which we're going to dive in deep today. Why don't you give us a brief history of your training and how you were worked with? I think it was Systems Pharmacology, is that-

Nichola Conlon:

Yes. Yeah. That's it.

Dr. Joseph Mercola:

You reel off from that. And to form own company, to apply the big benefits of Big Pharma. I mean, there are no question. They do a lot of great things. It's just that their implementation is just beyond fatally flawed, is focused on the bottom line, which is one of the reasons you left actually, I think when we were talking.

Nichola Conlon:

Yeah.

Dr. Joseph Mercola:

Why don't you talk about that transition from the dark side over to nutritional supplement side?

Nichola Conlon:

Okay. Yeah, I certainly will. Because I have to say, a lot of people did think I was crazy when I left my excellent job in the world of Big Pharma to start a supplement company. I'll give you a bit of a backstory of why that happened. I think as I said from my training, I've always just been really, really interested in how the body works and how it is so complex. I actually did my Ph.D. in understanding how when we take any molecule that goes into the body, whether that's going to be a supplement, a drug, something that we've eaten, a nutrient, how does that actually go from being in our mouths to then actually ending up in the cells where our body can actually use them and benefit from them. That's called the bioavailability, looking at bioavailability of molecules.

Nichola Conlon:

After I did my Ph.D, in that, that sort of naturally led me to think about, you know, it seems like the right thing to do, to go and work in drug discovery. Because there's all this amazing science going on, and surely it's the drugs companies that are the ones that are actually getting this amazing science out to the people who can actually benefit from it. So I went to work in Big Pharma. I actually worked for an early-stage drug development company, which is the part of the drug development process where you look at what targets that you're going to hit with the drug, basically. There were two things I sort of learned very early on. The first was that the drug development process was very, very long and very, very expensive.

Nichola Conlon:

You're looking at about 10 to 15 years on average from the work that I was doing in the lab to actually getting it to people that could benefit from it and probably a cost of hundreds of millions of pounds to actually do that. It was a little bit disappointing because the area that I was working on was really exciting and I was sort of like, okay, this isn't going to benefit anyone for absolutely ages, so that was disappointing. The second thing was part of my job was literally looking at lists of molecules. These were lists of molecules that we got back from the lab where our clinical partners would be actually testing molecules to see what worked in cells and what didn't. And quite often the top 10 molecules that worked really, really well, the drugs companies simply weren't interested in them because they couldn't patent them.

Nichola Conlon:

In order for a drug company to move forward with developing a molecule, it has to absolutely own it and hold the patent for that molecule, which is understandable from a commercial perspective because they wouldn't put hundreds of millions of pounds in developing something that they couldn't own. But from an ethical perspective, I found that quite challenging because there was a lot of data that I saw that actually showed that a lot of the molecules that were simply being put in the bin were things that were quite well-known that had good safety profiles already, but they just weren't interested in developing them any further. I actually decided that I was going to leave the world of Pharma. What I wanted to do was actually say, “Hang on a minute, we've got this amazing science that's going on.”

Nichola Conlon:

“We've definitely got molecules that don't have to be drugs that have good safety profiles that could be used now, but we need to move them out of this world pharma and put them into the nutritional supplement route.” Nuchido, which is the company I founded back in 2017 is all about, how do we develop this science, but using the rigor and the techniques that are actually used in drug development and bringing that into the nutritional supplement space.

Dr. Joseph Mercola:

Well, thank you for explaining that. It's, I guess, easy to understand that they wouldn't want to go into nutritional supplements because the industry as a whole, not necessarily the company you were working for, but the industry as a whole has very cleverly constructed barriers to entry and obstacles for any nutrition supplement company, essentially at least in the United States. I'm sure it's similar in the U.K. and other places. If you have a supplement, it's generally considered you cannot market it or make claims on it, otherwise it's in a drug. Then you've got it through drug testing, and it has the same challenges of barrier to entry. They don't want to do that from practical reasons. We see the same thing, too, with COVID.

Dr. Joseph Mercola:

I mean, we have just as a failure of commitment to integrity as an example of the industry as a whole, I mean, we had two drugs that were incredibly well that were clearly approved, previously approved, hydroxychloroquine and ivermectin, and found it be of great utility for COVID-19, but all that information was suppressed because they had bigger and better plans to launch a product, a pharmaceutical product that was exponentially more. And I mean, exponentially not, that's not hyperbole, more profitable than that. I mean, probably two or three orders of magnitude, maybe even four orders. I mean, it made Pfizer $36 billion last year alone than they could have ever hoped to make from those drugs. Your assessment is correct. It's really focused on the bottom line. It's not really focused on helping humanity or lessening pain and suffering in the human race.

Nichola Conlon:

Yeah. It's a tricky one. That is the reason why I decided, as a scientist, at the very beginning of this drug development process, I'm continually exposed to breakthrough science. A lot of that gets lost in the drug development process. Actually, somebody needs to take some of this science and actually turn it into something that's beneficial that you can actually get to market pretty quickly. But as you say, it becomes tricky with claims and things like that.

Dr. Joseph Mercola:

For sure. All right. Well, enough of a framework or background. Let's dive into the science, actually, because we've talked a lot about NAD. NAD is an incredible biomolecule, but you're the molecular biologist so I'll let you give a description of it. I'll maybe point some things you don't mention to reinforce it and then ask some questions.

Nichola Conlon:

Yeah, absolutely. NAD is actually something I ended up, believe it or not, working on in the drug development industry, because I was actually a lower slate in drug development. I was

fortunate enough to work for a company that was forward-thinking. It actually started looking at developing molecules that would improve our healthspan, which is the proportion of the life that we live in good health. Rather than just focusing on individual diseases, actually looking at underlying mechanisms of cellular aging and looking at slowing cellular aging so that you can improve healthy lifespan. This is when I came across NAD, which as you mentioned is an incredibly important molecule in the body. Going back to molecular biology roots, as you said, NAD is important for two critical things in the body. The first is energy production.

Nichola Conlon:

The conversion and the process that takes the energy out of the food we eat and converts into ATP (adenosine triphosphate), which is the form of energy currency that our cells can use to survive and do all the functions that they need to do. That process absolutely requires NAD. Without it, we simply wouldn't be alive because our bodies wouldn't be able to make any energy. It's estimated that if we didn't have any NAD in our body, we'd literally be dead in 30 seconds, which shows how critical it is to our cells. The second thing that it's really important for is cellular maintenance and repair. What NAD does is it almost acts as a sensor in the body and it enables the cell to react to changes in what we call energetic stress, which is basically how much energy or what lack of energy the cell has.

Nichola Conlon:

Let's say things like exercise and fasting, they will reduce cellular energy. NAD will sense this and increase its levels. This increase in the level of NAD actually tells the cell that the cell is in a state of stress, therefore it needs to switch on cellular maintenance and repair processes in order to survive this period of stress. They are the two major things that NAD is known for, and because of these roles, it's absolutely fundamental to overall cellular health.

Dr. Joseph Mercola:

Thanks for that. I just want to add a little bit of context to that in that anyone watching this who's taking a biochemistry course knows about NAD because it's taught. I mean, it's a fundamental basics. It's part of the Krebs citric acid cycle. It essentially passes the electrons along in the mitochondria to produce oxidative phosphorylation and produce that ATP you mentioned. It was first discovered I think in 1905 by Arthur Hayden. That's over a century ago but no one was – When I was in school in the last century, no one was thinking about this. I think until David Sinclair in the late '90s, when he was at MIT in Leonard Guarente's lab, realized that it's the fuel for these longevity proteins, these sirtuins.

Dr. Joseph Mercola:

That's when it started getting prominence. I first became enamored with it in five, six, seven years ago and started really looking into literature in this because it seemed like such intriguing molecule, which is probably about the time you started doing that. When did you start working at your previous position?

Nichola Conlon:

Yeah, so this would've been about 2014 that I started getting involved in the aging field. This was a time when a lot of scientists were talking about this idea that we could slow cellular aging,

but it perhaps hadn't really hit the mainstream yet. It was still something that was sort of brewing in the background. I think even scientists within our field still needed to be convinced, but that's absolutely changed now. There isn't a single scientist that works in the field of biogerontology, which is the study of aging that doesn't say that you can slow biological age and things like NAD are a good thing.

Dr. Joseph Mercola:

Okay. We're going to go deep now. I think it's important to understand why this is such an enigma because there's a lot of hype around NAD and a lot of people promoting supplements that may or may not work as well as you think they do. Before you can begin to evaluate them, it's really crucially important to understand that [inaudible 00:13:29] to see, to measure NAD. There are loads of problems with testing NAD, which makes it beyond a simple challenge to implement a strategy to identify what the results of your intervention are. Why don't you tell us the problems with measuring NAD? Because they are profound.

Nichola Conlon:

Yes. NAD is a bit of a complicated thing to measure. The reason everyone wants to measure it is because NAD has been found to decrease with age and that's one of the reasons why people actually want to boost their NAD back to youthful levels to be able to have the correct cellular energy and to be able to switch on these cellular maintenance and repair processes. In laboratories and scientific laboratories, we use some fairly sophisticated techniques to be able to measure NAD. But now there's been an emergence of companies sort of saying, “Well, you know, send your blood away and we'll measure it for you.” The reality is unfortunately, as good as that would be, it just doesn't work that way. The reasons are, if you think of what NAD does, NAD is described as a redox molecule. What that means basically is it’s continually flipping states.

Nichola Conlon:

You mentioned that it carries electrons in the electron transport chain and the mitochondrial reactions. This means that by its very nature, NAD is designed to flip between different states so it's really, really unstable. Literally, as soon as NAD is taken out of the body, out in the blood, it starts to break down, it starts to break down into its precursors. It starts to change form, therefore, if you don't do something to stop those reactions very, very quickly, what you end up measuring is not a correct reflection of what is actually in the body and in the cell. When we measure NAD in the laboratory, what we have to do is make sure that as soon as it is taken out of the person, it's actually put straight on ice to stop any reactions and then immediately prepped to be able to take out the cells that we want to measure the NAD from and they're cryogenically frozen to stop any changes or any reactions until we actually measure NAD.

Nichola Conlon:

And then after that, actually work out how much NAD is in the sample, you use techniques such as mass spec, which is where you can compare the amounts of the NAD in the sample compared to what we call standards, which are known amounts of NAD. These are not simple techniques. These are quite advanced laboratory techniques that you need a good setup and you need to know what you're doing to be able to measure this. Yeah, unfortunately, companies that are

saying they can provide this service at the moment, I'm quite skeptical of what they are actually measuring. But it would be good if someone could develop something to be able to test it easier because it is such a critical molecule. We know it declines. We know we want to boost levels back up to youthful levels, so if there was a way of easily measuring this, it would be brilliant.

Dr. Joseph Mercola:

Yes, indeed. I mean, it'd be so nice to have a little finger prick that you do, which measure your blood sugar, but we're pretty far away from there so far. Thank you for that description. I was just curious of few things. How long from the time it's drawn and put on ice does it take to prepare the cells before you can cryogenically freeze it? Is that like 10 minutes, a half hour, an hour, days?

Nichola Conlon:

Your optimum time will be looking at about 30 minutes. We've done tests to look at what happens to the NAD and blood samples if you just leave it on the bench, or if you leave it in ice. You can see quite rapidly after this time, it does really start to degrade. You've got like about a 30-minute window to get this done.

Dr. Joseph Mercola:

Okay. Thank you for that backstory. This is so important to understand, because if you're interested in NAD, you have to know this part of the equation. Because if you don't, you're going to get a lot of misinformation. I'm curious from your perspective, you cannot get this test on a Quest or LabCorp commercial laboratory. This is a laboratory research assay only. How many labs in the world do you think can make this, do this assay accurately?

Nichola Conlon:

I think a lot of labs can do mass spec. They can do the way that the blood extractions, they can do the mass spec readings of the NAD samples. The bit that's the sort of missing link is being able to offer this offsite. The key bit is that, yeah, as long as you've got the people in the lab who know what they're doing and you have the person coming to the actual lab to get the blood taken and prepped immediately, then it is entirely possible if you have people that specialize in that laboratory technique. The caveat is actually people don't want to be going to an academic lab to go and get some bloods drawn. I certainly don't think academics will want random people turning up to get their bloods drawn. It's trying to find a way to commercialize it, some way to kind of preserve the NAD or some way to really quickly prep it offsite and then transport it to the lab is kind of the missing link at the moment.

Dr. Joseph Mercola:

Yeah. All right, well, that's good to know. It's really an important part of the equation when you're seeking to optimize NAD, because many of the studies that are out there are based on flawed information from my perspective. But let's go into the details now of how your body makes NAD. I think you can, not only makes it, but how it's depleted in your body, which is a good part of the equation. Yes, you want your body to produce it, but it's a dual equation. So the total NAD, the net is a sum of what your body makes minus what it loses. If you can really limit how much is being lost, you can maintain your NAD levels. And sort of an artifact of this and an

aspect I'd like to dialogue with you about is the observation that NAD tends to decrease with age. My guess is that it's only partially related to metabolic issues and more likely related to lifestyle issues. But before we dive into that part of the conversation, why don't we talk about how your body makes and loses NAD?

Nichola Conlon:

Yeah, absolutely. I think what's becoming increasingly apparent as there's more research done on this role of NAD in the cell is that it's incredibly complex. It's not just a simple case of "adding two things together makes more NAD and that's the end of it." It's very, very complicated. Within the cell, there are five different what we would call precursors that NAD can be made out of. These are the raw materials that your body uses to manufacture NAD, because NAD is quite a big molecule and it can struggle to get over some cell membranes and into the cell so the cell likes to make it inside the cell where it's actually needed. What it does is it effectively ships all this raw material into the cell and it actually assembles it inside the cell.

Nichola Conlon:

Basically, you've got five precursors. You've got the B vitamin like nicotinic acid, nicotinamide. Then you've got other various of the precursors such as nicotinamide riboside, nicotinamide mononucleotide or NMN, which some people might be familiar with if they've took NAD supplements. Once these are inside the cell, they enter various different pathways which then assemble them into NAD. There are three main pathways. The most important pathway for NAD production is something called the NAD salvage pathway. This is because not only can it make NAD from these external raw materials that come into the cell, but it can also recycle NAD as it is broken down.

Nichola Conlon:

Because a key thing that many people don't realize is that when NAD is being used up in all of these beneficial processes in the cell such as in DNA repair and activating other cellular pathways like the sirtuins, it actually gets broken down and it gets broken down back into one of its precursors and that is nicotinamide. Now, instead of this nicotinamide-

Dr. Joseph Mercola:

Or niacinamide, same thing.

Nichola Conlon:

Same thing. Nicotinamide and niacinamide are the same thing. They can be used interchangeably, the names. But the key thing is that this is what NAD gets broken down into when it's used up in the cell. The cell is really clever because what it's evolved to have is this salvage pathway that is actually a recycling pathway for this nicotinamide. It means that when NAD is used up, it gets broken down in nicotinamide and this nicotinamide then just gets recycled straight back into fresh NAD again, which makes absolute sense, because why on Earth would the body want to rely on generating such critical molecules using external precursors? It needs to use something endogenous, something that is always going to have a ready supply of.

Nichola Conlon:

This also means that as demand for NAD goes up, technically, that means as the NAD is broken down, there's more raw material that can simply get recycled straight back into fresh NAD again. This has been demonstrated to be the most important pathway for NAD production in the body. That's the sort of production path. That's what happens when we're young, we've got this abundant supply of NAD that's continually being recycled via the salvage pathway. But unfortunately, as we get older, NAD declines. The two main reasons for this are firstly, more NAD is actually used up. We can go into all the different reasons, but you know, the lifestyle reasons and things like that, but ultimately more NAD is used.

Nichola Conlon:

When more NAD is used up that means more really needs to be recycled to replenish this NAD. But it's been found that that salvage pathway, that critically important NAD production pathway, also declines with age. Right at this point in your life, when you've got this increased demand for NAD, you've also got this reduction in the body's ability to regenerate it via this recycling route. When you put those two things together, what you get is an exponential decline in NAD which is exactly what we see in human tissues throughout life. We look at about a 50% reduction in NAD levels in our tissues every 20 years, which is quite shocking considering how important it is to our lives.

Dr. Joseph Mercola:

Yes, indeed. NAD deficiency can be terminal, fatal. It used to be pretty common actually at the beginning of the 20th century, and it is known, it has given a name. It's actually known to be niacin deficiency or nicotinic acid. Those two are also interchangeable. But the name of the disease is pellagra. Basically, it's niacin deficiency and you'll develop dermatitis or skin rash, diarrhea, dementia and death from not enough vitamin B3. You definitely need it. I'm convinced, and we can have this discussion, too, that part of the reason that people are more susceptible to dying from SARS-CoV-2 would be an NAD deficiency. This is good to keep up for a lot of reasons aside from longevity. It'll keep you alive a lot longer. I'm curious, another molecule in NAD aside from the vitamin B3 would be, is it true that ADP is part of that?

Nichola Conlon:

ATP?

Dr. Joseph Mercola:

No, ADP. ADP.

Nichola Conlon:

ADP. Not directly so, that's more looking when you're looking in the redox reactions. In the redox reactions where NAD is acting as moving the electrons around, it's not actually getting used up in that sort of role. The more critical role where it does actually get used up and it causes its decline is actually when it's acting as a co-factor for other enzymes. Things like the sirtuins, things like the DNA repair enzymes, it's almost acting as a fuel in that role. It actually gets degraded and declines, whereas in its role in energy production, it just flips between states so the overall amount is not really changing.

Dr. Joseph Mercola:

When it's being consumed as a fuel, and we'll talk about those two enzymes that consume it, then the ADP is liberated from molecule?

Nichola Conlon:

Well, literally, yeah, it's just broken down. It's just split back into some of its original components.

Dr. Joseph Mercola:

Okay, good. Why don't we talk about the two primary enzymes that consume it? Because understanding what these enzymes are could significantly help your strategy to make sure that you're maintaining healthy NAD levels.

Nichola Conlon:

Yeah. The two main ones are DNA repair enzyme called PARP (poly[ADP-ribose] polymerase) or PARP1. As we get older, we have increased levels of DNA damage in our cells. This is caused by, you know, in our skin by continually being exposed to UV radiation. It's caused by our metabolism which is constantly producing reactive oxygen species, which is damaging our DNA. It's caused by our bad diet. It's caused by just living and breathing. Our cells are continually damaged. This causes DNA damage. It accumulates as we get older. This DNA damage has to be repaired. One of the key enzymes that repairs this damage is called PARP1 and that's DNA repair enzyme. For that enzyme to work, it uses NAD as a fuel. It literally takes NAD, breaks it down to form its reaction in the DNA repair action.

Nichola Conlon:

Then it moves off, gets another NAD molecule, uses that one, breaks it down. What you see is that if you've got increased levels of DNA damage in your tissues, you get increased activity of this enzyme and you get NAD depletion. There's been some studies that have shown that if you have a lot of DNA damage in a cell, it can deplete the NAD level in that cell to about 5% to 10% of what it started at very, very quickly within five minutes. So that's a huge, huge decrease.

Dr. Joseph Mercola:

Now I've done some previous work with my interest in the EMF (electromagnetic fields) and PARP activation was a real important factor. From the papers I reviewed, it seems like every time PARP is activated for DNA repair, it consumes 150 NAD molecules. Is that consistent with what your understanding is?

Nichola Conlon:

I'm not 100% sure that it's that much in for the PARPs, but I know that there is another enzyme called CD38. That one definitely does consume about a hundred molecules of NAD for every cycle of its reaction. CD38 isn't a DNA repair enzyme, but it's another cell signal enzyme which is involved in sending these calcium signals throughout the cell to activate parts of our immune system. Now CD38 is perhaps the biggest NAD consumer in the body because of the fact that it is so inefficient at using NAD. Like you said, it takes a lot of NAD molecules just to have one

cycle of its reaction to set off its cell signal and cycle. It's been found that actually even if you can inhibit CD38 by just a very, very small amount, you can actually have a significant impact on NAD levels because it is so inefficient.

Nichola Conlon:

This CD38 molecule has been demonstrated to actually increase – the expression of it increases on the cell surface of our cells as we get older. This correlates really nicely with the decline that we see in NAD levels. Putting the combination of more DNA damage as we get older, which is activating the PARP DNA repair enzymes that's using NAD combined with higher levels of inflammation as we get older, which is well-known, which is activating CD38, which is also chewing up loads and loads of NAD, you can very quickly see why we end up in this situation where NAD is declining. Then just couple this with the fact that it's very well-known that our salvage pathway doesn't function as well as we get older. You can see how we're in a bit of a sticky situation as far as NAD production is concerned as we're getting into the older decades of our lives.

Dr. Joseph Mercola:

Okay. Thank you for that primer. Many people understand this and they've been exposed to this information before, but I wanted to get everyone up to speed for those who haven't. Now that we're at this point, those who have come to that understanding clearly want to make a change to improve their health. They seek to improve their NAD levels. The two most popular strategies are nutrients that you previously recommended as the precursors and those would be nicotinamide riboside and nicotinamide mononucleotide or NR and NMN. There's a lot of people taking these. You thought that there was likely a better strategy to do this. I used to take them, but when I did take them, I realized right off the bat that swallowing them was a bad idea.

Dr. Joseph Mercola:

It's kind of like swallowing bioidentical hormones. Yes. It's the real deal when you swallow it, but your liver has this tendency to want to detoxify and typically conjugates or adds in these molecules, specifically methyl groups, so it can excrete them. These don't work too well so it never really transfers into your blood the way it was supposed to. It was the main problem. But some does get through, but you think there's a better way and you were convinced from your study. Why don't you explain what you uncovered?

Nichola Conlon:

Yes. Well, when we started looking at NAD, the first thing we did was look at what evidence there was there that you could use molecules or supplements to boost NAD at that time. Everyone, as you said, was looking at enhancing NAD levels with nicotinamide riboside or nicotinamide mononucleotide, which are the precursors or the raw materials that the body uses to make NAD. But what there was definitely a lack of was any evidence that the reason that NAD was declining was because the body had a lack of availability of these precursors. In fact, still to this day, there's no evidence that our bodies have a reduced capacity to absorb these or that there's a reduced amount circulating in the plasma for the cells to use. It was actually like, well, let's take a deeper look at what is actually causing this NAD decline or the root causes of this NAD decline.

Nichola Conlon:

When we looked into this further and over the last couple of years, all of this more understanding of NAD decline has emerged. It's clearly now demonstrated that actually to restore NAD, you need to fix the root causes. You need to fix that salvage pathway. You need to increase the enzymes in that pathway that are actually declining with age so that your body can recycle NAD like it did naturally when it was younger. You also need to look at these processes that are, quite frankly, wasting NAD. You need to look at inhibitor CD38 and stopping this chronic low level inflammation that's using up all this NAD. You also need to actually look at reducing DNA damage and being more efficient in its repair so you haven't got these constant chronic activation of DNA repair, which is also using up NAD.

Nichola Conlon:

We said, "Look, let's take a multi-target strategy. Rather than just putting more raw material into the cell, let's actually look at fixing the cell." Because I always get people to think of the cell as like a factory and get people to think of, if you had this cell that's this NAD-production factory and production in the factory declined, and you knew it was because the machines were broken and the workers weren't there and the pipes were leaking, would you, as the owner of the factory, just say, "Well, just order more raw material and somehow we'll get more NAD out the end." That's exactly what I sort of compare a precursor approach to, it's completely ignoring what is actually causing the decline. That's when we started saying, "Let's look at this differently." In experiments that we've done, we've demonstrated that you can boost NAD levels in the cells without putting any precursor in. You can actually just use ingredients that inhibits CD38, activate NAMPT, and they will actually boost NAD levels without having to put any raw materials in there.

Dr. Joseph Mercola:

All right. I don't think you previously mentioned, but NAMPT is really important because that's the bottleneck, the rate-limiting step enzyme for the production of NAD. Why don't you expand on that?

Nichola Conlon:

Yes. The reason that the salvage pathway declines with age is because of this one key enzyme. NAMPT actually recycles nicotinamide and converts into NMN which then gets converted back into NAD. As you mentioned, the rate-limiting step, so the bottleneck in that process is NAMPT. Lo and behold, that is the key enzyme that declines as we get older. There've been studies that have been done and they've demonstrated that you get around to 50% decrease in this enzyme between the ages of 45 and 60. So that's a significant decline considering how important this is in new NAD production. The decline in the levels of this enzyme again correlate with the decline in NAD that we experience. Many diseases and issues that are associated with NAD decline are actually because of a reduction in this enzyme. So it's absolutely critical to try and improve the activation and improve the actual expression of this enzyme in the body to contribute to enhance NAD because it worked brilliantly to give us high NAD levels when we were younger, so why not restore it back to that?

Dr. Joseph Mercola:

Yes, indeed. Focusing on the NAMPT, you've got a 50% reduction over a 15-year period from 45% to 60%, but it's worse than that because you've got the CD38 levels increasing and PARP activation going along with, so that synergistically contributes to the decline. I'm wondering, you mentioned the decrease in NAMPT, but what is the decrease in NAD, the functional thing that we are experiencing in society? What are the typical levels you find at a 40-year old, maybe 20-, 40-, 60-, and 80-year old? Or around there, whatever numbers you have access to, because I think that will help people understand. Because my understanding is that you get 90%, 95% reduction as you age in NAD youthful level.

Nichola Conlon:

I think that the best way to sort of visualize it, because sometimes numbers don't really mean much to people, but it's looking at it more in the fact that it literally is declining from the day you're born. Within the first 20 years of your life, you've lost 50%. By age 20, 50% is gone. Then between age 20 and 40, you've lost another 50% of that 50% that you already had. Then it keeps going down. If you look at the curve, it's an exponential curve so it's starting very, very steep and you know, like that. Looking in elderly people's tissues, they really, really don't have very much left at all. Again, I just find that incredibly frightening because it's so important.

Dr. Joseph Mercola:

Absolutely. I think this is one of the reasons why people, elderly people are so susceptible to COVID. That no one, no, I've never seen anyone or study recommend this as a comorbidity, but it's just, it's there. It's probably the primary one.

Nichola Conlon:

Have you seen, there is a paper that-

Dr. Joseph Mercola:

Oh, okay. I did not see it. Okay. Tell me the paper.

Nichola Conlon:

Yeah. Actually, there's a couple of reviews in this one paper. It's been demonstrated that infection of cells with the COVID virus, basically it actually causes a huge depletion in NAD levels. It does this by really over-activating the PARPs.

Dr. Joseph Mercola:

That was the PARP?

Nichola Conlon:

Yeah, because although you've got PARP1 that's involved in DNA repair, some of the other PARP, and it's a big family of proteins, they're actually involved in inflammatory responses. As part of their activation process, they obviously need NAD to do that. So there's a huge depletion in NAD levels in infected cells. The running theory is that if we're older or sicker and we have lower levels of NAD to begin with, when we get infected, we're already at a lower starting point. As opposed to someone that's younger and healthy and has high NAD, means that when they get

infected, they've already got quite a good level to begin with. So even when they get that depletion, they can actually get by because they had adequate supplies to begin with.

Nichola Conlon:

The other really interesting thing from this research is that what they've looked at, what the cell does in response to the virus to try and mitigate this, and all of the genes that the cell regulates to try and protect itself are all to do with NAD salvage. It actually increases the expression of NAMPT so the body is going to try and increase NAMPT to try and protect itself because it knows that's the best way to produce its NAD and rectify the problem. Again, that just emphasizes the importance of that pathway in the body, even the body is trying to rescue it and switch it back on in its time of need. That's incredibly, you know, it makes perfect sense what you say about older people and the comorbidities.

Dr. Joseph Mercola:

Well, the reason I wanted to get the numbers out there was because – we'll get into this in a bit and with respect to what these interventions do in producing and increasing NAD levels. But if you don't know what the story is, as you just so eloquently explained, that a 40% increase may seem like a lot, but the reality is you got to get like a thousand-percent increase before it's going to be clinically significant because it's almost irrelevant to double or even triple sometimes when the level is so darn low to begin with.

Nichola Conlon:

Yes, exactly this. I think this is one of the issues why – in the preclinical studies, so in the studies involving like mice and cells, et cetera, it was found that the benefits of NAD restoration in terms of what the clinical outcome was, so in terms of actually reversing disease and actually really improving healthspan were great. There's a huge amount of evidence to show it can reverse metabolic disease, insulin resistance, obesity, it can regenerate organs. It can protect nerve damage. It has function in Alzheimer's. Loads of preclinical data that show that NAD restoration is [a] very, very good thing to do. However, the studies — I think there's been about 10 studies to date in humans using NR — haven't been as brilliant, shall we say, the results. They haven't been able to replicate many of the actual benefits that were shown in preclinical models.

Nichola Conlon:

I think this really is because NR and other precursors simply aren't really addressing the root causes of NAD decline. So as a result, they're only really reporting about 40% to 60% increase in NAD levels. The question is, like you say, is that enough to actually translate to some health benefit that you can perceive and feel or measure? I think as we move forward, actually looking at strategies which not only is a precursor but use a precursor alongside CD38 inhibitor and NAMPT activator, and things looking at reducing DNA damage, things like that, and use more of a whole systems approach. I think that's when we'll actually start seeing some real, you know, translate into some real clinical benefit in these actual human studies, because at the end of the day, we want it to work in humans.

Dr. Joseph Mercola:

Yeah. Many people may have missed what you said, but what you didn't say, you talked about a CD38 inhibitor but you didn't talk about a PARP inhibitor. PARP inhibitors actually exist. They're used in treating many cancers, but you did not mention that. You mentioned minimizing PARP activation, which I think is 100% correct. Why don't you explain why we don't want to inhibit PARP? And then maybe some of the consequences of inhibiting CD38, because I'm not, I mean, it's not as dangerous as inhibiting PARP but we can discuss that too.

Nichola Conlon:

Yeah. I think this goes back to this idea of the body is very, very complex and we can't just single out very specific enzymes or targets in the body because there's always a consequence of what you do on their whole biological network. So yeah, PARP is a DNA repair enzyme. DNA repair, despite it using a lot of NAD is actually critical. Every day, our cells, each cell is being exposed to tens of thousands of pieces of DNA damage. If we let that happen and we didn't have these DNA repair enzymes, we would get cancer. This is absolutely not something we want to inhibit. Now you mentioned there are PARP inhibitors, and these are actually used as a cancer treatment.

Nichola Conlon:

The idea behind this is that because cancer cells are actually replicating really quickly, they end up accumulating a lot of DNA damage. What the cancer cells actually do is they upregulate PARP so that they can keep on top of this DNA damage and survive. What these drugs are designed to do is to specifically target cancer cells, knock down DNA repair, so they accumulate too much damage where it kills and wipes out the cancer cell. But as with any cancer treatment, you've got the problem that it also affects healthy cells as well.

Dr. Joseph Mercola:

It's a race. Kill the cancer cells before your cells.

Nichola Conlon:

Yeah. It's certainly not the type of treatment you want to be taking when you're healthy and trying to improve your healthspan. I think you've got to, again, look at a bit more of a holistic approach and that, “Well, why is all my levels of DNA damage increasing as we're getting older?” What can I actually do to reduce the levels of DNA damage higher up in the chain? If you want to put it that way. CD38, that's a perfect example of, yes, you can inhibit CD38 and it doesn't have as big consequence as inhibiting a PARP. But at the end of the day, CD38 still does have a function in increasing immune activation, which again is critically important. I think the thing with inhibiting CD38 is you don't need to inhibit it that much to actually have an effect because of the amount of NAD it uses in one cycle. However, CD38 is known to be increased unnecessarily with age because of this chronic low-level inflammation that we have, this “inflammaging” that it's sometimes referred to as. If you can find a way to actually get in control your inflammation or your inflammatory levels in the body, then you are ultimately going to be helping your NAD levels.

Dr. Joseph Mercola:

Okay, great. That's a good background to help understand the strategy that you actually formulate and put together to refine a product that you actually brought to market and is available. Why don't you discuss that? And then we can go about ways that we can augment it. Because I don't want people to believe this is a magic bullet, because we're going to talk about other strategy you can use in conjunction with this, which will synergistically magnify it.

Nichola Conlon:

Yeah. Like I said, when we started looking at ways to boost NAD more effectively, we didn't want to just take a precursor approach so we developed a product, Nuchido TIME+, which was designed to use a whole-systems approach to NAD restoration and actually address each of those root causes that we have actually been discussing today. Not only does it have a precursor in there, but it also has a combination of ingredients in which we have demonstrated address the underlying root causes. We've got ingredients in there that actually boost NAMPT. We have demonstrated in our clinical studies that you can literally see the expression of NAMPT going from fairly detectable in the people cells to actually increasing over a period of 16 days so we know that we are improving that salvage pathway. The types of ingredients we-

Dr. Joseph Mercola:

Excuse me for a moment. Is it easier to measure NAMPT than it is NAD?

Nichola Conlon:

Yes, absolutely. The way you measure NAMPT, it's an enzyme, you can get antibodies, which will selectively attach to it. We use something called a western blot, which basically measures the amount of protein, the enzymatic protein that is available in the cell. It shows as a dark band. Basically, the darker the band, the more expression. On baseline samples, it's literally blank like there is no band because there's so little NAMPT, it's not picked up. As you go out through 16 days of supplementation, you can literally see it getting stronger and stronger throughout the time taking Nuchido TIME+. We were really excited about that because for us, that's addressing a major root cause of NAD decline. The types of ingredients that we used to actually boost that one you'll be very familiar with is quercetin.

Nichola Conlon:

We actually use rutin, which has a combination of troxerutin and quercetin in there which all have been demonstrated to increase the levels of NAMPT. We also use another ingredient called alpha lipoic acid. Now that actually increases NAMPT a little more indirectly. The way that works is it increases the activation of another energy sensor in the body called AMPK (AMP-activated protein kinase). AMPK is like a real sensor of any energy stress. When there's an energy stress in the body, AMPK goes up and it basically activates NAMPT so that it can increase NAD levels in the cells. That's an activator that we've contained within then. The other thing is we have the precursor in there so that the cell does have the availability of the raw material to make NAD.

Dr. Joseph Mercola:

What are you using for a precursor? Niacinamide?

Nichola Conlon:

We use nicotinamide. In our studies, we tested NR against nicotinamide. We did not find that NR worked any better than just using nicotinamide. As far as we're concerned, nicotinamide is the salvage pathway's preferred source of actual precursor to recycle to produce NAD. Also, it is bioavailable. It's got great bioavailability. It actually freely diffuses through cell membranes, whereas NR and NMN actually need to be transported through a cell membrane which is a barrier to entry.

Dr. Joseph Mercola:

And more importantly, it's not patented and it's cheap.

Nichola Conlon:

Exactly.

Dr. Joseph Mercola:

Fortunately, free. But in higher doses, it clearly has been shown to inhibit sirtuins. So I think you use a low level like 25, 50 milligrams?

Nichola Conlon:

Yeah. The thing with that is this is something that is widely talked about, about nicotinamide being a sirtuin inhibitor. Yes. If you work in absolute ton of nicotinamide onto some cells that are not in a human body, it does inhibit sirtuins. However, in the body, the body likes to maintain homeostasis. The levels that are used in these studies will never be reached inside a normal cell because the cell has pathways that get rid of nicotinamide before it ever becomes an inhibitor in the cell. That's one thing just to point out.

Dr. Joseph Mercola:

When you look at the studies that show this, they never really give a dosage. I've never seen any study that show dosage. Did you have any insights on what that dosage is? Like [1] gram, 2 grams, 5 grams, 10 grams, 20 grams before it's [crosstalk 00:52:21]. It just never happens.

Nichola Conlon:

Yeah. It wouldn't be, so when you're looking at, the translation is quite difficult because when you look in all of the studies being done in cells, so in vitro, so in Petri dishes, and when you're looking at that, you would say – I can't remember off the top of my head what it is, but you might say, "Oh, we'll use it at a 1 millimolar dose, or we'll use it at a 500 micromolar dose and that's what you'd put it on." Now obviously you can back-calculate what that would have to be orally, accounting for everything that's broken down, everything that's lost in the gut, everything that's metabolized in the liver to what that actually gets into the cell. You would never be anywhere near those levels that are actually just put pure onto the cell.

Nichola Conlon:

This leads me to one of the other ingredients that we've actually used in the product which is an NNMT (nicotinamide N-Methyltransferase) inhibitor. Now this is an enzyme that we haven't

actually even spoke about. If any of your listeners are familiar with this idea that when you take precursors, that you may suffer from methyl donor depletion. I don't know if that's something you are familiar with.

Dr. Mercola:

Sure, sure.

Nichola Conlon:

But basically a lot of people report that when they take precursors such as NR, they have to take something like a betaine or trimethylglycine to replenish methyl donors. The reason for this or the sort of science, a bit of chemistry behind it is that as your cells get older and they don't have that recycling capacity because their salvage pathway and that NAMPT enzyme has declined.

Nichola Conlon:

What happens is when NAD is used up in DNA repair or whatever other processes that it's being used in and it gets broken down in nicotinamide, the cell does not like nicotinamide building up, which as we've just said, because it could inhibit the sirtuins if it gets too high. What happens is it actually increases the expression of this other enzyme which is NNMT. What this enzyme does is it adds a little methyl group onto nicotinamide. This is called methylation and it's like a tagging process. When the methyl and nicotinamide becomes tagged with a methyl group, that signals for its excretion out of the cell so that it never gets into the state where it could be inhibiting anything that it shouldn't be. Because cells don't like things building up, they like to maintain homeostasis.

Nichola Conlon:

You see, in older cells that don't have salvage pathway working correctly that they increase the expression of NNMT. Now this makes the whole situation worse because the cell has become so dysregulated that it's now trying to chuck out all this useful nicotinamide that it could be recycling and instead it's excreting it because it doesn't have the capacity to recycle it. This actually leads to methyl donor depletion because all of the methyl groups which are important for things like epigenetics and switching genes on and off are actually being targeted towards getting rid of this excess nicotinamide. Now, what we've done is we demonstrated that actually if you can fix a salvage pathway, you don't need to have this, this other methylation process switched on because there's no need for it anymore. You can actually increase NAD a bit more by inhibiting that enzyme, which means that all of that useful nicotinamide, rather than getting excreted is going round and round in the salvage pathway. The way we inhibit that-

Dr. Joseph Mercola:

Brilliant.

Nichola Conlon:

Yeah. The way we inhibit that is with something called EGCG (epigallocatechin gallate), which is a compound that's really powerful found in green tea and that's an inhibitor of that enzyme.

That is what we would describe as a whole-systems approach. It's targeting every little bit of that NAD system [inaudible 00:56:02] that has gone wrong rather than ignoring it.

Dr. Joseph Mercola:

It's interesting because the ECGC also activates FOXO3, which I want to talk about in a bit. So you get two for the price of one. So that is good. You mentioned the methylation and that is an issue more so when people take NAD+ intravenously, which is pretty pricey. Typically, hundreds of dollars, if not, a thousand dollars for an infusion and usually taking over hours and hours. I am sure you've been asked this question before, but why don't you give us your perspective on that pathway? Because it's historically been used and promoted for people with drug dependencies or alcoholism. It seems to be worked quite effectively, but doesn't mean it's the only way to achieve that. I'm sure you have some views on it.

Nichola Conlon:

Yes. IV NAD is an interesting one. It's something where there is a lot of anecdotal evidence of people saying that it works for various different things. However, the evidence, the published evidence is actually very thin. There's not much out there. One of the arguments against IV NAD is that it doesn't, NAD is a big molecule and it struggles to get into the majority of cells, which as far as I can see from the literature at the moment is still an issue. However, there are some cells that NAD does definitely get into, and these are the neuronal cells. They have Cx43 channels, which allow NAD to pass in. It could be that some of the beneficial effects that people are feeling are because it's actually getting into the nervous system and into the neuron. Especially when you're thinking of things like addiction, et cetera, that could be the mechanism of action there.

Nichola Conlon:

But one of the things that I always talk about is no matter how you are planning to boost your NAD levels, whether that be take NR, take NMN, do an IV infusion. If you don't have an effectively functioning salvage pathway, it's a waste of time, because what it means is say, take the IV example. You are paying a lot of money to have this lovely, pristine NAD put into your cells. It gets its first pass so it gets used by the repair proteins, et cetera. It gets broken down into nicotinamide. If you don't have that salvage pathway working, it's going to get excreted. Whereas if you had the salvage pathway working, it could actually get recycled and used again and recycled and used again so you would get a lot more longevity, pardon the pun, out of your NAD infusion or out of your NAD supplement if you can actually fix that salvage pathway.

Dr. Joseph Mercola:

Yeah. I want to put this into a different context too and the amount of NAD your body needs per day. It's probably a few grams. You can tell us what that is. But from my memory of it, it's like upwards of 99% of that gets recycled through the salvage pathway, 99%. If your NAMPT is inhibited or impaired in some way or form, that's going to radically impair your body's ability to maintain healthy levels.

Nichola Conlon:

Yeah. It's absolutely fundamental to it. It's not surprising that a lot of diseases that are associated with low NAD are actually due to reduced NAMPT levels.

Dr. Joseph Mercola:

Yeah. That's what you focused on. I think you've found a good thing, found a good approach to do this. Why don't you share some of the data that you've accumulated through your studies and using a validated way to accurately determine what the true NAD levels are? Because again, that is enormously challenging to do.

Nichola Conlon:

The initial pilot studies that we did, the benefits of having actual, using actually supplement molecules that already have good safety profiles. It meant we could go straight into humans, which again is where we want to be measuring the beneficial effects. Our pilot study, we took two human volunteers. We actually did quite a comprehensive study where we hooked them up to a cannula. We were actually taking blood samples every two hours to measure really robustly what was happening to the NAD levels over the time of taking the supplement. This was for a period of 16 days. We found that using this multi targeted approach of really addressing the root causes of NAD decline with multiple different ingredients, we could actually boost NAD levels by an average of 242% over the period of 16 days, which is, you know, it's significantly more than the 40 to 60% that's being demonstrated with precursors.

Nichola Conlon:

As I mentioned previously, we demonstrated that this formulation was indeed boosting NAMPT levels. The other thing we measured were activity of the sirtuin enzymes. The sirtuins are almost the key effectors of the benefits of NAD because they use NAD to switch on and off lots of genes involved in longevity. Again, we demonstrated that. Prior to using the supplement, they were effectively switched off, and using the supplement increased their activity and expression of these enzymes. We've since actually, well, this was long before COVID, started a much larger study of 28 people, which is a double-blind, placebo-controlled, crossover study. Taking an element out of that rigorous testing that I've been brought up with in drug development. That is all tied up and all finished now. We're hoping to be able to publish the results of that very soon. So that's exciting for us.

Dr. Joseph Mercola:

Have you unblinded it yet? Do you have any idea what the result is?

Nichola Conlon:

It's not unblinded yet.

Dr. Joseph Mercola:

Okay. All right. Well, look forward to seeing those results. So that's great. That's really good. I'd like to get back to adding the synergistic lifestyle strategies that I mentioned that could also activate NAMPT. We had discussed this offline before. A strategy that I'm very, very fond and passionate about which is exercise, because that has been a well-documented strategy to also increase NAMPT. Not only that, but, well, I think fasting will do it too. Those are two well-

documented strategies that will also increase the AMPK. Are those associated, moves in the same direction? So when AMPK is increased, NAMPT is activated? Or is there a causal relationship there?

Nichola Conlon:

Exactly that, yeah. The energy stress basically upregulates the activity of AMPK. Then AMPK then goes and activates NAMPT, and then that increases NAD.

Dr. Joseph Mercola:

So it's causal? Yeah.

Nichola Conlon:

Yup.

Dr. Joseph Mercola:

If there's anything you could do, increase AMPK. My two favorite strategies and ones I use almost every day are the exercise and the time-restricted eating, which is a form of intermittent fasting. Perhaps you can comment on those. And if you're aware of any of the literature that looks at NAD increases directly or NAMPT activation, which would be easier to measure, probably better study at this point.

Nichola Conlon:

Yeah. No, it is a lot easier to measure. Like I said before, it is well-correlated with NAD decline or increase depending on which way the enzyme goes. So yeah, there have been studies, especially with exercise that have demonstrated that. I think it was about three weeks of resistance training. So relatively short period of time and amount of training resulted in an increase in NAMPT levels, which actually resulted in turn I think it was about, I want to say 127% increase in NAD levels. Again, that's way better than NR.

Dr. Joseph Mercola:

Yeah. Not quite as-

Nichola Conlon:

Or precursor alone.

Dr. Joseph Mercola:

Yeah. Not quite as good as the ones you said.

Nichola Conlon:

Not quite as good.

Dr. Joseph Mercola:

Yeah. The data you were reporting earlier, that was for the 16-day trial with two people. Right?

Nichola Conlon:

Yeah.

Dr. Joseph Mercola:

Over 16 days. And the two hours, were they hooked up to a catheter doing blood measuring it every two hours for 16 days?

Nichola Conlon:

Yeah. We just put a cannula in the back of the hand and then drew blood samples off every two hours for 12 hours throughout the day on the testing day.

Dr. Joseph Mercola:

Wow. Perseverance for those.

Nichola Conlon:

Yeah. It was. They were very good to have done that. There's no way we would've been able to do that with a bigger group of people. They were a month's worth of supplement and measuring their NAD levels once a week.

Dr. Joseph Mercola:

Oh, once a week. Big difference, big difference. But I feel and see it less costly and easier to do.

Nichola Conlon:

Yeah.

Dr. Joseph Mercola:

All right. Well, that's good. Part of the reason I've been passionate about NAD. Well, actually, let me just trail back to the PARP. My guess on, my best strategy for inhibiting PARP is one that's not very popular but I think really important. And one that we didn't have to worry about last century for the most part, which was limiting your exposure to EMFs. Because I'm convinced that that really activates PARP quite extraordinarily, especially in almost anyone who's in an urban area. Unless you're taking hyper-diligent actions to limit their exposure, which is beyond pervasive. Cell phones and Wi-Fi routers are the two most common contributors. That's my strategy, because you know, I think you're absolutely on target. You've got to limit PARP activation and CD38 inhibit in some way, if you can, or limit it. Do you have any other strategies to inactivate PARP or limit its activation?

Nichola Conlon:

Again, I think as boring as it sounds, it is the lifestyle side of it. Because if you can limit the amount of DNA damage that's happening, ultimately PARP naturally will not be activated as much. Like with the EMFs, but you know, other things like UV exposure and all the usual things that were told.

Dr. Joseph Mercola:

Well, like CAT (computed tomography) scans.

Nichola Conlon:

Yeah. X-ray, anything like that is causing DNA damage.

Dr. Joseph Mercola:

Yeah. One of my other passions though is one that you're involved with, is biogerontology or longevity work. That's one of the reasons I was so interested in NAD, but another biomolecule that's really important and I'm not sure which one is more important. It's hard to tell because I don't think there's been any head to head studies, but it's FOXO3 or FOXO3a. That is another incredible biomolecule and it's been associated. I think the study showed that interestingly that your body has an ability to upregulate this gene. There's many poly or SNPs (single-nucleotide polymorphisms) or polymorphisms that have that. It seems that in populations that have a higher expression of FOXO3, they live, they have a 2.7 times, 270% increased likelihood of living 200. It's associated pretty strongly with being a centenarian. It's a master regulator. It also activates DNA repair. Now, I'm not sure exactly how it does it, but it does it. It increases antioxidant genes, improves autophagy, and has impacts on the immune system and stem cells. I'm wondering if you could comment, as a molecular biologist, the connection or the relationship between FOXO3 and NAD.

Nichola Conlon:

Yeah. FOXO3, like you say is almost like one of these wonder molecules in the body that is so associated with longevity as is NAD. The kind of difference between them is the way they work. You could probably describe that NAD is more of a signaling molecule because its levels and its ratios basically turn on and off other things. Whereas FOXO3 is what you would call a transcription factor. What [a] transcription factor does is it binds to specific areas on your DNA, and then it initiates the transcription or these genes being turned into proteins that then actually go and have an effect on the body. The reason that FOXO3 is thought to be so influential in longevity is that its location and its proximity to particular genes that are involved in longevity that it can activate when it's switched on.

Nichola Conlon:

You mentioned it's like a master regulator. What is a master regulator is basically our response to stress. It's so critical in the response to multiple different types of stress. Everything from energy stress to like hypoxic stress, or lack of oxygen, lack of nutrients, DNA damage. Any of those things, ultimately, can lead to the activation of FOXO3 which then goes off and sets off the transcription of genes that are designed to alleviate the stress or protect from the stress, or just basically so that the cell can survive through whatever period of stress it is by activating appropriate genes to do this.

Dr. Joseph Mercola:

Okay. With NAD, it's a fuel for PARP. My understanding of the way PARP works is that, well, its technical name is Poly ADP Ribose Polymerase. It takes the ADP from the NAD, and this makes this matrix of ADP molecules which somehow, and I don't really understand it, but it forms this matrix which facilitates the actual DNA repair enzyme. Because I don't think the

PARP actually repairs it. It sets a substrate for other enzymes to come in and do their work. Is that right?

Nichola Conlon:

Yeah, exactly that. It's called power relation reaction. It's almost like tagging, this idea of almost tagging where the damage is so it's like alerting the rest of the cell that this is where the damage actually is occurring and it needs to be fixed. Yeah, that's exactly what happens.

Dr. Joseph Mercola:

The FOXO3 is a transcription factor, actually turns down the enzymes that the PARP would set up to actually work?

Nichola Conlon:

Yes. FOXO3 is actually involved in sort of like there's a few different types of DNA repair enzymes so there's not just PARP. There's multiple different ones. There's ones called XRCC1 which repairs a different type of DNA damage. Sometimes you get what are called single-strand breaks or double-strand breaks or where the DNA is being swapped around and it needs to be repaired in a different way. What FOXO3 actually does is it almost activates proteins that are like the DNA damage response proteins. They're like alerting the cell to basically coordinate this response of all different proteins and all different enzymes all coming in and having their own little role in fixing the DNA repair. Whether that's literally fixing it or providing this scaffolding so that the DNA repair enzyme can lock on and then do the repair effectively.

Nichola Conlon:

When you're looking at DNA repair, FOXO3 is the main links that it's almost coordinating, helping to coordinate this response. But also, it does a lot in terms of preventing the damage in the first place. A lot of damage from DNA damage can be caused by oxidative stress in the cell through one thing or another. There's been lots of links between FOXO3 and its ability to activate lots of factors that actually limit oxidative stress so that you don't get that DNA damage in the first place. Just going back to what you asked before as I realized I didn't mention it, the sort of link between FOXO3 and NAD is that as well as FOXO3 being directly activated through various types of stress, it can also be activated indirectly via NAD. What happens is say you have energetic stress, NAD goes up, NAD activates SIRT1. One of SIRT1's downstream targets is FOXO3. NAD activates FOXO3.

Dr. Joseph Mercola:

Terrific. Terrific. It may seem like an intellectual curiosity but it actually ties in really well. Because if your goal is longevity, and I think my goal is just not to increase NAD, we want to increase healthspan as you mentioned earlier. It would seem wise to integrate the lifestyle interventions. Interestingly, fascinatingly, the body is so wonderfully put together that if you target activating FOXO3, you will increase NAMPT because they're the same darn strategies, same darn strategies, identical. Whatever you do to increase FOXO3 increases NAMPT. What are those? Exercise, as you mentioned. Heat stress, sauna. That's why I do sauna three or four times every week. I used to do it every day but that was too much. Four times a week typically. In addition to that, being in cyclical ketosis does it, that will increase FOXO3. As I mentioned

earlier, the ECGC, which is in your supplement. All those things work. It's totally compatible and synergistic and they work to improve the body in all these different variety of ways.

Nichola Conlon:

Yeah. And you know, what I always like to say is we're coming back to this now where we're like it's all linked and it is.

Dr. Joseph Mercola:

Yeah. Absolutely.

Nichola Conlon:

Everything's so complex. If there's one thing for improving longevity, I mean, there isn't. The whole point is there isn't just one thing. It's a combination of things that need to be done to have the best chance of improving longevity, because aging is a huge, complicated mess of all sorts of things that are going on. Actually, the best interventions that we have are the things like calorie restriction and exercise because they are like right at the top of this pyramid of complexity that is biology. They're the things that are actually hitting the top layer and then that filters down to getting to the bottom where there's FOXO3 or SIRT or an individual protein. But really, you've got to go in nearer the top to have those maximal effects.

Dr. Joseph Mercola:

We didn't talk about senescent cells but many people are familiar with them. Those are cells that stop replicating and produce these inflammatory molecules that really contaminate the cells around them and essentially cause them to become senescent. Ideally, you want to have a process activated to remove those because I think that decreases NAD levels, too, these senescent cells.

Nichola Conlon:

Yep. It does.

Dr. Joseph Mercola:

Yeah. My strategy is activate autophagy, which FOXO3 does. What I've done, I'd like to get your feedback on this, sort of integrating everything I've learned into a lifestyle strategy. I do the intermittent fasting for 16 to 18 hours typically. So I stop eating at three or four o'clock and then I'll workout in the morning at seven, about six or seven, seven o'clock in the morning. And so I'm exercising, fasting. And then right after the exercise, I jump into the sauna. So you're getting the exercise, you're getting the ketosis, and you're doing it in a fasted state so you're reactivating even more autophagy. I just think it's just a winner to do that because I mean, exercise is good. The studies you quoted with the increase didn't really look at the timing of the exercises. You know, timing is critical, but I think if you do it while you're fasting, you're going to get even more benefits because it's just going to activate AMPK even higher.

Nichola Conlon:

Yeah. And all of the times that these longevity proteins and these proteins that are absolutely critical to healthspan are upregulated is in response to cellular stress. You look at everything. It's

always it's counterintuitive because you think, “Well, why would stress be a good thing on the body?” But it's this idea of hormesis that our body is actually reacting positively to the stress to be able to overcome it, make our bodies and our cells more resilient so that if we encounter the stress again, we're almost prepared for it. One of the things we talk about with our supplement is actually people say, “When do you want to take it?” We say, “Well, if you're fasting, finish your fast. Then take it because your fast will have activated AMPK.” As soon as you start eating, as soon as any food goes into your body, it's going to downregulate AMPK. However, in the supplement, you've got AMPK activators. It's kind of mitigating that decrease that you are going to get and trying to just keep it up as long as possible.

Dr. Joseph Mercola:

Yeah. So there's no real reason or benefit to take it when you're fasting because you're already-

Nichola Conlon:

No.

Dr. Joseph Mercola:

Yeah.

Nichola Conlon:

We would say just after to try and prolong the effects of the fast, even when you're not actually fasting anymore.

Dr. Joseph Mercola:

That's a good strategy. The name of your supplement again is?

Nichola Conlon:

It's Nuchido TIME+.

Dr. Joseph Mercola:

Nuchido. Nuchido TIME+. That's available pretty much anywhere, or?

Nichola Conlon:

Yeah, it's available on our website, www.Nuchido.com. I'm sure we can make a code available to your listeners if they wanted to try it.

Dr. Joseph Mercola:

Okay. Well, it seems like a good strategy, especially if you integrate it with the lifestyle strategies. The challenge is, as you mentioned earlier, is just unless you've got a relationship and you live not too far from a research laboratory that measures this, you're not going to know. You're just going to have to sort of trust that it's going to work. But I guess maybe you could share some of the anecdotal observations for people who have taken it but not done the testing to document either the increases of NAMPT or NAD.

Nichola Conlon:

Yeah. The main, we have top three things that people always report back on. The first is energy levels, which is not surprising whatsoever given the key role that NAD has in the body of producing our energy. People from the [inaudible 01:19:57] describe it using the same sort of language. It's not of like an energy where they feel like wired and like caffeined up. It's more they say, you know, "We just had a lot more enthusiasm about the day, about getting on with things rather than procrastinating and not really having the drive to get on." Which is funny because the very first two people that did that study, that was what they said. They said, we've got more get up and go. And when we did a study with them, when we give them a placebo and they didn't know, they said, "This isn't the same stuff because we can feel it."

Dr. Joseph Mercola:

[inaudible 01:20:33].

Nichola Conlon:

Yeah. They were right. The other thing is not just like physical energy but mental clarity and focus. We get a lot of reports of people, especially people who've been suffering from brain fog. A lot of perimenopausal and menopausal women, it's very big with where they'll say, we didn't realize how much brain fog we had till it was gone. That actual mental focus and clarity and just not having that fuzzy brain all the time. The final thing, which actually we haven't spoke about today is sleep. NAD is actually circadian and cyclical which is why when we did our first trial, we measured every two hours to check that we were measuring real increases in NAD and not just a natural fluctuation throughout the day because it does go up and down.

Nichola Conlon:

As you get older, the NAD levels decline, the peaks and troughs of NAD actually hamper your circadian rhythm, which means your sleep quality isn't as good. And yeah, a lot of people report back to say that actually their sleep has improved dramatically. A lot of our customers track with things like an Oura Ring or various other watches and monitors for their sleep. They've actually got some data to show to say, "Look, you can see the difference which is always nice." They're the three main things. The other thing which we always get reported is skin, hair and nails, which is cliché as it sounds [inaudible 01:22:10]. The amount of people, especially men actually who report this is really fascinating. But again, if you've got the cells running well and the fundamental critical parts of the body, that's when you start noticing the more things with your hair and the less important parts of the body as far as your physiology is concerned.

Dr. Joseph Mercola:

Well, I've got a new indication for you.

Nichola Conlon:

Okay.

Dr. Joseph Mercola:

Long-haul COVID.

Nichola Conlon:

Yes. Well, this is something we are really interested in, because of the papers and the studies that have come out.

Dr. Joseph Mercola:

Because it makes perfect sense. I mean, it's a real problem. I think we're going to see a lot more of it. Not only people with the infection, but also through the getting of the jab. So their mitochondria become damaged because they've been exposed to the spike protein. It crosses. It's a toxin, it's a poison, its spike protein. It's not something that should be given to anyone. As a result, they grew these complications, but you need strategies to mitigate it, remediate it actually. This could be a useful one to increase NAMPT levels and secondarily, NAD.

Nichola Conlon:

Yeah. I think it's going to be a really exciting area of research to follow. I'm sure there'll definitely be some more studies coming out on the links, you know, the links between NAD and COVID. I would be very surprised if we don't see anything within the next couple of months. That's new.

Dr. Joseph Mercola:

Well, great. This has been delightful. Do you have anything else you'd like to add?

Nichola Conlon:

No, it's a really good chat. I love getting into the complexity of the science, because I think it is, you know, although not everyone is a scientist, I think it's really important to understand why we're doing the things that we're doing and actually what they're doing within our bodies to have the beneficial health outcomes that we're looking to achieve.

Dr. Joseph Mercola:

Yeah. I really want to thank you for taking the time to help enlighten our audience about these really important strategies that can have a powerful influence on your life, because I mean, you highlighted very well the radical, absolutely radical and shocking, surprising, exponential decline that we have in NAD levels from early, early on. It really makes a lot of sense. I think the sciences help us understand some really powerful strategies and interventions we can do to address this, and secondarily, give your body what the raw materials it needs. It knows how to stay healthy. You just got to activate the factors that it wants. Once you understand that, it's a pretty simple strategy. Your supplement can be clearly one, but the exercise, the fasting, the ketosis, these are all powerful interventions that don't cost very much at all that can have radical improvements and add many, many years of not only just years but years of vitality and resilience where you can really enjoy your life.

Nichola Conlon:

Yeah, no, I am a huge advocate of all things, you know, a multiple strategy. It's got to be a multi targeted approach, whether that's in the cell or with our regimes that we're following. You've got

to be doing multiple different things if you really want to have a good go at it, it's very, very important.

Dr. Joseph Mercola:

All right. Well, thank you so much. I really appreciate your time and all the work you're doing. It's been great.

Nichola Conlon:

No, thank you so much. Thank you. That was really good.