#20 – NAD, Longevity, and the Line Between Promise and Proof Transcript

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Introduction to NAD and Longevity Medicine

[music] Welcome to the Trip Lab, kitchen table conversations about integrative medicine and psychedelics. [music] I'm your host and attending physician, Dr. Mariela Wood.

Hi everyone, welcome back. Today we're going to talk about a topic that has become almost unavoidable in wellness, longevity clinics, and supplement conversations right now, and that is NAD and longevity medicine. If you've spent any time in this space, whether on social media or outside, you've probably heard NAD described as a kind of master molecule for aging. Something that declines as we get older and if restored might improve energy, slow aging, or even extend lifespan. And it shows up in supplements, IV clinics, lab testing, and a lot of very confident claims. And like many things in medicine that sound compelling, there is real biology underneath it. But there's also a lot of oversimplification layered on top. So in this episode, we're going to break all of that down. We're going to talk about what NAD actually is and why it's getting so much attention. Then I want to zoom out a bit and use NAD as an entry point into the broader field of longevity medicine and what it's trying to do, why it's very exciting, why it's also prone to hype, especially when human outcome data is still emerging. From there, we'll go even deeper. We'll look at what NAD does in the body, why levels may decline with age, inflammation, and lifestyle factors, and what that decline actually represents. We'll also talk about testing, whether or not NAD can be measured, whether those tests are validated, and what they do and don't tell us clinically. And finally, of course, we'll talk about supplementation, what the data supports, what actually is still theoretical, what's definitely overhyped, and why NAD supplementation might still be reasonable in certain contexts, even though we don't yet have the kind of outcome data that would justify universal recommendations.

What Longevity Medicine Is Trying to Solve

So, spoiler alert, this episode is not about declaring NAD a miracle or dismissing it. It's about drawing a line between promise and proof and using NAD as a case study for how longevity medicine is evolving in real time. So let's just get into it. To really understand NAD, we first have to talk about longevity medicine and how aging is being studied.

So big picture, longevity medicine shifts the focus of healthcare earlier. So away from reacting to disease once it's established and toward understanding the biological processes that drive aging and age related decline in the first place. So the goal isn't simply to live longer lifespan but to extend health span the number of years we spend functioning well with resilience mobility cognitive clarity and metabolic flexibility. So this is part of what makes the field so compelling. Longevity medicine draws from systems biology, metabolism, immunology, neuroscience and a whole lot more to ask a different set of questions than our traditional medicine has historically asked. So instead of waiting for diabetes or cardiovascular disease or neurodeeneration to happen, it asks what is happening now at the cellular level and molecular level that could lead to disease or signs of aging and whether or not those processes are actually modifiable. One of the most influential frameworks to come out of this research is the concept of the hallmarks of aging. So these are shared biological processes that tend to change as we age and are thought to contribute to both the visible features of aging and to many chronic diseases. So some notable examples include mitochondrial dysfunction, deregulated nutrient sensing, impaired autoagi, epigenetic alterations, tieumir attrition, chronic inflammation, and stem cell exhaustion.

We could easily do an entire episode breaking those down in more detail, and maybe we will. But the brief point here is that aging isn't viewed as one single process. It's understood now as a network of interconnected biological changes. And this actually is where NAD enters the conversation. NAD plays a role in several of these hallmarks of aging. Mitochondrial energy production, DNA repair pathways, and cellular stress responses. So because of this, it has become a very attractive target within longevity medicine. So at high level, it certainly does sound pretty straightforward. NAD declines with age.

NAD is involved in many of the hallmarks of aging. So supplementing NAD should improve aging outcomes. And

that might be true, but this is also where longevity medicine becomes vulnerable to oversimplification.

Many of these hallmarks are supported by strong mechanistic and animal data. But translating that biology into meaningful human interventions is far more complex.

Aging happens over decades, which means outcomes take years, decades to measure. So, this doesn't mean that our theoretical lab studies are wrong. It just means that we don't have long-term data in humans yet, and it's pretty hard to assess, which we'll get into later. But with all that being said, one nuance that I often emphasize when discussing integrative or longevity focused therapies is this. The decision to use a treatment doesn't necessarily need to be based solely on whether or not we have definitive proof that it works.

Sometimes the data suggests something might help. And in those cases, the decision also hinges on other questions. Does it cause harm? Is the cost reasonable? How strong is the biological rationale? and how uncertain is the evidence? And truthfully, most of these longevity medicine treatments live right at the intersection of those questions.

How NAD Works in Cells

The field is quite scientifically sophisticated and genuinely promising, but it also is incomplete at this stage. But we could also argue that all of medicine is incomplete. But I will say longevity medicine is still relatively new and how it's being applied clinically, which makes careful interpretation especially important.

So with all that in mind, let's dive deeper. What do we actually know about NAD? To start, NAD stands for nicotenomide adinine ducleotide and it's a molecule that exists in every living cell. At its most fundamental level, NAD is essential for energy metabolism. It carries electrons during metabolic reactions, which essentially means that it helps convert the food we eat into usable cellular energy or ATP. Without adequate NAD, these pathways, particularly in the mitochondria, just simply don't function efficiently. So, this alone makes NAD very important. But that's actually not all that it does. It also functions as a signaling molecule and fuel when our cells are under stress, either from inflammation, oxidative damage, environmental exposures, or just wear and tear, aka aging. So for example, our DNA is constantly being damaged. This happens every day from metabolic processes, exposure to UV light, environmental toxins, oxidative stress, inflammation, or even just plain old normal cell division. And when that damage occurs, the cell activates repair pathways to fix it. The enzymes involved in those repair pathways require NAD to function. They literally use NAD as fuel to do their work. This is a key idea because it helps explain why NAD levels tend to be lower with age and in chronic disease. So over time, cells are naturally exposed to more cumulative stress and damage and they burn through more NAD trying to keep things functioning and stable. This is also why NAD levels are often lower, not just with aging, but in states of chronic inflammation, insulin resistance, mitochondrial dysfunction, and prolonged physiological stress. Lifestyle factors of course play a role here as well. Poor sleep, sedendary behavior, excess caloric intake, and ongoing psychological stresses appear to increase the metabolic and inflammatory burden on cells, which of course increases NAD demand. With this, I do want to note an important conceptual shift here. Declining NAD over time may not be the cause of aging so much as a marker of cumulative cellular stress and damage. As cells are forced to respond to more injury over time, they consume more NAD, and the systems responsible for regenerating can't keep up with the less NAD available. So, we get it. Yes, NAD important. But where does it actually come from? Well, our bodies make it primarily from B vitamins like B3 or niacin, which are found in foods like meats, fish, dairy, legumes, nuts, and whole grains. All of those contain different forms of B3 that our body can use as building blocks for NAD. Our bodies also have what's called a salvage pathway, which is the primary way we maintain NAD levels dayto-day. So instead of constantly building NAD from scratch, cells actually recycle the breakdown products, especially nicotinomide back into NAD.

This recycling process is efficient, but it's also where problems can arise as we age or experience chronic inflammation and stress. The demand for NAD increases as we talked about and also the salvage pathways may not keep up with how much NAD is being consumed. So even though we can make NAD, our levels do depend on a balance between production, recycling, and consumption. If consumption goes up because of ongoing inflammation, oxidative stress, repeated DNA repair, NAD levels fall unless our production and recycling keep up the pace. This is also why lifestyle factors matter.

Measuring NAD and B Vitamins

Adequate nutrition can provide the raw materials. Sleep, exercise, and metabolic health influence how efficiently NAD is recycled. On the other hand, chronic stress and inflammation increases demand. So, when we talk about quote unquote low NAD, what we're often really describing is an imbalance in this system rather than a simple lack of intake. I think understanding this is very important because it helps us reframe how we actually think about supplementation. Taking an NAD supplement, which is actually an NAD precursor, which we'll get to, isn't introducing something foreign into the body. It is providing additional raw materials for a system that already exists. But the question is, which we will get into right now, is whether adding more raw materials meaningfully changes outcomes in humans.

So to understand whether supplements work, we have to first talk about can we actually measure NAD and its building blocks like B vitamins. Technically, yes, NAD can be measured. There are blood tests that look at NAD levels and/or its related metabolites. And there are actually now commercial tests, including fingerstick options that claim to assess NAD status. In research settings, these measurements are done using very precise laboratory techniques. But in clinical practice, right now, the picture is a little bit more complicated. The first challenge is what are we actually measuring? Most available tests do measure NAD, but they measure NAD in the blood. What we need to remember is that NAD is used inside the cells, muscle, liver, brain, and all of those tissues have very different NAD dynamics. So, a blood value doesn't necessarily tell us what's going on inside the tissues that we actually most care about for aging, performance, and cognition.

So right away there is one limitation on how directly actionable these numbers are. The second is interpretation. Right now we don't have wellestablished clinical reference ranges for NAD that are clearly tied to outcomes like improve function, reduce cardiovascular risk, or longer health span. All of what our goal of supplementation, which we will get to later, would address. In many cases, testing can tell us whether NAD levels change after an intervention, but not whether the change actually translates into a meaningful benefit.

However, this doesn't mean that it's not helpful. It can serve as a biioarker that gives us just one piece of the puzzle. A related question that often comes up now that we know that NAD is made from B vitamins is whether testing B vitamins, particularly B3, is useful. This is where nuance really matters.

While B vitamin deficiencies certainly exist and can be clinically important, blood testing for B vitamins is surprisingly imperfect. Again, blood levels don't reflect the intracellular status, functional adequacy, or how efficiently those vitamins are being used inside the cells.

NAD Supplements: NR and NMN

So, what that means, someone can have a quote unquote normal B vitamin level in blood work and still have impaired utilization due to inflammation, metabolic dysfunction, or genetic variation. Conversely, elevated levels can sometimes reflect recent supplementation rather than true tissue sufficiency.

So, while B vitamin testing can be helpful in specific clinical scenarios, it doesn't reliably tell us whether the body is effectively producing or maintaining NAD. This also highlights a broader theme in longevity medicine.

Just because we can measure something doesn't mean it's necessarily useful and certainly does not give us the whole picture. Okay, so testing may be helpful if we look at it just one piece of the puzzle. But what about supplements?

Well, to start, the first thing to know is that most NAD supplements are not actually NAD. Instead, they are blends of NAD precursors, which are molecules that the body can then convert into NAD. And the two most common ones we see are nicotenomide riocide, NR, and nicotenomide monucleotide, NMN. So, here's what we do know with fairly good confidence. In many studies, NR does increase blood NAD levels. A well-sighted trial in healthy middle-aged and older adults showed that NR was well tolerated, which is important, and also increased NAD over 6 weeks. In another study looking at obese men, NR was also safe, also important. It raised NAD like the other one, but it did not improve insulin sensitivity over the study period. Follow-up studies also found that NR did not improve

skeletal muscle mitochondrial respiration or content which is an important note because mitochondria are one of the major reasons people take these products. So essentially NR does increase NAD levels but the actual functional impact of that is pretty inconsistent so far. For NMN, a randomized multic-center placeboc controlled dose ranging trial in healthy middle-aged adults found that NMN did increase blood NAD concentrations and was well tolerated. More recent NMN work in older adults also suggest potential improvements in areas like sleep quality and walking speed, but these are still early and not definitive yet.

Additionally, further systematic reviews and meta analysis are basically telling the same thing. NMN reliably increases NAD levels, but most clinically relevant metabolic outcomes are either small, inconsistent, or not statistically significant across trials. And they did show a big risk of bias common in several of the big studies. There also are disease specific studies worth mentioning as well. So in one randomized trial in peripheral arterial disease, NR meaningfully improved 6-minute walk distance compared with placebo over 6 months for mild cognitive impairment. A small randomized pilot study showed NR increased blood NAD, which we know happens, and was generally well tolerated, also important, but did not show clear cognitive improvement over the short duration, which is what they were looking at. Ultimately, the data isn't quite there for the clinical outcomes, but the theory behind supplementation is interesting. And again, we're thinking of this more long-term longevity, and these studies were done over pretty short terms. But what we do know is that most supplementation was pretty safe in all the clinical trials so far. Next, let's talk about the different delivery types with all of these highly marketed supplements. We have those regular capsules or tablets. We have sublingual or dissolving products. and we have IVs which are very hyped. So let's talk about each of them and look at what the data shows. To start the oral capsules actually have the most data to support it primarily because these are what are being used in the clinical trials.

Next when we look at the liposal or sublingual the dissolving under the tongue ones the thought is that supplements are better absorbed or delivered into the tissues this way. So liposal meaning better absorbed in the gut, sublingual dissolves directly into the bloodstream. And that does sound plausible, but we actually don't have robust evidence or clinical trials that show superior outcomes with these formulations over our regular capsules.

Last, the most highly marketed route, IVs.

IV NAD, Delivery Methods, and Lifestyle Strategies

But before we ask whether it helps, there's another basic question we need to answer first. What happens to NAD when you infuse it? A human study done to document plasma and urine NAD metabolites during and after a six-hour NAD infusion highlights that directly infusing NAD has a pretty complex metabolism and excretion dynamics, meaning it's not just as simple as IV NAD go straight into the cells. Separately, there's ongoing debate in the scientific community about whether intact NAD can cross cell membranes in meaningful amounts. More practically, the larger problem is that IVNAD is being sold from everything from detox or anti-aging in ways that really really exceed the quality of evidence and often at a very high cost. So ultimately, we just don't know how helpful NAD supplementation is. Theoretically, it should be very helpful and so far it hasn't shown to be harmful, but we just don't know yet. We do know NAD is essential for longevity and quote unquote anti-aging and supplementing may be helpful, but so might many other lifestyle strategies that actually have more evidence than NAD does right now. I will add though right now I would definitely say IV NAD is probably not worth the cost. So I mentioned these lifestyle longevity strategies.

These are essential because they can improve NAD levels and actually work more broadly for longevity. And it truly is back to lifestyle basics like exercise, metabolic health, sleep, and inflammation reduction. But of course, let's look at the data. Strength training appears to upregulate NAD salvage capacity in human skeletal muscle, which is one of the more compelling non-supplement strategies that we have.

There are also reviews and newer work supporting the idea that exercise acutely and chronically influences NAD metabolism and NAD biosynthesis pathways. Add in other fundamentals like maintaining adequate dietary B3 intake, improving insulin sensitivity, treating sleep disruption, and reducing chronic inflammation burden. And you're often addressing the real upstream reasons NAD gets stressed in the first place. So to conclude, NAD is very important and it clearly plays a role in energy repair and aging related pathways. We know that we can raise NAD

levels with supplementation, but we don't have strong evidence that doing so reliably improves long-term health outcomes. The promise is very real, but the proof is still emerging. And I think that is the larger point of longevity medicine right now. The field is so exciting because it is asking the better questions earlier, but it also sits in a space where mechanisms often get mistaken for answers and molecules get more attention than systems do. In my opinion, longevity is probably less about finding the right supplement and more about understanding why the body is under so much stress in the first place.

Aging isn't just something to quote unquote fix. It's something to understand. And the most powerful longevity interventions are still lifestyle, diet, nutrition, sleep, stress reduction, and social connection.

Thanks for listening to the Trip Lab. If you liked this episode, please subscribe and share so we can get the conversation started about integrative medicine and psychedelics to destigmatize it and fully explore what this could mean in the world. [music]