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The Crucial Role of NAD+ in Optimal Health

Analysis by Dr. Joseph Mercola | December 03, 2023

STORY AT-A-GLANCE

- NAD+ (nicotinamide adenine dinucleotide) is one of the most important biomolecules in your body. It's involved in the conversion of food to energy, maintaining DNA integrity and ensuring proper cell function. Together, these functions help protect against or delay aging and disease
- NAD also acts as fuel for longevity proteins called sirtuins
- NAD levels dramatically decline with age, contributing to aging and chronic disease states. NAD is also used up by DNA repair enzymes and enzymes involved in inflammation and immunity, such that chronic inflammation, or acute illness in old age, can rapidly result in depletion
- To restore NAD, you need to fix the root cause for NAD depletion, which primarily involves addressing the decline in the NAD salvage pathway. By increasing enzymes in that pathway, which decline with age, your body can recycle NAD like it did naturally when it was younger

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In this interview, Nichola Conlon, Ph.D., a molecular biologist, antiaging specialist and founder of a nutraceutical company that produces an NAD+ boosting supplement.

NAD+ (nicotinamide adenine dinucleotide) is one of the most important biomolecules in your body. It's involved in the conversion of food to energy, maintaining DNA integrity

and ensuring proper cell function. Together, these functions help protect against or delay aging and disease. As explained by Conlon:

> *"NAD is actually something I ended up working on in the drug development industry. I was fortunate enough to work for a company that was forward thinking. It actually started looking at developing molecules that would improve our health span, which is the proportion of the life that we live in good health.*
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> *So, rather than just focusing on individual diseases, we were actually looking at underlying mechanisms of cellular aging and looking at slowing cellular aging to improve healthy lifespan.*
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> *This is when I came across NAD, which is an incredibly important molecule in the body. Going back to molecular biology roots, NAD is important for two critical things in the body.*
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> *The first is energy production. The process that takes the energy out of the food we eat and converts it into ATP, which is the form of energy currency that our cells can use to survive and do all the functions that they need to do, absolutely requires NAD.*
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> *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.*
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> *The second thing that it's really important for is cellular maintenance and repair. NAD almost acts as a sensor in the body. It enables the cell to react to changes in energetic stress, which is basically how much energy or lack of energy the cell has ... These are the two major things that NAD is known for, and because of these roles, it's absolutely fundamental to overall cellular health."*

As an example, if you were to exercise or fast, that uses up cellular energy. NAD will sense this raised energy demand and increase its levels. Elevated NAD is actually a

signal that the cell is in a state of stress. In response, cellular maintenance and repair processes are switched on to preserve the cell and help it survive the stress.

Some History

NAD plays a large role in the Krebs citric acid cycle as it helps to pass the electrons along in the mitochondria in the electron transport chain to facilitate oxidative phosphorylation and generate cellular ATP. While discovered in 1905, well over a century ago, few scientists have paid much attention to it.

In the late 1990s, David Sinclair, Ph.D., while working in Leonard Guarente's lab at Massachusetts Institute of Technology (MIT), realized that NAD is the fuel for longevity proteins called sirtuins. That's when it started coming into prominence as an anti-aging agent.

> *"It was around 2014 that I started getting involved in the aging field,"* Conlon says. *"This was a time when a lot of scientists were talking about this idea that we could slow cellular aging ... [Today], there isn't a single scientist that works in the field of biogerontology — the study of aging — who doesn't say that you can slow biological."*

Testing NAD Levels Is Complicated

Oftentimes, before you start supplementing something, you'll want to find out what your level is. Unfortunately, that's extremely difficult to do with NAD. We do know that NAD levels decrease with age, which is one of the reasons why people want to boost their NAD back to youthful levels.

> *"In scientific laboratories, we use some fairly sophisticated techniques to measure NAD,"* Conlon says, *"But now there's been an emergence of companies saying, 'Send your blood and we'll measure it for you.' The reality is, unfortunately, that as good as that would be, it just doesn't work that way.*

If you think of what NAD does, NAD is described as a redox molecule. What that means is, that it is continually flipping states. It carries electrons in the electron transport chain and [is involved in] 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, 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, we have to make sure that as soon as it is taken out of the person, it's put straight on ice to stop any reactions and then immediately prepped to take out the cells that we want to measure the NAD from. They're then cryogenically frozen to stop any changes or any reactions until we measure the NAD. You've got around a 30-minute window to get this done.

After that, to work out how much NAD is in the sample, you can then use techniques such as mass spectrometry, which compares the amount of NAD in the sample to standards, which are known amounts of NAD.

These are not simple techniques. They are quite advanced laboratory techniques. So, when companies that say they can provide this as a postal service, at the moment, I'm quite skeptical of what they are actually measuring."

How NAD Is Made and Regenerated

Your net NAD level is the sum of what your body makes minus what it loses. If you can successfully limit the amount being lost, then you can maintain your NAD level. So, how is it made, and how is it lost? Conlon explains:

"It's incredibly complex. It's not just a simple case of adding two things together to make more NAD and that's the end of it. Within the cell, there are five

different precursors that NAD can be made out of. These are the raw materials that your body uses to manufacture NAD ...

You've got the B vitamins and derivatives nicotinic acid (nicotinamide), niacin, nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN). And also the amino acid tryptophan. 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.

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 into one of its precursors, nicotinamide.

The cell is really clever because what it's evolved to have is this salvage pathway, a recycling pathway for this nicotinamide (niacinamide). Which 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.

This makes absolute sense, because why would the body want to rely on generating such a critical molecule using external precursors? It needs to use something endogenous, something that it's always going to have a ready supply of.

This also means that as demand for NAD goes up, more NAD is broken down in to nicotinamide, so technically there's more raw material that can simply be recycled straight back into fresh NAD again. This has been demonstrated to be the most important pathway for NAD production in the body.

So when we're young, we've got this abundant supply of NAD that's continually being recycled via the salvage pathway. Unfortunately, as we get older, NAD declines. There are two main reasons for this. Firstly, more NAD is used up.

When more NAD is used up, this means more needs to be recycled to replenish NAD. But it's also been found that that salvage pathway also declines with age. So right at this point in your life when you've got an increased demand for NAD, you've also got a reduction in the body's ability to regenerate NAD 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 see 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."

How NAD Is Depleted

The thing that depletes NAD the most is when it's acting as a cofactor for other enzymes, such as the sirtuins and DNA repair enzymes. In that role, NAD acts much like a fuel, so it gets used up, causing your level to decline. In its energy production role, it merely flips between states, so the overall amount doesn't really change. The two primary enzymes that consume NAD are:

- **Poly ADP ribose polymerases (PARPs), especially PARP1, a DNA repair enzyme —** With age, the amount of DNA damage increases, which has to be repaired. One of the key enzymes that repairs this damage is called PARP1. For that enzyme to work, it needs NAD as a fuel. It literally takes NAD and breaks it down to form its reaction in the DNA repair action.

  "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," Conlon says. Studies suggest extensive DNA damage within a cell can within five minutes deplete the NAD level in that cell to about 5% to 10% of what it started out with.

One common exposure that causes DNA damage is electromagnetic field exposures (EMFs) from cell phones and wireless technologies. Some studies have shown that every time PARP1 is activated for DNA repair, it consumes 150 NAD molecules.[1]

- **CD38 —** Another enzyme called CD38, found on the surface of many immune cells, also consumes about 100 molecules of NAD for every cycle of its reaction. CD38 is a cell signal enzyme involved in sending calcium signals throughout the cell to activate parts of your immune system.

  "CD38 is one of the biggest NAD consumer in the body because of the fact that it is so inefficient at using NAD," Conlon says. "It's been found that even if you can inhibit CD38 by just a very, very small amount, you can have a significant impact on NAD levels because it is so inefficient."

The Challenges of Exogenous NAD Supplementation

Unfortunately, boosting NAD is no easy feat either. Many use NR or NMN, but the bioavailability of these is quite poor. It's kind of like swallowing bioidentical hormones. It's the real deal when you swallow it, but your liver has a tendency to want to detoxify and typically conjugates or adds in methyl groups to facilitate excretion. So, they don't really have time to transfer into your blood.

> **“ It's clearly now demonstrated that 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. ~ Nichola Conlon, Ph.D. ”**

Conlon and her team discovered another way of boosting NAD.

"When we started looking at NAD, the first thing we did was to look for evidence that you could use molecules or supplements to boost NAD. At the time, everyone 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 there was no 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.

Over the last couple of years, more understanding of NAD decline has emerged. It's clearly now demonstrated that 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 wasting NAD. You need to look at inhibiting CD38 and stopping chronic low level inflammation that's wastefully using up NAD. You also need to look at reducing DNA damage and being more efficient in its repair so you don't have this constant chronic activation of DNA repair, which is also using up NAD."

Conlon and her team decided to pursue a multi-target strategy. Rather than just putting more raw material into the cell, the aim is to fix the cell. In experiments, they've demonstrated that you can boost NAD levels in the cells without putting any precursor in. You can actually just use ingredients that inhibit CD38 and activate nicotinamide phosphoribosyltransferase (NAMPT). This will boost NAD without having to add more raw materials to the cell.

NAMPT Is a Rate Limiting Enzyme for NAD Production

NAMPT is really important because that's the bottleneck, the rate limiting enzyme for the production of NAD. Conlon explains:

> *"The reason the salvage pathway declines with age is because of this one key enzyme. NAMPT actually recycles niacinamide and converts it into NMN, which then gets converted back into NAD. The rate limiting step, the bottleneck in that process, is NAMPT. And lo and behold, that is the key enzyme that declines as we get older.*
>
> *Studies have demonstrated that you get a 50% decrease in this enzyme between the ages of 45 and 60. That's a significant decline considering how important this is for 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 found to be because of a reduction in this enzyme. So, it's absolutely critical to try and improve the activation and expression of this enzyme in the body to enhance NAD. It worked brilliantly to give us high NAD levels when we were younger, so why not restore it back to that?"*

How Much Does NAD Decline Over Time?

NAD starts declining from the day you're born. For every 20 years thereafter, you lose about 50%. So, by the time you're 20, your NAD level is half of what you had at birth. By age 40, it's halved again from what you had at age 20, and so on. "It's an exponential curve," Conlon says, "Looking in elderly people's tissues, they really don't have very much left." I believe this may be one of the many reasons why elderly people are so susceptible to COVID. Perhaps even a primary one.

Conlon cites research showing SARS-CoV-2 infection does cause massive NAD depletion by over activating the PARPs. While PARP1 is involved in DNA repair, some of the other PARPs are involved in inflammatory responses, and they too need NAD.

"The running theory is that if we're older or sicker we have lower levels of NAD to begin with, so when we get infected, we're already at a lower starting point. So in someone who's younger and healthy and has high NAD, when they get infected, they've already got quite a good level to begin with, so even when they get that depletion, they can get by because they had adequate supplies to begin with.

The other really interesting thing is what the cell does in response to the virus to try and mitigate this. All of the genes that the cell regulates to try and protect itself are all to do with NAD salvage. The body actively tries to increase NAMPT to protect itself because it knows that's the best way to produce NAD and rectify the problem."

NAD Restoration for Optimal Health

According to Conlon, preclinical animal studies have shown NAD restoration really does help reverse disease and improve health span. In humans, using NR supplementation, the benefits have been less stellar. So far, they've not been able to replicate the preclinical models. Conlon suspects this is because NR and other precursors simply don't address the root causes of NAD decline.

"NAMPT is an enzyme, and you can get antibodies which will selectively attach to it. To measure it, we use a Western blot, which basically measures the amount of NAMPT protein that is available in the cell and it shows as a dark band. Basically, the darker the band, the more expression.

Alpa lipoic acid works by increasing the activation of another energy sensor in the body called AMPK. AMPK is a 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," Conlon explains.

Best and Least Expensive Way to Improve Your NAD+ Levels

So deeply appreciate Dr. Conlon's insights and expertise on NAD+ precursors. Although I have read dozens if not hundreds of papers on NAD+ the entire subject is confusing and I now realize it is likely because of financial interests that the best precursor is not recommended more frequently. Dr. Conlon has concluded, and I thoroughly agree with her, that the best single NAD+ precursor is niacinamide, not niacin, NR or NMN.

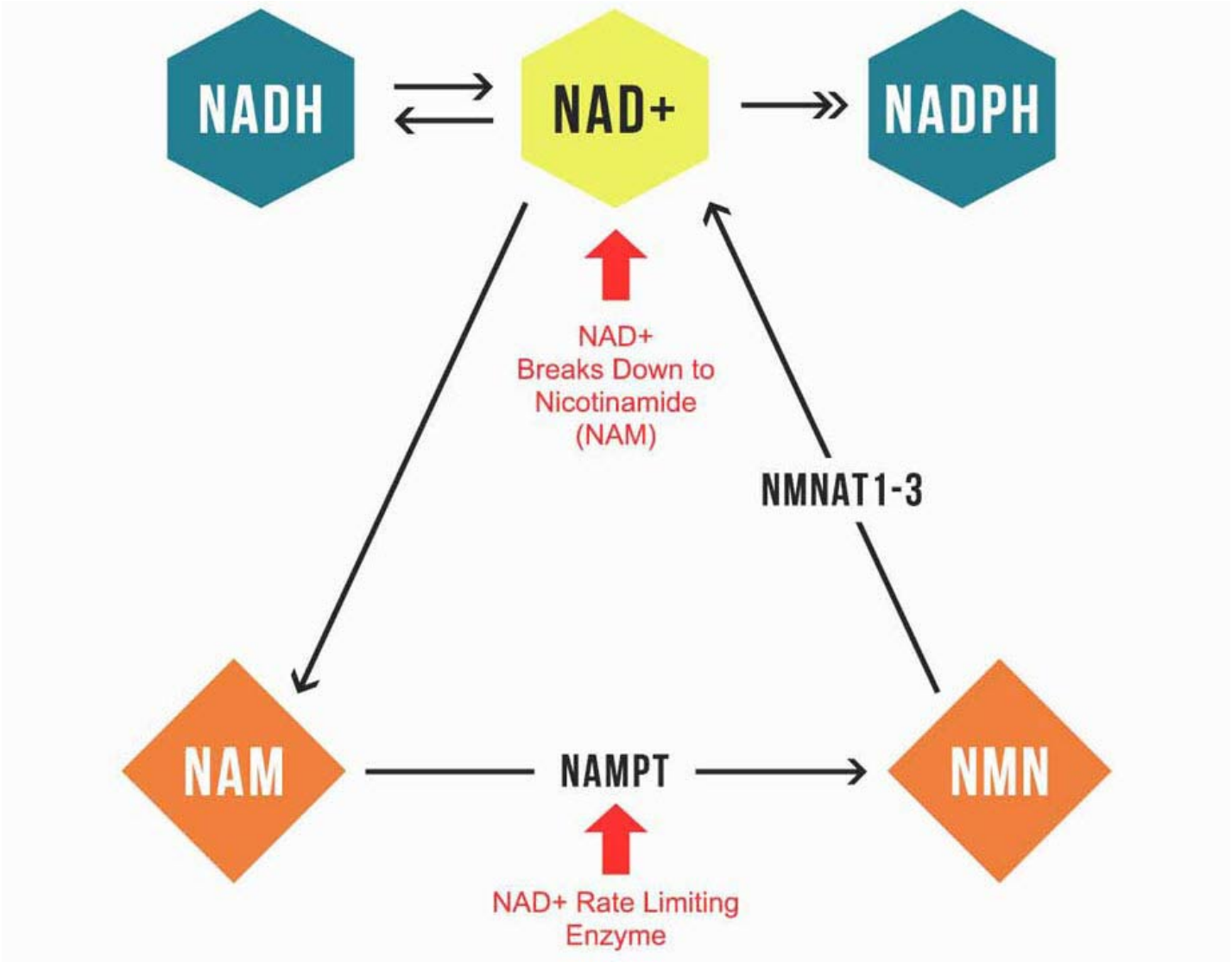
It is now beyond obvious to me why no one is promoting niacinamide. This is because it costs less than one cent a day and as a result there is simply no money to be made in promoting it. Ideally you buy **niacinamide powder** and use 1 to 1/2 of 1/64th of a teaspoon three times a day (25-50 mg).

You will need **special measuring spoons** to measure this small a dose. This is important as more is most definitely not better and much worse. If you use too much you will actually inhibit sirtuins which are important longevity proteins.

Spending $11 on 250 grams of niacinamide powder will give you a nearly four year supply of niacinamide. That pencils out to 23 cents a month or less than one penny a day. It is basically free. NMN in therapeutic doses of 1-2 grams/day can be one to two hundred dollars a month or 400-800X more expensive than niacinamide powder.

So let me review the reasons why Dr. Conlon and I both are convinced that niacinamide is the best NAD+ precursor. The immediate breakdown product of NAD+ is niacinamide and the enzyme NAMPT is the rate limiting enzyme in the salvage pathway to restore niacinamide back to NAD+. As you can see by the pathway below niacinamide is actually first converted to NMN before NAD+. This is likely why researchers like David Sinclair and others promote NMN.

However the enzyme NMNAT1-3 that converts NMN to NAD+ is not the rate limiting enzyme. Recall that NAMPT is what controls how much NAD+ you make. So you flooding your body with NMN is not going to be as useful as using small amounts of niacinamide and activating NAMPT as discussed below. Ideal dosing of niacinamide is from 25 to 50 mg three times a day. It is the rare person that will not respond favorable to this simple intervention for increasing NAD+.



Synergistic Lifestyle Strategies

While supplementation can be very valuable, it's not a magic bullet. In most cases, supplementation needs to be done in conjunction with other healthy lifestyle changes for lasting, optimal results. So, to boost and maintain youthful NAD levels, consider the following healthy lifestyle strategies:

- **Physical exercise —** Naturally increases NAMPT by activating AMPK, which in turn increases NAD. Conlon cites research showing about three weeks of resistance training will boost NAMPT by about 127%, which again is far greater than what you can get from an NR supplement alone.

- **Fasting or time-restricted eating —** Naturally increases NAMPT by activating AMPK, which in turn increases NAD.
- **Circadian rhythm optimization** by going to bed at sunset and getting up at sunrise and avoiding blue light after sunset will have profound impacts on increasing NAMPT.
- **Avoid radiation exposure —** To protect your NAD by preventing its consumption by PARPs, consider avoiding EMFs in the form of your cell phone and Wi-Fi and other forms of DNA damaging radiation, such as unnecessary medical x-rays and CAT scans.
- **Sauna bathing —** Heat stress also helps boost NAD.

Considering you can't really measure your NAD level, how can you your levels are improving? Conlon replies:

> *"We have 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. It's not an energy boost where people feel wired... It's more like having enthusiasm about the day — more 'get up and go.'*
>
> *The other thing is mental clarity and focus. And the final thing is sleep. NAD levels are actually circadian and cyclical and can fluctuate throughout your day ... As you get older and NAD levels decline, the peaks and troughs of NAD decline too which can hamper your circadian rhythm, which means your sleep quality isn't as good. Those are the three main things."*

I have a very optimized lifestyle that optimizes my NAD+ to youthful levels. I do this through an 18-hour daily fast in which I start my resistance training, and most days will follow that with an EMF-free sauna at 160 degrees F. for 20 minutes. I use 50 mg of the niacinamide powder I described above.

Even though I am rapidly approaching 70, my levels are that of someone much younger because of the activities I engage in that radically upregulate NAMPT. If you want to optimize your levels of NAD+, I encourage you to incorporate some of these strategies.

Sources and References

- [1] Nucleic Acids Research. Vol. 47, no. 8. (February 25, 2019): 3811–3827. doi: 10.1093/nar/gkz120