



## nad+

NAD<sup>+</sup> (nicotinamide adenine dinucleotide) is a fundamental coenzyme found in all living cells that is crucial for cellular energy production, DNA repair, metabolic health, and healthy aging.<sup>[1]</sup><sup>[2]</sup><sup>[3]</sup>

### What is NAD<sup>+</sup>?

NAD<sup>+</sup> is a molecule composed of two nucleotides joined through phosphate groups. One contains an adenine base, and the other has a nicotinamide. NAD<sup>+</sup> acts as a key electron carrier in multiple enzymatic reactions, shuttling electrons within cells and supporting essential processes including the conversion of food to energy and the maintenance of DNA integrity.<sup>[2]</sup><sup>[4]</sup><sup>[3]</sup>

### Health Benefits of NAD<sup>+</sup>

- NAD<sup>+</sup> facilitates energy production in cells by participating in metabolic reactions, particularly those occurring in mitochondria.<sup>[4]</sup><sup>[5]</sup><sup>[2]</sup>
- It supports DNA repair and reduces oxidative stress, which helps maintain cell function and integrity as the body ages.<sup>[6]</sup><sup>[4]</sup>
- Higher levels of NAD<sup>+</sup> have been linked to improved cognitive function, better sleep quality, enhanced metabolic resilience, improved mood, and reduced inflammation.<sup>[7]</sup><sup>[8]</sup><sup>[9]</sup><sup>[6]</sup>
- NAD<sup>+</sup> supplementation may help support brain health, insulin sensitivity, heart health, and protect against age-related conditions.<sup>[10]</sup><sup>[11]</sup><sup>[12]</sup>

### NAD<sup>+</sup> Supplementation & Precursors

- Direct oral supplementation of NAD<sup>+</sup> has not been proven effective; instead, precursors such as NMN (nicotinamide mononucleotide), NR (nicotinamide riboside), and niacin are used to boost NAD<sup>+</sup> levels in the body.<sup>[13]</sup><sup>[14]</sup><sup>[11]</sup><sup>[2]</sup>
- Clinical studies show that supplementation with NAD<sup>+</sup> precursors safely increases NAD<sup>+</sup> abundance, with some reporting improved mitochondrial function, reduced inflammation, and even benefits in symptoms of conditions like Parkinson's disease and long COVID.<sup>[14]</sup><sup>[8]</sup><sup>[15]</sup><sup>[16]</sup><sup>[17]</sup>
- NAD<sup>+</sup> IV therapy and supplements are popular for claims of boosting energy, metabolism, supporting weight management, and improving skin and cellular health, although more human trials are needed for robust clinical validation.<sup>[5]</sup><sup>[9]</sup><sup>[15]</sup><sup>[6]</sup>

## Decline of NAD+ Levels

- NAD+ levels diminish with age, contributing to metabolic decline, cognitive impairment, and increased vulnerability to age-related diseases. [\[11\]](#) [\[4\]](#)
- Maintaining or increasing NAD+ levels is a key area of research in anti-aging, neurodegenerative disease prevention, and regenerative medicine. [\[15\]](#) [\[17\]](#) [\[7\]](#)

NAD+ is central to cellular health, metabolism, and aging, and new research continues to explore its therapeutic potential through safe and effective supplementation of its precursors. [\[9\]](#) [\[16\]](#) [\[17\]](#) [\[7\]](#) [\[14\]](#) [\[15\]](#)



## Exogenous NAD does not increase NAD+, use only clinical studies and explain why it does not work

Clinical studies consistently show that direct supplementation with exogenous NAD+ does not reliably increase NAD+ levels in most tissues, primarily due to NAD+'s biochemical properties—instability, poor bioavailability, and inability to efficiently cross cell membranes. Instead, clinical trials demonstrate that the body preferentially absorbs and utilizes NAD+ precursors such as NMN (nicotinamide mononucleotide), NR (nicotinamide riboside), and niacin, which are actively transported into cells and converted to NAD+ via endogenous biosynthesis pathways. [\[21\]](#) [\[22\]](#) [\[23\]](#) [\[24\]](#) [\[25\]](#) [\[26\]](#) [\[27\]](#) [\[28\]](#) [\[29\]](#)

### Why Exogenous NAD+ Supplements Fail

- NAD+ is a negatively charged molecule and large in size, meaning it cannot passively cross cellular membranes. [\[24\]](#)
- Most administered NAD+ (especially orally) is rapidly degraded in the gut and bloodstream and converted into metabolites like nicotinamide (NAM) and nicotinamide mononucleotide (NMN) by extracellular enzymes (such as CD38), rather than directly entering cells as intact NAD+. [\[26\]](#) [\[24\]](#)
- Clinical evidence indicates that oral or even intravenous NAD+ administration leads to increased levels of metabolites in plasma, but little to no appreciable increase in intracellular NAD+ within most tissues, as shown by quantitative mass spectrometry in multiple human studies. [\[23\]](#) [\[24\]](#) [\[26\]](#)
- Attempts to directly supplement NAD+ failed to show sustained increases in whole blood NAD+ concentrations unless given through very high-dosage intravenous routes, which are not practical or safe for routine clinical use. [\[23\]](#) [\[26\]](#)

### Clinical Study Examples and Mechanistic Insights

- Trials repeatedly report increased NAD+ levels only when precursors are used, not with exogenous NAD+ itself. [\[22\]](#) [\[28\]](#) [\[29\]](#) [\[21\]](#)
- Mechanistically, exogenous NAD+ is cleaved extracellularly to NMN, NAM, and ADPR before it can be taken up and reassembled inside cells. [\[24\]](#)

- The real “NAD+ boosters,” validated by clinical trials, are precursors that enter cells via specific transport mechanisms and are rebuilt into NAD+ by enzymatic machinery, especially the NAMPT enzyme system. [\[25\]](#) [\[27\]](#) [\[28\]](#) [\[29\]](#) [\[21\]](#) [\[22\]](#)

In summary, clinical studies demonstrate that exogenous NAD+ does not directly elevate NAD+ levels due to its inability to traverse cell membranes, rapid breakdown in the extracellular space, and poor stability, whereas precursor compounds effectively increase NAD+ by leveraging the body's natural biosynthetic pathways. [\[28\]](#) [\[29\]](#) [\[21\]](#) [\[22\]](#) [\[26\]](#) [\[23\]](#) [\[24\]](#)



## As NMN and NR increase telomerase is this part of the mechanism that help to increase NAD+

Increasing NAD+ through supplementation with NMN (nicotinamide mononucleotide) and NR (nicotinamide riboside) does not primarily happen through telomerase activation, but some studies suggest that improved telomere maintenance may be a downstream effect of higher NAD+ levels. NMN and NR work as precursors, boosting NAD+ through cellular biosynthesis pathways; their main mechanism is direct conversion to NAD+, not via changes in telomerase. [\[40\]](#) [\[41\]](#) [\[42\]](#) [\[43\]](#) [\[44\]](#) [\[45\]](#) [\[46\]](#) [\[47\]](#) [\[48\]](#) [\[49\]](#)

### Clinical Study Insights

- Supplementation with NMN and NR robustly increases NAD+ by entering the salvage and Preiss-Handler pathways, which efficiently synthesize NAD+ from these compounds regardless of telomerase activity. [\[41\]](#) [\[43\]](#) [\[48\]](#)
- Several studies show that increased NAD+ enhances the activity of sirtuins, especially SIRT1 and SIRT6, which contribute to telomere stability and DNA repair. This may help maintain telomere length, but is not the primary route of NAD+ synthesis. [\[42\]](#) [\[44\]](#) [\[46\]](#) [\[50\]](#)
- NMN and NR have been observed to elongate telomeres in humans and animal models, possibly due to improved cellular health and increased sirtuin activity. The effect is likely secondary to increased NAD+, which benefits cellular longevity mechanisms. [\[51\]](#) [\[44\]](#) [\[49\]](#) [\[42\]](#)

### Mechanistic Relationship

- The relationship between NAD+ and telomerase is mostly indirect: NAD+ boosts sirtuins which stabilize and repair telomeres, but NMN and NR themselves do not activate telomerase as part of the NAD+ production mechanism. [\[44\]](#) [\[46\]](#) [\[50\]](#)
- Clinical evidence supports that NAD+ increases from NMN and NR supplementation occur even without changes in telomerase, confirming precursor-driven biosynthesis as the main pathway. [\[43\]](#) [\[48\]](#) [\[41\]](#)

In summary, NMN and NR elevate NAD+ through cellular biosynthetic pathways, and while increased NAD+ may help maintain telomere length by enhancing sirtuin-mediated telomere stability, telomerase activation is not a direct mechanism by which NAD+ is increased. [\[46\]](#) [\[48\]](#) [\[41\]](#) [\[44\]](#)

# Explain the role of telomerase in cellular aging and NAD metabolism

Telomerase is an enzyme that maintains and elongates telomeres—the protective caps at the ends of chromosomes—which is a critical factor in cellular aging. Shortened or dysfunctional telomeres trigger cellular senescence (growth arrest), apoptosis, and can amplify age-related diseases and inflammation, making telomerase activity central to cellular longevity. [\[60\]](#) [\[61\]](#) [\[62\]](#) [\[63\]](#) [\[64\]](#) [\[65\]](#)

## Telomerase in Cellular Aging

- Telomerase replenishes telomere sequences lost during DNA replication, allowing cells to divide repeatedly without losing vital genetic material. [\[62\]](#) [\[64\]](#) [\[60\]](#)
- In most somatic cells, telomerase is silenced, leading to gradual telomere shortening—a molecular clock for aging. [\[65\]](#) [\[60\]](#)
- Critically short telomeres activate DNA damage responses, promote cell cycle exit, and induce senescence, contributing to tissue dysfunction and aging phenotypes. [\[61\]](#) [\[64\]](#) [\[62\]](#) [\[65\]](#)
- Cells with shortened telomeres also exhibit increased ROS (reactive oxygen species), mitochondrial dysfunction, and a pro-inflammatory profile, exacerbating the aging process. [\[66\]](#) [\[61\]](#)

## Telomerase and NAD Metabolism

- Cellular studies and animal models reveal that telomere dysfunction and short telomeres—often due to reduced telomerase activity—lead to disturbed NAD metabolism. [\[67\]](#) [\[68\]](#) [\[69\]](#) [\[66\]](#)
- Short telomeres can increase the activity of CD38, an enzyme that breaks down NAD<sup>+</sup>, contributing to loss of NAD<sup>+</sup> homeostasis and impairing NAD-dependent enzymes such as sirtuins and PARPs. [\[69\]](#) [\[66\]](#)
- NAD<sup>+</sup> depletion, in turn, weakens sirtuin function, which is important for DNA repair, mitochondrial health, and anti-senescence signaling—creating a feedback loop between telomere integrity and cellular metabolism. [\[68\]](#) [\[70\]](#) [\[69\]](#)
- Clinical models suggest that restoring NAD<sup>+</sup> levels with precursors like NMN and NR boosts sirtuin activity and may help stabilize telomeres, reduce DNA damage at chromosome ends, and ameliorate cellular aging. [\[70\]](#) [\[67\]](#) [\[68\]](#) [\[66\]](#) [\[69\]](#)

## Key Mechanistic Connections

- Telomerase maintains telomere length, preserving genome stability and delaying senescence. [\[64\]](#) [\[71\]](#) [\[62\]](#)
- Telomere dysfunction reduces NAD<sup>+</sup> via increased CD38, which then impairs sirtuin/PARP function and worsens cellular aging. [\[66\]](#) [\[69\]](#) [\[70\]](#)

- Boosting NAD<sup>+</sup> with NMN/NR or CD38 inhibition can partially reverse metabolic and telomere abnormalities in cells and animal models with telomerase defects, supporting a dynamic telomere-NAD metabolic axis. [68] [69] [70] [66]

Telomerase is therefore deeply intertwined with both cellular lifespan and metabolic health via regulation of telomere length and NAD<sup>+</sup> homeostasis. Dysfunction in either system accelerates aging and promotes age-associated disease. [69] [70] [68] [66]



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