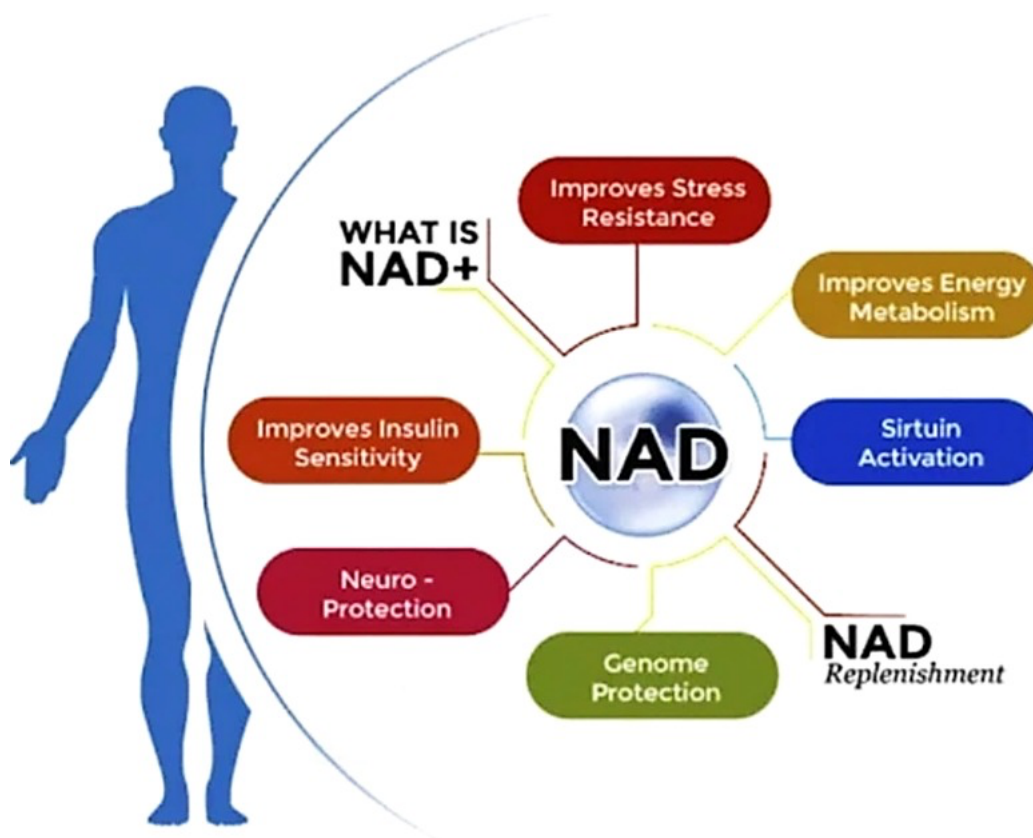


Overview of Nicotinamide Adenine Dinucleotide (NAD⁺) Infusion



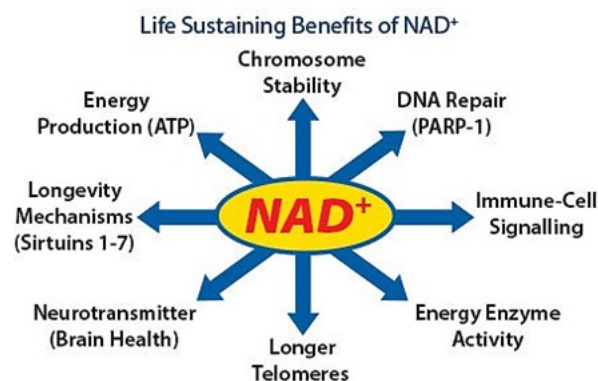
General Information

Nicotinamide Adenine Dinucleotide (NAD⁺) is a universal cellular electron transporter, coenzyme, and signaling molecule present in all cells of the body and is essential for cell

function and viability. Along with NAD⁺, its reduced (NADH) and phosphorylated forms (NADP⁺ and NADPH) are also important. NAD⁺ and its redox partner NADH are vital for energy (ATP) production in all parts of cellular respiration: glycolysis in the cytoplasm and the Krebs cycle and electron transport chain in the mitochondria.

NADP⁺ and NADPH tend to be used in anabolic reactions, including biosynthesis of cholesterol and nucleic acids, elongation of fatty acids, and regeneration of glutathione, a key antioxidant in the body. In other cellular processes, NAD⁺ and its other forms are used as substrates by NAD⁺-dependent/-consuming enzymes to make post-translational modifications to proteins. NAD⁺ also serves as a precursor for the secondary messenger molecule cyclic ADP ribose, which is important for calcium signaling.

NAD⁺ is naturally synthesized *de novo* in the body from the amino acid tryptophan or vitamin precursors, nicotinic acid and nicotinamide, collectively known as vitamin B3 or niacin; it can also be synthesized from biosynthetic intermediates, including nicotinamide mononucleotide and nicotinamide riboside. Within salvage pathways, NAD⁺ is continuously recycled within cells being interconverted to and from its other forms. Cell culture studies also suggest that mammalian cells can take up extracellular NAD⁺. NAD⁺ levels are highest in newborns and steadily decline with increasing chronological age. After age 50, they are approximately half of the levels seen in younger adults. The question of why NAD⁺ levels decline with age has been investigated in model organisms. During redox reactions NAD⁺ and NADH are not consumed but continuously recycled; however, during other metabolic processes, NAD⁺ is consumed by NAD⁺-dependent enzymes and thus could become depleted over time, contributing to increased DNA damage, age-related conditions and diseases, and mitochondrial dysfunction. Age-related decline in mitochondrial health and function is prominent in theories of aging and senescence, and studies of NAD⁺ depletion and subsequent oxidative damage and stress support these ideas.



A 2016 study in mice, which present age-related declines in NAD⁺ levels similar to those observed in humans, revealed that the age-related decline in NAD⁺ levels is driven by increasing levels of CD38, a membrane-bound NADase that breaks down both NAD⁺ and its precursor nicotinamide mononucleotide. The study also confirmed elevated CD38 gene expression in human adipose tissue from older adults (mean age, 61 years) relative to younger adults (mean age, 34 years). However, other studies in mice have

demonstrated that inflammation and oxidative stress caused by aging reduce NAD⁺ biosynthesis. Thus, it is likely that a combination of mechanisms contribute to age-related decline of NAD⁺ in humans.

The clinical importance of maintaining NAD⁺ levels was established in the early 1900s, when it was discovered that the disease pellagra, which is characterized by diarrhea, dermatitis, dementia, and death, could be cured with foods containing NAD⁺ precursors, in particular vitamin B3. Notably, in contrast to vitamin B3 (niacin) supplementation, which causes the skin to flush, this side effect has not been observed with NAD⁺ injection. In recent years, low NAD⁺ levels have been linked to a number of age-related conditions and illnesses associated with increased oxidative/free radical damage, including diabetes, heart disease, vascular dysfunction, ischemic brain injury, Alzheimer's disease, and vision loss.

IV infusion of NAD⁺ has been used extensively for the treatment of addiction, stemming from a study a 1961 report by Paul O'Hollaren, MD, of Shadel Hospital in Seattle, Washington. Dr. O'Hollaren described the successful use of IV-infused NAD⁺ for the prevention, alleviation, or treatment of acute and chronic symptoms of addiction to a variety of substances, including alcohol, heroin, opium extract, morphine, dihydromorphine, meperidine, codeine, cocaine, amphetamines, barbiturates, and tranquilizers, in over 100 cases. However, no clinical trials to date have evaluated the safety and efficacy of NAD⁺ treatment in addiction.

NAD⁺-replacement therapy may promote mitochondrial health and homeostasis, genome stability, neuroprotection, healthy aging, and longevity and may aid in treating addiction. Clinical trials evaluating these effects in humans treated with NAD⁺ injection have not yet been published; however, numerous clinical trials evaluating the efficacy and safety of NAD⁺-replacement therapy or augmentation in the context of human disease and aging have recently been completed, and many others are ongoing.

Mechanisms of Action

The exact mechanisms of NAD⁺ restoration or augmentation for potential health benefits, such as supporting healthy aging and treating age-related conditions, metabolic and mitochondrial diseases, and addiction, are unknown.

NAD⁺ replacement may counterbalance age-related degradation of NAD⁺ and its precursor nicotinamide mononucleotide by NADases, in particular CD38, thereby preventing mitochondrial dysfunction and maintaining metabolic function/energy (ATP) production. However, studies in animal models and humans (and/or samples and cell lines) indicate that NAD⁺ replacement supports several other biological pathways via NAD⁺-dependent enzymes.

There are several notable NAD⁺-dependent enzymes. Poly-ADP ribose polymerases (PARP 1-17) control DNA repair and nuclear stability. CD38 and CD157 are NADases whose products (cADP-ribose, ADP-ribose and nicotinic acid adenine dinucleotide) are used in Ca²⁺ signaling and intercellular immune communication. Sirtuins (Sirt 1-7) are a

family of histone deacetylases that regulate of several proteins associated with cellular metabolism, cellular stress responses, circadian rhythms, and endocrine functions; Sirt3s have also been linked to longevity in model organisms and protective effects in cardiac and neuronal models. Sterile Alpha and Toll/Interleukin-1 Receptor motif-containing 1 (SARM1), is a recently discovered NAD⁺ hydrolase involved in neuronal degeneration and regeneration.

Some insight into the mechanism of action of NAD⁺ replacement has been obtained from studies of progeroid (premature aging) syndromes, which mimic the clinical and molecular features of aging. Werner syndrome (WS) is believed to most closely resemble natural aging and is characterized by extensive metabolic dysfunction, dyslipidemia, premature atherosclerosis, and insulin-resistant diabetes. WS is caused by mutations in the gene encoding the Werner (WRN) DNA helicase, which regulates transcription of a key NAD⁺ biosynthetic enzyme called nicotinamide nucleotide adenylyl transferase 1.

A 2019 study found that NAD⁺ depletion is a major driver of the metabolic dysfunction in WS through dysregulation of mitochondrial homeostasis. Cells with depleted NAD⁺ from samples of WS patients and WS animal models showed impaired mitophagy (selective degradation of defective mitochondria). NAD⁺ repletion restored NAD⁺ metabolic profiles, improved fat metabolism, reduced mitochondrial oxidative stress, and improved mitochondrial quality by restoring normal mitophagy in human cells with mutated WRN. In animal models, NAD⁺ repletion significantly extended lifespan and delayed accelerated aging, including increased numbers of proliferating stem cells in the germ line. Replacement of NAD⁺ by administering various NAD⁺ precursor molecules recapitulated the results, confirming that the beneficial effects are due to NAD⁺ repletion.

Providing additional support for the role of NAD⁺ in promoting mitochondrial and metabolic health, murine cells overexpressing the NADase CD38 consumed less oxygen, had increased lactate levels, and possessed irregular mitochondria, including features such as lost or swollen cristae. Isolated mitochondria from these cells showed severe loss of NAD⁺ and NADH compared to controls. In mice lacking CD38, NAD⁺ levels, mitochondrial respiratory rates, and metabolic functions were preserved during aging.

Pharmacokinetics

One pharmacokinetic study has evaluated changes in concentrations of NAD⁺ and its metabolites in a cohort of healthy male participants (n=11; NAD⁺ n=8 and control n=3) during NAD⁺ IV infusion. Participants received a 6-hour continuous IV infusion of NAD⁺ (750 mg dose at 3 μmoles/min), which resulted in a significant increase in plasma levels of NAD⁺ (398%), nicotinamide (409%), adenosine phosphoribose (ADPR; 393%) at the end of infusion relative to baseline (p <.0001); these levels were all significantly different than in the control group (p <.001, p<.001, and p<.0001, respectively). After 8 hours, differences between the groups remained significant for levels of NAD⁺ but not of nicotinamide and ADPR. Within both groups, levels of these two NAD⁺ metabolites were

significantly correlated over the 8-hour timeframe ($\rho=1.0$, $p < .001$), suggesting cleavage of NAD⁺ to nicotinamide and ADPR by NADases, such as CD38.

Consistent with increased nicotinamide, plasma levels of its metabolites methyl nicotinamide (350%) and nicotinamide mononucleotide (NMN; 472%) also significantly increased at the end of the NAD⁺ infusion relative to baseline ($p < .0001$ and $p < .05$) and the control group ($p < .0001$ and $p < .05$, respectively).

In the NAD⁺ group, levels of NAD⁺ excreted in the urine significantly increased (538%) after infusion (at 6 h) relative to that measured at 30 minutes ($p < .001$); it was also significantly different from the controls ($p < .05$). This level decreased by 43% at the 8-hour time point relative to the peak at 6 hours ($p < .05$).

Excess NAD⁺ and its metabolites are excreted in urine. Urine excretion levels of nicotinamide did not change over the 8-hour period in the NAD⁺ group; however, those of methyl nicotinamide significantly increased (403%) after infusion (at 6 h) relative to that measured at 30 minutes ($p < .01$). This level also decreased by 43% at the 8-hour time point relative to the peak at 6 hours ($p < .05$).

Notably, no significant increases in plasma or urine levels of NAD⁺ or its metabolites were observed within the first 2 hours of infusion, indicating rapid and complete tissue uptake and/or metabolism (at least for the first 2 hours).

Intracellular concentrations of NAD⁺ are maintained between 0.2 and 0.5 mM, and intracellular NAD⁺ pools are believed to be compartmentalized among the nucleus, cytosol, and mitochondria with NAD⁺ salvage pathways functioning according to compartment-specific needs. However, it is currently unknown how NAD⁺ injections affect intracellular and compartmental NAD⁺ pools.

NAD Summary

Aging is a natural process that occurs as a part of the cycle of life. Yet even though aging is inevitable, how well you age can be influenced by a number of lifestyle factors over which you have a great deal of control. Your nutritional status, physical activity level, sleep quality and stress levels all play important roles in governing the rate at which you age. In recent decades, science and technology have made important inroads in identifying the specific mechanisms of aging at the cellular level. A significant discovery is the role of nicotinamide adenine dinucleotide (NAD⁺), the central redox coenzyme in cellular metabolism. In clinical trials, NAD⁺ treatment was found to reverse aging in laboratory mice. NAD⁺ is naturally present in every cell of your body, and plays a significant role in a number of cellular processes, including the repair of DNA. However, as humans age, we lose about 50 percent of our NAD⁺ levels, impeding the body's ability to repair cells and prevent degenerative health issues.

Indications

NAD+ AND BRAIN HEALTH

One of the most feared and devastating signs of aging is cognitive decline. Advanced brain disorders like dementia and Alzheimer's disease are on the rise, appearing in ever-younger populations and taking a toll on patients and their loved ones.

NAD+ stimulates the neogenesis of neurons to promote brain neuroplasticity and reduce inflammation. NAD+ also supports the production of norepinephrine and serotonin, important hormones that help regulate mood, suppress anxiety and promote healthy sleep.

BENEFITS OF NAD+ THERAPY

- Improved muscle function
- Reduced insulin resistance
- Reduced risk of cancer
- Improved cognitive function
- Improved liver function
- Reduced risk of hearing loss
- Increased basal metabolism
- Protection of cellular mitochondria
- Improved sleep
- Enhanced DNA repair
- Increased longevity

NAD+ ANTI-AGING INFUSION

NAD+ plays an important role in the series of chemical responses that convert food to energy. When readily available, it activates several enzymes that are important for health, including:

Sirtuins: Sometimes called the housekeeping genes, sirtuins regulate a number of key genes responsible for metabolism, cellular defense, reproduction, brain plasticity and memory.

PARP (Poly (ADP-ribose) polymerase): This family of proteins is involved in a myriad of cellular processes, including DNA repair, genomic stability, and programmed cell death.

CD38: (cluster of differentiation 38): The glycoprotein CD38 is found on the surface of white blood cells (immune cells), and also functions in cell adhesion, signal transduction and calcium signaling. It plays an important role in glucose-induced insulin secretion in the pancreas.

**As an anti-aging remedy,
NAD+ has been listed as GRAS
(Generally Recognized as Safe) by the US FDA**

CONDITIONS IMPROVED BY NAD+ THERAPY

- Loss of skin elasticity
- Sun damaged skin
- Hypertension
- Abdominal obesity
- Poor liver function
- Metabolic disease
- Chronic fatigue
- Difficulty sleeping
- Sarcopenia (loss of muscle mass)
- Brain fog and memory loss
- Hearing loss
- Withdrawal symptoms from drugs and alcohol

NAD+ ANTI AGING IV THERAPY IN BIOMED CLINIC

The remarkable anti-aging effects of NAD+ IV therapy are growing in popularity among celebrities, athletes and health-conscious people who want to maintain youthful robust health for decades on end. For the best NAD+ treatment in BioMed, contact Advanced BioMed Clinic Bangkok. Our spa-like clinic is staffed by professional clinicians who will administer your NAD+ treatment in a safe and spotless environment.

Research and Therapeutic Uses

- The Role of NAD+ in Anti-Aging Therapies <https://www.researchgate.net/publication/338820894> The Role of NAD in Anti-Aging Therapies
- Why NAD+ Declines during Aging: It's Destroyed <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5088772/>
- NAD+ can restore age-related muscle deterioration <https://advancedcryonyc.com/nad-iv-therapy-for-reversal-of-age-related-muscle-loss/>
- Clinical Evidence for Targeting NAD Therapeutically <https://www.mdpi.com/1424-8247/13/9/247>
- NAD metabolism in aging and cancer <https://journals.sagepub.com/doi/abs/10.1177/1535370220929287>