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Nicotinamide adenine dinucleotide (NAD+) Support:

Safety, Efficacy, and Delivery Approaches

Whitepaper

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Abstract

Nicotinamide adenine dinucleotide (NAD+) is a central coenzyme in cellular metabolism. Levels of NAD+ naturally decline with age and are linked to reduced mitochondrial function, lower energy production, impaired DNA repair, and increased susceptibility to metabolic and neurodegenerative diseases. Supplementation works by restoring NAD+ availability. Research indicates that supplementation with NAD+ precursors can safely increase NAD+ levels, thereby supporting healthy aging, reducing fatigue, enhancing mood, improving physical performance, and mitigating inflammation. Emerging evidence suggests that intravenous and intranasal administration of NAD+ may benefit cognitive and neurological function. However, oral NAD+ itself has low bioavailability due to degradation in the gut and poor cellular uptake. Fridays' innovative delivery systems, including subcutaneous injection, intranasal spray, and StatRX sublingual technologies, overcome these challenges. These approaches bypass digestive barriers, enabling reliable and convenient methods to support healthy NAD+ levels. Overall, NAD+ provides a safe and effective means of supporting cellular energy, healthy aging, and overall wellness.

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1 Introduction

Nicotinamide adenine dinucleotide (NAD+) was first discovered by biochemists in 1906 as a crucial component for fermentation[1]. Over the next century, it has been recognized as an essential coenzyme in cellular biology, playing a central role in processes such as energy metabolism, DNA repair, and cell signalling[1,2]. Growing evidence links age-related declines in NAD+ to impaired mitochondrial function, reduced cellular repair, and increased susceptibility to chronic disease[3]. As a result, interest in NAD+ has expanded rapidly among clinicians and health-conscious consumers seeking strategies to support healthy aging, longevity, and overall wellness. At Fridays, our mission is to provide scientific evidence-based longevity solutions, ensuring cutting-edge science is at the center of our products.

2 Biology of NAD+ and Precursors

The body does not rely solely on direct NAD+ intake, instead, it can also be synthesized from the metabolic conversion of several dietary sources known as NAD+ precursors[1,2,4,5]. These precursors include the amino acid tryptophan as well as several forms of vitamin B3, including nicotinic acid (NA), nicotinamide (NAM), and nicotinamide riboside (NR)[1,2,4,5]. Each precursor enters a metabolic pathway for conversion into NAD+ (Table 1). For example, in the salvage pathway, NR is converted to NMN by the enzyme nicotinamide riboside kinase. After this, NMN is converted to NAD+ by NMN adenyltransferase (NMNAT)[5]. Also in the salvage pathway, NMN can be formed from NAM by the rate-limiting enzyme nicotinamide phosphoribosyltransferase and converted into NAD+ by NMNAT[5]. The existence of these multiple pathways and precursors allows the body to maintain healthy NAD+ levels even if dietary intake or physiological needs change. Foods rich in vitamin B3, as well as NAD+ or precursor supplementation, enable sustained healthy NAD+ levels to support optimal cellular function and health.

Table 1: Dietary precursors essential for NAD+ synthesis.

Dietary Source	Class	Conversion pathway
Tryptophan	Amino acid	De novo/ Kynurenine pathway
Nicotinic acid (NA)	Vitamin B_3 derivative	Preiss-Handler pathway
Nicotinamide (NAM)	Vitamin B_3 derivative	Salvage pathway
Nicotinamide riboside (NR)	Vitamin B_3 derivative	Salvage pathway
Nicotinamide mononucleotide (NMN)	Vitamin B_3 derivative	Salvage pathway intermediate

Much of the existing clinical research has focused on NAD+ precursors, including NR and NMN, which have been proven in clinical studies to increase NAD+ levels through metabolic conversion via these various pathways (Table 1)[6–8]. Numerous clinical trials have also investigated the effects of NAD+ precursors on different aspects of human health. This body of clinical evidence is highly relevant to NAD+ supplementation as it demonstrates the wide range of physiological benefits associated with elevated NAD+[8–10]. However, the efficiency of precursor conversion depends on factors such as age, tissue distribution, and enzyme availability, meaning that precursor supplementation may not always result in efficient increases in cellular NAD+[11].

Fridays' NAD+ formulations, delivered by injectable, intranasal, and sublingual, bypass the metabolic steps precursors require by providing NAD+ directly. This approach builds upon the strong foundation of precursor research while potentially offering a more reliable method for increasing NAD+ levels rapidly and effectively.

2.1. Key Biological Roles of NAD+

Cellular energy metabolism (ATP production): NAD+ plays a central role in mitochondrial energy metabolism. It acts as an electron carrier in glycolysis, the tricarboxylic acid (TCA) cycle, and fatty acid oxidation. In these processes, NAD+ is reduced to NADH, which then donates electrons to the mitochondrial electron transport chain, supporting efficient ATP production[1,2,12.]

DNA repair and sirtuin activation: NAD+ is essential for DNA repair, as poly(ADP-ribose) polymerases (PARPs) consume NAD+ in response to DNA damage, a process that is closely linked to cellular longevity. NAD+ also acts as a cofactor for sirtuins, also known as "longevity genes," which regulate stress resistance, gene expression, and healthy aging[2,5].

Neurotransmitter regulation and brain function: NAD+ contributes to neurotransmitter synthesis and overall brain function. It is highly expressed in neural tissues where it supports cognition, plasticity, and resilience[13,14].

NAD+ is most abundant in tissues with high metabolic requirements, such as the heart, skeletal muscle, and the brain[4,12]. However, NAD+ levels decline naturally with age, leading to impaired mitochondrial function, energy production, DNA repair, skeletal muscle quality, and increased susceptibility to metabolic and neurodegenerative diseases[3,12–15]. Maintaining optimal NAD+ may therefore have benefits in terms of overall health and longevity.

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3 Clinical Data Supporting NAD+ or Precursor Supplementation

Supplementation of NAD+ and its precursors has been studied since the early 2000s, with over 100 clinical trials conducted to date. Clinical research is still ongoing, however, current evidence demonstrates that NAD+ and precursor supplementation can provide anti-aging effects, improve energy and fatigue, support mood and cognitive function, enhance physical performance and muscle function, and offer anti-inflammatory benefits.

3.1. Anti-Aging Effects

In a clinical study involving 80 midlife or older adults, participants received either 300 mg/day, 600 mg/day, or 900 mg/day of NMN or placebo over 60 days[16]. Blood NAD+ concentrations were increased in the NMN groups dose-dependently, whereas the placebo groups remained unchanged[16]. Additionally, those who received NMN walked significantly further during a 6-minute walking test, and biological age was unchanged in the NMN groups, whereas in the placebo group, biological age increased[16]. Indicating that NMN supplementation may have benefits for increasing cellular NAD+ levels, improving physical function, and helping to maintain biological youth in midlife and older adults.

Additionally, a clinical trial was carried out in 33 participants where each participant received either Nuchido TIME+® (NT), a supplement that contained ingredients that targeted multiple points in the NAD+ salvage pathway, or placebo for 28 days, followed by a wash-out period, then participants switched interventions for a further 28 days[9]. They found that the NT supplement increased NAD+ levels in whole blood, lowered concentrations of pro-inflammatory cytokines, and reduced glycated serum protein, shifting the glycosylation profile of immunoglobulin G (IgG) towards a younger biological age, which promotes a healthier age trajectory[9]. Overall, these results suggest that NT may enhance cellular NAD+ production, reduce markers of inflammation, and promote biological youth.

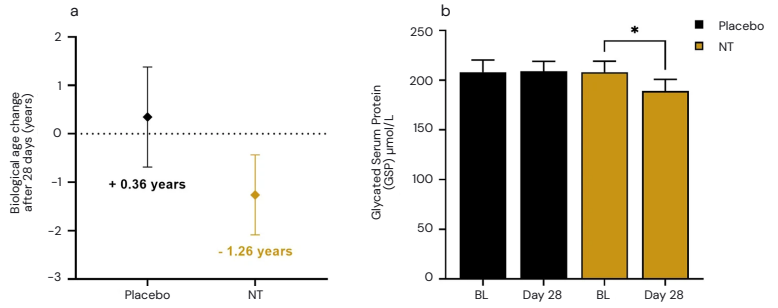

Figure 1. After 28 days of supplementation with a formulation targeting multiple points in the NAD+ salvage pathway (NT), participants had improvements in biomarkers of aging. Image adapted from Henderson et al., 2024[9]. BL = Baseline. Image used under Creative Commons License.

3.2. Supported Cellular Energy

A clinical trial was conducted over 6 weeks, comparing 1,200 mg/day coenzyme Q or 1,000 mg/day NR supplementation to placebo in 25 individuals with moderate to severe chronic kidney disease[17]. Supplementation with NR improved oxidative stress, inflammation, and cell bioenergetics[17]. These findings indicate NR supplementation may have potential benefits for mitochondrial function, energy production, and inflammation.

Furthermore, a clinical study involving 20 pairs of identical twins with significantly different body masses was conducted, where they received NR supplementation, gradually increasing from 250–1,000 mg/day over 5 months[18]. They found that NR improved systemic NAD+ metabolism, muscle mitochondrial number, myoblast differentiation, and gut microbiota composition in both cotwins[18]. They also found that NR was able to modulate epigenetic gene expression in muscle and adipose tissue in both cotwins[18]. The results from this study suggest that NR supplementation may support energy production, muscle and mitochondrial health, and improve gut microbiota composition.

Additionally, a clinical study involving 30 newly diagnosed Parkinson's disease patients who received either 1,000 mg/day NR or placebo was conducted over 30 days[19]. They found that NR significantly increased cerebral NAD+ levels, reduced inflammatory cytokines, and upregulated pathways related to mitochondrial, lysosomal, and proteasomal function, which are essential for efficient energy metabolism[19]. Together, these findings indicate that NR supplementation may increase NAD+ levels in the brain, improve energy metabolism, and reduce inflammation.

3.3. Improved Mood, Fatigue, and Cognitive Function

A study was conducted involving 145 colorectal cancer survivors to investigate cross-sectional associations between dietary intake of NAD+ precursors and patient-reported outcomes. They found that high daily intake of NAM, a main NAD+ precursor, was significantly associated with lower levels of fatigue, depression, and anxiety, and improved emotional functioning in colorectal cancer survivors[20].

NAD+ has also been investigated in clinical studies involving patients with Parkinson's disease. In one case report, an 80-year-old man with a history of Parkinson's Disease received intravenous NAD+ therapy at 500-1,500 mg/day over 8 days, which was associated with improvements in physical tremors and a reduction in visual hallucinations[21]. Maintenance therapy with an intranasal NAD+ spray at 300 mg/mL, administered as two sprays per nostril daily, was used to sustain symptom improvement[21].

Furthermore, a descriptive investigation involving 3 Parkinson's disease patients used an initial course of intravenous NAD+ followed by intranasal administration of 200 mg/mL NAD+, 0.5 mL per nostril[22]. Participants reported improvements in quality of life, cognitive function, tremor severity, and pain[22]. Together, these studies indicate that NAD+ may be effective in improving some of the symptoms associated with the DNA damage caused by Parkinson's disease.

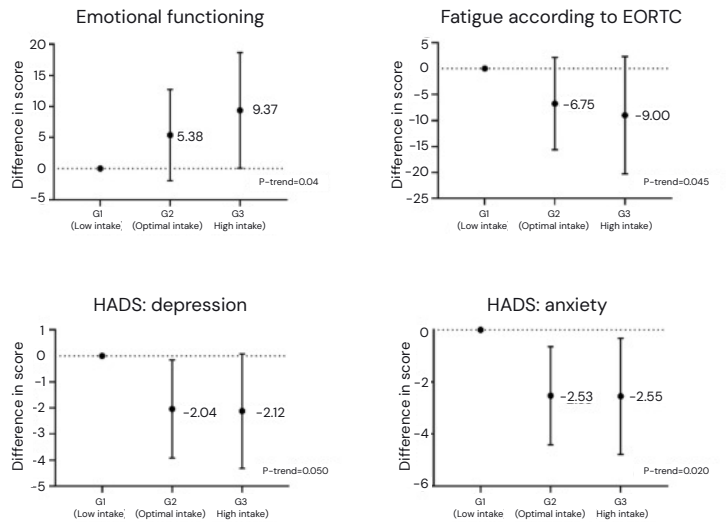

Figure 2. High daily intake of NAM was associated with significantly improved emotional function and reduced fatigue, depression, and anxiety in colorectal cancer survivors. Image adapted from Wu et al., 2021[20]. Image used under Creative Commons License.

3.4. Enhanced Physical Performance and Overall Wellness

Two clinical trials were conducted involving older adults who received either 250 mg/day NMN or a placebo over 12 weeks, and both studies found that NMN supplementation increased NAD+ levels[8,10]. The first study also found that NMN supplementation led to significantly increased NAD+ levels and improvements in motor function, including increased gait speed and grip strength, and therefore may be effective in preventing age-related decline in muscle functions[10]. The second study also found that NMN supplementation maintained walking speed and improved sleep quality[8].

Additionally, a clinical study carried out over 6 weeks in 48 young and middle-aged recreational runners found that 600 mg/day and 1,200 mg/day NMN led to increased oxygen uptake (VO2), percentages of maximum oxygen uptake (VO2 max), power at first ventilatory threshold, and power at second ventilatory threshold when compared with the control group[23]. They concluded that medium and high doses of NMN likely increase aerobic capacity during training due to enhanced oxygen utilization in skeletal muscle[23]. This study suggests that supplementation with NMN may improve physical performance, potentially due to enhanced ability of the muscles to use oxygen and produce energy more efficiently.

Another clinical study with 12 young and 12 older men was carried out, where participants either received a total dose of 500 mg NR or placebo, and blood and urine samples were collected pre- and 2 hours post-supplementation[24]. They found that in older adults who received NR, oxidative stress decreased, which may protect against mitochondrial damage, and physical performance improved[24].

Moreover, in a clinical study involving 20 patients with amyotrophic lateral sclerosis (ALS), daily supplementation with 1,200 mg/day EH301 (a combination therapy containing NR and the antioxidant pterostilbene) for 16 weeks resulted in improvements in body composition, physical function, and muscle function compared with placebo[25,26].

Furthermore, a 12-week clinical study in 108 older adults found that 250 mg/day NMN taken in the afternoon prevented loss of physical performance and improved fatigue, indicating NMN may be beneficial for overall wellness[27].

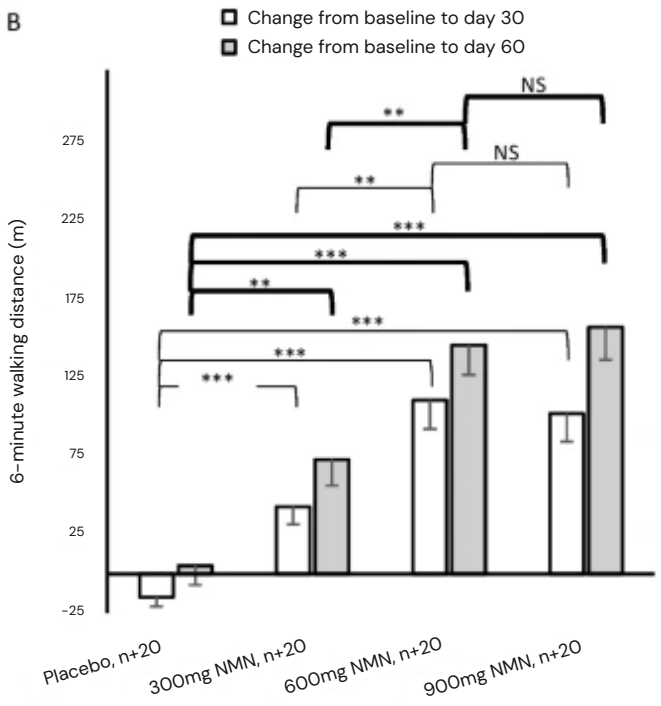

Figure 3. An increase in 6-minute walking distance was observed in participants who received NMN supplementation. Image adapted from Yi et al., 2022[16]. Image used under Creative Commons License.

3.5. Anti-Inflammatory Effects

A clinical study conducted over 21 days in 12 older men found that 1,000 mg/day NR increased NAD+ levels and decreased levels of circulating inflammatory cytokines[29].

Additionally, in a clinical study, 5 patients with advanced or end-stage heart failure received escalating doses of NR from 250 mg to 1,000 mg over 9 days[30]. After taking blood samples from these patients, they found that NR enhanced peripheral blood mononuclear cell respiration and reduced pro-inflammatory gene expression in 4 of the patients[30]. Together, these studies indicate that NR supplementation may have anti-inflammatory effects.

4 Safety and Dosing

NAD+ and its precursors are generally well-tolerated in human clinical trials[30]. Most human trials report no serious adverse effects or toxicity with 250-1,200 mg/day of oral NR over several weeks[30–32]. Mild side effects may include headache, muscle pain, flushing, nausea, diarrhea, and fatigue[31,33].

For intravenous delivery, studies indicate that 500-1,500 mg/day of NAD+ is well-tolerated with no significant adverse events reported[21,34]. Subcutaneous injection of NMN is well-tolerated in mouse models at 100 mg/kg body weight once daily, over several weeks[35–37]. Local injection site reactions such as redness or bruising may occur, if reactions persist, changing the needle site or discontinuation may be appropriate.

For intranasal delivery, studies report that the administration of intranasal NAD+ following initial intravenous NAD+ is safe between 200-300 mg/mL[21,22]. Treatment with NAD+ nasal sprays has been used chronically with no serious adverse events reported in the small patient cohorts[21,22].

5 Delivery Routes

NAD+ and its precursors, such as NR and NMN, are available in multiple formulations, including intravenous infusion, subcutaneous injection, oral supplementation, and intranasal sprays. Each delivery route offers different levels of bioavailability, practicality, and compliance.

Oral NAD+ administration has limited effectiveness in raising plasma or tissue NAD+[38]. When ingested, NAD+ undergoes degradation in the gastrointestinal tract, reducing its bioavailability. In addition, its large polarity and charge prevent passive transport across the plasma membrane, making direct cellular absorption difficult[38]. NAD precursors are more commonly administered orally, however, they require enzymatic conversion into NAD+. This process depends on factors such as age, tissue distribution, and enzyme availability, meaning that precursor supplementation may not always result in efficient increases in cellular NAD+[11].

Subcutaneous injection of NAD+ bypasses these metabolic and transport barriers, delivering NAD+ directly into systemic circulation[38,39]. However, this method requires a medical setting and professional supervision. Subcutaneous injections offer a less invasive alternative. By delivering NAD+ into adipose tissue, it bypasses first-pass metabolism in the gut and liver, allowing for slower, gradual absorption of NAD+ into the bloodstream.

Intranasal formulations offer non-invasive alternatives that also bypass first-pass metabolism in the gut and liver. This route of delivery offers potential improvements in bioavailability compared to oral routes, as NAD+ is absorbed directly into the systemic circulation through highly vascularized nasal mucosa, while being more practical than intravenous therapy for long-term use[21,22].

6 Fridays' NAD+ Therapies

Fridays offers longevity therapies, including physician-guided NAD+ therapies in multiple formulations, designed to maximize bioavailability and convenience. As direct oral NAD+ is not efficiently absorbed, Friday offers NAD+ in innovative delivery systems.

NAD+ Subcutaneous Injection: Direct delivery of NAD+ into adipose tissue, where it is gradually absorbed into systemic circulation, avoiding first-pass metabolism, providing steady exposure and reducing the need for clinical supervision.

NAD+ Nasal Spray: A needle-free option that bypasses first-pass metabolism, allowing NAD+ to be absorbed directly into the bloodstream, offering a practical option for ongoing supplementation.

StatRx Sublingual Liposomal Delivery: A cutting-edge delivery system now enables NAD+ to be taken sublingually, encapsulating NAD+ for potentially enhanced absorption and therapeutic effects. The StatRX delivery system, available exclusively at Friday's, enables easy and reliable delivery of NAD+ through the sublingual pathway, without the need for needles.

Fridays focuses on safety, education, and accessibility, helping individuals explore physician-guided wellness options that may support energy, recovery, and healthy aging. With transparent pricing and personalized care, Fridays make advanced therapies approachable and convenient for everyday life.

7 Conclusion

NAD+ represents a scientifically grounded and supported approach to enhancing cellular energy, promoting healthy aging, and overall wellness. By replenishing NAD+ levels that decline with age, supplementation supports mitochondrial function, DNA repair, and signaling pathways that underpin energy production and healthy aging. Clinical research on NAD+ precursors demonstrates consistent safety and ability to increase NAD+ availability, with reported benefits across fatigue, mood, inflammation, and physical performance. While clinical evidence on intravenous and intranasal administration of NAD+ is emerging, potential benefits include improved cognitive and neurological function. Reported side effects are typically rare or mild, underscoring NAD+'s favourable safety profile.

As direct oral NAD+ has limited bioavailability, advanced delivery technologies are enabling supplementation to be more effective, accessible, and convenient. Fridays' innovative approaches, including subcutaneous injection, intranasal spray, and StatRX sublingual system, bypass digestive barriers with the intent of enabling reliable absorption. These solutions lower barriers to therapy while maintaining effectiveness, making NAD+ supplementation practical for everyday use.

Taken together, the evidence supports NAD+ as a safe, effective, and patient-friendly therapy for promoting energy, recovery, and healthy aging. With the added advantage of StatRX delivery and physician-guided care, Fridays provides a trustworthy and innovative solution for individuals focused on longevity, vitality, and quality of life.


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NAD+
Liposomal Liquid

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8 References

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