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Nicotinamide Adenine Dinucleotide (NAD^+) and the Biology of Aging Mechanisms of Decline and Therapeutic Restoration

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Abstract

The inexorable process of aging is underpinned by a cascade of molecular deficits that erode cellular homeostasis and organismal function. A pivotal molecule within this cascade is nicotinamide adenine dinucleotide (NAD^+), a fundamental redox cofactor in energy metabolism and an essential substrate for signaling enzymes such as the sirtuin family of deacylases and poly (ADP-ribose) polymerases (PARPs). This review synthesizes current evidence establishing the age-related decline in NAD^+ bioavailability as a key driver of aging phenotypes and evaluates strategies for its therapeutic restoration. We detail the mechanisms of depletion, emphasizing heightened consumption by CD38 and PARP1 amid chronic inflammation and genomic stress. The review critically analyzes three principal intervention paradigms: supplementation with NAD^+ precursors like nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN); lifestyle modalities including caloric restriction and exercise; and pharmacological inhibition of NAD^+-catabolizing enzymes. Compelling preclinical data demonstrate that these approaches can rejuvenate mitochondrial function, improve metabolic health, and extend health span. Early human trials confirm precursor safety and bioavailability, indicating benefits for vascular and metabolic parameters. However, significant translational gaps remain, including questions of long-term safety, optimal dosing, tissue-specific delivery, and potential pro-tumorigenic effects in certain contexts. We conclude that NAD^+ repletion constitutes a potent, mechanism-based axis for aging intervention, yet its definitive clinical integration mandates rigorous long-term studies to transform robust biological insight into effective human therapeutics.

Introduction

Aging is the predominant risk factor for the development of chronic diseases, including cardiovascular disease, neurodegeneration, and cancer. As the global population ages, there is a critical need to develop interventions that target the fundamental biological processes of aging to extend health span, the period of life spent in good health. In recent years, the metabolism of nicotinamide adenine dinucleotide (NAD^+) has emerged as a central focal point in aging research [1, 26]. NAD^+ is an ancient and ubiquitous molecule that plays a dual role in cellular physiology: it is an essential redox coenzyme in hundreds of metabolic reactions governing energy production and, critically, it serves as a required co-substrate for several families of signaling enzymes involved in genomic maintenance, epigenetics, and stress responses [9, 20, 30]. These include the sirtuins (SIRT1-7), poly (ADP-ribose) polymerases (PARPs), and NADases such as CD38 [30].

Research has consistently shown that tissue NAD^+ concentrations decrease with age in both model organisms and people [5, 37]. Research suggests that NAD^+ levels in blood and tissues, including the brain and skin, are significantly lower in middle-aged and older persons compared to younger individuals. This depletion is not just a bystander effect; it actively contributes to physiological decline. Low NAD^+ levels affect the action of sirtuins and PARPs, enzymes essential for maintaining metabolic balance, repairing DNA damage, and supporting cellular survival. This deficiency exacerbates basic ageing markers such as mitochondrial failure, senescent cell accumulation, genomic instability, and persistent low-grade inflammation, sometimes known as "inflammaging" [8, 17].

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Preclinical study shows that preventing or restoring NAD^+ depletion can improve cell function. Restoring NAD^+ levels in old or sick mice improves metabolic health, mitochondrial energy generation, lowers inflammation, and even extends longevity [23, 36]. Recent findings have increased interest in "NAD^+ boosting" as a potential technique to counteract human ageing. Various approaches have been identified, including supplementation with NAD^+ precursor molecules such as NR and NMN, lifestyle interventions like caloric restriction and exercise, and pharmacological inhibition of NAD^+-consuming enzymes like CD38 [32, 33].

This review integrates information from mechanistic, preclinical, and upcoming clinical investigations to provide a comprehensive knowledge of NAD^+ in ageing biology. We first discuss the molecular origins and effects of age-related NAD^+ decrease. We evaluate the effectiveness, mechanisms, and limits of existing NAD^+-boosting methods. Finally, we examine the possible hazards, unanswered concerns, and future options for turning this fascinating biological target into safe and effective therapies that promote human health across the lifespan.

The Molecular Causes of Age-Related NAD^+ Decline

The depletion of cellular NAD^+ during aging is a well-documented phenomenon, yet its causes are multifactorial, stemming from a pronounced imbalance between its biosynthesis and catabolism. NAD^+ is not degraded in its redox cycling between NAD^+ and NADH; instead, its irreversible consumption occurs primarily through its role as a substrate for specific enzyme families [26, 30]. The dynamics of this balance shift unfavorably with age, leading to a systemic NAD^+ deficit.

Increased Catabolism: The Role of CD38 and PARPs

NAD^+ depletion is mostly caused by increased activity of NAD^+-consuming enzymes, including CD38 and poly (ADP-ribose) polymerases (PARPs). CD38, a key NADase, has considerably enhanced expression and activity in aged tissues [5]. This increase is intimately related to the persistent, low-grade inflammation associated with ageing ("inflammaging"). Senescent cells and pro-inflammatory M1-like macrophages in visceral adipose tissue secrete inflammatory cytokines that induce CD38 expression, creating a feed-forward loop where inflammation drives NAD^+ consumption. NAD^+ depletion further exacerbates metabolic dysfunction and inflammatory signaling [8, 26]. Genetic ablation or pharmacological inhibition of CD38 in aged mice robustly preserves tissue NAD^+ levels, restores mitochondrial function, and improves health span, underscoring its central role [5, 32].

Concurrently, genomic instability rises with age, resulting in more DNA damage. This damage activates PARP1, an enzyme that synthesizes poly (ADP-ribose) chains as part of the DNA repair response [2]. Chronic PARP1 activation can deplete cellular NAD^+ pools by up to 80%, competing with sirtuins for available substrate and restricting their action (Braidy et al., 2011). PARPs and sirtuins have different affinities for NAD^+. PARP1 has a low Michaelis constant (Km) and can effectively sequester NAD^+ even when concentrations fall, suppressing sirtuin-mediated longevity pathways [26].

Dysregulation of Biosynthesis: The Salvage Pathway

While consumption rises, the capacity for NAD^+ biosynthesis may also become compromised. The predominant route for maintaining cellular NAD^+ in most mammalian tissues is the salvage pathway, which recycles nicotinamide (NAM)—a product of NAD^+-consuming reactions—back into NAD^+. The rate-limiting step in this pathway is catalysed by nicotinamide phosphoribosyltransferase (NAMPT) (Revollo et al., 2004). Evidence suggests that NAMPT expression and activity may decline in certain tissues with age, although reports are mixed [1]. Furthermore, the activity of NAMPT can be inhibited by its own end-product, high levels of NAM, creating a potential negative feedback loop [20]. Lifestyle factors such as obesity can also suppress NAMPT expression in adipocytes, creating a tissue-specific bottleneck in NAD^+ synthesis that contributes to systemic metabolic dysfunction [34].

Compartmentalization and Systemic Effects

NAD^+ metabolism is compartmentalised in cells, having distinct pools and synthesis processes in the cytoplasm, nucleus, and mitochondria [6]. NAD^+ has a limited half-life (1-2 hours in the cytosol/nucleus) and requires continuous production to maintain equilibrium. Ageing affects this delicate equilibrium both inside cells and across the body. The gut flora, which provides NAD^+ precursors, may alter with ageing, impacting precursor availability [31]. Age-related NAD^+ deficit is caused by a combination of increased catabolic pressure from CD38 and PARPs, decreased NAMPT-mediated salvage, and changes in precursor supply. This defect directly impairs sirtuin activity, setting the scene for a wide range of age-related pathologies.

Physiological Consequences of NAD^+ Deficiency in Aging

The pathophysiology of age-related illnesses is driven by the systemic fall in NAD^+ bioavailability, which has significant negative impact on several organ systems. A key mechanism that interferes with vital metabolic, mitochondrial, and cellular integrity functions is the inhibition of sirtuin and PARP activity.

Metabolic Dysfunction and Insulin Resistance

The disturbance of energy homeostasis is one of the main effects of low NAD^+. Reduced sirtuin activity, especially of SIRT1 and SIRT3, causes a series of dysfunctions in metabolic tissues such skeletal muscle, adipose tissue, and the liver. Fatty acid oxidation and mitochondrial biogenesis depend on transcriptional coactivators like PGC-1α, which SIRT1 deacetylates and activates. Reduced oxidative capacity, insulin resistance, and fat build-up are all consequences of its

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impairment [7]. In a similar vein, SIRT3 deficiency in mitochondria accelerates the development of metabolic syndrome symptoms in model animals by promoting protein hyperacetylation, increasing oxidative stress, and compromising the activity of metabolic enzymes [18]. Systemic insulin sensitivity is directly compromised by reduced NAMPT-mediated NAD^+ production in adipocytes [34].

Mitochondrial Dysfunction and the Pseudohypoxic Shift

For mitochondrial oxidative phosphorylation (OXPHOS), NAD^+ is essential. Reduced ATP generation efficiency results from changes in mitochondrial metabolism caused by a decrease in the NAD^+/NADH ratio. Crucially, even under normoxic settings, NAD^+ shortage stabilizes hypoxia-inducible factor 1-alpha (HIF-1α) by inducing a pseudo hypoxic state (Gomes et al., 2013). Then, by downregulating the production of respiratory complexes I, III, and IV, HIF-1α suppresses mitochondrial OXPHOS while concurrently encouraging a shift towards glycolytic metabolism—a behavior that is similar to the Warburg effect. This metabolic reprogramming not only affects cellular energy output but also produces a milieu permissive to metabolic syndrome and cancer development [26]. A vicious cycle of dysfunction is also created by compromised SIRT3 activity, which makes it more difficult for antioxidant defences like manganese superoxide dismutase (MnSOD) to activate. This results in increased reactive oxygen species (ROS) and more mitochondrial damage.

Neurological Decline and Neurodegeneration

The brain is especially susceptible to NAD^+ depletion because of its extraordinarily high energy consumption. Maintaining neuronal health, promoting DNA repair through PARPs, controlling synaptic plasticity, and reducing neuroinflammation all depend on NAD^+. These functions are compromised by age-related NAD^+ depletion in the brain. NAD^+ replacement has been demonstrated to enhance cognitive function, reduce tau and amyloid pathology, and reduce neuroinflammation by suppressing the cGAS-STING pathway in Alzheimer's disease mice (Hou et al., 2021; Fang et al., 2016). Similarly, by improving mitochondrial quality control and reducing oxidative stress, NAD precursors shield dopaminergic neurons in Parkinson's disease models [28]. These findings underline the importance of NAD^+ depletion in weakening the brain's resistance to age-related stresses.

Cardiovascular Impairment

Age-related decreases in vascular endothelial function are partly caused by oxidative stress and decreased nitric oxide (NO) bioavailability. SIRT1 promotes vasodilation by deacetylating and activating endothelial NO synthase (eNOS) in response to NAD^+. Thus, endothelial dysfunction, arterial stiffness, and hypertension are all influenced by NAD^+ depletion [12]. Restoring NAD^+ levels in old mice reverses arterial dysfunction, enhances endothelium-dependent dilatation, and lowers oxidative stress, according to preclinical research, underscoring the therapeutic promise for cardiovascular ageing [10].

Immunosenescence and Chronic Inflammation

Immunosenescence and a persistent inflammatory state are linked to ageing. The creation of energy for immune cell multiplication and the activity of DNA-repair enzymes for antibody gene recombination depend on NAD^+. These procedures are hampered by its decrease. Moreover, as NAD^+ levels decline, the activity of SIRT1, which suppresses the pro-inflammatory transcription factor NF-κB, is lowered. As a result, aged and senescent cells release more inflammatory cytokines and exhibit the senescence-associated secretory phenotype (SASP) [24]. Ironically, this inflammation causes CD38 to be more upregulated, which speeds up the consumption of NAD^+ and creates a vicious loop that connects chronic inflammation to metabolic decline.

Muscle Wasting and Sarcopenia

Mitochondrial dysfunction and stem cell depletion are closely associated with sarcopenia, the age-related decrease of skeletal muscle mass and function. Muscle mitochondrial health and muscle stem cell (satellite cell) activity depend on NAD^+. Depletion of NAD^+ reduces satellite cells' ability to regenerate and causes mitochondrial dysfunction in muscle fibres [36]. Restoring NAD^+ in elderly mice successfully delays the onset of sarcopenia by improving exercise endurance, mitochondrial oxidative capacity, and muscle stem cell activity.

In conclusion, essential biological processes are disrupted by NAD^+ depletion, which functions as a shared upstream driver. It accelerates the systemic deterioration typical of ageing by disrupting sirtuin signalling and mitochondrial integrity, which spreads dysfunction throughout metabolic, neurological, cardiovascular, immunological, and musculoskeletal tissues.

Therapeutic Strategies to Restore NAD^+ Homeostasis

Given the established causal role of NAD^+ depletion in driving age-related pathologies, significant research efforts are focused on developing interventions to restore its bioavailability. These strategies can be broadly categorized into three complementary approaches: 1) supplementation with NAD^+ biosynthetic precursors, 2) lifestyle and dietary interventions that upregulate endogenous NAD^+ synthesis, and 3) pharmacological inhibition of NAD^+-consuming enzymes.

NAD^+ Precursor Supplementation

This direct approach involves administering molecules that serve as substrates in NAD^+ biosynthetic pathways. The primary candidates are vitamin B3 derivatives, which differ in their metabolic routes, efficiency, and side-effect profiles.

Nicotinamide Riboside (NR) and Nicotinamide Mononucleotide (NMN): These have become the most prominent NAD^+ boosters in longevity research. NR is

efficiently converted to NMN by NR kinases, and NMN is subsequently adenylated to form NAD^+. Both compounds show robust oral bioavailability and safely elevate NAD^+ levels in rodents and humans [22, 23, 33]. Preclinically, long-term administration mitigates a wide range of age-associated physiological declines, improving insulin sensitivity, mitochondrial function, cognitive performance, and extending health span and, in some studies, median lifespan [35, 36]. Human clinical trials, while still early-phase, confirm their safety and demonstrate increased circulating NAD^+ levels. Notably, NR supplementation in middle-aged and older adults has been associated with reduced arterial stiffness and blood pressure, as well as lowered levels of circulating inflammatory cytokines [13, 22]. A pivotal study showed NMN supplementation significantly improved muscle insulin sensitivity in prediabetic women [34].

Nicotinic Acid (Niacin) and Nicotinamide (NAM): While these classic vitamin B3 forms can raise NAD^+, their utility is limited. High-dose niacin causes prostaglandin-mediated flushing, and long-term cardiovascular benefit is debated [11]. High-dose NAM can act as a feedback inhibitor of sirtuins and PARPs, potentially counteracting the desired enzymatic activation, and carries a risk of hepatotoxicity [26].

Lifestyle Interventions: Diet and Exercise

Lifestyle modifications known to promote longevity naturally engage NAD^+ metabolism, offering a synergistic foundation for any therapeutic strategy.

Caloric Restriction (CR) and Fasting: CR robustly upregulates the expression and activity of NAMPT, the rate-limiting enzyme in the NAD^+ salvage pathway, via activation of AMP-activated protein kinase (AMPK) and circadian clock components [16]. This increases tissue NAD^+ levels and enhances SIRT1 activity, mimicking many of the molecular benefits of direct precursor supplementation.

Exercise: Physical activity is a potent physiological NAD^+ booster. Muscle contraction increases NAD^+ turnover and upregulates NAMPT expression in skeletal muscle, thereby enhancing the local NAD^+ pool [4]. Exercise-induced activation of AMPK also promotes NAD^+ synthesis. This elevation supports mitochondrial biogenesis and function, contributing to the well-documented metabolic benefits of regular physical activity [30].

Pharmacological Inhibition of NAD^+ Consumption

Targeting the enzymes responsible for age-related NAD^+ depletion offers a complementary strategy to precursor supplementation.

CD38 Inhibitors: In preclinical models, small-molecule CD38 inhibitors, such as the synthetic drug 78c and the flavonoid apigenin, have demonstrated considerable potential. CD38 suppression increases median longevity, improves metabolic health, increases exercise capacity, and raises tissue NAD^+ levels in old mice [14, 29, 32]. This technique directly counteracts a main cause of NAD^+ depletion.

PARP Inhibition: Although PARP inhibitors are therapeutically employed in cancer, their role in ageing is unclear. Pharmacological suppression of PARP1 in elderly mice has been demonstrated to enhance NAD^+ availability, accelerate mitochondrial metabolism, and improve muscular performance [3, 25]. However, long-term systemic PARP suppression has major dangers due to PARPs' critical function in DNA repair, potentially increasing genomic instability and cancer risk.

Other Targets: Inhibition of NNMT (nicotinamide N-methyltransferase), which methylates and thereby removes NAM from the salvage pathway, is another strategy to increase substrate availability for NAD^+ synthesis (Kraus et al., 2014).

In conclusion, it seems most logical to restore NAD^+ equilibrium using a multifaceted strategy. While targeted inhibition of certain consumers, such as CD38, provides a potential pharmaceutical approach, combining precursor supplementation with lifestyle therapies, such as exercise, may result in synergistic benefits. Depending on a person's age, health, and particular risk factors, the best course of action may vary.

Conclusion

Nicotinamide adenine dinucleotide (NAD^+) metabolism plays a crucial part in the biology of ageing, as demonstrated by the strong body of data compiled in this review. A multifactorial imbalance, including increased consumption by enzymes such as CD38 and PARP1 in response to chronic inflammation and genomic stress and possible inefficiencies in its salvage biosynthesis, is responsible for the age-dependent reduction in NAD^+, which is a conserved occurrence across animals. Sirtuins and other vital NAD-dependent enzymes are directly impacted by this deficiency, which is a pathogenic driver rather than a passive biomarker. Systemic effects include insulin resistance, cardiovascular impairment, neuroinflammation, immunosenescence, metabolic dysregulation, and mitochondrial dysfunction all of which are key components of age-related functional decline.

In preclinical animals, therapeutic approaches to restore NAD^+ homeostasis have shown significant success. Targeted pharmacological inhibition of NAD^+ consumers like CD38, lifestyle interventions like exercise and calorie restriction, and supplementation with next-generation precursors like nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN) can improve tissue health, prolong life, and restore cellular function. Important features of this biology have been effectively translated by early-phase human clinical studies, which have confirmed the safety and bioavailability of NAD precursors and shown encouraging, although early, signs of enhanced metabolic, vascular, and inflammatory health.

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However, there are several important obstacles and unanswered problems in the way of practical implementation. The indiscriminate use of high-dose supplements in some groups is contraindicated due to potential hazards, including the context-dependent potential to feed pre-existing malignancies. The factors influencing individual response variability, the best dosage and formulation techniques, and the long-term safety of persistently raised NAD^+ levels in humans are still mostly understood. Additionally, thorough research is needed to determine the relative effectiveness of various approaches and any possible synergies in combination therapy.

Consequently, even though NAD replacement is one of the most promising and mechanistically based therapies in geroscience, thorough, long-term, and ethically conducted clinical research is necessary to guide its future. To go beyond surrogate indicators, large-scale trials with concrete clinical objectives are necessary. To safely utilize this robust metabolic pathway, a customized, evidence-based strategy that may combine NAD^+ regulation with other geroprotective tactics would be essential. The ultimate objective is to transform this fundamental molecular knowledge into concrete expansions of human health span, enabling longer lives lived with vigour and resilience, rather than just improving a biochemical parameter.

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Declarations:

Authors' Contribution:

- a-b-c-dConceptualization, data collection, interpretation, drafting of the manuscript and intellectual revisions
- The authors agree to take responsibility for every facet of the work, making sure that any concerns about its integrity or veracity are thoroughly examined and addressed

Data Availability Statement

- No new data were created or analyzed in this study. Data sharing is not applicable to this article.

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