Therapeutic Use of Intravenously Administered Nicotinamide Adenine Dinucleotide

Tabitha Block, M.S. and Jonathann Kuo, M.D.

Nicotinamide adenine dinucleotide (NAD) is well-known as an electron carrier in redox reactions and has recently been studied extensively due to emerging knowledge about its role in intracellular signaling pathways. As an essential cofactor and substrate involved in a wide variety of key processes ranging from oxidative phosphorylation and ATP production to immunological functions and cell survival[1, 2], NAD has been suggested as a possible therapeutic target for the control of multiple pathological diseases including age-associated disorders, neurodegenerative diseases, and mental disorders[3].

Levels of NAD+, the oxidized form of NAD, decline across multiple tissues with age as a result of excessive DNA damage from free radical accumulation or ultraviolet exposure. This systemic decrease results in altered metabolic states and increased disease susceptibility. It has been predicted that restoring NAD+ levels can promote general health and even extend the human lifespan. This hypothesis has prompted many recent studies, many of which have shown NAD+ supplementation to increase the body's resilience to many different diseases[1].

A host of different NAD+ supplementation methods have been studied to date, including oral supplementation of NAD precursors such as vitamin B_3[4], nicotinamide riboside (NR), nicotinamide mononucleotide (NMN), and nicotinamide[1]. However, as opposed to supplementation via oral means, intravenous administration of nutrients is known to result in higher serum concentrations[5]. In addition, attempts to increase the levels of available NAD+ via the ingestion of NAD precursors is highly dependent on enzyme-limited synthesis pathways[2]. Thus, physician-guided intravenous NAD+ supplementation is believed to provide a more direct and effective approach of resolving NAD+ decline.

The family of NAD+-dependent enzymes called sirtuins play a central role in the translation of NAD+ levels to the regulation of key cellular processes like metabolism, DNA repair, stress response, or chromatin remodeling[3]. The deacetylase properties of sirtuins mediate broad functions involved in the regulation of aging and longevity. In mammals, there are seven sirtuin families, SIRT1-7, that function in various subcellular compartments. The activation of sirtuins generally triggers transcriptional pathways that enhance metabolic efficiency and upregulate resistance to oxidative stress[6]. By increasing antioxidant activity and activating DNA damage repair proteins, sirtuins have been shown to promote longevity in organisms ranging from yeast to mice and to mitigate diseases of aging in murine models[7]. Poly-ADP-ribose polymerases (PARPs) compose another category of enzymes that consume NAD+ and repair DNA strand breaks in the nucleus[8].

CONDITIONS BENEFITING FROM NAD+

Depression

Depression is a complex mood disorder that is associated with pathologies like inflammation, synaptic dysfunction, metabolic syndrome, and cognitive deficit. The modulation of sirtuin activity has been studied as a promising approach to prevent the development of depression[9], and a few possible mechanisms of sirtuin activity have been implicated: (1) SIRTs have been shown to suppress proinflammatory markers that are typical of patients with depression such as interleukin (IL)-6, tumor necrosis factor (TNF)-α, and C-reactive protein[10]; (2) SIRTs might regulate insufficient levels of neurotransmitters commonly seen in depression by modulating their expression, secretion, and uptake[11, 12, 13]; and (3) SIRT1 improves synaptic plasticity in depressive states[9]. It has been shown that defects in SIRT1 activity can be reversed by supplementation with NAD precursors[14], suggesting that the manipulation of sirtuins via NAD may be a therapeutic solution for depression.

Pain Syndromes and Inflammation

Every pain syndrome is associated with a set of inflammatory mediators. Thus, the key to treating conditions associated with pain is thought to lie in understanding their inflammatory profiles and subsequently inhibiting or suppressing the production of inflammatory mediators[15]. At Hudson Medical Group, conditions such as arthritis, back and neck pain, fibromyalgia, migraine, neuropathic pain, complex regional pain syndrome (CRPS), bursitis, shoulder pain, and many more are treated by limiting inflammation in affected areas. There is growing evidence that NAD is involved in anti-inflammatory processes. Studies performed by Elhossan et al. linked oral supplementation of NR to depressed circulating levels of inflammatory cytokines such as IL-6, IL-5, IL-2, and TNF-α[16]. Further, in murine models, treatment with NMN for time periods as low as one week caused a reduction in the expression of TNFα and IL-6 in skeletal muscle[14].

Skeletal Muscle Function

Many previous studies report a progressive, age-dependent decline in oxidative phosphorylation efficiency in skeletal muscle[17]. Mitochondrial dysfunction of this form manifests as muscle atrophy and inflammation, as well as impaired insulin signaling and glucose uptake. In studies performed by Gomes et al., treatment of old mice with NAD+ precursors dramatically improved muscle function by increasing mitochondrial efficiency, increasing ATP production, reducing inflammation and influencing muscle composition[14]. Similarly, improving mitochondrial function has been demonstrated to increase oxidative metabolism in muscle, thereby increasing endurance, thermogenic capacity, and recovery from muscle injury[18]. NR also increases the quantity and quality of muscle stem cells (MuSC) and enhances muscle regeneration in elderly mice models by preventing MuSC senesence[19]. For individuals affected by muscular dystrophy,

supplementation of NR is known to improve mobility and reduce the percentage of detached muscle fibers in *C. elegans* and zebrafish models, respectively[20, 21].

Longevity and Aging

A steady decline in total NAD+ levels over time is a common phenomenon that occurs naturally for all organisms[3]. This decrease parallels a progressive decline in mitochondrial function that leads to various age-related pathologies[17]. Considering the vital role of NAD+ in oxidative phosphorylation and mitochondrial homeostasis, it follows that restoring NAD+ levels in diseased and aged animals can extend productive lifespan. In models of mice with accelerated aging phenotypes, raising NAD+ levels has also been shown to be effective in extending lifespan. Treatment of elderly mice was shown to extend median lifespan by up to 58% in some studies. This increased lifespan was associated with many physiological improvements such as improved mitochondrial and stem cell function[19, 22]. Supplementation of NAD precursors initiated at a younger age has been observed to increase activity, improve insulin sensitivity, and yield greater bone-density, ultimately delaying aging and age-related physical decline[23].

A hallmark of aging is a decrease in neuronal function and impaired cognitive behaviors, often manifested as neurodegenerative disorders such as Alzheimer's disease. Administration of NAD precursors such as NMN and NR has been demonstrated to be effective in improving multiple aspects of neurodegenerative disease. For example, various studies have reported that NMN improves mitochondrial respiration, electrophysiological deficits, and neural stem cell proliferation and renewal[2]. The ability of NAD+ supplementation to restore health and extend lifespan in old and diseased animals is suggestive of the fact that this molecule is critical to achieve "productive aging" in humans[3].

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