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NMN

INTRODUCTION

Only recently have we begun to understand that the aging process itself is the primary driver for many chronic diseases. As a result, there has been growing effort to understand the mechanisms of aging and to find therapies that work to slow this process down and extend the "health span," the period of life characterized by the absence of severe disease with reasonably good health.[1]

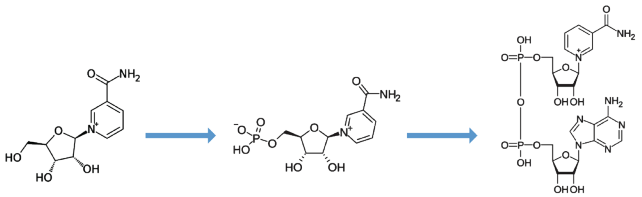
Many mechanisms characterize the aging process, often referred to as the "hallmarks of aging," including cellular senescence, telomere attrition, mitochondrial dysfunction, dysregulated nutrient sensing, etc.[2] A substantial and growing body of evidence suggests that waning levels of nicotinamide adenine dinucleotide (NAD^+), a metabolite with many different cellular functions, is intricately involved in the aging process. NAD^+ decline with age has been described as a "major player in aging-related diseases."[3] NAD^+ is a coenzyme needed for at least 500 enzymatic reactions, many crucial to a cell's metabolism, and it also catalyzes electron transfer in metabolic reduction-oxidation (redox) reactions.[4] In addition, NAD^+ is essential to important signalling proteins known as sirtuins, and to poly(ADP-ribose) polymerases (PARPs), a family of 17 enzymes including PARP1 (also known as NAD^+ ADP-ribosyltransferase 1), an enzyme that detects and repairs DNA damage. This partly explains the importance of NAD^+ to optimal cellular functioning.[5]

A decline in NAD^+ levels in both humans and experimental models of aging, as well as a decline in the proteins that require it for optimal function (including sirtuins and PARPs), have implicated this molecule as having an etiological role in many of the hallmarks of aging.[6] Strategies to boost NAD^+ levels have shown evidence of benefit for a wide range of age-related diseases in experimental models, including improved cognitive function, insulin secretion and sensitivity, hepatic function, and protection from cerebrovascular and cardiovascular disease.[7] By targeting a key driving process for aging itself, the hope is that many age-related diseases may be prevented or delayed.

WHAT IS NMN?

Nicotinamide mononucleotide (NMN) is a bioavailable precursor to NAD^+ that has been shown to increase cellular levels of NAD^+ in human trials.[8] Most cells cannot directly import NAD^+ and must synthesize it *de novo* using tryptophan (known as the kynurenine pathway) or recycle other compounds to produce it. These compounds include NMN and other forms of vitamin B3, such as nicotinamide or nicotinic acid, with the majority of NAD^+ production occurring through this process, known as the salvage pathway.

Most NAD^+ precursors (including nicotinamide riboside (NR)) require several steps to be converted to NAD^+ through enzymatic action that may be highly variable, potentially impairing NAD^+ synthesis. For example, the enzyme NAMPT is rate-limiting for the conversion of nicotinamide (NAM) to NMN, and may be inhibited by aging, obesity, inflammation, and a high-fat diet. Given that NMN is only one chemical step away from NAD^+ (as shown in the graphic below) and is not reliant on the enzyme NAMPT, it is an especially attractive candidate as an NAD^+ booster.[5,7]



NAD^+ Biosynthetic Pathway

In experimental models, supplementation with NMN has been associated with a wide range of benefits related to metabolism and cellular function. These benefits include suppression of weight gain, improved insulin sensitivity and plasma lipid profiles, enhancement of mitochondrial respiratory compatibility, and prevention of the decline of many physiological functions.[9]

Human trials of NMN supplementation have been encouraging. In a randomized and double-blind 10-week clinical trial, women with impaired glucose metabolism demonstrated signs of improved skeletal muscle insulin sensitivity and signalling, with an improvement similar to what would be observed with a 10% weight loss.[10] In a six-week double-blind trial, healthy amateur runners had improved aerobic capacity compared to a placebo, an effect attributed to enhanced oxygen use by skeletal muscle.[11] Trials with older adults have also demonstrated benefit; a double-blind controlled trial found that older adults receiving NMN (especially taken in the evening) reported reduced daytime drowsiness, as well as signs of improved muscle function (as assessed by a sit-to-stand evaluation) compared to a placebo.[12] A second trial with men aged 65 or older found that in addition to increasing NAD^+ levels, NMN supplementation improved muscle performance (as evaluated using gait speed and grip strength) compared to a placebo.[13]

Additionally, in a controlled trial with middle-aged adults, although no significant difference was found between NMN and a placebo, a trend toward reduced arterial stiffness was observed in a trial lasting only three months.[14] Arterial stiffness has emerged as an independent risk factor for cardiovascular and metabolic diseases, which appears to precede the onset of these diseases.[15]

MECHANISM OF ACTION

The benefits of NMN are likely to be mediated entirely by its effects on NAD^+, which itself has diverse metabolic and physiological actions. Sirtuins, for example, have many cardiac and metabolic effects, including upregulation of mitochondrial biogenesis, protection against atherosclerosis, improved endothelial function, enhanced insulin sensitivity, reduced inflammaging, etc.[16] Sirtuins impact inflammation, cell growth, circadian rhythms, energy metabolism, neuronal function, and stress resistance, playing a role in nearly all cellular functions.[7]

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ASSESSMENT

No specific contraindications have been described for NMN. It has an excellent safety profile in published clinical trials with both younger and older populations.

GENERAL RECOMMENDATIONS AND DOSING

The recommended adult dose of NMN is 1 capsule 2 times per day, consistent with the clinical trial dosing of 250–300 mg per day used in most trials. Higher doses (600–1200 mg per day) were used among younger adults to improve aerobic capacity.

SUMMARY

NMN has significant promise as an NAD^+ booster as it can increase levels of this metabolite, which has been clearly linked to many critical physiological functions that influence cellular metabolism and repair. Initial controlled trials suggest it not only increases NAD^+ levels, but also reflects the clinical improvements expected from increased NAD^+ availability.

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