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Review article

Anti-Aging Effects of Nicotinamide Riboside (NR) Supplementation

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ABSTRACT

Sirtuins show promise in prolonging lifespan, as shown by previous animal and human studies. They play a role in cellular responses against oxidative stress and in cellular metabolism while also maintaining the length of telomeres. To make sirtuins work, cells need NAD+. The bioavailability of NAD+ inside the cells decreases in normal aging and may add to physiological aging by decreasing the action of sirtuins. The NAD+ metabolites nicotinamide mononucleotide (NMN) and nicotinamide riboside (NR), which are forms of vitamin B3, can increase NAD+ levels and improves different physiological capacities in animal studies. Among these two metabolites, nicotinamide riboside (NR) is more available in food and has better cell permeability, since it does not require any transformation to different intermediates. NR is also proven to be safe by studies, while NMN is yet to demonstrate safety in human consumption. This article aims to discuss the anti-aging effects of nicotinamide riboside (NR), as well as its other health benefits. Overall, previous studies have shown that NR can increase mitochondrial biogenesis and oxidative metabolism, as well as prevent metabolic diseases, neurodegenerative disorders and age-related physiological decline. It effects on mitochondrial metabolism suggests that it could have significant applications in the treatment of age-related diseases.

Keywords: TSirtuins; Nicotinamide mononucleotide; Nicotinamide riboside; NMN; NR; Aging; Anti-aging; NAD+; Lifespan; Life extension; Vitamin B3; Niacin; NAD+ metabolites

INTRODUCTION

In the most recent decades, the overall population has displayed an increased life expectancy with a subsequent increase in seniors, bringing about upgraded health and social expenses. Aging is characterized by a decline and a deterioration of bodily functions and the body's metabolic processes. There are many theories about aging, but none of them is officially accepted [1].

There are some interventions which show promise in both animal and human studies, some of which has resulted in prolongation of lifespan. One of the well-studied targets in anti-aging studies are sirtuins. Sirtuins were once discovered in yeast as transcription repressors, but soon, they were found likewise in bacteria and eukaryotes, such as mammals. There are seven members of the sirtuin family in humans, and they play a role in cellular responses against oxidative stress and in cellular metabolism. These sirtuins protect the body from aging by maintaining the length of telomeres, which are end caps in the DNA that prevent unraveling of chromosomes. The longer the telomeres are, the longer the lifespan [2].

To make sirtuins work, the cells need NAD+. The bioavailability of NAD+ inside the cells decreases in normal aging and may add to physiological aging by decreasing the action of sirtuins. The NAD+ metabolites nicotinamide mononucleotide (NMN) and nicotinamide riboside (NR), which are forms of vitamin B3, can increase NAD+ levels and improve different physiological capacities in animal studies. Among these two metabolites, nicotinamide riboside (NR) is more available in food and has better cell permeability, since it does not require any transformation to different intermediates. NR is also proven to be safe by studies, while NMN is yet to demonstrate safety in human consumption.

This article aims to discuss the anti-aging effects of nicotinamide riboside (NR), as well as its other health benefits.

NICOTINAMIDE ADENINE DINUCLEOTIDE (NAD+) AND ITS METABOLITES

Nicotinamide adenine dinucleotide (NAD+) is a low molecular-weight substance that was previously discovered in boiled yeast extract. This substance was noted to stimulate fermentation and alcohol production outside the body. Studies were subsequently done over the next decades and determined that the structure of NAD+ consisted of two covalently-joined mononucleotides, nicotinamide mononucleotide or NMN, and AMP. The studies further showed that the main functions of NAD+ and NADH were

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as enzyme cofactors that intercede hydrogen transfer in oxidative and reductive metabolic reactions [3].

NAD+ and NADH varies with the availability of energy and nutrients from food. They were shown to control life extension and health through caloric restriction [4].

The main role of NAD+, as previously mentioned, is to encourage hydrogen transfer in various important metabolic pathways. For instance, NAD+ is converted to NADH in glycolysis, a metabolic pathway where glucose is converted into pyruvate. The conversion of NAD+ to NADH is also essential to mitochondrial metabolism. In this pathway, NAD+ is converted into NADH during oxidation of amino acids and fatty acids in the mitochondria. In these mitochondrial pathways, the NADH produced is an electron donor for oxidative phosphorylation and ATP creation [5].

The conversion of food, protein, fat, and sugar into energy requires NAD. Likewise, keeping up blood glucose during the evening and creating ketones requires NADH. It is reoxidized as NADH to NAD+. NADH is additionally re-oxidized to NAD+ when ATP is generated from food. This is required for basic processes in the body [5].

NAD+ controls sirtuins, so that the latter can react to stresses such as fasting, DNA damage, and oxidative stress. Once sirtuins are activated, transcription processes that enhance metabolic efficiency and control mitochondrial oxidative metabolism are also activated. Resistance to oxidative stress is also enhanced. Sirtuins enhance this resistance by promoting antioxidant pathways and facilitating repair of DNA damage by deacetylaton or ADP-ribosylation of proteins involved in repair. Many studies have also shown that sirtuins can prolong lifespan in animals and yeast, and it can moderate age-related diseases such as heart disease, dementia, cancer, type 2 diabetes and inflammatory diseases [6].

NAD+ levels decline by two-fold in aged worms and in the liver and skeletal muscle tissues of aged mice [7]. The bioavailability of NAD+ inside the cells decreases in normal aging and may add to physiological aging by decreasing the action of sirtuins [8]. It was shown that supplementation with NAD+ metabolites is able to restore NAD+ levels in both the nucleus and mitochondria of cells. In one study, aging led to the inactivation of SIRT1, which was reversed by NAD+ metabolites [9]. Despite the fact that NAD+ can be created anew within the body from the amino acid tryptophan, this does not happen in all tissues. Most cells rely on a rescue pathway for recovering NAD+ from other intracellular intermediates, which are available from food [10].

Certain forms of Vitamin B, such as Vitamin B3, enter this rescue pathway from food and goes about as a NAD+ precursor. 10 While the other forms of vitamin B do not have effects on sirtuins, the NAD+ metabolites nicotinamide mononucleotide (NMN) and nicotinamide riboside (NR) can increase levels of NAD+ and improve different physiological capacities in animal studies [11].

NICOTINAMIDE MONONUCLEOTIDE OR NICOTINAMIDE RIBOSIDE: WHICH ONE IS BETTER?

Among the various types of NAD+ precursors, only NMN and NR exhibited better pharmacokinetic and pharmacological properties. Also, these two intermediates are presently used for clinical studies. However, the question remains: which one is better? Investigators have their different supporting views. NR is more available in food and its cell permeability is straightforward as NR does not require any transformation to different intermediates. NR is also proven to be safe by studies, while NMN is yet to demonstrate safety in human consumption [12].

In a 12-week investigation where 2000 mg of NR supplementation was given per day, which was done to evaluate the adequacy of glucose metabolism and insulin sensitivity in obese subjects, NR treatment was safe despite the fact that it did not improve glucose metabolism and insulin sensitivity [13].

Martens et al in 2018 also utilized NAD+ precursors to expand NAD+ bioavailability as a process for improving cardiovascular and other physiological capacities in aging. They did a clinical trial, the results of which demonstrated that long-term supplementation with the NAD+ precursor nicotinamide riboside (NR), is very much tolerated and adequately stimulates NAD+ metabolism in middle-aged and older adults [10].

However, NMN may also have some advantages. In one study that evaluated the efficiency to treat Friedreich's Ataxia (FRDA), an uncommon congenital heart disease, NMN was discovered to be effective where NR treatment failed [14]. In this disease, the enhanced acetylation of a mitochondrial protein known as frataxin and reduced SIRT3 activity results in heart enlargement. NMN at a dose of 500 mg/kg two times each week for six weeks on FXN-KO mice caused improvements in diastolic function and systolic function, as compared with that of saline-treated control rodents. This positive outcome is controlled by expanding the deacetylase activity of SIRT3 on frataxin, while in another study, NR at a dose of 10 mg/kg for five weeks on FXN KO mice neither improved SIRT3 movement nor cardiovascular function [15].

In studies about cognitive impairment in Alzheimer's disease, where dementia was noted to be due to beta- amyloid plaques, NMN was sufficient enough to decrease the formation of beta amyloid plaques. In a study that lasted for six months, where NR was given at a dose of 12 mM in drinking water in rodents, it was seen that DNA damage, nerve inflammation and apoptosis of neurons in the hippocampus area of the brain were reduced. SIRT3 activity in the brain, however, was increased, leading to improved cognition, though there were no noted effects on beta amyloid production [15].

The subcutaneous injection of 100 mg/kg of NMN for 28 days diminished the loss of synapses in neurons, decreased inflammation and improved cognitive function by decreasing the production of beta amyloid protein in the brain. The reason behind this was the inhibition of the formation of amyloidogenic amyloid precursor protein (APP) and activation of non amyloidogenic APP by NMN. It is difficult to define the distinctions between the functions of NMN and NR. It is reasonable to say that they have overlapping activities, while they have their own individual positive and negative effects [16]. Also, in one study, supplementation of NMN in drinking water improved cardiovascular function in old mice [17].

In spite of the fact that NMN has appeared to have beneficial effects in animal studies, these studies still need sufficient clinical and pharmacologic evidence. NMN is expensive to manufacture and the patient has to shoulder these expenses. Though it has its own drawbacks, NMN may still have potential applications, as it can be used to treat Alzheimer's disease, diabetes, and heart diseases. NMN has already been capsulized and is now available in the market. With numerous clinical and preclinical studies going on

and with its potential pharmacological applications, NMN could be an effective treatment for a lot of disorders, especially those that are related to aging [16].

A GLIMPSE AT NICOTINAMIDE RIBOSIDE (NR)

Nicotinamide Riboside (NR) is a pyridine nucleoside type of vitamin B3 that is normally found in milk and is available as a supplement. NR is changed over by nicotinamide riboside kinases (NRK1,2) to NMN, which is then changed over to NAD+ by nicotinamide mononucleotide adenylyltransferase (NMNAT). Oral supplementation with NR has appeared to increase NAD+ in brown fat tissue, skeletal muscles and liver, and to enhance mitochondrial activities in obese mice [18].

Previous studies have shown that a single oral dose of NR can raise NAD+ levels to 2.7-fold. Subsequent studies have shown that supplementation with NR can increase mitochondrial biogenesis and oxidative metabolism. It can also prevent metabolic diseases, neurodegenerative disorders and age-related physiological decline [19]. NR supplementation also holds potential as an effective treatment for heart failure and other diseases with mitochondrial failure [20].

Airhart et al, in their study, found that an NR dose of 1000 mg twice a day increased steady-state, whole blood levels of NAD+ in subjects. The increases in NAD+ ranged from 35 to 168% from the baseline. The study also found that NAD+ effects are well-tolerated, with no side effects that are seen with Vitamin B3 (niacin) such as increased blood glucose levels, increased uric acid levels, flushing, itchiness, and elevated liver and muscle enzymes. Their findings confirmed that NR is potential treatment for diseases that are due to mitochondrial dysfunction [20].

Trammell et al conducted a similar study which evaluated the effects of three different doses of oral NR. The three doses were 30, 100 and 1000 mg respectively. Their findings showed that after 36 days of NR treatment at a final dose of 1000 mg daily, there were no serious adverse events and any events were dose-related. The average NAD+ concentration at 24 hours for the three doses were elevated from the baseline [21].

Oral NR supplementation viably raised levels of NAD+ by 60% as compared to placebo. Supplementation with NR can lower mean systolic and diastolic blood pressure in all subjects. The essential finding of this study is that long-term oral supplementation with 1000 mg of NR daily is an effective way for activating NAD+ metabolism in aged people [10].

Dolopikou et al in 2019 hypothesized that elderly people would benefit more from NR supplementation, and examined the effects of NR supplementation on redox homeostasis and physical capacity in young and elderly people. They have noted previously that nicotinamide riboside supplementation diminished exercise performance in young rodents. It was suggested that supplementation of redox operators applies an ergogenic effect just in people with deficiencies, particularly older people. In their investigation, twelve young and twelve elderly men got NR or placebo treatment. The results demonstrated that NR supplementation elevated NAD(P)H levels, diminished oxidative stress, and improved physical execution in old subjects. This only shows that redox supplementation may be useful only in people who are deficient in antioxidants [22].

A study by Martens et al has shown that supplementation with NR can lower mean systolic and diastolic blood pressure in subjects. Among those with Stage I hypertension, the mean SBP was 9 mmHg lower after NR supplementation. The researchers also observed a reduction in the mean carotid-femoral pulse wave velocity (PWV) after NR supplementation. The PWV is the clinical standard in measuring the stiffness of the aorta and is considered a risk factor for heart attacks related to aging [10].

Based on previous animal studies, it appeared that long-term NR supplementation may improve metabolism in people who consume unhealthy foods and those with metabolic disorders such as diabetes, obesity and metabolic syndrome [10].

A study by Wang et al explored the effects of NR on ethanol induced liver injuries and its underlying mechanisms. The results showed that NR was able to activate SirT1 by increasing NAD+ levels, decreasing oxidative stress, increasing deacetylation of PGC-1 alpha and mitochondrial function. This only shows that NR can protect against ethanol-induced liver damage by replenishing NAD+, decreasing oxidative stress and activating SirT1-PGC-1α mitochondrial biosynthesis [23].

CONCLUSION

Despite the fact that nicotinamide riboside has been known for a while as a NAD+ metabolite, it is only now that its properties and effects have been valued. There is growing evidence to propose that nicotinamide riboside could be a third major Vitamin B3 form which is distinctive from nicotinamide or nicotinic acid. Studies demonstrate that it has a different metabolism and function. It effects on mitochondrial metabolism suggests that it could have significant applications in the treatment of age-related diseases.

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