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Exploring the Therapeutic Potential of Nicotinamide Mononucleotide: A Review of Safety and Efficacy with Emphasis on Diabetes

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Abstract

Introduction: Nicotinamide mononucleotide (NMN) is a supplement that can boost nicotinamide adenine dinucleotide (NAD+) levels in the body, which is crucial for maintaining energy balance and stress response. Declining NAD+ levels with age contribute to aging and related diseases, making NMN supplementation a potential solution. Despite its potential benefits, NMN's safety and efficacy need further investigation.

Aim of the Study: This study aimed to analyze recent research on NMN supplementation regarding its safety and efficacy in improving human health, especially in patients with diabetes and prediabetes, and to suggest potential research directions for this compound.

Methods and Materials: Extensive research was conducted using PubMed and Google Scholar, focusing on literature from the past 5 years, primarily on randomized controlled trials. The databases were searched using the term "nicotinamide mononucleotide" to gather articles, and references from selected articles were included.

Conclusion: A beneficial direction for NMN research is an in-depth analysis of its effects on skeletal muscles in both healthy individuals and those with diabetes. Studies on larger groups, with higher doses, and over longer periods are crucial to determine the optimal supplementation protocol and assess individual variability in NMN's metabolic effects.

Keywords: Nicotinamide mononucleotide, Nicotinamide adenine dinucleotide, NMN supplementation

Introduction

Based on available, published national surveys conducted after 2000, the use of dietary supplements in some European countries exceeded even 50% of the population (Finland and Denmark) (Papatesta et al., 2023). Data pertaining to dietary supplement consumption in the United States between 2007 and 2018 indicate a growing trend in the use of such substances (Cowan et al., 2022). The market is continuously introducing new products that have the potential to enhance sports performance, maintain fitness in old age, or even reverse some effects of aging. However, the safety of their use and their actual impact on the human body are not fully understood. (Bayliak & Lushchak, 2021; Guest, 2019; Hargreaves & Mantle, 2019; Warsito & Kusumawati, 2019). One such substance is nicotinamide mononucleotide (NMN) (Arslan et al., 2024; Mills et al., 2016; Nadeeshani et al., 2022). This compound, like niacin and its ester inositol hexanicotinate, nicotinamide, and nicotinamide riboside, is one of the possible precursors for supplementation of nicotinamide adenine dinucleotide (NAD^+) (Li et al., 2023; Milton et al., 2013).

With age, due to the increasing imbalance between synthesis and consumption, the level of NAD^+ gradually declines. This dinucleotide is a crucial element in the activation of sirtuin pathways, is consumed by poly (ADP ribose) polymerase, and acts as a coenzyme in many diverse redox reactions. Consequently, it improves energy regulation balance, response to stress, and helps maintain cellular homeostasis. For these reasons, the progressive decline in NAD^+ levels is likely to promote the development of age-related diseases and is one of the causes of aging processes (Imai & Guarente, 2014; Yaku et al., 2018). Supplementation with NMN, a direct precursor

converted to NAD^+ by nicotinamide mononucleotide adenylyl transferase (NMNAT), could potentially halt or reverse some of the effects of decreased NAD^+ levels (Li et al., 2023).

Natural sources of NMN include vegetables and fruits, such as cucumber, cabbage, broccoli, avocado, and tomato. However, the content of this compound typically does not exceed 2 mg per 100 g. Even less NMN can be found in shrimp and raw beef meat (Mills et al., 2016). The doses used in presented studies range from 250 to 2000 mg per day, which is significantly higher than what can be ingested in food (Igarashi et al., 2022; Kim et al., 2022; Okabe et al., 2022; Pencina et al., 2023; M. Yoshino et al., 2021) . This discrepancy illustrates that the dosing regimen for NMN has not yet been fully developed. The impact of this substance on NAD^+ levels also appears to be highly variable between individuals, especially at lower doses around 300 mg (Kuerec et al., 2024).

Animal studies

Due to the growing interest in the use of NMN as a NAD^+ booster, numerous studies have been published aiming to identify new potential clinical scenarios, where this agent could be beneficial. This section of the article presents recently published studies showcasing the broad spectrum of directions that can be explored in the application of NMN. Currently, due to advertising by the nutraceutical industry, the use of NMN may primarily be associated with anti-aging effects (Nadeeshani et al., 2022) . However, Kawamura et al. investigated its neuroprotective effects in neonatal mice with hypoxic-ischemic brain injury. Administration of NMN to newborn mice was able to reverse some changes occurring in this condition, such as the reduction of NAD^+ and SIRT6 (protein involved in critical processes such as glucose and lipid metabolism, DNA repair, and telomere maintenance) in injured hippocampal cells (Kawamura et al., 2023; Smirnov et al., 2023) . Additionally, the intervention resulted in a decrease of releasing of hippocampal high mobility group box-1 (a pro-inflammatory cytokine) and the activity of caspase-3 (a protease involved in the apoptosis process) (Hyman & Yuan, 2012; Kawamura et al., 2023; Yang et al., 2013).

In the first part of their study on a mouse model, Wen et al. investigated how the use of doxorubicin, an anti-neoplastic drug known for its cardiotoxicity, affects NAD^+ levels in tissues (Octavia et al., 2012; Wen et al., 2024) . The results demonstrated a significant decrease in the level of this dinucleotide in the heart, liver, and lungs, likely contributing to multi-organ injury in mice. Subsequently, they examined whether NMN supplementation could reverse this adverse effect of doxorubicin administration. The findings indicated, that such intervention was effective in raising NAD^+ levels and reducing mortality in mice (Wen et al., 2024).

Another study, that also addressed the protective action of NMN on cells damaged by an anti-neoplastic drug, was conducted by Qiu et al. The authors compared the effects of NMN and nicotinamide riboside on HeLa cells with DNA damage induced by cisplatin. Qiu et al.'s work suggests that both NAD^+ precursors similarly enhance DNA damage repair in injured cells and protect them dose-dependently from decreased viability. Simultaneously, the DNA-protective effect in damaged cells is stronger for nicotinamide riboside (Qiu et al., 2024).

Human Studies

In the past five years, several randomized controlled trials (RCTs) have been published, attempting to verify, whether the promising results obtained in animal studies translate to equally satisfactory effects in humans supplementing with NMN (Arslan et al., 2024; Mills et al., 2016) . Due to the ongoing aging of the population in developed countries and the increasing average lifespan, discovering new agents with a satisfactory safety profile that have a clear positive impact on maintaining or improving functional capacity appears to be a worthwhile direction (Marois et al., 2020; Welsh et al., 2021). The aim of this section of the article is to provide comprehensive information on the outcomes of recent studies describing the effects of oral NMN supplementation in different age groups, doses, and supplementation periods on both physical performance and the metabolic and biochemical parameters of the body. An additional goal is to identify areas that require further exploration in future research on the use of NMN.

A randomized controlled trial by Kim et al., examining the impact of 250 mg oral supplementation over 12 weeks on the quality of sleep, fatigue, and physical performance in adults over the age of 65, indicated improvements only in the performance of the 5-times sit-to-stand test, with a medium to large effect size (Cohen’s d = 0.72) and self-perceived feelings of drowsiness, also with an effect size in the same range (Cohen’s d = 0.64). In both cases, improvement was observed in groups where the administration of the studied supplement occurred in the afternoon, whereas in groups taking the supplement in the morning, the effect size was notably lower (Kim et al., 2022).

Igarashi et al. investigated the effects of NMN supplementation in a similar study, also at a dose of 250 mg daily for 6 or 12 weeks. At the end of the randomized controlled trial, it was observed that in the group orally administered with NMN, concentrations of whole blood NAD^+ and its metabolites increased significantly. The authors noted a potential positive impact of the supplementation on muscle performance based on results of gait speed and grip

strength; however, they also highlighted the necessity for larger studies to confirm their observations. It is also noteworthy that, due to an error in the delivery of the appropriate placebo and NMN supplements in the described study, from the 6th week onwards, 11 participants in each group were receiving incorrect supplements. The conclusions regarding the 12-week supplementation were therefore drawn based on data from the remaining 10 participants in each group (Igarashi et al., 2022).

A six-week RCT conducted on healthy amateur runners investigating whether NMN supplementation has a synergistic effect with exercise training showed that taking 600 mg and 1200 mg daily can additionally benefit the improvement of parameters such as oxygen uptake, percentage of maximum oxygen uptake, or power at the first and second ventilatory thresholds in training individuals, with the effect being dose-dependent. Moreover, the authors indicate that skeletal muscles might be among the tissues most responsive to NMN supplementation in humans. Nevertheless, the study had several notable limitations, with the most significant being the marked predominance of men in the study groups and the use of a cycle ergometer rather than a treadmill in the CPET, while the primary form of physical activity participants were supposed to engage in was running (Liao et al., 2021).

In the subsequent RCT conducted on a slightly younger population of healthy middle-aged individuals (40-65 years old), Yi et al. investigated the effects of supplementation. The study included 80 participants, comprising 59% women, who were divided into four groups: placebo, 300mg, 600mg, and 900mg. The supplementation period lasted 60 days, with NMN administered orally before breakfast. The concentration of NAD in the blood significantly increased in all supplemented groups compared to the placebo group after both 30 and 60 days. Interestingly, NAD levels did not statistically differ between the 600mg and 900mg groups in both assessments. In the same groups, the 6-minute walking test distance also significantly increased compared to baseline after 30 and 60 days. No significant difference in walking test results was found between these two higher NMN dose groups. The conducted Homeostasis Model Assessment - Insulin Resistance (HOMA-IR) test did not reveal statistically significant differences between the groups (Yi et al., 2023) The increase in biological age calculated based on blood parameters in the placebo group compared to the NMN groups, where the measured value did not change, was statistically significant. However, it is concerning that the recorded increase in the placebo group was about 5.5 years over the 60-day duration of the study (Mamoshina et al., 2018; Yi et al., 2023) . In all supplementation groups, a statistically significant increase in 36-Item Short Form Health

Survey (SF-36) score was observed after 60 days, and in the 600mg and 900mg groups, also after 30 days of NMN use (Lins & Carvalho, 2016; Yi et al., 2023).

Katayoshi et al. examined the effects of NMN administration on metabolic and biochemical parameters, including those considered risk factors for cardiovascular disease, over a 12-week period at a dosage of 125 mg, twice daily, in middle-aged adults (40-59 years). Interestingly, when measuring the levels of NAD^+, NMN, and nicotinamide in serum, only the concentration of the latter was significantly higher in the NMN group compared to placebo. It is also noteworthy that the measured value of brachial-ankle pulse wave velocity, which did not differ significantly between the placebo and NMN-treated groups, significantly decreased in the NMN-supplemented subgroup with above-average BMI and level of blood glucose compared to the placebo group (Katayoshi et al., 2023).

Another study relevantly different from the previous RCTs was conducted by Pencina et al., describing the supplementation of NMN. This 14-day trial differs from the other studies by using the MIB-626 preparation, a microcrystalline unique polymorph of β-Nicotinamide Mononucleotide, and by the dosage, which was 1000 mg and 2000 mg daily in the supplementation groups. The study was conducted on a group of adults, 32 men and women in a 1:1 ratio, aged 55 to 80 years, with a body mass index ranging from 28 to 40 kg/m^2, without any important medical problems. The concentration of blood NAD^+ achieved in both supplementation groups after 14 days was significantly higher compared to the placebo group, and importantly, this increase was dose-related (Pencina et al., 2023).

In a study conducted by Okabe et al. on healthy adults aged 20-65 years, daily supplementation with 250 mg of NMN over a period of 12 weeks, revealed an interesting correlation between pulse rate values and the increase in NAD^+ levels ($R=0.768$) associated with oral NMN supplementation. The authors suggest that the cause of this relationship may be linked to energy consumption, but they themselves indicate the necessity for further studies to elucidate their findings (Okabe et al., 2022).

NMN Supplementation and Diabetes

One of the most crucial studies demonstrating the effects of NMN supplementation was conducted on transgenic mice overexpressing SIRT1 in pancreatic β cells, characterized by enhanced glucose-stimulated insulin secretion and improved glucose tolerance. As these mice aged, their NAD^+ synthesis levels decreased, and they lost their phenotype that was attributed

to the overexpression of SIRT1; however, NMN supplementation restored it. The described restoration was achieved only in female mice (Imai & Guarente, 2014; Ramsey et al., 2008). A slightly later study, also conducted on an animal model by Yoshino et al., indicated that administering NMN to mice with age-induced diabetes (type 2) may improve dysfunctional glucose tolerance. In this study, the effect of the intervention was also more pronounced in female mice (J. Yoshino et al., 2011) . It is therefore not surprising that some of the first disease-burdened groups in which the effects of NMN supplementation were studied included patients with diabetes, prediabetes, and obesity. Examples of such randomized controlled trials are those conducted by Yoshino et al. and by Akasaka et al. (Akasaka et al., 2023; M. Yoshino et al., 2021). In the first study, the effects of 250 mg daily NMN supplementation for 10 weeks on metabolic functions were evaluated in postmenopausal women with prediabetes who were either obese or overweight. In the NMN group, as opposed to the placebo group, a 25±7% increase in muscle insulin sensitivity and metabolic changes indicating enhanced remodeling were observed. Hepatic and adipose insulin sensitivity did not change significantly in either group, which corresponds with the findings from a slightly later study by Liao et al. regarding skeletal muscles being the most responsive to NMN supplementation (Liao et al., 2021; M. Yoshino et al., 2021). In the second RCT, conducted by Akasaka et al., the authors focused on investigating the effect of NMN supplementation on improving physical performance in patients with diabetes aged ≥ 65 years, who had baseline reduced physical performance, characterized by decreased handgrip strength and reduced gait speed. The study had a notably long supplementation period of 24 weeks, compared to the previously described studies, with a daily dose of 250 mg (Akasaka et al., 2023) . No statistically significant change in physical performance was observed in either the NMN or placebo groups; however, there were notable inverse trends in mean central retinal thickness in the intervention and placebo groups ($p=0.051$), which might suggest a potential anti-aging effect of NMN on the retina (Akasaka et al., 2023; Alamouti & Funk, 2003).

Safety of Supplementation and Recorded Adverse Effects

To consider NMN as a viable agent for chronic supplementation aimed at improving quality, and possibly even the length of life, it is essential that it is free from any serious adverse effects during both short-term and long-term use. Flushing reactions, along with rash, increased blood glucose or uric acid levels, and gastrointestinal disorders, are well-known and

common adverse events associated with another NAD^+ precursor, nicotinic acid, but they can also occur with the use of high doses of nicotinamide (Li et al., 2023; She et al., 2021; Song et al., 2023) . Based on studies in mice and initial trials in humans, NMN supplementation appears to be a safe NAD^+ booster. However, further detailed observation of this compound's effects regarding its safety is essential (Mills et al., 2016; Song et al., 2023) . Below, we present information on the safety of NMN supplementation derived from the latest available randomized controlled trials (RCTs) focused on this compound.

In the previously mentioned study examining the synergistic effects of NMN supplementation and exercise training, participants reported no side effects in any of the three groups, each consisting of 12 individuals, with oral supplementation for 6 weeks at doses of 300 mg, 600 mg, and 1200 mg. No abnormalities were detected in electrocardiograms either (Liao et al., 2021) . In the trial performed by Igarashi et al. a 12-week oral supplementation of 250 mg NMN daily in healthy men over the age of 65 also did not result in any serious adverse effects. Blood parameters (WBC, RBC, platelets, hemoglobin, CRP, hematocrit), assessed in 10 participants in the NMN supplementation group, as well as blood chemistry, including parameters primarily used to examine renal and liver function, did not exceed the normal range at the end of the trial (Igarashi et al., 2022). In the study by Katayoshi et al., a 12-week oral supplementation regimen of 250 mg, administered to 36 healthy men and women aged 40-59, also did not result in any reported adverse effects (Katayoshi et al., 2023). In the study by Yi et al., during a 60-day oral supplementation period with 300 mg, 600 mg, and 900 mg doses, a statistically significant change in blood and urine parameters compared to the placebo group was observed in the LDL and MCHC parameters in the 900 mg group, and in the uric acid nitrogen parameter in the 600 mg group. None of these changes were considered clinically meaningful abnormalities. Additionally, out of all nine reported adverse effects 6 were from the placebo group and 3 from the 300 mg NMN supplementation group, moreover reported only by 2 participants from this group. One of them reported hyperacidity, while the other reported a dermatological problem and a mouth ulcer. All adverse effects were considered unrelated to NMN supplementation (Yi et al., 2023) . In the case of MIB-626 supplementation over 14 days at doses of 1000 mg and 2000 mg, which is difficult to compare with the previously described studies on NMN administration, mild ALT and AST elevation was observed on the final day of the trial in one participant in the 1000 mg daily group and one in the placebo group. The levels of these liver enzymes returned to baseline values after the completion of supplementation. Additionally, one participant in the 1000 mg

group discontinued supplementation at some point after day 8 of the study due to diarrhea. No clinically significant changes in the QTc interval were observed in any of the participants. The presented adverse events were not considered by the authors to be a result of NMN supplementation (Pencina et al., 2023). Also, in the study by Okabe et al., all adverse events observed during the study in the placebo and NMN groups were not severe and were considered unrelated to supplementation. The most notable phenomenon was the occurrence of fever, fatigue, or joint pain in 6 individuals (40%) in the NMN group, but this was most likely due to the side effects of the COVID-19 vaccine administered to these participants (Okabe et al., 2022) . In the study conducted on patients aged ≥65 years with diabetes, published by Akasaka et al., where the longest described oral NMN supplementation, lasting 24 weeks at a dose of 250 mg, was used, no serious adverse effects were noted in the supplementation group. One individual in the NMN group prematurely discontinued supplementation due to the occurrence of diarrhea; however, the researchers excluded a causal relationship with the tested substance (Akasaka et al., 2023) . In the study involving prediabetic women by Yoshino et al., neither adverse events nor deviations in standard blood tests were noted. The supplementation in this RCT involved a 10-week oral administration of NMN at a dose of 250 mg by postmenopausal women (M. Yoshino et al., 2021).

Conclusion

The latest research seems to confirm previous findings regarding the safety of chronic oral supplementation of NMN in humans, even at doses exceeding 1000mg per day. Nevertheless, continued careful monitoring of patients taking this compound is necessary. The most pronounced effects of using the described supplement are largely centered around the skeletal muscle system, where it presumably positively impacts glucose metabolism and improves physical performance. Therefore, a reasonable direction for future research would be a detailed examination of the impact of NMN use on muscle tissue, especially in groups of patients burdened with diabetes. Conducting studies on larger groups with higher doses of NMN over longer periods could help determine the optimal supplementation dose and clarify the significance of individual variability and gender in increasing NAD+ levels and their effects on the human body.

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