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doi:10.36849/JDD.6870

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A Narrative Review of Nicotinamide Adenine Dinucleotide (NAD)+ Intermediates Nicotinamide Riboside and Nicotinamide Mononucleotide for Keratinocyte Carcinoma Risk Reduction

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ABSTRACT

Oral nicotinamide (NAM) supplementation has been shown to decrease the incidence of keratinocyte carcinoma (KC) in high-risk skin cancer patients. NAM is a nicotinamide adenine dinucleotide (NAD+) intermediate and thus directly leads to increased NAD+. This increase in NAD+ is believed to be responsible for NAM's impact on keratinocyte carcinoma risk. NAD+ has protective cellular effects and is a necessary cofactor for DNA repair, helping to prevent potentially oncogenic mutations. Nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN) are NAD+ intermediates like NAM; however, their protective roles on cellular DNA and effects on cancer have been under-explored. Research into cellular metabolism and aging suggests that NR and NMN can lead to greater increases in NAD+ vs NAM. NR and NMN are safe and well-tolerated and are consequently currently undergoing investigation as agents able to protect against age-associated disease caused by NAD+ depletion. We hypothesize that oral supplementation with NR or NMN may lead to greater reductions in KC than NAM.

J Drugs Dermatol. 2022;21(10):1129-1132. doi:10.36849/JDD.6870

INTRODUCTION

Oral supplementation of nicotinamide (NAM), a water-soluble vitamin B3 derivative, decreases incidence of keratinocyte carcinomas (KC), and decreases the size, number, and incidence of actinic keratoses (AKs) in high-risk skin cancer patients.[1-3] An analysis of 386 high-risk skin cancer patients treated with oral NAM demonstrated a significant 23% reduction in the incidence of new KCs vs placebo.[3]

NAM is a nicotinamide adenine dinucleotide (NAD+) intermediate and is used to create NAD+. NAD+ is cationic and unable to be directly supplemented orally. NAD+ acts as a cofactor in glycolysis and has a critical role in adenosine triphosphate (ATP) production. ATP, in turn, is essential for many basic cellular functions, including DNA repair. Pathways leading to NAD+ production are thus essential and interwoven into basic cellular metabolism. Interestingly, animal and human models have shown that physiologic levels of NAD+ naturally decrease with aging and in certain disease states, leading to the hypothesis that reduced NAD+ may be one causative factor in age-associated functional decline and disease.[4,5] Consistent with this hypothesis, ultraviolet radiation (UV) exposure further depletes NAD+, resulting in inhibition of glycolysis and a scarcity of ATP. The subsequent inhibition of DNA repair due to ATP scarcity predisposes cells to oncogenic DNA damage and tumor formation.[4,5]

Recent work demonstrates that keratinocytes supplemented with NAM in vitro had increased NAD+ levels, increased DNA repair, and reduced UV-induced inflammation.[6-8] This work prompted the hypothesis that NAM supplementation may replenish depleted NAD+ found in states associated with UV exposure, ultimately replenishing cellular ATP and promoting the repair of damaged DNA. This theory has gained widespread acceptance and is the primary proposed mechanism for NAM's effect in reducing KC.[6]

NAD+ biology is a strong focus of modern research into aging and age-associated disease. Given that NAD+ cannot be directly absorbed from the diet, research has been focused on alternative sources or intermediates from which NAD+ can be synthesized; specifically, niacin, NAM, nicotinamide riboside (NR), and nicotinamide mononucleotide (NMN) (Figure 1).[9,10] These NAD+ intermediates exhibit varying and unique effects on metrics of metabolism and health.[10-12] NR and NMR are more direct precursors in the biosynthetic pathway of NAD+ synthesis and increase NAD+ more effectively than NAM,[13] which, along with other results, has led investigators to believe NR and NMN are more potent anti-aging and anti-cancer molecules than NAM.[4,10] Here, we perform a narrative review investigating whether NR and NMN may have an equal or greater effect on KC chemoprevention to that of NAM.

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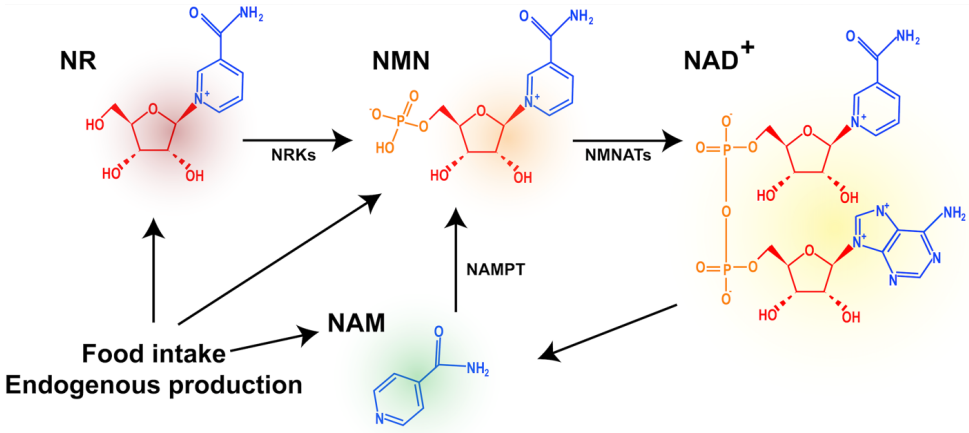
FIGURE 1. Biosynthetic pathway of nicotinamide synthesis.



MATERIALS AND METHODS

This narrative review considered all types of published journal articles (clinical trials, case studies, scientific reviews). Studies were identified by searching the PubMed database and reference lists of respective articles. Only articles available in English were considered for this review.

RESULTS

1: Increased NAD+ leads to KC chemoprevention.

NAM supplementation leads to decreased numbers of existing AKs, decreased development of new AKs, and decreased incidence of KC in high-risk skin cancer populations.[1-3] This effect is likely due to a NAM-induced increase in NAD+ availability within keratinocytes.[6,14] Animal models indicate that NAD+ deficiency increases cellular sensitivity to UV light, exhibits impaired ability to repair damaged DNA, and has increased genomic instability.[14] Correlation work in humans suggest that NAD+ levels also decrease with aging, leading to the hypothesis that NAD+ depletion is causally related to aging and age-associated disease, including oncogenesis.[4,5]

2: NMN and NR supplementation more efficiently increase NAD+ levels than NAM supplementation, making them more promising treatments for age-associated disease related to NAD+ depletion.

Recent work has suggested that supplementation with NR and NMN may be a more effective means than NAM to increase cellular NAD+ levels. Mice treated with oral NMN vs NAM have increased tissue levels of NAD+.[10,15] Humans and mice treated with oral NR vs NAM have, respectively, increased blood and hepatic levels of NAD+.[13,16] These results may be due to both pharmacokinetics and pharmacodynamics; NR and NMN are more directly synthesized to NAD+ (Figure 1).[13,17]

Preliminary animal models have shown promising effects of treatment with NR and NMN; specifically, work suggests that NR and/or NMN can: 1) help treat numerous age-associated diseases (such as hepatic steatosis), 2) improve measurements of metabolic outcomes, 3) improve skeletal muscle mitochondrial function in vitro, 4) mitigate against acute kidney injury, and 5) protect against cardiac ischemia-reperfusion injury.[10,15,18] Compared with untreated mice, NR-treated mice had longer lifespans, less cellular DNA damage, and improved mitochondrial and stem cell function.[11] Similar results were found in yeast and *C. elegans*.[19,20]

3: NMN and NR are safe and well tolerated.

Like NAM, both NR and NMN molecules are water-soluble vitamin B3 derivatives endogenously present in human cells and food. NMN and NR supplementation has been used extensively in animals with no reported toxicity or serious adverse side effects to date.[10,21] Over the past 2 years, several small trials of NMN and NR supplementation in humans have been published. One study used oral NMN supplementation in 25 pre-diabetic postmenopausal women at a dose of 250 mg / day and found that supplementation increased muscle insulin sensitivity without causing any adverse events.[22] A second study looked at the effects of NMN supplementation on the aerobic capacity of runners; 36 participants were given either 300 mg / day (n=12, 600 mg /day (n=12), or 1200 mg/day (n=12) of NMN, and no side effects or adverse events were reported at any NMN dose.[23] Several small trials have tested supplementation of NR at doses ranging from 300 to 2000 mg /day in adults without any reported adverse events.[24,25] Although the United States (US) Food and Drug Administration regulating body has not yet approved either molecule for healthcare purposes, both NMN and NR supplements are easily available online as unregulated supplements, and many consumers are already taking them at doses ranging from 500 mg to 1000 mg/day, with no published data on adverse outcomes.

DISCUSSION

NAM is an important chemopreventative molecule for KC, thought to primarily act via increasing intracellular NAD+. Recent in vivo work in humans and animals has shown that oral supplementation of NR and NMN may increase NAD+ levels

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more effectively than NAM. Consequently, we hypothesize that NR and NMN supplementation will lead to similar or greater reductions in KC rates in high-risk skin cancer patients compared with supplementation with NAM. Supporting this hypothesis, recent work using animal models has shown that both NR and NMN supplementation can mitigate DNA damage, improve cellular metabolic function, and reduce age-associated disease more effectively than NAM supplementation.

Chen et al recently published a model to investigate NAM on keratinocyte chemoprevention in high-risk human subjects, which can be adapted to investigate and compare the alternative NAD+ intermediates.[3] Specifically, we propose a randomized controlled trial, as the strongest level of evidence, with participants randomized to one of 4 groups: placebo, NAM, NR, or NMR. At present, it is unclear if either NR or NMN is superior, and thus both should be included in initial studies compared with NAM. Power analyses indicates that at least 400 to 500 participants should be enrolled. Participants will be supplemented for 18 months at 1000 mg/day, a concentration shown to be safe in prior studies.[10,24,25] The main outcomes would be development of AKs, BCCs, and SCCs. Participants would be evaluated by dermatologists at 3-month intervals for the duration of the study. Groups will be evaluated in a blind fashion with intention-to-treat analysis. Group differences would be analyzed at study end using an ANOVA with significance set to $P<0.05$. This study design would allow the impact of NR or NMR to be compared against both placebo and NAM for the reduction of skin cancers. Results should be presented at national and international levels, and ultimately can help influence our prophylactic and therapeutic management of patients with skin cancers.

CONCLUSIONS AND PERSPECTIVES

KCs are the most common malignancies in the US and worldwide, and rates continue to increase with the growing elderly population.[26,27] More than 4.9 million adults were treated annually for skin cancer from 2007 to 2011 in the US, with annual costs peaking at $8.1 billion.[28] The significant population-level morbidity and associated healthcare costs of KC means that any effective intervention to treat or reverse early KC has the potential to be hugely beneficial for patient outcomes and for reducing system costs.[29] Current methods for primary prevention of KC are largely through sun protection. However, most adults do not routinely use sunscreen despite decades of encouragement by dermatologists and public health campaigns.[30] Reasons for this include the perceived inconvenience of application and the perceived incompatibility of sun protective behaviors with outdoor activities.[31,32] Oral methods of skin cancer prevention may be more convenient and address these patient concerns.

Among the oral supplements for skin cancer chemoprevention currently under investigation, NAM is one of the best candidates.[33] A recent survey indicated that 76.9% of Mohs surgeons recommend NAM to prevent keratinocytes in their current patients.[34] Given the ubiquity of KC, if NR or NMN even confer a minimally superior effect reducing KC over NAM, this would lead to a meaningful decrease in KCs on a population level with a concordant decrease in healthcare system costs given the relative low cost of NMN and NR supplements in comparison to surgical interventions for KC.

A special population that may especially benefit from treatment with NAD+ intermediates is the organ transplant recipient (OTR) patients. OTRs develop SCC up to 250 times the rate of the general population.[1] Prevention of AKs and the reduction of risk of developing KC would have a valuable impact on these patients. Drago et al demonstrated a reduction in AKs and showed a decreased rate of AK progression to SCC in a small randomized controlled trial of transplant patients on NAM.[1] NR or NMN would be a valuable tool for dermatologists to reduce morbidity and mortality in OTR as well as other high-risk populations if they were to demonstrate greater efficacy than NAM in KC reduction.

DISCLOSURES

No funding was received for this manuscript and the authors state no conflict of interest. The content has not been previously presented.

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