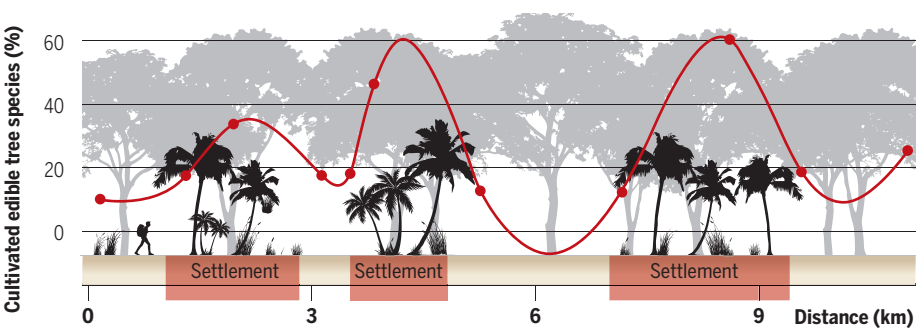
back between Indigenous peoples and food availability is one with the potential to transform forest composition and amplify food production at large scales. Positive feedback is a two-way interaction that may amplify changes in the system (*12*). When Indigenous and local peoples manage tropical forests by selecting, cultivating, and dispersing trees, palms, and other perennial plants, they interfere with ecological processes that shape forest composition, favoring edible species. As a result, patches of edible species increase in abundance. In managed landscapes, plant communities become dominated by multiple edible species clumped together around ancient settlements. To illustrate this, the abundance of edible species is depicted during a walk in the seemingly natural landscape of the Tapajós National Forest (Brazilian Amazonia), where the average distance between ancient settlements is 2 (±1) km (*11*) (see the figure). As one approaches the site of an ancient settlement, the abundance of edible (and cultivated) plant species rises steeply; as one walks away, the abundance diminishes in the same fashion until another ancient settlement site is approached.

One implication of this positive feedback is that where Indigenous and local peoples are excluded from the system, or when their practices are lost, landscapes are expected to change. Initially, the most domesticated plant populations begin to disappear because they depend on local management to persist (*6*). If anthropogenic dark soils erode—for example, owing to unsustainable land use and wildfires—edible species that are more nutrient demanding may also disappear. In the long run, natural ecological and evolutionary processes could reduce the abundance of edible species by up to 80%. With fewer fruits and seeds in the forest, the cascading effects on ecological interactions could negatively affect the populations of frugivore vertebrates, consequently affecting the availability of animal protein. Similarly, where Indigenous and local peoples have no access to the forest, their ancient ecological knowledge fades away over a few generations (*13*).

Globally, more than a billion people rely on forest resources for their nutrition and health, particularly in developing tropical regions (*14*). Indigenous and local peoples have historically contributed to the enrichment of tropical forests with food, and today their territories act as buffers against large-scale deforestation and degradation (*15*). The positive feedback between local peoples and food availability unveils the possibility of conserving tropical forests while boosting food security and sovereignty; hence, it might contribute to achieving the Zero Hunger goal of the Sustainable Development Goals. For this ancient feedback to continue functioning, societies need to recognize Indigenous and local peoples' rights to their ancestral forest lands. ■

A walk in the forest

When passing by ancient settlements, the proportion of edible arboreal species rises steeply as a result of Indigenous and local peoples' management.



GRAPHIC: C. BICKEL/*SCIENCE*

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METABOLISM

Supplements to treat prediabetes

Boosting nicotinamide adenine dinucleotide (NAD^+) improves health in a clinical study

By **Chelsea Hepler** *and* **Joseph Bass**

Nicotinamide adenine dinucleotide (NAD^+) is an essential metabolic cofactor that is central to energy metabolism. During aging, obesity, and diabetes, NAD^+ concentrations in cells decline. NAD^+ is synthesized de novo from tryptophan precursors, from nicotinic acid through the Preiss-Handler pathway, or from nicotinamide through the salvage pathway. The rate-limiting enzyme in the salvage pathway, nicotinamide phosphoribosyltransferase (NAMPT), recycles nicotinamide into nicotinamide mononucleotide (NMN), which is converted into NAD^+ (see the figure). Restoration of NAD^+ concentrations in cells of old or diseased mice through administration of NMN improves health; however, it is unclear whether NMN therapy is practical in humans. On page 1224 of this issue, Yoshino *et al.* (*1*) show in a randomized, placebo-controlled, double-blind trial that NMN supplementation promotes NAD^+ metabolism and improves skeletal muscle insulin sensitivity in postmenopausal prediabetic women who are overweight or obese. Thus, NMN may be a viable therapeutic strategy in humans to improve metabolic health during obesity.

Ingestion of NMN from supplements or various types of foods—such as edamame, broccoli, and cabbage—leads to rapid absorption into the circulation where it is used by tissues for NAD^+ biosynthesis. Studies have shown that NMN enters cells indirectly through dephosphorylation into nicotinamide riboside (NR) and subsequent reconversion to NMN inside the cell or directly by transport through SLC12A8 (solute carrier 12 member 8), although it remains unclear whether direct uptake occurs owing to difficulty in measuring NMN and NR

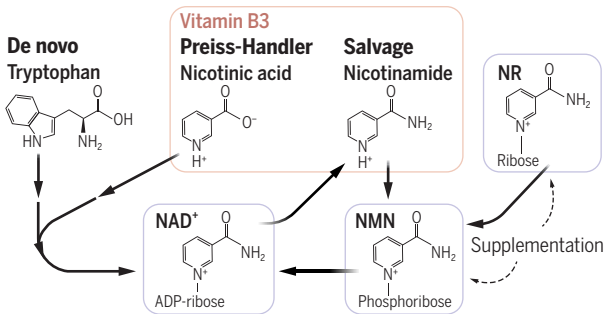
Department of Medicine, Division of Endocrinology, Metabolism, and Molecular Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA. Email: j-bass@northwestern.edu

(*2*, *3*). NMN treatment does not always lead to a measurable increase in tissue NAD^+, because measurements of steady-state metabolite concentrations alone do not provide information on metabolic flux, that is, the rates of production, consumption, and degradation of NAD^+ by cellular reactions. The use of NAD^+ by sirtuins and other NAD^+-consuming enzymes can also prevent an increase in total NAD^+ or even lead to a decline in NAD^+, which occurs during aging (*4*).

Several groups have demonstrated beneficial effects of NMN in mouse models of disease, including neurodegenerative disorders, cerebral and cardiac ischemia, age-associated complications, renal injury, obesity, and diabetes (*5*). A recent single-arm nonrandomized clinical study reported that administration of a single dose of 100 to 500 mg of NMN in healthy adult men was safe and effective with no adverse side effects (*6*). Yoshino *et al.* now report that daily administration of 250 mg of NMN to 13 women for 10 weeks produced no adverse events or abnormalities in routine blood tests. The participants showed improved skeletal muscle insulin sensitivity after receiving NMN, indicating that NMN may be a promising therapy in prediabetic individuals. This study supports the use of NMN as a safe and effective long-term treatment to increase NAD^+ metabolism in humans.

Therapeutic potential

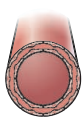
Three routes generate nicotinamide adenine dinucleotide (NAD^+): de novo synthesis, the Preiss-Handler pathway, and the salvage pathway. Supplementation with nicotinamide mononucleotide (NMN) and nicotinamide riboside (NR) to boost NAD^+ has tissue-dependent effects.



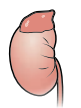
Adipose tissue
Enhance adiponectin secretion and reduce lipolysis in diabetes and dyslipidaemia

Brain
Improve cognitive and motor function during Alzheimer's and Parkinson's diseases

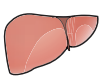
Pancreas
Improve insulin secretion and beta cell function in diabetes



Vasculature
Decrease atherosclerotic progression in coronary artery disease
Reduce blood pressure in hypertensive individuals

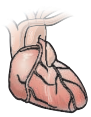


Kidney
Correct electrolyte disturbances during chronic kidney disease



Liver
Reduce hepatic lipid content in obesity

Skeletal muscle
Increase insulin sensitivity in postmenopausal prediabetes



Heart
Decrease incidence of heart attack in coronary artery disease

Immune system
Improve psoriasis outcomes

ADP–ribose, adenosine diphosphate–ribose

How does NMN improve insulin sensitivity? The studies by Yoshino *et al.* and others demonstrate that skeletal muscle insulin sensitivity is affected by NMN in mice and humans; however, the precise mechanisms remain to be determined. NMN is likely acting on a wide array of tissues and cell types to affect physiology. NAD^+ plays a key role in energy homeostasis in reduction-oxidation (redox) reactions, including glycolysis, the tricarboxylic acid (TCA) cycle, and fatty acid oxidation where it is reduced to NADH. NADH then serves as a hydride donor in mitochondrial oxidative phosphorylation to generate adenosine triphosphate (ATP). NAD^+ supports several cellular processes, such as mitochondrial respiration and circadian gene transcription, acting as a cosubstrate for the sirtuin family of deacylases. NAD^+ is a cofactor for the cyclic adenosine diphosphate (ADP)–ribose synthases and the poly(ADP-ribose) polymerases, influencing signaling and DNA repair, respectively. NAD^+ also regulates transcription and stability through the capping of RNA and through sirtuin-dependent pathways. It will be critical to determine the mechanisms and tissues through which boosting NAD^+ affects health, which likely include a combination of these functions to manipulate metabolism, transcription, and signaling.

Skeletal muscle from individuals in the group that received NMN had increased expression of genes in the platelet-derived growth factor (PDGF) pathway and increased expression of PDGF receptor β. This receptor is highly expressed on pericytes—cells that wrap around endothelial cells that line blood vessels—and its activation contributes to myogenesis and angiogenesis during muscle growth and regeneration. This suggests a critical role for muscle pericytes in the response to NMN therapy to improve metabolic health. This is also consistent with previous studies showing that pericytes are essential during adult skeletal muscle regeneration (*7*). It remains to be determined whether pericytes in additional tissues responded to NMN or whether this was an indirect effect through cross-talk between other cellular populations and pericytes.

Our knowledge of NAD^+ metabolism has greatly advanced since the first clinical trial on NAD^+-boosting through NR supplementation in 2016 (*8*). Several clinical studies have shown promising results on the delivery of NAD^+ precursors to improve health, although many have also shown little to no benefit (*5*). Metabolic conditions characterized by low tissue NAD^+ concentration may be the most amenable to the benefit of NMN supplementation. The positive effects of NMN on skeletal muscle in postmenopausal women, who experience muscle degeneration and loss, suggest that NAD^+ therapy may also be beneficial during diseases involving muscle atrophy. Additionally, NMN may play an important role in enhancing metabolic health in the context of mitochondrial dysfunction during aging.

Although NAD^+ depletion leads to degenerative diseases, an excess of NAD^+ may also be problematic during immune cell development and activation, senescent and stem cell function, and cancer growth, where NAMPT inhibitors are being tested for antitumor potential (*9*). For NAD^+-boosting therapies to be considered, it will be essential to thoroughly investigate the dose, duration of therapy, and context of disease. Because NAD^+ synthesis is controlled by the circadian clock, investigating the optimal timing of NMN delivery may maximize therapeutic efficacy (*10*). In addition, it will be critical to measure the entire NAD^+ metabolome and use isotope tracing to track the fate of NMN in a cell- and tissue-specific manner to determine how NMN affects NAD^+ flux. The findings of Yoshino *et al.* demonstrate that NMN is safe and effective in humans, although further research is warranted on therapies that manipulate NAD^+. ■

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Supplements to treat prediabetes

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