

# The NAD<sup>+</sup> Paradox: More Precursor Does Not Necessarily Mean More Repair

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*\*Abstract (original summary).\** Increasing a blood or tissue NAD<sup>+</sup> pool does not establish that an organ has repaired itself. Human evidence for precursor supplementation remains substantially more limited than popular longevity claims suggest. This essay examines compartment-specific NAD metabolism, pathway engagement and the requirement for meaningful functional outcomes rather than biomarker elevation alone.

## A compelling molecule, an incomplete prescription

Nicotinamide adenine dinucleotide participates in redox reactions and functions as a substrate for enzymes involved in DNA repair, signaling and cellular regulation. Its prominence in aging research has encouraged efforts to increase NAD<sup>+</sup> through precursor supplementation. Yet a 2025 review of human clinical evidence concluded that age-related declines in human NAD<sup>+</sup> have not been consistently established across many tissues and that clinical benefits from precursor trials remain limited. This should shift the question away from whether one can increase a biomarker toward what happens after the molecule enters a particular tissue.

## The compartment problem

Cells maintain mitochondrial, nuclear and cytosolic NAD-related pools with distinct local functions. Dietary precursor absorption, conversion pathways, transport, enzyme activity and disease-associated consumption can all affect where a precursor goes and what it changes. A rise in whole-blood NAD<sup>+</sup> does not necessarily prove improved neuronal metabolism or muscle repair. Likewise, changing an NAD-dependent enzyme's activity can have consequences not captured by measuring the metabolite alone.

## The repair hypothesis

The defensible idea is that NAD metabolism may constrain some cellular repair programs under some conditions. But an organism also requires perfusion, nutrient supply, correct cellular identity and tissue-level organization. Excessively broad supplementation claims ignore the possibility that distinct tissues respond differently or that another bottleneck dominates. A successful experimental strategy would link compartment-specific biochemical correction to restoration of a relevant function.

## What evidence should decide

A clinical trial should distinguish precursor uptake, changes in NAD pools, pathway engagement, clinical improvement and safety. If circulating NAD<sup>+</sup> increases without measurable benefit in an appropriately selected outcome, the intervention has achieved a biochemical effect, not demonstrated rejuvenation. That is not a reason to abandon NAD research. It is a reason to replace simplistic replacement narratives with tissue-specific metabolic science.

## A clinical thought experiment

A patient may demonstrate elevated NAD-related measurements after supplements while experiencing no improvement in muscle function, sleep or recovery. That observation does not disprove the biochemical pathway, but it is inconsistent with an unqualified therapeutic claim. The opposite pattern—clinical improvement without large circulating changes—would suggest the measured pool is an incomplete proxy.

## **What would discriminate among explanations**

The key experiment links tissue exposure to target engagement and functional outcomes in an appropriate population. Trials limited to small biomarker changes should not be translated into promises about lifespan or organ regeneration. Lack of clear human age-related NAD decline across every tissue is a reason to refine the mechanism, not to insist supplementation must help everyone.

## **A precursor is not an outcome**

Nicotinamide adenine dinucleotide participates in redox reactions and serves as a substrate for several families of enzymes involved in cellular regulation. Because NAD-related metabolism changes with age and disease in some settings, precursors have attracted substantial interest as potential interventions. The physiological problem is that NAD is not one homogeneous reservoir. Cytosolic, nuclear and mitochondrial pools interact with different processes, and changes in blood or tissue content may not correspond to changes where a particular enzyme operates.

Providing more precursor does not guarantee proportional increases in the desired intracellular pool, greater repair activity or improved patient function. Transport, biosynthetic capacity, consumption and clearance all influence the outcome. An intervention might raise a circulating metabolite while leaving a tissue-specific bottleneck untouched. The reverse is also possible: a functional benefit might occur without a large change in the easiest biomarker to measure.

## **The case of excess simplification**

NAD is often marketed as though age-related loss of a molecule explains fatigue, cognitive decline, muscle weakness and chronic disease through one pathway. These syndromes have many established causes, and evidence from selected animal models cannot establish broad clinical efficacy. A patient with anemia will not necessarily regain endurance because a supplement changes NAD metabolites; someone with severe neuropathy needs evaluation of the relevant neural disease.

The concept of 'more' also ignores regulatory balance. Enzymes that use NAD have distinct roles, and their activity is influenced by substrates, cellular localization and other cofactors. A change beneficial for stress resistance in one cell type may have a different consequence for proliferation or immune signaling in another. Some pathways consuming NAD are themselves responses to injury; lowering their activity to conserve NAD may interfere with other protective functions.

## **What a meaningful trial should measure**

A convincing study would define a patient population, specific biological deficit, administered precursor, evidence of target engagement and an outcome with clinical relevance. For muscle aging, this might include strength and functional performance; for a defined metabolic disorder, appropriate physiological endpoints. Changes in whole-blood NAD-related measures should be interpreted as evidence of exposure or metabolic alteration, not by themselves as proof of regeneration.

Long-term safety and clinical interaction data matter, particularly when interventions are taken alongside multiple medications or in the setting of cancer. There is no basis for assuming that increasing all NAD-related processes is universally safe or that precursor products interchangeably produce the same cellular state.

## **A compartment-based hypothesis**

The useful frontier is that a specific NAD-dependent process could be limiting in a particular cell compartment during repair. Demonstrating this would require showing that the compartment is functionally deficient, that an intervention corrects it, and that tissue recovery improves as a result. If added precursor raises NAD measures without improving repair, the causal claim weakens. If correction works only in a narrowly defined phenotype, that is still valuable and more clinically interpretable than a universal anti-aging claim.

The paradox is therefore straightforward: an essential molecule can be necessary for cellular life without its increased supply becoming a general therapy for aging. Regenerative medicine needs to locate the actual bottleneck before supplementing what is easiest to measure.

## **Why clinical heterogeneity is decisive**

An intervention studied in healthy volunteers may not have the same effect in people with severe metabolic illness, impaired renal function or chronic inflammatory disease. Baseline nutrient state and medication exposure can influence precursor handling. Such variability should prompt careful stratification rather than the assumption that people who fail to improve simply need higher doses. A dose-response relationship in blood metabolites does not establish one in organ function.

A useful clinical trial could predefine a tissue-related hypothesis, measure whether that tissue's NAD-dependent processes actually respond, and link those changes to patient-centered endpoints. If high systemic exposure is needed while meaningful target engagement remains absent, the strategy may be pharmacologically unsuitable. If a narrow subgroup improves, the result should be reported as subgroup-specific until replicated independently.

The lesson extends beyond NAD: biochemical necessity and therapeutic sufficiency are not the same proposition. Oxygen, iron and glucose are essential, yet supplying more of each is beneficial only under appropriately defined conditions. A precursor should be held to the same standard.

## **A normal measured concentration may hide a localized deficit**

A systemic measurement can appear normal while a compartment-specific enzyme experiences insufficient substrate or altered turnover. However, a hypothetical intracellular deficit should not be invoked merely because symptoms are unexplained. It requires direct or convincing indirect measurement, a plausible pathway and evidence that correcting it changes function. Otherwise, the concept becomes impossible to falsify.

The appropriate research strategy is targeted. Identify a specific NAD-dependent process implicated in a defined tissue disorder, test whether precursor supply or pathway regulation is limiting, and compare clinical outcomes with controls. A universal supplement recommendation cannot be built from the existence of compartmentalization alone. Complexity increases the need for evidence rather than weakening it.

There is another reason to resist a universal NAD narrative: the direction of a metabolite change can be disease-specific. A cell consuming more NAD might be mounting a response to damage rather than malfunctioning through wasteful depletion. Inhibiting that response could conserve measured substrate while worsening the underlying injury. Conversely, supplementing precursor may help when a genuine deficiency

limits a necessary process. The correct interpretation depends on what the pathway is doing in the affected tissue. Measurements should connect metabolite supply, enzyme activity and physiological consequences before the intervention is described as restorative.

## Selected scientific readings

- Vinten KT et al. (2025). NAD+ precursor supplementation in human ageing: clinical evidence and challenges. Nature Metabolism. <https://www.nature.com/articles/s42255-025-01387-7>

- López-Otín C et al. (2023). Hallmarks of aging: An expanding universe. Cell. <https://doi.org/10.1016/j.cell.2022.11.001>

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