TRU NIAGEN®

State of the Science | Clinical Research on Niagen®

Nicotinamide adenine dinucleotide (NAD+) is an essential coenzyme found in all living cells. Researchers have identified several molecules that can act as NAD+ precursors to elevate cellular levels of NAD+. These include the B3 vitamins niacin (NA) and nicotinamide (NAM), as well as the more recently discovered NAD+ precursor nicotinamide riboside (NR). Due to its strong bioavailability, safety, and ability to raise NAD+ levels, NR is rising as the leading candidate among other precursors. Accumulating evidence on the potential health benefits of NR has validated its efficacy across a variety of organisms ranging from yeast and worms to mice and humans. Niagen®, the active ingredient in Tru Niagen®, is the only patented form of NR that has been extensively studied in published human clinical trials. As summarized below, nine peer-reviewed clinical studies using Niagen® have been published in high-tiered biomedical journals, demonstrating an increase in NAD* [1-9]. These nine clinical studies include the first ever clinical NR trial supporting its bioavailability, safety, and efficacy, the pharmacokinetics of NR supplementation in humans, NR's dose-response effect on blood NAD+ levels, as well as the health benefits of NR supplementation, including improvements in cardiovascular health, liver health, body composition, and mitochondrial function. Because the safety profile of Niagen® is established, validated, and vetted, numerous additional studies in humans are ongoing or have recently completed. More specifically, an additional 45 completed or ongoing clinical trials investigating NR only are currently registered on www.clinicaltrials.gov.

**Defined as raising whole blood and/or tissue levels or raising NAD+ flux (indicated as an increase in the NAD metabolome or "NADome")*

Quick Overview

Author	Key Results
Trammell et al., 2016	First clinical NR trial demonstrates safety and efficacy in humans
Airhart et al., 2017	Second clinical NR trial corroborates safety and efficacy results of the first
Martens et al., 2018	Third clinical NR trial shows chronic use and promise for cardiovascular health
Dollerup et al., 2018	Fourth clinical NR trial shows promise for supporting liver health
Conze et al., 2019	Fifth clinical trial demonstrates dose-response effect of NR supplementation
Elhassan et al., 2019	Sixth clinical NR trial reported lower levels of proinflammatory cytokines
Remie et al., 2020	Seventh clinical NR trial shows minor changes in body composition and skeletal muscle acetylcarnitine concentrations
Zhang et al., 2020	Eighth clinical NR trial shows safety and tolerability of first metabolic cofactor combo product supplementation, including NR as an ingredient
Zhou et al., 2020	Ninth clinical NR trial shows reduction in inflammation, as well as improved mitochondrial respiration in bloods cells extracted from heart failure patients

Brief Summaries

1. Trammell et al., 2016
    - Researchers investigated the effect of NR (single oral doses of 100mg, 300mg, and 1000mg) supplementation in 12 healthy men and women, as well as in mice. This was the very first clinical trial of NR. It establishes both its safety and efficacy as an NAD+ precursor in humans. Importantly, NR increased NAD+ and related metabolites in peripheral blood mononuclear cells (PBMCs). Mouse pharmacokinetic data demonstrated that NR has unique and superior hepatic (liver) pharmacokinetics compared to the B3 vitamins niacin (NA) and nicotinamide (NAM).
2. Airhart et al., 2017
    - Researchers examined the pharmacokinetics of NR supplementation and its effects on blood NAD+ levels. No adverse events or side effects attributable to NR were reported. No significant changes were observed in blood pressure, body temperature, body weight, white blood cell count, lactate dehydrogenase (LDH), or aspartate aminotransferase (AST). All subjects showed an increase in blood NAD+ concentrations between baseline and Day 9. On average, NAD+ levels increased 2-fold. No further increase in blood NAD+ levels was observed after the final Day 9 dose.
3. Martens et al., 2018
    - Researchers investigated the effect of chronic NR supplementation in healthy, middle aged and older adults. Of the 30 subjects, 24 completed the study and were included in the final analyses. No adverse events or side effects were attributable to NR. NR significantly increased average NAD+ levels by 60% compared to placebo ($p < 0.05$). NR supplementation tended to lower both systolic and diastolic blood pressure. This decrease was more pronounced for subjects who began the study with elevated blood pressure (in the stage I hypertension range) compared to subjects with blood pressure in the normal range. NR tended to decrease aortic stiffness, assessed via carotid-femoral pulse wave velocity.
4. Dollerup et al., 2018
    - Researchers investigated the effects of 12 weeks of NR supplementation for a variety of metabolic parameters related to the development of type-2 diabetes. These included measurements of insulin sensitivity, body composition, fat distribution, and liver fat content at the beginning and end of the 12-week trial. No adverse events or side effects were attributable to NR, and no clinically relevant differences in blood biochemistry (to test for safety) were observed. Men taking NR had an average 2% absolute reduction in liver fat content compared to a 0.2% absolute reduction in the placebo group ($P=0.13$). Of the subset of men who started the trial with greater than 5% liver fat, 69% experienced a reduction in liver fat compared to only 39% of the men taking the placebo. NR supplementation tended to decrease circulating levels of alanine aminotransferase (ALT) in the blood ($p = 0.21$). Elevated ALT levels are a sign of liver damage. NR did not have any noticeable effect (positive or negative) on insulin sensitivity, energy expenditure, body composition, or body fat distribution.
5. Conze et al., 2019
    - Researchers evaluated the kinetics and dose-dependency of NR oral availability and safety in overweight, but otherwise healthy men and women. They found that consumption of 100mg, 300mg, and 1000mg of NR, dose-dependently and significantly increased whole blood NAD+ levels by 22%, 51%, and 142%, respectively, within two weeks. These levels were also maintained throughout the remainder of the study (study duration = 8 weeks).
6. Elhassan et al., 2019
    - Researchers aimed to establish whether oral NR supplementation in aged individuals can increase the skeletal muscle NAD+ metabolome and alter muscle mitochondrial bioenergetics. After 21 days of supplementation, they found that NR increased the muscle NAD+ metabolome and decreased levels of circulating inflammatory cytokines.

7. Remie et al., 2020
    - Researchers examined the effect of NR on metabolic health, muscle metabolism, and mitochondrial function in overweight/obese men and women. NR did not increase NAD+ levels in skeletal muscle, however NR significantly increased markers of NAD flux (NAAD and MeNam). Minor beneficial changes in body composition and skeletal muscle acetylcarnitine concentrations (a molecule that helps bring fuel into the mitochondria) were found. Consistent with Elhassan et al., 2020, NR supplementation significantly increased markers of enhanced NAD+ metabolism in human skeletal muscle.
8. Zhang et al., 2020
    - Researchers investigated the effects of a combination of NR with L-serine, N-acetyl-L-cysteine, and L-carnitine on liver fat as a potential treatment for NAFLD. The study included a rat toxicology study and pilot clinical study—both of which supported the initial safety and tolerability of this combination supplement in humans. It was found that this set of cofactors significantly decreased blood plasma levels of markers associated with increased liver fat, as well as blood plasma levels of branch chain amino acids associated with insulin resistance and development of type 2 diabetes. Both results suggest that this set of cofactors may provide a therapeutic strategy against the progression of NAFLD. Mathematical modeling results also showed that supplementation globally increased fat metabolism, decreased glucose metabolism, and increased synthesis/turnover of NAD, carnitine, and GSH.
9. Zhou et al., 2020
    - In this ex vivo and pilot clinical study, researchers investigated the mechanistic link between mitochondrial dysfunction and inflammatory activation in peripheral blood mononuclear cells (PBMCs), and the potential anti-inflammatory effect of boosting NAD levels in Stage D heart failure (HF) patients. It was found that HF PBMCs had reduced mitochondrial respiratory capacity and elevated proinflammatory cytokine gene expressions. In PBMCs isolated from HF patients, NR administration reduced interleukin (IL)-6 secretion and gene expressions of proinflammatory cytokines and increased basal and maximal mitochondrial respiration. Similar effects were seen in a small group of HF patients following NR supplementation (1000mg, 2x/day) for 5-9 days. NR supplementation increased whole blood NAD+ levels, increased the mitochondrial respiration rate of the patients' PBMCs, and reduced the production and gene expression of proinflammatory cytokines. Overall, these results suggest that systemic inflammation in HF patients is causally linked to the mitochondrial function of PBMCs.

References

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