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WHITE PAPER

Niagen™ Plus: Current Evidence and Clinical Outcomes

Intravenous, Intramuscular, and Subcutaneous Administration

August 2026

EXECUTIVE SUMMARY

Nicotinamide adenine dinucleotide (NAD+) is an essential coenzyme that supports cellular energy production, mitochondrial function, DNA repair, metabolic regulation, and cellular resilience. Because NAD+ levels naturally decline with age and exposure to metabolic stress, restoring NAD+ has become a central focus of healthy aging and metabolic health research.

Nicotinamide riboside (NR) is among the most extensively studied NAD+ precursors and has consistently been shown to safely increase blood and tissue NAD+ following oral supplementation. Parenteral administration offers a distinct pharmacological approach that bypasses the gastrointestinal (GI) and hepatic first-pass metabolism, potentially increasing delivery of intact NR to metabolically active tissues.

Niagen™ Plus is a pharmaceutical-grade nicotinamide riboside chloride formulation developed for parenteral administration [intravenous (IV), intramuscular (IM), and subcutaneous (SC)]. Preclinical research demonstrates that parenteral NR increases tissue NAD+ more efficiently than oral administration and produces favorable biological effects in multiple disease models.

Four pilot clinical studies have evaluated the safety and emerging clinical effects of Niagen™ Plus. Across all studies, parenteral administration demonstrated a favorable safety profile with no serious adverse events. Compared with conventional NAD+ IV therapy, Niagen™ IV was consistently better tolerated and allowed more efficient administration with fewer infusion-related adverse experiences.

Although primarily designed to assess safety, these studies also identified encouraging biological and patient-reported outcomes. Findings included transient increase in whole-blood NAD+, improvements in fatigue, sleep quality, and quality of life, favorable shifts in mitochondrial energy metabolism, reductions in oxidative stress biomarkers, and trends in inflammatory markers.

Collectively, these findings support continued investigation of Niagen™ Plus as a novel strategy for rapidly boosting or restoring NAD+ levels. The observed functional benefits are hypothesis-generating and require confirmation in larger randomized, placebo-controlled trials.

1. INTRODUCTION

NAD+ is an essential coenzyme involved in mitochondrial ATP production, DNA repair, oxidative stress defense, cellular signaling, and metabolic regulation. NAD+ declines with age and chronic exposure to metabolic stress [1–3], making restoration of NAD+ an important goal in healthy aging [4].

Oral supplementation with Niagen® (a patented form of Nicotinamide Riboside Chloride [NRCl]) has been consistently demonstrated to safely increase blood and tissue NAD+ in humans [5–28]. Niagen™ Plus offers a complementary strategy to circumvent first-pass metabolism in the GI tract and liver, potentially increasing delivery of intact NR to metabolically active tissues.

2. WHY PARENTERAL NR?

Parenteral NR alters pharmacokinetics by avoiding first pass metabolism through the GI tract and liver. Preclinical studies suggest IV administration produces greater tissue NAD+ elevation than oral administration in skeletal muscle, liver, and kidney [29,30]. Niagen™ Plus is considered complementary to oral Niagen®, with each route of administration providing distinct biological advantages [31–33].

To date, four clinical studies provide encouraging evidence of safety and biological activity for NR. Larger randomized, placebo-controlled trials are needed to confirm efficacy and optimize dosing (Table 1).

Table 1: Summary of Niagen® IV and Injection Studies

Study	Design	Purpose	Key Outcomes
Hawkins et al. 2024	RCT	Safety & PK	>20% blood NAD+ increase; superior IV tolerability
Reyna et al. 2026	Retrospective	Real-world safety	Better tolerability than NAD+ IV
Nkrumah-Elie et al. 2026	Randomized	Injection safety	Favorable safety and exploratory benefits
Russ et al. (manuscript in process)	Open label	Long-term safety	Improvements in fatigue, sleep, QoL, mitochondrial function, oxidative stress, transient NAD+ increase

3. CLINICAL SAFETY OF NIAGEN™ PLUS

The primary objective of the clinical development for Niagen™ Plus has been to establish the safety and tolerability. Across four pilot clinical studies evaluating parenteral administration, Niagen™ Plus demonstrated a favorable safety profile. No serious adverse events were reported, and adverse events were generally mild, transient in nature and self-resolving. Common experiences included temporary tingling during IV administration, mild muscle cramping, localized injection-site discomfort, redness, or sensitivity with IM or SC administration. Niagen™ IV was consistently better tolerated than conventional NAD+ IV.

3.2.1. Toxicity and Safety biomarkers

Preclinical oral toxicology data for Niagen® established a no observed adverse effect level (NOAEL) of 300 and 500 mg/kg body weight per day [34,35]. Published clinical studies have demonstrated oral NR to be well tolerated at

doses up to 2-3 g/day [5,9,10,13–15,22,25,36–41]. Across the four parenteral pilot studies, laboratory safety markers remained within expected ranges without consistent patterns of concern[1].

Takeaway: Across four pilot clinical studies, Niagen™ Plus demonstrated a favorable short-term safety profile with no serious adverse events following IV, IM, or SC administration and was consistently better tolerated than conventional NAD+ IV therapy.

3.2.2. Whole blood NAD+

Niagen™ Plus rapidly increases circulating NAD+. In Hawkins et al. (2024) [39], a single 500 mg IV infusion increased whole-blood NAD+ by more than 20% within three hours (Figure 1).

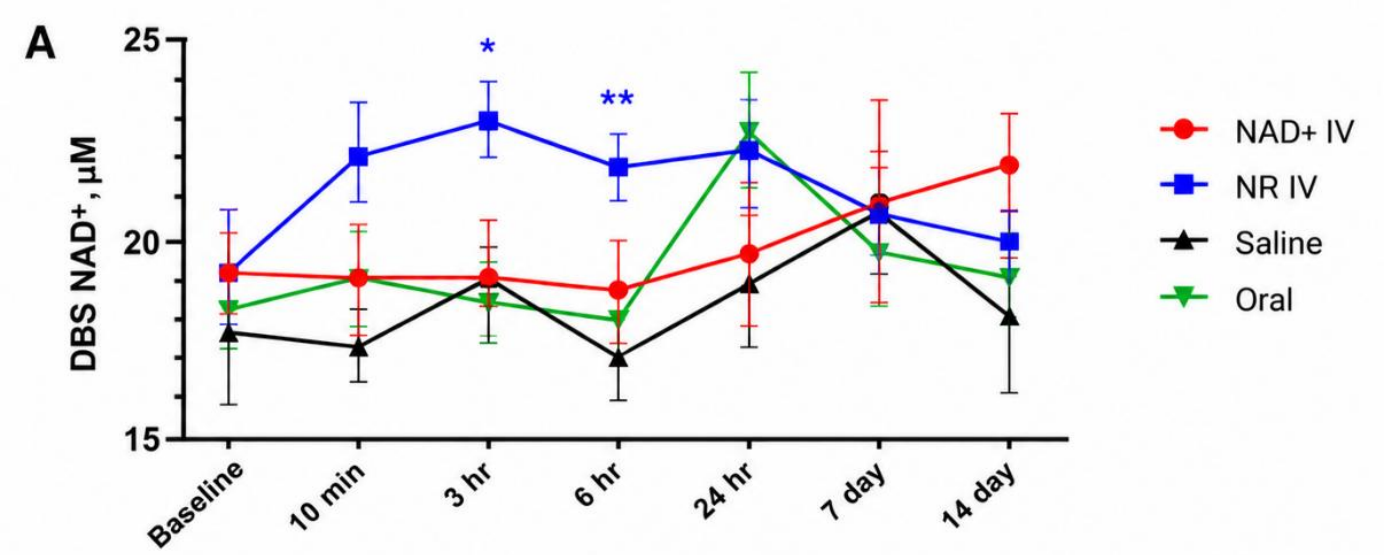

Figure 1. NAD+ measured by capillary whole blood NAD+ captured by dried blood spot (DBS). Levels are reported as the mean ± SEM, *p<0.05, **p<0.01 of NR relative to saline.

In Russ et al. (manuscript in process), IM and SC administration produced significant transient increases of up to 6%, peaking after three consecutive days of injection. NAD+ levels were monitored throughout the dosing period. A transient peak was observed on Day 3, with levels increasing 6.4% above baseline (p = 0.001), before returning to baseline by Day 4 and remaining stable through Day 100. Baseline NAD+ concentrations did not change significantly over the course of the study (Figure 2).

Together, these pilot studies demonstrate that parenteral Niagen produces rapid, but transient increases in whole-blood NAD+ that warrant confirmation in larger clinical studies.

[1] These pilot studies were conducted in generally healthy adults and have not been validated in larger or diseased populations. Periodic blood chemistry monitoring is recommended, and drug-drug and drug-nutrient interactions have not been evaluated.

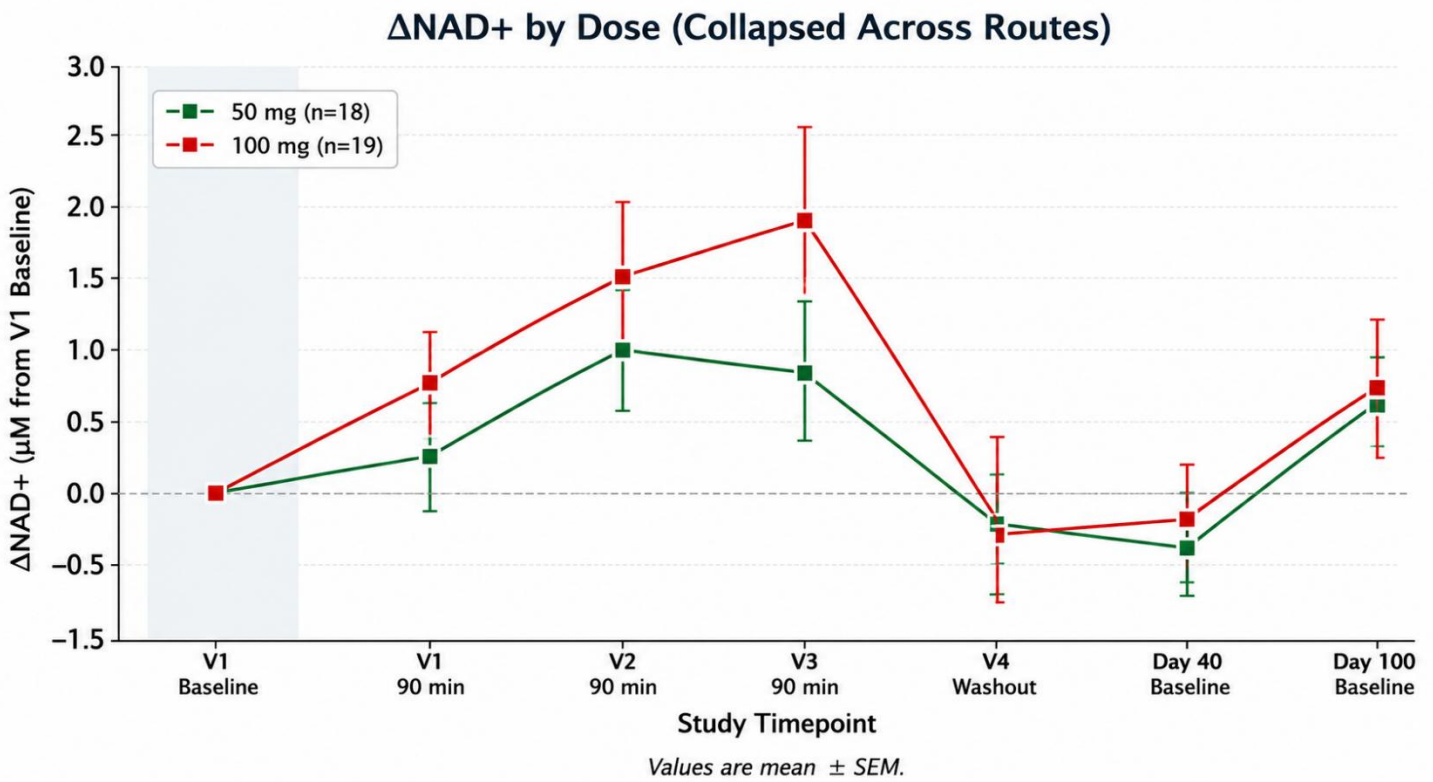

Figure 2. NAD+ kinetics by dose in Russ et al. (manuscript in process). NAD+ increased through V3, with a greater response in the 100 mg group, returned below baseline after washout, and showed modest recovery by Day 100.

4. UNDERSTANDING BLOOD AND TISSUE NAD+ FROM ORAL AND PARENTERAL NIAGEN ADMINISTRATION

Whole blood is a complex mixture of plasma, red blood cells (RBCs), white blood cells, and platelets. RBCs account for ~40–45% of blood volume but have limited capacity to utilize NR for NAD+ synthesis. In contrast, NRK expression varies across metabolically active tissues, with particularly high NRK1 expression in kidney and NRK2 expression in skeletal muscle. Preclinical isotope-tracing studies demonstrate that IV NR can be delivered intact to peripheral tissues and increase tissue NAD+. Together, these findings suggest that changes in whole-blood NAD+ may not fully reflect tissue exposure following parenteral NR [30,42].

For clinicians, the primary point is that whole-blood NAD+ is a useful pharmacodynamic biomarker of exposure to NAD+ precursors but may not be a direct measure of tissue NAD+ status. Blood measures may not fully capture NR activity in metabolically active tissues where NAD+ supports mitochondrial function, cellular repair, and metabolic regulation.

4.1. Oral Niagen®: Systemic Exposure with First-Pass Metabolism

Oral Niagen increases NAD+ levels in both blood and tissues in humans [8,17,20,24,27,28]. However, oral NR undergoes first-pass metabolism in the GI tract and liver and interactions with the gut microbiome before it reaches systemic circulation [26]. A portion of NR is converted to downstream metabolites including nicotinamide (NAM) and nicotinic acid (NA), which may also contribute to NAD+ biosynthesis and the biological effects of oral NR [26].

4.2. Parenteral Niagen: Direct Systemic Delivery

IV, IM and SC administration bypass gastrointestinal and hepatic first-pass metabolism [26], altering the pharmacokinetic profile of NR. IV administration delivers intact NR directly into circulation, while IM and SC administration provide gradual systemic absorption without GI metabolism.

Preclinical research demonstrates IV administration of NR produces greater increases in NAD+ in metabolically active tissues including skeletal muscle, kidney, liver and brain [30] compared to oral administration. Skeletal muscle also expresses high levels of NRK [43], making it a potentially important target for circulating NR [44].

Conversely, oral NR may support NAD+ biology through both intact NR and downstream metabolites generated during GI and microbiome metabolism. These differences suggest that oral and parenteral NR should be viewed as complementary rather than competing approaches to NAD+ restoration, with distinct pharmacokinetic profiles and potentially different biological strengths. Table 2 summarizes the key differences between the two routes and their potential clinical relevance.

TAKEAWAY: NIAGEN PLUS BYPASSES GASTROINTESTINAL AND LIVER METABOLISM AND THEREFORE INCREASES SYSTEMIC EXPOSURE TO INTACT NR, WHILE ORAL NIAGEN PROVIDES SUSTAINED NAD+ SUPPORT THROUGH COMPLEMENTARY METABOLIC PATHWAYS.

Table 2: Comparison of Oral Niagen® and Niagen™ Plus

Characteristic	Oral Niagen®	Niagen™ Plus	Clinical Perspective
Administration	Capsule or powder	IV, IM, or SC	Niagen Plus offers rapid, flexible delivery; oral Niagen supports convenient daily use.
Intact NR Exposure	Shaped by GI absorption and metabolism	Greater initial systemic exposure before metabolism	Niagen Plus increases initial intact NR exposure, complementing oral metabolic pathways.
Blood NAD+	Gradual increase with consistent daily use	Rapid, transient increase after administration	Niagen Plus provides rapid elevation; oral Niagen supports sustained NAD+ levels.
Tissue NAD+	Human studies demonstrate increases in multiple tissues	Preclinical studies suggest greater tissue delivery; human data remain limited	Niagen Plus may enhance tissue delivery, complementing established oral tissue effects.
Primary MOA	NAD+ biosynthesis through intact NR and downstream metabolites	Direct systemic delivery of intact NR before metabolism	Distinct metabolic pathways provide complementary approaches to NAD+ support.
Clinical Evidence	Extensive human clinical evidence	Early human evidence for safety, pharmacokinetics, and exploratory outcomes	Niagen Plus extends an established oral evidence base through a distinct delivery approach.

Table 2. Oral Niagen® and parenteral Niagen™ Plus offer complementary approaches to NAD+ support: sustained daily supplementation and rapid systemic delivery through parenteral administration.

5. CLINICAL OUTCOMES OF PARENTERAL NIAGEN

Although the Niagen Plus clinical studies were primarily designed to evaluate safety, exploratory biological and patient-reported outcomes were also assessed. Findings across fatigue, sleep, quality of life, mitochondrial bioenergetics, oxidative stress, inflammation, and skin health provide direction for larger efficacy-focused trials.

5.1. Energy and Fatigue

NAD+ is essential for cellular energy production, making fatigue and perceived energy important exploratory outcomes for Niagen™ Plus.

Across multiple pilot studies, participants reported improvements in fatigue and selected measures of perceived energy (Figure 3). In Russ et al. (manuscript in process), repeated SC administration significantly reduced PROMIS Fatigue scores by Day 100 in both the 50 mg and 100 mg groups. PROMIS (Patient-Reported Outcomes Measurement Information System) measures self-reported fatigue over the past 7 days. Hawkins et al. 2025 (manuscript in process) reported improvements in general, emotional, and overall energy following IV administration. There was decline in physical energy, but fatigue showed improvement and a favorable trend toward reduced fatigue 30 days after a four-day IV loading protocol was also reported [45].

Together, these exploratory findings suggest that Niagen™ Plus may reduce perceived fatigue and influence energy-related outcomes. Larger randomized, placebo-controlled trials are needed to confirm these effects and determine their durability.

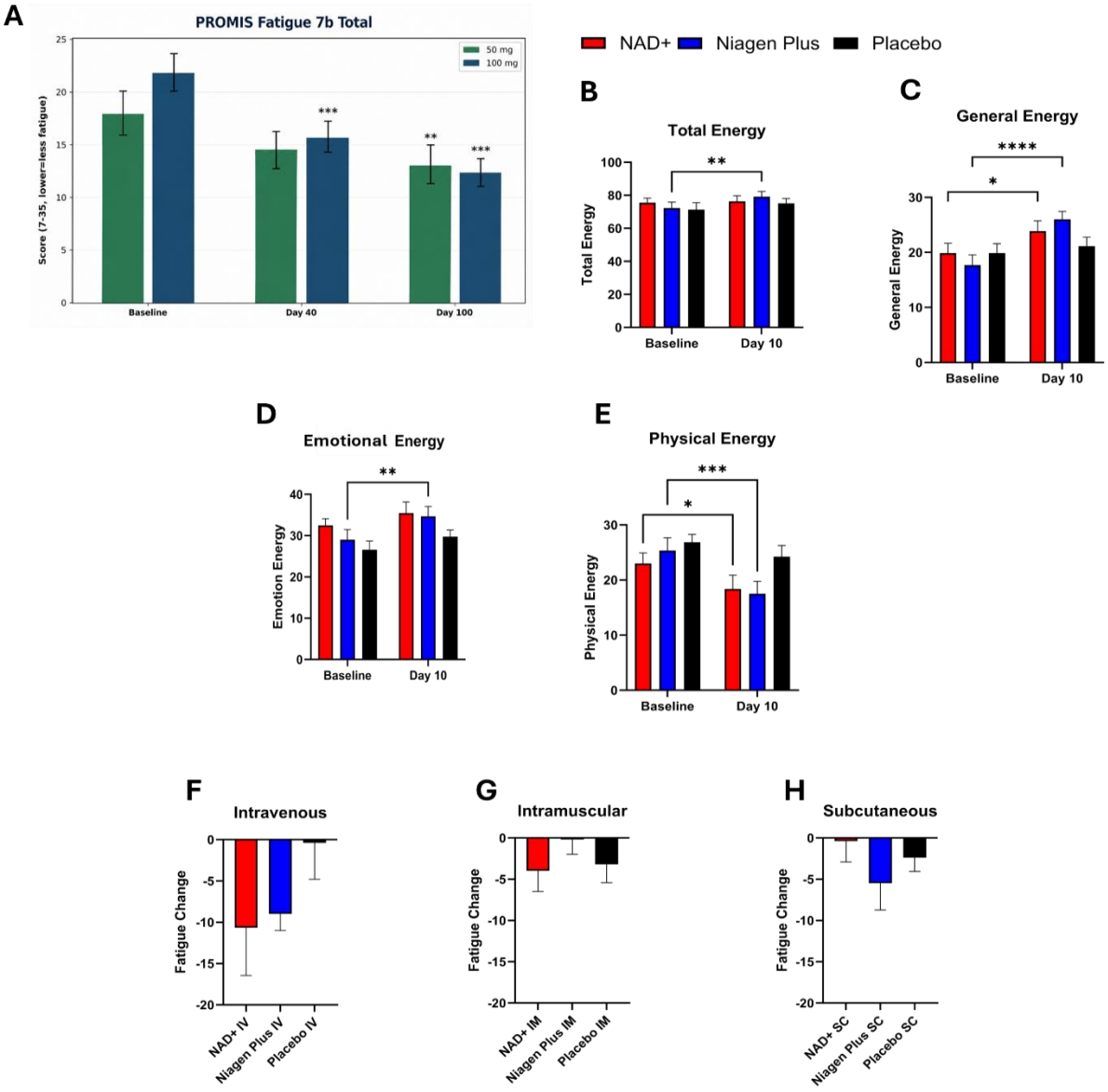

Figure 3. Changes in fatigue and energy following Niagen™ Plus. (A) PROMIS Fatigue scores following repeated 50 mg and 100 mg SC administration. (B–E) Changes in total, general, emotional, and physical energy. (F–H) Changes in fatigue by IV, IM, and SC administration. Data are mean ± SEM; *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

Mitochondrial Function

Improvements in fatigue were accompanied by measurable changes in mitochondrial bioenergetics. In Russ et al. (manuscript in preparation), MeScreen™ test was used to assess ATP production from mitochondrial oxidative phosphorylation relative to glycolysis. This at-home test measures mitochondrial efficiency and cellular energy production to provide personalized health insights.

Repeated injections of Niagen™ Plus increased the mitochondrial ATP-to-glycolytic ATP ratio by 44.5% from baseline to Day 40 (p=0.005), which was sustained through Day 100 (p=0.003) (Figure 4). This shift toward oxidative phosphorylation suggests greater reliance on mitochondrial energy metabolism and provides a potential biological link to the observed improvements in fatigue [46,47].

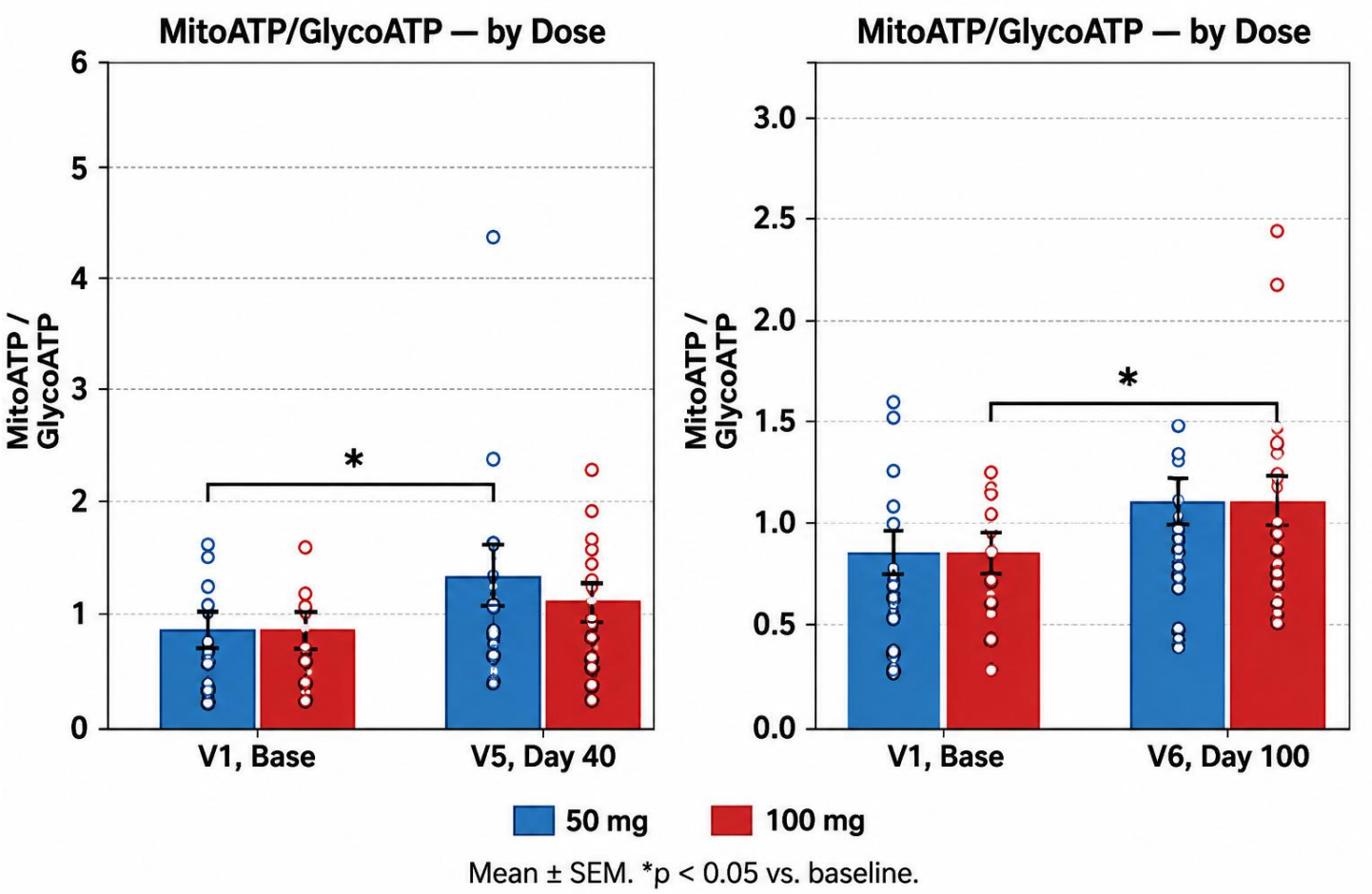

Figure 4. Mitochondrial ATP-to-glycolytic ATP ratio following repeated Niagen™ Plus administration. The MitoATP:GlycoATP ratio increased from baseline to Day 40 and remained elevated through Day 100, as measured using the MeScreen™ Mitochondrial Efficiency assay from dried blood spots.

TAKEAWAY: REPEATED ADMINISTRATION OF NIAGEN™ PLUS WAS ASSOCIATED WITH IMPROVED MITOCHONDRIAL BIOENERGETICS, PROVIDING A POTENTIAL BIOLOGICAL MECHANISM FOR THE OBSERVED IMPROVEMENTS IN FATIGUE AND ENERGY.

5.2. Sleep

NAD+ plays an important role in circadian regulation and cellular metabolism age [48–52] making sleep quality an important exploratory outcome for Niagen™ Plus.

In Russ et al. (manuscript in process), repeated administration of Niagen™ Plus was associated with progressive improvements in self-reported sleep quality. While improvements following the initial three injections did not reach statistical significance, sleep quality improved significantly across all participants by Day 40 ($p < 0.0001$) and remained improved through Day 100 ($p < 0.001$).

These findings suggest that repeated NAD+ restoration may support healthy sleep, although larger placebo-controlled studies are needed to confirm these observations.

TAKEAWAY: REPEATED ADMINISTRATION OF NIAGEN PLUS WAS ASSOCIATED WITH SUSTAINED IMPROVEMENTS IN SELF-REPORTED SLEEP QUALITY.

5.3. Quality of Life

Quality of life was assessed using the PROMIS Global Health Rating (GHR), a validated measure of overall physical and mental well-being. It is a 10-item patient-reported questionnaire developed by the National Institutes of Health (NIH) to assess an individual's overall health across physical, mental, and social domains.

In the Russ et al. study, participants reported improvements in global health ratings as early as Day 10, with significant improvements across the study population by Day 40 ($p < 0.001$) that were maintained through Day 100 (Figure 5).

Although exploratory, these findings are consistent with the concurrent improvements observed in fatigue, sleep quality, mitochondrial function, and oxidative stress.

TAKEAWAY: PARTICIPANTS RECEIVING REPEATED NIAGEN PLUS INJECTIONS REPORTED SUSTAINED IMPROVEMENTS IN OVERALL QUALITY OF LIFE.

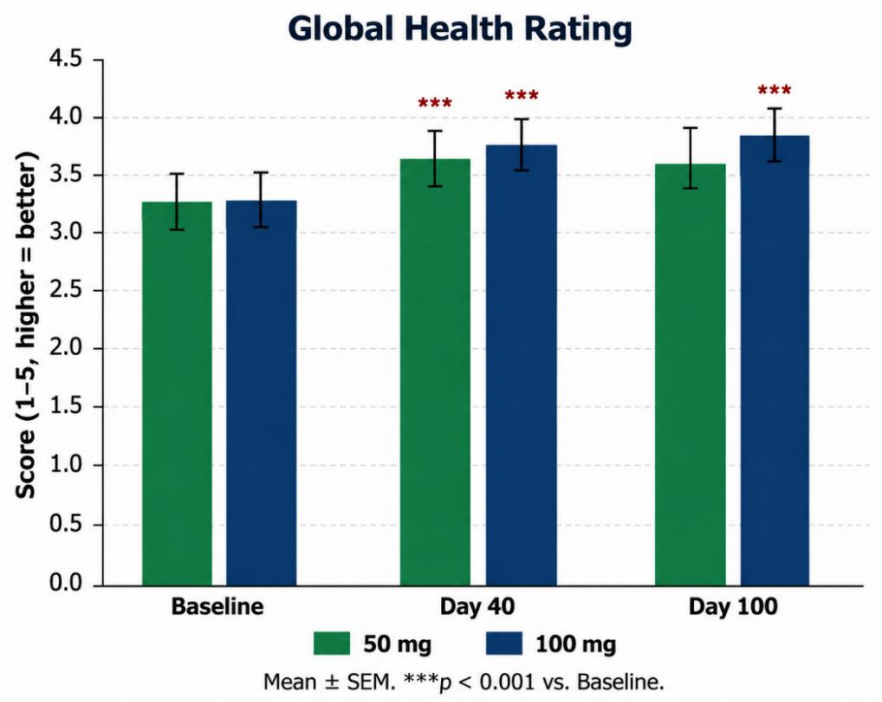

Figure 5. Global Health Rating, a QoL measurement, was sustainably improved with 100 mg SC injections three times per week. Bars represent the mean ± SEM. (***p<0.001)

5.4. Oxidative Stress

Oxidative stress was evaluated in Russ et al (manuscript in process) using 17 urinary biomarkers spanning multiple oxidative pathways. Repeated Niagen Plus administration was associated with reductions in several biomarkers of oxidative stress.

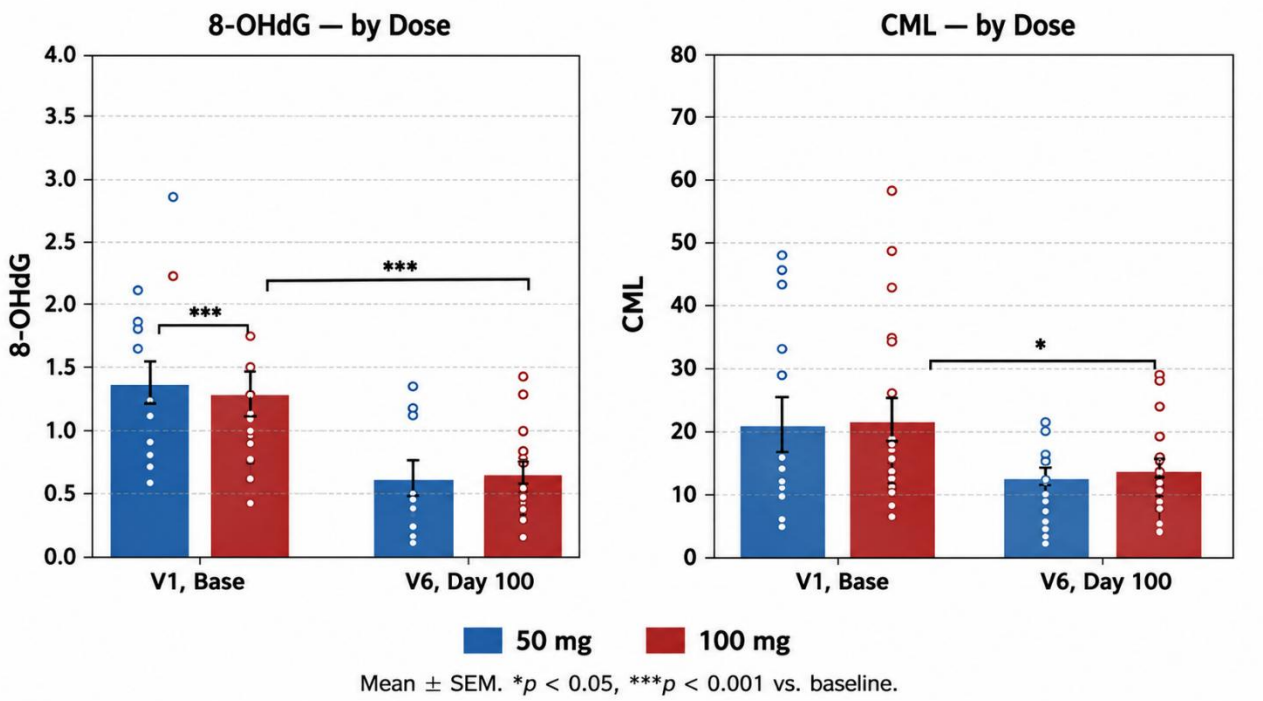

Figure 6. Changes in 8-OHdG and CML from baseline to Day 100 by Niagen™ Plus dose

By Day 100, key oxidative stress biomarkers improved significantly. 8-OHdG, a marker of oxidative DNA damage, decreased by more than 50% ($p<0.001$), while carboxymethyl lysine (CML), a marker of advanced glycation, decreased by approximately 35% ($p<0.003$) relative to baseline (Figure 6).

Together, reductions across multiple oxidative stress biomarkers suggest that repeated Niagen Plus injections may support cellular redox balance. These exploratory findings are consistent with the role of NAD+ in supporting antioxidant defense and mitochondrial function and warrant confirmation in larger placebo-controlled studies [53–55].

5.5. Skin

In Russ et al., participant-reported skin improvements increased from 0% at baseline to 34% by Day 100, including 27% reporting improved facial appearance. These exploratory findings warrant confirmation using objective dermatologic endpoints.

5.6 Inflammation

Oral Niagen® has been shown to reduce proinflammatory cytokines in clinical studies [10,11,17,20,25,28,56], providing a rationale for evaluating inflammatory outcomes with Niagen™ Plus. In Hawkins et al. [57] changes in IL-1β, IL-6, IL-10, and TNFα were not significantly different from saline control. Exploratory patterns were observed including increases in IL-6, IL-10, and TNFα after NAD+ IV that were not seen with NR IV; however, these findings require confirmation in larger studies (Figure 7).

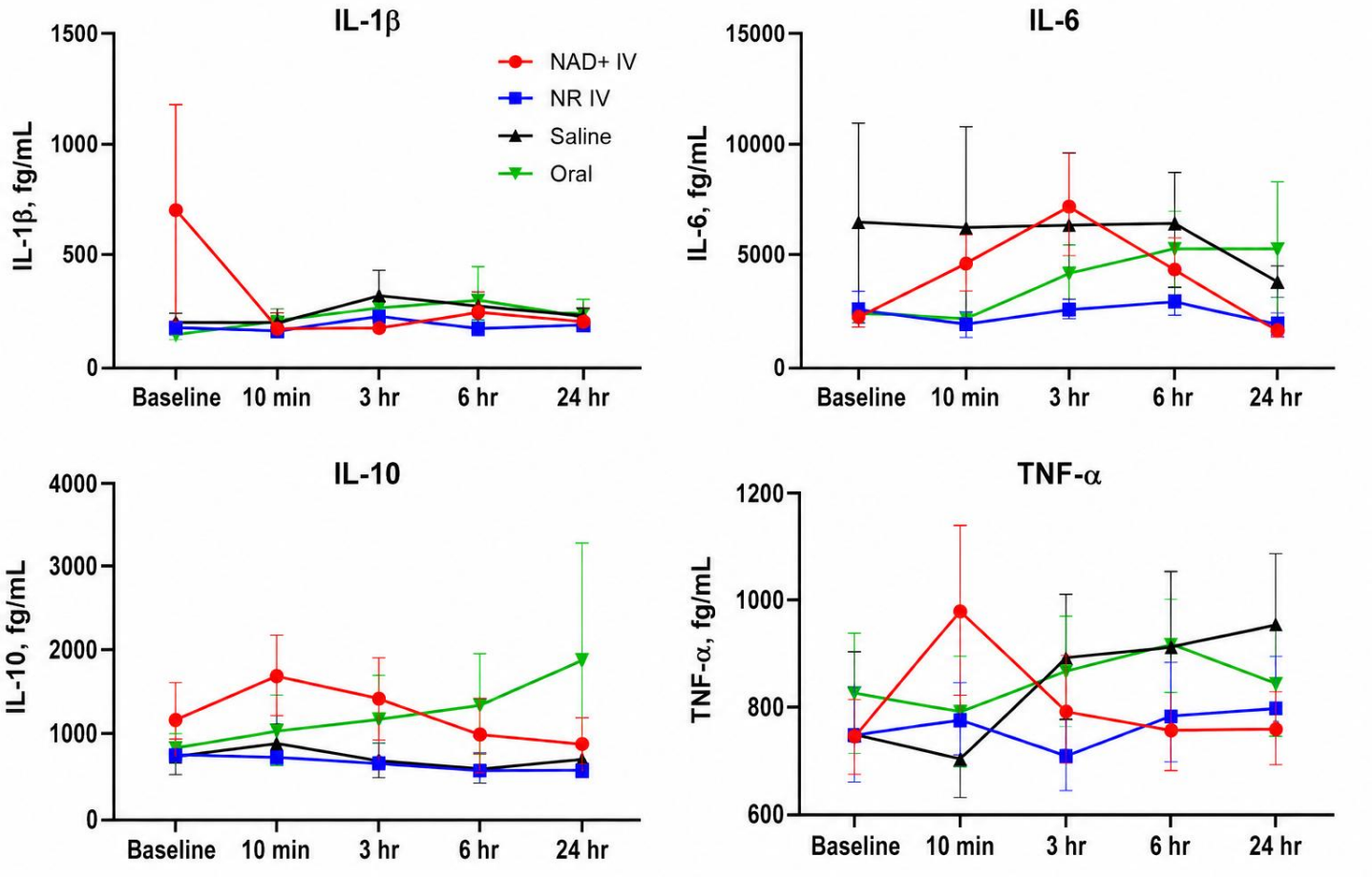

Figure 7. Changes in IL-1β, IL-6, IL-10, and TNFα following IV administration in Hawkins et al. (2024; unpublished data). No significant treatment differences were observed.

Clinical markers of inflammation, including hsCRP, serum viscosity, and erythrocyte sedimentation rate (ESR), were also evaluated. Nkrumah-Elie et al. (2026)[58] observed nonsignificant trends toward reductions in hsCRP and ESR (Figure 8), while Russ et al. found no significant changes in hsCRP over time.

Overall, Niagen™ Plus did not increase the inflammatory markers evaluated. Larger studies are needed to determine whether parenteral NR has clinically meaningful anti-inflammatory effects, especially in populations with elevated baseline inflammation.

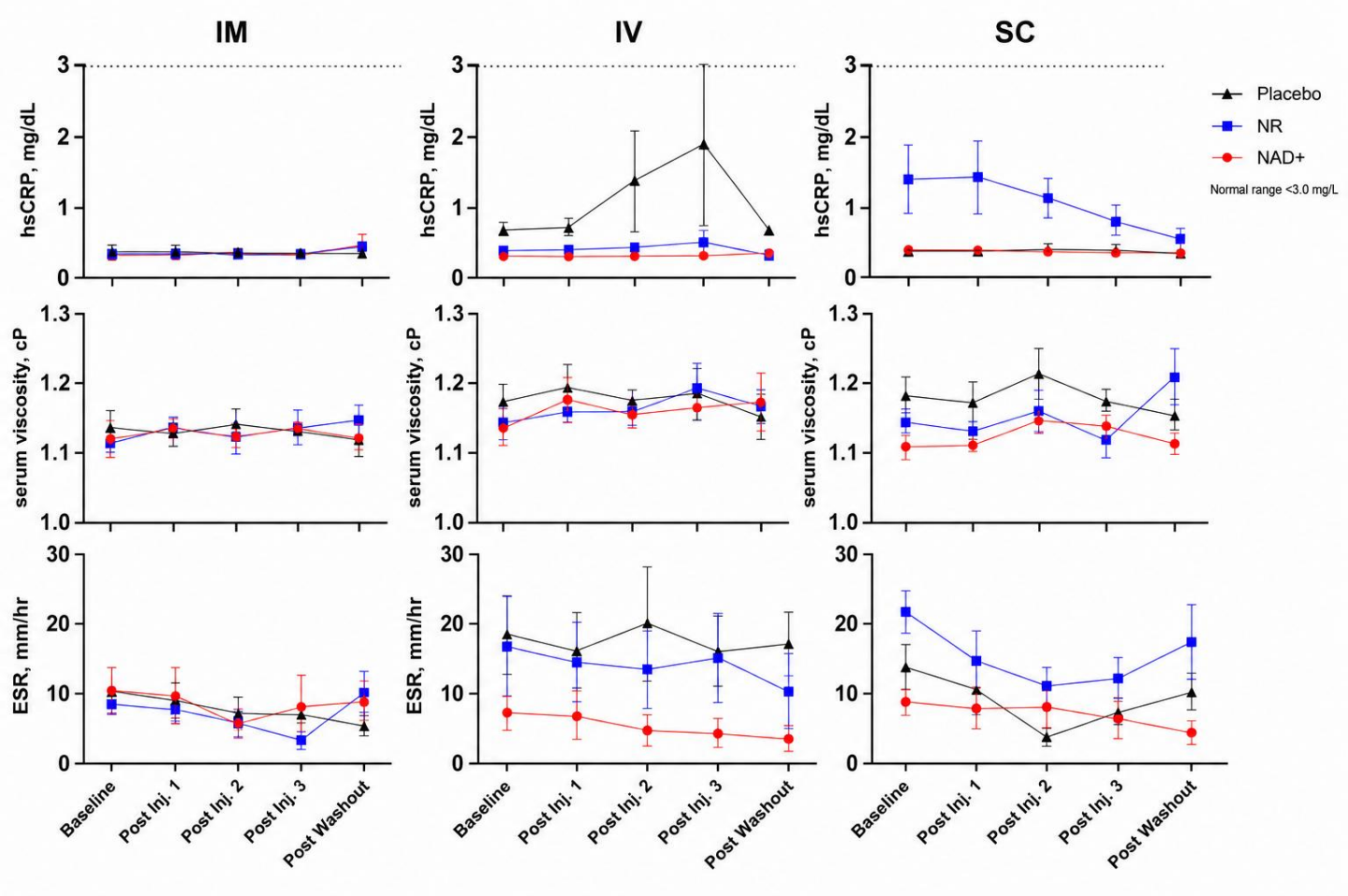

Figure 8. Clinical inflammatory markers following Niagen™ Plus administration, including hsCRP, serum viscosity, and ESR.

6. CONCLUSION

Across four pilot clinical studies, parenteral Niagen™ Plus administered by IV, IM, and SC routes demonstrated a favorable short-term safety and tolerability profile with no serious safety signals. Niagen™ Plus administration produced rapid, transient increases in whole-blood NAD+, while Niagen IV was better tolerated and administered more efficiently than conventional NAD+ IV.

Importantly, these studies also generated encouraging biological and participant-reported outcomes beyond NAD+ elevation. Repeated Niagen™ Plus administration was associated with improvements in fatigue, sleep quality, and quality of life, alongside favorable changes in mitochondrial bioenergetics and markers of oxidative stress. Exploratory inflammatory findings further suggest that parenteral NR does not increase inflammation and warrant investigation in populations with elevated baseline inflammation.

Together, these findings demonstrate biological activity across multiple domains relevant to cellular and metabolic health and support the potential of parenteral Niagen™ Plus as a distinct approach to NAD+ restoration. While the efficacy findings remain preliminary, their consistency across objective biomarkers and participant-reported outcomes provides a strong rationale for larger randomized, placebo-controlled trials to confirm clinical benefits, optimize dosing, and identify populations most likely to benefit.

REFERENCES

[1] Massudi, H., Grant, R., Braidy, N., Guest, J., Farnsworth, B. and Guillemin, G.J. (2012) Age-Associated Changes In Oxidative Stress and NAD+ Metabolism In Human Tissue. *PLoS ONE*, **7**, e42357. https://doi.org/10.1371/journal.pone.0042357

[2] Janssens, G.E., Grevendonk, L., Perez, R.Z., Schomakers, B.V., Bosch, J. de V. den, Geurts, J.M.W. et al. (2022) Healthy aging and muscle function are positively associated with NAD+ abundance in humans. *Nature Aging*, **2**, 254–63. https://doi.org/10.1038/s43587-022-00174-3

[3] Bagga, P., Hariharan, H., Wilson, N.E., Beer, J.C., Shinohara, R.T., Elliott, M.A. et al. (2020) Single-Voxel 1H MR spectroscopy of cerebral nicotinamide adenine dinucleotide (NAD+) in humans at 7T using a 32-channel volume coil. *Magnetic Resonance in Medicine*, **83**, 806–14. https://doi.org/10.1002/mrm.27971

[4] Vinten, K.T., Trętowicz, M.M., Coskun, E., Weeghel, M. van, Cantó, C., Zapata-Pérez, R. et al. (2025) NAD+ precursor supplementation in human ageing: clinical evidence and challenges. *Nature Metabolism*, **7**, 1974–90. https://doi.org/10.1038/s42255-025-01387-7

[5] Dollerup, O.L., Christensen, B., Svart, M., Schmidt, M.S., Sulek, K., Ringgaard, S. et al. (2018) A randomized placebo-controlled clinical trial of nicotinamide riboside in obese men: safety, insulin-sensitivity, and lipid-mobilizing effects. *The American Journal of Clinical Nutrition*, **108**, 343–53. https://doi.org/10.1093/ajcn/nqy132

[6] Martens, C.R., Denman, B.A., Mazzo, M.R., Armstrong, M.L., Reisdorph, N., McQueen, M.B. et al. (2018) Chronic nicotinamide riboside supplementation is well-tolerated and elevates NAD+ in healthy middle-aged and older adults. *Nature Communications*, **9**, 1286. https://doi.org/10.1038/s41467-018-03421-7

[7] Orr, M.E., Kotkowski, E., Ramirez, P., Bair-Kelps, D., Liu, Q., Brenner, C. et al. (2024) A randomized placebo-controlled trial of nicotinamide riboside in older adults with mild cognitive impairment. *GeroScience*, **46**, 665–82. https://doi.org/10.1007/s11357-023-00999-9

[8] Nanga, R.P.R., Wiers, C.E., Elliott, M.A., Wilson, N.E., Liu, F., Cao, Q. et al. (2024) Acute nicotinamide riboside supplementation increases human cerebral NAD+ levels in vivo. *Magnetic Resonance in Medicine*, **92**, 2284–93. https://doi.org/10.1002/mrm.30227

[9] Airhart, S.E., Shireman, L.M., Risler, L.J., Anderson, G.D., Gowda, G.A.N., Raftery, D. et al. (2017) An open-label, non-randomized study of the pharmacokinetics of the nutritional supplement nicotinamide riboside (NR) and its effects on blood NAD+ levels in healthy volunteers. *PLoS ONE*, **12**, e0186459. https://doi.org/10.1371/journal.pone.0186459

[10] Zhou, B., Wang, D.D., Qiu, Y., Airhart, S., Liu, Y., Stempien-Otero, A. et al. (2020) Boosting NAD Level Suppresses Inflammatory Activation of PBMC in Heart Failure. *Journal of Clinical Investigation*, **130**, 6054–63. https://doi.org/10.1172/jci138538

[11] Wu, J., Singh, K., Lin, A., Meadows, A.M., Wu, K., Shing, V. et al. (2022) Boosting NAD+ blunts toll-like receptor-4 induced type-I interferon in control and systemic lupus erythematosus monocytes. *Journal of Clinical Investigation*, **132**, e139828. https://doi.org/10.1172/jci139828

[12] Martens, C.R., Decker, K.P., DeConne, T.M., Sanjana, F., Horvat, F., Rizzi, N.A. et al. (2026) A phase-II randomized controlled pilot study of nicotinamide riboside supplementation in older adults with amnestic mild cognitive impairment. *Alzheimer's & Dementia*, **22**. https://doi.org/10.1002/alz.71605

[13] Dollerup, O.L., Trammell, S.A.J., Hartmann, B., Holst, J.J., Christensen, B., Møller, N. et al. (2019) Effects of Nicotinamide Riboside on Endocrine Pancreatic Function and Incretin Hormones in Nondiabetic Men With Obesity. *The Journal of Clinical Endocrinology & Metabolism*, **104**, 5703–14. https://doi.org/10.1210/jc.2019-01081

[14] Wu, C.-Y., Reynolds, W.C., Abril, I., McManus, A.J., Brenner, C., González-Irizarry, G. et al. (2025) Effects of nicotinamide riboside on NAD+ levels, cognition, and symptom recovery in long-COVID: a randomized controlled trial. *eClinicalMedicine*, **89**, 103633. https://doi.org/10.1016/j.eclinm.2025.103633

[15] Thomas, S., Ben-Davies, R., Cetinkaya-Fisgin, A., Hu, X., Li, X., Stewart, S. et al. (2026) Evaluation of Nicotinamide Riboside in Prevention of Small Nerve Fiber Axon Degeneration and Promotion of Nerve Regeneration. *Journal of the Peripheral Nervous System*, **31**. https://doi.org/10.1111/jns.70101

[16] Presterud, R., Deng, W.H., Wennerström, A.B., Burgers, T., Gajera, B., Mattsson, K. et al. (2024) Long-Term Nicotinamide Riboside Use Improves Coordination and Eye Movements in Ataxia Telangiectasia. *Movement Disorders*, **39**, 360–9. https://doi.org/10.1002/mds.29645

[17] Elhassan, Y.S., Kluckova, K., Fletcher, R.S., Schmidt, M.S., Garten, A., Doig, C.L. et al. (2019) Nicotinamide Riboside Augments the Aged Human Skeletal Muscle NAD+ Metabolome and Induces Transcriptomic and Anti-inflammatory Signatures. *Cell Reports*, **28**, 1717-1728.e6. https://doi.org/10.1016/j.celrep.2019.07.043
[18] Lapatto, H.A.K., Kuusela, M., Heikkinen, A., Muniandy, M., Kolk, B.W. van der, Gopalakrishnan, S. et al. (2023) Nicotinamide riboside improves muscle mitochondrial biogenesis, satellite cell differentiation, and gut microbiota in a twin study. *Science Advances*, **9**, eadd5163. https://doi.org/10.1126/sciadv.add5163
[19] Trammell, S.A.J., Schmidt, M.S., Weidemann, B.J., Redpath, P., Jaksch, F., Dellinger, R.W. et al. (2016) Nicotinamide riboside is uniquely and orally bioavailable in mice and humans. *Nature Communications*, **7**, 12948. https://doi.org/10.1038/ncomms12948
[20] Remie, C.M., Roumans, K.H., Moonen, M.P., Connell, N.J., Havekes, B., Mevenkamp, J. et al. (2020) Nicotinamide riboside supplementation alters body composition and skeletal muscle acetylcarnitine concentrations in healthy obese humans. *The American Journal of Clinical Nutrition*, **112**, 413–26. https://doi.org/10.1093/ajcn/nqaa072
[21] Stocks, B., Ashcroft, S.P., Joanisse, S., Dansereau, L.C., Koay, Y.C., Elhassan, Y.S. et al. (2021) Nicotinamide riboside supplementation does not alter whole-body or skeletal muscle metabolic responses to a single bout of endurance exercise. *The Journal of Physiology*, **599**, 1513–31. https://doi.org/10.1113/jp280825
[22] Berven, H., Kverneng, S., Sheard, E., Søgnen, M., Geijerstam, S.A.A., Haugarvoll, K. et al. (2023) NR-SAFE: a randomized, double-blind safety trial of high dose nicotinamide riboside in Parkinson's disease. *Nature Communications*, **14**, 7793. https://doi.org/10.1038/s41467-023-43514-6
[23] Vreones, M., Mustapic, M., Moaddel, R., Pucha, K.A., Lovett, J., Seals, D.R. et al. (2022) Oral nicotinamide riboside raises NAD+ and lowers biomarkers of neurodegenerative pathology in plasma extracellular vesicles enriched for neuronal origin. *Aging Cell*, **22**, e13754. https://doi.org/10.1111/acel.13754
[24] Conze, D., Brenner, C. and Kruger, C.L. (2019) Safety and Metabolism of Long-term Administration of NIAGEN (Nicotinamide Riboside Chloride) in a Randomized, Double-Blind, Placebo-controlled Clinical Trial of Healthy Overweight Adults. *Scientific Reports*, **9**, 9772. https://doi.org/10.1038/s41598-019-46120-z
[25] Wang, D.D., Airhart, S.E., Zhou, B., Shireman, L.M., Jiang, S., Rodriguez, C.M. et al. (2022) Safety and Tolerability of Nicotinamide Riboside in Heart Failure With Reduced Ejection Fraction. *JACC: Basic to Translational Science*, **7**, 1183–96. https://doi.org/10.1016/j.jacbts.2022.06.012
[26] Christen, S., Redeuil, K., Goulet, L., Giner, M.-P., Breton, I., Rota, R. et al. (2026) The differential impact of three different NAD+ boosters on circulatory NAD and microbial metabolism in humans. *Nature Metabolism*, 1–12. https://doi.org/10.1038/s42255-025-01421-8
[27] Berven, H., Svensen, M., Eikeland, H., Tvedten, N., Sheard, E.V., Geijerstam, S.A.A. et al. (2026) The NAD-brain pharmacokinetic study of NAD augmentation in blood and brain using oral precursor supplementation. *iScience*, 114764. https://doi.org/10.1016/j.isci.2026.114764
[28] Brakedal, B., Dölle, C., Riemer, F., Ma, Y., Nido, G.S., Skeie, G.O. et al. (2022) The NADPARK study: A randomized phase I trial of nicotinamide riboside supplementation in Parkinson's disease. *Cell Metabolism*, **34**, 396-407.e6. https://doi.org/10.1016/j.cmet.2022.02.001
[29] Yaku, K., Palikhe, S., Iqbal, T., Hayat, F., Watanabe, Y., Fujisaka, S. et al. (2025) Nicotinamide riboside and nicotinamide mononucleotide facilitate NAD+ synthesis via enterohepatic circulation. *Science Advances*, **11**, eadr1538. https://doi.org/10.1126/sciadv.adr1538
[30] Liu, L., Su, X., Quinn, W.J., Hui, S., Krukenberg, K., Frederick, D.W. et al. (2018) Quantitative Analysis of NAD Synthesis-Breakdown Fluxes. *Cell Metabolism*, **27**, 1067-1080.e5. https://doi.org/10.1016/j.cmet.2018.03.018
[31] Ratajczak, J., Joffraud, M., Trammell, S.A.J., Ras, R., Canela, N., Boutant, M. et al. (2016) NRK1 controls nicotinamide mononucleotide and nicotinamide riboside metabolism in mammalian cells. *Nature Communications*, **7**, 13103. https://doi.org/10.1038/ncomms13103
[32] Ma, S., Feng, J., Lin, X., Liu, J., Tang, Y., Nie, S. et al. (2021) Nicotinamide Riboside Alleviates Cardiac Dysfunction and Remodeling in Pressure Overload Cardiac Hypertrophy. *Oxidative Medicine and Cellular Longevity*, **2021**, 5546867. https://doi.org/10.1155/2021/5546867
[33] Hong, G., Zheng, D., Zhang, L., Ni, R., Wang, G., Fan, G.-C. et al. (2018) Administration of nicotinamide riboside prevents oxidative stress and organ injury in sepsis. *Free Radical Biology and Medicine*, **123**, 125–37. https://doi.org/10.1016/j.freeradbiomed.2018.05.073

[34] Conze, D., Crespo-Barreto, J. and Kruger, C. (2016) Safety assessment of nicotinamide riboside, a form of vitamin B3. *Human & Experimental Toxicology*, **35**, 1149–60. https://doi.org/10.1177/0960327115626254
[35] Marinescu, A.G., Chen, J., Holmes, H.E., Guarente, L., Mendes, O., Morris, M. et al. (2020) Safety Assessment of High-Purity, Synthetic Nicotinamide Riboside (NR-E) in a 90-Day Repeated Dose Oral Toxicity Study, With a 28-Day Recovery Arm. *International Journal of Toxicology*, **39**, 307–20. https://doi.org/10.1177/1091581820927406
[36] Yulug, B., Altay, O., Li, X., Hanoglu, L., Cankaya, S., Velioglu, H.A. et al. (2025) Multi-omics characterization of improved cognitive functions in Parkinson's disease patients after the combined metabolic activator treatment: a randomized, double-blinded, placebo-controlled phase II trial. *Brain Communications*, **7**, fcae478. https://doi.org/10.1093/braincomms/fcae478
[37] Yulug, B., Altay, O., Li, X., Hanoglu, L., Cankaya, S., Lam, S. et al. (2023) Combined metabolic activators improve cognitive functions in Alzheimer's disease patients: a randomised, double-blinded, placebo-controlled phase-II trial. *Translational Neurodegeneration*, **12**, 4. https://doi.org/10.1186/s40035-023-00336-2
[38] Peluso, A.A., Lundgaard, A.T., Babaei, P., Mousovich-Neto, F., Rocha, A.L., Damgaard, M.V. et al. (2023) Oral supplementation of nicotinamide riboside alters intestinal microbial composition in rats and mice, but not humans. *Npj Aging*, **9**, 7. https://doi.org/10.1038/s41514-023-00106-4
[39] Zeybel, M., Altay, O., Arif, M., Li, X., Yang, H., Fredolini, C. et al. (2021) Combined metabolic activators therapy ameliorates liver fat in nonalcoholic fatty liver disease patients. *Molecular Systems Biology*, **17**, e10459. https://doi.org/10.15252/msb.202110459
[40] Altay, O., Arif, M., Li, X., Yang, H., Aydın, M., Alkurt, G. et al. (2021) Combined Metabolic Activators Accelerates Recovery in Mild-to-Moderate COVID-19. *Advanced Science*, **8**, 2101222. https://doi.org/10.1002/advs.202101222
[41] Dollerup, O.L., Chubanava, S., Agerholm, M., Søndergård, S.D., Altıntaş, A., Møller, A.B. et al. (2020) Nicotinamide riboside does not alter mitochondrial respiration, content or morphology in skeletal muscle from obese and insulin-resistant men. *The Journal of Physiology*, **598**, 731–54. https://doi.org/10.1113/jp278752
[42] Fletcher, R.S., Ratajczak, J., Doig, C.L., Oakey, L.A., Callingham, R., Xavier, G.D.S. et al. (2017) Nicotinamide riboside kinases display redundancy in mediating nicotinamide mononucleotide and nicotinamide riboside metabolism in skeletal muscle cells. *Molecular Metabolism*, **6**, 819–32. https://doi.org/10.1016/j.molmet.2017.05.011
[43] Ahmad, F. and Qaisar, R. (2024) Nicotinamide riboside kinase 2: A unique target for skeletal muscle and cardiometabolic diseases. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, **1870**, 167487. https://doi.org/10.1016/j.bbadis.2024.167487
[44] Turner, D.C., Raastad, T., Ullrich, M., Christiansen, S.F., Sutherland, H., Boot, J. et al. (2026) Repeated Disuse Atrophy Imprints a Molecular Memory in Skeletal Muscle: Transcriptional Resilience in Young Adults and Susceptibility in Aged Muscle. *Advanced Science*, e22726. https://doi.org/10.1002/advs.202522726
[45] Reyna, K., Heinzen, G., Patel, N., Ritter, M., Siojo, A., Legere, H. et al. (2026) Intravenous infusion of nicotinamide adenine dinucleotide (NAD+) versus nicotinamide riboside (NR): a retrospective tolerability pilot study in a real-world setting. *Frontiers in Aging*, **7**, 1652582. https://doi.org/10.3389/fragi.2026.1652582
[46] Vercellino, I. and Sazanov, L.A. (2022) The assembly, regulation and function of the mitochondrial respiratory chain. *Nature Reviews Molecular Cell Biology*, **23**, 141–61. https://doi.org/10.1038/s41580-021-00415-0
[47] Sundberg, C.W. and Fitts, R.H. (2019) Bioenergetic basis of skeletal muscle fatigue. *Current Opinion in Physiology*, **10**, 118–27. https://doi.org/10.1016/j.cophys.2019.05.004
[48] Sato, S., Solanas, G., Peixoto, F.O., Bee, L., Symeonidi, A., Schmidt, M.S. et al. (2017) Circadian Reprogramming in the Liver Identifies Metabolic Pathways of Aging. *Cell*, **170**, 664-677.e11. https://doi.org/10.1016/j.cell.2017.07.042
[49] Ramsey, K.M., Yoshino, J., Brace, C.S., Abrassart, D., Kobayashi, Y., Marcheva, B. et al. (2009) Circadian Clock Feedback Cycle Through NAMPT-Mediated NAD+ Biosynthesis. *Science*, **324**, 651–4. https://doi.org/10.1126/science.1171641
[50] Nakahata, Y., Sahar, S., Astarita, G., Kaluzova, M. and Sassone-Corsi, P. (2009) Circadian Control of the NAD+ Salvage Pathway by CLOCK-SIRT1. *Science*, **324**, 654–7. https://doi.org/10.1126/science.1170803
[51] Asher, G., Gatfield, D., Stratmann, M., Reinke, H., Dibner, C., Kreppel, F. et al. (2008) SIRT1 Regulates Circadian Clock Gene Expression through PER2 Deacetylation. *Cell*, **134**, 317–28. https://doi.org/10.1016/j.cell.2008.06.050

[52] Levine, D.C., Hong, H., Weidemann, B.J., Ramsey, K.M., Affinati, A.H., Schmidt, M.S. et al. (2020) NAD+ Controls Circadian Reprogramming through PER2 Nuclear Translocation to Counter Aging. *Molecular Cell*, **78**, 835-849.e7. https://doi.org/10.1016/j.molcel.2020.04.010
[53] Singh, C.K., Chhabra, G., Ndiaye, M.A., Garcia-Peterson, L.M., Mack, N.J. and Ahmad, N. (2017) The Role of Sirtuins in Antioxidant and Redox Signaling. *Antioxidants & Redox Signaling*, **28**, 643–61. https://doi.org/10.1089/ars.2017.7290
[54] Massudi, H., Grant, R., Guillemin, G.J. and Braidy, N. (2012) NAD+ metabolism and oxidative stress: the golden nucleotide on a crown of thorns. *Redox Report*, **17**, 28–46. https://doi.org/10.1179/1351000212y.0000000001
[55] Merksamer, P.I., Liu, Y., He, W., Hirschey, M.D., Chen, D. and Verdin, E. The sirtuins, oxidative stress and aging: an emerging link | Aging [Internet].
[56] Han, K., Singh, K., Meadows, A.M., Sharma, R., Hassanzadeh, S., Wu, J. et al. (2023) Boosting NAD preferentially blunts Th17 inflammation via arginine biosynthesis and redox control in healthy and psoriasis subjects. *Cell Reports Medicine*, **4**, 101157. https://doi.org/10.1016/j.xcrm.2023.101157
[57] Hawkins, J., Idoine, R., Kwon, J., Shao, A., Dunne, E., Hawkins, E. et al. (2024) Randomized, placebo-controlled, pilot clinical study evaluating acute Niagen®+ IV and NAD+ IV in healthy adults. *medRxiv*, 2024.06.06.24308565. https://doi.org/10.1101/2024.06.06.24308565
[58] Nkrumah-Elie, Y., Kwon, J., Simpson, S., Idoine, R., Mavoyan, J., Russ, A. et al. (2026) Preliminary Safety Analysis of Two Pilot Clinical Trials Involving Injections of Niagen ®, Nicotinamide Riboside Chloride. https://doi.org/10.64898/2026.04.28.26352007