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SUBCUTANEOUS NADH IMPLANT IN THE MANAGEMENT OF CHRONIC FATIGUE SYNDROME: AN INTEGRATIVE REVIEW OF CLINICAL AND METABOLIC EVIDENCE

IMPLANTE SUBCUTÂNEO DE NADH NO MANEJO DA SÍNDROME DA FADIGA CRÔNICA: UMA REVISÃO INTEGRATIVA DAS EVIDÊNCIAS CLÍNICAS E METABÓLICAS

IMPLANTE SUBCUTÁNEO DE NADH EN EL TRATAMIENTO DEL SÍNDROME DE FATIGA CRÓNICA: UNA REVISIÓN INTEGRADORA DE LA EVIDENCIA CLÍNICA Y METABÓLICA

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Valéria Goulart Viana[1], Guilherme Tunckus Balderrama[2], Isisnaldo Silva Correia[3], Giovanna Abe Rodrigues de Melo[4], Marcelo de Araújo Lopes Júnior[5], Lucas Emericiano de Morais[6], Bruna Bastos Bezerra[7], Luisa Bastos Bezerra[8], Diego Quirino Cadete[9], Diegomaier Nunes Neri[10], David de Sousa Cortez Barros[11], Patrícia Lemos dos Santos[12], Davi Cardoso Bezerra[13], Winna Maciel Nunes Chen[14], Deir Grassi Ribeiro da Silva[15], Murilo Almeida[16], Matheus Magalhães Cesana de Oliveira[17], Ana Paula Martins Pereira[18], Pedro Henrique Souza e Silva[19], Rhaí Víctor Andrade Borges[20], Karla Mickaela Araújo dos Santos[21]

ABSTRACT

This integrative review aimed to gather, analyze, and synthesize the available clinical, metabolic, and pharmacological evidence on the use of NADH in the management of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), with emphasis on evaluating the therapeutic potential of the subcutaneous route as an alternative to oral administration. The methodology followed the model proposed by Whittemore and Knafl (2005), complemented

[1] Medical Doctor. Faculdade de Medicina de Itajubá. E-mail: dravaleriagoulart@yahoo.com.br
[2] Medicine. Universidade Nove de Julho. E-mail: guitunckus42@gmail.com
[3] Medicine. Universidade Federal do Maranhão. E-mail: isisnaldocorreia@gmail.com
[4] Medicine. Centro Universitário de Brasília. E-mail: giovannameloxi@gmail.com
[5] Medicine. Centro Universitário de Brasília. E-mail: marcelo.araujo1296@gmail.com
[6] Medicine. Faculdade de Medicina Juazeiro do Norte (Idomed). E-mail: lucas.hidan@hotmail.com
[7] Medical Doctor. Universidade Federal de Uberlândia. E-mail: dra.brunabastosb@gmail.com
[8] Medical Doctor. Universidade Federal de Uberlândia. E-mail: draluisabastosb@gmail.com
[9] Undergratuated student. Universidade Potiguar (UNP). E-mail: diego.cadete@hotmail.com
[10] Medical Doctor. Universidade Potiguar (UNP). E-mail: diego.cadete@hotmail.com
[11] Medicine. UNIFACID. E-mail: davidcortez908@gmail.com
[12] General Practitioner. Universidade do Estado do Amazonas (UEA). E-mail: pls.lemoss@gmail.com
[13] Medical Doctor. Universidad Nacional de Rosario. E-mail: davicardosobezerra@gmail.com
[14] Medical Doctor. Fundación H. A. Barceló. E-mail: winnamnc@gmail.com
[15] Medical Doctor. Universidade Federal de Uberlândia (UFU). E-mail: deirgrassi00@gmail.com
[16] Medical Doctor. Centro Universitário Estácio de Sá. E-mail: murilo_6_a@icloud.com
[17] Medical Doctor. Faculdade Pitágoras de Medicina de Eunápolis. E-mail: matheus.mag05@hotmail.com
[18] Medical Doctor. Centro Universitário Unieuro. E-mail: anapaulamp14@icloud.com
[19] Cardiologist. Universidade Estácio de Sá. E-mail: pedrohens.med@outlook.com
[20] Undergratuated student. Faculdade de Medicina de Campos. E-mail: rhaivictor@hotmail.com
[21] Medicine. Faculdade de Medicina de Campos. E-mail: rhaivictor@hotmail.com

by the guidelines of Mendes, Silveira, and Galvão (2008), encompassing six structured stages. In total, 31 scientific studies were selected from recognized databases such as PubMed, ScienceDirect, Scopus, and SpringerLink. Inclusion criteria comprised clinical, experimental, and review studies addressing interventions with NADH, its precursors (such as NMN and nicotinamide riboside), energy metabolism, and alternative routes of administration. Evidence indicates that NADH exerts positive effects on cellular energy levels, fatigue symptoms, and quality of life in individuals with ME/CFS, especially through oral supplementation. However, the low bioavailability of this route has stimulated interest in alternative delivery forms. Recent pharmacokinetic studies, including experiments with nanoencapsulation, enzymatic regeneration, and injectable systems, support the theoretical feasibility of subcutaneous NADH administration, although specific clinical trials confirming its efficacy are still lacking. It is concluded that the subcutaneous route represents a promising and rational alternative to enhance the therapeutic effects of NADH in ME/CFS patients, mainly due to its greater stability, continuous absorption, and systemic availability. Controlled clinical trials are needed to confirm the safety, applicability, and efficacy of this route.

Keywords: NADH. Chronic Fatigue Syndrome. Subcutaneous Administration. Energy Metabolism. Supplementation.

RESUMO

Esta revisão integrativa teve como objetivo reunir, analisar e sintetizar as evidências clínicas, metabólicas e farmacológicas disponíveis sobre o uso do NADH no manejo da Síndrome da Fadiga Crônica/Encefalomielite Miálgica (ME/CFS), com ênfase na avaliação do potencial terapêutico da via subcutânea como alternativa à administração oral. A metodologia seguiu o modelo proposto por Whittemore e Knafl (2005), complementado pelas orientações de Mendes, Silveira e Galvão (2008), abrangendo seis etapas sistematizadas. Foram selecionados 31 estudos científicos publicados entre 2015 e 2025, extraídos de bases reconhecidas como PubMed, ScienceDirect, Scopus e SpringerLink. Os critérios de inclusão contemplaram estudos clínicos, experimentais e revisões que abordassem intervenções com NADH, seus precursores (como NMN e nicotinamida ribosídeo), metabolismo energético e vias alternativas de administração. As evidências indicam que o NADH exerce efeitos positivos sobre os níveis de energia celular, sintomas de fadiga e qualidade de vida em indivíduos com ME/CFS, especialmente por via oral. No entanto, a baixa biodisponibilidade dessa via tem impulsionado o interesse por formas alternativas de administração. Estudos farmacocinéticos recentes, incluindo experimentos com nanoencapsulamento, regeneração enzimática e sistemas injetáveis, sustentam a viabilidade teórica do uso subcutâneo do NADH, embora ainda não existam ensaios clínicos que confirmem sua eficácia. Conclui-se que a via subcutânea representa uma alternativa promissora e racional para potencializar os efeitos terapêuticos do NADH em pacientes com ME/CFS, sobretudo por sua maior estabilidade, absorção contínua e disponibilidade sistêmica. São necessários ensaios clínicos controlados para comprovar a segurança, a aplicabilidade e a eficácia dessa via.

Palavras-chave: NADH. Síndrome da Fadiga Crônica. Administração Subcutânea. Metabolismo Energético. Suplementação.

RESUMEN

Esta revisión integrativa tuvo como objetivo recopilar, analizar y sintetizar la evidencia clínica, metabólica y farmacológica disponible sobre el uso de NADH en el tratamiento del síndrome de fatiga crónica/encefalomielitis miálgica (EM/SFC), con énfasis en la evaluación del

potencial terapéutico de la vía subcutánea como alternativa a la administración oral. La metodología siguió el modelo propuesto por Whittemore y Knafl (2005), complementado con las guías de Mendes, Silveira y Galvão (2008), que comprende seis pasos sistematizados. Se seleccionaron 31 estudios científicos publicados entre 2015 y 2025 de bases de datos reconocidas como PubMed, ScienceDirect, Scopus y SpringerLink. Los criterios de inclusión comprendieron estudios clínicos, estudios experimentales y revisiones que abordaran intervenciones con NADH, sus precursores (como NMN y ribósido de nicotinamida), el metabolismo energético y vías de administración alternativas. La evidencia sugiere que el NADH ejerce efectos positivos sobre los niveles de energía celular, los síntomas de fatiga y la calidad de vida en personas con encefalomielitis miálgica/síndrome de fatiga crónica (EM/SFC), especialmente por vía oral. Sin embargo, la baja biodisponibilidad de esta vía ha impulsado el interés en métodos de administración alternativos. Estudios farmacocinéticos recientes, incluyendo experimentos con nanoencapsulación, regeneración enzimática y sistemas inyectables, respaldan la viabilidad teórica del uso subcutáneo de NADH, aunque aún faltan ensayos clínicos que confirmen su eficacia. Se concluye que la vía subcutánea representa una alternativa prometedora y racional para potenciar los efectos terapéuticos del NADH en pacientes con EM/SFC, particularmente debido a su mayor estabilidad, absorción continua y disponibilidad sistémica. Se necesitan ensayos clínicos controlados para confirmar la seguridad, aplicabilidad y eficacia de esta vía.

Palabras clave: NADH. Síndrome de Fatiga Crónica. Administración Subcutánea. Metabolismo Energético. Suplementación.

1 INTRODUCTION

Chronic Fatigue Syndrome, also called Myalgic Encephalomyelitis (ME/CFS), is a debilitating condition of multifactorial etiology, characterized by persistent fatigue, cognitive disorders, non-restorative sleep, and intolerance to physical exertion. It is estimated that millions of people are affected worldwide, with a significant impact on quality of life and functionality (Castro-Marrero et al., 2021; Dehhaghi et al., 2022). Recent studies indicate that the pathophysiology of ME/CFS involves metabolic and mitochondrial dysfunctions, associated with central inflammatory processes in the hypothalamic-pituitary axis (Hoel et al., 2021; Hatziagelaki et al., 2018).

Among the biochemical mechanisms involved in ME/CFS, the dysfunction in the metabolism of nicotinamide adenine dinucleotides (NAD^+ and NADH), which are essential for cellular energy metabolism and redox processes, stands out. Research indicates that changes in NAD^+ regeneration and its redox cycle are associated with mitochondrial exhaustion and reduced ATP production in patients with ME/CFS (Dehhaghi et al., 2022; Navarro et al., 2021). The modulation of these metabolic pathways, therefore, represents an emerging and promising therapeutic strategy for the management of this complex syndrome (Kavyani et al., 2022; Roh et al., 2018).

Several clinical studies have investigated the effects of NADH supplementation, alone or in association with coenzyme Q10, as a potential therapeutic for fatigue in individuals with ME/CFS. Positive results were observed in parameters such as perception of fatigue, quality of life, and physical performance (Castro-Marrero et al., 2016; Xue et al., 2022; Maksoud et al., 2021). In addition, a recent systematic review highlighted the efficacy and safety of oral supplementation with NADH and its precursors, such as NMN and nicotinamide riboside, in modulating energy metabolism (Brito et al., 2025; Dewi et al., 2024).

Despite the advances observed, most research focuses on the oral route of administration, which has limitations in terms of bioavailability, intestinal absorption, and molecular stability. Pharmacokinetic studies demonstrate that the degradation of NADH in the gastrointestinal tract can compromise the systemic levels achieved (Chen et al., 2025; Ma et al., 2025). **This pharmacokinetic limitation** has driven the development of alternatives, such as extended-release formulations, polymeric encapsulation, and the use of subcutaneous implants, strategies already studied in other areas of medicine to enhance the absorption and systemic effects of bioactive compounds (Gruszczyńska et al., 2025; Lu & Zhou, 2025).

In view of the therapeutic relevance of NADH and the limitations associated with the oral route, this study proposes an integrative literature review with the objective of critically analyzing the available clinical and metabolic evidence on the use of NADH in the treatment of ME/CFS, with emphasis on **the translational potential of the subcutaneous** implant as an alternative route of administration, considering bioavailability, pharmacokinetics, and molecular stability data present in the scientific literature (Pan & Luo, 2025; Mishra et al., 2025; Block & Kuo, 2022).

2 METHODOLOGY

This is an integrative review of the literature, whose purpose was to gather, analyze and critically synthesize the available knowledge on the use of reduced dinucleotide NADH (nicotinamide adenine dinucleotide) in the therapeutic approach of ME/CFS, with emphasis on the translational potential of the subcutaneous route as an alternative to oral administration. Integrative review, as a scientific method, allows the incorporation of different types of study, quantitative, qualitative, theoretical, and clinical, and is widely used in health research to support evidence-based practices and identify knowledge gaps (Whittemore; Knafl, 2005).

Based on this methodological approach, the following guiding question was elaborated, which guided the entire process of searching and selecting the studies:

"What is the clinical and metabolic evidence available on the use of NADH in the treatment of Chronic Fatigue Syndrome, and what is the feasibility of subcutaneous implantation as an alternative route of administration?"

This question was constructed from the PICO model adapted for integrative reviews, in which the target population (individuals with ME/CFS), the intervention (NADH), the comparison (alternative routes of administration), and the outcome (clinical benefits and pharmacological plausibility) are defined.

The bibliographic search was carried out systematically in the **PubMed**, **ScienceDirect**, **SciELO, SpringerLink**, **Web of Science** and **Scopus databases**. The following descriptors were used, adjusted according to each base and combined with Boolean operators: *"Myalgic Encephalomyelitis", "Chronic Fatigue Syndrome", "NADH", "Nicotinamide Adenine Dinucleotide*", *"Subcutaneous*", *"Supplementation", "Pharmacokinetics", "Bioavailability"* and *" Energy Metabolism".* The selection covered

publications in the period from 2015 to 2025, available in English or Portuguese. The search was last updated on **November 5, 2025**.

We included studies published in peer-reviewed journals that directly addressed the use of NADH, NAD^+, NMN, or nicotinamide riboside in ME/CFS, as well as investigations on alternative routes of administration, pharmacokinetics, and bioavailability of these molecules. Clinical trials, systematic reviews, narrative reviews, experimental studies, and translational articles were accepted. Duplicate papers, editorials, congress abstracts, dissertations, theses, and articles without access to the full text were excluded.

Data analysis and extraction were performed manually and recorded in a spreadsheet with the following variables: authors, year, country of publication, type of study, population and intervention, route of administration, main clinical outcomes, and conclusions. For analytical purposes, the studies were organized into three thematic axes: (1) clinical and metabolic aspects of ME/CFS, (2) evidence on supplementation with NADH/NAD^+ and its precursors, and (3) studies on bioavailability and alternative routes of administration, with emphasis on extended-release strategies and subcutaneous use.

All stages of the survey, analysis, and categorization were conducted by two independent reviewers, with cross-validation of the data and consensus in case of divergences. Methodological rigor was guaranteed by the exclusive use of indexed sources and by the use of explicit and transparent selection criteria, according to methodological recommendations for integrative reviews in the field of health (Mendes; Scott; Galvão, 2008).

The absence of prior registration in specific protocol platforms, such as PROSPERO, is recognized as a limitation of this integrative review, which, although not mandatory for this type of study, could reinforce methodological transparency. In addition, the selection of studies was limited to publications available in full text and in English, Portuguese, and Spanish, which may have restricted the sample size. Sources of gray literature, such as theses, dissertations, or technical reports, were also not considered, which may result in the exclusion of relevant data not yet published. Finally, the heterogeneity of the methodological designs and outcomes evaluated among the included studies made it difficult to make direct comparisons and to carry out a quantitative synthesis of the results.

3 RESULT AND DISCUSSION

3.1 CLINICAL AND METABOLIC FINDINGS OF NADH USE IN ME/CFS

The literature analyzed shows that Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (ME/CFS) is strongly associated with mitochondrial and metabolic dysfunctions, especially in cellular energy metabolism, which justifies the growing interest in interventions that act on bioenergetics, such as NADH. Studies have shown that patients with ME/CFS have alterations in oxidative metabolism, decreased ATP production, and accumulation of metabolites indicative of hypometabolism (Hoel et al., 2021; Germain et al., 2017).

In this context, supplements such as NADH and coenzyme Q10 have been evaluated as potential modulators of mitochondrial function and bioenergetic response. Castro-Marrero et al. (2021) demonstrated that combined supplementation of NADH and CoQ10 improved the perception of fatigue and quality of life of individuals with ME/CFS. Similar results were observed by Calvo et al. (2015), reinforcing the therapeutic potential of modulation of energy metabolism in such patients.

In addition, NAD^+ metabolism and its relationship with the kynurenine pathway, which regulates the immune system and tryptophan levels, have been pointed out as central elements in the pathophysiology of ME/CFS (Dehhaghi et al., 2022; Kavyani et al., 2022). The reduction in the availability of NAD^+ compromises fundamental processes such as DNA repair, oxidative stress control, and intracellular communication, which amplifies the fatigue and immune dysfunction observed in these patients (Navarro et al., 2021).

Recent studies have also investigated the immunological and metabolic aspects of NK cells and T lymphocytes, demonstrating a pattern of energy dysfunction characteristic of ME/CFS, with reduced mitochondrial activity and alteration in the biochemical profile (Maya, 2023). These findings reinforce that fatigue in the syndrome is not limited to isolated psychological or neurological factors, but results from a systemic imbalance involving the energetic, immunological and redox axes.

Thus, NADH, by acting as an essential cofactor in mitochondrial energy production, has a plausible biological basis for clinical application in ME/CFS. However, it is important to consider that most documented interventions use the oral route, whose effectiveness may be limited by low gastrointestinal absorption and degradation (Xue et al., 2022; Dewi et al., 2024). **This pharmacokinetic limitation motivates the search for alternative routes of administration**, a topic addressed in the following subsection.

3.2 NADH BIOAVAILABILITY AND SUBCUTANEOUS VIABILITY AS A THERAPEUTIC PROPOSAL

Although the positive effects of NADH supplementation in patients with ME/CFS are well documented, especially through oral formulations, recent studies have drawn attention to the limitations of this route of administration. **This pharmacokinetic limitation** stems from the instability of the compound in the gastrointestinal environment, subject to enzymatic degradation and pH variations, which may compromise clinical efficacy in conditions requiring rapid or sustained restoration of cellular NAD^+/NADH levels.

In view of these restrictions, there is growing interest in alternative routes of administration that allow greater control of the release and absorption of the compound. The subcutaneous route, for example, has been widely used for extended-release drugs and molecules with low oral bioavailability, due to its ability to maintain more stable plasma levels and reduce metabolic losses in the digestive tract (Lu & Zhou, 2025). **There are still no clinical trials evaluating the subcutaneous use of NADH in ME/CFS**, but technological advances demonstrate its pharmacological feasibility, as evidenced by studies using nanostructured polymers and sustained-release systems for similar compounds (Gruszczyńska et al., 2025).

The plausibility of the subcutaneous use of NADH is reinforced by experimental models that simulate its direct absorption into tissues, with increased cell penetration and prolonged half-life in the body (Mishra et al., 2025). These models demonstrate that **by avoiding first-pass hepatic metabolism, NADH preserves its molecular integrity for longer, increasing its potential efficacy**, especially in chronic conditions such as ME/CFS, in which continuous redox cofactor replacement is desirable.

In addition, studies investigating the intracellular regeneration of NADH through photocatalytic reactions or stabilized enzymes in polymeric supports suggest the possibility of developing therapeutic strategies based on bioactive implants or controlled infusion systems. These resources could be adapted for long-term administration of NADH, offering a rational alternative for patients who require constant metabolic support (Lu & Zhou, 2025; Pan & Luo, 2025). Such advances strengthen the scientific rationale for translational proposals involving subcutaneous use as the route of choice in contexts of metabolic dysfunction.

Therefore, although specific clinical trials are still needed to directly investigate the application of NADH subcutaneously in patients with ME/CFS, the convergence of

experimental, pharmacokinetic, and technological evidence indicates that this approach has solid theoretical support and clinical potential. This gap in the literature represents a relevant opportunity for future investigations, especially in view of the need for more effective and bioavailable strategies for the management of chronic fatigue.

3.3 METHODOLOGICAL CHALLENGES AND HETEROGENEITY OF THE INCLUDED STUDIES

Despite the scientific advances observed, it is essential to recognize the methodological challenges and heterogeneity of the studies included in this review. Wide variation was identified in the experimental designs, sample sizes, types of intervention, and forms of administration of NADH and its precursors. This diversity makes it difficult to directly compare the results and limits the generalization of conclusions about their clinical efficacy.

Many studies have small sample sizes, no control groups, and use of non-standardized secondary outcomes. In addition, there are considerable differences in the doses used, follow-up time, and metabolic evaluation parameters, which compromises the statistical consistency between the investigations. These limitations, although expected in an area that is still emerging, reinforce the need for more robust clinical protocols, with adequate sampling, standardization of outcomes, and longitudinal analysis of therapeutic effects.

Another important challenge is the scarcity of comparative studies that directly evaluate the different routes of administration of NADH, such as oral, intravenous, and subcutaneous. The lack of randomized clinical trials focused on the subcutaneous route limits the understanding of its safety, pharmacokinetics, and real efficacy in clinical settings. In view of this, it is recommended that future studies adopt multicenter designs, use objective biomarkers of energy metabolism, and consider direct comparisons between routes of administration, aiming to expand the translational evidence base on the therapeutic use of NADH in ME/CFS.

4 CONCLUSION

This integrative review gathered and critically analyzed the scientific evidence on the use of NADH as a therapeutic intervention in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (ME/CFS), highlighting its relevance in modulating energy metabolism and restoring mitochondrial function. The findings confirm that immunometabolic disorders and mitochondrial hypofunction are among the main pathophysiological mechanisms of the

syndrome, justifying the growing interest in strategies aimed at optimizing cellular redox balance.

Clinical and experimental evidence indicates that NADH and its precursors, such as NMN and nicotinamide riboside, exert positive effects on fatigue, quality of life, and metabolic performance. However, the oral route, predominant in the interventions studied, has relevant pharmacokinetic limitations, such as gastrointestinal degradation and low systemic bioavailability. **This pharmacokinetic limitation** has motivated the exploration of more effective alternatives, capable of providing continuous release and enhanced absorption of the compound.

Among the emerging approaches, the subcutaneous route emerges as a promising strategy, based on principles of molecular stability, prolonged absorption, and reduction of first-pass hepatic metabolism. Although there is still a lack of clinical trials that directly evaluate this form of administration in patients with ME/CFS, pharmacological and technological studies support its theoretical plausibility and translational potential.

It is concluded, therefore, that the subcutaneous implantation of NADH represents a rational and innovative alternative to increase the therapeutic efficacy of this cofactor in conditions of chronic bioenergetic dysfunction. The development of **controlled clinical trials, translational studies, and multidisciplinary approaches** that integrate pharmacology, bioengineering, and regenerative medicine is recommended in order to validate the safety, applicability, and clinical impact of this pathway in the management of ME/CFS.

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