v. 5, n. 27, 2025

International Journal of Health Science

Acceptance date: 29/07/2025

NEPHROGENIC SYSTEMIC FIBROSIS AND GADOLINIUM-BASED CONTRAST AGENTS: AN INTEGRATIVE REVIEW OF RISKS AND PREVENTION

Daniella Nogueira Ferreira
Hospital Municipal Ronaldo Gazolla (HMRG)
Rio de Janeiro, RJ

Márcio Antonio Lyra Quintaes Junior
Hospital Municipal Ronaldo Gazolla (HMRG)
Rio de Janeiro, RJ
Hospital Municipal Albert Schweitzer (HMAS)
Rio de Janeiro, RJ

Danielle Furtado de Oliveira
Hospital Municipal Ronaldo Gazolla (HMRG)
Rio de Janeiro, RJ

Nathalia Lopez Duarte
Hospital Municipal Ronaldo Gazolla (HMRG)
Rio de Janeiro, RJ
Universidade Federal do Rio de Janeiro (UFRJ)
Rio de Janeiro, RJ
Instituto Nacional de Ciência e Tecnologia em Biologia do Câncer Infantil e Oncologia Pediátrica (INCT BioOncoPed)
Porto Alegre, RS

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Abstract: Introduction: Nephrogenic systemic fibrosis (NSF) is a rare, progressive, and debilitating condition that primarily affects patients with chronic kidney disease (CKD), often associated with exposure to Gadolinium-based contrast agents (GBCAs). Although gadolinium (Gd) exposure is a well-recognized risk factor, NSF has a multifactorial and a not fully understood etiology. **Objective:** To analyze the risks critically associated with Gd exposure in CKD patients, focusing on pathophysiological mechanisms, clinical manifestations, diagnostic challenges, and preventive strategies, while considering health system limitations in vulnerable settings. **Methods:** This is an integrative literature review conducted through searches in PubMed and SciELO databases from 2019 to 2024. Descriptors related to NSF, Gd, and kidney disease were used in both English and Portuguese. After applying inclusion and exclusion criteria, seven studies were selected for analysis. **Results and Discussion:** The reviewed literature confirmed a strong association between GBCA use and NSF in patients with GFR < 30 mL/min/1.73m². Nonetheless, reports of NSF in the absence of Gd exposure suggest additional contributing factors, including immunosuppressive therapy, chronic inflammation, erythropoietin use, and vascular manipulation. Clinical manifestations are predominantly cutaneous, with possible systemic involvement. Diagnosis requires clinical-pathological correlation and high clinical suspicion. Preventive measures include strict renal function screening and the use of more stable contrast agents. **Conclusion:** Understanding NSF requires a comprehensive approach that integrates its multifactorial nature, emphasizes prevention, and promotes professional training for early detection. Further research is needed, particularly in vulnerable populations, to develop evidence-based and context-specific protocols for public health systems such as the Brazilian Unified Health System (SUS).

Keywords: Nephrogenic systemic fibrosis; chronic kidney disease; gadolinium; contrast agents; public health.

INTRODUCTION

Nephrogenic Systemic Fibrosis (NSF) is a rare, progressive, and potentially debilitating condition characterized by collagen accumulation and fibroblast proliferation in the dermis and, in more severe cases, in systemic tissues such as muscles, lungs, and heart. It predominantly affects patients with chronic kidney disease (CKD), especially those undergoing dialysis or with severely reduced glomerular filtration rate (typically below 30 mL/min/1.73 m²), corresponding to stages 4 and 5 of CKD. Initially described as Nephrogenic Fibrosing Dermopathy (NFD), the syndrome was first recognized in 1997 following the identification of 15 cases in dialysis patients who presented with cutaneous changes such as hyperpigmentation, skin thickening, and development of subcutaneous nodules (MUNDIN et al., 2009). In 2005, the terminology shifted to NSF due to increasing reports of internal organ involvement, reflecting its systemic nature (BASAK; JESMAJIAN, 2011; LEITE, 2007).

The main risk factor associated with NSF is exposure to gadolinium-based contrast agents (GBCAs), which are widely used in magnetic resonance imaging (MRI) procedures. In individuals with normal renal function, Gadolinium (Gd) is promptly cleared by the kidneys. However, in CKD patients, its elimination is impaired, leading to tissue deposition of the metal and potentially initiating inflammatory and fibrotic processes (SHAMAN, 2023). Studies by Prince et al. (2020) and Kuo et al. (2007) reinforce the pathogenic role of Gd by documenting multiple cases of NSF associated with its use, including histological detection of the metal in skin lesions. Nevertheless, the etiology of NSF remains incompletely understood.

In recent years, evidence has emerged challenging the notion of Gd as the sole trigger for NSF. Cases documented by Wahba, Simpson, and White (2007) reported the development of the disease in renal transplant recipients without prior exposure to Gd-based contrast agents. These findings suggest that other factors may be involved in the pathogenesis of NSF, such as the use of immunosuppressive drugs, systemic inflammation, vascular manipulation, and the high-dose erythropoietin administration. These factors, whether individually or in combination, may contribute to the activation of circulating fibroblasts and promote fibrotic tissue formation, reinforcing the hypothesis of a multifactorial etiology.

From a clinical perspective, NSF initially manifests as skin induration, thickening, and hyperpigmentation, primarily affecting the extremities. In more advanced cases, fibrosis may extend to the joints, leading to pain, contractures, and marked functional impairment. There are also reports of visceral involvement, including lungs and heart, which worsens the prognosis. Due to its clinical resemblance to other fibrosing dermatoses, such as systemic sclerosis, scleromyxedema, and eosinophilic fasciitis, a thorough differential diagnosis is essential. These conditions share manifestations like skin stiffness and contractures and must be differentiated based on clinical history, presence of renal comorbidities, absence of specific autoantibodies, and, most importantly, characteristic histopathological findings.

Thus, a definitive diagnosis of NSF requires a high degree of clinical suspicion and confirmation by biopsy, highlighting the importance of integrating clinical and histopathological evaluation. Currently, no specific or definitive treatment is currently available for the syndrome. Therapeutic strategies such as phototherapy, plasmapheresis, and, in some cases, renal transplantation may provide stabilization or partial symptom improvement, though outcomes remain inconsistent (SAWAL; GNANASEKARAN, 2021).

In this context, prevention becomes the primary strategy in addressing NSF. Judicious selection of patients for Gd-enhanced imaging procedures, the use of more stable formulations, and the implementation of tailored clinical protocols are fundamental measures. Additionally, the literature highlights the importance of multidisciplinary follow-up and early rehabilitation to mitigate functional consequences of the disease. The recognition of multiple potential pathogenic factors further reinforces the need for clinical vigilance and future investigations aimed at deepening the understanding of NSF's pathophysiological mechanisms and their implications in clinical practice.

This study aimed to provide a thorough and critical analysis of NSF, focusing on the risks linked to Gd-based contrast agent exposure in patients with CKD. It covered the key pathophysiological aspects of the syndrome, its most frequent clinical manifestations, and the challenges inherent to differential diagnosis. The review also sought to discuss preventive strategies and the relevance of a multidisciplinary approach in the management of NSF, especially in resource-limited settings. Additionally, it explored the underdiagnosis and underreporting of the condition and the scarcity of studies targeting vulnerable populations, emphasizing the need to expand the scientific debate and foster the production of evidence applicable to clinical practice, particularly within the scope of Brazil's Unified Health System (SUS).

METHODS

This integrative literature review was developed based on a bibliographic search, gathering relevant information from books, scientific articles, theses, and academic documents that contributed to the theoretical foundation of the study. The search was conducted in the SciELO and PubMed databases, both widely recognized for their editorial quality and peer-reviewed indexed publications.

The data collection followed the methodological framework previously established by Souza, Silva, and Carvalho (2010), who outline the essential steps for conducting an integrative review in the health field. The review applied a five-year time frame (2019–2024) to ensure the scientific rigor and timeliness of the selected literature. Controlled descriptors were used in both Portuguese and English, to encompass high-quality international evidence. Key search terms included: *Nephrogenic Systemic Fibrosis / Fibrose Sistêmica Nefrogênica*; Renal insufficiency / Insuficiência renal; *Causes of Nephrogenic Systemic Fibrosis / Causas da Fibrose Sistêmica Nefrogênica*; *Complications inherent to Nephrogenic Systemic Fibrosis / Complicações inerentes à Fibrose Sistêmica Nefrogênica*; and *Adverse effects of gadolinium / Efeitos adversos do gadolínio*.

Finally, inclusion and exclusion criteria were established to refine the selection of studies, as specified in Table 1, aiming to ensure thematic and methodological relevance. After screening and selecting the articles, a descriptive narrative analysis was applied. This consisted of a critical synthesis of the findings based on the objectives, methods, and results of each study. This approach allowed for the identification of patterns, convergences, and gaps in the available evidence, without applying formal categorization or thematic coding.

RESULTS

Following a thorough and methodologically sound review process, seven articles were selected as highly pertinent to the study's focus. The selection of these publications was based on their thematic relevance, timeliness, and scientific contribution, ensuring consistency and depth in the proposed analysis.

The results are organized in table (Table 2) and figure (Figure 1), with the aim of presenting the information in a clear and accessible manner. The adopted structure follows methodological recommendations for literature reviews, inspired by guidelines aimed at the systematization and synthesis of data in systematic reviews and meta-analyses of randomized clinical trials. These guidelines emphasize the importance of transparency, reproducibility, and clarity in the presentation of findings, facilitating critical analysis and reader comprehension (MINISTÉRIO DA SAÚDE, 2023).

DISCUSSION

PATHOPHYSIOLOGY AND RISK FACTORS

This review identified a substantial body of studies, both national and international, conducted by experts in the health sciences. Among the analyzed publications, there was strong evidence convergence regarding the role of GBCAs, used in MRI for the development of NSF, particularly in patients with CKD. Studies such as those by Fernandes and Picka (2019), Mathur et al. (2019), Silva and Fazenda (2022), and Woolen et al. (2019) discuss the association between Gd toxicity and the increased risk of NSF, while also recognizing the condition's multifactorial etiology.

DIAGNOSTIC APPROACH AND CLINICAL CHALLENGES

Despite advances in understanding the pathogenesis of NSF, there is no clear consensus on its triggering mechanisms (SHAMAN & DE JESUS, 2023). Factors such as systemic inflammation, metabolic acidosis, hyperphosphatemia, and erythropoietin use are considered relevant to disease progression. Furthermore, attention has been drawn to documented cases of NSF in patients who had not been exposed to GBCAs, as reported by Wahba, Simpson, and White (2007). These authors described two renal transplant patients with impaired kidney function who developed NSF with no confirmed prior exposure

Inclusion	Exclusion
Peer-reviewed academic studies in Portuguese or English;	Academic studies in languages other than Portuguese or English;
Articles published within the defined time frame;	Articles outside the defined publication window;
Articles directly relevant to the proposed topic;	Articles unrelated to the study's proposed topic;
Articles that provide relevant contributions to the subject under study;	Articles that do not provide substantial contributions to the topic;
Academic articles available in full text.	Academic articles not fully available in their entirety.

Table 1 - Inclusion and Exclusion Criteria of the Study

Source: Ferreira DN, et al., 2025.

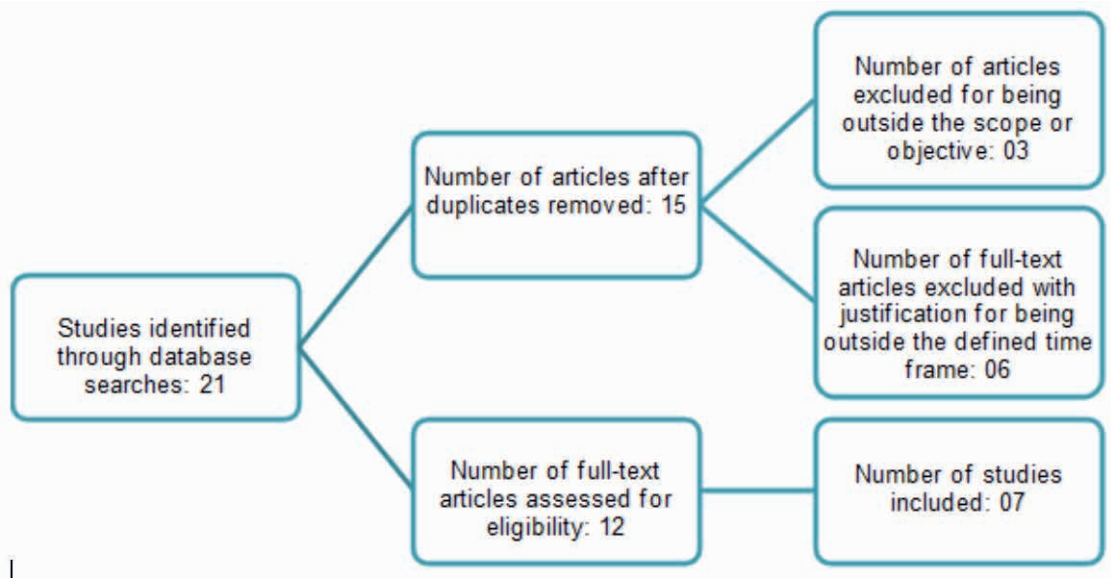

Figure 1 – Article Selection Flowchart

Source: Ferreira DN, et al., 2025.

Author (Year)	Study Title	Study Design	Objective	Sample/ Population	Main Findings	Main Conclusions
Silva e Fazenda (2022)	Toxicidade do gadolínio por meio de contraste em EM RM	Narrative Review	To evaluate Gd toxicity in MRI contrast agents	MRI patients	Gd is a toxic metal in its free form, but when chelated, it is used as intravenous contrast in MRI. In patients with renal dysfunction, incomplete excretion leads to agent accumulation and a risk of fatal NSF.	GBCA use should be cautious in patients with renal impairment to avoid NSF.
Mathur et al. (2019)	Gadolinium Deposition and Nephrogenic Systemic Fibrosis	Systematic Review	To review NSF cases and safety of GBCA, focusing on reduced incidence and current safety	Patients with and without renal dysfunction	NSF cases declined significantly over the last decade due to stricter renal screening protocols, use of stable thermodynamic agents, and proper dosing. Concerns remain regarding Gd deposition and retention.	Safety has improved with current protocols, but attention must remain due to Gd retention.
Malikova (2019)	Nephrogenic systemic fibrosis: a closed chapter?	Critical Review	To assess actual incidence and underreporting of NSF	Biopsy-confirmed cases	The actual number of NSF cases may be higher than estimated due to underreporting, non-indexed publications, unconfirmed cases, and stigma around Gd toxicity.	NSF is likely underestimated; increased surveillance and reporting are needed.
Woolen et al. (2019)	Risk of Nephrogenic Systemic Fibrosis in Patients With CKD Stage 4-5	Systematic Review and Meta-analysis	To assess the risk of NSF in patients with severe CKD exposed to Group II GBCA	CKD stage 4 or 5 patients	NSF risk is lower than 0.07% with Group II GBCA use. Withholding contrast-enhanced imaging may cause more harm than the actual risk of NSF.	Guidelines allow liberal use of Group II GBCA in advanced CKD, considering the greater diagnostic benefit.
Fernandes e Picka (2019)	Depósito do agente de contraste à base de Gadolínio no cérebro	Narrative Review	To investigate Gd deposition in the brain and clinical implications	Various groups	It is not yet determined whether specific groups are at higher risk of deposition. Main affected areas are related to motor coordination. The clinical significance is still unclear.	More studies are needed to understand the clinical impact of brain Gd deposition.
Shaman e De Jesus (2023)	Nephrogenic Systemic Fibrosis	Narrative Review	To review prevalence, diagnosis, and management of NSF	Patients with advanced kidney disease	Higher prevalence in patients with severe kidney disease. High-risk GBCA should be avoided in eGFR < 30 mL/min/1.73m^2. Multidisciplinary management is essential.	Accurate diagnosis and multidisciplinary collaboration are fundamental for proper NSF management.
Wahba, Simpson e White (2007)	Gadolinium is not the only trigger for nephrogenic systemic fibrosis	Case Report and Review	To describe NSF in transplant patients without GBCA exposure and discuss multifactorial causes	Renal transplant patients	Two cases of NSF occurred in renal transplant patients without Gd exposure. Immunosuppressants and vascular manipulation were suggested as contributing factors.	NSF has a multifactorial etiology, not limited to Gd exposure.

Table 2 - List of Relevant Articles for the Study.

Source: Ferreira DN, et al., 2025.

to contrast agents. A thorough review of the medical records, along with the exclusion of other contrast-enhanced diagnostic procedures, reinforced the hypothesis that additional triggers (such as immunosuppression, vascular manipulation, and even genetic predisposition) may also play a role in the syndrome's pathogenesis. This finding broadens the scope of analysis and highlights the need to avoid attributing causality solely to Gd, especially in complex clinical contexts.

THERAPEUTIC STRATEGIES AND INTERDISCIPLINARY MANAGEMENT

Given this multifactorial scenario, the therapeutic approach to NSF must go beyond primary prevention and include supportive and rehabilitative measures aimed at improving patients' functionality and quality of life (FAROOQI et al., 2023; RICHMOND et al., 2007). The specialized literature recommends the implementation of strategies based on individualized and multidisciplinary care, focusing on symptom mitigation, preservation of mobility, and psychosocial support. Interventions such as regular physiotherapy, strict metabolic control (especially of calcium, phosphorus, and pH levels), phototherapy, and immunomodulation have been explored as palliative alternatives, with varying outcomes. The restoration of renal function, when feasible, has also shown to be beneficial in some cases, although it does not necessarily result in full clinical reversal (FAROOQI et al., 2023; RICHMOND et al., 2007; LIM et al., 2020).

Shaman and De Jesus (2023) advocate for individualized care in patients with advanced CKD, with particular attention to carefully selecting contrast agents. This approach aims not only to prevent complications but also to enhance safety in managing the underlying condition. Additionally, Gallo-Bernal et al. (2022) emphasize that multidisciplinary teams, including nephrologists, radiologists, dermatologists, and physiotherapists, involved from early diagnosis through post-symptom rehabilitation can contribute significantly to improving functionality, autonomy, and overall well-being in NSF patients.

LIMITATIONS IN HEALTHCARE AND INEQUITIES IN ACCESS

In public healthcare contexts such as SUS, the applicability of NSF findings must consider structural limitations and restricted access to high-complexity exams, such as skin biopsy or contrast-enhanced magnetic resonance imaging (PRINCE et al., 2019; EDWARDS et al., 2008). In these scenarios, early clinical recognition of NSF becomes essential to prevent disease progression. Authors such as Igreja et al. (2012) and Madke & Khopkar (2011) emphasize that clinical identification based on characteristic cutaneous signs, combined with a history of renal insufficiency and Gd exposure, may be sufficient to raise diagnostic suspicion in resource-limited settings.

Healthcare professionals in nephrology, radiology, and primary care must be trained to recognize clinical signs suggestive of the syndrome and critically evaluate the indication for Gd use, especially in patients with impaired renal function (SHAMAN & DE JESUS, 2023). According to StatPearls (2024), adequate renal function assessment before administering contrast agents and the preferential selection of stable macrocyclic agents are key strategies to mitigate risks. Ongoing education of these teams is essential to support more informed clinical decision-making, reduce complications, and improve interdisciplinary management of the disease even in low-resource environments (STATPEARLS, 2024; IGREJA et al., 2012).

FUTURE PERSPECTIVES AND RESEARCH GAPS

In this context, it is evident that additional studies are warranted to deepen the understanding of NSF pathophysiology, particularly regarding mechanisms that are not dependent on Gd. Madke and Khopkar (2011) emphasize that factors such as systemic inflammation, procoagulant states, erythropoietin use, liver diseases, and microvascular injuries may significantly contribute to dermal fibroblast activation and fibrosis progression. Igreja et al. (2012) add that the inflammatory response may facilitate the release of pro-fibrotic cytokines, while oxidative stress and elevated serum iron may promote Gd release and tissue deposition. Future investigations should explore the influence of these factors, as well as potential genetic determinants that remain poorly understood.

Moreover, there is a lack of studies examining the progression of NSF in specific populations, such as patients treated within public healthcare systems, limiting insight into the disease's impact on socially vulnerable populations. There are also considerable gaps in knowledge about the efficacy of unconventional therapies, such as phototherapy, intravenous immunoglobulin, and tyrosine kinase inhibitors. Multicenter studies with prospective designs and a focus on early clinical and laboratory markers may aid in refining diagnostic criteria and guide more effective therapeutic protocols (STATPEARLS, 2024; MADKE & KHOPKAR, 2011; IGREJA et al., 2012).

Therefore, the management of NSF requires an integrated approach that encompasses both the prevention of exposure to potential triggers, such as Gd, and the prompt identification and treatment of established cases. The multiplicity of factors involved in the development of the disease suggests that isolated therapeutic strategies may be insufficient (GALLO-BERNAL et al., 2022). Thus, it is essential to adopt a broad, patient-centered, and evidence-based perspective that integrates clinical, functional, and social aspects in addressing NSF.

FINAL CONSIDERATIONS

This review has demonstrated that, although Gd exposure is a recognized contributor in patients with chronic kidney disease in the pathophysiology of NSF, the disease has a multifactorial etiology that demands attention to additional factors such as immunosuppression, inflammation, and vascular intervention. This reinforces the critical role of prevention, early diagnosis, and multidisciplinary care, especially in low-resource settings. Underreporting, the scarcity of studies focused on vulnerable populations, and existing therapeutic gaps underscore the urgency for new clinical and translational research. Incorporating international evidence, while also valuing the Brazilian context, is essential to strengthen the response to NSF within the framework of SUS.

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