Review Article

Gadolinium Toxicity: Mechanisms, Clinical Manifestations, and Nanoparticle Role

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Gadolinium-based contrast agents (GBCAs), essential for MRI, are facing renewed scrutiny due to gadolinium (Gd) retention and emerging toxicity profiles. While the link between less stable agents and Nephrogenic Systemic Fibrosis (NSF) in renal impairment is established, gadolinium (Gd) deposition is also observed in the brain, bone, and skin across all GBCA classes, even in patients with normal renal function. This finding has raised concerns and led to the controversial concept of Gadolinium Deposition Disease (GDD). The present review synthesizes current evidence on clinical manifestations and underlying mechanisms. It highlights pathways beyond traditional transmetallation, particularly endogenous nanoparticle formation as a key mechanism for Gd release and retention, potentially challenging the stability assumptions for even macrocyclic agents. Structural factors (linear/macrocyclic; ionic/non-ionic) and stability parameters (thermodynamic log K; kinetic kobs) influencing risk are evaluated alongside regulatory responses. GBCAs should be viewed not as inert diagnostics but as agents with complex, cumulative biological interactions. Future research should focus on developing non-gadolinium alternatives, validating biomarkers for early detection of Gd retention, and conducting controlled trials on chelation therapy efficacy. Clinicians must balance the diagnostic benefits of GBCAs with potential long-term risks, ensuring informed patient consent and judicious use.

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1. Introduction

In contemporary medical diagnostics, contrast-enhanced magnetic resonance imaging (MRI) serves as a crucial modality, providing superior soft tissue visualization and functional data[1][2]. Central to this technique are gadolinium-based contrast agents (GBCAs). These agents employ the paramagnetic characteristics of the gadolinium ion (Gd^{3+}) to shorten T1 relaxation times, thereby enhancing image contrast[3][4][5]. This enhancement capability is often essential for diagnosing and tracking a broad spectrum of conditions, such as cancer, inflammatory processes, and neurological issues, yielding information not attainable with other imaging methods or non-contrast MRI. Their substantial contribution to diagnostic precision and patient care management solidifies their essential place in modern medicine, despite ongoing safety discussions[6]. Since the US FDA first approved a GBCA in 1988, millions of doses have been utilized worldwide. Initially, GBCAs presented a robust safety record, with adverse event rates documented between 0.001% and 0.01%[7][8].

GBCAs feature a trivalent gadolinium ion (Gd^{3+}) enclosed within an organic ligand chelate. Chelation is vital because the unbound Gd^{3+} ion is highly toxic. Its ionic radius is similar to calcium's, allowing interference with critical calcium-dependent biological processes[9]. The ligand isolates Gd^{3+}, reducing toxicity and enabling rapid elimination via the kidneys[10]. The perception of GBCA safety was dramatically altered in 2006 with the identification of nephrogenic systemic fibrosis (NSF). This severe fibrotic illness showed a strong connection to GBCA administration in individuals with profound renal impairment[11][12][13][14][15]. Implementing screening practices and favoring more stable GBCAs significantly reduced NSF incidence[16]. Nonetheless, a new safety question surfaced in 2014 with reports of increasing signal hyperintensity on non-contrast T1-weighted MRI scans in specific brain regions after multiple doses, predominantly involving linear GBCAs. Significantly, this was observed even in individuals with normal renal function[17][18][19][20]. Later research confirmed Gd presence in various tissues like the brain, bone, and skin among people previously given GBCAs[21][22]. This phenomenon of Gd deposition, occurring to varying degrees, is linked with all GBCA categories[23][24][21][25]. A more contentious subject concerns patients reporting lasting symptoms post-GBCA exposure, giving rise to the controversial and not universally accepted concept of "Gadolinium Deposition Disease" (GDD)[26][27]. Davies et al.[28] provided a comprehensive summary detailing the contemporary understanding of Gd pharmacokinetics, toxicity pathways, and the range of clinical issues, emphasizing chelate stability and the generally better safety record of macrocyclic versus linear agents.

Mechanistic investigations have challenged established notions of Gd toxicity. While transmetallation (the displacement of Gd^{3+} by endogenous metals) was considered the principal mechanism for Gd release from less stable chelates[29], subsequent findings suggested more complex pathways[30][31]. Transmetallation occurs when Gd^{3+} is displaced from its chelating ligand by metals naturally occurring in the body. Intriguingly, emerging data indicate that the *in vivo* generation of Gd-containing nanoparticles could be a significant factor in Gd retention and toxicity[25]. Endogenous molecules like oxalate might initiate this process within specific biological microenvironments[30][32].

Considering this context, the present review intends to synthesize the current knowledge base on GBCA-associated toxicity. It concentrates on clinical manifestations, deposition patterns, and the evolving understanding of underlying mechanisms. By integrating recent findings, particularly regarding nanoparticle formation, this review presents a detailed view of the risk-benefit profile of these agents, while also identifying critical areas needing further research. GBCAs are classified by key characteristics that dictate their stability and safety. Understanding these categories is essential for evaluating the variable toxicity risks among different agents.

2. Search strategy

An extensive search of the literature was executed using Scopus, PubMed and Embase, spanning publications from the late 1980s to April 2025. The search involved free-text terms and MeSH terms where applicable, utilizing keywords like: “gadolinium,” “gadolinium-based contrast agents,” “GBCA,” “MRI contrast,” “toxicity,” “adverse effects,” “safety,” “nephrogenic systemic fibrosis” (NSF), “Gadolinium Deposition Disease” (GDD), “transmetallation,” “nanoparticles,” “kidney disease,” “chelating agents,” and “chelation therapy.” Boolean operators (AND, OR) were employed to refine queries. Manual review of bibliographies from significant studies, reviews, and guidelines supplemented the electronic search. Regulatory documents from agencies such as the US Food and Drug Administration (US FDA) and the European Medicines Agency (EMA) were also consulted. Materials included comprised original preclinical, clinical, and in vitro research; systematic reviews; meta-analyses; case reports/series (especially for NSF/GDD); authoritative reviews; clinical guidelines; and regulatory statements, confined to English-language publications. Titles and abstracts were initially screened, followed by full-text assessment based on inclusion criteria. Preference was given to studies significantly enhancing comprehension of the pathophysiology, clinical aspects, risks, diagnosis, treatment, and regulatory dimensions of GBCA toxicity, emphasizing novel concepts like nanoparticle formation.

3. Structural Classification

GBCAs are primarily categorized by ligand structure: 1) linear GBCAs, which are characterized by flexible, open-chain ligands surrounding the Gd ion. Examples include gadodiamide (Omniscan), gadopentetate dimeglumine (Magnevist), and gadobenate dimeglumine (MultiHance). Typically, linear agents have lower stability and are more prone to releasing Gd[33][24], and 2) macrocyclic GBCAs, which employ rigid, cage-like ligands providing more secure encapsulation of the Gd ion. Examples are gadoterate meglumine (Dotarem), gadobutrol (Gadavist/Gadovist), and gadoteridol (ProHance).

3.1. Ionic Classification

GBCAs are further subdivided by electrical charge. Thus, ionic GBCAs carry a net charge and interact ionically with counterions, while non-ionic GBCAs are electrically neutral While charge contributes to classification, the main factors influencing *in vivo* Gd chelate stability and dissociation are ligand structure (linear vs. macrocyclic) and kinetic inertness, more so than just the ionic property[23][34]. Non-ionic linear agents might show better tolerability but potentially slightly lower stability than their ionic linear counterparts[35].

3.2. Stability Parameters

Two key metrics define GBCA stability: a) thermodynamic stability, quantified by log K(GdL), represents the equilibrium constant for the Gd-ligand binding. Higher values signify stronger binding and increased stability. Log K(cond) denotes stability at physiological pH. Macrocyclic agents generally have higher thermodynamic stability (log K(GdL) ~20-25) compared to linear ones (log K(GdL) ~16–22)[36][37], and b) kinetic inertness, measured by the dissociation rate constant (kobs), shows how rapidly the Gd-ligand complex disassembles. Lower values indicate slower dissociation and enhanced *in vivo* stability, even under demanding biological conditions. Macrocyclic agents typically show much greater kinetic inertness (kobs ~10^{-7} s^{-1}) versus linear agents (kobs ~10^{-4} s^{-1})[38][39].

3.3. Clinical Classification

For clinical practice, the American College of Radiology (ACR) provides a categorization of GBCAs into three groups based on NSF risk[40]. Group I (Highest Risk) contains linear agents like gadodiamide (non-ionic) and gadopentetate dimeglumine (ionic), group II (Intermediate Risk) encompasses linear ionic

agents with some protein binding, such as gadobenate dimeglumine, and group III (Lowest Risk) includes all macrocyclic agents, for example, gadoterate meglumin, gadobutrol, and gadoteridol. This classification system helps guide clinical choices, particularly regarding patients with compromised renal function or those anticipated to undergo multiple contrast examinations[41][42].

4. Clinical Spectrum of Gadolinium Toxicity

4.1. Nephrogenic Systemic Fibrosis (NSF)

NSF is the most widely known and severe manifestation of Gd toxicity[6][42]. First identified in 1997 as "nephrogenic fibrosing dermopathy" and later recognized as systemic, NSF causes fibrosis in skin, joints, and internal organs, primarily affecting patients with severe kidney problems[43][12][44]. NSF commonly presents as symmetrical thickening and hardening of the skin, typically initiating in the lower limbs and progressing upwards. Skin might take on a *"peau d'orange"* texture with discoloration, bumps, and plaques. Joint contractures frequently occur, severely restricting movement. In advanced stages, fibrosis can affect internal organs like the heart, lungs, liver, and muscles, leading to higher mortality[45][46]. NSF has been reported almost in individuals with severe renal impairment (eGFR <30 mL/min/1.73m^2), particularly those on dialysis. Incidence rates peaked in the early 2000s but decreased sharply after the link with GBCAs was recognized and preventive measures were adopted[47][48].

The pathogenesis of NSF is believed to stem from the activation and multiplication of circulating fibrocytes. These cells enter tissues and transform into collagen-producing fibroblasts[49]. Gadolinium is thought to initiate this cascade through various mechanisms, like upregulating monocyte chemoattractant protein-1 (MCP-1), transforming growth factor-beta (TGF-β), and possibly NADPH oxidase 4 (Nox4)[50]. Diminished renal clearance extends GBCA circulation time in patients with kidney impairment, enlarging the window for Gd release, especially from less stable linear agents, thereby facilitating this pathological process[51]. The connection between GBCAs and NSF is robust, with epidemiological data indicating a dose-dependent risk[52][53]. Linear, non-ionic agents like gadodiamide present the highest risk. Macrocyclic agents, at standard doses in patients with renal impairment, have not shown a conclusive link to NSF[54].

The spectrum of Gd toxicity spans acute, subacute, and chronic manifestations (Table 1). While NSF represents the most severe acute presentation, emerging evidence highlights long-term deposition-

related effects even in patients with normal renal function.

4.2. Gadolinium Deposition and Retention

Beyond NSF in kidney impairment, broader anxieties about Gd retention have emerged[55]. Since 2014, mounting evidence demonstrates Gd accumulation in diverse tissues, even among patients with normal kidney function, contradicting the prior assumption of complete GBCA clearance[18][19]. Regarding tissue localization, deposition happens in the brain, bone, and other tissues. Within the brain, progressive T1 signal hyperintensity within the dentate nucleus and globus pallidus was noted after multiple administrations of primarily linear GBCAs[56][57][58]. Post-mortem analyses verified Gd presence in these regions, correlating with the number of prior GBCA exposures[59]. Although early studies emphasized linear agents, later research also found Gd in the brain following macrocyclic agent use, albeit usually at lower concentrations[60][61]. Bone serves as a major Gd reservoir, showing higher concentrations than other tissues[62][63]. This bone deposition can last for years, potentially acting as a long-term source for slow Gd release[62]. Gd has also been identified in the skin, liver, and kidneys of individuals after previous GBCA exposure[64]. Animal studies revealed wider distribution across various organ systems[60][65], while Le Fur et al.[66] demonstrated in rats that Gd from both linear and macrocyclic GBCAs distributed to multiple tissues, including brain, bone, and kidneys, with varying chemical speciation. These findings suggest that Gd may persist as intact chelates, free ions, or precipitated forms, highlighting the complexity of long-term retention mechanisms[66].

Although most GBCA is eliminated within days by individuals with normal kidney function, trace Gd levels remain detectable in urine months or years later, suggesting slow release from tissue reservoirs[67][68][69]. The clinical relevance of Gd deposition, particularly in the brain, is not yet fully established. While some studies hint at possible links to subtle neurological problems like cognitive shifts or fatigue, causality remains unproven. Most research has not shown overt neurological issues directly caused by brain Gd deposition, although subtle effects, particularly from repeated exposure, cannot be definitively excluded[70][71][72]. Gulani et al.[73] provided consensus guidelines, recommending judicious GBCA use while noting the limited evidence of clinical harm from brain deposition. In turn, Choi and Moon[74] reviewed deposition pathways and patterns, highlighting differences between linear and macrocyclic agent types.

4.3. Gadolinium Deposition Disease (GDD)

Some patients experience persistent symptoms following GBCA administration, leading to the proposed, although controversial, diagnosis termed Gadolinium Deposition Disease (GDD)[75][76]. Individuals reporting symptoms frequently describe debilitating conditions, including diffuse pain, cognitive challenges, and skin changes, which significantly affect their quality of life[77]. Patient advocacy groups have surfaced, increasing awareness and urging further investigation. Establishing causality and precise diagnostic criteria remains problematic[26][27][78]. Critics note symptom similarities with conditions like fibromyalgia, while others highlight the absence of definitive biomarkers[79]. Reported symptoms cover persistent headaches, bone/joint discomfort, chronic fatigue, mental fog, skin alterations (thickening, rash), burning/tingling sensations, and sensory disturbances. Parillo et al.[80] reviewed skin deposition and toxicity in patients whose renal function was normal, suggesting a possible mechanistic link to Gd exposure. However, objective diagnostic markers for GDD are lacking[27][78]. Symptom overlap with fibromyalgia and chronic fatigue syndrome complicates diagnosis. The temporal connection to GBCA use forms the primary basis for suspicion[81]. While Gd deposition is confirmed, its direct causal role in these reported symptoms isn't definitively proven. Nonetheless, from the patient's view, the temporal association between receiving a GBCA and symptom onset is often compelling, motivating the search for answers and therapies. Suggested potential mechanisms include immune responses, mitochondrial damage, and direct cellular injury from free Gd or nanoparticles[82][5]. GDD research remains in early stages, relying mainly on case reports/series[26][83]. Controlled studies are necessary to better define this condition and establish diagnostic criteria. Lyapustina et al.[84] pointed out evaluation difficulties, stressing the need to exclude other conditions due to non-specific symptoms and the lack of validated GDD biomarkers. Semelka et al.[27][78] proposed diagnostic criteria, indicating symptom onset within hours to a month post-GBCA, with a cluster including central torso pain, neuropathy, headache, and cognitive issues.

4.4. Other Potential Toxicities

Rare occurrences of Acute Kidney Injury (AKI) after GBCA administration have been noted, though the frequency has been substantially lower than with iodinated contrast agents[85][86]. Furthermore, local problems from contrast extravasation are a consideration. Granata et al.[87] reviewed contrast media extravasation, observing that while usually mild, severe instances needing surgery can happen,

highlighting correct injection protocols. Regarding hypersensitivity reactions, immediate reactions occured in ~0.01-0.3% of cases, with severe anaphylactoid events being very uncommon (0.001-0.01%)[88][87]. Neurotoxicity has also been documented with accidental intrathecal injection or significant blood-brain barrier compromise, manifesting as confusion, drowsiness, visual problems, and seizures[89][90][91].

5. Mechanisms of Gadolinium Release, Deposition, and Toxicity

Understanding how Gd detaches from chelates, deposits in tissues, and causes toxicity is key for creating safer agents and reducing risks. Some findings have suggested mechanisms are more complex than initially believed[25].

5.1. Traditional View

Transmetallation involves Gd^{3+} exchange with endogenous metals (like Zn^{2+}, Cu^{2+}, Fe^{3+}, Ca^{2+}), releasing free, toxic Gd^{3+}[92][29]. The relative stability of metal-ligand complexes influences the likelihood of this exchange[93]. Key determinants include GBCA stability (linear agents are more susceptible than macrocyclics)[94], exposure duration (prolonged with renal impairment)[69], concentration of competing metals[95], and the biological milieu (pH, protein binding)[96]. However, transmetallation alone fails to fully explain all observed Gd deposition patterns, particularly the detection of Gd within the brain following administration of highly stable macrocyclic agents[97][98][99].

5.2. Role of Acidic Environments

Acidic conditions markedly influence Gd release, potentially explaining deposition in specific cellular compartments[100]. GBCA stability generally lessens at lower pH, with linear agents being especially vulnerable to acid-driven dissociation. Macrocyclic agents usually maintain better stability under acidic conditions[101][102].

5.3. Precipitation/Nanoparticle Pathway

Figure 1 provides a visual summary of the proposed mechanisms by which Gd is released from contrast agents and subsequently exerts toxic effects, including the roles of transmetallation, acidic dissociation in lysosomes, and nanoparticle formation. Some studies have suggested an alternative pathway: the generation of insoluble Gd-containing nanoparticles. This might occur with both linear and macrocyclic

agents[31][30]. A recent investigation by Henderson et al.[32] provided strong experimental support for this mechanism. These authors showed that both linear and macrocyclic GBCAs can dechelate and subsequently precipitate as gadolinium oxalate in acidic, lysosome-like environments. That *in vitro* study confirms even macrocyclics like Dotarem can be susceptible to oxalate-induced precipitation, especially when proteins are present and pH is low. It supports the biological feasibility of nanoparticle formation contributing to Gd retention and toxicity. The process yields gadolinium oxalate precipitates, potentially serving as precursors to observed intracellular nanoparticles. The body's environment actively affects Gd dechelation and precipitation. Proteins like bovine serum albumin (BSA) have demonstrated an ability to accelerate dechelation, suggesting biological molecules actively participate[103]. The complex chemistry, involving ligand design and metal coordination, impacts stability and dechelation potential[104]. Besides oxalate, other endogenous anions like phosphate and citrate can also promote Gd precipitation and nanoparticle formation, highlighting intricate *in vivo* interactions[105][106][107]). This mechanism offers a plausible rationale for Gd deposition beyond just transmetallation, covering observations with both linear and macrocyclic types. It implies even highly stable macrocyclics might dechelate under specific biological conditions[108]. Frenzel et al.[109] measured residual Gd in the brain after repeated GBCA administrations, finding a significant amount present in a soluble, but not necessarily fully chelated form, further supporting complex retention mechanisms. Emerging data suggest Gd-containing nanoparticles could initiate neuroinflammatory or fibrotic processes, acting either as inert storage or as active toxic agents via interactions with cells and organelles[32]. Whether these nanoparticles are biologically inactive or harmful remains under investigation. While transmetallation was historically considered the primary pathway for Gd release, recent evidence demonstrates that nanoparticle formation via endogenous ligands (e.g., oxalate in lysosomal environments) may represent a parallel mechanism—even for macrocyclic agents[110][25]. This challenges the assumption that kinetic inertness alone ensures safety and underscores the need for agent-specific risk assessments.

5.4. Downstream Cellular Effects

Once Gd is released (as free Gd^{3+} or within nanoparticles), several toxic pathways can be activated: 1) Free Gd^{3+}, owing to its ionic radius similarity to Ca^{2+}, can disrupt voltage-gated calcium channels and calcium-dependent enzymes, impairing cellular functions[111][29]; 2) Inflammation arises when Gd deposits provoke local inflammatory reactions, including macrophage activation and cytokine release, contributing to tissue damage and fibrosis[112][113]; 3) Gd can also promote the generation of reactive

oxygen species (ROS), inflicting oxidative damage on proteins, lipids, and DNA[114][115][116]; 4) Evidence indicates Gd can impede mitochondrial function, affecting energy production and potentially triggering apoptosis[117]; 5) *In vitro* studies as that conducted by Erdoğan et al.[118], revealed dose-dependent GBCA toxicity on neuronal cells, with linear agents causing more damage than macrocyclics; 6) In NSF, Gd appears to stimulate fibroblast growth and collagen synthesis through upregulation of profibrotic cytokines and growth factors like TGF-β[119][120]; and 7) Gd-containing nanoparticles might exert biological effects distinct from free Gd^{3+}, interacting with cell membranes, proteins, or organelles, or acting as a reservoir for gradual Gd release[121][25].

6. Risk Factors for Gadolinium Toxicity/Retention

Identifying factors elevating susceptibility to Gd toxicity assists in risk assessment and prevention.

6.1. Renal Function

Compromised renal function is the most critical risk factor for Gd toxicity, especially NSF. Risk inversely correlates with eGFR; the highest risk is in patients with eGFR <30 mL/min/1.73m^2, particularly those on dialysis or with AKI[52][122]. Reduced renal clearance prolongs GBCA circulation, increasing opportunities for Gd release via transmetallation or other pathways[119][123]. Standard eGFR calculations might not always accurately reflect true GFR, particularly in individuals with unusual body size, critical illness, or fluctuating renal status, potentially leading to flawed risk assessment[124][125].

6.2. GBCA Type and Stability

The chemical structure and stability of GBCAs heavily impact toxicity risk. Thus, linear agents, especially non-ionic types like gadodiamide, pose a substantially higher NSF risk than macrocyclic agents[99][126]. Linear agents also exhibit greater tissue deposition, though all classes contribute somewhat[127]. Among linear agents, ionic ones generally possess better stability than non-ionic ones, potentially implying lower risk[128]. The American College of Radiology's three-group classification has provided a practical guide for agent selection based on risk[40]. A meta-analysis by Woolen et al.[44] supported this, finding a very low (possibly zero) NSF risk with Group II agents even in patients with stage 4/5 CKD, unlike the higher risk with Group I agents.

6.3. Cumulative Dose

Data consistently demonstrate a dose-dependent link for both NSF risk and tissue deposition. Repeated GBCA administrations increase cumulative Gd burden. Studies connect the number of prior administrations to the extent of brain signal alterations or tissue Gd levels[73][129][130][131]. The interval between administrations might also influence risk, but optimal timing was unclear[17].

6.4. Other Potential Risk Factors

Evidence for other factors modifying Gd toxicity risk is less definitive. Concurrent inflammation might enhance Gd release and tissue injury through increased vascular permeability and acidic conditions[132][133][104]. Gadolinium also crosses the placenta, causing fetal deposition. Although teratogenicity isn't confirmed, caution is advised[134][135][136]. Moreover, conditions like multiple sclerosis, tumors, or inflammation disrupting the BBB can facilitate Gd entry into brain parenchyma[137][138]. Furthermore, children might be more vulnerable due to developing organs, maturing BBB, and a longer potential lifespan for effects[139][140]. Additionally, individual genetic variations in metal handling or inflammatory responses could affect susceptibility, but specific markers are yet to be identified[141][142].

7. Diagnosis and Monitoring

Reliable diagnosis and monitoring for Gd-related toxicities, particularly beyond NSF, remain challenging.

7.1. Clinical Assessment

For NSF, diagnosis combines characteristic clinical signs (skin thickening, contractures) with histopathology (increased dermal cells, CD34+ fibrocytes, collagen) within the context of GBCA exposure and renal dysfunction[143][144]. For GDD, no standardized diagnostic criteria exist. Assessment involves documenting symptom timing relative to GBCA use, excluding other causes, and potentially confirming Gd retention[63][80]

7.2. Imaging Assessment

Progressive T1 hyperintensity noted in the dentate nucleus and globus pallidus on unenhanced MRI acts as a radiological sign of brain Gd deposition, mainly linked to linear agents[60][115][116][145]. These signal

changes don't perfectly align with Gd concentration and might miss deposition below detection limits. The link between signal changes and clinical symptoms remains uncertain[146].

7.3. Laboratory Assessment

Definitive proof of Gd deposition needs tissue sampling, typically restricted to research or post-mortem studies due to invasiveness[147]. Urine/blood Gd measurements confirm recent exposure but reflect clearance or mobilization, not total body burden or tissue levels. Normal elimination kinetics complicate interpretation, as Gd might be detectable for days/weeks even without abnormal retention[148][149]. Currently, no validated biomarkers exist for Gd toxicity or problematic retention, hindering early detection and prognosis[150].

7.4. Monitoring Challenges

The potential for delayed symptom onset and the uncertain clinical meaning of Gd deposition complicate long-term monitoring[27][78]. Monitoring approaches must balance surveillance needs with resource use and potential patient anxiety arising from uncertain findings[151]. The lack of clear clinical correlation for findings like brain hyperintensity can cause significant worry for patients undergoing monitoring.

8. Management and Mitigation

Managing Gd-related risks involves prevention, careful agent choice, and weighing benefits against risks[152].

8.1. Risk Stratification and Informed Consent

Screening for risk factors (renal impairment, inflammation, prior reactions) should inform decisions[153]. Patients need information about potential risks, including Gd retention, tailored to their individual factors and the selected agent[40]. Effective risk communication is crucial. This requires explaining not only established risks like NSF (in susceptible patients), but also uncertainties surrounding Gd deposition and GDD, ensuring patients can make truly informed choices collaboratively with their clinicians. Openly addressing patient concerns and questions is paramount.

8.2. Agent Selection and Dose Optimization

Balancing diagnostic need with safety is essential, especially in high-risk individuals[154][155]. Macrocyclic agents are generally preferred due to higher stability and lower deposition, particularly for patients with risk factors or needing repeat scans[156]. Specific guidance exists for high-risk groups like those with chronic kidney disease (CKD), reinforcing risk stratification by agent class and renal function[157]. Group I agents should be avoided in patients with severe renal impairment (eGFR <30 mL/min/1.73m^2) and used very cautiously, if ever, in those requiring multiple scans[40]. Employing the lowest effective diagnostic dose minimizes total Gd exposure and risks[158][159], while careful planning can prevent unnecessary repeat scans, especially at short intervals[16]. For high-risk patients, consider non-contrast MRI or alternative imaging methods if suitable[160][161]. Current risk mitigation strategies emphasize agent selection, dose optimization, and patient screening (Table 2). These measures are particularly critical in high-risk populations, such as those requiring repeated GBCA exposure.

8.3. Management of Established Toxicity

For NSF management, primarily supportive care focusing on physical therapy, skin treatments, and optimizing renal function (including transplantation) is recommended[162]. No definitive cure exists; therefore, management relies on symptom control. Various treatments (anti-inflammatories, chelation) have been tried with inconsistent outcomes[163]. Ramalho et al.[63][164] reviewed potential therapies for Gd retention/toxicity, noting anecdotal evidence for chelation (e.g., with DTPA) but lack of standardized protocols.

8.4. Chelation Therapy

Chelation therapy is a well-established approach for treating heavy metal poisoning, utilizing agents such as ethylenediaminetetraacetic acid (EDTA), 2,3-dimercapto-1-propanol (BAL), and D-penicillamine (D-PA) since the 1950s, with more recent agents including dimercaptosuccinic acid (DMSA), 2,3-dimercaptopropane-1-sulfonate (DMPS), and Tiron. These agents effectively counteract heavy metal toxicity but can also cause adverse effects and deficiencies in essential elements, often necessitating mineral supplementation[165][166][167]. Recent research has also explored bioactive compounds with antioxidant and anti-inflammatory properties for chelation, alongside the development of orally administrable chelators suitable for home health care. Balali-Mood et al.[168] reviewed current antidotes

for metal poisoning, highlighting DMSA and DMPS as safe oral chelators for various metal toxicities, which may have relevance for Gd.

In the context of Gd, chelation therapy for this element removal remains controversial and is primarily used off-label[169]. Layne et al.[79] reviewed the topic, concluding that there is insufficient evidence to define Gadolinium Deposition Disease as a distinct condition and cautioning against chelation therapy due to unproven effectiveness and potential risks. Very few controlled studies validate the efficacy or safety of chelation for Gd, with most data derived from case reports or series[163][169][170][171]. Semelka and Ramalho[77] suggested that diethylene triamine penta-acetic acid (DTPA) was the most effective chelating agent for Gd due to its high affinity, proposing its use to mitigate GDD. Animal studies suggest chelation reduces Gd burden[172][173], with DTPA decreasing bone retention by 40% in rats[110], but human data remain rather limited. Risks of hypocalcemia, nephrotoxicity, and essential metal depletion necessitate caution until controlled trials validate protocols[174], while Henderson et al.[32] advised against chelation without stronger evidence, citing the lack of robust data on its benefits for Gd retention. However, recently, Schilling et al.[175] assessed in volunteers the efficacy of EDTA in mobilizing toxic metals, including lead, cadmium, and Gd, while minimizing the loss of essential elements such as Mn and Cu. Gd excretion increased by up to 78 000% even at 0.5 g. This finding would highlight the potential use of EDTA to reduce long-term Gd burden post-MRI. Anyhow, controlled clinical trials are essential to determine the optimal chelating agents, timing, dosage, and patient selection for Gd-related toxicities, building on the general chelation principles outlined in earlier studies.

9. Regulatory Perspectives

Global regulatory bodies have addressed emerging Gd safety evidence, balancing diagnostic utility and potential harm. The US FDA implemented several actions: issued a boxed warning in 2007 for NSF risk; added class warnings for Gd retention in 2017; recommended restricted use of specific linear agents, and mandated distribution of medication guides to inform patients[176][177]. The US FDA focused on risk mitigation like medication guides for all GBCA classes, permitting continued use of linear agents with precautions. In turn, the European Medicines Agency (EMA) enacted more restrictive measures[178][179]: suspended marketing for four linear GBCAs in 2017 (gadodiamide, gadopentetate dimeglumine, gadoversetamide, gadobenic acid); restricted gadobenic acid to liver imaging; and maintained approval for macrocyclics and liver-specific gadoxetic acid. This divergence highlights challenges regulators face

balancing established benefits against emerging, sometimes uncertain, risks. Practice patterns and GBCA availability consequently vary significantly across regions. Some nations follow EMA's restrictions, others align with the US FDA, while some, like Japan, maintain linear agent approval with specific warnings[180][181]. Other regulatory bodies, such as Health Canada or Australia's Therapeutic Goods Administration (TGA), have also issued communications and restrictions, often aligning closely with either the US FDA or EMA approach depending on their assessment. Regulatory actions have markedly impacted clinical practice, favoring macrocyclics, improving screening, emphasizing benefit-risk assessment, and enhancing patient communication[73][63][182].

10. Conclusions and Future Directions

Gadolinium toxicity ranges from the established NSF entity to the increasingly acknowledged issue of widespread tissue deposition, whose clinical relevance is debated. Emerging mechanistic understanding points to complex processes beyond simple transmetallation, potentially involving Gd-containing nanoparticle formation via interactions with endogenous molecules in specific microenvironments[30][31][32][183].

Key implications of this expanded view include: a) even highly stable macrocyclic GBCAs might dechelate under certain biological circumstances[108][184], b) the biological environment plays an active role in Gd release, not just a passive one[103], c) nanoparticle formation could represent a distinct toxicity pathway beyond free Gd^{3+} effects[121][185][186]. Despite progress, critical knowledge gaps persist. These include: a) the long-term clinical impact of brain and tissue deposition[59], b) validating "Gadolinium Deposition Disease" as a specific clinical condition[77], c) the need for reliable biomarkers for Gd toxicity or problematic retention[74], d) effective treatments for symptomatic Gd retention[63], and e) understanding individual susceptibility and risk prediction[187].

Future research priorities should involve longitudinal studies linking Gd deposition to histopathology, developing non-gadolinium alternatives (e.g., iron oxide nanoparticles), validating biomarkers for early retention detection, and conducting controlled trials on chelation therapy efficacy[129][65][188]. Until these gaps are filled, a cautious approach remains necessary: judicious GBCA use (reserving for clinical need)[40], preferring macrocyclics (especially in high-risk patients or those needing multiple scans)[189], considering cumulative dose[190], thorough documentation of GBCA administration to facilitate long-term monitoring[156], and open patient communication about risks and uncertainties[24]. Engaging

patients in shared decision-making, supported by clear and balanced information, will remain essential as understanding evolves.

Balancing Benefits and Risks

GBCAs are indispensable diagnostic tools that have significantly advanced medical imaging and patient care. The ongoing task is to balance their clear clinical advantages against potential long-term risks. It is crucial to remember that for many patients, the diagnostic information gained from a GBCA-enhanced MRI significantly outweighs the currently known potential risks, especially when using more stable agents and adhering to screening guidelines. For example, accurate tumor staging, assessment of treatment response in oncology, or identification of inflammatory lesions in multiple sclerosis often relies heavily on GBCA enhancement. The potential harm of a missed or delayed diagnosis must be carefully weighed against the risks tied to Gd exposure. This necessitates refining risk stratification methods[5], developing patient-specific protocols[191], adapting practices as new data become available[161], and ensuring transparent communication among healthcare professionals and patients[192]. Recent insights into Gd precipitation and nanoparticle formation highlight the intricate nature of GBCA-biological system interactions and emphasize the need for continued research to optimize the safety of these valuable diagnostic agents[184][193][194][195]

11. Limitations of Current Knowledge and this Review

Although the present review synthesizes a broad range of literature on Gd toxicity, several limitations should be acknowledged, both within the current body of knowledge and in the scope of this review. There are gaps in evidence. For example, definitive understanding of the long-term clinical significance of Gd deposition, particularly in the brain with normal renal function, remains elusive. Robust longitudinal studies correlating deposition levels with specific clinical outcomes are still needed. Moreover, the existence and diagnostic criteria for 'Gadolinium Deposition Disease' (GDD) remain highly controversial and lack universal acceptance within the medical community. Much of the evidence relies on case reports and series, often subject to selection bias, making causality difficult to establish. There is also a lack of validated, accessible biomarkers to reliably quantify Gd body burden or identify individuals experiencing Gd-related toxicity beyond NSF. While this review synthesizes preclinical and clinical data, the lack of standardized Gd speciation methods in human tissues limits mechanistic certainty. Additionally, heterogeneity in GBCA dosing protocols across studies complicates cumulative risk

assessments. Regarding mechanistic uncertainty, while transmetallation and nanoparticle formation offer plausible mechanisms, the precise in vivo processes, their relative contributions, and the exact molecular triggers under various physiological conditions require further elucidation.

It should also be noted that this review primarily focused on English-language publications identified through Scopus, PubMed and Embase up to April 2025. Relevant studies in other languages or additional databases may have been missed. Furthermore, the rapid evolution of this field means new findings may emerge after this review's completion. In addition, studies often vary significantly in methodology, patient populations, GBCA types used, and outcome measures, making direct comparisons and meta-analyses challenging.

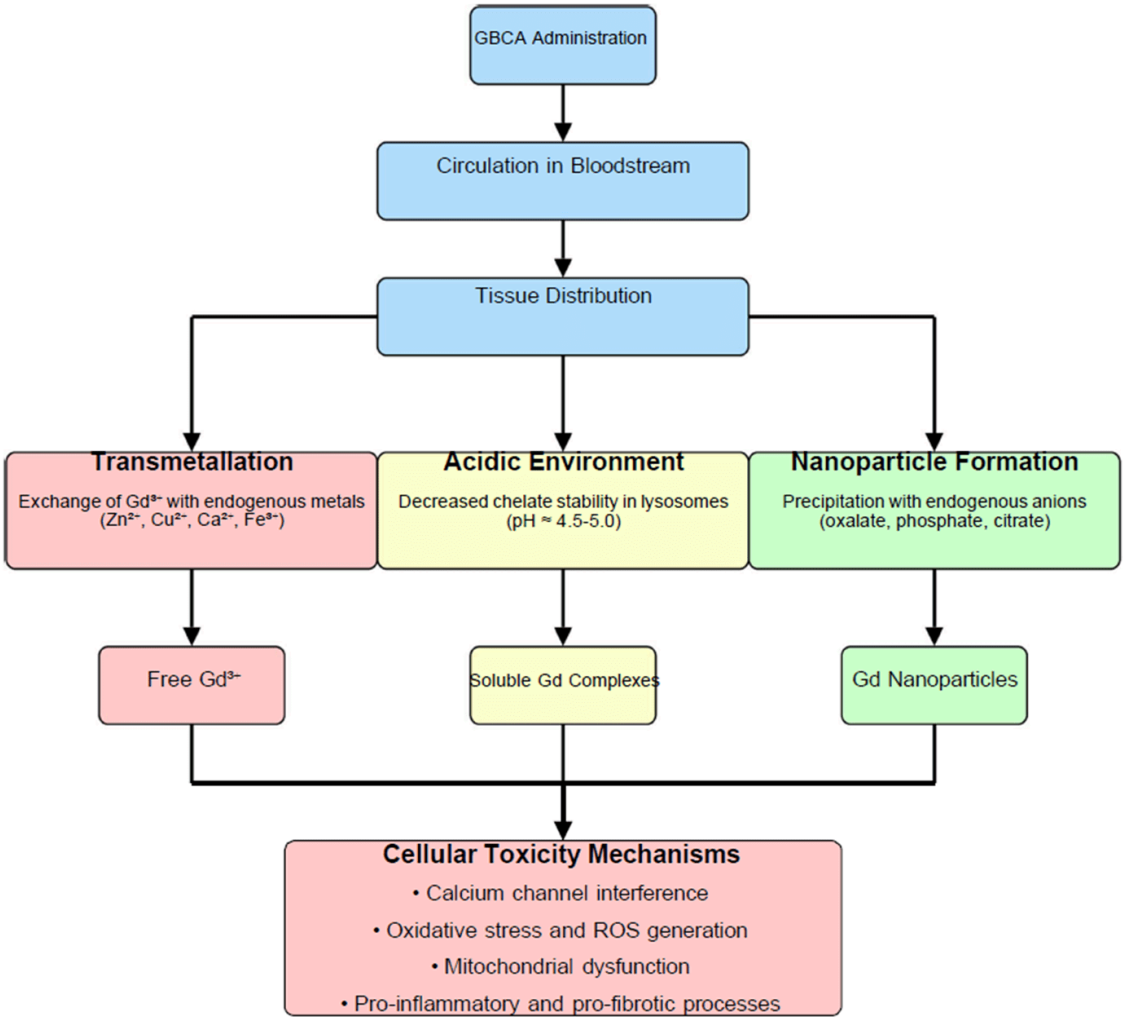

Figure 1. Proposed Mechanisms of Gadolinium Release and Toxicity

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Entity	Patient Population	Temporal Association	Major Clinical Manifestations	Objective Findings	Strength of Evidence
Nephrogenic Systemic Fibrosis (NSF)	Primarily patients with severe renal impairment (eGFR <30 mL/min/1.73m^2)	Weeks to months after GBCA exposure	• Skin thickening and hardening • *"Peau d'orange"* appearance • Joint contractures • Pain and pruritus • Possible internal organ fibrosis	• Characteristic histopathology • CD34+ fibrocytes • Increased dermal cell count • Collagen deposition • Gd detection in tissue	Strong • Epidemiological studies • Clear dose-response relationship • Plausible biological mechanism
Brain Gadolinium Deposition	Patients with normal or impaired renal function receiving multiple GBCA doses	Cumulative over multiple exposures	• Generally asymptomatic • Possible cognitive changes (controversial)	• T1 hyperintensity in dentate nucleus and globus pallidus • Gd detection in brain tissue on autopsy	Moderate • Signal changes well-documented • Tissue Gd confirmed • Clinical significance unclear
Gadolinium Deposition Disease (GDD)	Patients with normal renal function	Hours to weeks after GBCA exposure	• Persistent headache • Bone/joint pain • Chronic fatigue • Mental fog/confusion • Skin changes • Burning/tingling sensations	• No standardized objective findings • No established biomarkers • Symptom overlap with other conditions	Limited • Primarily case reports/series • No controlled studies • Subjective symptoms • No specific diagnostic test
Acute Reactions	General population	Minutes to hours after GBCA exposure	• Nausea, vomiting • Skin rash/hives • Anaphylactoid reactions (rare)	• Objective physical findings of hypersensitivity	Strong • Well-documented adverse events

Entity	Patient Population	Temporal Association	Major Clinical Manifestations	Objective Findings	Strength of Evidence
			• Pain at injection site	• Vital sign changes in severe cases	• Clear temporal association • Established incidence rates

Table 1. Clinical Manifestations of Gadolinium Toxicity

doi.org/10.32388/S711CO

Patient Risk Category	Risk Assessment	Agent Selection	Dose Considerations	Monitoring Recommendations	Alternative Approaches
Severe Renal Impairment (eGFR <30 mL/min/1.73m²)	• Measure eGFR prior to GBCA • Assess hydration status • Review prior GBCA exposure	• Macrocyclic agents only (Group III) • Avoid linear agents (Group I/II)	• Minimum effective dose • Avoid repeat injections • Minimum 7-day interval between doses	• Document GBCA type and dose • Clinical follow-up for NSF symptoms • Consider dermatology evaluation if skin changes	• Non-contrast MRI protocols • Alternative imaging modalities • Ultrasound or CT when appropriate
Moderate Renal Impairment (eGFR 30–60 mL/min/1.73m²)	• Measure eGFR prior to GBCA • Review prior GBCA exposure • Consider risk factors	• Preferably macrocyclic agents (Group III) • May use Group II with caution • Avoid Group I	• Standard dose • Minimize repeat injections • At least 48-hour interval between doses	• Document GBCA type and dose • Routine clinical follow-up	• Consider non-contrast MRI if diagnostically adequate • Lower dose protocols
Normal Renal Function with Multiple Exposures	• Review prior GBCA exposure • Estimate lifetime cumulative dose	• Preferably macrocyclic agents (Group III) • May use Group II • Consider Group I only if specific indication	• Standard dose • Minimize unnecessary repeat scans	• Document GBCA type and dose • Consider baseline MRI for future comparison	• Optimize protocols to reduce need for repeat scans • Consider alternative sequences
Pediatric Patients	• Assess renal function • Consider developmental	• Macrocyclic agents	• Weight-based dosing • Minimum effective dose	• Document GBCA type and dose • Long-term follow-up consideration	• Non-contrast protocols when possible • Alternative

doi.org/10.32388/S711CO

Patient Risk Category	Risk Assessment	Agent Selection	Dose Considerations	Monitoring Recommendations	Alternative Approaches
	factors • Evaluate long-term risk	preferred (Group III)			imaging modalities
Pregnant/Breastfeeding	• Assess benefit vs. risk to mother and fetus/infant • Consider gestational age	• Macrocyclic agents if GBCA necessary	• Minimum effective dose	• Document GBCA type and dose • No specific monitoring required for breastfeeding	

Table 2. Risk Management Strategies for GBCA Use

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