

Coordination chemistry as the governing principle of gadolinium biology: from GBCA design to dissociation, endogenous coordination, and chelation

Abstract

Coordination chemistry provides a continuous molecular framework for gadolinium from the manufacture of a gadolinium-based contrast agent (GBCA) through biological retention, ligand exchange, endogenous re-coordination, and eventual chelation. A GBCA begins as a deliberately engineered Gd(III) coordination complex in which water accessibility, relaxivity, solubility, thermodynamic stability, kinetic inertness, distribution, and elimination must be balanced. If the original pharmaceutical coordination environment is disrupted, gadolinium does not become chemically undefined; it enters new coordination environments involving endogenous ligands. Phosphate-containing species have the strongest direct support as an inorganic binding environment for released Gd, while proteins, carbonate, other oxyanions, and mixed mineral-organic phases may also participate. Therapeutic chelation addresses the same coordination chemistry from the opposite direction. The chelator must reach retained Gd, compete with the existing coordination environment, form a sufficiently stable complex under physiological conditions, keep that complex soluble during transport, and permit elimination. Recent human data comparing four chelators illustrate why stability of a preformed complex alone does not establish in vivo performance. Paired urinary data demonstrate mobilization and increased excretion of an accessible Gd pool, but they do not identify its tissue or molecular origin, quantify total-body removal, or establish that retained Gd is causal for Gadolinium Deposition Disease (GDD). Clinical evidence for DTPA remains observational, and its use for GDD is off-label. This review develops accessibility as the connecting concept across the gadolinium molecular life cycle and presents DTPA-mediated decorporation as a mechanistically testable therapeutic approach requiring further controlled clinical evaluation.

Keywords: gadolinium, coordination chemistry, gadolinium-based contrast agents, DTPA, chelation, ligand exchange, phosphate, gadolinium retention, decorporation, accessibility

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Introduction

From formulation of an MR contrast agent to therapeutic decorporation, gadolinium remains subject to the same basic chemical rules. Gd(III) is strongly paramagnetic because of its seven unpaired electrons, which makes it useful for shortening proton relaxation times. The same highly charged, oxophilic ion is unsuitable for direct biological administration. Clinical use therefore depends on surrounding Gd(III) with a multidentate ligand that changes its solubility, kinetic behavior, distribution, and biological accessibility.^{1,2}

The clinically familiar term “contrast agent” can obscure this molecular fact: a GBCA is a preformed coordination complex. Its performance depends not only on the affinity of the ligand for Gd but also on how fast the complex forms or dissociates, how readily water can approach the paramagnetic center, whether endogenous competitors can gain access, and whether the intact complex leaves the body before important ligand exchange occurs.¹⁻⁵

The same framework continues after administration. Retained Gd may remain within the original pharmaceutical complex, become partially altered, undergo ligand exchange, enter intracellular compartments, associate with proteins or macromolecules, or participate in phosphate-rich and other mineral-like coordination environments. Therapeutic chelation is therefore not a chemically separate topic. It is a second coordination problem imposed on Gd that is already coordinated elsewhere.

This review develops a molecular-life-cycle model in which the governing variable is accessibility. The meaning of accessibility changes at each stage: water must approach Gd for MRI; competing endogenous ligands ideally should not disrupt an intact GBCA; released or labile Gd becomes accessible to biological ligands; and an effective therapeutic chelator must ultimately gain access, form a new complex under physiological conditions, and carry that complex to an excretory pathway.

Coordination chemistry and the molecular identity of a GBCA

Coordination chemistry concerns a metal center and surrounding donor atoms that contribute electron density to that center. Gd(III) behaves primarily as a hard Lewis acid and therefore favors hard donor atoms, especially oxygen. Polyaminocarboxylate ligands used in GBCAs provide multiple oxygen and nitrogen donor sites that can envelop Gd within a multidentate coordination environment.^{1,2}

Linear agents use flexible acyclic ligands such as DTPA and its derivatives, whereas macrocyclic agents use preorganized ring systems such as DOTA derivatives. This architectural distinction influences both complex formation and complex dissociation. Macrocyclic Gd complexes are generally much more kinetically inert once fully formed, while formation of a metal complex inside a rigid macrocyclic cavity can be slower and more stepwise than coordination by an open-chain ligand.³⁻⁵

That asymmetry is central to the therapeutic discussion. The question “How difficult is it to break an already formed complex?” is not equivalent to “How readily can this ligand capture a metal under physiological conditions?” A ligand can generate an extremely inert final complex yet still be a poor practical decorporation agent if absorption, distribution, access, or formation kinetics are unfavorable.

Table 1 Accessibility across the molecular life cycle of gadolinium

Stage	Required or relevant accessibility	Functional consequence
GBCA design	Controlled water access to the paramagnetic center	Useful proton relaxation while preserving complex integrity
GBCA circulation	Minimal disruptive access by endogenous competitors	Intact distribution and elimination
Dissociation / transformation	Access of endogenous donor atoms to labile or released Gd	Re-coordination, sequestration, or aggregation
Tissue retention	Variable access within proteins, particles, and mineral-like phases	Persistence, biological interaction, or relative sequestration
Therapeutic chelation	Physical and chemical access of a chelator to retained Gd	Ligand exchange, capture, soluble transport, and decorporation

GBCA design: water should get in, gadolinium should not get out

A useful shorthand for GBCA engineering is that water should be able to get in, whereas Gd should not get out. Relaxivity depends on the relationship between the paramagnetic center and nearby water, including inner-sphere water coordination, water-exchange rate, second-sphere hydration, molecular tumbling, and, for some agents, protein interaction.¹ A complex that excluded water too completely could be chemically robust but diagnostically inefficient.

At the same time, the pharmaceutical ligand must limit access by biological competitors during the clinically relevant residence interval. The design problem is therefore an optimization problem rather than maximization of any single parameter. Greater relaxivity, higher equilibrium affinity, greater kinetic inertness, rapid clearance, low osmolality, and appropriate distribution are desirable, but improving one property can alter another.

This is a molecular version of the Goldilocks principle: sufficient water accessibility for imaging, sufficient ligand protection for safety, and sufficiently favorable pharmacokinetics for timely elimination.

Stability and formation are separate problems

The word stability is often used too broadly. Intrinsic thermodynamic stability describes equilibrium favorability under specified reference conditions. Conditional or physiological thermodynamic stability incorporates ligand protonation and other features relevant to physiological pH. Kinetic behavior concerns a separate dimension: the time required for an already assembled complex to release its metal. Acid-challenge dissociation and behavior in serum at 37 °C provide useful but nonidentical experimental views.^{3–5}

Frenzel and colleagues demonstrated large differences in Gd release among marketed agents incubated in human serum at 37 °C, with substantially greater release from less stable linear compounds and no measurable release from the tested macrocyclic agents during the observation interval.⁴ Such experiments are important because they place stability in a biologically competitive medium rather than in a purely idealized equilibrium system.

For therapeutic chelation, however, a second kinetic question becomes equally important: can the new metal-ligand complex actually form fast enough, at approximately 37 °C and physiological pH, in the presence of competing endogenous ligands and metals? A

Accessibility is not one thing

Accessibility is useful because it forces the molecular question to be specified. The form of access that is desirable during MRI is not the form desired during chelation, and the form that promotes tissue sequestration may be the opposite of the form that permits removal (Table 1).

very stable final complex does not by itself answer that question.

Dissociation is a change of coordination environment

A binary model in which retained gadolinium exists only as intact GBCA or as persistent freely solvated Gd(III) is chemically incomplete. If Gd leaves or becomes accessible outside its pharmaceutical ligand, the strongly Lewis-acidic metal immediately encounters water, oxyanions, carboxylates, proteins, and other donor-rich structures. Persistent free Gd(III) is therefore not required for biological transformation.

A more realistic molecular sequence is: pharmaceutical Gd-ligand complex → transient exchange state → endogenous Gd coordination environment. Proton-assisted dissociation, metal-assisted exchange, ligand competition, endosomal processing, or combinations of these processes can contribute depending on the original agent and biological compartment.^{5,6}

Di Gregorio and colleagues provided direct evidence that linear GBCAs can undergo extensive degradation after endosomal internalization in living cells.⁷ This observation is important because intracellular acidity, ligand composition, macromolecular crowding, and compartmental confinement differ from plasma. The chemical identity of retained Gd can therefore diverge substantially from the identity of the originally injected agent.

Endogenous re-coordination: phosphate, proteins, and mixed mineral-organic phases

Among candidate inorganic binding environments, phosphate has the strongest direct support. Human NSF tissue has shown Gd associated with phosphate-rich material by synchrotron methods, including a sodium-calcium-phosphate environment, and multiorgan autopsy observations have demonstrated insoluble Gd-phosphate-containing deposits.^{8,9} Cellular studies also implicate phosphate as an important scavenger when Gd becomes chemically accessible.⁶

Renal and experimental tissue studies have identified Gd-rich particles containing phosphorus and oxygen, supporting the concept that retained Gd may enter nanoscale or mineral-like structures rather than remain exclusively as a small molecular complex.¹⁰ More recent EPR/ENDOR work distinguished complex-bound from released Gd after a linear GBCA and identified phosphorus-containing molecules in the immediate chemical environment of released Gd, adding independent support for phosphate-rich re-coordination.¹¹

A recent review focused specifically on post-dissociation salt formation and emphasized an important mechanistic distinction: an endogenous oxyanion may scavenge Gd that has already become accessible without being the process that caused the intact GBCA to dissociate.¹² That distinction prevents two separate reactions - destabilization of the pharmaceutical complex and subsequent sequestration of released Gd - from being treated as though they were identical.

The term “gadolinium salt” is therefore useful shorthand but not a complete structural description. A retained phase may include multiple Gd centers bridged by phosphate or other oxygen donors, associated water and hydroxide, adsorbed proteins, or mixed inorganic-organic components. Proteins may bind Gd at discrete coordination sites, associate with the surface of an inorganic particle, or participate within a heterogeneous deposit.

Tissue microenvironments, water access, and biological activity

Total elemental Gd does not specify molecular form. The same tissue concentration could represent intact GBCA, soluble endogenous complexes, protein-associated Gd, nanoscale phosphate-rich material, or more ordered mineral-like deposits. Those forms need not have the same mobility, biological activity, MRI visibility, or chelator accessibility.

This distinction is particularly relevant to relaxometry. MRI-visible retained Gd must occupy a coordination environment in which water retains sufficient access to influence proton relaxation. A densely coordinated or highly mineralized deposit may contain substantial elemental Gd while being relatively relaxometrically silent. Conversely, a hydrated, dynamically exchanging coordination environment may contribute disproportionately to T1 shortening despite representing only part of the total retained Gd pool.

Sequestration should also not be equated automatically with biological inertness. *In vitro* work has shown that insoluble gadolinium phosphate and carbonate particles can attach to human dermal fibroblast surfaces and stimulate proliferation over a defined concentration range, with cytotoxicity at higher concentrations.¹³ These experiments establish biological interaction under experimental conditions; they do not establish that such particles cause GDD. More broadly, the existence of retained or biologically interactive Gd does not by itself prove that retained Gd is the cause of persistent symptoms in an individual patient. Causal attribution remains unsettled and is likely to depend on both the retained chemical species and host susceptibility.²⁶

Aggregate size and surface chemistry are likely to matter therapeutically. Gd exposed at the surface of a small particle or microaggregate should be more accessible to an incoming ligand than Gd buried within a mature lattice. Tissue turnover, dissolution, cellular trafficking, and remodeling may subsequently expose additional sites, providing one route by which a retained pool can change its chelatability over time.

Therapeutic chelation is the mirror-image accessibility problem

GBCA formulation and therapeutic chelation are molecular mirror images only in a limited but useful sense. Both involve controlling access to Gd, yet the starting conditions and objectives are opposite. The GBCA is administered as an already formed complex; its task is to remain intact while permitting enough water interaction for MRI.

Therapeutic chelation begins with Gd already coordinated within a biological reservoir; the new ligand must find that reservoir, compete successfully, form a new complex *in vivo*, and escort the metal to elimination.

The contrast-agent problem can be summarized as: preserve the manufactured Gd-ligand complex during distribution and clearance. The decorporation problem is: gain access to retained Gd, create a new soluble coordination environment, prevent rerelease during transport, and remove the product from the body.

An effective chelator therefore requires more than a favorable intrinsic log K. It needs physical access to the retained compartment, suitable donor chemistry, competitive affinity, biologically useful formation kinetics, sufficient persistence of the new complex, water compatibility, an effective route of administration, and an excretory pathway.

Why a stable final complex is not enough to select a chelator

Macrocyclic ligands illustrate the difference between final-complex stability and practical capture. DOTA-based Gd complexes are exceptionally inert after formation, but lanthanide-DOTA complexation proceeds through intermediates and incorporation of the metal into the macrocyclic cavity; formation can therefore be kinetically demanding.^{14,15} The properties that make a preformed macrocyclic GBCA resistant to dissociation do not automatically make uncomplexed DOTA the best ligand for rapidly capturing retained Gd *in vivo*.

Recent human proof-of-concept data provide a real-world test of this distinction. In an intra-individual comparison of four chelators, candidate selection was interpreted using metal-ligand stability, physiological accessibility, ability to form the complex under biological conditions, route of administration, and measured 24-hour urinary decorporation.¹⁶ Intravenous Ca-DTPA increased 24-hour urinary Gd 164-fold, oral HOPO increased it 9.4-fold, while oral DOTA and oral Emeramide produced no substantial Gd increase under the doses, formulations, and routes tested.¹⁶

The experiment does not establish population-level superiority of one chelator, nor does failure of an oral formulation prove that the ligand cannot bind Gd. It does demonstrate the methodological point: coordination chemistry should identify plausible candidates, but the final test of a decorporation agent requires evidence that the complete sequence - delivery, access, complex formation, transport, and elimination - occurs *in vivo*.

DTPA and the chemically accessible retained pool

DTPA is an open-chain aminopolycarboxylate that forms a highly stable complex with Gd and can undergo metal exchange under physiological conditions. Its flexibility and rapid coordination behavior distinguish it from a rigid macrocycle during the complex-formation step, even though preformed macrocyclic GBCAs are more kinetically inert.¹⁻⁵

Three routes of DTPA-facilitated Gd removal can be considered. First, DTPA can capture Gd that has already separated from its original GBCA and resides in an accessible endogenous coordination environment. A second pathway becomes possible when the original GBCA has acquired sufficient lability - through opening, degradation, or other kinetic alteration - for DTPA to win the coordination competition. Both are conventional ligand-exchange processes. Third, an intact GBCA might theoretically be displaced from a tissue

compartment toward circulation without transfer of Gd to DTPA; this “tugging” concept remains conjectural and requires speciation studies.

Animal experiments demonstrate why original-agent identity matters. Ca-DTPA administered after prior gadodiamide produced a substantial rise in urinary Gd and reduced brain Gd, whereas little additional removal occurred after gadobutrol over the studied interval.¹⁷ The result is consistent with a larger dechelated or chemically accessible pool after the less inert linear agent and a predominantly intact retained pool after the macrocyclic agent at that time point.

Human chelation as an in vivo coordination-chemistry experiment

Human chelation studies provide an unusual opportunity to perturb the proposed chemistry directly. In the initial clinical series, intravenous Ca-/Zn-DTPA substantially increased 24-hour urinary Gd in patients treated for presumed GDD.¹⁸ A later prospective study found at least a fourfold increase in 24-hour urinary Gd after 87% of 30 Ca-DTPA sessions.¹⁹

Those observations have a limited but important chemical implication: at least part of the retained human Gd pool remains accessible to a new ligand. A reproducible increase in 24-hour urinary Gd after DTPA demonstrates increased movement of Gd into an excretory compartment and increased elimination during that collection interval. It does not identify the source tissue, establish the molecular identity of every excreted species, quantify the fraction of total-body burden removed, or prove that the mobilized pool is pathogenic. This use of paired pre- and post-chelation urine as a pharmacodynamic endpoint should also be distinguished from diagnostic post-chelator or “provoked” urine testing, which has been criticized in clinical toxicology when used to infer total-body metal burden, diagnose metal poisoning, or justify treatment by comparison with non-provoked reference ranges.³⁰ No such diagnostic inference is made here.

Natural elimination data after a single lifetime GBCA administration further show that retained Gd is not necessarily a completely static compartment; urinary Gd can remain measurable for months after exposure.²⁰ Chelation should therefore be considered against a background of ongoing exchange among compartments rather than a model of permanently fixed, chemically inaccessible deposits.

Source-directed treatment as a mechanistic framework

Reduction or elimination of a causal source is a recurring therapeutic principle in medicine, but this is an analogy of mechanism rather than an assertion of evidentiary equivalence. Source control in sepsis, removal of selected retained foreign material, cancer-directed treatment, and toxicologic decorporation each rest on their own disease-specific evidence bases.^{21,22} The narrower point relevant here is that, if retained Gd contributes causally to symptoms in a susceptible patient and an accessible fraction can be transferred into a stable excretable complex, chelation is mechanistically directed at the proposed causal material rather than solely at downstream symptoms.

This framework does not establish that Gd is causal for GDD or that DTPA is clinically effective. Those are separate empirical questions. Retention is well documented, and human chelation studies demonstrate that an accessible fraction can be mobilized and excreted; the clinical significance of that removal requires independent evaluation.

Clinical observations provide supportive but still limited context. DTPA treatment has been associated with symptomatic improvement in earlier GDD cohorts, substantial recovery has been described in selected patients, and an eight-year expert-observer series has documented sustained near-complete recovery in a selected responder cohort.^{18,23,27} These reports are uncontrolled and do not establish a population response rate, causality, or comparative efficacy. Much clinical use of DTPA for GDD has developed outside university-based controlled trials; this may partly explain why clinical practice has outpaced the formal literature, but frequency of use is not evidence of efficacy.

Accordingly, the present evidence supports a mechanistic hypothesis rather than a settled clinical doctrine: if retained Gd contributes causally to disease, decorporation of a clinically meaningful accessible fraction could be beneficial. Conversely, clinical improvement cannot be assumed from urinary removal alone. Irreversible tissue injury, an inaccessible residual reservoir, self-sustaining inflammatory or neural pathways, placebo and expectation effects, concomitant treatments, and natural symptom fluctuation can all complicate interpretation. Prospective controlled studies with standardized outcomes and independent assessment remain necessary.

Re-equilibration, renal elimination, and repeated removal

Le Chatelier’s principle provides a useful qualitative analogy for repeated decorporation. If an accessible Gd species is transferred into Gd-DTPA and the product is promptly removed through the kidneys, depletion of that accessible compartment can permit additional Gd to move from less accessible reservoirs into exchangeable states.

At a compartmental level the sequence can be written as: less-accessible retained Gd $\leftrightarrow$ more-accessible Gd $\rightarrow$ Gd-DTPA $\rightarrow$ urine. The human body is an open, heterogeneous, nonequilibrium system, so this is not a quantitative pharmacokinetic equation. It is a conceptual description of why repeated removal of an accessible fraction can be followed by redistribution or re-equilibration from deeper stores.

The concept also helps separate a single-session urinary signal from cumulative decorporation. A large post-chelation increase documents access to a pool at that moment. Long-term treatment depends on how quickly other compartments re-supply the accessible pool, how much can be captured during subsequent sessions, and whether repeated treatment remains safe and tolerable.

DTPA safety, essential metals, and regulatory context

DTPA is not selective only for exogenous or toxic metals. Ca-DTPA can increase urinary loss of endogenous zinc and manganese and can transiently alter serum zinc, manganese, magnesium, and the activity of selected metal-dependent enzymes. In a controlled volunteer study, the reduction in serum zinc after Ca-DTPA recovered after subsequent Zn-DTPA in the combination protocol, and several other biochemical changes were transient.²⁸ These findings support acknowledging essential-metal effects while distinguishing transient biochemical perturbation from sustained clinically important depletion.

The Ca-DTPA followed by Zn-DTPA sequence used in published GDD treatment series is intended in part to address this issue.¹⁸ U.S. prescribing information for radionuclide contamination similarly recommends only a single initial Ca-DTPA dose and, when continued chelation is required, subsequent Zn-DTPA because repeated Ca-DTPA can deplete endogenous trace metals.²⁹ Thermodynamic preference for Gd(III) over many abundant endogenous divalent

cations reduces but does not abolish competition with native metals. With repeated treatment, dose, interval, nutritional status, renal function, and monitoring of relevant electrolytes and trace metals remain clinically important.

Ca-DTPA and its metal complexes are eliminated predominantly by glomerular filtration; impaired renal function may therefore slow clearance and warrants additional caution.²⁹ Use of DTPA for GDD is off-label: the FDA-approved indication for Ca-DTPA is decorporation of internal contamination with plutonium, americium, or curium.²⁹ Off-label status is a regulatory descriptor rather than evidence for or against efficacy, but it reinforces the need for informed consent, appropriate monitoring, and prospective controlled study of this indication.

Where gadolinium deposition disease enters the model

Retention is not synonymous with symptomatic disease. Individuals can retain Gd without developing the characteristic persistent symptom complex termed Gadolinium Deposition Disease (GDD); asymptomatic retention has been described as gadolinium storage condition.²⁴ Toxicologic and mechanistic literature describes several plausible pathways by which retained or transformed Gd could remain biologically active, including calcium interference, oxidative stress, immune signaling, and particle-associated effects, but causality for the clinical syndrome remains incompletely established.²⁶ The molecular substrate and host response therefore need to be separated conceptually.

Coordination chemistry defines what forms of Gd are present, how they transform, where they reside, whether water can approach them, and whether a therapeutic ligand can reach them. Immune, cellular, neural, and genetic factors help determine whether those retained forms produce symptoms in a particular host.

Studies performed during Ca-DTPA chelation have demonstrated both urinary Gd mobilization and temporally structured cytokine responses.^{19,25} These data do not establish a single immune pathway, but they are consistent with the idea that movement of a retained metal can be accompanied by measurable biological signaling. The characteristic post-chelation Flare described clinically is therefore relevant to host response, whereas the urinary Gd increase is evidence of metal movement; the two outcomes should not be conflated.

A unified molecular life cycle

The complete sequence can be expressed without changing chemical disciplines at each step: Gd(III) + pharmaceutical ligand → preformed GBCA → controlled water access and intact circulation → intact elimination or ligand exchange/dissociation → endogenous re-coordination → soluble complexes, protein association, phosphate-rich particles, or mixed phases → tissue persistence and further transformation → variable chelator access → new Gd-chelator complex → excretion.

Seen this way, GBCA engineering, gadolinium retention, salt formation, tissue microenvironments, and chelation are not separate chemical stories. They are successive states of the same metal as its coordination partners, compartment, accessibility, and biological purpose change.

Conclusions

Coordination chemistry supplies a continuous framework for the clinically relevant life cycle of gadolinium. A GBCA is a

deliberately engineered coordination complex whose success depends on permitting the right kind of access - particularly water access for relaxation - while resisting disruptive ligand exchange during distribution and elimination.

If the pharmaceutical coordination environment changes, Gd enters endogenous coordination chemistry rather than persisting as a chemically undefined free ion. Phosphate-containing species have the strongest direct evidence as a recurring inorganic environment for released Gd, with proteins, carbonate, other oxyanions, and mixed mineral-organic structures contributing additional possibilities.^{7–13}

Therapeutic chelation applies the same discipline in the opposite functional direction. The central challenge is not simply to identify the ligand capable of forming the most stable final complex, but to identify a chelator that can reach retained Gd, form the complex under physiological conditions, keep the captured metal soluble and bound during transport, and produce measurable decorporation. The recent four-chelator human comparison makes this distinction experimentally visible.¹⁶

Finally, if retained Gd contributes causally to symptoms, removal of an accessible fraction is mechanistically consistent with source-directed treatment. Current human data establish chemical accessibility and chelator-associated urinary elimination, but they do not by themselves establish the pathogenic source of the excreted Gd, the magnitude of total-body burden reduction, or clinical efficacy. Observational reports of improvement and sustained recovery support further study rather than definitive therapeutic conclusions.^{18,23,27} The most important remaining questions are therefore both chemical and clinical: which retained species are accessible, how accessibility changes with time and GBCA type, what molecular species appear in urine after chelation, how cumulative decorporation changes tissue burden, and whether controlled reductions in retained Gd produce reproducible clinical benefit.

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Conflicts of interest

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References

1. Caravan P, Ellison JJ, McMurry TJ, et al. Gadolinium(III) chelates as MRI contrast agents: structure, dynamics, and applications. *Chem Rev.* 1999;99(9):2293–2352.
2. Sherry AD, Caravan P, Lenkinski RE. A primer on gadolinium chemistry. *J Magn Reson Imaging.* 2009;30(6):1240–1248.

3. Cacheris WP, Quay SC, Rocklage SM. The relationship between thermodynamics and the toxicity of gadolinium complexes. *Magn Reson Imaging*. 1990;8(4):467–481.
4. Frenzel T, Lengersfeld P, Schirmer H, et al. Stability of gadolinium-based magnetic resonance imaging contrast agents in human serum at 37 degrees C. *Invest Radiol*. 2008;43(12):817–828.
5. Baranyai Z, Palinkas Z, Uggeri F, et al. Dissociation kinetics of open-chain and macrocyclic gadolinium(III)-aminopolycarboxylate complexes related to magnetic resonance imaging: catalytic effect of endogenous ligands. *Chem Eur J*. 2012;18(51):16426–16435.
6. Cabella C, Geninatti Crich S, Corpillo D, et al. Cellular labeling with Gd(III) chelates: only high thermodynamic stabilities prevent the cells acting as 'sponges' of Gd3+ ions. *Contrast Media Mol Imaging*. 2006;1(1):23–29.
7. Di Gregorio E, Gianolio E, Stefania R, et al. On the fate of MRI Gd-based contrast agents in cells: evidence for extensive degradation of linear complexes upon endosomal internalization. *Anal Chem*. 2013;85(12):5627–5631.
8. George SJ, Webb SM, Abraham JL, et al. Synchrotron X-ray analyses demonstrate phosphate-bound gadolinium in skin in nephrogenic systemic fibrosis. *Br J Dermatol*. 2010;163(5):1077–1081.
9. Sanyal S, Marckmann P, Scherer S, et al. Multiorgan gadolinium (Gd) deposition and fibrosis in a patient with nephrogenic systemic fibrosis—an autopsy-based review. *Nephrol Dial Transplant*. 2011;26(11):3616–3626.
10. DeAgüero J, Howard T, Kusewitt D, et al. The onset of rare earth metallosis begins with renal gadolinium-rich nanoparticles from magnetic resonance imaging contrast agent exposure. *Sci Rep*. 2023;13:2025.
11. Anderhalten L, Hofer N, Dymnikova D, et al. EPR-based assessment of gadolinium-based contrast agent retention and gadolinium transchelation in inflamed murine brain. *Invest Radiol*. 2026.
12. Semelka RC, Ramalho M. Gadolinium salt formation after dissociation of MR contrast agents: physiologic sequestration and tissue retention. *Int J Radiol Radiat Ther*. 2026;13(4):89–93.
13. Bleavins K, Perone P, Naik M, et al. Stimulation of fibroblast proliferation by insoluble gadolinium salts. *Biol Trace Elem Res*. 2012;145(2):257–267.
14. Baranyai Z, Tircso G, Rosch F. The use of the macrocyclic chelator DOTA in radiochemical separations. *Eur J Inorg Chem*. 2020;2020(1):36–56.
15. Chang CA, Liu YL, Chen CY, et al. Ligand preorganization in metal ion complexation: molecular mechanics/dynamics, kinetics, and laser-excited luminescence studies of trivalent lanthanide complex formation with macrocyclic ligands TETA and DOTA. *Inorg Chem*. 2001;40(14):3448–3455.
16. Semelka RC, Ramalho M. Selecting chelators for heavy metals: integrating coordination chemistry with *in vivo* decorporation (an intra-individual proof-of-concept study). *J Appl Biotechnol Bioeng*. 2026;13(4):117–121.
17. Boyken J, Frenzel T, Lohrke J, et al. Impact of treatment with chelating agents depends on the stability of administered GBCAs: a comparative study in rats. *Invest Radiol*. 2019;54(2):76–82.
18. Semelka RC, Ramalho M, Jay M, et al. Intravenous calcium-/zinc-diethylene triamine penta-acetic acid in patients with presumed gadolinium deposition disease: a preliminary report on 25 patients. *Invest Radiol*. 2018;53(6):373–379.
19. Maecker HT, Siebert JC, Rosenberg-Hasson Y, et al. Acute chelation therapy-associated changes in urine gadolinium, self-reported flare severity, and serum cytokines in gadolinium deposition disease. *Invest Radiol*. 2021;56(6):374–384.
20. Ramalho J, Ramalho M, Semelka RC. Gadolinium elimination in a gadolinium deposition disease population after a single exposure to gadolinium-based contrast agents. *Invest Radiol*. 2025;60(7):429–433.
21. Evans L, Rhodes A, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock 2021. *Crit Care Med*. 2021;49(11):e1063–e1143.
22. Rupert J, Honeycutt JD, Odom MR. Foreign bodies in the skin: evaluation and management. *Am Fam Physician*. 2020;101(12):740–747.
23. Semelka RC, Ramalho M. Effective cure with iv DTPA in gadolinium deposition disease sufferers: description of factors. *Int J Radiol Radiat Ther*. 2025;12(6):161–166.
24. Semelka RC, Ramalho M. Gadolinium deposition disease: current state of knowledge and expert opinion. *Invest Radiol*. 2023;58(8):523–529.
25. Maecker HT, Siebert JC, Rosenberg-Hasson Y, et al. Dynamic serial cytokine measurements during intravenous Ca-DTPA chelation in gadolinium deposition disease and gadolinium storage condition: a pilot study. *Invest Radiol*. 2022;57(2):71–76.
26. Domingo JL, Semelka RC. Gadolinium toxicity: mechanisms, clinical manifestations, and nanoparticle role. *Arch Toxicol*. 2025;99:3897–3916.
27. Semelka RC, Ramalho M. Eight-year expert-observer longitudinal case series of intravenous DTPA chelation for gadolinium deposition disease: from standardized protocols to patient-engaged care. *Int J Radiol Radiat Ther*. 2026;13(4):101–107.
28. Tominaga T, Shimomura S, Tanosaki S, et al. Effects of the chelating agent DTPA on naturally accumulating metals in the body. *Toxicol Lett*. 2021;350:283–291.
29. U.S. Food and Drug Administration. Pentetate calcium trisodium injection (Ca-DTPA): prescribing information. DailyMed. 2026.
30. American College of Medical Toxicology. ACMT recommends against use of post-chelator challenge urinary metal testing. *J Med Toxicol*. 2017;13(4):352–354.