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Gadolinium salt formation after dissociation of MR contrast agents: physiologic sequestration and tissue retention

Abstract

Gadolinium-based contrast agents (GBCAs) may undergo time-dependent dissociation according to their kinetic stability and the physicochemical conditions of the biological environment. Once gadolinium has separated from its original chelating ligand, it may bind to endogenous oxyanions, including phosphate, carbonate, and oxalate, as well as to proteins and other biological macromolecules. These retained forms are better conceptualized as mixed coordination networks, particles, or mineral-like aggregates than as simple one-to-one ionic salts. This review examines the available literature regarding the interaction of these oxyanions with gadolinium released from GBCAs. Particular emphasis is placed on the mechanistic distinction between sequestration of gadolinium after dissociation and destabilization or disruption of the intact GBCA complex. These processes are not equivalent: an oxyanion may bind and sequester gadolinium that has already become kinetically accessible without having caused the original GBCA to dissociate. Oxalate can participate in the downstream sequestration of released gadolinium; however, the available chemical evidence does not support the conclusion that physiologic oxalate concentrations initiate or materially accelerate disruption of intact GBCAs. Clear separation of these mechanisms is necessary for accurate interpretation of experimental observations and their physiologic relevance.

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Introduction

Gadolinium-based contrast agents (GBCAs) contain Gd3+ enclosed within an organic ligand intended to prevent the toxic metal ion from interacting directly with organic structures. If gadolinium dissociates from its original ligand, it does not remain as an unbound aqueous ion for a meaningful period. Its high positive charge density leads to rapid interactions with available proteins, macromolecules, and endogenous anions. Among the relevant inorganic anions are phosphate, carbonate, and oxalate, which may be described collectively as endogenous oxyanions.

The formation of poorly soluble metal–oxyanion species is not unique to gadolinium. It is a general physicochemical fate of several toxic metals, including lead. Conversion of a mobile metal ion into a poorly soluble phosphate, carbonate, oxalate, hydroxide, or mixed mineral-like species may limit its immediate movement through the circulation and its access to vulnerable cell elements.[1] This apparent protective effect has an important adverse consequence: poorly soluble metal species are difficult to remobilize and eliminate and may therefore remain within tissues for prolonged periods.

These retained forms are not necessarily pure, stoichiometrically defined salts. They may instead consist of mixed inorganic precipitates, mineral-like phases, nanoparticles, or protein-associated metal complexes and other macromolecules. Nevertheless, the central principle remains the same: conversion of a soluble or chemically accessible metal ion into a poorly soluble species limits mobility while favoring retention.

Importantly, the term metal salt in this setting should not be interpreted as a simple one-metal/one-anion ionic pair. In a solid or mineral-like deposit, a Gd3+ ion may be coordinated by oxygen donor atoms from several phosphate, carbonate, oxalate, hydroxide, or water ligands, and individual oxyanions may bridge more than one metal center. The resulting material is therefore better understood as a three-dimensional coordination lattice or coordination network containing multiple metal ions and multiple ligands. The individual metal–oxygen interactions have mixed ionic and covalent (coordinate) character. In biological tissue, additional proteins and other macromolecules may become incorporated into, adsorbed onto, or associated with these inorganic structures.

This distinction is fundamental. Endogenous oxyanions may scavenge gadolinium that has already dissociated from a GBCA, but their presence does not establish that they caused the original GBCA to dissociate.

Physiological oxyanion speciation

Phosphate, carbonate, and oxalate exist in physiological fluids primarily as ionized species. They are not present in substantial concentrations as fully protonated phosphoric acid, carbonic acid, or oxalic acid.

At physiological pH, phosphate is present principally as HPO_4^{2-} and $H_2PO_4^-$. Fully protonated phosphoric acid, H_3PO_4, is negligible. The physiological carbon dioxide–bicarbonate system consists predominantly of bicarbonate, HCO_3^-, together with dissolved carbon dioxide, a small quantity of carbonic acid, and a much smaller fraction of carbonate dianion, CO_3^{2-}.[2] Carbonic acid therefore exists physiologically, but not as a concentrated acid capable of reproducing strongly acidic laboratory conditions.

Oxalic acid is a diprotic acid with pK_a values of approximately 1.25 and 4.2–4.3.[3,4] At physiological pH 7.4, soluble oxalate is present almost entirely as the oxalate dianion, $C_2O_4^{2-}$. The calculated proportion present as fully protonated oxalic acid, $H_2C_2O_4$, is less than one part per billion of the total soluble oxalate. The terms oxalate and oxalic acid therefore do not describe equivalent chemical species under physiological conditions.

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These oxyanions are solvated components of biological electrolyte solutions. In extracellular fluid, sodium is the predominant cation, whereas potassium predominates intracellularly. Although phosphate, carbonate, and oxalate may originate from soluble sodium or potassium salts, they do not persist in solution as fixed molecular pairs in which each anion remains attached to a specific sodium or potassium ion. They exist as independently solvated ions within a complex electrolyte environment.

The relevant biological reaction is therefore the encounter between a chemically accessible multivalent metal ion and an available oxyanion, which can produce a poorly soluble metal-containing species.

Phosphate: best-supported inorganic Gd-binding environment

The available experimental and human evidence most consistently identifies phosphorus-containing species as an important inorganic environment for retained, dissociated gadolinium.

In human nephrogenic systemic fibrosis specimens, synchrotron-based analyses demonstrated gadolinium associated with phosphorus-containing and phosphate-like deposits.[5,6] Sanyal et al.[7] additionally demonstrated insoluble Gd–phosphate-containing deposits in multiple organs at autopsy, providing direct evidence that phosphate-associated gadolinium is not restricted to skin.

Electron microscopy and elemental analyses of human kidney specimens have also identified intracellular gadolinium-rich particles containing gadolinium, oxygen, and phosphorus. Comparable gadolinium-rich, phosphorus-containing particles were observed in the kidneys of GBCA-exposed experimental animals.[10] These findings support phosphate-mediated immobilization of dissociated gadolinium in both humans and animals. In complementary cellular work, Cabella et al.[8] found that components of the incubation medium mediated transfer of Gd3+ from a less-stable linear chelate, with phosphate anions having a dominant role in that process.8 Di Gregorio et al.[9] subsequently demonstrated extensive degradation of linear Gd chelates after endosomal internalization, providing a mechanistic pathway through which dissociated Gd3+ can become available for endogenous scavenging.

Phosphorus-containing gadolinium deposits have been demonstrated in vivo as nanoscale particles in kidney tissue.10 Such small particles or microaggregates have a high surface-area-to-volume ratio and, as a structural principle, would be expected to leave a larger fraction of their metal coordination environment exposed to an incoming chelator. Gadolinium oxalate, by contrast, is a poorly soluble precipitated coordination solid.14 Oxalate-containing particles can potentially grow or aggregate into larger mineral structures; where such macroaggregation occurs, a smaller fraction of Gd would remain surface-accessible and chelator access to metal sites buried within the lattice would be expected to decrease. Thus, aggregate size and mineral structure may materially influence the ability of a chelator to engage retained Gd. However, the available literature does not yet establish a universal in vivo rule that phosphate-bound Gd occurs only as microaggregates while oxalate-bound Gd occurs only as macroaggregates, nor has comparative chelator accessibility of these two retained forms been directly quantified.

Experimental studies also demonstrate that the retained chemical form strongly depends on the stability of the originally administered GBCA. Frenzel et al.[11] found that repeated exposure to linear GBCAs produced substantial water-insoluble gadolinium fractions in rat brain. In contrast, gadolinium retained after administration of macrocyclic agents remained predominantly in soluble fractions compatible with the intact contrast agent.

Boyken et al.[12] subsequently examined rats that had been previously administered either linear gadodiamide or macrocyclic gadobutrol. Ca-DTPA administered 7 weeks after GBCA exposure increased urinary gadolinium excretion approximately 10-fold after gadodiamide and reduced the corresponding brain gadolinium burden. In contrast, Ca-DTPA did not significantly increase gadolinium elimination after gadobutrol. The findings indicated that a dechelated and chelatable gadolinium pool was present after gadodiamide, whereas the gadolinium measured after gadobutrol was predominantly consistent with intact gadobutrol.

More recent EPR- and ENDOR-based experimental work distinguished complex-bound from released gadolinium after linear GBCA administration and detected phosphorus-containing molecules within the microenvironment of released Gd3+.[13] Complementary experiments supported an association between released gadolinium and inorganic ligands.

Summary of evidence for major oxyanion candidates

Table 1 summarizes the relative evidentiary support for phosphate, carbonate, and oxalate as endogenous binding environments for chemically accessible gadolinium. The categories distinguish direct human tissue observations from animal and in-vitro/cellular evidence.

GBCA dissociation / kinetic accessibility	→	**Endogenous scavenging of released Gd3+**	→	**Phosphate-containing binding / mineral phase***	→	**Reduced mobility / tissue retention**

Figure 1 Proposed sequence from GBCA dissociation to endogenous scavenging and tissue retention.

*Phosphate is shown as the best-supported inorganic pathway. Proteins/macromolecules, carbonate, hydroxide, oxalate, and mixed mineral phases may also participate in scavenging and retention.

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Table 1 Comparative evidence for phosphate, carbonate, and oxalate as gadolinium-binding species.

Candidate	Human evidence	Animal evidence	*In-vitro* / cellular evidence	Overall interpretation
Phosphate	Direct phosphate-associated Gd in NSF skin and multiorgan autopsy tissues.5-7	Gd/O/P-rich renal nanoparticles and phosphorus-containing microenvironments of released Gd.10,13	Phosphate was a dominant medium component mediating Gd3+ transfer from a less-stable chelate; endosomal degradation of linear chelates provides released Gd3+ for scavenging.8,9	Strongest and most repeated evidence; best-supported major inorganic scavenger.
Carbonate	No comparably consistent direct demonstration of Gd-carbonate as a dominant retained human tissue species.	Biologically plausible, but direct retained-tissue evidence is limited.	Coordination chemistry supports carbonate as a plausible ligand/precipitation partner for released Gd3+.17	Plausible secondary contributor; quantitative importance remains uncertain.
Oxalate	No evidence that Gd-oxalate is the predominant systemic retained species in human tissue.	No convincing evidence that oxalate is a dominant systemic retained form.	Concentrated oxalic acid precipitated Gd oxalate from Omniscan and Dotarem under nonphysiological concentrations and protonation conditions.14	Can bind chemically accessible Gd3+; systemic importance is uncertain and may be greatest in renal/urinary compartments.

Proposed Sequence of Gd Dissociation and Retention

1. A fraction of a sufficiently labile GBCA dissociates, degrades, or becomes kinetically accessible.
2. Endogenous ligands rapidly scavenge released Gd3+.
3. Phosphate-containing species represent the most repeatedly demonstrated inorganic environment for this dissociated gadolinium.
4. Formation of poorly soluble or tissue-associated species limits mobility but promotes persistence.

Phosphate should therefore be considered the best-supported major inorganic scavenger of released gadolinium. The evidence does not establish the exact proportion of retained gadolinium that exists as phosphate, nor does it rule out the presence of proteins, other macromolecules, hydroxide, carbonate, or mixed mineral phases.

Carbonate: plausible but less-established

Carbonate is frequently identified in the coordination-chemistry and GBCA literature as a chemically plausible binding or precipitation partner for released Gd3+.[17] Gadolinium carbonate is poorly soluble, and carbonate is present physiologically as a small component of the much larger bicarbonate buffering system.

However, the direct biological evidence for gadolinium carbonate is substantially less developed than the evidence for phosphorus-containing gadolinium species. Carbonate-containing retained gadolinium has not been demonstrated in human tissues with the same consistency as phosphate-associated gadolinium.

Carbonate should therefore be described as a plausible contributor to gadolinium speciation rather than as an established dominant retained form. It may contribute to mixed phosphate–carbonate deposits or other mineral-like phases, but its quantitative role in human or animal gadolinium retention is still unclear.

Oxalate: limited systemic role

Oxalate differs from phosphate and bicarbonate in its physiological distribution. Normal plasma oxalate concentrations are approximately 1–5 µmol/L, whereas urinary concentrations may be approximately 100-fold higher.[3] The kidney and urinary tract are therefore the compartments in which oxalate is most concentrated and most readily observed.

This distribution may explain why gadolinium–oxalate species could become prominent when urine or renal material is examined. A urine-centered investigation could consequently overestimate the systemic importance of oxalate relative to phosphorus-containing tissue deposits. Identification of gadolinium oxalate in urine would establish the chemical form being eliminated in that specimen. It would not establish that gadolinium oxalate is the predominant retained gadolinium species throughout the body.

Oxalate may potentially serve an eliminative function. If already dissociated gadolinium encounters oxalate within the renal or urinary compartment, formation and excretion of a gadolinium–oxalate species could contribute to reduction of the total body burden. This remains a reasonable hypothesis rather than an established major pathway for gadolinium elimination.

The existing evidence does not justify concluding that oxalate is the dominant systemically bound gadolinium-binding oxyanion. Its prominence in urine may primarily reflect renal concentration and elimination of oxalate rather than its relative abundance in tissues.

The important distinction is again between scavenging and dissociation. Oxalate can bind or precipitate Gd3+ that is already chemically available. This does not demonstrate that physiological oxalate can remove Gd3+ from an intact GBCA.

Oxalic acid experiments: physiological relevance

Henderson et al.[14] reported precipitation of gadolinium oxalate after exposing Omniscan and Dotarem directly to oxalic acid. The study demonstrated that gadolinium oxalate could be produced from these agents under the selected experimental conditions. However, those conditions differed profoundly from human physiology. The physiological interpretation of the observations was subsequently debated: Do et al.[18] pointed out the marked differences between the

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experimental conditions and physiological oxalate concentrations, protonation state, and pH. Wagner responded that bulk extracellular fluid may not be the most relevant biological environment and highlighted acidic intracellular compartments, particularly lysosomes, along with protein-mediated reactions, as potentially more favorable settings for GBCA destabilization.[19] These latter contentions are, at present, hypotheses, with no evidence that they are correct.

The experiments used GBCA concentrations of approximately 166.7 mmol/L and oxalic acid concentrations of approximately 250–333 mmol/L.14 Normal circulating oxalate is approximately 1–5 µmol/L.[3] The experimental oxalic acid concentration was therefore approximately 50,000 to more than 300,000 times the total oxalate concentration normally present in blood.

More importantly, the experimental reagent was concentrated oxalic acid, whereas physiological oxalate at pH 7.4 is almost entirely $C_2O_4^{2-}$, with essentially no fully protonated oxalic acid present. Wagner's response emphasizes biological compartmentalization. However, there is presently no evidence that clinically relevant concentrations of intact GBCA, oxalate, and protein coexist within lysosomes for sufficient periods to produce quantitatively meaningful dechelation in vivo.[19] Moreover, it is highly unlikely that an intracellular compartment could sustain a pH low enough, by itself, to destabilize highly kinetically inert macrocyclic agents without causing severe cellular injury or loss of viability. Any proposed intracellular mechanism would therefore need to involve more than acidity alone and should be demonstrated under biologically plausible conditions.

Requirements for In vivo extrapolation

1. Physiological pH of approximately 7.4.
2. Micromolar rather than molar oxalate concentrations.
3. Physiological ionic strength.
4. Competing phosphate, bicarbonate, proteins, and other endogenous ligands.
5. Tissue, extracellular, intracellular, and renal compartmentalization.
6. Blood flow, distribution, metabolism, and renal clearance.
7. The thermodynamic stability and kinetic inertness of the individual GBCA.

This distinction is particularly important for macrocyclic agents. Gadoterate meglumine has a reported thermodynamic stability constant of approximately log K 25.6 and a conditional stability constant at pH 7.4 of approximately log K 19.3.[15] Its reported dissociation half-life under the severe experimental condition of pH 1 at 25°C exceeds 338 hours.15 Studies performed in human serum at 37°C have demonstrated measurable gadolinium release from less-stable linear agents but no measurable release from macrocyclic agents during the experimental observation period.[16]

The pK_a of oxalic acid should not be interpreted as the lowest pH that a concentrated oxalic acid solution can achieve. Concentrated oxalic acid can produce a strongly acidic solution. Nevertheless, such a solution has no equivalent within circulating blood or extracellular tissues.

Accordingly, the ability of concentrated oxalic acid to force a reaction with Dotarem in a laboratory vessel does not establish that physiological oxalate can degrade Dotarem within the human body. Endogenous oxalate may scavenge Gd3+ if dissociation has already occurred, but it lacks the concentration, proton activity, and exposure conditions required to reproduce the reported in vitro reaction.

Clinical implications

The distinction between oxalic acid and physiological oxalate has practical clinical importance. Oxalate-containing foods include many fruits, vegetables, nuts, grains, and other nutritionally valuable foods. Dietary oxalate restriction is appropriate for selected patients with defined disorders such as primary or secondary hyperoxaluria or recurrent calcium oxalate nephrolithiasis.

There is presently no clinical evidence that consumption of oxalate-containing foods causes dissociation of an intravenously administered GBCA. No evidence restricting dietary oxalate improves gadolinium elimination, prevents gadolinium retention, or reduces symptoms attributed to gadolinium exposure.

A recommendation that GBCA-exposed patients broadly restrict oxalate-containing foods would therefore extend the findings of a concentrated in vitro experiment beyond the conditions that were actually studied. Such a recommendation could impose unnecessary dietary restrictions and reduce consumption of otherwise nutritious foods without a demonstrated chemical or clinical benefit.

Evidence needed before dietary oxalate restriction

1. Dietary oxalate meaningfully changes systemic oxalate concentrations.
2. This change increases GBCA dissociation under physiological conditions.
3. The effect occurs at clinically encountered GBCA and oxalate concentrations.
4. Dietary restriction improves an objective clinical or toxicological outcome.

No such evidence currently exists.

Current guidance in the 2026 ACR Manual on Contrast Media addresses GBCA selection, adverse reactions, and nephrogenic systemic fibrosis risk but does not recommend dietary oxalate restriction before or after GBCA exposure.20 This is consistent with the current absence of evidence that dietary oxalate materially destabilizes GBCAs in vivo.

The same general principle applies to acidic foods and beverages. Gastrointestinal acidity does not reproduce systemic acidity, and ingestion of an acidic beverage does not reduce blood or extracellular-fluid pH to the pH of that beverage. An intravenously administered GBCA remains within a tightly buffered physiological environment that is anatomically separate from the gastrointestinal lumen.

Conclusion

The formation of poorly soluble metal–oxyanion species is an important physiological and physicochemical mechanism for limiting the mobility of dissociated toxic metals. For gadolinium released from an MR contrast agent, the available human and animal evidence most consistently supports phosphorus-containing species as the principal demonstrated inorganic binding environment. This conclusion is strengthened by direct multiorgan human Gd–phosphate observations, cellular evidence identifying phosphate as a dominant mediator of Gd3+ transfer from a less-stable chelate, and endosomal degradation

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studies demonstrating a pathway for release of Gd3+ from linear complexes.[7-9]

This sequestration may limit immediate redistribution of released Gd3+ but has the undesirable consequence of facilitating long-term tissue retention.

Carbonate is chemically capable of playing a role in gadolinium speciation, but its role in retained biological gadolinium is less directly demonstrated and has not been quantitatively established. It should therefore be considered a plausible secondary contributor rather than a proven dominant retained species.

Oxalate appears to be a quantitatively minor systemic component, with greatest relevance in the kidney and urine. Its renal distribution may permit binding and urinary elimination of chemically available gadolinium, but this possibility should not be confused with degradation of the original GBCA.

The demonstration that concentrated oxalic acid can produce gadolinium oxalate from a GBCA in vitro does not establish that physiological oxalate initiates GBCA dissociation in humans. At physiological pH, fully protonated oxalic acid is essentially absent; circulating oxalate concentrations are micromolar; and macrocyclic GBCAs possess marked thermodynamic stability and kinetic inertness.

Endogenous phosphate, carbonate, and oxalate should therefore be viewed principally as potential scavengers of already dissociated gadolinium rather than as demonstrated causes of GBCA degradation. There is no scientific or clinical basis for advising patients to restrict oxalate-containing foods to prevent breakdown of MR contrast agents, particularly the most thermodynamically stable and kinetically inert macrocyclic agents.

Conflicts of interest

Richard C. Semelka, MD, and Miguel Ramalho, MD, are nonpaid board members of GadTTRAC. The authors declare that this affiliation does not constitute a conflict of interest.

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