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Peer Review

Review of: "Gadolinium Toxicity: Mechanisms, Clinical Manifestations, and Nanoparticle Role"

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Comment on “Gadolinium Toxicity: Mechanisms, Clinical Manifestations, and Nanoparticle Role”

Dear Editor,

We read the recent review article “Gadolinium Toxicity: Mechanisms, Clinical Manifestations, and Nanoparticle Role” with interest and acknowledge the author's effort to provide an overview of the literature on gadolinium-based contrast agent (GBCA) safety topics and offer some interpretation.

We would like to comment on some aspects and interpretation of the available literature by offering additional and in part contradicting aspects and thoughts. These are meant to add clarity and to help prevent readers from misunderstandings or premature conclusions on aspects that are emerging hypotheses or reflect artificial test conditions without apparent clinical relevance.

1. Use of misleading clinical terminology

The article repeatedly references “Gadolinium Deposition Disease” (GDD), a term that remains scientifically controversial and unvalidated, and its use in some literature does not mean acceptance. Neither has a specific disease entity been defined by accepted criteria, nor has there been any causal link between retained gadolinium and clinical symptoms in patients with normal renal function established as suggested by this term. This position aligns with statements from the U.S. Food and Drug Administration (FDA) [1]. To better reflect current understanding, the American College of Radiology has proposed the term “Symptoms Associated with Gadolinium Exposure (SAGE)” [2]. This terminology captures all symptoms that have been reported following the administration of GBCAs and identifies certain subgroups based on a holistic view of available evidence. The term avoids, however, premature conclusions on causality while acknowledging that a small subset of patients have reported symptoms.

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Importantly, SAGE has been meanwhile used in recent observational studies comparing different GBCAs [3,4], which were not cited in the review but would have strengthened its clinical relevance and balance.

2. Hypothesis of nanoparticle formation as the primary cause of instability

The review suggests that the formation of gadolinium-containing nanoparticles is a key mechanism driving GBCA instability. This interpretation reverses the direction of causality. Gd^{3+} ions must first dissociate from the GBCA complex before binding instantly to other molecular structures, including the formation of insoluble species such as phosphates or oxalates. Nanoparticle formation is a consequence, not a cause, of de-chelation. The statement that "nanoparticle formation... may represent a parallel mechanism—even for macrocyclic agents" risks undermining the well-established concept of kinetic inertness as the defining feature of macrocyclic GBCAs. Even if some dissociation occurs over time, the rate is minute and orders of magnitude lower than for linear agents due to their structural rigidity and very slow ligand exchange kinetics.

3. Use and far-reaching conclusions of in-vitro experiments under highly artificial conditions

The review references recent experiments (e.g., Henderson et al. [5]) that demonstrate gadolinium precipitation when GBCAs are mixed with large amounts of oxalic acid at pH values between 1 and 2. While technically valid, such experiments are performed under highly artificial, non-physiological conditions. Physiological plasma pH values are tightly regulated near 7.4, and endogenous oxalate levels are significantly lower than those artificially high oxalate concentrations as they were described and used in these in-vitro assays. The precipitation of gadolinium oxalate in a strong acid milieu is chemically expected and not clinically meaningful unless validated under physiological settings. Presenting this mechanism as a plausible in vivo pathway without highlighting that these data are obtained under conditions that, based on today's knowledge, cannot be reached in vivo is misleading.

4. Inaccurate statements on thermodynamic stability

The review states that macrocyclic GBCAs "generally have higher thermodynamic stability than linear ones." This is not universally correct. Thermodynamic stability constants depend on specific ligand design. For instance, Gd-DTPA (linear) has a log $K \approx 22$, while Gadobutrol (macrocyclic) has log $K \approx 20$. These values show that thermodynamic stability does not necessarily (closely) correlate with the structural class. The real critical difference between linear and macrocyclic GBCAs lies in their kinetic inertness, where macrocyclic agents exhibit greater resistance to de-chelation due to their constrained geometry. Confusing these two stability concepts may lead to wrong conclusions, mislead readers, and oversimplify a central tenet of GBCA chemistry.

General remarks

While the author provides an extensive literature overview, the review would benefit from clearer distinctions between hypotheses and established findings, particularly regarding speculative mechanisms like Gd-related nanoparticles and oxalate interactions. Furthermore, omitting important studies on SAGE and pharmacovigilance limits the clinical applicability of the discussion. Lastly, chelation therapy is mentioned only briefly without adequate critical appraisal, despite limited clinical evidence supporting its necessity or efficacy in patients with retained gadolinium.

Gadolinium safety remains an evolving research area. We encourage future reviews to integrate physiologically relevant data, apply clear distinctions between mechanisms and associations, and include a broader range of high-quality peer-reviewed studies. This will strengthen scientific discourse and help patients, clinicians, and researchers navigate this complex issue more accurately.

Sincerely,

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Declarations

Potential competing interests: No potential competing interests to declare.