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CONTROVERSIAL ISSUES REGARDING THE USE OF GADOLINUM-BASED CONTRAST AGENTS – THE LATEST REPORTS

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ABSTRACT

Introduction and objective: Gadolinium-based contrast agents (GBCAs) are paramagnetic substances that have been used over the past 30 years in MRI diagnostics, and have significantly improved imaging and diagnostic capabilities for many diseases. Although they are used in small amounts in individual patients, their use worldwide involves the consumption of many thousands of liters of GBCAs per year and is growing. With such widespread demand for contrast-enhanced MRI, there is a need for these agents to be as safe as possible.
Review methods: A comprehensive literature review was conducted, analyzing 33 studies from the PubMed and Google Scholar database (English-language, published within the last 8 years).
Brief description of the state of knowledge: In recent years, much attention has been paid to the fact of gadolinium deposition in tissues and accumulation in the environment, the risk of nephrogenic systemic fibrosis (NSF), and safety issues in use in pregnant patients and the pediatric population. The risk of the above-mentioned events has been shown to vary depending on the type of GBCA, with macrocyclic GBCAs having a lower risk than linear GBCAs. Despite a great number of studies, many issues regarding the clinical significance of the side effects of GBCAs still remain unclear and controversial. Therefore, even more stable and better-performing GBCAs, new MRI approaches requiring lower doses of GBCAs, and alternative contrast agents need to be developed to ensure patient welfare.
Summary: In this review, we will try to present the current state of knowledge on the above-mentioned issues with a perspective of the future of this branch of medicine.

KEYWORDS

Magnetic Resonance Imaging, Gadolinium, Gadolinium-Based Contrast Agents, Contrast Agents, Nephrogenic Systemic Fibrosis, Deposition, Pregnancy

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Introduction

Gadolinum-based contrast agents (GBCAs) are compounds of paramagnetic gadolinium (III) and various types of organic chelators that have found widespread use in magnetic resonance diagnostics. Since their approval by the Food and Drug Administration (FDA) in the 1980s, they have revolutionized the diagnostic capabilities of many diseases (such as neurological, metabolic, inflammatory and orthopedic disorders, cancer and cardiovascular diseases) by enabling detailed visualization of tissues and organs [1].

Their use has generally been considered safe, but over time it has become clear that they are not completely inert to human health and the environment [2].

In this review, we provide the latest information on challenges in the use of GBCAs such as tissue deposition, accumulation in the environment, the incidence of nephrogenic systemic fibrosis (NSF), the use of GBCAs in patients with chronic kidney disease (CKD) and during pregnancy or lactation. In addition, we discuss potential future directions for this branch of diagnostic imaging.

Materials and Methods

The review was based on the analysis of materials collected in "PubMed" and Google Scholar. The following keywords were entered in the search for scientific articles: „magnetic resonance imaging", „gadolinium", „gadolinium-based contrast agents"; „contrast agents", „nephrogenic systemic fibrosis", „deposition", „pregnancy". A total of 33 articles published between 2017 and 2025 were considered for research and verified for their relevance to the topic.

Results and Discussion

GBCAs classification

Gadolinium-based contrast agents can be classified according to the architectural structure of organic chelating ligands into: macrocyclic, which have a rigid, caged structure, are more stable and have a much lower dissociation rate, and linear, characterized by an open chain structure and weaker binding to Gd (III) [3]. Another division is based on charge and divides GBCAs into ionic, like acidic GBCAs, or non-ionic, like chelating agents with amide or alcohol groups [4]. (Table 1)

The optimal GBCA for use in clinical practice should have high stability, as rapid dissociation leads to higher circulating levels and increased tissue uptake of free Gd (III), which can be associated with long-term disorders in many organs.

Other desirable features include i) high water solubility, ii) rapid biodistribution and excretion, iii) good contrast performance at low doses, and iv) a good biosafety profile [5].

Table 1. GBCAs classification

	IONIC	NON-IONIC
LINEAR	Gadobenate dimeglumine (MultiHance®) Gadoxetic acid (Eovist® Primovist®) Gadopentetate dimeglumine (Magnevist®) Gadofosveset trisodium (Ablavar® Vasovist®)	Gadodiamide (Omniscan®) Gadoversetamide (Optimark®)
MACROCYCLIC	Gadoteric acid (Dotarem® Clariscan®)	Gadoteridol (ProHance®) Gadobutrol (Gadavist®, Gadovist®) Gadopiclenol (Vueway® Elucirem®)

GBCA and patients with NSF or CKD

NSF is a rare disease that was first described in 1997 and mainly affects patients with renal failure, as a result of slower excretion of GBCA due to impaired filtration mechanisms. It is characterized by thickening of the skin and subcutaneous tissue, as well as systemic symptoms. The process of sclerotization can also involve skeletal muscles and any fibrous tissues in the body, including internal organs such as the liver, heart and lungs. The severity of symptoms varies from mild to lethal forms [6]. Other factors predisposing to the development of NSF have been metabolic acidosis, ongoing inflammation, erythropoietin treatment and high serum calcium and phosphorus levels [7].

The risk of NSF is mainly associated with the use of a group of linear GBCAs. Studies have confirmed that the use of Group II GBCAs (Table 2) is associated with a very low rate of NSF occurrence, and this risk is estimated to be less than 0.07% in patients with stage 4 or 5 chronic kidney disease [8]. As a result, it is now recommended that Group II GBCAs not be withheld from patients with CKD when there is a compelling indication to use these agents for medical reasons for diagnosis. In addition, when a Group II GBCA is used in a clinically indicated trial, it is not necessary to measure eGFR [9]. The use of class III GBCAs (gadoxetic acid), for liver and biliary imaging studies, has also been associated with only minimal risk of NSF [10].

In stage 1, 2 or 3 CKD, no special precautions are usually necessary for patients [11].

To date, the effectiveness of prophylactic low-dose GBCA (lower than recommended for diagnostic purposes) in avoiding NSF has not been confirmed [12], and no known prophylaxis is available to reduce the risk of NSF [3].

Table 2. GBCA groups according to the risk of NSF [13]

GROUP I	GROUP II	GROUP III
Gadodiamide Gadopentetate dimeglumine Gadoversetamide	Gadobenate dimeglumine Gadoteridol Gadoterate meglumine Gadobutrol	Gadoxetate disodium

Group I - Agents associated with the greatest number of NSF cases

Group II - Agents associated with few, if any, unfounded cases of NSF

Group III - Agents with limited data regarding NSF risk, but for which few unfounded cases have been reported

GBCA and pregnant or breastfeeding patients

To date, no significant association has been shown between perinatal gadolinium exposure and the occurrence of serious mutagenic or teratogenic effects in all three trimesters of pregnancy [14,15]. However, we do not have sufficient prospective and longitudinal studies. Some studies indicate a potentially increased risk of stillbirth or neonatal death and differences in risk depending on the type of GBCA used [16,17], but these have important limitations such as small study trials and potential confounding factors.

Until conclusive evidence is available, management should be based first on consideration of the use of alternative imaging modalities, such as ultrasound or MRI without contrast, and in critical cases, with the benefit outweighing the risks on the possible administration of Group II GBCAs.

Breastfeeding cessation after GBCA administration is not required because less than 1% of a 0.04% intravenous dose of GBCA permeates into breast milk, so the likelihood of a negative effect on the newborn after absorbing such a small amount of GBCA is low [18].

GBCA and tissue deposition

In recent years, a growing number of in vivo and ex vivo studies have provided evidence of gadolinium accumulation in various tissues (such as liver, bone and skin [19]) after repeated administration of GBCA, even with normal renal function. Of most concern is the accumulation of gadolinium in brain tissues. Areas where GBCA accumulates include the globus pallidus, dentate nuclei, caudate nucleus, shell, posterior thalamus, black matter, red nucleus, superior and inferior thalamus, and superior cerebellar peduncle. [20] The risk is greater for linear compounds than for macrocyclics, and increases with the number of doses administered [21]; it occurs even in the absence of blood-brain barrier dysfunction [22]. Similar results have been obtained in the pediatric population [23].

However, the clinical significance of gadolinium accumulation in the brain remains unknown and controversial. The acute toxic effects of non-chelated Gd3+ have been demonstrated in animal models, but in the human population there has been no histopathological evidence of neuronal or neural interstitial damage or any other adverse clinical entity associated with GBCA retention in the brain [24].

GBCA and accumulation in environment

Since the first approval of GBCA (Gd(III)-DTPA) in 1988 until 2009, approximately 100 million applications have been performed worldwide, using 22-66 tons of Gd(III) as a contrast agent annually [5]. As much as a doubling of annual anthropogenic gadolinium has been observed over the past 15 years [25]. GBCAs enter the environment, mainly as liquids, through disposal of unused product or elimination after intravenous administration [26]. The relative persistence and mobility, as well as the high dosage of GBCAs, make them recorded in a wide range of environmental matrices [27]. The unequivocal environmental impact of one particular agent under conditions of multiple variables affecting biological systems in real-world contexts is difficult to assess, but there are already in vitro experiments showing that in biological models such as plants [28] or bivalves [29] biomarkers of metabolic capacity and oxidative stress are influenced by gadolinium accumulation, and in the freshwater parasitoid Hydra vulgaris, gadolinium exposure has even shown teratogenic effects [30].

Strategies to reduce GBCAs in the environment should be based on i) replacing (if possible) GBCAs with other CAs for MRI (e.g., Mn- or Fe-based CAs or diaCEST agents), ii) reducing the dose of GBCAs (with improved sequencing/analysis of MRI data or improved relaxivity), iii) recovering Gd(III) from the environment and recycling it in the context of a closed-loop economy and environmental sustainability. [5],[27]

Future development directions

Development of future gadolinium-based contrast agents should focus on increasing their stability and relaxivity. One promising molecule is gadopiclenol [31], recently approved by the Food and Drug Administration and the European Medicines Evaluation Agency. There are also studies underway to develop other macrocyclic agents with high relaxivity, notably gadoquatrane and gadoPlus [32], but their approval by regulatory authorities is expected within a few years.

Another proposal is to replace Gd(III)-based MRI contrast agents with alternative contrast agents (CA). Metal-free MR contrast agents are promising, but they are likely to take a long time to develop. To date, five major classes of CA MRI without Gd(III) can be considered in the future (see Figure 1) [5] [33].

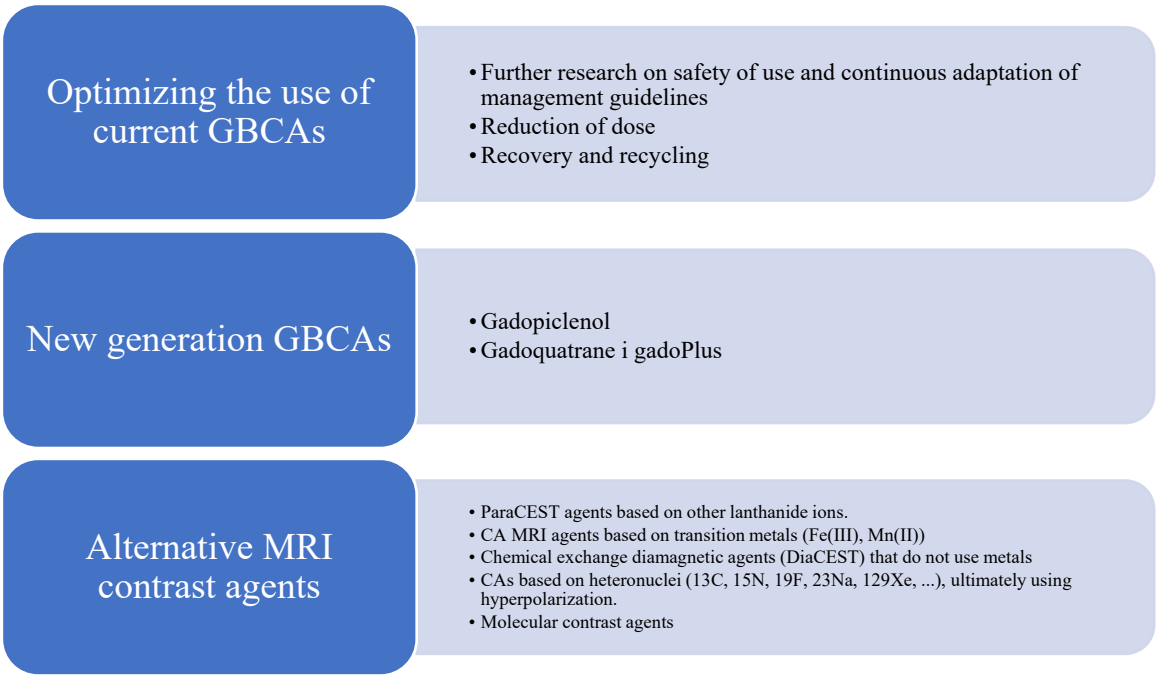

Fig. 1. *Key development directions*

Conclusions

GBCAs play an important role in MR diagnostics, enabling better visualization and diagnosis of various diseases. Despite their many advantages, over time they have been found to exhibit some side effects, but the significance of this phenomenon has not yet been fully investigated. Currently, the medical community faces numerous questions regarding the long-term safety of these contrast agents. In conclusion, this review underscores the importance of conducting further large sample studies to obtain clearer answers to these questions, aiming to optimize the administration of GBCAs and develop other contrast agents in parallel.

Author's contribution:
-Research koncept and design: Alicja Bury, Natalia Kraciuk
-Collection and/or assembly of data: Kacper Jankowski, Jan Kamiński
-Data analysis and interpretation: Anna Daniel, Jan Kamiński
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-Critical revision of the article: Karol Bartecki
-Final approval of the article: Małgorzata Piekarska-Kasperska, Radosław Kasperski

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