

Original Article

Gadolinium-based contrast agents and nephrogenic systemic fibrosis: a systematic review and meta-analysis

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Abstract

Background. In the past decade, more than 200 cases of nephrogenic systemic fibrosis (NSF) have been identified, primarily among patients with advanced kidney disease. Multiple studies have suggested an association between gadolinium-based contrast agents (GBCAs) and NSF. We performed a systematic review and meta-analysis to examine this potential association.

Methods. A systematic review of studies examining the association between any GBCA and NSF was performed. A search for controlled studies was conducted in MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials. If controlled data for a GBCA was not available, we searched for case reports and series. Relevant data were extracted and meta-analyses were performed.

Results. Seven of 144 identified studies met inclusion criteria; gadodiamide was the sole or predominant GBCA in four of these; one study exclusively examined gadopentetate. Other GBCAs were not specifically examined in controlled or uncontrolled studies. Meta-analysis of controlled trials demonstrated a significant association between GBCA exposure and NSF [odds ratio (OR) 26.7; 95% confidence interval (CI) 10.3–69.4] and gadodiamide and NSF (OR 20.0; 95% CI 3.7–107.8). Examination of the evidence using established criteria suggested that this association was causal.

Conclusions. The current state of evidence suggests an association and potentially causal link between the use of GBCAs and the development of NSF among patients with advanced kidney disease. Additional study is warranted to clarify the potential association of GBCAs other than gadodiamide with NSF.

Keywords: chronic kidney disease; gadolinium; meta-analysis; nephrogenic systemic fibrosis; systematic review

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Introduction

Nephrogenic systemic fibrosis (NSF), originally called nephrogenic fibrosing dermopathy (NFD), is a scleroderma like condition that primarily involves the skin but may also affect organs such as the liver, lung, heart and muscle and can lead to immobility [1,2]. More than 200 cases of NSF have been identified in the last decade, almost exclusively among patients with advanced kidney disease [3]. No consistently effective treatments are currently available, and prevention may be the best approach [4].

NSF is considered to be a systemic disease that involves aberrant recruitment, activation and proliferation of fibrocytes [5,6]. Grobner was the first to propose that gadolinium-based contrast agents (GBCAs) might cause NSF [7]. Subsequently, a number of studies have supported this association [8–22]. The mechanism by which this occurs is not well understood. It is speculated that a reduction in renal clearance of gadolinium increases its biological half-life and dissociation into an ionic state. This may then lead to increased tissue exposure to gadolinium, resulting in an inflammatory reaction and fibrosis [23–25]. It is unclear how the dissociated form triggers NSF [26], but its accessibility to tissues may be facilitated by vascular trauma and endothelial dysfunction [23]. Iron, zinc, copper, calcium and erythropoietin have also been associated with NSF when used concurrently with gadolinium [25], and there are reports that immunosuppressive agents in the setting of solid organ transplantation may also be associated [26].

Currently, five GBCAs have been approved by the US Food and Drug Administration (FDA) for use in magnetic resonance imaging: gadodiamide (Omniscan, GE Healthcare, Princeton, NJ, USA), gadopentetate dimeglumine (Magnevist, Berlex Imaging, Montville, NJ, USA), gadoversetamide (OptiMARK, Mallinckrodt, St. Louis, MO, USA), gadoteridol (ProHance, Bracco Diagnostics, Princeton, NJ, USA) and gadobenate dimeglumine (MultiHance, Bracco Diagnostics). With the rapid growth of diagnostic imaging, the use of GBCAs in advanced kidney disease has increased in the last decade [27]. According

to the FDA, NSF has been reported with all the GBCAs, although gadodiamide is the GBCA most commonly reported through their MedWatch program [28]. This has led some to suggest that gadodiamide compared with the other GBCAs presents a greater risk of NSF, while others explain that gadodiamide's large market share is responsible for the frequency of reports.

In this paper, we perform a systematic review and meta-analysis to (1) examine the association of GBCAs and NSF and precisely estimate the risk of NSF with the GBCAs currently approved for use, (2) use established criteria to assess whether causality may be inferred and (3) examine whether differences in NSF risk exist among the GBCAs currently approved.

Methods

Study selection

We searched MEDLINE (1950 to April 2008), EMBASE (1980 to April 2008) and the Cochrane Central Register of Controlled Trials (inception to April 2008) using keywords and/or medical subject headings (MeSH) for the GBCAs, NSF and NFD. The detailed search strategy can be found in the Appendix. We screened the titles and abstracts of references identified in our search, and those meeting our inclusion criteria were retrieved for full-text review. To be included, a study had to be a controlled trial examining the association between gadolinium and NSF. For those GBCAs not examined in controlled studies, we evaluated case series and case reports. We excluded articles that were not published in English.

Data extraction

The outcome of interest was the development of NSF/NFD as reported by the studies. We also extracted data on the study design, patient population, the specific contrast agent(s) used, the size of the study sample, the outcome measure and whether the study adjusted for potential confounders. Furthermore, we examined whether the studies reported a temporal sequence or a dose-response relationship between the administration of GBCAs and the development of NSF.

Statistical analysis

We performed meta-analysis of the included controlled studies using the Mantel-Haenszel procedure that assumes a fixed effect size [29]. We performed a meta-analysis for all studies of GBCAs, as well as those examining the association of gadodiamide with NSF, since it was the GBCA most commonly examined. We measured heterogeneity using both the Q and I^2 statistics. A non-significant P -value (≥ 0.10) based on the Q statistic and a low I^2 ($\leq 50\%$) would suggest that the differences in findings between studies could be ascribed to chance alone [30,31]. We also examined the influence of individual studies on the results of our meta-analyses using exclusion sensitivity plots, which

display the pooled values after excluding each study, one at a time.

If studies with positive results were more likely to be published than negative studies, a systematic review of only the published literature would lead to a bias in favor of the positive results. We explored publication bias using funnel plots, which graph the effect size versus the observed variance for each individual study. The symmetric distribution of studies in an inverse funnel shape suggests the absence of publication bias. To provide a quantitative estimate of publication bias, we used the Begg (rank correlation) and Egger (weighted regression) methods [32,33].

Meta-analyses were performed and funnel plots were obtained using RevMan version 4.2 (The Cochrane Collaboration, Oxford, UK). Publication bias was quantified using STATA version 9.0 (Stata Corporation, College Station, TX, USA). We used MIX version 1.61 [34] to generate the exclusion sensitivity plots.

Assessment of causality

We used established criteria to make judgments about causation from statistical associations [35]. This approach considers nine factors when judging whether an observed association was a causal relationship. We used data from the included studies to make assessments about all of the factors except 'biological plausibility', 'coherence' and 'analogy'. For these factors, we relied on additional sources of data [15,23,25,36,37].

Results

Study flow and characteristics

Our literature search yielded 144 references (Figure 1). Of these, 23 full-text articles were retrieved and 7 studies [8–

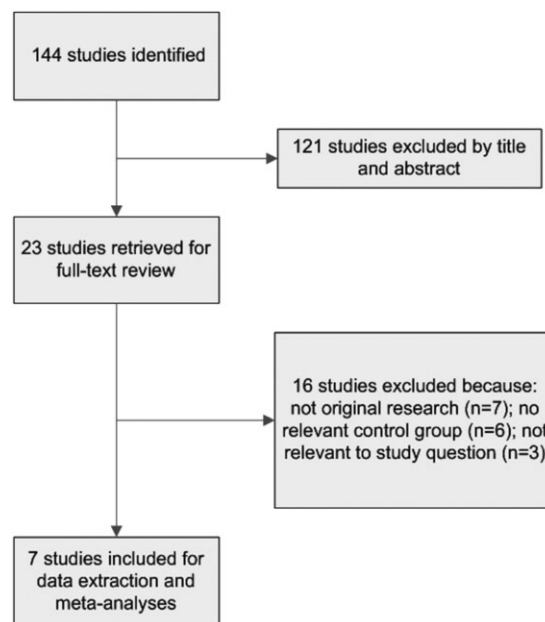


Fig. 1. Flow diagram for identification and selection of studies.

Table 1. Characteristics of included studies

Author (year)	Study design	Adjustment for potential confounders	Study duration	Population	N	GBCA ^a	NSF ^a assessment
Broome (2007) [8]	Retrospective cohort study	No	>6 years	Patients undergoing dialysis	238	Gadodiamide (Omniscan)	Clinical examination, skin biopsy, laboratory data
CDC (2007) [9]	Case-control study	Yes	>6 years	Patients undergoing dialysis	76	Not specified	Clinical examination, skin biopsy
Collidge (2007) [10]	Retrospective cohort study	No	>6 years	Patients undergoing dialysis	1826	Multiple ^b	Clinical examination, skin biopsy, laboratory data
Deo (2007) [11]	Retrospective cohort study	No	18 months	Patients undergoing dialysis	467	Unspecified ^c	Clinical examination, skin biopsy
Marekman (2006) [12]	Retrospective cohort study	No	10 months	Patients with end-stage renal disease	800 ^d	Gadodiamide (Omniscan)	Clinical examination, skin biopsy
Othersen (2007) [13]	Retrospective cohort study	No	6 years	Patients undergoing dialysis	849	Gadodiamide (Omniscan)	Clinical examination, skin biopsy
Todd (2007) [14]	Prospective cohort study	No	2 years	Patients undergoing dialysis	90 ^e	Gadopentetate (Magnevist)	Clinical examination

^aGBCA, gadolinium-based contrast agent; NSF, nephrogenic systemic fibrosis.

^b88.6% MR exams were performed using gadodiamide.

^cThe cases were after exposure to gadodiamide and gadopentetate.

^dThe number of unexposed patients was given as a range from 430 to 630. The lower number was used for the odds ratio calculation in order to obtain a conservative estimate.

^eOnly a subgroup of the entire population that had data on gadolinium exposure.

14] met our inclusion criteria.

Study characteristics are shown in Table 1. No randomized controlled trials were identified. The seven studies identified included a total of 4 276 patients. All study participants had advanced chronic kidney disease (CKD). Study duration ranged from 10 months to >6 years. Gadodiamide was the sole or predominant GBCA examined in four studies [8,10,12,13]; one study examined gadopentetate [14]. We did not find any published controlled or uncontrolled reports of the association of the other GBCAs with NSF. All studies used a combination of clinical examination and skin biopsy to arrive at the diagnosis of NSF with the exception of one study [14] that used a clinical scoring system. The quality of the evidence base was generally poor with only one study [9] identifying and adjusting for confounders.

Association of GBCAs and NSF

Six of the seven studies demonstrated a significant association between GBCA exposure and NSF. Meta-analysis of these studies demonstrated a significant increase in the risk of NSF [odds ratio (OR) 26.71; 95% confidence interval (CI) 10.27–69.44] (Figure 2). There was no significant heterogeneity among studies (Q statistic = 1.44, P = 0.96; I^2 = 0%).

A meta-analysis of those studies exclusively examining gadodiamide also showed a significant increase in the risk of NSF (OR 20.04; 95% CI 3.72–107.78) (Figure 3). Again, there was no significant heterogeneity among studies (Q statistic = 0.27, P = 0.87; I^2 = 0%).

For both meta-analyses, there was no evidence of publication bias on visual inspection of the funnel plots (Figure 4). This was confirmed upon quantitative assessment using the methods of Begg (P = 0.76 and 1.00 for meta-analyses of all GBCAs and gadodiamide, respectively) and Egger (P = 0.46 and 0.96 for meta-analyses of all GBCAs and gadodiamide, respectively). In addition, it can be seen from the exclusion sensitivity plots that the pooled values after exclusion of each individual study were all similar to the overall estimate. Thus, no single study seemed to disproportionately influence the results of the meta-analyses (Figure 5)

One study was identified in which gadopentetate dimeglumine was the sole GBCA. This demonstrated a significant association with NSF (OR 14.74; 95% CI 1.86–117.00) [14]. We were unable to identify any controlled or uncontrolled reports studying the relationship of the other GBCAs to NSF.

Do GBCAs cause NSF?

Hill's criteria [35] were applied to assess whether a causal link exists between gadodiamide and other GBCAs, and the development of NSF/NFD (Table 2). For GBCAs in general and gadodiamide in particular, there was a *strong* and *consistent* association between exposure and the development of NSF. A clear *temporal sequence* was reported in six studies of GBCAs, including all three studies of gadodiamide. Among five studies examining a *dose-response relationship*, three demonstrated such an effect, including two of three gadodiamide studies.

Review: Gadolinium Based Contrast Agents and Nephrogenic Systemic Fibrosis - A Systematic Review
 Comparison: 01 All Gadolinium Based Contrast Agents vs. Control
 Outcome: 01 NSF

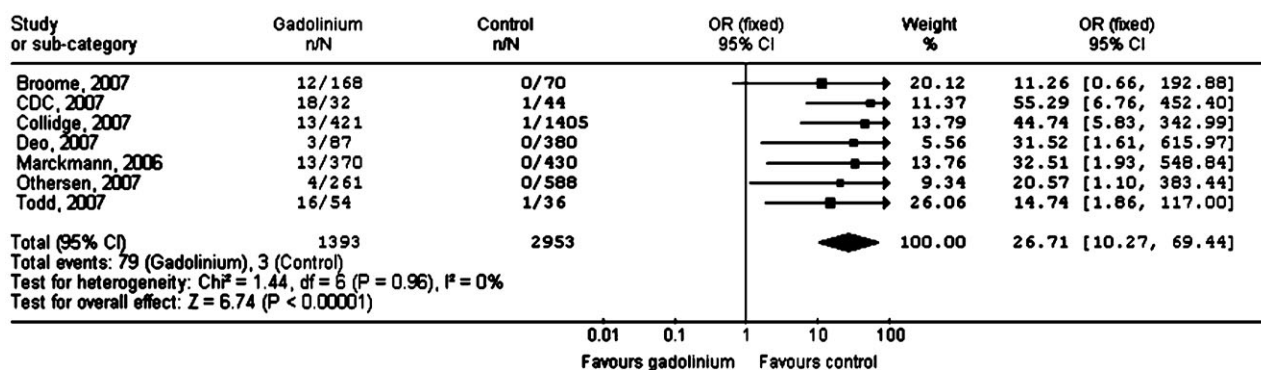


Fig. 2. Relationship between gadolinium and NSF. Results indicate a significant increase in the risk of NSF with gadolinium. The odds of developing NSF were 27 times greater in patients exposed to gadolinium compared to those who were not.

Review: Gadolinium Based Contrast Agents and Nephrogenic Systemic Fibrosis - A Systematic Review
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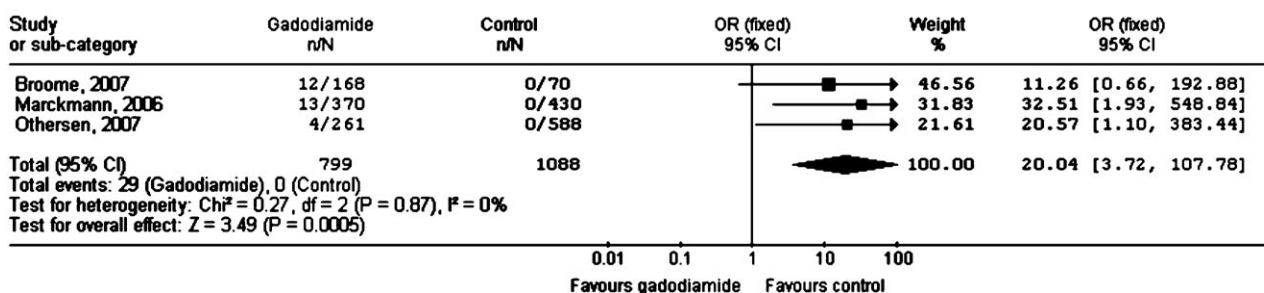


Fig. 3. Relationship between gadodiamide and NSF. Results indicate a significant increase in the risk of NSF with gadodiamide. The odds of developing NSF were 20 times greater in patients exposed to gadodiamide compared to those who were not.

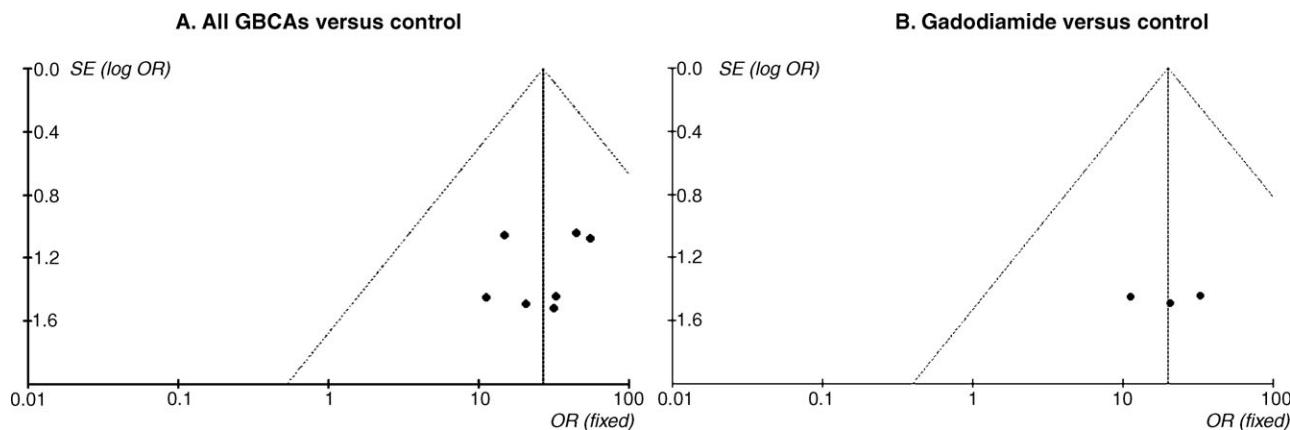


Fig. 4. Funnel plots for publication bias. The symmetrical distribution of studies in an inverse funnel shape suggests the absence of publication bias.

In terms of *biological plausibility*, the chemical structure of the GBCAs along with their pharmacokinetics supports a causal relationship with NSF (Table 3). For the chemical structure, the GBCAs are classified as either macrocyclic versus linear or ionic versus nonionic. Macrocyclic molecules are more stable and have lower dissociation rate when compared with linear molecules, and non-

ionic chelates are more likely to release free gadolinium in the body than ionic chelates. This would suggest that the non ionic linear configuration of gadodiamide would make it particularly prone to dissociation and release of free gadolinium, which may account for its association with NSF in the available data. Pharmacokinetically, GBCAs are almost exclusively excreted renally, and therefore have a

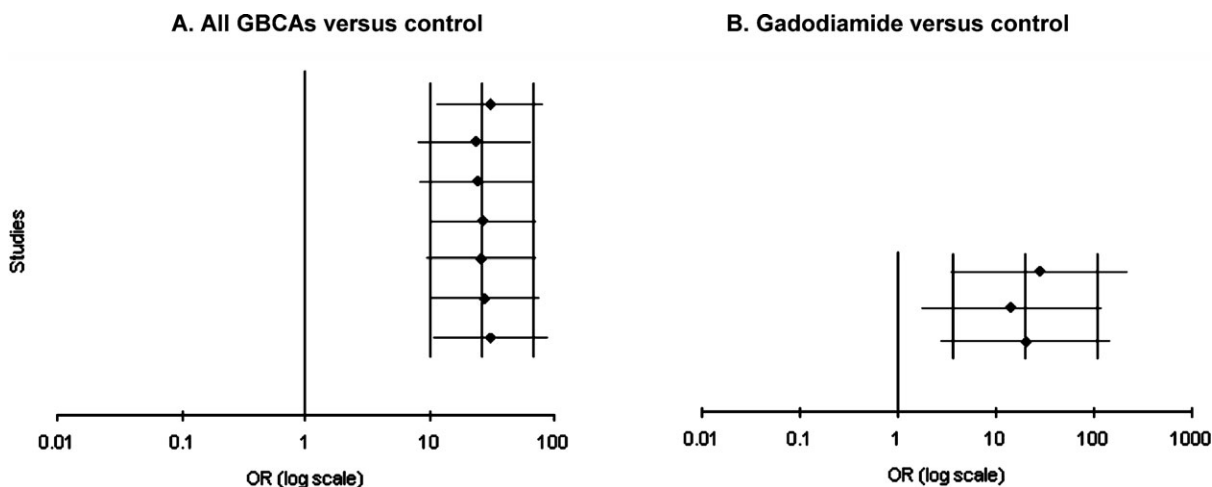


Fig. 5. Exclusion sensitivity plots: (A) all studies and (B) studies exclusively examining gadodiamide. Each diamond represents the pooled estimate after exclusion of individual studies in the order shown in the meta-analyses in the corresponding meta-analyses in Figures 2 and 3. The similarity among the pooled estimates suggests that no single study disproportionately influenced the results of the meta-analyses.

Table 2. Evaluation of evidence in support of a potentially causal association between gadolinium, gadodiamide and NSF

Hill’s criteria	What the evidence suggests	
	All GBCAs	Gadodiamide (Omniscan)
Strength of association	Six of seven studies reported a statistically significant association. Our meta-analysis showed that the odds of developing NSF were 27 times greater in patients exposed to gadolinium compared with those who were not	All three studies [8,12,13] reported a statistically significant association. Our meta-analysis showed that the odds of developing NSF were 20 times greater in patients exposed to gadodiamide compared with those who were not
Consistency	All studies reported consistently similar direction and a large magnitude of effect. Though studies were conducted in different countries (USA, Scotland and Denmark), the results were similar	All three studies [8,12,13] reported consistently a similar direction and a large magnitude of effect. Though studies were conducted in different countries (USA and Denmark), the results were similar
Specificity	With the exception of two studies [11,14], whenever a specific GBCA was implicated in the development of NSF, it was gadodiamide. Conclusions about differences in risk with individual GBCAs cannot be drawn with currently available data	
Temporal sequence	A temporal relationship was clearly reported in all studies except one [14]	All three studies [8,12,13] reported a clear temporal relationship of gadodiamide exposure with NSF
Biological gradient (dose–response relationship)	A dose–response relationship was demonstrated in three studies [8,10,13], but not in two studies [11,12]. The other studies did not report such a relationship	Two of the studies demonstrated a dose–response relationship [8,13] while one study did not [12]
Biological plausibility	Gadodiamide has an unstable non ionic linear configuration and is excreted renally	
Coherence	Gadolinium is both detectable and quantifiable within the tissues of patients with NSF/NFD [15,36]	
Experiment (e.g. removing the exposure)	When a patient who had clinical resolution of NSF was re-exposed to gadodiamide, NSF reappeared again [13]	
Analogy		

prolonged half-life in renal failure patients [37], supporting their association with NSF primarily in those with advanced kidney disease.

In terms of *coherence*, there have been reports that gadolinium is both detectable and quantifiable within the tissues of patients with NSF/NFD [15,36]. *Experiment* also suggests causation, as a patient who had a clinical

resolution of NSF relapsed when re-exposed to gadodiamide [13].

Are there differences in the risk of NSF between GBCAs?

Most studies examined GBCAs in general, or gadodiamide specifically. One study exclusively examined

Table 3. Characteristics of approved gadolinium-based contrast agents (GBCAs)^a

GBCA	Charge	Structure	Elimination ^b	Half-life (minutes) ^c
Gadodiamide (Omniscan)	Nonionic	Linear	Renal	62–94
Gadopentetate (Magnevist)	Ionic	Linear	Renal	90–102
Gadoversetamide (OptiMARK)	Nonionic	Linear	Renal	84–123
Gadoteridol (ProHance)	Nonionic	Cyclic	Renal	89–99
Gadobenate (MultiHance)	Ionic	Linear	Renal	54–156

^aSources: Peak *et al.* [25]; Issa *et al.* [23] and www.uptodate.com.

^bPrimary route of elimination.

^cMean elimination half-life in normal subjects.

gadopentetate. We found no other controlled or uncontrolled published reports examining the association of the other GBCAs with NSF. The odds of NSF were similar between the non-ionic linearly configured gadodiamide and the ionic linearly configured gadopentetate, suggesting that the other linearly configured GBCAs have similar risks. The only GBCA with a cyclic structure, gadoteridol, has not been specifically examined in any published study, so it is unclear whether the risk of NSF would be lower with this agent. The clearance and half-lives of the GBCAs appear to be similar, so pharmacokinetics may not be an important factor for any differences in NSF risk that might exist between the GBCAs.

Discussion

To our knowledge, this is the first meta-analysis of controlled studies examining the relationship between GBCAs and the development of NSF. Our analyses suggest a potent and significant association between GBCAs and NSF among patients with advanced CKD. Much of the evidence consisted of studies that either exclusively examined gadodiamide or did not specify the GBCA administered. One study exclusively examined gadopentetate. For GBCAs in general and gadodiamide in particular, application of Hill's criteria suggests a causal relationship.

FDA's most recent advisory and the American College of Radiology (ACR) both recommend withholding all GBCAs in patients with severe to end-stage (stage 4–5) CKD (glomerular filtration rate < 30 mL/min/1.73 m²). Our findings support these recommendations. In patients with stage 3 or moderate CKD, the ACR noted that there were insufficient data to make any recommendations, which was also consistent with our findings [28,38]. One study that did examine the association of gadodiamide and NSF in patients with mild to moderate CKD observed a prevalence of NSF in stage 1–4 CKD of 0% while among patients with stage 5 CKD of 18% ($P < 0.01$) [39]. The FDA also recommends that if patients with severe CKD need GBCAs, prompt haemodialysis following contrast administration should be considered [28]. The ACR, on the other hand, was concerned that this might result in greater risk to patients from inappropriate haemodialysis and recommended that such prophylactic use of dialysis be warranted only in patients who were already on dialysis. For patients not already on haemodialysis (e.g. stage 3 or 4 CKD), the ACR notes that the risks of initiating haemodialysis should be weighed

against that of developing NSF [38]. Our data do not permit examination of these issues.

The current state of evidence does not allow an assessment of the relative effects of gadodiamide compared with the other GBCAs. A recent systematic review found that of 195 cases of NSF described in the published literature, 157 were associated with exposure to gadodiamide, 8 to gadopentetate, 3 to gadoversetamide and 18 occurred after unspecified GBCA exposure. We could not identify the three gadoversetamide cases that the review included as the GBCA used was ascertained through personal communication with the original authors. No published cases ascribed to gadoteridol and gadobenate were identified [40]. Though there is a lack of published reports for these agents, cases with each of the currently approved GBCAs have been reported to FDA's MedWatch program [28,38]. However, the reliability of such reports has been questioned as the limitations of the program do not allow for accurate calculation of adverse event rates [41]. Thus, despite differences in the chemical structure of the GBCAs that might result in differences in NSF risk, no firm conclusions can be drawn at the present time. The FDA and the ACR assume in their recommendations that an association might exist for all currently approved GBCAs and that NSF may be a class issue rather than a specific agent issue. The ACR further recommends that gadodiamide should be avoided in patients with any level of renal dysfunction [28,38]. Again, our data do not permit examination of this recommendation.

This review is the first attempt to systematically identify all controlled evidence on the association between GBCAs and NSF and provide a summary estimate of the association. The absence of statistical heterogeneity, publication bias and the robustness of our findings on sensitivity analyses add to our confidence that the relationship between GBCAs and NSF is real and did not result from chance or bias. The evidence was also rigorously examined using existing criteria to assess for the presence of a causal link. Our findings are relevant to the numerous patients with advanced kidney disease, many of whom may be eligible for imaging with GBCAs.

The conclusions of our systematic review are limited by the quality of the constituent studies. We were unable to identify any randomized controlled trials on the subject, and the studies that we included, though the best available, were of relatively poor quality. There may have been unmeasured variables in the studies confounding the relationship between GBCAs and NSF. It is believed that meta-analyses of observational studies are prone to producing precise but

inaccurate summary estimates due to the presence of such confounding factors [30]. However, there was a consistently large effect observed in each of the included studies and no statistical heterogeneity was observed in the meta-analyses. Lastly, we looked only at peer-reviewed literature published in English, so our results may have suffered from publication bias even though we were not able to detect any in our analyses.

We were able to identify several gaps in the existing literature and this may help lay the foundation for future research. It would be beneficial to know if there are differing degrees of risk with GBCAs other than gadodiamide. Future studies should focus on reporting the association of NSF with gadoversetamide, gadoteridol and gadobenate. Additional research is also needed to quantify the risks of GBCAs in patients with lesser degrees of kidney disease (e.g. stage 1–4 CKD).

In conclusion, this analysis demonstrates the presence of a potentially causal link between GBCAs in general and the development of NSF among patients with advanced kidney disease. Much of the evidence is derived from studies that either exclusively studied gadodiamide or did not specify the agents that were administered. Thus, it is difficult to draw conclusions about differences in NSF risk that may exist between the GBCAs. Until such data become available, all GBCAs should be used only after a careful assessment of risks and benefits in patients with renal impairment in accordance with the FDA and ACR recommendations.

Conflict of interest statement. None declared.

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