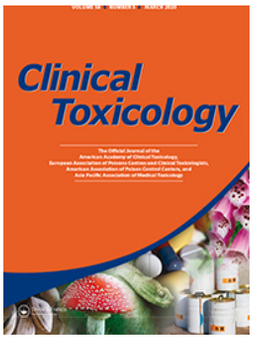

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REVIEW

Gadolinium-based contrast agents – what is the evidence for 'gadolinium deposition disease' and the use of chelation therapy?

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ABSTRACT

Introduction: Gadolinium-based contrast agents are widely used for magnetic resonance imaging and, until recently, had been generally considered to have an excellent safety profile in patients with normal renal function. Nephrogenic systemic fibrosis is a well-established disease process involving fibrosis of the skin and internal organs seen in some patients with severely impaired renal function following exposure to these agents. Following reports that individuals with normal renal function may experience gadolinium deposition within brain and bone tissue, the term "gadolinium deposition disease" has been proposed and the use of chelating agents has been recommended to treat this "disease".

Objectives: This review will address the clinical evidence for "gadolinium deposition disease" and discuss whether chelation therapy is appropriate for individuals who believe they have this condition.

Methods: Electronic databases (PUBMED, Ovid MEDLINE and EMBASE) were searched up to 1st October 2019 for all studies evaluating clinical signs or symptoms related to potential gadolinium toxicity post-gadolinium-based contrast agent exposure in subjects with normal renal function, or papers evaluating the potential chelation of gadolinium in humans.

Does "gadolinium deposition disease" exist as a novel condition? We identified four clinical studies relating to "gadolinium deposition disease", including one that included some discussion of the use of chelation therapy. Two of the clinical studies presented data from anonymous online surveys that recruited participants from support forums for people who self-identified as having gadolinium-based contrast agent–induced toxicity, with questions focussing on their reported symptoms and signs. The published literature to date has demonstrated that gadolinium deposition within the brain primarily occurs within the dentate nucleus and globus pallidus. These patients did not complain of movement disorders, but instead reported generalised sensory symptoms, which would not be expected to occur with pathology in these areas of the brain. There was considerable selection bias and a lack of available clinical information to exclude alternative medical diagnoses for these series, thus rendering the results difficult to interpret.

Role of chelation therapy in patients exposed to gadolinium-based contrast agent: One study reported data from 25 patients who were diagnosed with "gadolinium deposition disease" according to unspecified criteria and were treated with intravenous calcium or zinc trisodium pentetate. The authors reported an increase in urine gadolinium concentrations following administration of the chelating agents, which they attributed to re-chelation of gadolinium from tissue deposits, however, there are insufficient data to be able to substantiate this.

Conclusion: There is currently no published information from well-designed clinical studies that support a link between gadolinium deposition and the development of clinical sequelae in patients with normal renal function. Clinicians should exercise caution when considering whether or not gadolinium is of relevance in patients reporting symptoms after administration of gadolinium-based contrast agents. The inappropriate use of chelation therapy in patients with no clear evidence-based indication for their use potentially increases the risk of clinically significant harm to these patients from the adverse effects of chelation. Further research and well-designed clinical and epidemiological surveillance is needed to determine whether there are toxicological risks related to gadolinium exposure from the use of gadolinium-based contrast agents in patients with normal renal function.

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Introduction

Gadolinium is a rare-earth metal that has been used as a contrast agent for magnetic resonance imaging (MRI) scans since the late 1980s. It is bonded with either linear or macrocyclic ligands to form gadolinium chelates that are used as gadolinium-based contrast agents during MRI [1]. Macrocyclic chelates form stronger bonds with gadolinium ions, and therefore the gadolinium is less likely to dissociate from the gadolinium-based contrast agent complex compared with linear chelates [1–3]. Gadolinium-based contrast

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agents are an essential tool in MRI diagnostics and, until recently, had been generally considered to have an excellent safety profile, aside from the risk of nephrogenic systemic fibrosis in those patients with end-stage renal failure and very infrequent cases of acute neurotoxicity [4–6].

Recent radiological analyses and post mortem studies, however, have suggested that exposure to gadolinium-based contrast agents may result in gadolinium deposition in human brain and bone tissue in those patients with normal renal function [7–18]. In September 2017, the United States Food and Drug Administration (FDA) convened a Medical Imaging Drugs Advisory Committee meeting to review the emerging data related to gadolinium deposition in the brain and other body organs in patients with normal renal function. The team concluded that whilst current evidence shows that gadolinium is retained in human tissues post-exposure to gadolinium-based contrast agents, "for all or almost all of the millions of patients with normal renal function who have benefitted diagnostically from these drugs since 1988, the range of post-GBCA [gadolinium-based contrast agents] gadolinium retention probably falls below exposure thresholds that could induce grossly observable subacute/chronic adverse reactions" [6]. Subsequently, the UK Medicines and Healthcare products Regulatory Agency (MHRA) and the FDA released new guidance in December 2017 advising healthcare professionals to aim to minimise requests for gadolinium-enhanced MRI scans unless diagnostic information is essential, with the MHRA also suspending the licences for the linear agents, gadodiamide (Omniscan) and intravenous gadopentetic acid (Magnevist) [19,20]. The European Medicines Agency similarly issued recommendations to restrict the use of some linear gadolinium agents used in MRI body scans and to suspend the authorisations of others [21].

Although one study showed detectable gadolinium in the skin of a patient with normal renal function at a concentration of 0.057 μg/g tissue [15], a case report showed similar findings with a gadolinium concentration of 14.5 ± 0.4 μg/g tissue in a skin biopsy [22], and an additional case report described a male patient with normal renal function presenting with plaques with features typical for gadolinium deposition on his hands [23], to date, gadolinium deposits in humans have been primarily identified in bones [7–9,15], and two distinct areas of the brain: the dentate nucleus and the globus pallidus [12–14,16,24].

One study has additionally shown gadolinium present in the pons and thalamus, albeit at far lower concentrations than the dentate nucleus and globus pallidus [18], whilst another showed evidence of gadolinium deposition within the pons, putamen, caudate head, and centrum semiovale white matter, again at significantly lower concentrations than the dentate nucleus and globus pallidus [15]; whether this results in any neurological/other clinical sequelae has not been established and more research is required to determine the clinical relevance of these gadolinium deposits [1,25]. The majority of histopathological studies have favoured analysing tissue from sites where MRI scans have highlighted metallic deposits and it is important to consider that gadolinium deposition in other regions of the brain may also occur.

A number of online forums and support groups have been established since 2012 to discuss potential adverse effects occurring following an individual's exposure to a gadolinium-based contrast agent [26–29]. There have been increasing numbers of individuals reporting that they believed they have gadolinium toxicity based on their symptoms. In 2016 the term "gadolinium deposition disease" was first proposed to describe "symptomatic deposition of gadolinium in individuals with normal renal function" by Semelka and his colleagues [30] in the USA.

Public awareness of the potential diagnosis of "gadolinium deposition disease" has significantly increased following a series of interviews and press releases from celebrity martial artist, Chuck Norris, and his wife, Gena, who both state that she has developed chronic, multisystem symptoms as a result of gadolinium-based contrast agent-induced gadolinium toxicity [31,32].

The couple have engaged subsequently in a high-profile lawsuit against multiple pharmaceutical companies that are involved in the production of gadolinium-based contrast agents [33]. McNamara and Rahmani [34] discussed in a published letter the phenomenon of celebrity disclosures increasing public awareness of particular health issues. They state that the peak popularity for the search terms "gadolinium", gadolinium poisoning" and "gadolinium deposition disease" between January 2013 and January 2018 occurred over the fortnight following a televised interview with Chuck and Gena Norris on the American CBS television network in November 2017 [34].

Increasing public and media attention related to "gadolinium deposition disease" has naturally led to speculation regarding treatment options for those individuals who are concerned that they may have suffered harmful effects following exposure to gadolinium-based contrast agents.

Objectives

This review will address the clinical evidence for "gadolinium deposition disease" and discuss whether chelation therapy is appropriate for individuals who believe they have this condition.

Methodology

Electronic databases (PUBMED, Ovid MEDLINE and EMBASE) were searched up to 1st October 2019 for all studies evaluating clinical signs or symptoms related to potential gadolinium toxicity post-gadolinium-based contrast agent exposure in subjects with normal renal function, or papers evaluating the potential chelation of gadolinium in humans. All languages were searched. The Medical Subject Headings text words and key words used in the search were 'gadolinium' in combination with each of the following terms: 'deposition', 'toxic', 'toxicity, 'poisoning', 'disease', 'symptom', 'sign', 'sequelae', and 'chelation'.

The search yielded 9883 papers, 2079 of which were clinical studies, clinical trials, or case reports. A secondary search of the 2079 papers identified from the primary search was performed by hand, of which eight were considered relevant. Studies were deemed to be relevant if they related to potential adverse reactions to gadolinium-based contrast agents in humans with normal renal function. Of the eight identified relevant papers, four were studies that reportedly involved humans with presumed gadolinium toxicity and were thus included in this literature review (none of which were randomised controlled trials), and four case reports were additionally identified and included in this review. These eight papers are all described in Table 1.

In order to identify potentially relevant animal studies, a further database search was conducted using the search term "chelation" in combination with "gadolinium", plus one of the following: "mouse", "mice", "rat", "murine", "rabbit" or "animal". This search identified 52 studies, 4 of which were considered to be of relevance and are thus reported in this paper.

Does "gadolinium deposition disease" exist as a novel condition?

There are currently few published reports of patients with normal renal function who present with clinical sequelae that are potentially related to gadolinium deposition. One case report describes a 21-year-old male patient with a medical history that included a recurring rhabdomyosarcoma of the left orbit and an anaplastic astrocytoma of the left thalamus who underwent 35 contrast-enhanced MRI brain examinations with the linear gadolinium-based contrast agent, gadopentetate dimeglumine, throughout his treatment [36]. The patient's renal and hepatobiliary function

Table 1. Studies evaluating clinical signs and symptoms related to potential gadolinium toxicity post-gadolinium-based contrast agent exposure in subjects with normal renal function.

	Study design	Subject characteristics	Study findings
Leung et al. 2009 [35]	Case study	65 year old female kidney transplant recipient with biopsy-confirmed nephrogenic systemic fibrosis.	Deferoxamine was administered intramuscularly. Urine excretion of gadolinium increased, however serum gadolinium concentrations were unchanged. The patient felt that her symptoms had stabilised post-chelation therapy but there was no objective evidence provided to be able to substantiate.
Miller et al. 2015 [36]	Case study	21 year old male patient with rhabdomyosarcoma of the left orbit, who received who received 35 doses of a linear intravenous gadolinium-based contrast agent.	Review of the patient's later MRI scans showed increased regional signal intensity within the dentate nuclei, globus pallidus, and posterior thalamus. The patient had impaired cognitive function, however it was unclear whether the underlying cancer and the treatments that he received contributed to this.
Burke et al. 2016 [37]	Clinical study	50 patients who reported that they experienced gadolinium toxicity.	An anonymous online survey of patients who reported that they suffered from gadolinium toxicity showed that the most common reported symptoms included bone/joint pain, headache, vision change, and hearing change.
Roberts et al. 2016 [22]	Case study	30 year old female patient with glioblastoma who underwent 61 gadolinium-based contrast agent-enhanced MRI scans over an 11 year period, 8 months prior to review.	The patient denied experiencing any symptoms related to her skin, although skin biopsies showed increased CD34 (indicative of inflammation) and tested positive for gadolinium deposition.
Semelka et al. 2016 [38]	Case series	1. 29 year old female patient who had a contrast-enhanced MRI scan 2 months prior to review. 2. 43 year old female patient who underwent four contrast-enhanced MRI scans over a 2 month period, 3 months prior to review 3. 58 year old female patient who underwent a contrast-enhanced MRI scan 7 years prior to review 4. 55 year old female patient who underwent six contrast-enhanced MRI scans over a 13 year period, 8 years prior to review.	Patients reported symptoms including pain in the central torso, arms, and legs, plus skin thickening and clouded mentation. Detectable concentrations of gadolinium were present in samples, including: urine, hair, and a saphenous vein sample.
Semelka et al. 2016 [39]	Clinical study	42 patients, aged 28–69 years, who reported that they experienced gadolinium toxicity.	An anonymous online survey of patients who reported that they suffered from gadolinium toxicity showed that the most common reported symptoms included central/peripheral/bone pain, headache, skin thickening, and clouded mentation.
Semelka et al. 2018 [40]	Clinical study	25 patients, aged 26–76 years, who reportedly met criteria for a diagnosis of 'gadolinium deposition disease'.	Patients who were reportedly diagnosed with 'gadolinium deposition disease' received chelation therapy with intravenous Ca-/Zn-DTPA, and subsequently had increased urinary excretion of gadolinium. Symptoms reportedly improved in 13 of the 25 patients post-chelation.
Greenberg et al. 2019 [41]	Case study	55 year old male patient with zinc toxicity, who had undergone two gadolinium-based contrast agent-enhanced MRI scans. Incidentally found to have increased urine gadolinium excretion.	The patient was treated for zinc toxicity with a chelation regime of EDTA and DMSA. 24-h urine gadolinium concentrations showed a rise in gadolinium excretion post-chelation, compared with baseline gadolinium concentrations. The patient had, however, also undergone a subsequent enhanced MRI during this interval and it was unclear whether chelation therapy contributed to this rise.

were consistently normal. Retrospective review of his pre-contrast MRI scans showed increased regional signal intensity within the dentate nuclei, globus pallidus, and posterior thalamus [36], consistent with multiple studies that have linked gadolinium-based contrast agent exposure with signal changes in these regions [12,13,42].

The patient had no reported skin changes but the authors comment on observed deficits in executive functioning, visual memory and reasoning, reading comprehension, and mathematical abilities during neuropsychological testing despite no significant visible treatment-related intracranial structural abnormality or current medical problems [36]. Of note, however, the patient previously underwent multiple treatments with surgery, chemotherapy, external beam radiation and proton beam therapy, which are clear confounding factors when considering the underlying cause(s) of his impaired cognitive function [36].

A second case report documents the history of a 30-year-old female patient diagnosed with a glioblastoma with oligodendroglial components who underwent 61 gadolinium-based contrast agent-enhanced MRI scans over an 11 year period, and although there is a lack of clarity as to which agent(s) she received, the likely highest level of exposure was to gadobenate dimeglumine (a linear gadolinium-based contrast agent) [22]. The brain malignancy was treated with surgical resection and chemotherapy. The patient additionally had an extensive past medical history including cognitive and developmental delays, hypothyroidism, vagal nerve stimulator implantation, and laparoscopic cholecystectomy but was consistently reported to have normal renal function [22]. The patient denied experiencing any symptoms related to her skin and examination by a dermatologist identified no skin changes. Skin biopsy showed normal histological appearances, although there was increased CD34 indicative of inflammation [22]. Inductively coupled plasma mass spectrometry showed gadolinium deposition (14.5 ± 0.4 μg/g) within the skin biopsies [22]. Skin biopsies from patients with nephrogenic systemic fibrosis have previously shown gadolinium concentrations in the range of 57–718 μg/g [43]. Additionally, following a laparoscopic cholecystectomy 3 years prior to the skin biopsies being performed, the patient was reported to have developed severe joint contractures of the limbs and neck, a finding observed in patients with nephrogenic systemic fibrosis, although the authors accept that the underlying aetiology of this may be multifactorial, as the patient had an extensive medical history. The patient became non-ambulatory as a result of the joint contractures [22].

After Semelka and his colleagues [37] proposed the term "gadolinium deposition disease" in 2016, the same research group published results from an anonymous online survey that they conducted to try and describe the symptoms in individuals who believed that they had gadolinium toxicity. The research team posted links to the survey on a private blog, 'The MRI-Gadolinium-Toxicity Support Group', and on a public gadolinium toxicity page on the social media site Facebook. In total 50 people responded, all of whom had self-identified as having gadolinium-based contrast agent-induced gadolinium toxicity or "gadolinium deposition disease". Forty-seven subjects responded to a question regarding the gadolinium-based contrast agent that they had been exposed to, with one subject reporting that they were exposed to a single macrocyclic agent, 36 subjects reporting exposure to a single linear agent, four subjects reporting exposure to multiple agents, and 11 subjects stating that they were unsure. Thirty-three of the 50 subjects reported that their symptoms developed immediately following contrast administration, 16 reported a symptom onset of six weeks post-exposure, and the remaining one subject developed symptoms 6 months post-exposure [37].

The majority reported bone/joint pain and headache as their main complaints following exposure to gadolinium-based contrast agents, having selected options from a predetermined list that included: "skin, bones or joints, digestive system (nausea, vomiting, diarrhoea), chest (breathing issues), head and neck (headaches, vision, hearing), flu-like symptoms, generalized symptoms (whole body), other". The authors acknowledged the potential issues surrounding the validity of this study, focussing on the inevitable selection bias that was associated with recruiting subjects who had been self-diagnosed with gadolinium toxicity and were providing anonymised information [37]. Furthermore, there was no clinical review of the subjects and no information was reported on previous medical history or consideration of other conditions that may have been contributing to the reported symptoms.

Semelka and colleagues [37] reported that 41 of the 50 subjects had previously undergone testing for "gadolinium retention", with the majority having urine gadolinium concentrations measured; this was determined by the survey question, "Have you had gadolinium detected in your body by prior tests? (Urine, blood, other)", rather than by reviewing laboratory results or including detail on the methodology used for any testing undertaken. Furthermore, although there are isolated reports quantifying urine gadolinium concentrations in biological matrices from healthy subjects [44–47], the data provided in these reports are insufficient to characterise a reference range and it is therefore challenging to interpret the results from blood and/or urine gadolinium concentration measurements.

In the same month, the same group published a more detailed case series of four patients reviewed directly by the team [38]. All four individuals self-approached the group for assessment to identify potential gadolinium toxicity [38]. The patients described symptoms including widespread pain, headache, clouded mentation, and skin changes. One of the patients described generalised "skin tightening" and physical examination identified subcutaneous lesions, skin tightness, and shiny appearance of the skin overlying the fingers. Physical examination of another patient in the series identified "skin discoloration of the hands, discoloured legs and a red rubbery texture to the subcutaneous tissue", whilst a third patient was reported to have skin over the hands and feet that was "thickened and red with a doughy consistency". It is not documented whether or not the physicians reviewing these patients excluded other conditions that may have

contributed to the reported symptoms. The authors reported "elevations" in gadolinium concentrations in urine and serum samples from the patients, as well as hair and saphenous vein tissue, with all quantitative analyses (inductively coupled plasma-mass spectrometry) being performed at the Mayo Clinic and compared to reference ranges published on the Mayo Clinic internet site [38,48–50]. However, as noted above, there have been no validated gadolinium reference ranges published in the medical literature or confirmation from other analytical laboratories that the Mayo Clinic reference ranges are accurate.

This group then published results from a further online anonymous survey, which recruited people from a link posted on the aforementioned gadolinium toxicity support blog and Facebook page to try and further describe the features of "gadolinium deposition disease" [39]. It was unclear whether this study had excluded people who had participated in the earlier anonymous survey. They reported that 41 of the 42 respondents stated that they had "evidence of gadolinium presence beyond 1 month after exposure" in the form of urinalysis results, and that the "vast majority" of the surveyed subjects complained of central, peripheral and bone pain, headache, skin changes and clouded mentation [39]. However, as with the previous online survey, there was no clinical review of the subjects and no information was reported on previous medical history or consideration of other conditions that may have been contributing to the reported symptoms.

Additionally, there was no evidence provided that gadolinium concentration testing had been performed or if it had how these results had been interpreted. The authors concluded that these symptoms represent gadolinium toxicity in patients with self-reported normal renal function and that such findings comprised the initial description of "gadolinium deposition disease" [39].

The published literature to date has demonstrated that gadolinium deposition within the brain primarily occurs within the dentate nucleus and globus pallidus [12,17,42]. From a clinical perspective, damage to these areas of the brain would typically be expected to cause movement disorders, with globus pallidus lesions resulting in generalised dystonia or parkinsonism and the dentate nucleus being involved in voluntary motor function and cognition [51,52]. However, in the published studies by Semelka and his colleagues [37–39], the patients do not complain of movement disorders, but instead complain of generalised sensory symptoms, which would not be expected to occur with pathology in these areas of the brain.

There is therefore a discordance between the radiological evidence of where gadolinium is deposited in the brain and the clinical symptoms that individuals report and further work is required to determine whether or not the gadolinium deposited in these areas of the brain is associated with clinical sequelae [1,25]. As the patients in the aforementioned studies have reported a variety of sensory symptoms, including abnormal sensation in the 'glove and stocking' distribution, potential axonal peripheral neuropathies related to exposure to gadolinium-based contrast agents should be considered although histopathological evidence for this has not yet emerged. As discussed in a recently published commentary on the topic [53], whilst gadolinium deposition within the brain may not be harmful, there may be deposition at other sites in the body that could result in symptoms that as yet have not been linked to their cause.

It is impossible to ignore the selection bias associated with each of the three published clinical data sets [37–39], all of which recruited patients who reported self-diagnosed gadolinium toxicity and who, aside from those four patients reviewed directly by the group, were providing anonymous responses, with no past medical history, or examination reports available to Semelka and his colleagues. This includes renal function results, as well as other access to key investigations to enable exclusion of alternative diagnoses that may be contributing to the reported symptoms.

Furthermore, there are no published studies which have compared those who report symptoms after gadolinium-based contrast agent administration to those who are asymptomatic. As patients who have undergone a contrast-enhanced MRI typically have a neurological or cardiac condition, malignancy, or disseminated infection, it is difficult to clearly establish whether the variety of symptoms and signs that have recently been reported following exposure to gadolinium-based contrast agents are related to the contrast or the underlying pathology. There are currently no case-control studies to assess for differences in symptoms in patients who have received gadolinium-based contrast agents compared with matched patients with similar pathologies who have not undergone contrast-enhanced MRI scans. Additionally, there are no available studies to assess whether signs or symptoms develop when gadolinium-based contrast agents are administered to healthy subjects. Further well-designed studies to investigate potential clinical sequelae that may arise following gadolinium-based contrast agent exposure, particularly with macrocyclic agents (as these are now more commonly used), are needed.

In conclusion, we believe that there is currently insufficient evidence to confirm that gadolinium-based contrast agent use in those with normal renal function results in clinically significant adverse effects and therefore it is premature to consider "gadolinium deposition disease" to be a novel condition.

Role of chelation therapy in patients exposed to gadolinium-based contrast agents

A variety of chelating agents are used to treat patients with heavy metal toxicity and there are currently 11 FDA-approved chelators available in the United States by prescription [54]. Gadolinium-based contrast agents are comprised of gadolinium ions which are bonded to chelating ligands to improve stability and reduce toxicity [1]. Gadopentetate dimeglumine contains the chelate diethylenetriaminepentaacetic acid (DTPA) and was the first gadolinium chelate to be used as a gadolinium-based contrast agent in clinical practice [55]. Gadolinium-based contrast agent

preparations typically contain excess volumes of chelate to reduce free (unbound) gadolinium ions within the solution [56].

Dr Semelka's team [57] published a paper in 2016 which discussed the potential use of chelation as a method of removing gadolinium deposits, drawing inferences from work relating to the decorporation of radioactive actinides. As recent media coverage relating to potential gadolinium deposition post-gadolinium-based contrast agent exposure has intensified, there has been increasing interest regarding whether chelation therapy represents a potential intervention to remove gadolinium from the body.

Animal studies

In 2015, results from a study were published that utilised a murine model of nephrogenic systemic fibrosis to further investigate the underlying pathophysiology of the skin changes that can develop after gadolinium-based contrast agent exposure in patients with severe kidney disease [58]. Mice with surgically-induced renal impairment were exposed to a course of 10 injections (3 injections per week) of gadodiamide (linear agent) 0.5 mmol/kg, with the treatment group receiving deferiprone 125 mg/kg, a drug used to chelate iron, in their drinking water for 16 weeks [58]. The mice subsequently developed skin changes typical of nephrogenic systemic fibrosis. However the group that had received deferiprone had significantly ($p < 0.05$) decreased skin thickness and dermal fibrosis compared to the gadodiamide-only group [58]. The researchers concluded that catalytic iron plays a role in the development of nephrogenic systemic fibrosis although they did not present data to substantiate this [49].

Of note, deferiprone chelates multiple metals aside from iron, including copper, iron, and zinc and it is unclear whether gadolinium may also bind to this ligand, which may have had an impact on the results obtained. Over recent months animal models have been utilised by several groups to investigate the chelation of gadolinium *in vivo*.

Boyken et al. [59] compared the effects of administering a course of either intravenous calcium trisodium pentetate or sodium chloride 0.9% solution over a period of 3 weeks to rats that had received 1.8 mmol/kg of either a linear (gadodiamide) or macrocyclic (gadobutrol) gadolinium-based contrast agent, or an infusion of sodium chloride 0.9% solution ($n = 18$ per group) 7 weeks earlier. Six animals from each group were sacrificed at the 7 week post-gadolinium-based contrast agent timepoint. The team showed that calcium trisodium pentetate administration had no significant impact on urine gadolinium concentrations in rats that had initially received either gadobutrol or sodium chloride 0.9% solution. In contrast, those rats that had initially received gadodiamide had an increase in urine gadolinium excretion that exceeded the spontaneous urine gadolinium excretion by 26 ± 4.3 mmol within 24 h after the first dose of calcium trisodium pentetate [59].

The gadodiamide group had seven-fold higher concentrations of gadolinium (0.74 ± 0.052 nmol gadolinium/g brain tissue (brain homogenates comprising brainstem, cerebellum, and cerebrum)) 7 weeks later, compared with those that had received gadobutrol (0.11 ± 0.029 nmol gadolinium/g tissue) [59]. The group that had received sodium chloride 0.9% solution had gadolinium concentrations that were close to or below the limit of quantification, as detected by inductively coupled plasma mass spectrometry [59].

Furthermore, the team reported that there was a significant reduction ($p = 0.009$) in brain tissue gadolinium concentrations post-calcium trisodium pentetate treatment from 0.74 ± 0.052 nmol gadolinium/g brain tissue to 0.56 ± 0.13 nmol/g tissue in the gadodiamide group. The authors did not comment on whether there was a significant difference between the gadolinium concentrations in the rats that received the course of calcium trisodium pentetate (to 0.56 ± 0.13 nmol gadolinium/g tissue), compared with those that received the 3 week course of sodium chloride 0.9% solution (0.66 ± 0.081 nmol gadolinium/g tissue) [59]. When comparing chelation results from studies involving other heavy metals, this approximately 25% reduction in brain tissue gadolinium represents a considerable yield.

A series of animal models have been used to assess the efficacy of succimer in reducing brain lead burdens and these have demonstrated variable results, with a 19 day chelation course showing no evidence of a significant reduction in brain lead concentrations in primates exposed to lead [60] and a further study in rodents exposed to lead for their first 40 postnatal days showing that a three week course of succimer (50 mg/kg/day for 1 week followed by 25 mg/kg/day for an additional 2 weeks) caused a significantly superior reduction in both blood and brain lead concentrations compared with vehicle, although succimer-induced reductions in brain lead concentrations lagged behind reductions in blood lead concentrations and were generally smaller in magnitude [61]. Of note, a rebound was detected in blood, but not brain, lead concentrations and the authors comment in a later paper that blood lead concentrations represent a relatively poor surrogate of brain lead concentrations [61,62].

Another study has assessed whether gadolinium can be 're-chelated' in rats who have received gadolinium-based contrast agents [63]. The rats were injected for 10 days with intravenous gadodiamide (linear gadolinium-based contrast agent) at a dose of 1 mmol/kg and the treatment groups were subsequently given intravenous zinc trisodium pentetate (0.03 mmol/kg) concomitantly or 1, 4 or 8 h after gadolinium-based contrast agent administration, whilst the control groups received no intervention. Three days later, the rodents were euthanised and their femurs, blood, brain, kidneys and liver were harvested [63]. Treatment with zinc trisodium pentetate did not produce a significant reduction in gadolinium concentration, regardless of timing, in any organ, although the 1 h timepoint was associated with a non-significant trend ($p = 0.07$) in reduced kidney, brain and femur gadolinium relative to untreated controls [63].

Rees et al. [64] additionally used a murine model to compare the efficacy of calcium trisodium pentetate with the orally-available metal decorporation agent 3,4,3-lithium(1,2-hydroxypyridinone) (3,4,3-Li(1,2-HOPO)) in promoting the

clearance of the radiotracer ^{153}Gd. ^{153}Gd 0.1 mmol/kg was administered intravenously, and calcium trisodium pentetate, 3,4,3-Li(1,2-HOPO) or control sodium chloride 0.9% solution were administered intraperitoneally to groups of mice either prophylactically (at either 1 h or 24 h pre-^{153}Gd) or at 1 h, 24 h, or 48 h post-^{153}Gd [64]. In the control groups, 57% of the ^{153}Gd was retained in the body after 4 days, primarily within the skeleton. Intraperitoneal administration of both HOPO and calcium trisodium pentetate was found to promote the clearance of ^{153}Gd, and for both chelators, with prophylactic chelation being more effective than post-^{153}Gd chelation [64]. Approximately 11% of the administered gadolinium dose was recovered from the liver in the control group and all of the treatments reduced this burden to <2%, aside from the group where calcium trisodium pentetate was administered 1-h post-^{153}Gd administration that was found to have a burden of 6.3 ± 1.6% of the radiotracer [64]. Animals were sacrificed at 4 days post-^{153}Gd administration, so there was no information available regarding the clearance of ^{153}Gd in the control mice beyond this timepoint [64].

Clinical studies

A recently published review [65] identified only two case reports [35,41] that assessed the effect of chelation therapy. The first [35] described a patient with nephrogenic systemic fibrosis who received a 12 day course of intramuscular deferoxamine chelation therapy that was associated with an increase in urine gadolinium excretion from 6.0 μg/day to 11.6 μg/day and subsequently to 13.0 μg/day with deferoxamine 500 mg/day and deferoxamine 1000 mg/day respectively, but no change in serum gadolinium concentrations and no symptomatic improvement [35].

The second paper [41] reported a patient who was treated for zinc toxicity who had undergone two gadolinium-based contrast agent-enhanced MRI scans and was incidentally noted to have increased urine gadolinium excretion. His chelation therapy consisted of a regimen of 3–5 capsules per day of a dietary supplement that contained (per capsule) sodium calcium edetate 75 mg and succimer 25 mg, followed by 22 intravenous chelation infusions with edetate disodium or sodium calcium edetate 1500–3000 mg per infusion.

The patient had initially presented with a progressive myelopathy with distal sensory loss, a sensory ataxia and brisk reflexes and the MRI scans had been performed to investigate this; he had no signs or symptoms of nephrogenic systemic fibrosis [41]. His renal function was reportedly normal throughout the course of his evaluation. The patient's 24-h urine gadolinium concentrations during chelation were periodically measured as a component of a large panel of elements by inductively coupled plasma mass spectrometry. In comparison to a pre-chelation gadolinium baseline of 0.8 μg/day, a 24-h urine sample collected on day 17 of chelation therapy contained 89 μg/day. He had commenced chelation therapy 12 days after the second MRI scan.

One retrospective study assessed the hepatic gadolinium burden in 21 allogeneic haematopoietic stem cell transplant patients aged 2–17 years who underwent one or more contrast-enhanced MRI scan(s) with the macrocyclic agent, gadoterate meglumine (0.1 mmol/kg), to investigate for suspected infection or relapse [66]. A control group of 4 patients who did not undergo contrast-enhanced MRI scans was also included. All patients had undergone serial liver biopsies to assess for possible graft-versus-host disease and had either normal renal function, or only mild renal impairment (estimated glomerular filtration rate $\geq$60 mL/min/1.73 m^2). A positive correlation between the total gadolinium-based contrast dose received and the gadolinium concentrations within the liver, as measured by inductively coupled plasma mass spectrometry, were identified in the 21 patients from the study group ($r = 0.4486$; $p < 0.05$) [66]. Organ siderosis occurs frequently following allogeneic stem cell transplantations and in this study 19 of the 21 (90.5%) study group patients had evidence of iron overload on histological examination of the liver [66]. A positive correlation between the liver gadolinium concentration and the liver iron concentration was also identified in the 21 patients from the study group ($r = 0.56$; $p < 0.05$) [66]. Five of the study group patients were treated with chelation therapy for siderosis with deferoxamine and one was treated with deferasirox. In the deferoxamine group, chelation therapy was associated with a significant reduction of liver gadolinium concentration from 0.64 to 0.20 μg/g ($p < 0.05$), and the patient who underwent the longest chelation therapy (14 weeks vs the mean of 9.6 weeks) achieved nearly complete gadolinium clearance [66]. The authors hypothesise that a transmetallation mechanism may occur between ferric iron and gadolinium-based contrast agents, resulting in gadolinium deposition within the liver of patients with siderosis. There was no concern that these patients had signs or symptoms related to gadolinium deposition although the authors concluded by recommending that physicians consider administering chelation therapy in patients with iron overload and a history of exposure to gadolinium-based contrast agents [66].

Semelka and his colleagues [40] published the results of a preliminary investigation into the administration of intravenous calcium and/or zinc trisodium pentetate to patients with "gadolinium deposition disease", a diagnosis made by an author who is a board-certified internist if they met criteria that were not specified in the paper [40]. It is therefore not possible to determine on what basis the diagnosis of "gadolinium deposition disease" was made or the pattern of clinical features present in those patients recruited. Patients in this study were managed at a unit which treats patients with a variety of conditions thought to be caused or potentiated by heavy metal toxicity [67]. This unit is reported to be well-regarded by many patients and their families who value the opportunity to access alternative therapies from medical practitioners [67]. However, concerns have been raised at this clinic by other authors relating to treatment and diagnosis of certain conditions, including amyotrophic lateral sclerosis, and the use of post-chelation urinary heavy metal testing for the diagnosis of heavy metal toxicity [67,68]. Of the 25 patients studied, it was self-reported by 13 that their symptoms had "improved", were "unchanged" in 10, and

"worsened" in 2 following chelation therapy [40]. However, as this was an uncontrolled study it is not possible to be certain what "improvement" meant to each individual patient and the extent to which any improvement (or deterioration) in clinical features related to calcium and/or zinc trisodium pentetate therapy.

Semelka et al. [40] also reported an increase in urine gadolinium concentrations following calcium and zinc trisodium pentetate administration, which they attributed to *in vivo* re-chelation of gadolinium from tissue deposits and describe improvement in various symptoms in 13 of the 25 patients. They stated that one of the criteria for "gadolinium deposition disease" in patients is "evidence of gadolinium in their system beyond 30 days."

Firstly, it is important to note that low-level background environmental exposure typically results in detectable blood and urine concentrations of heavy metals in healthy individuals [69,70], and as there are currently no published data in the literature regarding reference intervals for either blood or urine gadolinium concentrations there are no data to substantiate this statement. Furthermore, increased urine concentrations of heavy metals is the expected and predictable outcome following the administration of a chelating agent such as calcium trisodium pentetate. Hence, this does not indicate, as suggested by the authors, that baseline concentrations of gadolinium were elevated or that gadolinium was being removed from excess tissue reservoirs in these patients related to previous gadolinium-based contrast agent administration. It is also important to consider that if, as was suggested in the aforementioned paper, chelation therapy does remove gadolinium from tissue stores, there have historically been extensive conflicting reports as to whether chelation therapy may actually mobilise heavy metals deposited in bone into the circulation and subsequently lead to increased deposition in soft tissues, such as the brain and heart [71–74]. Whilst urine heavy metal concentrations can be helpful in assessing the impact of chelation therapy [75,76]; it is essential that these are not considered in isolation as an indicator of therapeutic efficacy.

The American College of Medical Toxicology issued a position statement in 2010 cautioning against the use post-chelation urine heavy metal testing to diagnosis heavy metal toxicity/poisoning, because this: "has not been scientifically validated, has no demonstrated benefit, and may be harmful when applied in the assessment and treatment of patients in whom there is concern for metal poisoning" [77]. The statement references multiple reports of poor patient outcomes, including deaths, as a result of electrolyte depletion following inappropriate use of chelation therapy [77–79].

Numerous toxicologists and experts in heavy metal toxicity have continued to express concern regarding inappropriate use of chelation challenge testing and reports of significant adverse events in patients who receive chelation therapy in the absence of heavy metal toxicity as an 'alternative medicine', including the death of a 5 year old child who was receiving succimer infusions as treatment for an autistic spectrum disorder [62,78,80].

Although the incidence of nephrogenic systemic fibrosis has dramatically declined in recent years, predominantly due to increased awareness of the risk of using gadolinium-based contrast agents in individuals with impaired renal function, patients with this condition could represent a suitable group in which to assess the efficacy of therapies to treat gadolinium excess. One case series reviewed the outcomes of eight patients with a clinical and histopathologic diagnosis of nephrogenic systemic fibrosis and the authors showed that there was a significant correlation ($p = 0.0286$) between the improvement of renal function and the improvement of nephrogenic systemic fibrosis symptoms [81]. Of the four patients who had an improvement in their renal function, two were patients with end-stage renal failure who underwent successful kidney transplant and two had acute kidney injury that resolved; all of these four patients had improvements in their symptoms of nephrogenic systemic fibrosis [81]. Of the remaining four patients, all had end-stage renal failure that progressed. This includes one patient who developed nephrogenic systemic fibrosis during an episode of acute kidney injury that subsequent resolved, As the patient's renal function recovered, her symptoms of nephrogenic systemic fibrosis improved, but she subsequently developed end-stage renal failure and underwent a kidney transplant that failed and her nephrogenic systemic fibrosis symptoms progressed [81].

Conclusions

The potential that gadolinium-based contrast agents may result in retention of gadolinium following administration in those with normal renal function has resulted in increased lay and scientific interest in the last few years. However, there is currently no published information from well-designed clinical studies that support a link between gadolinium deposition and clinical sequelae. Further research is required to determine whether there are risks associated with exposure to gadolinium-based contrast agents in patients with normal renal function, and clinicians should exercise caution when considering whether or not gadolinium is of relevance in patients reporting symptoms after administration of contrast agents. The inappropriate use of chelation therapy in patients with no clear evidence-based indication for their use potentially increases the risk of clinically significant harm to these patients from adverse effects of the chelation therapy.

Disclosure statement

No potential conflict of interest was reported by the authors.

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