Impact of Impaired Renal Function on Gadolinium Retention After Administration of Gadolinium-Based Contrast Agents in a Mouse Model

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Objectives: The aim of this study was to investigate the impact of impaired renal function on gadolinium (Gd) retention in various organs after Gd-based contrast agent injection.

Materials and Methods: After local animal care and review committee approval, 23 normal mice and 26 with renal failure were divided into 4 treatment groups (Gd-DTPA-BMA, 5 mmol/kg; Gd-DOTA, 5 mmol/kg; $GdCl_3$, 0.02 mmol/kg; and saline, 250 μL). Each agent was intravenously administered on weekdays for 4 weeks. Samples were collected on days 3 (short-term) and 45 (long-term) after the last injection. Gadolinium concentrations were quantified by inductively coupled plasma-mass spectrometry.

Results: Three mice with renal failure and 2 normal mice in the $GdCl_3$ group and 1 mouse with renal failure in the Gd-DTPA-BMA group died. In the Gd-DTPA-BMA group, impaired renal function increased short-term Gd retention in the liver, bone, spleen, skin, and kidney ($P < 0.01$) but did not affect long-term Gd retention. Gd-DTPA-BMA showed higher Gd retention than Gd-DOTA. Although Gd retention in the Gd-DOTA group was generally low, impaired renal function increased only long-term hepatic Gd retention. Hepatic and splenic Gd retentions were significantly higher than other organs' Gd retention in the $GdCl_3$ group ($P < 0.01$). Renal function did not affect brain Gd retention, regardless of the Gd compound used.

Conclusions: The tendency of Gd retention varied according to the agent, regardless of renal function. Although renal impairment increased short-term Gd retention after Gd-DTPA-BMA administration, long-term Gd retention for Gd-based contrast agents was almost unaffected by renal function, suggesting that the chemical structures of retained Gd may not be consistent and some Gd is slowly eliminated after initially being retained.

Key Words: gadolinium, gadolinium-based contrast agent, renal function, retention, mouse

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Gadolinium (Gd)-based contrast agents (GBCAs) are globally used on a daily basis in the field of diagnostic radiology,[1,2] and they are considered safe for use in clinical practice due to the low incidence of acute adverse reactions and rapid elimination by the kidneys.[3] However, a report published in 2006 suggested an association between GBCA exposure and nephrogenic systemic fibrosis (NSF) in patients with impaired renal function.[4] Furthermore, recent studies have shown that multiple administrations of GBCAs may lead to Gd retention in various tissues, even when renal function is normal.[5–7]

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Commercially available GBCAs can be characterized as linear or macrocyclic. Macrocyclic GBCAs are more stable and have lower dissociation rates compared with linear chelate GBCAs.[8,9] The Gd^{3+} in linear chelate GBCAs dissociates at a higher rate than that in macrocyclic GBCAs and then may bind to endogenous molecules or organic chelators such as phosphate or carbonate, resulting in Gd retention in various tissues.[9,10] Elimination of GBCAs from the human body primarily depends on renal function. In addition, NSF was reported in patients with chronic kidney disease, suggesting that renal function is one of the most important risk factors for the development of NSF.[11,12] However, it must be noted that the pathogenesis of NSF remains unclear, and the role of other confounding factors makes it more difficult to decipher the etiology.[13,14]

It has been assumed that NSF is related to delayed Gd elimination and accumulation in target organs, but several studies have shown that, in both animals and humans, Gd is retained in the kidneys, liver, bone, and brain despite the absence of renal failure.[15–18] The aim of this study was to investigate the impact of impaired renal function on Gd retention in various organs after multiple administrations of GBCAs, for better understanding the effect of renal function on the tissue retention of Gd.

MATERIALS AND METHODS

GBCAs and $GdCl_3$

Two GBCAs, listed with the respective pharmaceutical companies, were used in this study: Omniscan (Gd-DTPA-BMA, 0.5 mol/L; Daiichi-Sankyo Co, Ltd, Tokyo, Japan) and Magnescope (Gd-DOTA, 0.5 mol/L; Terumo Co, Tokyo, Japan). Gd(III) chloride hexahydrate ($GdCl_3$; molecular weight, 371.70) was purchased from Sigma-Aldrich Corporation (St Louis, MO). A solution of $GdCl_3$ was diluted with 0.9% saline to a concentration of 1.0 mol/L.

Animals

All study protocols were approved by the Institutional Animal Care and Use Committee of our institution. Forty-nine female ddY mice (aged 6-7 weeks; mean weight, 25.7 ± 0.7 g) were purchased from Japan SLC, Inc (Tokyo, Japan). Twenty-three normal mice were randomly divided into 4 groups to receive injections of the following agents: Gd-DTPA-BMA (n = 6), Gd-DOTA (n = 6), $GdCl_3$ (n = 6), and saline (n = 5).

To produce models of renal failure, electrocoagulation of the kidney was performed on 26 mice using the methods reported by Gagnon et al,[19] with some modifications. In brief, the mice were anesthetized by inhaled isoflurane (5% for induction; 2% for maintenance) supplemented with 2 mL/min of air and placed on their left side (ie, the opposite side of the incision site) on a heating pad. A 2-cm incision was made along the lumbar spine, and the kidney was exteriorized while keeping the capsule intact. Electrocoagulation of the entire kidney excluding the hilum was then performed. The electrocoagulated lesions were 2 mm apart and 1 mm deep, surrounded by blanched areas so as to cover the majority of the kidney. The treated kidney was returned to the retroperitoneal cavity. After a 10-day recovery period, the other

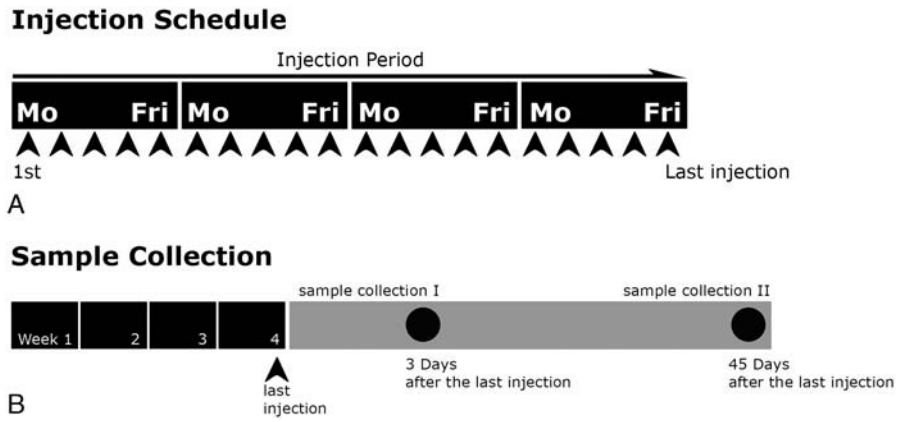

FIGURE 1. Injection and sample collection schedule. Three mice of each treated group was euthanized on days 3 after the last injection to analyze short-term Gd retention, while the other 3 mice were euthanized on days 45 after the last injection to analyze long-term Gd retention.

kidney was similarly treated. Confirmation of renal failure was performed by measuring the urea nitrogen level in the blood (BUN). Urea nitrogen is a waste product that is eliminated by the kidneys and thus may reflect the function of the kidneys.[20,21] We used a commercially available kit to measure the BUN (Wako Pure Chemical Industries, Ltd, Osaka, Japan). Based on a previously reported study,[22] BUN level of 30 mg/dL or higher was classified as impaired renal function. These mice with renal failure were randomly divided into 4 groups to be injected with the following injection agents: Gd-DTPA-BMA (n = 7), Gd-DOTA (n = 7), $GdCl_3$ (n = 7), and saline (n = 5). All authors were blinded with regards to the biological profile (eg, weight, BUN) of these mice.

All mice were housed in an approved animal facility at room temperature (27°C-28°C) with ad libitum access to food and water. The dorsal surface of the animals was shaved at the beginning of the study for skin observation and then reshaved every week. The mice were observed daily, and body weights were measured every weekday.

Injection Protocol

Each agent was intravenously administered via the tail vein every weekday for 4 weeks (Figs. 1, 2). Gd-DTPA-BMA and Gd-DOTA were injected at a dose of 5 mmol/kg, while $GdCl_3$ solution was injected at a dose of 0.02 mmol/kg. These GBCA doses were identical to those in to previous reports by Grant et al.[23] Mice in the control group received injections of 250 μL saline.

Retained Gd Analysis by Mass Spectrometry

Three days after the final injections, 3 mice from each group were euthanized by cervical dislocation to obtain the following organ samples: brain, liver, spleen, kidney, femoral bone, and skin. The samples were analyzed for Gd retention on days 3 after the last injection (short-term Gd retention). Cardiac perfusion was performed after cervical dislocation to remove the blood from the circulation. To prepare the anticoagulant solution, 3 mg of ethylenediaminetetraacetic acid (disodium EDTA; Dojindo, Inc, Tokyo, Japan) was added to 500 mL of phosphate-buffered saline solution. The solution was stirred using a magnetic glass stirrer while the pH level was adjusted to 8.1 by adding sodium hydroxide (NaOH). Before the cardiac perfusion, the heart was exposed by carefully cutting the ventral skin and the rib cage. The heart was then separated from the surrounding connective tissue. A flowing needle with anticoagulant solution was placed in the left ventricle, and then the right atrium was cut. Ten milliliters of EDTA solution

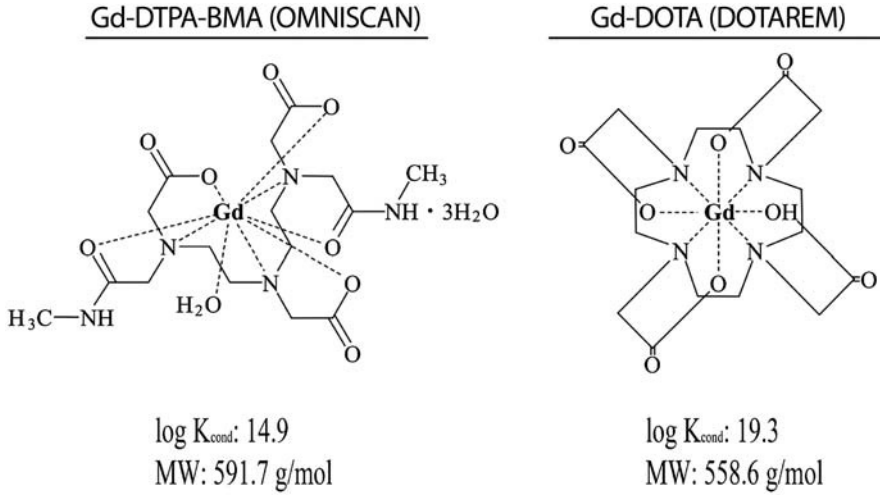

FIGURE 2. Chemical structure of Gd-DTPA-BMA and Gd-DOTA. log K_{cond} = conditional stability constant at pH 7.4; MW = molecular weight. Gd-DOTA show higher stability constant compared with Gd-DTPA-BMA.

was injected into the left ventricle, followed by 30 mL of phosphate-buffered saline (total 60 μg EDTA per 40 mL solution). Then, each sample was weighed, sealed in a perfluoroalkoxy vial along with 500 μL of nitric acid and 100 μL of hydrogen peroxide, and then subjected to sample digestion with 8 sequences of microwave program for 125 minutes (MLS 1200 Mega; Milestone Inc, Shelton, CT). After this procedure, ultrapurified water was added to each sample for a total volume of 10 mL. Finally, the accumulation of the stable Gd isotope (^{158}Gd) in each sample was measured by inductively coupled plasma-mass spectrometry (ICP-MS) using the ELAN DRC II instrument (PerkinElmer, Inc; Waltham, MA). The remaining mice were kept for 45 days after the final injection, whereupon the same organs were collected and analyzed using the same protocol to analyze Gd retention at 45 days after injection (long-term Gd retention).

Statistical Analysis

All data are expressed as means ± standard deviations. Analysis of variance was performed to analyze the main effect of renal function and specific organs on Gd retention, followed by the post hoc Tukey honest significant difference test. The effect size was determined by partial eta squared (η_p^2). SPSS software (version 23; IBM-SPSS, Inc, Chicago, IL) was used for data analyses. A P value of greater than 0.05 was considered statistically significant.

RESULTS

Animal Observations and ICP-MS Validation Experiments

All mice with renal failure survived the electrocoagulation surgeries. Similar with the previous study,[19] BUN levels in all of the electrocoagulated mice were greater than those in the control mice (58.4 ± 27.5 vs 6.3 ± 1.6 mg/dL, respectively, $P < 0.01$), whereas there was no difference in body weight between the treatment and control groups after 20 injections (29.0 ± 1.6 vs 29.8 ± 0.8 g, respectively, $P = 0.31$). Three of 7 mice with renal failure treated with $GdCl_3$ died during the injection period, whereas 2 of 6 normal mice treated with $GdCl_3$ died on days 11 and 17 after injection. Because of these deaths, we could not analyze long-term Gd retention in the $GdCl_3$ group due to an insufficient number of samples. One of 7 mice with renal failure in the Gd-DTPA-BMA group died on day 16.

Quantification of ICP-MS experiment was calculated by a linear regression graph of standard Gd solution. Linearity of the ICP-MS experiment was verified in the concentration up to 300 μg/g. The limit of detection was determined to be 0.015 μg/g; limits of detection for normal mice and renal failure mice were 0.015 μg/g and 0.005 μg/g, respectively. The limit of quantification was determined to be 0.05 μg/g.

Short-Term Gd Retention in Normal and Mice With Renal Failure

Gadolinium retention of Gd-DTPA-BMA depended on the renal function ($P < 0.01$, $\eta_p^2 = 0.58$). Renal failure increased total Gd concentrations in all tested tissue, except the brain and skin, indicating that delayed elimination of Gd-DTPA-BMA increased Gd retention. Each organ has different total Gd concentrations ($P < 0.01$, $\eta_p^2 = 0.71$) and was found to be significantly higher in the liver, bone, spleen, and kidney than in the brain (Fig. 3A).

In the Gd-DOTA group, Gd retention was much more affected by the organs ($P < 0.01$, $\eta_p^2 = 0.97$). Renal failure reduced total Gd concentration in the kidney ($P = 0.003$, $\eta_p^2 = 0.30$), but no significant difference was found in the other organs. Gadolinium retention was significantly higher in the kidney compared with the other organs (Fig. 3B).

Similar to the Gd-DOTA group, the $GdCl_3$ group was less affected by renal function, although the total Gd concentration in each organ was found to be completely different from the others. Gadolinium retention of $GdCl_3$ was much more affected by the organs ($P < 0.01$, $\eta_p^2 = 0.95$). Although renal failure reduced the total Gd concentration in the liver and spleen ($P < 0.01$, $\eta_p^2 = 0.31$), it did not affect the rest of the organs. Nevertheless, Gd retention was significantly higher in the liver and spleen than in the other organs (Fig. 3C).

Under conditions of normal renal function, we found a significant difference in Gd retention between Gd-DTPA-BMA and Gd-DOTA. Gadolinium retention was found to be higher in the brain ($P = 0.02$), bone ($P < 0.01$), and skin ($P = 0.04$) of the mice injected with Gd-DTPA-BMA, whereas Gd retention of Gd-DOTA was higher in the kidney ($P < 0.01$). In the impaired renal function group, Gd retention of Gd-DOTA was significantly lower than Gd-DTPA-BMA in the brain ($P = 0.01$), liver ($P = 0.03$), bone ($P < 0.01$), and spleen ($P < 0.01$) (Table 1).

Long-Term Gd Retention in Normal and Mice With Renal Failure

In the Gd-DTPA-BMA group, the long-term Gd retention varied among organs ($P = 0.01$, $\eta_p^2 = 0.61$), whereas no significant difference of Gd retention was found in the normal mice and renal failure mice ($P = 0.79$, $\eta_p^2 = 0.004$). These results indicated that long-term Gd retention in the Gd-DTPA-BMA group was not affected by renal function (Fig. 4A). Gadolinium retention was significantly higher in the liver and bone than in the brain.

Similar with the Gd-DTPA-BMA group, the long-term retention of Gd-DOTA group varied among organs ($P < 0.01$, $\eta_p^2 = 0.75$), whereas renal function did not affect Gd retention ($P = 0.69$, $\eta_p^2 = 0.007$). The

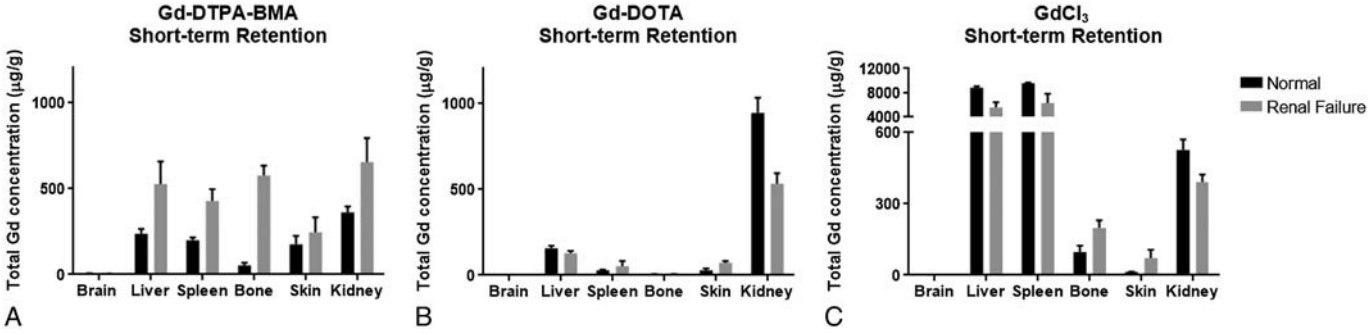

FIGURE 3. Short-term Gd retention in the organs after injections of Gd-solution. A, Renal failure increases the short-term Gd retention in the liver, spleen, bone, and kidney of Gd-DTPA-BMA group. B, Gd retention in the kidney was significantly higher than the other organs ($P < 0.01$). C, Gd retention was significantly high in the liver and spleen compared with the other organs ($P < 0.01$).

TABLE 1. Gd Concentration in the Normal Mice After Multiple GBCA Administrations

	Short-Term			Long-Term		
Organs	**Gd-DOTA (n = 3, μg/g)**	**Gd-DTPA-BMA (n = 3, μg/g)**	***P***	**Gd-DOTA (n = 3, μg/g)**	**Gd-DTPA-BMA (n = 3, μg/g)**	***P***
Brain	1.4 ± 0.2	5.04 ± 1.6	0.02*	0.2 ± 0.04	2.6 ± 0.5	<0.01
Liver	156.8 ± 25.7	236.8 ± 48.3	0.06	21.9 ± 0.9	250.0 ± 54.2	<0.01
Spleen	28.5 ± 7.7	198.1 ± 28.2	<0.01*	5.8 ± 3.2	67.9 ± 83.0	0.3
Bone	6.3 ± 0.6	52.9 ± 27.4	0.04*	6.7 ± 4.6	203.3 ± 33.4	<0.01
Skin	28.6 ± 19.3	175.0 ± 83.8	0.04*	1.4 ± 0.5	76.2 ± 50.2	0.06
Kidney	942.5 ± 152.5	360.5 ± 59.5	<0.01*	186.9 ± 39.3	40.6 ± 17.8	<0.01

Each value represents mean ± SD of 3 mice. Values are expressed as a total Gd dose per gram of organ (μg/g).

*Significant difference in Gd concentrations between 2 groups with different GBCA administrations.

Gd indicates gadolinium; GBCA, gadolinium-based contrast agents.

long-term Gd retention in the kidney and liver was significantly higher than in the brain (Fig. 4B).

We found significant differences in Gd retention between the Gd-DTPA-BMA and Gd-DOTA groups. Total Gd concentrations of Gd-DTPA-BMA in the brain, liver, and bone were higher than those of the Gd-DOTA group ($P < 0.05$) (Table 2).

DISCUSSION

Although renal impairment was found to affect short-term Gd retention for each agent differently, it hardly affected long-term Gd retention. In the Gd-DTPA-BMA group, renal impairment increased short-term Gd retention in most organs, whereas in the Gd-DOTA group, renal impairment increased long-term Gd retention only in the liver. In the $GdCl_3$ group, renal impairment had a limited effect on short-term retention. Long-term Gd retention could not be analyzed due to animal death.

Each agent used in this study exhibited a different tendency of Gd retention. In the Gd-DTPA-BMA group, Gd retention in the liver, spleen, bone, and kidney was significantly higher than that in the brain, whereas in the Gd-DOTA group, Gd retention in the kidney and liver was significantly higher than that in the brain. In the $GdCl_3$ group, Gd retention in the liver and spleen was significantly higher than that in other organs. Moreover, Gd retention in the Gd-DOTA group was lower than that in other agents.

Chelation changes the chemical properties of Gd, reducing its toxicity and enabling its elimination by the kidney.[24] An in vitro study of human serum showed that macrocyclic GBCAs remained stable even after 2 weeks, suggesting that Gd-DOTA was stable and remained concentrated in the kidney until eliminated.[10] Because high doses were injected, the kidney likely required more time to eliminate the remaining GBCA. After the series of injections was completed, Gd was gradually eliminated and only a small amount remained in the kidney. Under conditions of renal failure, the elimination rate of Gd-DOTA by the kidney may be decreased, thus resulting in a higher Gd concentration in not only the kidney but also the liver at 45 days. This finding is consistent with a previous study by Wadas et al,[22] which demonstrated that the biodistribution of $^{153/Nat}$Gd-DOTA at 7 days after injection was higher in the liver of renal-impaired mice than normal mice. Both short-term and long-term Gd retentions in other organs of the Gd-DOTA group were significantly lower than those of the Gd-DTPA-BMA group.

The lower stability and higher dissociation rate of linear GBCAs[8,9] may have influenced Gd retention in the Gd-DTPA-BMA group. The use of Gd-DTPA-BMA has been associated with high Gd retention in bone,[15,25] especially in the renally impaired mice,[22] and with skin fibroblast stimulation.[26–28] The dissociation of chelated Gd releases Gd^{3+} ions, which may form Gd-complexes with endogenous molecules, such as phosphate, carbonate, hydroxide, or citrate.[29] However, these unchelated Gd compounds may not be eliminated by the kidney, resulting in long-term retention in the tissues. Although these chemical structures may have been retained in the organs of the Gd-DTPA-BMA group, the organ Gd retention was different from that of the $GdCl_3$ group. The insoluble form of Gd in $GdCl_3$ was mostly phagocytosed by Kupffer cells and splenic macrophages,[3,30] resulting in remarkably high retention in the liver and spleen, which was not affected by renal impairment.

These results suggest that retained Gd in various tissues, especially when Gd-DTPA-BMA is administered, may have 2 or more

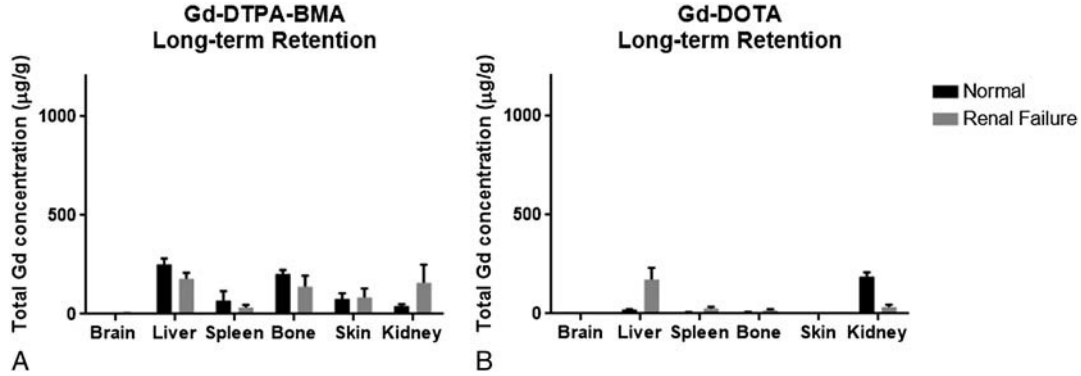

FIGURE 4. Long-term Gd retention in the organs after injections of Gd solution. A, In Gd-DTPA-BMA group, the amounts of Gd retention between the normal mice and renal failure mice were similar. B, In Gd-DOTA group, renal failure increases the long-term Gd retention in the liver.

TABLE 2. Gd Concentration in the Renal Failure Mice After Multiple GBCA Administrations

	Short-Term			Long-Term		
Organs	**Gd-DOTA (n = 3, μg/g)**	**Gd-DTPA-BMA (n = 3, μg/g)**	***P***	**Gd-DOTA (n = 3, μg/g)**	**Gd-DTPA-BMA (n = 3, μg/g)**	***P***
Brain	0.6 ± 0.1	4.05 ± 1.44	0.01*	0.1 ± 0.02	3.76 ± 1.11	<0.01*
Liver	127.7 ± 23.8	525.4 ± 226.7	0.03*	173.3 ± 100.4	179.3 ± 50.3	0.9
Spleen	52.6 ± 53.3	426.3 ± 119.3	<0.01*	25.3 ± 17.9	33.4 ± 22.2	0.6
Bone	5.8 ± 2.1	574.4 ± 98.0	<0.01*	16.2 ± 11.5	138.4 ± 97.6	0.09
Skin	72.3 ± 18.6	245.1 ± 152.0	0.1	0.4 ± 0.04	84.6 ± 78.2	0.1
Kidney	531.3 ± 106.3	653.0 ± 240.9	0.4	33.4 ± 22.2	157.7 ± 159.0	0.2

Each value represents mean ± SD of 3 mice. Values are expressed as a total Gd dose per gram of organ (μg/g).

*Significant difference in Gd concentrations between 2 groups with different GBCA administrations.

Gd indicates gadolinium; GBCA, gadolinium-based contrast agents.

different chemical structures. Some of the unchelated Gd compounds (eg, $GdPO_4$, and $Gd_2(CO_3)_3$) are insoluble and may not be eliminated by the kidney, resulting in their longer retention in tissues. Other Gd compounds, including chelated Gd, may be slowly eliminated even if initially retained in the tissues. Birka et al[31] found both insoluble and chelated Gd in a skin sample of a 25-year-old woman with NSF.

Retained Gd in brain tissues with an intact blood-brain barrier (BBB) challenges our current understanding of the biodistribution of GBCAs in the brain. Because systemic hypertension in patients with renal failure may disrupt the BBB,[32,33] it was expected that Gd retention in the brain of mice with renal failure would be higher than that of normal mice. However, there was no difference in Gd retention between normal mice and mice with renal failure, regardless of the Gd compound used. These data suggest that the mechanism of Gd retention in the brain was not affected by renal function.

There were some limitations to this study. First, the organ sample analysis process included nitric acid digestion, so it was not possible to determine whether the retained Gd was chelated Gd, free Gd, or some other Gd complex. Furthermore, the use of EDTA as an anticoagulant may have led to a reduction of Gd in the sample, particularly Gd-DTPA-BMA, because the thermodynamic stability constant of EDTA toward Gd (Log K' = 14.7) is almost the same as DTPA-BMA (Log K' = 14.9).[34] However, it must be noted that only 60 μg of EDTA was added to each wash blood from the carcass of each animal. Thus, the maximum amount of Gd that can be lost by EDTA is only 0.5% of the average Gd retention in the Gd-DTPA-BMA group (2 μmol EDTA may lead to the loss of 25 μg Gd in a 30-g mouse). In addition, the EDTA was restricted primarily to the blood part of the sample due to the saline flush. Hence, with all of these factors put together, we considered that the effect of the EDTA is negligible. Second, other target organs for Gd retention, such as the bowel, which may be involved in Gd elimination, were not evaluated.

The use of linear GBCAs in patients with renal impairment has been associated with NSF,[11,35] whereas the use of macrocyclic GBCAs has not.[36] Although renal impairment increases exposure time, which increases the potential of dissociation of GBCA, Gd-DOTA remained mostly stable and was continuously eliminated by the kidney. The lower Gd retention suggests that high-dose injections of Gd-DOTA were safer than those of Gd-DTPA-BMA. Although the effect of Gd retention remains unclear, these differences in retention may influence the adverse effects of Gd, especially the development of NSF. The results of this study showed less Gd retention in the Gd-DOTA group than in the Gd-DTPA-BMA group for most of the analyzed organs. This finding is consistent with that of previous reports.[10,11,16]

In conclusion, the retention of each Gd-based agent tended to differ among the studied organs, regardless of renal function, and Gd retention was greater when Gd-DTPA-BMA was administered, as compared with Gd-DOTA. Although renal impairment increased short-term Gd retention in various organs after Gd-DTPA-BMA administration, long-term Gd retention for the GBCAs was almost unaffected by renal function. These findings suggest that the chemical structures of retained Gd may not be homogenous and some Gd could be slowly eliminated after being initially retained in the tissues. Meanwhile, Gd retention in the brain may not be affected by renal function, and the presence of the BBB likely plays a role in the mechanism of Gd retention in the brain.

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