Gadolinium Retention from Contrast MRIs in 70 Cases with Normal Renal Function

24-hour Urine Test Results

Abstract:
In 2006, a connection was made between Gadolinium-based Contrast Agents (GBCAs) administered for contrast-enhanced MRIs and Nephrogenic Systemic Fibrosis (NSF). NSF is a potentially fatal disease that has been diagnosed almost exclusively in patients with end-stage renal disease (ESRD). Prolonged excretion times and the instability of the GBCA results in the toxic gadolinium ion separating from the ligand and remaining in the body, where it can cause extensive fibrosis and calcification of tissues. Aside from their role in NSF, GBCAs have historically been considered safe. Patients with normal renal function are told that the contrast agent will be out of their body within a few days. We first reported evidence of long-term gadolinium retention in October, 2013[1]. In December of 2013, Kanda published the first paper to report evidence of gadolinium deposition in the brains of patients with normal renal function. Although more studies are being conducted, very little is known about long-term retention of gadolinium in patients with normal renal function.

In this study, 70 cases are analyzed involving 120 tests for gadolinium in 24-hour urine collections, performed from as few as 4 days to as long as 10 years after contrast administration. The subjects for the analysis are patients who believe they have symptoms of gadolinium toxicity caused by their contrast-enhanced MRIs. In cases where urine tests were performed within the 3 months following contrast administration, none had a result that was within the reference range used by Mayo Clinic Laboratories. Cases with multiple contrast MRIs show elevated gadolinium levels for longer time periods than those with a single contrast administration. Overall, the results of this study conflict with the published clearance times of GBCAs and indicate levels of increased chronic toxicity from multiple contrast administrations. Both of these results have the potential to produce Gadolinium Toxicity with NSF-like symptoms in patients with normal renal function. Further investigation by researchers, GBCA manufacturers, and licensing agencies is warranted.

No attempt is made to determine what, if any, level of gadolinium is safe to remain in the body. The authors, who are study participants, take sole responsibility for the content of this document.

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We began releasing our research papers regarding gadolinium toxicity in March of 2013[2]. The material in the three papers was drawn from published medical research papers and information we collected from members of a support group created for people who are gadolinium toxic from receiving a Gadolinium-based Contrast Agent (GBCA) for their MRIs. Our most recent paper, Survey of the Chronic Effects of Retained Gadolinium from Contrast MRIs [3], was released in April, 2014. Since then it has been increasingly recognized that gadolinium from contrast-enhanced MRIs is retained in the body of patients with normal kidney function. On July 27, 2015, the FDA issued its first Safety Announcement regarding brain deposits of gadolinium following repeated use of a GBCA, even in patients with normal kidney function[4]. From the initial 2013 study by Kanda et al.[5] to the recently published description of Gadolinium Deposition Disease by Semelka et al.[6], we have seen many new studies that describe various aspects of retention of toxic gadolinium by people with normal kidney function. In addition, the authors have seen new information shared by the many people who have joined the MRI-Gadolinium-Toxicity support group since early 2014. These people all have normal renal function and report having symptoms of gadolinium toxicity.

We present further documentation of high gadolinium levels in urine well beyond the clearance times indicated on GBCA product labeling. The consistent results demonstrate the levels of gadolinium that can be expected depending on the time since the last administration of a Gadolinium-based Contrast Agent. For the first time, we show how the results vary depending on the number of doses of contrast received.

We believe that the people from whom we have gathered this information provide the most fertile study opportunity regarding the clinical implications of retained gadolinium and therefore make the case that those looking for clinical implications should take the opportunity to study these individuals by contacting the authors.

Gadolinium Urine Test Results for 70 Cases

In our Survey of the Chronic Effects of Retained Gadolinium from Contrast MRIs, we presented updated gadolinium retention information observed in 24-hour urine collections for 15 cases that included 40 standard urine test results. We now present results for 70 cases with 120 urine tests performed without provocation by a chelating agent that might increase the excretion of gadolinium. With the higher number of tests and additional information from the people tested, we are now able to analyze the results based on the number of contrast MRIs received. The only criteria for inclusion of individuals was that they had normal kidney function, had received a contrast-enhanced MRI, and had a 24-hour urine test for gadolinium. There was no range requirement for the test results. Although we did not have any requirement for the symptoms experienced, it is not likely that these people would have found our Support Group or www.GadoliniumToxicity.com if they were not experiencing symptoms that they attributed to their contrast MRI.

Data Collection and Reporting

In 2012, a Yahoo Group was created to provide collective support to those people with gadolinium toxicity from contrast MRIs. It is a closed group with membership limited to affected people or members of their families. As of this writing, the group has over 225 members. All postings are private to the group. In addition to providing mutual support, we have invited members to share their test results with the authors and we have surveyed them on multiple occasions regarding the symptoms they have experienced since their MRIs. Each of the individuals has agreed to the anonymous inclusion of his or her information.

We did not control any of the urine testing done by the individuals and their doctors. We have simply used their self-reported results retrospectively. With the exception of one case in which the participant was tested in

Europe, the tests were performed by three labs - Mayo Medical Laboratories, Genova Diagnostics, and Doctor's Data. Many people had testing performed at more than one lab, and from that information we have determined that the results are consistent across labs within expected accuracy levels. There is no broadly utilized acceptable range for gadolinium in a 24-hour urine collection. Mayo Clinic has established a reference range that was recently updated to be 0.0-0.6 mcg Gd/24-hour urine specimen collected more than 96 hours after administration of a GBCA.

Since we now have many more test results, we use, at most, three results from any individual - their first test result, their last test result, and a result from the middle time frame. Not all individuals had three test results. We have also collected information on the number of contrast MRIs each person has undergone and the agent received, when available. Because of the small per-agent sample size, we decided not to report test results by agent administered except to note that both linear and macrocyclic agents were reported for 34 unconfounded cases (28 single contrast and 6 multiple contrast).

Gadolinium Retention - Urine Test Results

The information presented in Tables 1 and 2 demonstrates that, contrary to what GBCA product labeling indicates should occur, the gadolinium in our study group did not clear the body within a few days. As a result, this finding conflicts with what most practitioners believe will happen.

Table 1: Early Urine Test Results

Case #	Months Since Last Contrast	mcg Gd/24hr	# of Contrast MRIs
844	0.13	507.0	6
424	0.30	182.0	3
749	0.33	272.0	8
782	0.40	240.0	2
436	0.40	68.0	1
817	0.46	29.9	1
533	0.46	60.0	7
838	0.50	95.0	1
506	0.56	72.0	1
520	0.56	39.7	1
835	0.59	55.0	3
427	0.69	49.8	4
562	0.73	77.0	2
132	0.79	17.0	2
239	0.79	16.0	2
658	0.79	56.8	3
375	0.83	17.0	1
126	0.83	27.0	1
625	0.83	30.0	3
914	0.92	17.9	1
289	0.96	82.0	4

Table 1 shows the early urine test results for the 21 cases in which urine testing was performed in the first month following their contrast MRI. Gadolinium content in urine was considerably high even at 4 weeks following a contrast-enhanced MRI, and it had not cleared the body in a few days as most medical practitioners believe will occur. Note that we have shown results for all people who had a 24-hour urine test for gadolinium performed in the first 30 days after their contrast MRI. The results are considerably higher than Mayo Clinic's reference range of 0.0-0.6 mcg Gd/24-hour specimen even after 30 days.

Table 2: Long-term Urine Test Results

Case #	Months Since Last Contrast	mcg Gd/24hr	# of Contrast MRIs
178	38.94	0.1	2
804	42.71	0.5	6
916	57.49	0.5	3
503	57.43	0.2	3
407	70.99	0.3	5
322	71.00	0.6	7
201	86.04	0.6	9
876	124.85	0.1	1

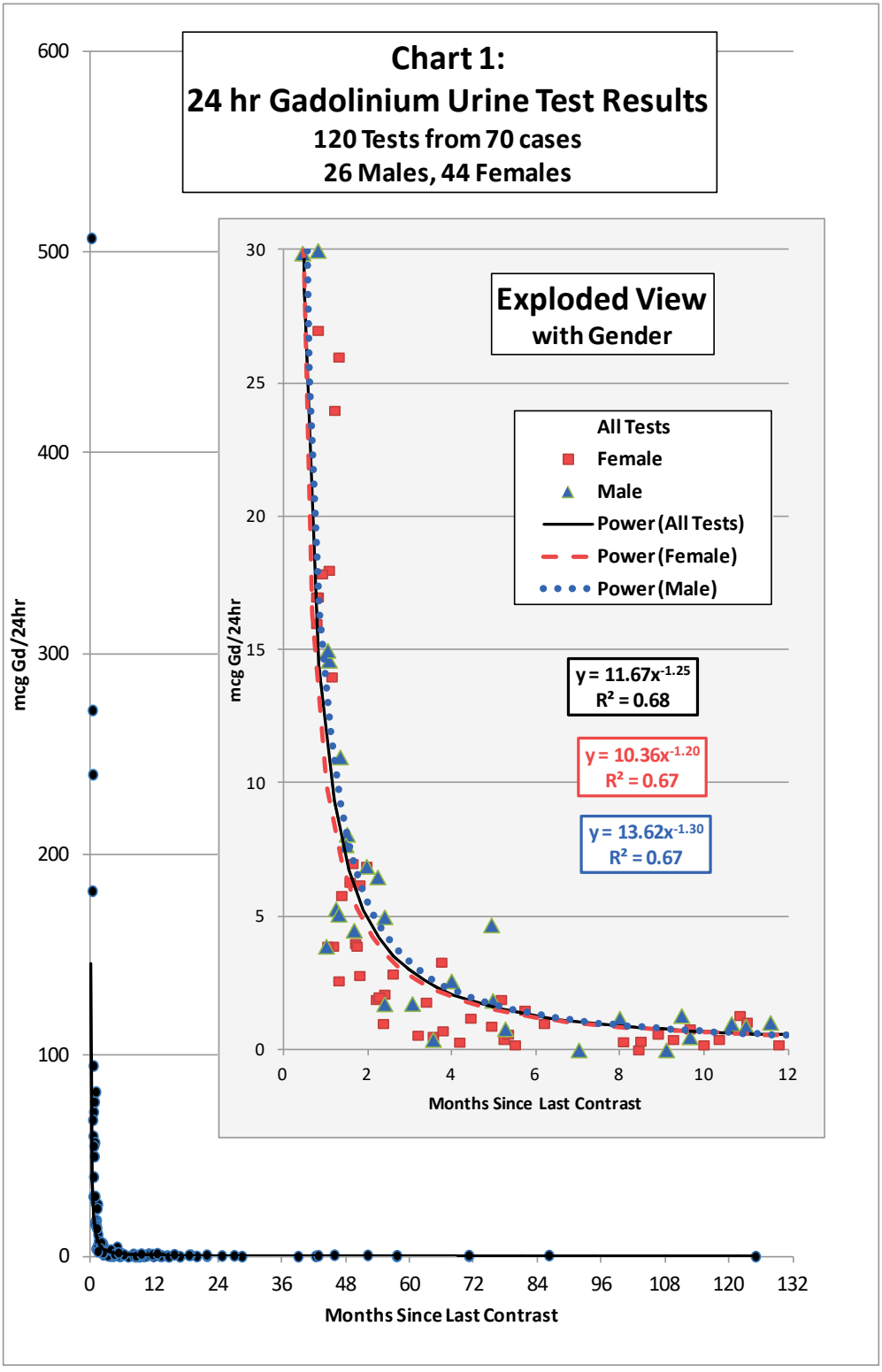
At the other end of the time spectrum are 8 cases in which the individual had urine testing performed more than 3 years after his/her last contrast MRI. The results in Table 2 demonstrate long-term gadolinium retention in the body. Although this is a small sample, the urine test result levels appear to be related to the number of contrast MRIs.

All Gadolinium Urine Test Results

Chart 1 presents all test results for all months and all values without regard to the number of contrast MRIs the patient had received (the same format we used in our prior report). The Exploded View with Gender shows additional detail including gender for tests in the first 12 months and up to 30 mcg Gd/24hr. Note that the results follow the trend line in an orderly manner with only a few outliers. Information about the outliers is presented later in this paper.

The gender information indicates that there is no discernible difference in the test results. Even the trend lines are nearly identical. We speculate that the difference in the number of cases, 26 males and 44 females, simply reflects the greater propensity for females to join support groups.

The r-squared value for all tests of 0.68 is an indication of closeness of fit for the trend line. In the next section, we present separate trend lines based on the number of contrasts received, improving the r-squared value.



All Gadolinium Urine Test Results - by number of contrast MRIs received

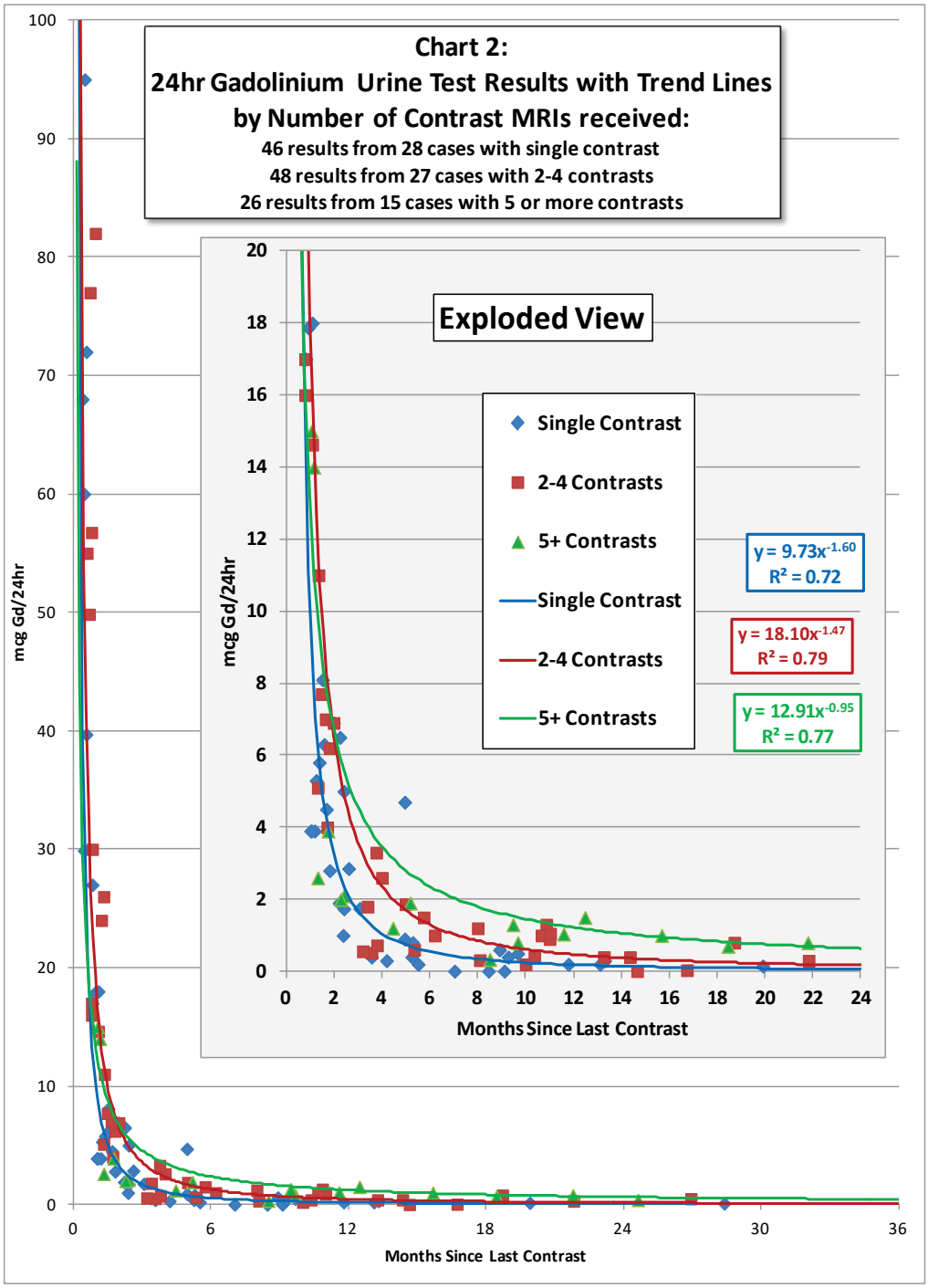
Chart 2 separates the results by the number of contrast MRIs received - grouped as:

- Single contrast
- 2-4 contrasts
- 5 or more contrasts

All test results are included in the trend line computations, but the axes are truncated to enable greater visibility of the results. An exploded view shows results for the first 12 months following contrast MRI and up to 20 mcg Gd/24hr. Tables 3 and 4 show the raw values used in creating these charts.

Note that the data points and trend lines for Single Contrast results (blue diamond) are lower earlier, followed by the 2-4 Contrasts (red square), and then the 5+ Contrasts (green triangle) are markedly higher later, indicating a cumulative effect from multiple contrast MRIs.

The r-squared values for each of the trend lines (0.72 for test results of cases with a single contrast, 0.79 for test results of cases with 2 to 4 contrasts, and 0.77 for test results of cases with 5 or more contrasts) are higher than the r-squared value (0.68) for the trend line of all tests as shown in Chart 1. This indicates that separating test results by number of contrast MRIs produces more accurate trend lines.



Test Results by Case

In our previous publications, we have shown test results without reference to the individuals receiving those results. Test results by case number are shown below in Table 3 for those with a Single Contrast MRI, and then separately in Table 4 for those with Multiple Contrast MRIs. Please note that we have shown all of the results we have received, even those that may seem to be outliers.

Table 3: 24 hr Gadolinium Urine Test Results for 28 Cases with a Single Contrast MRI

		24hr Unprovoked Test Results							Month time blocks since last contrast (if a case had two results in a time block, average was used)									
		1st		2nd		3rd												
Line	Case #	**mcg Gd**	Mo.	**mcg Gd**	Mo.	**mcg Gd**	Mo.	Contrasts	0-0.5	0.5-1	1-3	3-6	6-12	12-24	24-36	36-48	48-60	60-132
1	436	**68.00**	0.40	**0.40**	3.56			1	68.00			0.40						
2	533	**60.00**	0.46	**5.30**	1.25			1	60.00		5.30							
3	817	**29.90**	0.46					1	29.90									
4	838	**95.00**	0.50	**18.00**	1.09	**2.86**	2.61	1	95.00		10.43							
5	520	**39.70**	0.56	**3.90**	1.19			1		39.70	3.90							
6	506	**72.00**	0.56	**8.10**	1.52	**6.90**	1.98	1		72.00	7.50							
7	126	**27.00**	0.83	**0.40**	5.25	**0.01**	8.45	1		27.00		0.40	0.01					
8	375	**17.00**	0.83					1		17.00								
9	914	**17.87**	0.92	**0.10**	28.38			1		17.87					0.10			
10	134	**3.90**	1.02					1			3.90							
11	574	**3.90**	1.06	**1.00**	2.38			1			2.45							
12	863	**5.80**	1.39	**1.90**	2.21	**0.30**	4.19	1			3.85	0.30						
13	215	**6.30**	1.58					1			6.30							
14	741	**4.50**	1.68					1			4.50							
15	709	**2.80**	1.82					1			2.80							
16	542	**6.50**	2.24					1			6.50							
17	356	**1.74**	2.41	**0.01**	9.11			1			1.74		0.01					
18	353	**5.00**	2.41					1			5.00							
19	243	**1.75**	3.07					1				1.75						
20	271	**4.70**	4.95	**0.01**	7.03			1				4.70	0.01					
21	329	**0.90**	4.95	**0.60**	8.91	**0.30**	13.30	1				0.90	0.60	0.30				
22	640	**0.80**	5.28					1				0.80						
23	490	**0.20**	5.51					1				0.20						
24	654	**0.50**	9.67	**0.15**	19.90			1					0.50	0.15				
25	230	**0.40**	9.27					1					0.40					
26	287	**0.20**	11.78					1					0.20					
27	328	**0.20**	13.10					1						0.20				
28	876	**0.10**	124.85					1										0.10
	28	**Total**						**Average**	**63.23**	**34.71**	**4.94**	**1.18**	**0.25**	**0.22**	**0.10**			**0.10**

Notes to Table 3:

We would call the reader's attention to the following:

1. There is consistency in the pattern of urine test results across the cases.
    a. If tested within the first month, the results are always in double digits.
    b. The results always go down as time passes.

2. In lines 7, 17, and 20, the boxed 0.01 mcg Gd/24hr results reflect the only cases in which people received a result of "less than detectable limit of the test". The notation of 0.01 is used as a convenience. Note that they are all in the 7 to 9-month time period since the contrast MRI.

3. For the case on Line 20, the result of 4.70 mcg Gd/24hr at 4.95 months since the contrast MRI appears to be an outlier. A result of approximately 1.0 mcg Gd/24hr would have been more typical. It is then followed by the "less than detectable limit" result at 7.03 months since contrast, a remarkable change from exceedingly high to very low in a short time period. We have no explanation but simply include it in our results. Since the test results are time dependent, repeating the test is not possible.

4. On line 28, we report a test result of 0.1 mcg Gd/24hr at 10 years following a single contrast MRI. This is the longest time period for which we have a test result. A positive result this long after contrast administration is surprising since the trend line for single contrast results shown in Chart 2 would predict a value of 0.004 mcg Gd/24hr. Interestingly for this case, approximately one week following this urine test, a provoked test was done following IV Chelation with a result that was approximately 25 times higher than the unprovoked result. We will provide a review of gadolinium urine test results with chelation in a future paper.

Table 4: 24 hr Gadolinium Urine Test Results for 42 Cases with Multiple Contrast MRIs

		24hr Unprovoked Test Results							Month time blocks since last contrast (if a case had two results in a time block, average was used)									
		1st		2nd		3rd												
Line	Case #	mcg Gd	Mo.	mcg Gd	Mo.	mcg Gd	Mo.	Contrasts	0-0.5	0.5-1	1-3	3-6	6-12	12-24	24-36	36-48	48-60	60-132
1	844	**507.00**	0.13	**15.00**	1.06			6	507.00		15.00							
2	424	**182.00**	0.30	**11.00**	1.35			3	182.00		11.00							
3	749	**272.00**	0.33	**2.00**	2.28			8	272.00		2.00							
4	782	**240.00**	0.40	**24.00**	1.22			2	240.00		24.00							
5	835	**55.00**	0.59					3		55.00								
6	427	**49.84**	0.69					4		49.84								
7	562	**77.00**	0.73	**5.10**	1.32			2		77.00	5.10							
8	658	**56.75**	0.79	**1.80**	3.40			3		56.75		1.80						
9	132	**17.00**	0.79	**0.31**	8.09			2		17.00			0.31					
10	239	**16.00**	0.79	**1.50**	5.74	**0.40**	13.27	2		16.00		1.50		0.40				
11	625	**30.00**	0.83	**7.70**	1.49			4		30.00	7.70							
12	289	**82.00**	0.96	**3.30**	3.76	**1.00**	6.20	4		82.00		3.30	1.00					
13	383	**14.63**	1.09					2			14.63							
14	484	**14.00**	1.16					9			14.00							
15	360	**26.00**	1.32	**0.60**	5.35			2			26.00	0.60						
16	680	**2.60**	1.32					10			2.60							
17	157	**7.00**	1.65					2			7.00							
18	488	**3.90**	1.75					5			3.90							
19	503	**6.20**	1.82	**0.50**	26.93	**0.20**	57.43	3			6.20					0.50	0.20	
20	631	**4.00**	1.95					2			4.00							
21	537	**6.90**	1.98	**1.05**	11.02			4			6.90		1.05					
22	521	**2.10**	2.41	**0.80**	9.67			5			2.10		0.80					
23	185	**0.56**	3.20	**0.20**	10.00	**0.01**	14.65	3				0.56	0.20	0.01				
24	359	**0.52**	3.56					2				0.52						
25	586	**0.72**	3.80					2				0.72						
26	402	**2.60**	4.00	**1.20**	8.00	**0.90**	11.00	2				2.60	1.05					
27	377	**1.20**	4.46					5				1.20						
28	869	**1.87**	4.98					2				1.87						
29	366	**1.90**	5.18	**1.50**	12.48			11				1.90		1.50				
30	423	**0.30**	8.50					10					0.30					
31	168	**1.30**	9.47					6					1.30					
32	467	**0.40**	10.36					4					0.40					
33	345	**1.00**	10.66	**0.40**	14.36			3					1.00	0.40				
34	916	**1.30**	10.86	**0.80**	18.71	**0.50**	57.49	3					1.30	0.80			0.50	
35	201	**1.04**	11.58	**0.79**	45.74	**0.61**	86.04	9					1.04			0.79		0.61
36	650	**1.00**	15.68	**0.80**	21.78			9						0.90				
37	761	**0.04**	16.73					2						0.04				
38	804	**0.70**	18.45	**0.50**	42.71			6						0.70		0.50		
39	379	**0.30**	21.82					3						0.30				
40	407	**0.40**	24.62	**0.24**	42.24	**0.30**	70.99	5							0.40	0.24		0.30
41	178	**0.08**	38.94					2								0.08		
42	322	**0.70**	52.00	**0.60**	71.00			7									0.70	0.60
	42	**Total**						**Average**	**300.3**	**47.9**	**9.5**	**1.5**	**0.8**	**0.6**	**0.4**	**0.4**	**0.5**	**0.5**

Notes to Table 4: Gadolinium Test Results for Cases with Multiple Contrast MRIs

1. On line 23, the boxed 0.01 mcg Gd/24hr result reflects the only Multiple Contrast Case in which the participant received a result of "less than detectable limit of the test". This occurred approximately 15-months after the participant's last contrast MRI.
2. We would call the reader's attention to the fairly consistent test results in the 0.5 mcg Gd/24hr range for years 2 through 7 following the last contrast MRI.

Average Results by Time Period

Looking at both sets of averages, we see the following:

Comparison of Average Results

	Months since last contrast									
	0-0.5	0.5-1	1-3	3-6	6-12	12-24	24-36	36-48	48-60	60-132
Single Contrast MRI Average	**63.23**	**34.71**	**4.94**	**1.18**	**0.25**	**0.22**	**0.10**			**0.10**
Multiple Contrast MRIs Average	**300.25**	**47.95**	**9.51**	**1.51**	**0.81**	**0.56**	**0.40**	**0.42**	**0.47**	**0.50**

Notes to Comparison of Average Results:

1. As would be expected, the results for cases with Multiple Contrast MRIs are higher than those with a Single Contrast MRI. A closer look at the results in the time period from 0 to 0.5 months (the first two weeks) following contrast administration reveals that the very large difference between Single Contrast cases and Multiple Contrast cases is strongly influenced by the timing of the tests in the different groups. In the Single Contrast cases, the earliest test was at 0.40 months following contrast, while in the Multiple Contrast cases there were 3 very high results between 0.13 months and 0.33 months as can be seen in the previous tables.
2. In the 3-6 month time frame, the Single Contrast Average of 1.18 mcg Gd/24hr is strongly influenced by the outlier result of 4.70 mcg Gd/24hr at 4.95 months on line 20 of Table 3. If we exclude that outlier result, the Single Contrast Average would be 0.68 mcg Gd/24hr for that time frame. A comparison of the time periods from month 3 through the end of the table would then indicate that mcg Gd/24hr for cases with multiple contrasts is two or more times the result for cases with a single contrast.

Possible Influencing Factors

There are two factors that appear to contribute to higher urine levels of gadolinium, but we have an insufficient number of results to present them statistically. We believe it is important to present them here for possible future focus by professional researchers.

1. Extravasation of the contrast agent into the surrounding tissue seems to cause higher test results for an extended period of time, and with that increase, an increase in the associated symptoms, particularly chronic burning pain near the site of the extravasation.
2. For cases with multiple contrast MRIs, the time interval between contrast-enhanced MRIs appears to affect the gadolinium urine levels. Shorter intervals appear to produce higher urine test results for longer time periods. Some support group members with the highest long-term test results and chronic symptoms received multiple doses of contrast within days, weeks, or a few months of each other. A study of this relationship would require a much larger universe of cases and test results.

Discussion

From the material presented, we believe the following are noteworthy:

- To the best of our knowledge, this is the most comprehensive reporting of retained gadolinium as evidenced by gadolinium concentration in 24-hour urine collections. While we understand that our methods do not meet the rigor associated with a clinical trial, our results are the best information presently available to the public on this topic. The gathering of this type of testing information is non-invasive and can be easily undertaken by professional researchers, and we encourage them to conduct similar studies.
- One thing we do not know is whether the results shown here would apply to all patients receiving a contrast MRI, or whether there is something different or unique about the people whose test results are shown here. Because of the consistency of these urine test results and particularly the lack of outliers on the low side, we believe there is the possibility that similar urine gadolinium levels will be found in all people who receive contrast-enhanced MRIs.
- Although we did not present any data based on the agents administered, it is important to note that the agents reported by study participants include unconfounded cases of both linear and macrocyclic GBCAs as noted above. We believe that further investigation by researchers, GBCA manufacturers, and licensing agencies is warranted.
- We find it revealing that for 70 cases, only a few have test results that are not close to the results expected by looking at the other people's results. Even with the differences in people, their medical conditions, medications, diet and exercise habits, the results are rather predictable.

Conclusion

These findings present a strong case that gadolinium from contrast-enhanced MRIs may be present in patients with normal renal function for considerably longer than would be expected based on the elimination rates reported in GBCA product labeling. We believe this study, when combined with the chronic symptoms reported by Semelka et al.[6] in 2016 and by us in 2014[3], indicate stronger action is needed by the FDA and others to inform patients about possible gadolinium retention from contrast-enhanced MRIs and the potential for side-effects.

This study does not stand alone in reporting unexpected long-term gadolinium retention. We believe it confirms the published reports from Kanda[7], McDonald[8], Murata[9] , Radbruch[10] , Ramalho[11], and others, about unexpected gadolinium retention in patients with normal renal function.

The authors are eager to collaborate with researchers in studying these findings or conducting new gadolinium-related research in patients with normal renal function.

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