

Gadolinium Toxicity

A Group Self-Study of Retained Gadolinium from Contrast MRIs

This small group retrospective Self-Study of Gadolinium Toxicity examines urine test results which show long-term retention of Gadolinium occurs in patients with normal kidney function who had contrast MRI/MRA procedures. Unprovoked and Provoked urine testing results are presented documenting the retention of Gadolinium at toxic levels for as long as 79 months after their most recent contrast procedure.

The information and conclusions presented here should not be interpreted as medical advice.

The conclusions are based on a small sample and suggest that a larger study should be conducted. This Study references only the amount of Gadolinium that was detected in 24-hour urine samples. The test results are as reported by Study participants normalized to a common measuring unit. No attempt is made to link the amount of Gadolinium to any symptoms or conditions, and no attempt is made to determine what, if any, level of Gadolinium, is safe to remain in anyone's body.

All Study participants consented to inclusion of their test results and they were provided a copy of the document prior to publication. The author, one of the Study participants, takes sole responsibility for the content of this document.

Team of Patient Advocates
October 1, 2013

Background

Gadolinium is the paramagnetic element in the contrast material infused into a patient's body for an MRI or MRA with contrast. This contrast material is known as a Gadolinium-Based Contrast Agent or GBCA. The medical community and government agencies have recognized the toxicity of retained Gadolinium from GBCAs as the primary contributor to the development of Nephrogenic Systemic Fibrosis (NSF) in patients with compromised renal function. Although the precise mechanism is not known, it is generally accepted that patients with renal problems retain the GBCA for an extended period of time, allowing the toxic Gadolinium to separate from the ligand to which it was bound during manufacture. Since not all patients with impaired renal function contract NSF after receiving contrast, other co-factors not yet understood are likely involved. Cautions now included on the GBCA packaging as well as in medical literature have reduced new occurrences of NSF in renally impaired patients. However, despite numerous medical research publications noting that Gadolinium from GBCAs is also retained by patients with normal kidney function, no studies have been done to document and understand the retention of Gadolinium from GBCAs using simple urine testing. Patients without any record of renal disease are simply told that the contrast agent is safe and will be excreted within a few days. This Study will demonstrate otherwise.

Support Groups have been formed by individuals who have developed troubling, unexplained symptoms following a contrast MRI or MRA. As they share their experiences, they realize that there are other people with similar as well as different symptoms. They also find people who understand the frustration of seeing doctors who are unable to help. Some doctors dismiss the possible connection of symptoms to Gadolinium because the patient has normal kidney function (impaired kidney function is presumed to be a requirement for NSF). Those doctors who are open to the possible involvement of Gadolinium have no information on how to evaluate or treat any Gadolinium-related health issues. As a result, many patients have sought out doctors experienced in chelation in an attempt to remove the Gadolinium from their body. Neither the patients nor the doctors have any guidelines as to what they should expect to achieve through removal of the Gadolinium.

Thus we have a condition that we call Gadolinium Toxicity. Medical literature is of little help regarding this condition, its possible effects (other than NSF), or its treatment, despite volumes of published medical research confirming that Gadolinium is toxic to the kidneys, nervous system, vascular system, and many other body systems. The medical community knows that Gadolinium is toxic to humans. They also know that having too much Gadolinium in the body for too long is the common element in those who have contracted NSF. But how much is "too much"? And how long is "too long"? There appear to be no answers. We would hope that our Self-Study will be a stimulus for a re-evaluation of contrast MRI guidelines and more broad-based research of Gadolinium Toxicity.

Group Self-Study

With no published literature regarding retention of Gadolinium from contrast MRIs in patients with normal kidney function, the author sought to gather data for collective publication. This Group Self-Study is the result of that effort. We believe that even though we are small in number, sharing our information may prove useful to other affected patients as well as medical professionals.

All of the individuals whose test results are included have given their permission for that inclusion and have seen the Group Self-Study before publication.

Scope

The scope is only to gather and report data from patients with normal renal function who have had urine testing for Gadolinium. The results are shown in relation to the number of months following their last contrast MRI, separating Unprovoked tests from Provoked (chelated) tests. The only intention is to see if any patterns result which others may use to evaluate their situation and that we might use to stimulate

medical researchers to undertake professional studies of Gadolinium Toxicity. We do not attempt to make any connection between the level of Gadolinium in one's urine and any medical symptom or condition. We just want to show others that Gadolinium from contrast MRIs is retained long after the MRI by patients with normal kidney function.

Statistical Precision

This is a retrospective study of urine test results for Gadolinium from 13 people with 47 test results - 31 Unprovoked and 16 Provoked. We acknowledge the small sample-size of this study but believe the results are relevant because we have not found any published studies of retained Gadolinium from GBCAs based on urine testing.

The urine tests were performed by four different testing organizations - Mayo Clinic Laboratories, Genova Diagnostics, Doctor's Data, and Rocky Mountain Analytical. For Mayo, Genova, and Doctor's Data we have enough comparable reports on the same person to feel confident that the labs' results are comparable. We have no reason to believe Rocky Mountain Analytical results are not also comparable, but we only have test results from one person, and that person was not tested elsewhere, so we cannot validate comparability. Nonetheless, all results were taken and used as reported.

The provocation protocol used in each of the Provoked tests may vary from patient to patient, and even from test to test for the same patient. This might produce some variability, but the test results were used as reported.

Neither the author nor anyone in the group has medical statistical training. We were careful to gather and report the information accurately.

There are many other variables that could influence the results. The following differences are noted but no attempt has been made to separate these variables: total number of contrast magnetic resonance studies varied from one to twelve, the cumulative dosage ranged from 13 cc to over 170 cc, and the time between dosages ranged from several days to many years. Some patients had immediate negative reactions while others did not. Some may have had extravasation. None of these variables was separated because of the overall small sample-size.

Urine Testing Results

First, an explanation of provoked versus unprovoked urine testing is warranted. A normal urine sample, either just a small volume or a timed collection taken with no special medications, is an unprovoked urine test. Reference ranges are established based on unprovoked testing. With provoked urine testing, the doctor infuses the patient with a chelating agent via IV or has the patient take an agent orally. The chelating agent has the ability to extract elements from tissue in much higher quantity than would normally be excreted in urine. For our purposes, the use of a chelating agent for provoked tests will demonstrate that there is Gadolinium in the tissue to a much greater extent than would be revealed in an unprovoked urine collection. We will not compare Provoked results to unprovoked reference ranges.

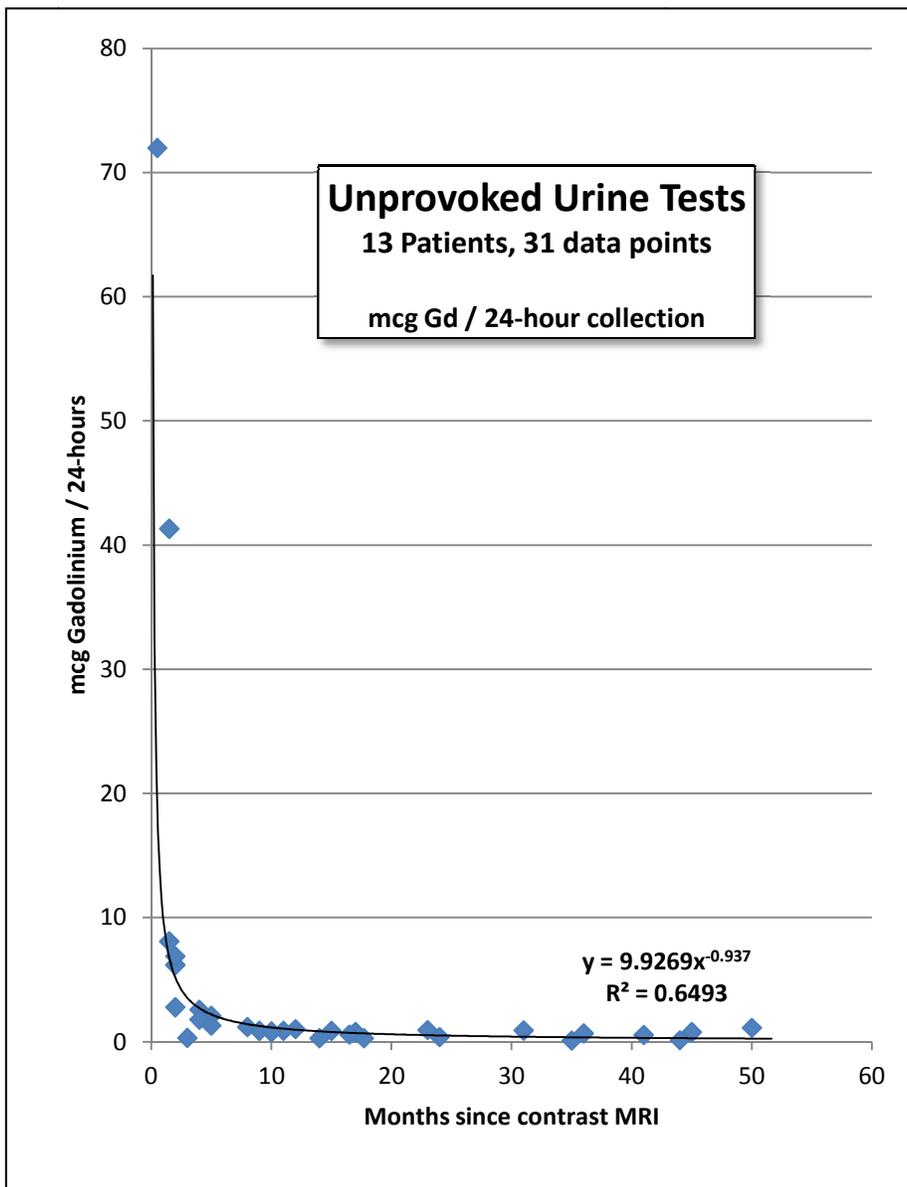
The units of measure for Gadolinium found in urine testing will normally be either mcg Gd/g Creatinine or mcg Gd/24-hour collection. (The mcg is read microgram, which is 1,000th of a milligram {mg} and is shown in some literature as μg). We have chosen to normalize all of the results to mcg Gd/24-hour collection. There were a few cases requiring estimation, but we do not believe this to have any significant impact on the results.

A word about reference ranges for mcg Gd/24-hour collections. Since there is no biological use for having Gadolinium in one's body, the establishment of a reference range is challenging. Mayo Clinic Labs developed an acceptable range of 0.0 - 0.4 mcg Gd/24-hours. While Genova Diagnostics uses a much lower limit of 0.019 mcg Gd/24-hours, we will use the Mayo Reference Range in our commentary.

Unprovoked Results

We had 31 Unprovoked test results from 13 different people. A table of the test results sorted by the number of months since contrast infusion is shown alongside a chart of the results below. The chart also includes a trendline developed automatically from the data points.

Months	mcg Gd/24-hr
0.5	72.0
1.5	41.3
1.5	8.1
2	6.9
2	6.2
2	2.8
3	0.3
4	2.6
4	1.8
4	1.3
5	2.1
8	1.2
9	0.9
9	0.8
10	0.8
11	0.9
12	1.0
14	0.3
15	0.9
17	0.6
17	0.8
18	0.3
23	1.0
24	0.4
31	0.9
35	0.1
36	0.7
41	0.6
44	0.1
45	0.8
50	1.1



Although a general pattern can be seen, the scale of the higher results makes the pattern difficult to interpret visually.

Before we look a little closer at portions of the chart, let me comment about the R-squared value seen in the lower right-hand corner. R-squared is called the Coefficient of Determination, and it describes how well the trendline fits the data points. In this case it is 0.6493 or approximately 65%. The higher the number, the closer the fit. We will not go into this measure of trendline characteristics in any greater depth, but we will compare the goodness of fit for this line with the trendlines on other charts.

Looking more closely now at the Unprovoked urine test results between 0 and 10 mcg Gd/24-hours, we observe the following:

First, the trend line curve visually matches the data points in this area rather well. Looking at particular groupings of data points (and referring to the table placed alongside the previous chart), we can see results of 6 to 8 mcg Gd/24-hours in the first several months. Note that there are even higher results of 41 and 72 mcg Gd/24-hours during this time frame that we cannot see in this chart.

With the exception of the data point at 3 months and 0.3 mcg Gd/24-hours, the values through 8 months are at least 1.2 mcg Gd/24-hours, three times the Mayo Reference Range.

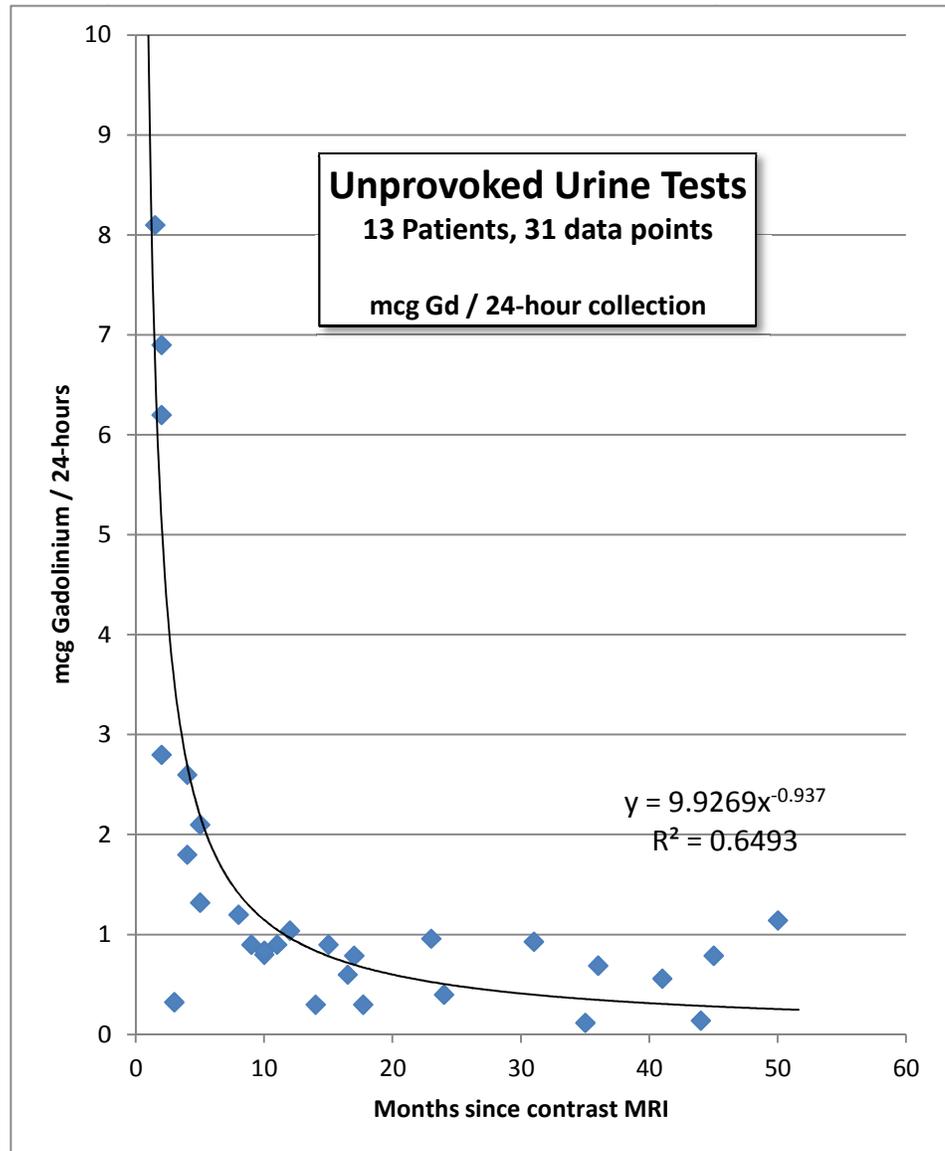
What should we think of the data point at 3 months and 0.3 mcg Gd/24-hours? Simply that we used test scores from anyone who would participate. Some people may have test results that appear to be outliers.

We are not attaching any symptoms or severity to any data points, so there

is no need to attempt to find an explanation for outliers. Also, we know from published reports regarding renally impaired patients that Gadolinium affects different people in different ways that are not understood. Likewise, retained Gadolinium might result in Gadolinium Toxicity at different levels in different people.

From 9 to 18 months we have ten data points and seven of them are 0.8 mcg Gd/24-hours or higher, more than twice the Mayo Reference Range.

Beyond 18 months we see six of the nine results are over the Mayo Reference Range of 0.4 mcg Gd/24-hours, with a test result at 50 months of 1.1 mcg Gd/24-hours.

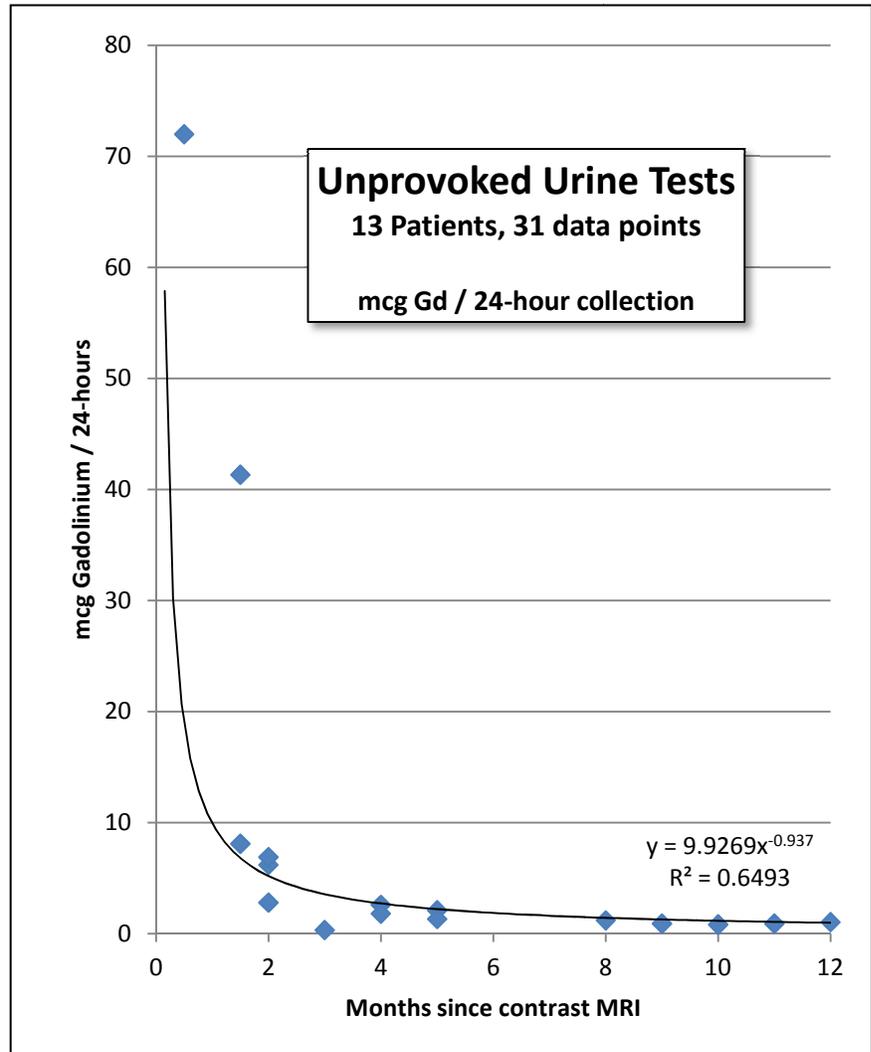


Looking at a chart that only shows the first 12 months of data points we can see the higher numbers.

Test results before 2 months are excessively high, with one after only 2 weeks reaching 72 mcg Gd/24-hours.

It is very unusual for a person to suspect Gadolinium from the contrast agent as being responsible for symptoms in just two weeks and get a urine test that soon. The person with the 72 mcg Gd/24-hours result also received the 8.1 mcg Gd/24-hours result at six weeks, so we only have two people tested before two months. Their results are remarkably high. We have no reason to think that many, if not most, of those who started testing later would have had similar results at two weeks.

To conclude the Unprovoked Results section, we believe this is much more information than has been available previously, and it can serve as a guidepost for those who suspect Gadolinium Toxicity. For researchers, it provides evidence that further study of Gadolinium retention and Gadolinium Toxicity will be fruitful.

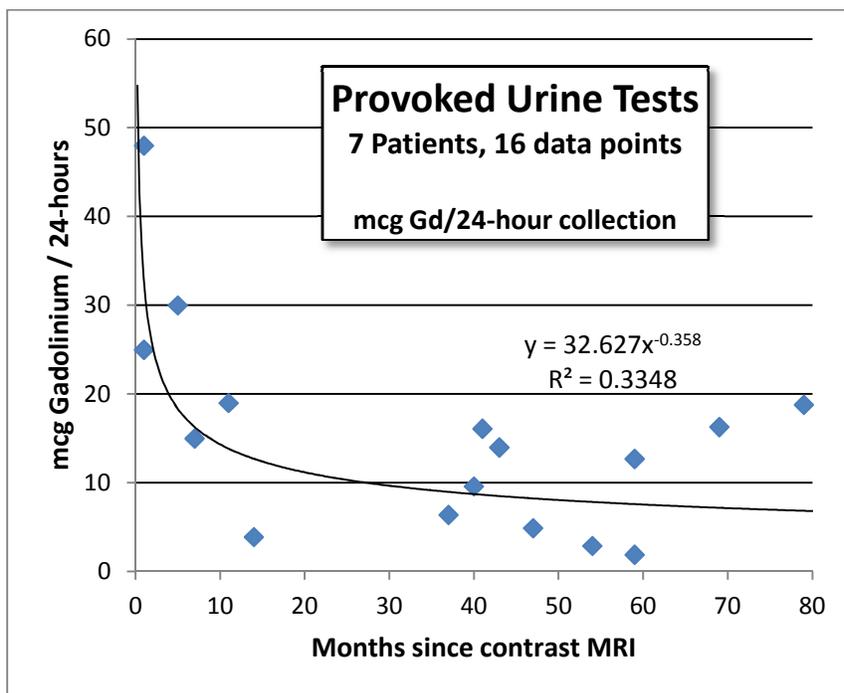


Provoked Results

Provoked results have a different starting point, as they are usually initiated by a patient who already suspects some level of toxicity from the Gadolinium-Based Contrast Agent (GBCA). When people have multiple provoked results, it is usually because they have chosen to begin a course of chelation treatments and the tests are a way to measure individual progress. The provoking or chelation process will produce significantly higher urine test results than as are seen for Unprovoked results.

The following chart shows the Provoked results in the same format as was used for the Unprovoked:

Months	mcg Gd/24-hr.
1	48.0
1	25.0
5	30.0
7	15.0
11	19.0
14	3.9
37	6.4
40	9.6
41	16.1
43	14.0
47	4.9
54	2.9
59	12.7
59	1.9
69	16.3
79	18.8



You will notice several things:

The number of data points is smaller, with 7 patients and 16 urine test results.

The levels of Gadolinium are much higher as would be expected with Chelation. Ten of the 16 test results exceed 10 mcg Gd/24-hours with a maximum of 48 mcg Gd/24-hours.

The test results extend out longer, now going to 79 months after the last contrast MRI with a provoked result of 18.8 mcg Gd/24-hours.

The numbers have less of a pattern, and the trend line is considerably less effective in predicting the values, 33% here versus 65% for the Unprovoked results. The different chelation protocols used to remove the Gadolinium could play a role in this dispersion.

What observations are most striking in these Unprovoked results? First, Gadolinium remains in tissue even after 79 months as evidenced by the last entry in the table showing that 18.8 mcg Gd/24 hours could be chelated from an individual 79 months after the last exposure. Second, even with regular chelation, high levels of Gadolinium continue to be reported in provoked urine tests.

Note that we are not comparing Provoked results with the Mayo Reference Range for unprovoked testing. But we are showing that considerable Gadolinium can remain in a patient for as long as 79 months and likely much longer.

In viewing these Provoked results and previously the Unprovoked results, one is led to the question of "is there any way to compare Provoked urine test results with Unprovoked urine test results, or to determine the effect of Chelation?".

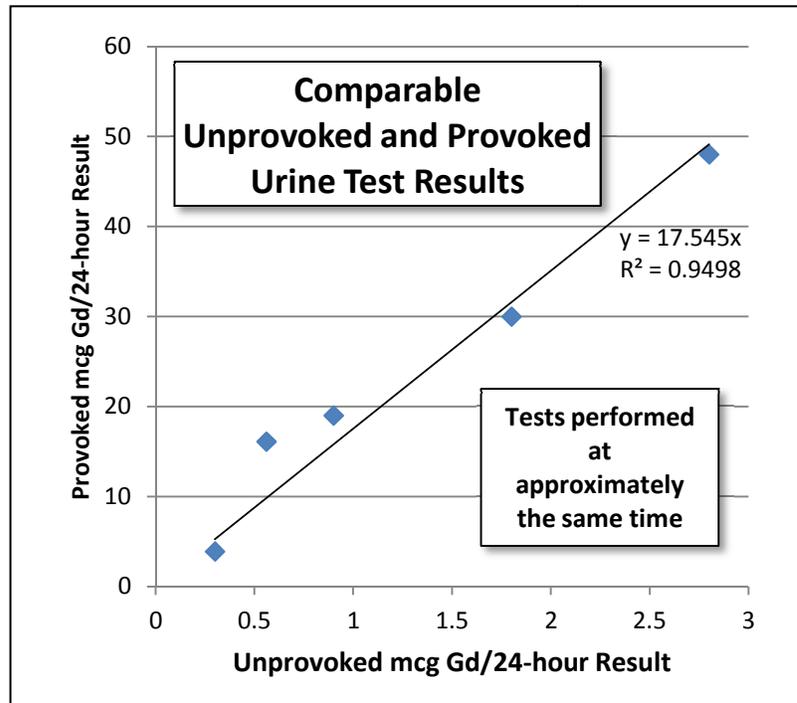
Comparison of Provoked and Unprovoked results

The comparison of Provoked with Unprovoked results yields an even smaller set of data points because the individual would have had to do an unprovoked test and a provoked test within a short enough time frame to consider the tests equivalent. We have only five such data points:

mcg Gd/24-hours	
Unprovoked	Provoked
0.3	3.9
0.6	16.1
0.9	19
1.6	30
2.8	48

It is important to note the scale on the axes because they are measuring similar items but they have vastly different scales.

Note also that the relationship fits a straight line rather well, with an R-Squared value of 95% and a simple linear expression for the trend line. Expected Provoked values are approximately 18 times the Unprovoked value.



Although the sample-size is small, the closeness of the trend line to the data points indicates that the formula might provide a valuable estimate when comparing provoked and unprovoked test results

Applying the chart's equation to the last Provoked value (79 months) of 18.8 mcg Gd/24-hours, the expected Unprovoked result would be about 1.0 mcg Gd/24-hours, still above the Mayo Reference Range limit of 0.4 mcg Gd/24 hours after 79 months.

Final Thoughts

We believe this Self-Study shows that people with normal renal function retain significant amounts of Gadolinium from Gadolinium-Based Contrast Agents used for contrast MRIs and MRAs. Since Gadolinium is known to be toxic to humans, we believe retained Gadolinium results in Gadolinium Toxicity which may present clinically with a variety of symptoms.

For those of us in the Self-Study, it is very frustrating that so little research has been done into the retention of Gadolinium from GBCAs in patients with normal renal function. To us individually, the need for this research has been very clear. As an individual patient talking to our doctor(s) who has never heard of or recognized Gadolinium Toxicity-caused problems in patients with normal renal function, it has been difficult to connect our symptoms to Gadolinium. The doctors apply what they have been told by others, and they have been told that patients with normal renal function are not at risk from GBCAs. It is our hope that this Self-Study can be the catalyst to change this understanding.

For many of us, the road ends with our symptoms or condition being described as idiopathic, and we are told that a high percentage of patients with our symptoms have this same assessment. Idiopathic does not mean that there is no cause; it just means that medical science has not yet found the cause for the patient's symptoms or condition. With appropriate research, Gadolinium Toxicity may prove to be the cause of many presently idiopathic diagnoses.

Some have been told that their symptoms are atypical for specific diseases or conditions based on their test results. While it could be that Gadolinium Toxicity is responsible for these atypical presentations, there are no tests or diagnostic procedures to make that determination. So doctors continue to look for some cause other than Gadolinium that is typical for their patients' symptoms.

When research is conducted on patients with normal renal function, medical science may gain the knowledge to make these connections, and possibly change standard practices regarding the administration of Gadolinium-Based Contrast Agents.

The results of this Self-Study suggest that a larger study should be conducted. It is time for medical research that will document the amount of Gadolinium being retained by patients with normal renal function. Additionally, a review should be conducted of Gadolinium-exposed patients whose symptoms or conditions are presently labeled as idiopathic or atypical so that those non-specific descriptions can be replaced with proper diagnoses and treatment plans can be developed that will do more than relieve patients' symptoms.

Despite the limitations of our small sample size, no other study exists, to our knowledge, that would refute the information presented here.

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