Texila International Journal of Academic Research
ISSN: 2520-3088
DOI: 10.21522/TIJAR.2014.09.04.Art010

Gadolinium Distribution in the Kidney, Liver, and Heart of Wistar Rats after Administration of Gadolinium-Based Contrast Agents

Oluwafemi Olumide Egbeyemi[1*], Anthony Chukwuka Ugwu[2]
[1]*Radiodiagnostic Department, City Gate Health Diagnostic Services, Ogijo, Ogun state Nigeria*
[2]*Nnamdi Azikiwe University, Nnewi, Anambra State Nigeria*

Abstract

Magnetic resonance imaging (MRI) is an established non-invasive and non-destructive medical imaging modality for the assessment of various organ systems in the human body. Gadolinium-Based Contrast Agent (GBCA) enhanced and improved images from MRI and was believed to be entirely excreted through urine in normal kidney function within 24 hours after injection. Previous studies identified gadolinium accumulations in the brain, bones, and skin of animals. This study evaluated gadolinium retention in normal kidneys, Liver, and heart of Wistar rats after administration of GBCAs in male Wistar rats. Twenty-five male Wistar rats of ages ≥ 5 weeks or ≤ 6 weeks in 4 experimental and 1 control groups were studied. Ethical considerations were obtained from the Institutional Review Board (IRB) of the Nigerian Institute of Medical Research (NIMR), Nigeria. Samples in experimental groups each administered 2.5 mls of 4 different GBCAs, and the control group same per day of saline intravenously through the lateral tail for five days a week and continued for 4 weeks. The kidney, Liver, and Heart tissues of these samples were harvested 4 weeks after the last injection and sent for spectrometry evaluation. Samples in the control group had no gadolinium accumulation. Groups administered gadopentetate dimeglumine, and gadodiamide had greater cardiac metrics (0.397 and 0.390). The higher renal metric was experienced by samples that received dotarem and cyclolux (0.397 and 0.377), though the sample exposed to cyclolux reported more Liver metric (0.407) than other concentrations. Wistar rats' Kidneys, Liver, and Heart retained gadolinium weeks after injection of GBCAs.

Keywords: *Dotarem and Cyclolux, Gadolinium, Gadodiamide, Gadopentetate dimenglumine, Magnetic resonance imaging.*

Introduction

Magnetic resonance imaging (MRI) is a well-established non-invasive, and non-destructive medical imaging modality for the assessment of various organ systems in the human body [1], including the kidney, hepatic structures, and cardiovascular system. They often provide images that are superior to those obtained with computed tomography (CT) scans and have the advantage of avoiding iodinated radio-contrast agents having more overall toxicity [2]. Impaired or pathologic organs may retain gadolinium after injection of GBCAs during MRI scan and should therefore be used with extreme caution [3, 4]. Lately, a growing body of data [5-7] demonstrated that gadolinium gathers in tissue (brain, bone, and kidney) of patients exposed to GBCAs during MRI. Retention of gadolinium has been studied to increase in those who have repeated GBCAs exposure [5, 6]. Studies found that linear GBCAs cause much greater brain deposition of gadolinium than macrocyclic GBCAs in

Received: 10.08.2022 ***Accepted: 23.08.2022*** ***Published on: 29.10.2022***
****Corresponding Author: femijoseph3@yahoo.co.uk***

animals and humans [8,9]. Many arguments were generated about the use of linear GBCAs in 2017 despite continuous use for nearly 30 years with the only reported major adverse event being NSF [10]. [11], reported on the behavioral abnormalities of fetal mice when exposed to 100 doses of linear GBCAs, and rats live approximately 3 years and assume sexual maturity in ≥ 6 weeks [12-14]. The American College of Radiology and the US Food and Drug Administration (FDA) refused to restrict the use of linear GBCAs (FDA). The decision on the use of the linear GBCAs during MRI studies in the USA, Japan, and Europe are totally different because it is still unclear whether the gadolinium accumulation in the brain is toxic [10], though the Japanese radiologists use of the agent has drastically decreased from 64.7 % in 2014 to 24.7 % in 2016[15]. Gadolinium depositions in the human body have received fundamental interest associated with impaired or pathologic organs after injection of GBCAs during MRI; this retention had been documented with the brain, bone, and soft tissues following repeated administrations and has resulted in numerous lawsuits. There is, however, concern for normal major organs to prevent unforeseen toxicity. We hypothesized the following: i) there is no concentration of gadolinium in the tissue of the kidney, Liver or heart of Wistar rats and that there is no statistically significant difference in the concentration distributions of the four different GBCAs on the Kidney, Liver, and Heart of male Wistar rats. Therefore, this study aimed to determine the concentration distributions of the gadolinium-based contrast agents after administration in the kidney, Liver, and heart of Wistar rats.

Materials and Methods

Research Design

This was an experimental study. This design was adopted because the animal understudy have biological and behavioral characteristics closely resemble to those of humans, and animal-like rats are susceptible to most similar health conditions as humans. All variables and their relationships were carefully identified. Predictions that are specific and testable were decided.

Area of Study

The animals were housed and later sacrificed at the physiology laboratory of Bayero University, Kano State, Nigeria, under standard conditions. They had free access to water and diet (normal rat foodstuff). They were acclimatized for two weeks prior to the onset of this experiment. The histology and mass spectrometry was conducted at histology and chemical pathology laboratories Ysusuf Maitama Sule University, Kwanar Dawaki Campus Kano, Nigeria.

Ethical Consideration and Selection Criteria

All methods adopted in this study were conventionally in line with Nigerian animal welfare law and experimental protocols, compliance with the “Guide for Care and Use of Laboratory Animals” summarized by [16]. The experiments were conducted after an ethical approval (IRB/21/038) was obtained from the Institutional Review Board (IRB) of the Nigerian Institute of Medical Research (NIMR), Yaba Lagos, Nigeria.

Inclusion Criteria

1. Male Wistar Rats.
2. Ages ≥ 5 ≤ 6 weeks.

Exclusion Criteria

1. Female Wistar Rats due to hormonal fluctuations.
2. < 5 weeks of age not equating to adult human.

Sample Size Determination and Sampling Technique

A simple approach to calculating sample size was adopted in this study since the effect of different GBCAs is to be examined, plus to

avoid complex statistical calculations and ethical issues. This method is based on ANOVA calculations and the sample size for this study was reached at twenty-five (25) Wistar rats. A simple random technique was adopted to group the animals.

Animal Specimen

The animals studied were twenty-five (25) healthy male wistar albino rats, and their health condition was only determined by thorough observations, body weight, age, and assessment. No blood or urine volume, heart rate, allergens and respiratory rate taken. This model was selected for this study owing to their smaller body size, high rate of survival, and lower tumor or lesion incidence compared to other outbreed rats. The ages of the animal were $\geq 5 \leq 6$ weeks old, because they have reached maturity at this time [14, 17]. The male breeds were studied since the female hormones fluctuate during the reproductive cycle and could influence the outcome of the experiment (18]. The animals received 20 intravenous injections each of 2.5 mmol GBCA per kilogram (gadolinium-exposed group) or saline (control group) over a period of 28 days (4 weeks). The animals were killed without anaesthesia. The kidney, Liver, and heart tissues of each of the animals were harvested for histological changes and subjected to plasma mass spectrometry (PMS) for assessment and quantification of gadolinium retention.

Experimental / Test Agents

The contrast media used for this study were:

1. Gadopentetate dimeglumine known as magnetect (Gd-DTPA), is an ionic Gd complex with a linear polyaminocarboxylic acid ligand. The chemical formula is $C_{28}H_{54}GdN_5O_{20}$.
2. Gadodiamide, also known as Omniscan (Gd-DTPA-BMA), a linear, non-ionic Gd complex with the chemical formula of $C_{16}H_{28}GdN_5O_9$.
3. Gadoterate meglumine, known as doterem by Guerbet (DOTA-Gd), a macrocyclic ionic GBCA having the chemical formula of $C_{23}H_{42}GdN_5O_{13}$.
4. Gadoterate meglumine, known as cyclolux by Sanochemia (DOTA-Gd), also a macrocyclic ionic.

Instrument and Procedures for Data Collection

Instrument used in this study are:

1. Microscope.
2. Spectrophotometer.

Method of disposal of Animal

The incineration method through the licensed commercial medical waste company was used after the body parts, and carcasses of the Rats are bagged in a seal bag provided by division of laboratory animals.

Statistical Analysis

Data were categorized into groups A, B, C, D, and E based on the type of contrast administered. Statistical analysis was done on the statistical package for the social science SPSS version 23 (SPSS incorporated, Chicago) using descriptive statistics (mean values, frequency, and percentages).

Results

GBCAs in the Tissues of the Kidney, Liver and Heart of Male Wistar Rats

Table 1 shows the absorbance values of gadolinium in tissues of the organs studied from concentration of different GBCAs administered. The group that received gadodiamide had gadolinium absorbance, Heart > Kidney > Liver (0.404, 0.397, 0.376). Kidney > Heart > Liver absorbance of Gd^{+3} (0.383, 0.359, 0.346) in group that received dot area, whereas Heart > Liver > Kidney absorbance of Gd^{+3} (0.394, 0.371, 0.386) in group that received gadopentetate dimeglumine. The group that received cyclolux had Gd^{+3} Liver > Kidney >Heart (0.412, 0.405, 0.389). The only

group with Liver =kidney=Heart =0 from concentration was the group that received normal saline. Figure 1 shows the spectrometric curve of absorbance gadolinium plotted against the GBCAs concentration, and Figure 2 illustrates the graphical distribution of the GBCAs in the Kidney, Liver, and heart tissue of samples studied.

Table 1. Gadolinium Absorbance and GBCAs Concentration in the Kidney, Liver, and the Heart of Male Wistar Rats

Gadopentetate Dimeglumine	**Kidney**			**Liver**			**Heart**		
	Abs.	**Conc.**	**Total**	**Abs.**	**Conc.**	**Total**	**Abs.**	**Conc.**	**Total**
1	0.363	1.523	1.886	0.377	1.579	1.956	0.394	1.647	**2.0410**
2	0.369	1.547	1.916	0.386	1.615	2.001	0.384	1.607	**1.9910**
3	0.366	1.559	1.925	0.372	1.559	1.931	0.389	1.627	**2.0160**
4	0.371	1.587	1.958	0.379	1.587	1.966	0.394	1.647	**2.0410**
Total	**1.469**	**6.216**	**7.685**	**1.514**	**6.340**	**7.854**	**1.561**	**6.528**	**8.0890**
Gadodiamide									
1	0.363	1.523	1.886	0.352	1.479	1.831	0.391	1.635	**2.0260**
2	0.366	1.535	1.901	0.331	1.395	1.726	0.396	1.655	**2.0510**
3	0.397	1.659	2.056	0.360	1.511	1.871	0.397	1.659	**2.0550**
4	0.365	1.531	1.896	0.390	1.631	2.021	0.397	1.659	**2.0560**
5	0.368	1.543	1.911	0.376	1.575	1.951	0.404	1.687	**2.0910**
Total	**1.859**	**7.791**	**9.650**	**1.809**	**7.591**	**9.400**	**1.985**	**8.295**	**10.279**
Dotarem									
1	0.372	1.559	1.931	0.332	1.399	1.731	0.352	1.479	**1.831**
2	0.371	1.555	1.926	0.329	1.387	1.716	0.359	1.507	**1.866**
3	0.383	1.603	1.986	0.331	1.395	1.726	0.335	1.411	**1.746**
4	0.374	1.567	1.941	0.346	1.455	1.801	0.355	1.491	**1.846**
5	0.372	1.559	1.931	0.336	1.415	1.751	0.352	1.479	**1.831**
Total	**1.872**	**7.843**	**9.715**	**1.674**	**7.051**	**8.725**	**1.753**	**7.367**	**9.120**
Cyclolux									
1	0.370	1.551	1.921	0.398	1.663	2,061	0.389	1.627	**2.016**
2	0.401	1.675	2.076	0.406	1.695	2.101	0.376	1.575	**1.951**
3	0.405	1.691	2.096	0.407	1.699	2.106	0.380	1.591	**1.971**
4	0.405	1.691	2.096	0.412	1.719	2.131	0.376	1.575	**1.951**
5	0.402	1.679	2.081	0.410	1.711	2.121	0.374	1.567	**1.941**
Total	**1.983**	**8.287**	**10.270**	**2.033**	**8.487**	**10.520**	**1.895**	**7.935**	**9.830**
Normal Saline									
1	0.000	0.0712	0.0712	0.000	0.0712	0.0712	0.000	0.0712	**0.0712**
2	0.000	0.0712	0.0712	0.000	0.0712	0.0712	0.000	0.0712	**0.0712**
3	0.000	0.0712	0.0712	0.000	0.0712	0.0712	0.000	0.0712	**0.0712**
4	0.000	0.0712	0.0712	0.000	0.0712	0.0712	0.000	0.0712	**0.0712**
5	0.000	0.0712	0.0712	0.000	0.0712	0.0712	0.000	0.0712	**0.0712**
Total	**0.000**	**0.3560**	**0.3560**	**0.000**	**0.3560**	**0.3560**	**0.000**	**0.3560**	**0.3560**

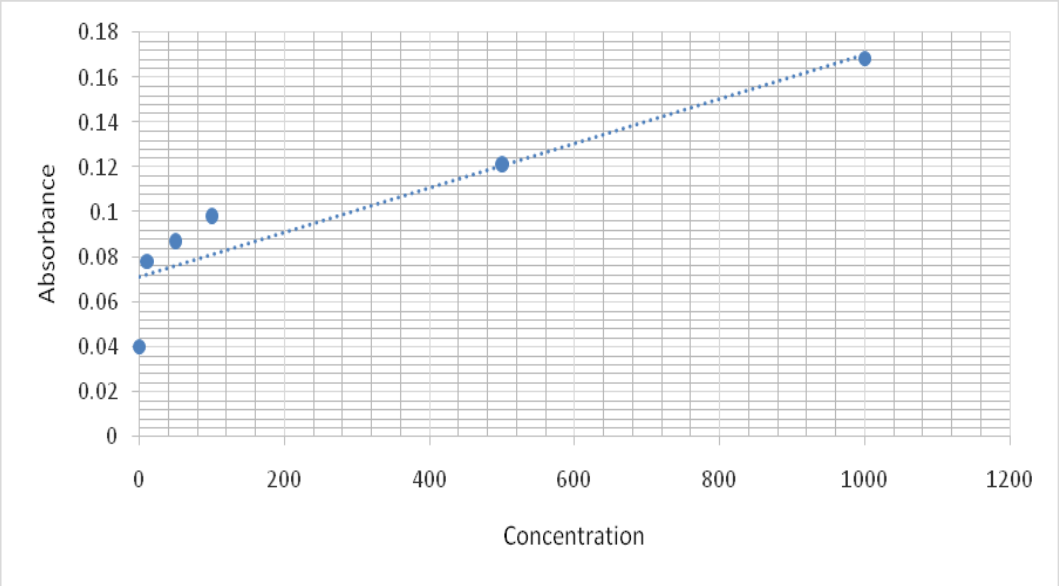

Figure 1. Spectrometry Curve of Absorbance Gadolinium against GBCAs Concentration in the Tissues of the Kidney, Liver, and Heart of Male Wistar Rats

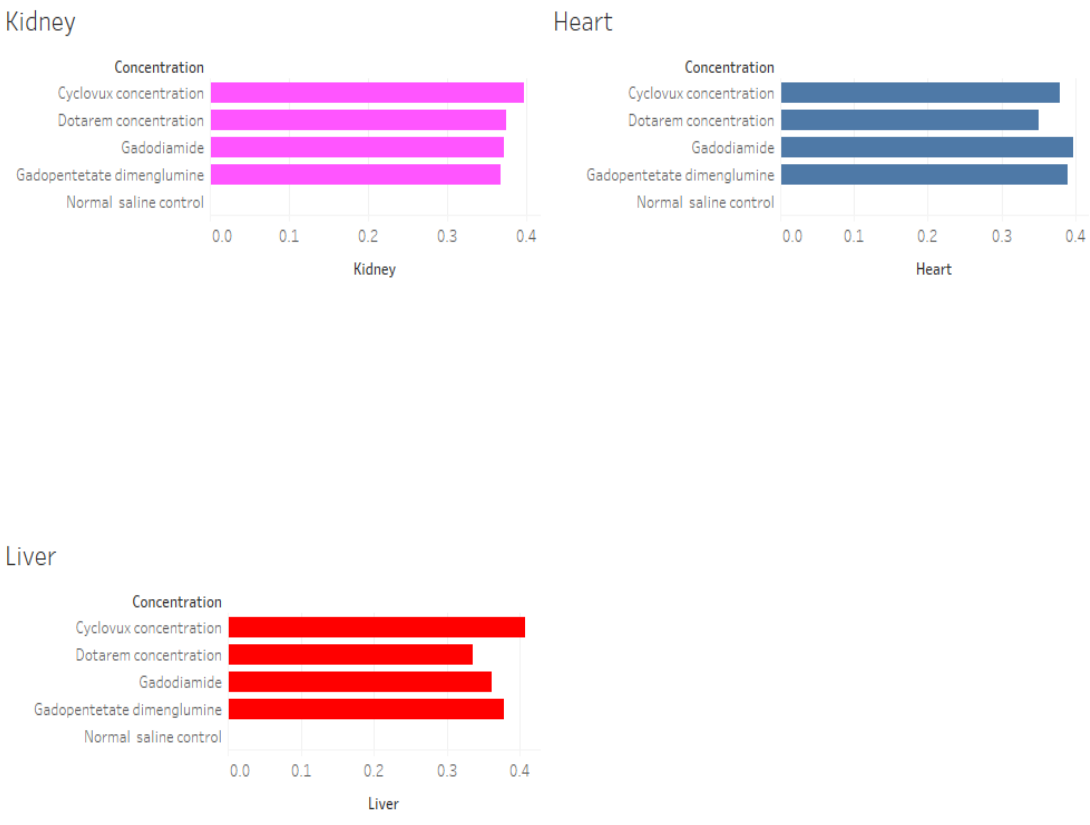

Figure 2. Distribution of GBCAs in the Tissues of the Heart, Liver and Kidney of Male Wistar Rats

Discussion

This current study utilized two linear (gadopentetate dimeglumine and gadodiamide), together with two macrocyclic, brands of gadoterate (dotarem and cyclolux) and was observed that all the GBCAs had deposition of gadolinium in the tissue of the organs studied as this was confirmed through the spectrophotometric readings, in agreement with previous study [19]. We found that the Gadopenetate Dimeglumine absorbance and concentration in the organs studied were highest in the heart, followed by the kidney and the least was found in the Liver. The absorbance and concentration of Gadodiamide was found to be highest in the heart, followed by kidney, and the least was recorded in the Liver of the Wistar rats. With regards to the Dotarem contrast agent, both the absorbance and concentration were mostly found in the kidney, followed by the heart and the least in the Liver of the animals. The Liver had the highest absorbance and concentration of the Cyclolux contrast agent. These findings imply that different contrast agents accumulate or are being retained at different amount depending on the types of the agent as well as the tissues of the organ under investigation. These findings agree with the findings of the studies conducted by [8, 20-23], which also reported that the degree of deposition of contrast agents used MRI varies with the types of agent used as well as the tissues of the organs examined. According to [24], gadolinium is a none naturally occurring biological component, and once administered into the tissues of an animal, it is retained for a long duration.

Conclusion

All the GBCAs had deposition of gadolinium in the tissue of the organs studied, as this was confirmed through the spectrophotometric readings. The concentration of the agents' deposition varies with the types of the agent administered as well as the tissues of the organ under investigation.

Conflict of Interest

None declared among the authors.

Acknowledgement

Dr. O. Dixon, Dr. K. Gopal, Dr. S. Mohammed, Mr. M.P. Ogolodom.

References

[1] Yadollahpour, A., Venkateshwarlu, G., 2016, Applications of gadolinium nanoparticles in magnetic resonance imaging: A review on recent advances in clinical imaging. *International Journal of Pharmacology and Technology*, 8: 11379-11393.

[2] Perazella, M., 2009, Status of gadolinium toxicity in patients with kidney disease. *Clinical Journal of American Society of Nephrology*, 4,461-469.

[3] Ramalho, J., Semelka, R.C., Ramalho, M., Nunes, R., Obaidy, M.A.I., Castillo, M., 2016, Gadolinium-based Contrast Agent Accumulation and Toxicity: An Update. *American Journal of Neuroradiology*. 37(7),1192-1198.

[4] Leyba, K.., Wagner, B., 2019, Gadolinium-based contrast agents: why nephrologists need to be concerned. Current Opinion in Nephrology and Hypertension, 28(2),154–162. https://doi.org/10.1097/MNH.0000000000000475

[5] Rogosnitzky, M., Branch, S., 2016, Gadolinium-based contrast agent toxicity: a review of known and proposed mechanisms. Biometals 29,365–376 https://doi.org/10.1007/s10534-016-9931-7.

[6] Quattrocchi, C. C., van der Molen, A. J. ,2017, Gadolinium Retention in the Body and Brain: Is It Time for an *International Joint Research Effort*?. Radiology, 282(1),12–16. https://doi.org/10.1148/radiol.2016161626.

[7] Gale, E. M., Caravan, P., 2018, Gadolinium-Free Contrast Agents for Magnetic Resonance Imaging of the Central Nervous System. ACS Chemical Neuroscience, 9(3), 395–397. https://doi.org/10.1021/acschemneuro.8b00044.

[8] Kanda, T., Fukusato, T., Matsuda, M., Toyoda, K., Oba, H., Kotoku, J., Haruyama, T., Kitajima, K., Furui, S., 2015a, Gadolinium-based Contrast Agent Accumulates in the Brain Even in Subjects without Severe Renal Dysfunction: Evaluation of Autopsy Brain Specimens with Inductively Coupled Plasma Mass Spectroscopy. *Radiology*, *276*(1), 228–232. https://doi.org/10.1148/radiol.2015142690.

[9] Radbruch, A., Weberling, L.D., Kieslich, P.J., Eidel, O., Burth, S., Kickingereder, P., Heiland, S., Wick, W., Schlemmer, H., Bendszus., 2015, Gadolinium retention in the dentate nucleus and globus pallidus is dependent on the class of contrast agent. Radiology 275:783–791.

[10] Kanda, T., Ishii, K., Kawaguchi, H., Kitajima, K., Takenaka, D., 2014, High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images: relationship with increasing cumulative dose of a gadolinium-based contrast material. Radiology, 270(3),834–841. https://doi.org/10.1148/radiol.13131669.

[11] Khairinisa, M. A., Takatsuru, Y., Amano, I., Erdene, K., Nakajima, T., Kameo, S., Koyama, H., Tsushima, Y., Koibuchi, N., 2018, The Effect of Perinatal Gadolinium-Based Contrast Agents on Adult Mice Behavior. Investigative Radiology, 53(2), 110–118.

[12] Pass, D., Freeth, G.,1993, The rat. Anzccart News. 6,1–4.

[13] Quinn, R., 2005, Comparing rats to human's age: How old is my rat in people years? Nutrition. 21:775–7.

[14] Sengupta, P., 2012, A Scientific Review of Age Determination for a Laboratory Rat: How old is it in comparison with Human age? Biomedical International, 2,81–9.

[15] Mugikura, S., Takase, K., 2017, Fear of linear gadolinium-based contrast agents and the Japanese radiologist's choice. *Japanese Journal of Radiology*. 35(11), 695–696.

[16] Davidson, M. K., Lindsey, J. R., Davis, J. K., 1987, Requirements and selection of an animal model. *Israel Journal of Medical Sciences*, 23(6), 551–555.

[17] Sengupta, P., 2013, The Laboratory Rat: Relating Its Age with Human's. *International Journal of Preventive Medicine*, 4(6), 624–630.

[18] Shirani, F., Teimoori, A., Rashno, M., Latifi, S. M., Karandish, M., 2017, Using rats as a research model to investigate the effect of human adenovirus 36 on weight gain. Arya Atherosclerosis, 13(4), 167–171.

[19] Lohrke, J., Frisk, A. L., Frenzel, T., Schöckel, L., Rosenbruch, M., Jost, G., Lenhard, D. C., Sieber, M. A., Nischwitz, V., Küppers, A., Pietsch, H.,2017, Histology and Gadolinium Distribution in the Rodent Brain After the Administration of Cumulative High Doses of Linear and Macrocyclic Gadolinium-Based Contrast Agents. Investigative Radiology, 52(6), 324–333. https://doi.org/10.1097/RLI.0000000000000344.

[20] Parasuraman, S., 2011, Toxicological screening. Journal of Pharmacology and Pharmacotherapy, 2(2),74-79. doi: 10.4103/0976-500X.81895

[21] Kanda, T., Osawa, M., Oba, H., Toyoda, K., Kotoku, J., Haruyama, T., Takeshita, K., & Furui, S. (2015b). High Signal Intensity in Dentate Nucleus on Unenhanced T1-weighted MR Images: Association with Linear versus Macrocyclic Gadolinium Chelate Administration. Radiology, 275(3), 803–809. https://doi.org/10.1148/radiol.14140364.

[22] McDonald, R. J., McDonald, J. S., Kallmes, D. F., Jentoft, M. E., Paolini, M. A., Murray, D. L., Williamson, E. E., Eckel, L. J., 2017a, Gadolinium Deposition in Human Brain Tissues after Contrast-enhanced MR Imaging in Adult Patients without Intracranial Abnormalities. Radiology, 285(2), 546–554. https://doi.org/10.1148/radiol.2017161595.

[23] Murata, N., Gonzalez-Cuyar, L.F., Murata, K., Fligner, C., Dills, R., Hippe, D., Maravilla, K.R., 2016, Macrocyclic and other nongroups 1 gadolinium contrast agents deposit low levels of gadolinium in brain and bone tissue: preliminary results from 9 patients with normal renal function. Investigative Radiology. doi:10.1097/rli.0000000000000252.

[24] Wáng, Y. X., Schroeder, J., Siegmund, H., Idée, J. M., Fretellier, N., Jestin-Mayer, G., Factor, C., Deng, M., Kang, W., Morcos, S. K., 2015, Total

gadolinium tissue deposition and skin structural findings following the administration of structurally different gadolinium chelates in healthy and ovariectomized female rats. Quantitative Imaging in Medicine and Surgery,5(4),534–545. https://doi.org/10.3978/j.issn.2223.4292.2015.05.03.

[25] Gibby, W.A., Gibby, K.A., Gibby, W.A., 2004, Comparison of Gd DTPA-BMA (Omniscan) versus Gd HP-DO3A (ProHance) retention in human bone tissue by inductively coupled plasma atomic emission 2 eespectroscopy. Investigative Radiology, 39,138–142.