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MRI demonstration of gadolinium deposition in bone after monthly triple-dose gadopentetate dimeglumine and correlation with frequency of hypophosphatemia

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ABSTRACT

Objectives: We retrospectively analyzed data of the BECOME trial to investigate whether serial administration of triple-dose (3-dose) gadopentetate dimeglumine would result in the development of T1 signal-to-noise (S/N) changes in the cranial diploic space and whether S/N changes correlated with on-study hypophosphatemia.
Methods: Signal intensity analysis was performed on the first year's data of the BECOME trial using 3-dose Gd (14 months, maximum number of doses, 39, mean: 36). Routine blood and urine tests were obtained each month for safety monitoring. Linear mixed regression modeling with random intercept was used to analyze monthly signal-to-noise ratio (S/N = Bone/Air) using an ROI of the diploic space created from T2W images and overlaid on T1FS (T1 fat-saturated) images. Incidence of phosphate abnormalities was analyzed using the general estimation equation; correlation of phosphate and S/N change was achieved with type 3 test of fixed effects.
Results: Cranial diploic space T1FS S/N increased over 14 months: S/N = 0.039 mean monthly increase (S.E. 0.008; $p < 0.0001$). Subjects with consistently normal phosphate levels (n = 32) experienced more of a S/N increase than patients with at least one episode of hypophosphatemia (n = 35) (0.057 *vs.* 0.023, respectively, $p = 0.037$). Those with moderate hypophosphatemia demonstrated no significant S/N increase.
Conclusion: Monthly administration of 3-dose gadopentetate dimeglumine is associated with development of increased S/N on T1FS imaging in the cranial diploic space, suggesting Gd retention in bone. Our data suggests MRI could be used as a noninvasive method of tracking Gd retention in bone, which was *more pronounced* in patients with normal phosphate levels.

1. Introduction

In 1994, Wolansky et al., conducted the first intrapatient study in multiple sclerosis patients demonstrating significantly improved contrast-to-noise ratio and improved lesion detection rate with cumulative 0.3 mmol/kg dose of GBCA as opposed to standard 0.1 mmol/kg dosing [1]. Several years later, monthly scanning was combined with 0.3 mmol/kg (3-dose) gadopentetate dimeglumine (Magnevist®, Bayer) administration in the BECOME trial, which was the first head-to-head clinical trial comparing what were at the time the two fundamental medications for treating MS: Interferon beta-1b (Betaseron®, Bayer) and glatiramer acetate (Copaxone ®, Teva) [2]. In the BECOME trial, 3-dose gadopentetate dimeglumine was administered monthly to 75 patients with MS randomized to interferon beta-1b or glatiramer acetate for 14 consecutive monthly scans [2].

Abbreviations: T1FS, T1 fat-saturated; FSE, Fast Spin-Echo; SI, signal intensity; Gd, gadolinium; CE-MRI, contrast-enhanced MRI; S/N, signal-to-noise ratio; GBCA, gadolinium-based contrast agents; 3-dose, triple dose; CBC, complete blood count; FSL, FMRIB Software Library; PTH, parathormone; CaSR, Calcium Surface Receptor

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Since the 3-dose gadopentetate dimeglumine used in BECOME was an off-label dosage for that particular contrast agent, close monitoring of clinical adverse events and potential toxicity was performed using monthly blood chemistry, CBC with differential and urinalysis [3]. The researchers reported a statistically significant rise in the frequency of hypophosphatemia attributable to GBCA administration [4].

The past decade of research has established the tendency for gadolinium agents, particularly class I linear agents, to deposit in various body tissues, including deep gray matter nuclei of the brain, bone, as well as skin and soft tissues in patients with normal renal function [5–17]. Study of gadolinium retention in bone has been less extensive than the brain; analyses of morselized samples of cortical and cancellous bone have demonstrated Gd deposition *ex vivo* [14–16]. Currently, the only *in vivo* method proposed for the detection of osseous gadolinium is based on a small pilot study using x-ray fluorescence [18], which is only available on specialized experimental equipment. While increased T1 signal of gray matter nuclei is well-established, MR demonstration of T1-weighted SI change secondary to osseous gadolinium retention has not been described in the literature.

Approximately 85% of the body's phosphate is present in the hydroxyapatite form in the skeleton and the transcellular movement of phosphate between intracellular fluid and the bone storage pool contributes significantly to phosphate homeostasis. Blood phosphate is regulated by several hormones, principally parathyroid hormone (PTH), 1,25-dihydroxycholecalciferol (1,25 DHCC), and fibroblast growth factor 23 (FGF23), the latter of which is produced by osteocytes in the marrow [19]. While most of the known actions of gadolinium are on the kidney due to its action on various renal tubular receptors, specific receptor actions of gadolinium in bone are yet unknown. However, it is well-documented that the lanthanide ion Gd (III) has an almost identical ionic radius to that of divalent Ca^{2+} and acts competitively, therefore displaying actions similar to calcium *in vivo*, including influences on PTH, 1,25 DHCC, both of which impact phosphorus levels [20].

The purpose of the current study is to retrospectively analyze the population of patients receiving monthly, 3-dose gadopentetate dimeglumine in the BECOME trial in order to study the retention of gadolinium in cranial bone and – given the importance of bone in phosphorus metabolism – to correlate bone signal with monthly phosphate levels.

2. Methods

Institutional Review Board approved the BECOME study and informed consent was obtained from the subjects.

2.1. Patients

The original study cohort consisted of 75 patients with MS or Clinically Isolated Syndromes typical of MS who were randomized ~1:1 to Betaseron or Copaxone, the details of which have been described elsewhere [2]. Of the original cohort, analyzable data from 67 patients was available for retrospective analysis of monthly gadolinium retention over the first year (mean number of scans 12.2, mean cumulative Gd doses 36.6).

2.2. Image acquisition and time point terminology

All images had been obtained on a single 3 T MRI by three technologists directly trained and supervised by the original BECOME Radiology Principal Investigator. For consistent positioning on serial imaging, axial images were obtained using a reference line drawn along the inferior surfaces of the genu to splenium (corpus callosum line). To avoid inconsistencies due to partial volume artifact, technologists were trained to obtain one section precisely through the corpus callosum line. Scanning was carried out with 3-mm slice thick sections including unenhanced spin-echo T1FS, T2-FSE images. Further details for the MRI protocol and analysis of the BECOME trial are provided elsewhere [21,22].

The initial visit in the original BECOME trial was a screening visit (S), during which eligibility to be enrolled was confirmed. At this visit, blood and urine were collected for analysis, and an MRI (including pre- and post-contrast T1-weighted imaging) was obtained. One month later, patients returned for a baseline visit (B), and underwent the same sequence of testing described above. This second visit is referred to as baseline because it was completed prior to randomization into treatment arms. Therefore, at baseline, each patient had a history of one triple dose of Gd administered the month prior during their screening visit. Following the baseline visit, subjects were randomized into treatment groups, and each subsequent time point (M1–M12) was named to indicate the number of months since the start of treatment. The number of prior administrations of 3-dose gadopentetate dimeglumine at each time point for the study is described in Supplemental Table 1.

2.3. ROI segmentation and analysis

ROI masks were manually traced by a single reader (J.D.) on T2 images at the M12 time point (when available). For cases in which the M12 time point was not acquired, or degraded due to motion artifact, the time point closest to M12 was chosen. ROIs were assessed by a second reader (D.B) as part of the registration process described below. Both readers were blinded to all clinical and demographic information for each patient. A single multi-voxel ROI was placed in air outside of the skull to be used in S/N calculation. A contiguous 2-slice axial binary ROI was placed within the medullary cavity of the inion region or the clivus dependent on the size of the medullary cavity. For each patient, the same ROI was used for all serial analysis. A 1–2 mm border was preserved around the ROI in order to avoid inadvertent inclusion of adjacent cortical bone after transformation to different time points.

All serial intensity analysis was performed on T1FS images using the same ROI as a mask. To account for potential movement between scans, the T2 image used for ROI placement was registered onto a T1FS image from the same time point using rigid body transformation in FSL. Registration quality was visually assessed to ensure accuracy. The transformation matrix calculated through this process was used to transform the bone ROI onto the T1FS scan. Bone ROIs for non-segmentation time points were then produced using rigid body transformation from the segmentation time point to each monthly time point. The final bone ROI for all patients at all timepoints underwent a visual quality assurance process by a single reader (D.B.) to ensure accuracy.

After transformation onto each time point, ROIs were rebinarized after interpolation at threshold of 0.5 to approximately preserve their original size. Finally, the mean intensity and total volume of each ROI at the target time point was calculated.

2.4. Measurement of serum phosphate

At each time point, blood samples were collected immediately prior to Gd administration and processed in the standard fashion. Hypophosphatemia was defined in accordance with standard clinical guidelines as at least one occurrence of phosphate levels < 2.5 mg/dL, and moderate hypophosphatemia was defined as at least one occurrence < 2.0 mg/dL [23].

2.5. Statistical analysis

At each time point, the signal to noise ratio within the bone ROI was determined:

$$S/N = \text{Bone (medullary cavity)}/\text{Air}$$

Since all scans were collected on the same MRI unit, air was used to approximate noise. Measurements at different time points from the same patient were considered a correlated cluster. Linear mixed regression modeling with random intercept using the data from the time point S

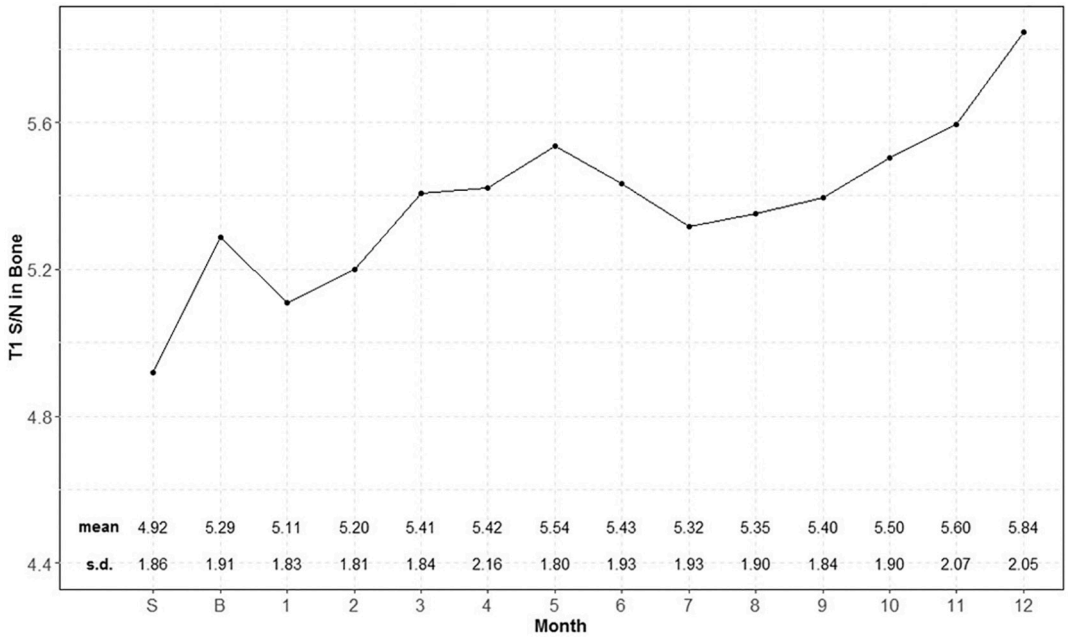


Fig. 1. T1 S/N of bone tissue demonstrates steady increase over the year with monthly 3-dose. The increase averages 0.039 S/N per month ($p < 0.0001$).

through M12 was performed to test the linear trend in monthly imaging data. Month was used as a continuous variable in the model, and the regression coefficient estimate represents monthly change of S/N. The interaction between month and phosphate-level subgroup was included in the model to test for difference in time trend between phosphate-level subgroups. All statistical analyses were conducted using SAS 9.4. All the tests were two-tailed with a significance level of 0.05.

3. Results

Data of 67 patients from monthly (or nearly monthly) scanning over the 14 months (mean number of scans = 12.2, mean cumulative Gd doses 36.6) were analyzed. During monthly scanning, bone demonstrated a statistically significant increase in S/N of 0.039 per month (S.E. 0.008; $p < 0.0001$) (Fig. 1).

Patients with consistently normal phosphate levels (n = 32) experienced a significantly higher rate of S/N increase than patients who experienced at least one episode of hypophosphatemia (n = 35) during that time with a monthly S/N difference of 0.034 ($p = 0.037$). (Fig. 2).

When subjects were grouped based on the occurrence (n = 9) or absence (n = 58) of at least one recorded episode of moderate hypophosphatemia over the course of the study, these two groups also had different monthly rates of change in T1FS S/N in bone (difference in rate of change of S/N = 0.063) ($p = 0.0082$). Patients with no occurrences of moderate hypophosphatemia had a statistically significant increase in monthly bone S/N of 0.048 (S.E. 0.0088, $p < 0.0001$), while patients who experienced at least one episode of moderate hypophosphatemia experienced a mean decrease in S/N of 0.015, S.E. 0.022, which was not significant ($p = 0.50$) (Fig. 3).

Notably, incidence of hypophosphatemia increased significantly over the course of the study in both treatment arms (Fig. 4). A detailed discussion of these findings is available in previously published work [4].

4. Discussion

To the authors' knowledge, the BECOME Trial administered a larger monthly dose of Gd contrast over the course of > 1 year to a greater number of patients than any other randomized clinical trial to date. The prospective design of the original BECOME dataset analyzed in this study offers a major strength with regard to periodicity of scanning and clinical data collection as well as consistent timing, contrast administration, image acquisition. Due to the interim accrual of medical knowledge regarding Gd safety, it is unlikely that such a study could be conducted at the present time. The prospective nature of the original study design provides a unique opportunity to retrospectively characterize a kind of "imaging pharmacokinetics," the month-to-month cumulative effect and longitudinal behavior of the retention phenomenon. Here, retrospective analysis of the BECOME trial reveals both a progressive increase in the T1 S/N of bone associated with serial Gd administration and S/N changes within bone that were more pronounced in patients with normal phosphate levels compared to hypophosphatemic patients.

Currently, the only *in vivo* method proposed for the detection of gadolinium is based off a small pilot study using X-ray fluorescence [18]. This methodology does not appear to discriminate between the different bone compartments and would require specialty equipment not available at most institutions, while MRI is ubiquitous in most tertiary care hospitals.

Gadolinium has previously been shown to accumulate in bone in histological studies [16,24]. However, in those studies, "bone" consisted of large quantities of cortical bone, which is exceedingly difficult to image due to the relative lack of mobile protons (*i.e.* water). This leads to an important question that has remained unanswered: is the presumed accumulation of gadolinium in the medullary cavity of bone – observed *via* progressive T1 signal increase – accumulating in the trabecular bone or the red marrow? Although trabecular bone may seem to be unable to facilitate gadolinium induced proton-electron dipole-dipole relaxation-enhancement for T1 shortening, due to the relative paucity of mobile protons in trabeculae, the large surface area at interfaces between finely spaced bone trabeculae could theoretically cause direct T1 shortening of water protons in the adjacent red marrow. This is akin to the mechanism that has been theorized as the cause of FLAIR related CSF suppression failure in the sulci between closely spaced gyri [25]. Alternatively, the gadolinium could be accumulating in an altogether different tissue of bone – in the red marrow itself.

Hypophosphatemia is not a known side effect of either Copaxone of Betaseron, both drugs under study in the original BECOME trial. Yet, hypophosphatemia represents a significant abnormality seen in the blood of our subjects particularly during the latter 6 months of the first year. We observed an increased incidence of hypophosphatemia that reached statistical significance after five months, peaking at month 10 to include

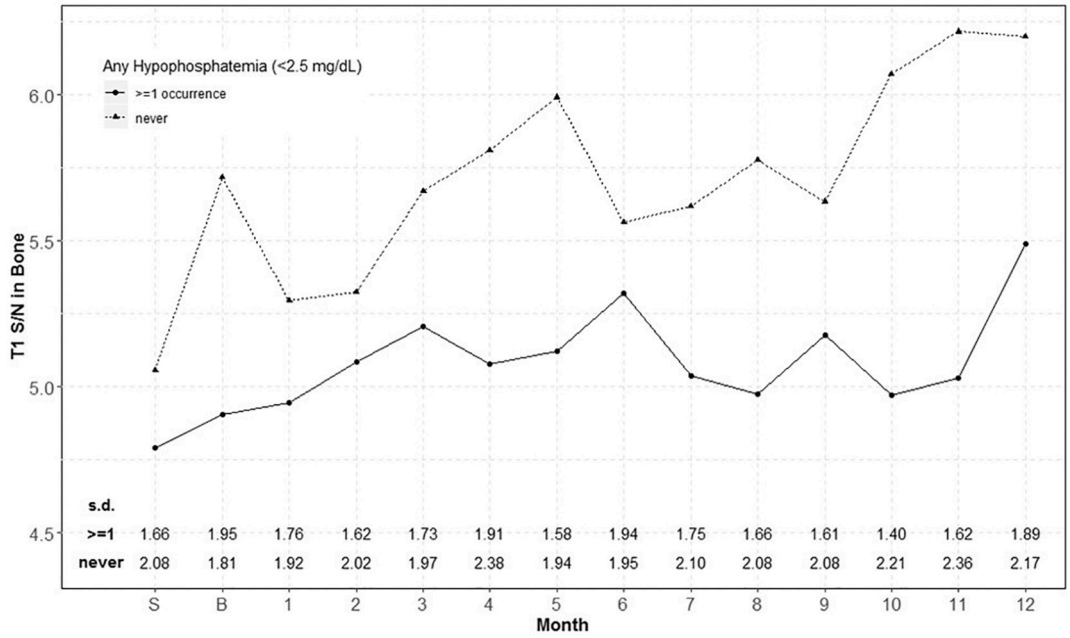


Fig. 2. Monthly T1FS S/N in bone tissue demonstrates more pronounced increase in patients with consistently normal phosphate levels when compared to those who experienced at least one episode of hypophosphatemia ($p = 0.037$).

26% of our study population. A detailed discussion of these findings can be found in a previously published analysis of this cohort [4].

4.1. Potential mechanisms

There are several theoretical mechanisms, by which gadolinium is known to affect phosphate handling; however, most of these mechanisms result in elevated phosphate levels. The cause of hypophosphatemia from prolonged gadolinium exposure may be a paradoxical decrease in phosphate as an overexpressed response to hyperphosphatemia or could be due to a novel effect of gadolinium on phosphate homeostasis.

Phosphate balance is regulated by parathyroid hormone (PTH), Vitamin D, and 'phosphatonins' which include fibroblast growth factor 23 (FGF-23), matrix extracellular phosphoglycoprotein (MEPE), stanniocalcin, and Frizzled-related protein 4 (FRP4) [26]. The gadolinium (III) or Gd^{3+} cation belongs to the lanthanide family of ions, colloquially known as "super calcium," [27] and acts as a Calcium Surface Receptor (CaSR) agonist. Increased CaSR action suppresses PTH release in the parathyroid gland, while in the kidneys, it decreases excretion of phosphate due to decreased removal of type IIa Na-Pi channels from the apical brush border wall of proximal renal tubular cells [28], thereby elevating body phosphate levels.

Increased phosphate levels in the body are known to stimulate PTH production and secretion [29] but this effect will be offset by constant

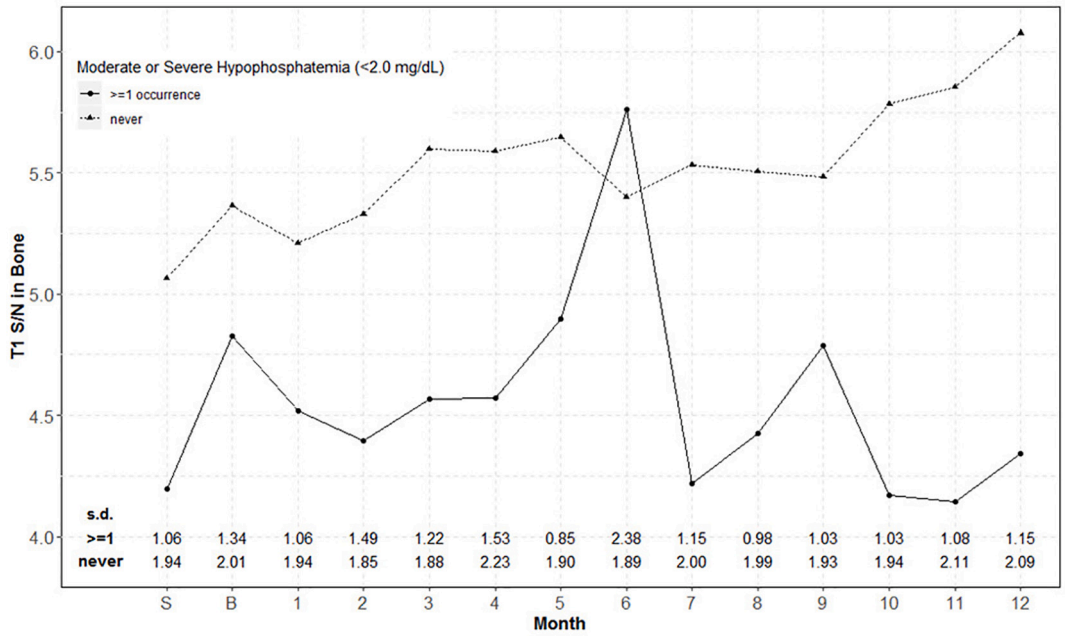
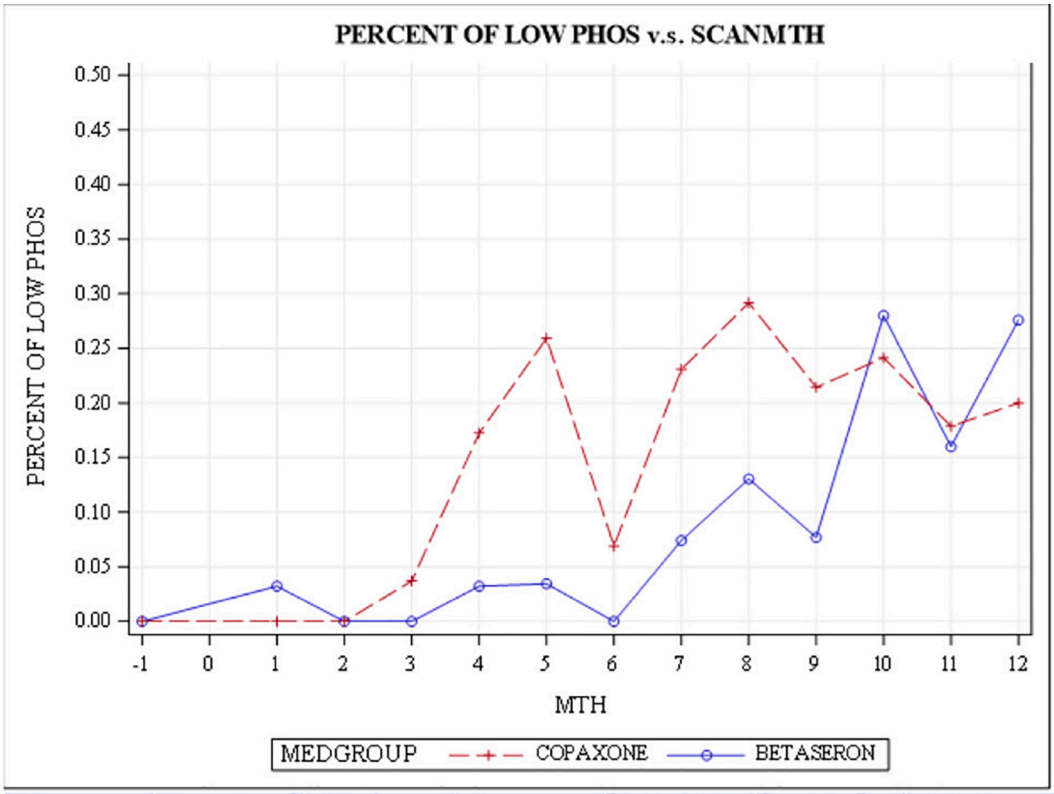


Fig. 3. Monthly T1 S/N in bone tissue demonstrates S/N increase in (N = 57) patients that never experienced moderate hypophosphatemia as opposed to (N = 9) patients who had at least one episode of moderate hypophosphatemia who showed no increase in signal, leading to increasing splaying of the respective curves.



BIO	TREAT	STAT	EST	CI_LOW	CI_HIGH	P_VALUE
PHOS	COPAXONE	ESTIMATOR	0.1869	0.1315	0.2423	<.0001
		ODDS RATIO	1.2055	1.1406	1.2742	_
	BETASERON	ESTIMATOR	0.3501	0.2095	0.4907	<.0001
		ODDS RATIO	1.4192	1.2331	1.6334	_

Fig. 4. Highly significant increase in frequency of hypophosphatemia. This is also significant in each arm when stratified by treatment.

CaSR activation by Gd^{3+}, while it is present in the body. However, once it is sufficiently eliminated from the body, PTH production may very well rebound strongly due to a long suppression, with an added synergistic stimulation from increased phosphates. Conceivably the rebound in PTH could cause serum phosphorus to overshoot, becoming depressed until the PTH subsides back to normal. This could be thought of as a “long term paradoxical effect” of Gd on phosphate levels.

24 h after IV administration of Gd-DTPA, 91% is excreted from the body, the lowest fractional excretion when compared to other GBCAs [30]. In a study involving dogs, gadolinium levels as high as 2.05 ± 0.17 ppm were seen in the kidney 2 weeks after injection of 0.2 mmol/kg of Gd-DTPA [31]. Gd even when released in small quantities by transmetallation, is known to initially go to the liver and then transferred to bone, and has negligible elimination over the next 3 weeks [32]. Therefore, Gd takes several days to weeks for complete elimination from the body. The use of consecutive monthly 3-dose should theoretically lead to more bone and tissue deposition with each passing month.

Apart from mechanisms described above, there are many independent, direct actions of gadolinium that may lead to hypophosphatemia. *In vitro* studies to compare the cytotoxicity of iodinated contrast and GBCA at angiographic concentrations on LLC-PK1 cells (a proximal tubular epithelial cell line of porcine origin) showed that Gd-DTPA induced significant necrosis and apoptosis of these cells [33]. Ultrastructural damage to proximal tubular cells is known to affect reabsorption of phosphates and lead to hyperphosphaturia, similar to that in Fanconi's syndrome [34], with resultant hypophosphatemia. Additionally, as a potent activator of Calcium Surface Receptor (CaSR), gadolinium may lead to decreased Vitamin D3 levels, thereby adding to the development of hypophosphatemia [35]. Hence, the ‘long term paradox’ hypotheses along with the above mentioned mechanisms may work in tandem or independently to cause hypophosphatemia after serial 3-dose gadolinium exposure.

There are several limitations to this study. First, this is a retrospective analysis of a randomized clinical trial originally designed to determine the relative efficacy of two different treatments for MS. As such, retention rates observed here may not be generalizable to healthy subjects, or those not undergoing similar drug therapy. This study also lacks a gadolinium-free control group. Like other investigators of Gd deposition, we lack information on prior administration of either linear or macrocyclic GBCA agents administered prior to initiation of the BECOME trial, which could contribute to signal changes encountered. This does not change the fact that over the 14 scans, the signal increased from its baseline, whether or not the patients were “gadolinium-naive.”

Triple-dose is now rarely utilized. MS clinical trials depend more heavily on annual quantification of FLAIR burden, rather than on detection of new enhancing lesions with frequent scanning. The authors acknowledge the frequent high dosing of linear chelate may have enabled detection of retention which may otherwise have gone undetected. Further investigations will be helpful to determine whether MRI detectable T1 hyperintensity can occur after a single administration of standard 0.1 mmol/kg dosage of a macrocyclic agent. Furthermore, research into the pathophysiology of gadolinium-related hypophosphatemia is recommended and the clinical significance of hypophosphatemia in this setting remains unknown.

Finally, what we have observed is T1 hyperintensity presumably due to macromolecule bound gadolinium. We cannot be certain this represents Gd, since other factors can result in hyperintensity. In our study, the use of fat-sat prevented fat from confounding the signal change.

5. Conclusion

Utilizing a systematically administered, high-dose gadolinium data set, this retrospective study demonstrated progressive development of intraosseous T1 hyperintensity, indirect MRI evidence of Gd retention in bone, as well as blunted development of T1 hyperintensity in patients who developed hypophosphatemia. This unique imaging-hematologic correlation may provide indirect evidence for *in vivo* transmetallation of gadolinium and should prompt further investigation into possible clinical sequelae that could arise due to retention within bone, as well as into the underlying pathophysiologic mechanisms. The fact that T1 hyperintensity was more pronounced in patients with normal phosphate as opposed to hypophosphatemic patients is puzzling. It is speculated that this could be the result of some sort of metabolic polymorphism wherein the heavy gadolinium load impacts on one or the other system, but not both. Alternatively, it is conceivable that depositing excess gadolinium in bone is protective against a separate, but yet unknown toxic effect causing hypophosphatemia. Future studies in which T1 hyperintensity is correlated with pathologic specimens could conceivably pave the way for a widely available *in vivo* method of monitoring bone gadolinium with MRI.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinimag.2020.07.022.

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1. The current retrospective study was sponsored by Guerbet, but was Investigator-initiated.
2. The original BECOME Trial was sponsored by Bayer, but was Investigator-initiated and the intellectual property remains that of the original investigators' institution.
3. At the time of subject participation in the randomized trial, gadopentetate dimeglumine was FDA approved but not at the 0.3 mmol/kg dose utilized.

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