Incorporation of gadolinium into hydroxyapatite: elucidating the accumulation of Gd in bone after MRI contrast agent administration

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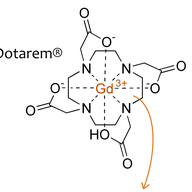
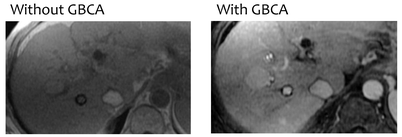
Introduction

Gadolinium-based contrast agents (GBCAs):
Currently the only available contrast agents for magnetic resonance imaging (MRI)

Example: Dotarem®





Malignant liver lesion: hepatocellular carcinoma
(Courtesy of Dr R Schubert, Radiopaedia.org, rID: 15858)

- GBCAs (chelators) may partly dissociate and release free Gd^{3+}
  → ongoing safety concerns: GBCAs linked to nephrogenic fibrosis and deposition in the brain [1]
- Gd^{3+} **deposition observed in bone** several years after administration (at levels much higher than in the brain) [2] → long term storage!

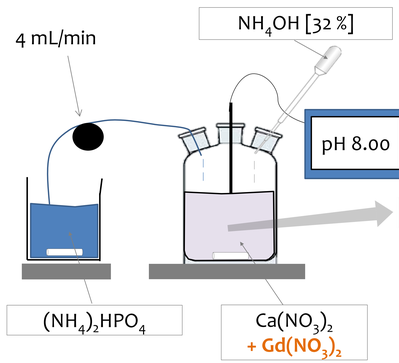
- But how is Gd^{3+} incorporated into bone ?
  - Organic phase of bone ?
  - $GdPO_4$ (known to be insoluble in physiological medium [3]) ?
  - Gd-substituted bone mineral (hydroxyapatite) ?

Goal of the present work:

- To investigate whether Gd^{3+} precipitated along with Ca^{2+} and PO_4^{3-} from a supersaturated solution is incorporated into the crystal structure of a bone-like calcium phosphate phase

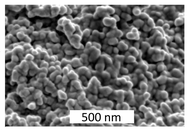
Method

Precipitation of **calcium deficient hydroxyapatite (CDHA)**



CDHA with
nominal (Ca+3/2·Gd)/P molar ratio: 1.50
nominal Gd/(Gd+Ca) molar ratios: 0, 0.01 and 0.05

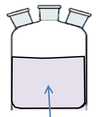
Filtering → Rinsing in H2O → Drying



Rinsing solution (1% Gd sample) → Elemental quantification by inductively coupled-plasma mass spectrometry (**ICP-MS**)

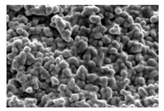
Solid → Crystallographic characterization by powder X-ray diffraction (**XRD**) and Rietveld refinement

Results & Discussion



Incoporated into crystals (1% Gd sample):
→ 99.99 mol% of all Gd^{3+} ions
→ only 96 to 97 mol% of Ca^{2+} and PO_4^{3-} ions

Gd/(Gd+Ca) = 1% → Rinsing solution → Gd/(Gd+Ca) <0.01%



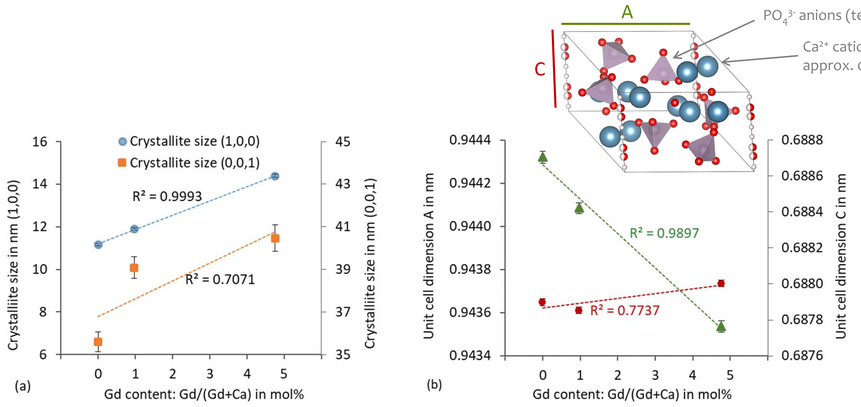
Gd/(Gd+Ca) = 0.97%

- Gd^{3+} is highly insoluble and was permanently incorporated into the precipitated crystals

Chemical and crystallographic parameters of the Gd-containing precipitate

Gd / (Gd+Ca) nominal in mol%	**Gd / (Gd+Ca) (ICP-MS)** in mol%	**Phases detected (XRD)**	**Amorphous fraction (XRD)** in wt%
0%	0%	CDHA	14%
1%	0.97%	CDHA	14%
5%	4.76%	CDHA	19%

- The precipitate consisted of phase-pure CDHA with a Gd content close to nominal quantities, and accompanied by an amorphous fraction of <20 wt%



Crystallite size (a) and unit cell dimensions (b) of the CDHA crystal lattice as a function of Gd content. Error bars designate the estimated standard deviation associated with the Rietveld refinement.

- Gd content affects the CDHA crystallite size
- Unit cell dimension A decreases with increasing Gd content → a contracted unit cell is in line with the smaller Gd^{3+} ionic radius compared to Ca^{2+} [4]
- These findings imply that Gd^{3+} was most likely incorporated into the apatite crystal lattice rather than forming a separate $GdPO_4$ phase

Conclusions

- Chemical and crystallographic analysis of the precipitate formed from a supersaturated solution of Gd^{3+}, Ca^{2+} and PO_4^{3-} provided strong evidence of a Gd-containing apatite crystal structure
- Thus, Gd^{3+} ions dissociated from their chelators *in vivo* after GBCA administration may be directly incorporated into the mineral phase of bone during bone formation or remodeling

References

[1] Grobner, *Nephrol Dial Transplant* 2006; **21(4)**:1104-8
[2] Murata et al, Invest Radiol 2016; **51(7)**:447-53
[3] Bleavins et al, Biol Trace Elem Res 2012; **145(2)**:257-67
[4] Shannon, *Acta Cryst A* 1976; **32(5)**:751-67

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