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)

- GBCAs (chelators) may partly dissociate and release free Gd³⁺
- Ongoing safety concerns: GBCAs linked to nephrogenic fibrosing and deposition in the brain

- Gd³⁺ deposition observed in bone several years after administration (at levels much higher than in the brain)
- But how is Gd³⁺ incorporated into bone?
- Organic phase of bone
- GdPO₄ (known to be insoluble in physiological medium)
- Gd-substituted bone mineral (hydroxyapatite)

Goal of the present work:
- To investigate whether Gd³⁺ precipitated along with Ca²⁺ and PO₄³⁻ from a supersaturated solution is incorporated into the crystal structure of a bone-like calcium phosphate phase

Method

Precipitation of calcium deficient hydroxyapatite (CDHA)

4 mL/min

\[(\text{NH}_4)_2\text{HPO}_4 \quad \rightarrow \quad \text{Ca(NO}_3\text{) } \quad \rightarrow \quad \text{Gd(NO}_3\text{)}\]

\[\text{CDHA with nominal (Ca+3/2-Gd)P molar ratio: 1.50 nominal Gd/(Gd+Ca) molar ratios: 0, 0.01 and 0.05}\]

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Elemental quantification by inductively coupled plasma mass spectrometry (ICP-MS)

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

Results & Discussion

Incorporated into crystals (1% Gd sample)

- Gd³⁺ is highly insoluble and was permanently incorporated into the precipitated crystals
- The precipitate consisted of phase-pure CDHA with a Gd content close to nominal quantities, and accompanied by an amorphous fraction of <20 wt%

Gd³⁺ ions after GBCA administration may be directly incorporated into the mineral phase of bone


Stähli et al, Invest Radiol 2016; 51(3):447-53

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Gd³⁺ 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


Conclusions

Chemical and crystallographic analysis of the precipitate formed from a supersaturated solution of Gd³⁺, Ca²⁺ and PO₄³⁻ provided strong evidence of a Gd-containing apatite crystal structure

Thus, Gd³⁺ 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

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