

**Supplementary information**

**Bioinorganic supplementation in calcium phosphate-based bone substitutes for improvement of biological performance: a systematic review and meta-analysis**

*Irene Lodoso-Torrecilla, Raquel Klein Gunnewiek, Eline-Claire Grosfeld, Rob B de Vries, Pamela Habibovi, John A Jansen, Jeroen JJP van den Beucken*

**Table S1: Literature search-strategy for PubMed**

|                                       |  |
|---------------------------------------|--|
| <p>Component 1: Bone regeneration</p> | <p>("Bone regeneration"[Mesh] OR "Osteogenesis"[Mesh] OR "Fracture healing"[Mesh] OR (Bone regeneration[Tiab]) OR ((Bone[Tiab] AND (regeneration[Tiab])) OR Osteogenesis[Tiab] OR (Fracture healing[Tiab]) OR ((Fracture[Tiab] AND (Healing[Tiab])) (Bone Formation[Tiab]) OR ((Bone[Tiab] AND (Formation[Tiab])) OR (Bone repair[Tiab]) OR ((Bone[Tiab] AND (Repair[Tiab])) OR (Bone healing[Tiab]) OR ((Bone[Tiab] AND (Healing[Tiab])) OR (new bone[Tiab]) OR (new formed bone[Tiab]) OR (newly formed bone[Tiab]) OR (bone forming[Tiab]) OR (formation of bone[Tiab]) OR (formation of new bone[Tiab]))</p>   |
| <p>Component 2: Bone substitutes</p>  | <p>("Bone Substitutes"[Mesh] OR "Bone Cements"[Mesh] OR "Bone Transplantation"[Mesh] OR "Calcium phosphates"[Mesh] OR Beta-tricalcium Phosphate[Supplementary Concept] OR Alpha-tricalcium Phosphate[Supplementary Concept] OR Tricalcium Phosphate[Supplementary Concept] OR Bone substitute*[Tiab] OR ((Bone[Tiab] OR Bones[Tiab]) AND (Substitute[Tiab] OR Substitutes[Tiab])) OR ((Artificial[Tiab] OR Artificials[Tiab]) AND (Bone[Tiab] OR Bones[Tiab])) OR ((Bone[Tiab] OR Bones [Tiab]) AND (Replacement[Tiab] OR Replacements[Tiab])) OR (Calcium[Tiab] AND Phosphate[Tiab]) OR Calcium phosphate*[Tiab] OR CPC[Tiab] OR CPCs[Tiab] OR ((Bone[Tiab] OR Bones[Tiab]) AND (Cement[Tiab] OR Cements[Tiab])) OR Tricalcium phosphate[Tiab] OR Tricalcium phosphates[Tiab] OR Tricalcium orthophosphate[Tiab] OR Tricalcium Diphosphate[Tiab] OR</p> |

|                             |   |
|-----------------------------|---|
|                             | Tricalcium Phosphate Ceramic[Tiab] OR Beta-tricalcium Phosphate[Tiab] OR Calcium Superphosphate[Tiab] OR $\alpha$ -TCP[Tiab] OR $\beta$ -TCP[Tiab] OR $\alpha$ -TCP[Tiab] OR $\beta$ -TCP[Tiab] OR alpha-TCP[Tiab] OR beta-TCP[Tiab] OR alpha-tricalcium[Tiab] OR beta-tricalcium[Tiab] OR tetracalcium phosphate[Tiab] OR TTCP[Tiab] OR Dicalcium Phosphate[Tiab] OR DCPA[Tiab] OR hydroxyapatite*[Tiab] OR Synthetic bone[Tiab])  |
| Component 3: Bioinorganics  | ("Copper"[Mesh] OR "Fluorides"[Mesh] OR "Fluorine"[Mesh] OR "Magnesium"[Mesh] OR "Silicon"[Mesh] OR "Silicates"[Mesh] OR "Strontium"[Mesh] OR "Zinc"[Mesh] OR "Chlorine"[Mesh] OR "Chlorides"[Mesh] OR "Sulfur"[Mesh] OR "Sulfides"[Mesh] OR Inorganic*[Tiab] OR Bioinorganic*[Tiab] OR Trace elements [Mesh] OR Trace element*[Tiab] OR Copper[Tiab] OR Fluorine*[Tiab] OR Fluoride*[Tiab] OR Magnesium[Tiab] OR Silicon[Tiab] OR Silicate*[Tiab] OR Strontium[Tiab] OR Zinc[Tiab] OR Chlorine[Tiab] OR Chlorite[Tiab] OR Chloride*[Tiab] OR Sulfur[Tiab] OR Sulphur[Tiab] OR Sulfide*[Tiab] OR Sulphide*[Tiab]) |
| Component 4: Animal studies | Search filter for animal studies [1]  |

**Table S2: Literature search-strategy for Embase**

|                                |  |
|--------------------------------|--|
| Component 1: Bone regeneration | exp bone defect/ OR exp bone regeneration/ OR exp bone development/ OR exp bone transplantation/ OR (bone regeneration OR fracture healing OR bone formation OR bone repair OR bone healing OR new bone OR new formed bone OR newly formed bone OR bone forming OR formation of bone OR formation of new bone).ti,ab.  |
| Component 2: Bone substitutes  | exp bone graft/ OR exp bone implant/ OR exp calcium phosphate/ OR exp bone cement/ OR exp bone cement device/ OR (bone substitute* OR bone cement* OR calcium phosphate* OR alpha tricalcium phosphate* OR bone transplantation OR tricalcium phosphate* OR beta tricalcium phosphate* OR artificial bone* OR bone replacement OR CPC* OR tricalcium orthophosphate* OR tricalcium diphosphate* OR tricalcium phosphate ceramic* OR calcium superphosphate* OR a-TCP OR b-TCP OR alpha-TCP OR beta-TCP OR tetracalcium OR TTCP OR dicalcium phosphate* OR DCPA OR hydroxyapatite OR synthetic bone).ti,ab. |
| Component 3: Bioinorganics     | exp copper/ OR exp fluoride/ OR exp sulfur/ OR exp sulfide/ OR exp fluorine/ OR exp magnesium/ OR exp silicon/ OR exp silicate/ OR exp strontium/ OR exp strontium 90/ OR exp zinc/ OR exp chlorine/ OR (inorganic* OR bioinorganic* OR trace element* OR copper OR fluoride* OR fluorine OR magnesium OR silicon OR silicate* OR strontium OR zinc OR chlorine OR chloride* OR sulphide* OR sulphur OR sulfide*).ti,ab.   |
| Component 4: Animal studies    | Search filter for animal studies[2]  |

**Table S3: Inclusion and exclusion criteria used for study selection**

|  | Inclusion criteria  | Exclusion criteria  |
|--|---|---|
| Type of study (design)                                       | - Primary research paper presenting pre-clinical animal data (in vivo)  | - Not an original article<br>- Research paper presenting in vitro data or clinical data   |
| Type of animals/population (e.g. age, gender, disease model) | - Animals used should have reached the age of skeletal maturity   | - Skeletally immature animals   |
| Type of intervention (e.g. dosage, timing, frequency)        | - Data should be presented for animals that received a calcium phosphate based bone substitute with inclusion of one (not multiple) bioinorganic element (i.e. Mg, Sr, Zn, F, Cu, Si, S or Cl) (experimental group) vs. animals that received a calcium phosphate based bone substitute without inclusion of a bioinorganic element (control group) | - No CaP-based bone substitute<br>-No bioinorganics<br>- Multiple bioinorganics added to a calcium phosphate based bone substitute<br>- No relevant control group<br>- No bone defect |
| Outcome measures   | - Histological or (histo)morphometrical data about bone formation and/or material degradation should be presented   | - Other outcome measures  |

**References**

[1] C.R. Hooijmans, A. Tillema, M. Leenaars, M. Ritskes-Hoitinga, Enhancing search efficiency by means of a search filter for finding all studies on animal experimentation in PubMed, *Laboratory animals* 44(3) (2010) 170-5.

[2] R.B. de Vries, C.R. Hooijmans, A. Tillema, M. Leenaars, M. Ritskes-Hoitinga, Updated version of the Embase search filter for animal studies, *Laboratory animals* 48(1) (2014) 88.