Properties of commonly used calcium phosphate cements in trauma and orthopaedic surgery

Technical note

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Abstract

Since the introduction of calcium phosphate cements (CPCs) in 1985, a number of CPCs became predominantly commercially available for use in trauma and orthopaedic surgery. The aim of this technical note was to provide the relevant knowledge about CPCs that may improve the selection of CPCs for bone defects encountered in trauma and orthopaedic surgery. This includes a classification based on the chemical composition, and details about structural, mechanical and biological properties. Furthermore, the biological performance of each CPC was assessed in an animal study. And finally, a systematic literature search was conducted to provide a comprehensive overview of currently available clinical literature of these CPCs in trauma and orthopaedic surgery.

Keywords

biocompatibility, bone defects, bone graft, calcium phosphate cement, osteoconduction
Introduction

Halve of the population sustains at least one fracture during their lifetime\(^1\), and the majority of these fractures heal successfully. Successful fracture healing requires the following five elements; (i) osteogenic cells (\textit{e.g.}, osteoblasts), (ii) osteoinductive stimuli (\textit{e.g.}, bone morphogenetic proteins); (iii) an osteoconductive matrix; (iv) adequate blood and nutrient supply, and (v) sufficient mechanical support\(^2\). One or more elements can be compromised due to the existence of a bone defect. Bone defects are treated with bone grafts in order to avoid insufficient fracture healing. Insufficient fracture healing is encountered in 5 to 10% of the fractures, resulting in delayed union, malunion, or non-union\(^3\).

Most commonly used bone graft material is autologous bone. Autologous bone is usually harvested from the iliac crest\(^4\). However, harvesting autologous bone lengthens the surgical procedure and is associated with complications in 8-39\% of patients (\textit{e.g.}, infection, nerve and urethral injury, and postoperative or chronic pain)\(^5\). An alternative option is to use allogeneic bone. However, allogeneic bone grafting is considered suboptimal since it has biocompatibility disadvantages\(^6\). The disadvantages of autologous and allogeneic bone grafts have resulted in the development of alternative (synthetic) bone substitute materials. The most interesting group of bone substitute materials is probably calcium phosphate (CaP), because CaPs mimic the mineral part of natural bone\(^7\).

CaP-based bone substitutes have been studied for several decades\(^8\) and they can be categorized into CaP ceramics and CaP cements (CPC)\(^7\). CaP ceramics are obtained by thermal treatment (sintering), generally resulting in solid grafting materials (\textit{e.g.}, blocks or granules). CPCs, on the other hand, consist of CaP powder that forms a paste upon mixing with a liquid. Mixing is usually done during surgery and the resulting paste becomes solid within several minutes through an isothermic chemical setting reaction. During this setting
reaction, the CPCs can be moulded by the surgeon into any desired shape in order to completely fill the defect.

Since the introduction of CPC in 1985 by Brown and Chow, a number of CPCs have become commercially available for trauma and orthopaedic surgery. Trauma or orthopaedic surgeons are therefore given the opportunity to select a CPC that meets the specific demands of each bone defect that requires bone grafting. The aim of this technical note was to provide a comprehensive overview of knowledge of commonly used CPCs that may improve this selection for bone defects encountered during fracture treatment. The chemical composition and structural, mechanical and biological properties of the four predominantly used CPC products (Table 1) are discussed. In addition, the biological properties were evaluated in a large animal bone defect model. Finally, a systematic literature search was conducted in order to provide insight into the available clinical evidence supporting to use of these CPC products to graft bone defects encountered during fracture treatment.

**Calcium phosphate cements**

CPCs can be classified based upon the setting product of the CPC into apatite-forming and brushite-forming CPCs. This classification refers to the degree of crystallinity of the CaP formed and has a direct impact on their resorption rate. The resorption of an apatite-forming CPCs is very limited and takes many years, whereas the resorption of brushite-forming CPCs takes place within several months. Commercially available apatite-forming CPCs are BoneSource®, Calcibon®, and Norian SRS®, a brushite-forming CPC is ChronOS™ Inject (Table 2). CPC products are available in several quantities, ranging from 1.5 cc to 30 cc (Table 1), and depending on the CPC product the setting reaction will take five (Calcibon®) or fifteen minutes (Norian SRS®) to be completed once the components are mixed (Table 2).
It is necessary to distinguish CPCs from ceramic CaPs. The ceramic CaPs are acquired from heating (sintering) of calcium phosphate powder up to 800-1300 ºC. This heating results in formation of solid porous blocks or granules that can consist of hydroxyapatite (HA), tricalcium phosphate (TCP) or a combination HA and TCP (composites). Examples of commercially available CaP ceramics are BoneSave®, Camceram®, Cerabone®, ChronOSTM, Endobon®, Ostim®, Pro Osteon 500®, and Vitoss®

Structural properties
CPCs are generally described as being osteoconductive. Osteoconduction is defined as the ability of a graft material to function as a scaffold that allows ingrowth of bone and vascular tissues. A scaffold that offers an open porous structure with pore dimensions of 150-500 μm is considered optimal for bone ingrowth. CPCs generally form dense structures with limited porosity (Table 3). In vitro micro-CT measurements indicate that the porosity of ChronOSTM Inject is only 5±1 %, and that the porosity of apatite-CPCs does not exceed 5 % (BoneSource® 0.4±0.3 %, Calcibon® 0.9±0.5 %, Norian SRS® 0.3±0.2 %). Furthermore the majority of these pores is smaller than 150 μm. Average pore size of ChronOSTM Inject is 100 μm, and 18 % of these pores exceed the size of 150 μm. Average pore sizes of other apatite-CPCs is ~50 μm and the fraction that exceeds the size of 150 μm is less than 4 %.

Mechanical properties
The mechanical properties of a bone substitute material should ideally be comparable to the bone being replaced. However, the mechanical properties of bone differ according to their structure (cortical or trabecular bone) and function (weight-bearing or non-weight-bearing). Compression strength of human cortical bone is in the range of 130 to 190 MPa, whereas trabecular bone has a compression strength of 8 to 38 MPa. Apatite-CPCs were found to have
a compression strength in the range of trabecular bone (Table 3); Calcibon® has the highest compression strength (34±7 MPa), followed by Norian SRS® (26±7 MPa) and BoneSource® (14±3 MPa). The brushite-CPC ChronOS™ Inject has a compression strength that is much lower and does not exceed values of 1 MPa13.

**Biological properties**

Biological properties of four CPCs were studied in a drill-hole tibia bone defect model in goats14. This model allows for a direct comparison of different CPCs. Three months after grafting the drill-hole defects with different CPCs, resorption and bone formation were determined using micro-CT scanning, histology, and fluorochrome labeling (Supplementary Materials and Methods). The study was approved by the institution’s Animal Ethics Committee (EUR1540).

The micro-CT scans acquired at three months after grafting showed that drill-hole defects remained adequately filled by apatite-based CPCs (BoneSource®, Calcibon®, and Norian SRS®). This indicates limited resorption of apatite-CPCs whereas using ChronOS™ Inject resulted in a partially remaining bone defect (Figure 1); the latter is most likely the result of fast resorption of this brushite-CPC. Detailed views of defects with CPCs showed that it is difficult to distinguish CPC from native bone as the radiographic density is very close (BoneSource®, Norian SRS®) or even similar (Calcibon®, ChronOS™ Inject) to native bone. These similar radiographic densities obstruct a quantitative analysis from these micro-CT images of newly formed bone and remaining CPC volumes.

Histology confirmed that resorption rate of apatite-CPCs is very limited and that, as a result, these CPCs remained largely intact (Figure 2). Calcibon® still covered almost the complete defect and hardly any bone ingrowth had appeared within three months. Furthermore little activity of bone formation at the CPC-interface, indicated by the
fluorochrome labels, was found in defects grafted with Calcibon®. Although BoneSource®
also covered the majority of the defect, some resorption did take place within the three
months follow-up. The fact that BoneSource® resorbed slowly was also shown by Welch et
al. In their study, subchondral femoral bone defects in goats were grafted with
BoneSource®, and 38 % of the CPC was still present after two years. A similar resorption
pattern was also seen for Norian SRS®. Apelt et al. indicated that approximately 5 % of
Norian SRS® was resorbed at six months after grafting a comparable subchondral bone defect
in sheep. The minimal appearance of fluorochrome labels at CPC-interface of tibia defects
grafted with BoneSource® and Norian SRS® also indicate little bone forming activity (Figure
2).

Histology of the only brushite-based CPC, ChronOS™ Inject, indicated indeed that
most of CPC was resorbed within three months time. This was also shown by Apelt et al.,
who found that only 20 % of ChronOS™ Inject was still present six months after grafting
subchondral bone defects in sheep. In the periphery of the defect, ChronOS™ Inject had
resorbed and was replaced by new bone. After three months, only some bits of CPC were
found within the center of the defect (Figure 2). Contrary to the limited bone forming activity
found for apatite-CPCs, this brushite-CPC seemed to elect a bone formation activity almost
throughout the complete CPC-interface (Figure 2).

Clinical evidence in fracture treatment
A systematic literature search was conducted using the product names of all products (Table
1) as search terms in PubMed database. PubMed database was searched from the earliest date
available until October 26, 2012. The following filters were used: species (human), languages
(Dutch, English, or German), search fields (Text word). Retrieved manuscripts were only
included when they contained original research on CPC use in trauma and orthopaedic related
indications. Manuscripts were excluded when they only contained data describing in vitro (e.g. cellular response or cadaver studies) or animal experiments, or when the CPC was used in other than trauma and orthopaedic related indications (e.g. dental or craniofacial surgery). All references of included manuscripts were reviewed in order to ensure that no relevant papers had been missed.

The systematic literature search resulted in seventy-eight eligible manuscripts. Thirty-three of these manuscripts were selected for final inclusion, including one additional reference (Table 4). The included manuscripts consisted of ten clinical trials, two case-control studies, twenty case-series and one case-report. The four CPC have been used to graft bone defects encountered in treatment of humerus, radius, femur, tibia, calcaneus, vertebra, and odontoid fractures (Table 5), as well as bone defect encountered during knee or hip revision surgery and treatment of endochondrale bone cysts.

BoneSource® was subjected to one multicenter prospective randomized trial. Metaphyseal bone defects of thirty-eight fractures, including femur, tibia, calcaneus, humerus, and distal radius fractures were grafted with either BoneSource® or autologous bone. Adequate reduction was maintained in 83 % of the defects treated with BoneSource® versus 67 % of the defect treated with autologous bone. Furthermore, reduction and injection of BoneSource® was compared with reduction and fixation with K-wires as a treatment for displaced distal radius fractures. In their study, all clinical and radiographic parameters were worse after twenty-six weeks in the BoneSource® groups, and they concluded that BoneSource® alone does not provide sufficient fixation after reduction of displaced radial fractures.

Calcibon® is mostly used for grafting defects resulting of (osteoporotic) vertebral fractures. One prospective trial, several prospective and retrospective case-series all
indicate that grafting with Calcibon® gives comparable results to using polymethylmethacrylaat (PMMA).

Norian SRS® is described in more than twenty manuscripts and has been used as a bone graft for filling bone voids resulting of fractures of the proximal humerus, distal radius, proximal femur, proximal tibia, or calcaneus, as well as in odontoid fractures. Keating et al. treated 49 lateral tibia plateau fractures with internal fixation and Norian SRS®. After one year, 95 % had good or excellent Rasmussen knee scores but also 20 % showed radiological evidence of post-traumatic osteoarthritis. In a randomized controlled trial including 323 patients, percutaneous injection of Norian SRS® after closed reduction of displaced distal radius fractures resulted in accelerated rehabilitation and improved clinical outcomes after two years compared with reduction only. Norian SRS® was used for grafting defects resulting from calcaneal fractures and it allowed full weight bearing as early as three weeks after open reduction and internal fixation. Furthermore, the use of Norian SRS® has used in acetabular cup revision surgery (case-report), knee replacement surgery (case-series). One study that was designed to treat enchondromas with Norian SRS® was stopped because three of the four included patients had severe pain after curettage of enchondroma and subsequent grafting with Norian SRS®.

ChronOSTM Inject is indicated for use in femur, tibia, calcaneus, humerus, and radius fractures by the manufacturer, however there were no clinical studies found that describe the use of ChronOSTM Inject in this indication (Table 5). ChonOS™ Inject has been used to treat benign bone cysts in children. After treating twenty-four pediatric patients, ChonOS™ Inject was found to be safe and therefore could provide an alternative treatment for benign bone cysts in children.
Discussion

Commercially available CPCs have different mechanical, structural and biological properties. Mechanical, structural and biological properties are mainly explained by their chemical composition. Based on chemical composition, CPCs can be classified into apatite-forming and brushite-forming CPCs. This classification may prove helpful in selection of CPCs for bone defects at specific fracture sites. In general, apatite-forming CPCs offer more mechanical strength and have a low resorption rate. Brushite-forming CPCs, on the other hand, offer only limited mechanical strength and have a high resorption rate.

Bone graft materials should offer mechanical support to surrounding bone and soft tissues in order to facilitate fracture healing. Apatite-forming CPCs have compression strengths in the range of trabecular bone (Table 3), and may therefore be most suitable to graft defects of metaphyseal bone defect. Brushite-forming CPCs only offer minimal mechanical strength, and they should therefore only be used in situations in which sufficient mechanical stability can already be acquired using fixation hardware. Overall, CPCs do not possess sufficient mechanical strength to be used in cortical or weight-bearing bone defect.

Micro-CT data indicates that CPCs form a rather dense structure with only a limited amount of pores that may allow bone and vessel ingrowth. The working mechanism in which CPCs can support bone formation is therefore more likely based on gradual resorption of the CPC and subsequent bone formation. Resorption of CPCs is an active process mediated by osteoclasts. The resorption rate is an interplay of chemical composition, structure and volume of the CPC and the availability and activity of osteoclasts. Resorption of CPC should be followed by bone formation until complete regeneration of the bone defects has occurred. The regenerative potential of the surrounding bone should therefore be taken into account, and
when rapid bone formation can be expected, fast resorbing brushite-forming CPCs, such as ChronOSTM Inject, may be preferred over apatite-forming CPCs.

CPCs are mostly studied as a bone substitute material to graft metaphyseal bone defects (Table 5). Grafted metaphyseal bone defects include fractures of the femur, tibia, calcaneus, humerus, radius, and vertebra. The majority of the studies included in the systematic literature search consist of case-series. Case-series can provide relevant knowledge about the specific indication in which a CPC can be used and the relative safety, however they are not the preferred evidence to draw well-founded conclusions on the clinical benefits of using CPCs. Furthermore, the average number of clinical studies performed with each CPC product is surprisingly low, especially for BoneSource®, ChronOSTM Inject and Calcibon® (Table 4). More clinical studies, preferably randomized controlled trials, are therefore desired and can contribute to better understanding of the potential indications and benefits of different CPC products.

**Limitations**

There are limitations to this work. Firstly, the selection of CPC products was based upon their availability for use in trauma and orthopaedic surgery in the Netherlands. The included products are widely available and used worldwide, which supports a wide relevance of this paper. On the other side, several other CPC products such as Norian Drillable®, HydroSet®, alpha-BSM® and Callos® were not included. Furthermore, biological properties were studied in a tibia drill-hole defect model. This model has the advantage over other models that it allows for evaluation of multiple CPCs within one animal. This makes direct comparison of the studied CPCs more relevant. On the other hand, it model might be a clinically less relevant, since CPC products are predominantly used to graft metaphyseal bone defects. Therefore, whether metaphyseal bone defects can successfully be grafted with the studied
CPC cannot be directly translated from their performance in this model. The biological properties as described here provide important clues that can help to determine which product is most suitable for each type of bone defect encountered during clinical practice. Finally, the systematic literature search may not have been able to retrieve all relevant publications of the included CPC products. This risk is minimized through performing the search with the product name as search term in two different databases (Embase and PubMed) and screening reference lists of the included articles for additional publications (one publication found). Missing publications that did not specify the product name is not considered a limitation, since this systematic search was conducted to provide insight into the available clinical evidence of the commercially available CPC products, helping trauma and orthopaedic surgeons to select the most suitable product. Mentioning the product name was therefore essential for this study.

**Acknowledgements and affiliations**

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References


Figure captions

Figure 1: Filling capability of CPCs in a drill-hole defect

Micro-CT and corresponding Goldner’s trichrome histological images. S, substitute material; B, bone. Bar indicates 1 mm.
Figure 2: CPC integration and bone forming activity at the CPC-interface

Goldner’s trichrome histological images of the CPC-interface and corresponding fluorochrome images. S, substitute material; B, bone. Red label is tetracycline and green label is calcein green. Bar indicates 1 mm.
Supplementary Materials and Methods

Animal experiment

In five skeletally mature female milk goats, each weighing 50-60kg, a drill-hole bone defect model was used in which three holes were created at the diaphysis of the right tibia. Two of the holes were grafted with a CPC and one was left empty, serving as a control. All products were tested in duplicate and randomized over the proximal, distal and middle holes. After three months, the goats were killed and the grafted bone defects were analyzed using micro-CT, histology, and fluorochrome labeling.

Surgical procedure

The operation was performed under general anesthesia induced by an intravenous injection of 0.3ml medetomidine (1mg/ml) followed by 20ml propofol (10mg/ml) and maintained by isoflurane 1.5% through a constant volume ventilator, administered through an endotracheal tube. The goats received prophylactic antibiotics according to the following scheme: 12.5ml amoxicillin (48mg/ml) at the start of the operation and 7.5ml ampicillin (100mg/ml) during the operation; and two and four days after the operation.

Before surgery, the animal was immobilized on its right side and the right limb was shaved, washed, and disinfected with povidone-iodine. A longitudinal incision was made on the medial surface of the tibia, and the bone was exposed by blunt dissection. Three unicortical 2.0mm diameter holes were drilled at low rotational drill speeds and continuous cooling with cold physiologic saline, with an interspace of 2.5cm. The 2.0mm diameter holes were enlarged to 5.0mm diameter and irrigated and packed with sterile cotton gauze, and the calcium phosphate cements were then prepared. Subsequently, the cements were injected into the bone defects and allowed to solidify. Any extruding material was removed. The soft
tissues and skin were closed in separate layers with Vicryl sutures. Post operative analgesia consisted of 0.8ml buprenorphine (300μg/ml) and 1.0ml flunixin (50mg/ml) on day zero to three post surgery.

**Fluorochrome labeling**

The fluorochrome labels were administered intravenously at 14 days (tetracycline hydrochloride, 30 mg/kg (Sigma)) and four days (calcein, 10 mg/kg intravenously (Sigma)) before they were killed using an overdose pentobarbital.

**Micro-CT evaluation**

The right tibias were taken out and trimmed to a suitable size for micro-CT scanning. A 9 μm-resolution protocol (75 kV energy, 133 μA current, 1.0 mm Al filter) was used with a SkyScan 1076 micro-CT scanner (Bruker micro-CT N.V., Kontich, Belgium). The CT images were reconstructed using NRecon software version 1.5 (Bruker micro-CT N.V., Kontich, Belgium).

**Histological evaluation**

After micro-CT scanning, each tibia was trimmed to a size suitable for histological processing. Subsequently, all specimens were fixed in paraformaldehyde (4%) overnight, dehydrated in a graded series of ethanol, and embedded in methylmethacrylate (MMA). After polymerization, undecalcified thin (6μm) sections were made with a heavy duty microtome in a transverse direction through the middle of the defect area. Sections were stained using Goldner’s trichrome and evaluated with a light microscope (Olympus BX50). Fluorochrome labels were evaluated in unstained sections using an epifluorescence microscope (Axiovert 200MOT/Carl Zeiss) equipped with a double filter block.
### Table 1. Product specifications

<table>
<thead>
<tr>
<th>Product</th>
<th>Manufacturer</th>
<th>Available volumes</th>
</tr>
</thead>
<tbody>
<tr>
<td>BoneSource®</td>
<td>Stryker</td>
<td>1.5 cc, 3 cc, 6 cc, 15 cc, 30 cc</td>
</tr>
<tr>
<td>Calcibon®</td>
<td>Biomet</td>
<td>4 cc, 8 cc, 16 cc</td>
</tr>
<tr>
<td>ChronOS™ Inject</td>
<td>DePuy Synthes</td>
<td>2.5 cc, 5 cc, 10 cc</td>
</tr>
<tr>
<td>Norian SRS®</td>
<td>DePuy Synthes</td>
<td>3 cc, 5 cc, 10 cc</td>
</tr>
</tbody>
</table>

### Table 2. Chemical composition and mixing properties

<table>
<thead>
<tr>
<th>Product</th>
<th>Chemical composition</th>
<th>Mixing time</th>
<th>Final setting time</th>
<th>Final setting product</th>
</tr>
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<tbody>
<tr>
<td>BoneSource®</td>
<td>80% TCP / 20% HA</td>
<td>2-4 m</td>
<td>5-10 m</td>
<td>apatite</td>
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<tr>
<td>Calcibon®</td>
<td>62.5% α-TCP / 26.8% DCPA / 8.9% CaCO₃ / 1.8% HA</td>
<td>1 m</td>
<td>5 m</td>
<td>apatite</td>
</tr>
<tr>
<td>ChronOS™ Inject</td>
<td>73% β-TCP / 21% MCP.H₂O / 5% MHPT</td>
<td>1 m</td>
<td>11 m</td>
<td>brushite</td>
</tr>
<tr>
<td>Norian SRS®</td>
<td>α-TCP / CaCO₃ / MCP.H₂O</td>
<td>1 m</td>
<td>15 m</td>
<td>apatite</td>
</tr>
</tbody>
</table>

CaCO₃, calcium carbonate; DCPA, dicalcium phosphate anhydrous; HA, hydroxyapatite; MCP.H₂O, monocalcium phosphate monohydrate; MHPT, magnesium hydrogen phosphate trihydrate; TCP, tricalcium phosphate.

### Table 3. Structural and mechanical properties

<table>
<thead>
<tr>
<th>Product</th>
<th>Porosity (%)¹³</th>
<th>Compression strength (MPa)¹³</th>
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</thead>
<tbody>
<tr>
<td>BoneSource®</td>
<td>0.4</td>
<td>14</td>
</tr>
<tr>
<td>Calcibon®</td>
<td>0.9</td>
<td>34</td>
</tr>
<tr>
<td>ChronOS™ Inject</td>
<td>4.5</td>
<td>1</td>
</tr>
<tr>
<td>Norian SRS®</td>
<td>0.3</td>
<td>26</td>
</tr>
</tbody>
</table>
Table 4: Number of publications retrieved during the systematic literature search

<table>
<thead>
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<th>Inclusion</th>
<th>Exclusion</th>
<th>Final</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PubMed Search</td>
<td>In vitro experiments</td>
<td>Animal experiments</td>
</tr>
<tr>
<td>Apatite-CPC</td>
<td></td>
<td></td>
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<tr>
<td>BoneSource®</td>
<td>23</td>
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<td>1</td>
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<td>0</td>
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<td>Norian SRS®</td>
<td>48</td>
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<td>0</td>
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<td>Brushtite-CPC</td>
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<tr>
<td>ChronOS™ Inject</td>
<td>2</td>
<td>1</td>
<td>0</td>
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</table>

Table 5: Clinical evidence for CPC use in fracture surgery

<table>
<thead>
<tr>
<th>Products</th>
<th>Proximal Humerus</th>
<th>Distal Radius</th>
<th>Proximal Femur</th>
<th>Proximal Tibia</th>
<th>Calcaneal</th>
<th>Vertebral</th>
<th>Odontoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apatite-CPC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BoneSource®</td>
<td>IV¹⁷</td>
<td>IV¹⁷,¹⁸</td>
<td>IV¹⁷</td>
<td>IV¹⁷</td>
<td>IV¹⁷</td>
<td>N.D.</td>
<td>N.D.</td>
</tr>
<tr>
<td>Calcibon®</td>
<td>N.D.</td>
<td>x</td>
<td>N.D.</td>
<td>x</td>
<td>x</td>
<td>II¹⁹, 20, 22, 23</td>
<td>N.D.</td>
</tr>
<tr>
<td>Norian SRS®</td>
<td>V³¹,³²</td>
<td>II²⁵, ³³-⁴³</td>
<td>II⁴⁴-⁴⁷</td>
<td>V⁴⁸-⁵¹</td>
<td>V²⁶, ⁵², ⁵³</td>
<td>N.D.</td>
<td>VI⁵⁴</td>
</tr>
<tr>
<td>Brushtite-CPC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ChronOS™ Inject</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>N.D.</td>
<td>N.D.</td>
</tr>
</tbody>
</table>

I–VI, the highest clinical level of evidence according to Mahid *et al.*¹⁵⁵ supporting the use for specific indication; x, indicated by manufacturer only; N.D., no data available.