Bone substitutes in the Netherlands - a systematic literature review

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Abstract

BACKGROUND: Autologous bone grafting is currently considered as the gold standard to restore bone defects. However, clinical benefit is not guaranteed and there is an associated 8-39% complication rate. This resulted in the development of alternative (synthetic) bone substitutes. The aim of this systematic literature review was to provide a comprehensive overview of literature data of bone substitutes registered in the Netherlands for use in trauma and orthopaedic surgery.

METHODS: Brand names of selected products were used as search terms in three available databases: Embase, PubMed, and Cochrane. Manuscripts written in English, German or Dutch that reported on structural, biological or biomechanical properties of the pure product or on its use in trauma and orthopaedic surgery were included.

RESULTS: The primary search resulted in 475 manuscripts for PubMed, 653 for Embase, and 10 for Cochrane. Of these, 218 met the final inclusion criteria. Of each product, structural, biological and biomechanical characteristics as well as their clinical indications in trauma and orthopaedic surgery are provided. All included products possess osteoconductive properties but differ in resorption time and biomechanical properties. They have been used for a wide range of clinical applications; however the overall level of clinical evidence is low.

CONCLUSION: The requirements of an optimal bone substitute are related to size and location of the defect. Calcium phosphate grafts have been used for most trauma and orthopaedic surgery procedures. Calcium sulphates were mainly used to restore bone defects after tumour resection surgery and offer minimal structural support. Bioactive glass remains a potential alternative; however its use has only been studied to a limited extent.

Keywords

bone substitutes, biomaterials, review, calcium phosphate, calcium sulphate, bioactive glass
1. Introduction

The treatment of fractures remains a continuous challenge for trauma and orthopaedic surgeons. Although most fractures heal uncomplicated, 5-10% of patients encounter problems due to bone defects, impaired fracture healing, or a combination of both [1]. Significant bone defects or post-traumatic complications such as delayed union, non-union or malunion may require bone-grafting in order to fill the defect. Bone grafts fill voids, provide support, and therefore may enhance the biological repair of the defect. Bone grafting is a common surgical procedure, carried out in approximately 10% of all skeletal reconstructive surgery cases [2]. Worldwide, an estimated 2.2 million grafting procedures are performed each year [3, 4].

Bone healing differs from any other soft tissue since it heals through the generation of new bone rather than by forming fibrotic tissue. Bone repair requires four critical elements: (1) osteogenic cells (e.g., osteoblasts or progenitor cells); (2) osteoinductive signals provided by growth factors; (3) an osteoconductive matrix; and (4) adequate blood and nutrient supply [5]. Therefore, bone grafts are often described by the terms osteogenicity, osteoinductivity and osteoconductivity. Osteogenicity is the presence of bone forming cells within the bone graft [6, 7]. Osteoinductivity is the ability of a graft to stimulate or promote bone formation [8]. Osteoconductivity is the ability of the graft to function as a scaffold for ingrowth of new bone and sprouting capillaries [9].

Autologous bone, mostly harvested from the iliac crest, is considered the gold standard since it provides a scaffold for bone ingrowth, contains living bone cells that offer osteogenesis, and contains growth factors that stimulate osteoinduction [6]. However, as the cellular elements do not necessarily survive transplantation, the clinical benefit is not guaranteed [10]. In addition, the harvesting of autologous bone lengthens the surgical procedure, and the graft amount may be insufficient, or the form inappropriate. Moreover,
autograft harvesting is associated with an 8-39% risk of complications, e.g., infection, hematoma, nerve and urethral injury, pelvic instability, cosmetic disadvantages, postoperative pain and chronic pain at the donor site [11-14]. Furthermore, autografting is normally not recommended for elderly or paediatric patients or for patients with malignant or infectious disease. Alternative strategies like allo-, and xenotransplantation have major biocompatibility disadvantages compared with autografting [15, 16], and as such their use is suboptimal.

Due to complications and limitations associated as reported, alternative bone substitutes were needed. Based upon the above, the perfect bone substitute is osteoconductive, osteoinductive, biocompatible, and bioresorbable. Moreover, it should induce minimal or no fibrotic reaction, undergo remodelling and support new bone formation. From a mechanical point of view bone substitutes should have similar strengths to that of the bone being replaced. Finally, it should be cost-effective and ought to be available in the amount required.

Technological evolution and better understanding of bone-healing biology resulted in the development of numerous alternative bone substitutes. Multiple products, containing (combinations of) hydroxyapatite, tricalcium phosphate, dicalcium phosphate, calcium sulphate (plaster of Paris), or bioactive glass are currently available for use in trauma and orthopaedic surgery. However, an evidence-based guideline to assist surgeons in selecting the best product for specific clinical indications is not available yet. The aim of the current study was to provide a comprehensive overview of literature data of bone substitutes registered in the Netherlands for use in trauma and orthopaedic surgery. An overview of products, their composition, their biological and biomechanical characteristics as well as their clinical indications in trauma and orthopaedic surgery is provided.
2. Methods

2.1. Product selection

Products were selected based upon the following criteria: (1) products composed of (combinations of) calcium phosphate, calcium sulphate or bioactive glass; (2) indicated for use in trauma and orthopaedic surgery; and (3) available in the Netherlands on October 12, 2009. Products were excluded if they could only be used in combination with adjunctive (e.g., bone marrow aspirate, growth factors, or antibiotics) or if they were only indicated for use in craniomaxillofacial surgery.

2.2. Literature search

Brand names of all products (see Table 1) were used as search terms in three available online databases: Embase, PubMed, and Cochrane. Databases were searched from the earliest date available until July 1, 2010. Titles and abstracts were screened by two researchers (JVDS and YEM). Only papers that reported on structural, biological or biomechanical properties, or on clinical indications in trauma and orthopaedic surgery, and were written in English, German, or Dutch were considered eligible. The full text of all eligible papers retrieved from PubMed and Cochrane were read by two researchers (JVDS and YEM), papers found in Embase were read by three researchers (JVDS, GHVK, and YEM). All references in the selected manuscripts were reviewed in order to ensure that no papers had been missed with the chosen search strategy. For final inclusion a manuscript had to report on structural, biological or biomechanical properties of the pure product or on their use in trauma and orthopaedic surgery. Data regarding study design, species, structural, biological, biomechanical, and clinical findings were collected in a database, and are summarized below. Manuscripts
reporting on clinical indications of bone substitutes for trauma and orthopaedic surgery were given a level of evidence as described by Mahid et al [17].

3. Results

Eighteen bone substitute products were selected. All products were commercially available at July 1, 2010 and the costs per unit range between 100 and 750 Euro. The initial literature search for product name resulted in 475 manuscripts for Pubmed, 653 for Embase and 10 for Cochrane. After screening of all titles and abstracts, 195 manuscripts for Pubmed, 230 for Embase and 1 for Cochrane were considered eligible. Exclusion of 159 duplicates resulted in a total of 267 eligible manuscripts, as shown in Figure 1. After reading the full text of all eligible manuscripts 67 papers had were excluded and 18 were added based upon the reference list. Finally, 218 articles were found to fulfil all inclusion criteria. A detailed overview of the final inclusion per product and subdivision in pre-clinical and clinical studies is given in Table 2.

3.1. Calcium phosphate

In the eighties, calcium phosphate salts such as tricalcium phosphate (TCP) and hydroxyapatite (HA) were introduced for clinical use [18]. Multiple calcium phosphate grafts are available with different application forms (e.g., pastes, putties, solid matrices, granules). Based upon their chemical composition, calcium phosphates can be separated into hydroxyapatite (HA), tricalcium phosphate (TCP) and composite grafts (Table 1). The latter simply indicating a combination of two or more calcium phosphates.
3.1.1. Structural properties

Structural properties are related to production methods. Therefore a further subdivision can be made between ceramics and cements. A ceramic is defined as an inorganic, non-metallic solid prepared by thermal treatment and subsequent cooling [19], for calcium phosphates ceramics thermal treatment is called sintering. The sintering process removes volatile chemicals and increases crystal size, resulting in a porous and solid material. Cements, first introduced by Brown and Chow [20], consist of a mixture of calcium phosphates which can be applied as a paste and harden in situ due to precipitation reactions.

Hydroxyapatite grafts of ceramic origin are Cerabone®, Endobon® and Pro Osteon 500®. Ostim® is a hydroxyapatite cement. Hydroxyapatite ceramics have a stoichiometry similar to that of bone mineral [7, 21]. Cerabone® and Endobon® are grafts of bovine origin and Pro Osteon 500® is derived from sea coral (genera goniopora). Endobon® has a highly crystalline grain size (1.57±0.78 µm) with an apparent density of 0.35-1.25 g/cm³ [22, 23], and has a porosity of 60-80% [24], including 18% micropores and a pore size of 390-1,360µm [22]. Pore sizes of Cerabone® and Pro Osteon 500® stated in the product information were 100-1,500µm and 280-770µm, respectively. Ostim® is a hydroxyapatite suspension in water, available as a paste.

ChronOS™ and Vitoss® consist of tricalcium phosphate and are both ceramic materials. Tricalcium phosphate has a stoichiometry similar to that of amorphous bone precursors [21]. ChronOS™ has a particle size of 1.4-2.8 mm [25], and has a porosity of 60-75% [26-28] and a pore size of 100-400µm [26, 28].

Included composite grafts of ceramic origin were BoneSave® and Camceram®. BoneSave® consists of 80% TCP and 20% HA. Camceram® consist of 60% HA and 40% β-TCP. BoneSource®, Calcibon®, ChronOS™ Inject, HydroSet™ and Norian SRS® are calcium phosphate cements. The setting reaction of calcium phosphate cements leads to the formation
of either precipitated hydroxyapatite (PHA) or dicalcium phosphate dihydrate (DCPD). Cements have a solid structure characterized by limited porosity and pore size [21]. BoneSource®, composed of tetracalcium phosphate and dicalcium phosphate anhydrous, has a porosity of 46% [29, 30] and pore size of 2-50μm [31]. Calcibon® consists of α-tricalcium phosphate, and has a porosity of 30-40% [32, 33] with a pore size of <1μm [33]. Calcibon® has a density of 1.84 g/cm³[32] whereas Norian SRS® has a density of 1.3 g/cm³ [34].

3.1.2. Biological properties

Although highly crystalline TCP and HA derived through thermal treatment do not exist naturally, they have been shown to induce a biologic response similar to that of bone [21]. In general, calcium phosphates are considered to be osteoconductive. However under certain conditions calcium phosphates might also possess osteoinductive properties [35, 36]. Osteoconductive properties were confirmed for most calcium phosphate products (Table 3), however no data were found for BoneSave®, Camceram® and HydroSetTM. BoneSource® implanted in an extra skeletal side was able to induce bone formation, and is therefore considered to possess osteoinductive properties [29]. Extra skeletal implantation of Calcibon®[37] and Endobon®[38] did not initiate bone formation.

Biodegradability of HA seems related to its appearance. HA ceramics like Endobon® and Pro Osteon 500® are rather inert [39-44], whereas the HA cement Ostim® was shown to be biodegradable by osteoclastic activity [45-50]. After one year, 70% of the implanted material was resorbed in tibia bone of minipigs [50], but a recently published study only found minimal resorption of Ostim® after an implantation period of 12 weeks in rabbits femora [51].
Vitoss® elicits no cytotoxic reaction in *in vitro* cell cultures [52]. ChronOS™ and Vitoss® are both resorbed over time [25, 53]. Resorption of these TCP products is mediated by osteoclastic activity and resorption time varies between 6-24 months [21].

BoneSource® and Calcibon® support cell-growth of osteoblasts in *in vitro* cell cultures, eliciting no cytotoxic reactions [54-56]. Resorption of composite ceramics is unknown; no data on biodegradation was found for BoneSave® and Camceram®. All composite cements were shown to be biodegradable. In vertebral bodies, 20% of the applied Calcibon® was resolved after one year [57]. ChronOS™ Inject is almost completely resorbed by osteoclastic activity within six months [58]. Norian SRS® was biodegraded by osteoclasts [59-62], however one study found no resorption of Norian SRS® at 12 weeks after implantation in sheep tibia [63].

### 3.1.3. Biomechanical properties

Calcium phosphates generally provide limited biomechanical support, because they are brittle and have little tensile strength [64]. Tricalcium phosphates are less brittle compared with hydroxyapatite; however, their degradation results in subsequent loss of mechanical strength over time. An overview of compression strength, Young’s modulus, tensile strength and shear strength of each product is given in Table 4. No data was found for BoneSave®, Camceram®, ChronOS™, ChronOS™ Inject, Ostim®, Pro Osteon 500®, and Vitoss®.

Endobon® has an *in vitro* strength of 1-11MPa with a Young’s modulus of 20-3,100MPa [22]. *In vivo* tests showed a 2-20MPa compression strength and a Young’s modulus of 20-1,200MPa [24, 65]. Push-out testing of Endobon® after 26 weeks implantation in femoral metaphysair bone of rabbits showed in an interfacial shear stress of 7MPa [24]. Hing *et al* measured compression strength of Endobon® before (*in vitro*) and after implantation into rabbit femur condyles for five weeks (*in vivo*). The *in vitro* compression
strength was 2-9MPa and the in vivo compression strength was 6-11MPa, an increase of 195% [39].

Tricalcium phosphate grafts, ChronOS™ and Vitoss®, were implanted in rabbit tibia and subsequently subjected to torque force. During the study period, torque failure of the grafted tibia increased from 1800Nm after two weeks to 3400Nm after 26 weeks, however torque failures at both time point did not differ significantly between ChronOS™ and Vitoss® [25].

The composite cements BoneSource®, Calcibon®, HydroSet™ and Norian SRS® have been tested in various biomechanical experiments. Norian SRS® has an compression strength of 23-55MPa [34, 66, 67], with a tensile strength of 2.1MPa [66, 67], and a shear strength of 0.85-1.3MPa [68]. In addition, Norian SRS® may also be used to augment cortical screws, this results in an increased resistance to torque forces [69]. BoneSource® has a compression strength of 6.3-34MPa [70, 71] with a Young’s modulus of 3.6-4.7MPa [72, 73]. Interfacial bonding strength of BoneSource® implanted in dog femora was superior to that of the implanted polymethylmethacrylaat (PMMA), which served as a control group [74]. Calcibon® has a compression strength of 35-55MPa [32, 75], with a Young’s modulus of 2,500-3,000MPa [32] and a tensile strength of 4.5MPa [76]. Of HydroSet™, compression strength of 14-24MPa and Young’s modulus of 125-240MPa [77] and a tensile strengths of 0.11-0.17MPa were recorded [78].

3.1.4. Clinical indications

Each clinical indication requires specific structural, biological and biomechanical properties of graft material. An overview of clinical indications in trauma and orthopaedic surgery of each product is given in Table 5.
Hydroxyapatite ceramic Endobon® can be used to fill bone defects of several fracture sites; specifically proximal tibia [43, 79-82], distal tibia [82], distal radius [83, 84] and calcaneus [82]. It provides adequate mechanical stability in open [43, 81, 82] and arthroscopic [80] management of tibia plateau fractures. However, in one case refracture of the proximal tibia occurred seven years after implantation [79]. Huber et al showed treated 24 tibia plateau fractures by using a combination of Ostim® and Cerabone® resulting in an average Rasmussen tibia score of 26 after one year [46]. Ostim® may also be used as sole product for the treatment of fractures of the Tibia [85], calcaneus [85], or radius [85-87]. Bone voids resulting of benign bone tumour resections, located in the humerus, tibia, femur, calcaneus, ileum, fibula, and ulna bone were successfully grafted with Pro Osteon 500® [88]. Besides, Pro Osteon 500® was also used for distal radius fractures [89].

Tricalcium phosphate grafts may be used in the upper and lower extremity. Vitoss® is an option to treat fractures of the tibia or calcaneus, but was also used in the upper extremity, especially in the humerus [90]. ChronOS™ was used as bone graft in the posterior stabilization and interlaminar fusion of a vertebral fracture type Magerl B2.3 [88].

Of the calcium phosphate cements, Norian SRS® have been tested most extensively. In the upper extremity, union of fractures of the humerus [91] and distal radius [92-100] has been achieved. Norian SRS® is effective in maintaining realignment of fracture parts after reduction of displaced or comminuted distal radius fractures. This technique resulted in accelerated rehabilitation, and better final outcomes after two years [93, 96, 97]. In the lower extremities, Norian SRS® can be used to fill metaphyseal bone defects in tibia plateau fractures [101-106]. Good to excellent results at one year after trauma was shown in 95% of cases [106]. Nonetheless, loss of reduction occurred in 8-20% of cases and long term results showed a 20% post-traumatic osteoarthritis rate [105, 106]. Adding Norian SRS® to sliding screw fixation for unstable trochanteric fractures resulted in modest improvement of fracture
healing [107]. Average movement of sliding screw was significantly reduced by augmentation with Norian SRS® after six weeks [108]. In calcaneal fractures this grafting material allows full weight bearing four weeks after surgery compared to eight weeks with autologous augmentation [109]. Another study shows postoperative full weight bearing as early as three weeks shows in standard open reduction with internal fixation in calcaneal fractures [60].

BoneSource® can be used safely when filling of traumatic bone voids is required. Graft sites included the humerus (1), radius (3), femur (1), tibia (9), and calcaneus (7) and reduction was maintained in 83% [110]. However, BoneSource® alone does not provide adequate fracture stability in distal radius fractures [111]. Calcibon® is used for filling of metaphyseal cancellous bone defects and is was used to stabilize traumatic Magerl type A thoracolumbar fractures [112]. Calcibon® augmentation in vertebral bodies improves pain and function en enables the treated vertebral body to regain height [113, 114].

Reports on clinical experience with the use of BoneSave®, Camceram®, ChronOS™ Inject and HydroSet™ without adjunctive in trauma and orthopaedic surgery has not been found.

3.2. Calcium sulphate

Calcium sulphates (CaSO₄) or Plaster of Paris have been used as bone void filler since the late 1800’s [115]. Calcium sulphate is produced by heating gypsum, resulting in a dry powder. Adding water to this powder results in an exothermic reaction leading to crystallization and hardening of the preparation. Four calcium sulphate products are available in the Netherlands: Bone Plast®, MIIG® X3, OsteoSet®, and Stimulan®. MIIG® X3 and OsteoSet® are chemically identical; however, MIIG® X3 is available in paste, were as OsteoSet® is available in granules or blocks.
3.2.1. Structural properties

No data on structural properties of calcium sulphate grafts has been found.

3.2.2. Biological properties

Calcium sulphates appear to function as a resorbable osteoconductive scaffold that provides the structural framework necessary for angiogenesis and osteogenesis while preventing soft tissue invasion by acting as a void filler; however, they lack not only osteogenic but also osteoinductive properties. Calcium sulphate is considered biocompatible, eliciting little or no macrophagic reaction, and is fully dissolved within 6-12 weeks [116]. MIIG® X3 was found to be osteoconductive [117-119]. The use of OsteoSet® resulted in a 8-35% new bone ingrowth in animal experiments [116, 120-123] which was found to be equivalent to autogenous and allogenic bone grafts [116]. However, in two studies no osteoconductive potential of OsteoSet® was noted [124, 125]. No data on osteoconductive properties of Bone Plast® and Stimulan® were found.

3.2.3. Biomechanical properties

Compression strength of OsteoSet® and MIIG® X3 were attained in similar experiments, using in vivo samples which were implanted in for 26 weeks in the humerus of dogs. Compression strength of OsteoSet® was 0.6-0.9MPa [121, 123] and of MIIG® X3 0.6MPa [123]. Young’s modulus of OsteoSet® was 59MPa [121]. No data on biomechanical properties of Bone Plast® and Stimulan® was found.

3.2.4. Clinical indications

Calcium sulphate grafts are mainly used to fill bony voids resulting of tumour resection surgery. Kelly et al used MIIG® X3 to graft bone defects of the distal tibia, patella, calcaneus,
ileum, femur, and humerus [117]. But MIIG® X3 may also be used to treat both proximal [118, 123] and distal tibia fractures [123] Twenty-one tibia plateau fractures were treated with MIIG® X3 and internal fixation, resulting in complete fracture healing and graft resorption after 12 weeks [118].

OsteoSet® fills defects of the humerus, radius, ulna, femur, tibia, fibula and calcaneus [126-130]. However, OsteoSet® may not provide sufficient biomechanical support as several stress fractures after grafting have been reported [129, 131] and a self-limiting local sterile inflammatory reaction occurred in 4 to 20% of graft sites [129, 132, 133]. In one case convulsions as complication with elevated calcium was reported after use of OsteoSet® in a lumbar fracture [134]. Also Bone Plast® may be indicated as it has been used in pelvic, humerus, calcaneus and femoral bone after aspiration of recurrent aneurysmal bone cysts [135]. No data on Stimulan® was found.

3.3. Bioactive glass

Bioactive glasses are hard, solid (non-porous), materials consisting of four components: sodium oxide, calcium oxide, silicon dioxide (silicate, the main component) and phosphorous [7]. By varying the proportions of sodium oxide, calcium oxide and silicon dioxide, soluble and non-resorbable grafts can be made [136]. Cortoss® is the only bioactive glass that is available in the Netherlands.

3.3.1. Structural properties

Bioactive glasses can be manufactured into microspheres, fibers and porous implants. Cortoss® is available as a paste, but no data concerning other structural properties of Cortoss®, such as porosity and pore size, was found.
3.3.2. Biological properties

Bone substitute materials within the group of bioactive glass display osteoinductive and osteoconductive properties [7]. They are bioactive, as they interact with the body [137]. Bioactivity depends upon the SiO$_2$ content; the bonding between bone and glass is best if the bioactive glass contains 45-52% SiO$_2$ [137]. The strong graft-bone bonding occurs as a result of the formation of a silicate rich layer after contact with body fluids. On top of this, a layer of hydroxyapatite will form, which directs new bone formation together with protein absorption. The extracellular proteins attract macrophages, mesenchymal stem cells, and osteoprogenitor cells. Subsequently, the osteoprogenitor cells proliferate into matrix-producing osteoblasts [137, 138]. Cortoss® has osteoconductive properties [139], but is not resorbed [140]. It does not induce cytotoxicity [141], and offers biocompatibility and reduced risk of thermal necrosis [142].

3.3.3. Biomechanical properties

Bioactive glass possesses superior mechanical strength compared with calcium phosphate products, as a result of a strong graft-bone bonding [7]. Cortoss® has a compression strength of 91-179MPa with a shear strength of 8.4MPa, which is significantly higher than PMMA bone cements [143, 144]. Manufactures information also provides a Young’s modulus of 6,400MPa and a tensile strength of 52MPa; however this was not confirmed in other studies.

3.3.4. Clinical indications

The first reports on clinical applications of bioactive glass emerge in the 1980s [145]. Since then, bioactive glass has been applied for craniofacial reconstructive surgery, dental surgery and trauma or orthopaedic surgery. Reports on clinical applications of Cortoss® are few; no randomized controlled trials have been conducted. Andreassen et al evaluated the use of
Cortoss® for screw augmentation in 37 Weber type B ankle fractures. After two years, no screw loosening occurred [146]. The use of Cortoss® may relieve pain when used in vertebroplasty [147, 148]. One case report was published in which successful treatment of an unstable distal radius fracture was described [140].

4. Discussion

The repair of large bony defects resulting of trauma or disease remains a major problem in trauma and orthopaedic surgery. Treatment options depend upon size and location of the defect, but patient characteristics like bone quality, age, and co-morbidities also affect outcome. The past decade, an increasing number of bone substitute materials became available for use in trauma and orthopaedic surgery. This systemic literature review was conducted in order to provide a comprehensive overview of characteristics and clinical indications of products available in the Netherlands. Eighteen products, varying in composition and structure, have been reviewed. These products are widely available worldwide, therefore the information provided is relevant for many other countries as well.

Structural, biological and biomechanical properties of bone grafts are critical in their clinical success. Calcium phosphates may possess osteoinductive properties under certain conditions [35, 36]. Of the 18 selected products, osteoinductivity was only found with the use of BoneSource®. Overall, osteoconductive properties could be confirmed for almost all included calcium phosphates, calcium sulphates and for bioactive glass. Unfortunately, major differences in experimental design (e.g., animal model) and absence of a standardized scoring system to define quality and quantity of new bone formation troubles the direct comparison among included grafts.
In order to acquire osteoconductive properties, pore size and porosity, and the degradation potential of the bone substitute material are essential. A macroporous structure of pores ranging 150-500μm in size is considered optimal for ingrowth of new bone [149, 150]. In addition, interconnective pores increases new bone ingrowth [149, 151, 152]. Microporosity (e.g., pores <5μm) is considered important for bioresorbable properties of the material [153]. Resorption rates differ substantially between the products, mainly due to their chemical composition. On average, sintered HA is rather inert, and hardly shows any resorption even after ten years. Tricalcium phosphate and calcium phosphate cement composites, on the other hand, are degraded within approximately two years as a result of osteoclastic activity [21]. Calcium sulphates are generally dissolved within 8-12 weeks [154]. Resorption of bioactive glass is variable, and depends upon the relative amounts of sodium oxide, calcium oxide, silicon dioxide, and phosphorous present [7].

Based upon their structure, hydroxyapatite and tricalcium phosphate ceramics have the advantage of offering a sufficient macroporous structure to facilitate new bone ingrowth. Optimized pore size was confirmed for the products Endobon® and ChronOS™ (Table 3). On the other hand, rather quick resorption of calcium sulphate products provides space for new bone formation and prevents the early formation of fibrotic tissue; however, resorption may be completed before sufficient new bone formation. The same accounts for the biodegradable calcium phosphate cements, however their resorption time is slower compared with calcium sulphate products and depends mainly on chemical composition of the graft.

Besides optimal biological properties, bone substitutes should offer direct structural support to surrounding bone and soft tissues. The biomechanical strength is the resultant of a complex interplay between the bone and bone substitute material. In an ideal situation a bone void is grafted by a bone substitute material that offers biomechanical strength similar as the bone being replaced. However, the biomechanical behavior of implanted material may
undergo changes as a resultant of in vivo interactions, e.g. osteointegration, bone incorporation, or bioresorption of the substitute material. The biomechanical properties of bone itself, on the other hand, differ according to their structure (cortical or cancellous) and function (weight-bearing or non weight-bearing). Grafting a defect with a bone substitute material that has a higher initial biomechanical strength than the surrounding bone may result in stress-shielding and subsequent bone resorption at the bone-implant interface, or may lead to delayed fractures along the bone-implant interface. Using a bone substitute material with a lower biomechanical strength than the surrounding bone may lead to delayed fractures due to the lack of biomechanical stability. As mentioned above, the different products have different resorption rates. Provided that the biodegradation process works as designed, each product may ultimately resorb and remodel back into normal bone. If that holds true, the long-term strength of the restored bone may be similar for different products.

Human cortical bone has a compression strength of 130-290MPa and a tensile strength of 90-190MPa, whereas the compression strength of cancellous bone ranges between 2 and 38MPa [155]. None of the included bone substitutes offers biomechanical strengths similar to cortical bone, although bioactive glass (Cortoss®) has a compression strength of 91-197MPa, tensile strength does not reach values comparable to cortical bone [144, 146]. Calcium phosphate grafts possess compression strengths comparable to cancellous bone, but the main drawback of calcium phosphates remains their limited resistance to tensile and shear forces, making it vulnerable to crackling and subsequent material failure. Calcium sulphates only provide minimal structural support and are not suitable in cases were structural support is required (Table 4).

All included bone substitutes are available for use in skeletal surgery in the Netherlands and an overview of clinical indications is given in Table 5. No bone substitute seems to be suitable for grafting of significant cortical bone defects without additive support.
Calcium phosphate grafts may be used to fill metaphyseal bone defects at various locations of the lower extremity. The use of Norian SRS®, in femur fractures is supported by level II evidence (Table 5). Norian SRS®, BoneSource®, Endobon® and Ostim® have also been used to fill bony defects of the calcaneus, proximal tibia, distal tibia, or proximal femur, but the clinical evidence remains limited to level IV and consists mainly of level V evidence. In the lower extremity, calcium sulphate is rarely used. Most likely because the minimal structural supportive function. Although bioactive glass offers acceptable biomechanical strength, no evidence was found for their use in the lower extremity. Again in the upper extremity, calcium phosphate grafts are most frequently used. The use of Norian SRS® in distal radius fractures is supported by level II evidence. In addition, hydroxyapatite ceramics may also be used in open surgical technique to treat distal radius fractures. Furthermore, bioactive glass Cortoss® (Level V) and calcium phosphate Calcibon® (Level II) can be used in vertebral fractures as alternative for PMMA. Calcium sulphate grafts are generally used to fill bone defects after tumour resection surgery, however their minimal biomechanical support may result in secondary fractures.

This data of the current systematic literature review show that vital data concerning structural, biological, biomechanical behavior and also the use of bone substitute for specific clinical indications is limited or incomplete. Additional high-quality scientific evidence is necessary in order to adequately state the clinical benefit of those products as a bone substitute. Evidence regarding their clinical use in trauma and orthopaedic surgery comes mainly from uncontrolled case series (clinical evidence level V). The absence of a control group in this type of research makes it difficult to draw sound conclusion regarding the beneficial effects except the avoidance of auto- or allograft related complications. Three products have been tested in randomized controlled trials (RCTs); Calcibon®, BoneSource® and Norian SRS®. Although not available for use in the Netherlands, and hence not included
in this review, a properly designed RCT, and within the literature more well conducted RTCs has also been published on the use of α-BSM [156]. This shows that RCTs on efficacy of bone substitutes in trauma and orthopaedic surgery are feasible.

A potential weakness of this study could be the used search strategy which forms the basis of our conclusions. Included products were searched in multiple databases by using product name as search term. By this method we might have missed studies which did not specify the product being used. However, the aim of this systematic review was to provide an overview of available pre-clinical and clinical evidence for the use of bone substitute materials in clinical practice that may guide surgeons for selecting the best product for a particular clinical indication. Therefore manuscripts not specifying the product being used could not be included. The data shown in this manuscript also show that materials consisting of similar chemical compositions do not necessarily possess the same structural, biological and biomechanical properties. Differences in production methods (sintered materials versus cements), or in micro- and macrostructure also influence the biological and biomechanical behavior of the material in situ.

This review focuses on the first and vital step to facilitate new bone formation: the creation of an osteoconductive scaffold, as this will be the first clinical step in the treatment of bone defect. In a majority of cases, an osteoconductive scaffold will provide adequate support and will sufficiently facilitate new bone formation by the invasion of nearby bone forming cells. Only in cases where the surrounding bone has insufficient osteoinductive potential, adjunctive growth stimuli such as bone morphogenetic proteins (BMPs) or bone marrow aspirate may be needed in combination with a void filler. The use of growth factors has been reviewed elsewhere [157, 158].
5. Summary

The eighteen bone substitute materials available in The Netherlands represent a variety of forms, structure and chemical composition. Some of them have been investigated thoroughly, for other there is limited data available. Determining which material to use for different clinical indications is based on many factors including the size and location of the bone tissue defect as well as structural, biological and biomechanical properties of the graft itself. Calcium phosphate grafts have been used for most trauma and orthopaedic surgery procedures when a grafting is necessary to restore bone defects. Calcium sulphates were mainly used to restore bone defects after tumour resection surgery and do not offer sufficient structural support to be used even in minimal weight baring bones. Bioactive glass remains an interesting alternative; however its use in trauma and orthopaedic surgery is only reported in a limited number of studies. To further improve decision making of bone substitute grafts to treat bony defects, more standardized research to explore the full potential of calcium phosphate, calcium sulphate and bioactive glass is recommended.

6. Acknowledgements

Fonds NutsOhra and Biomet Netherlands B.V. are acknowledged for financial support.
<table>
<thead>
<tr>
<th>References</th>
</tr>
</thead>
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Beuerlein, M. J. and McKee, M. D. Calcium sulfates: what is the evidence? J Orthop Trauma 24 Suppl 1, S46-51
Giannoudis, P. V. and Dinopoulos, H. T. BMPs: Options, indications, and effectiveness. J Orthop Trauma 24 Suppl 1, S9-16


Table 1: Overview of bone substitutes available for clinical use in the Netherlands

<table>
<thead>
<tr>
<th>Product name</th>
<th>Company</th>
<th>Origin</th>
<th>Chemical composition</th>
<th>Form</th>
<th>Ceramic/cement*</th>
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</thead>
<tbody>
<tr>
<td><strong>Hydroxyapatite</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerabone®</td>
<td>Fame Medical Products BV</td>
<td>Bovine</td>
<td>HA</td>
<td>solid</td>
<td>Ceramic</td>
</tr>
<tr>
<td>Endobon®</td>
<td>Biomet</td>
<td>Bovine</td>
<td>HA</td>
<td>solid</td>
<td>Ceramic</td>
</tr>
<tr>
<td>Ostim®</td>
<td>Heraeus</td>
<td>Synthetic</td>
<td>60% HA / 40% H₂O</td>
<td>paste</td>
<td>Cement</td>
</tr>
<tr>
<td>Pro Osteon 500®</td>
<td>Biomet</td>
<td>Coral</td>
<td>HA</td>
<td>solid</td>
<td>Ceramic</td>
</tr>
<tr>
<td><strong>Tricalcium phosphate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ChronOS™</td>
<td>Synthes</td>
<td>Synthetic</td>
<td>β-TCP</td>
<td>solid</td>
<td>Ceramic</td>
</tr>
<tr>
<td>Vitoss®</td>
<td>Orthovita</td>
<td>Synthetic</td>
<td>β-TCP</td>
<td>solid</td>
<td>Ceramic</td>
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<tr>
<td><strong>Composite</strong></td>
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</tr>
<tr>
<td>BoneSave®</td>
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<td>80% TCP / 20% HA</td>
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<td>Synthetic</td>
<td>TTCP / DCP</td>
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<td>Calcibon®</td>
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<td>Synthetic</td>
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<td>pellets</td>
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<td>Synthetic</td>
<td>CaSO₄</td>
<td>pellets/paste</td>
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<td></td>
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<tr>
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<td>N.S.</td>
<td>paste</td>
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</tbody>
</table>

*ceramic* is defined as an inorganic, non-metallic solid prepared by thermal treatment and subsequent cooling [19]; *cement* is defined as a product consisting of a liquid solution which hardens in situ through a chemical reaction.

Table 2: Number of publications retrieved from the systematic literature review on bone substitutes

<table>
<thead>
<tr>
<th>Product name</th>
<th>PubMed</th>
<th>Embase</th>
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<th>Exclusion</th>
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<th>Field of study</th>
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</table>

Database searches were performed until July 1, 2010 (PubMed, Embase and Cochrane). * Pre-clinical studies including biomechanical studies.
Table 3: Overview of porosity, pore size and biological properties

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<tr>
<th>Product name</th>
<th>Porosity (%)</th>
<th>Pore size (μm)</th>
<th>Osteogenic</th>
<th>Osteoinductive</th>
<th>Osteoconductive</th>
<th>Biodegradable</th>
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</tr>
<tr>
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</tr>
<tr>
<td>Cerabone</td>
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<td>(100-1,500)</td>
<td>N.D.</td>
<td>N.D.</td>
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<td>(280-770)</td>
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<td>N.D.</td>
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<tr>
<td>Vitos</td>
<td>(88-92)</td>
<td>(1-1,000)</td>
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<tr>
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Data obtained from the suppliers are given between brackets.
N.D.: no data available.
### Table 4: Overview of biomechanical properties

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<th>Product name</th>
<th>Compression Strength (MPa)</th>
<th>Young's modulus (MPa)</th>
<th>Tensile strength (MPa)</th>
<th>Shear strength (MPa)</th>
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<tbody>
<tr>
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<td></td>
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<tr>
<td><em>Hydroxyapatite</em></td>
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<tr>
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<tr>
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<td>N.D.</td>
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<td>N.D.</td>
<td>N.D.</td>
</tr>
<tr>
<td><strong>Bioactive glass</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortoss®</td>
<td>91-179[143, 144]</td>
<td>(6400)</td>
<td>(52)</td>
<td>8.4[144]</td>
</tr>
</tbody>
</table>

Data obtained from the suppliers are given between brackets.  
N.D.: no data available.
**Table 5: Overview of applications in trauma and orthopaedic surgery**

<table>
<thead>
<tr>
<th>Product name</th>
<th>Fractures</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Femur</td>
<td>Tibia plateau</td>
</tr>
<tr>
<td><strong>Calcium phosphate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxyapatite</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerabone®</td>
<td>N.D.</td>
<td>V [46]</td>
</tr>
<tr>
<td>Pro Osteon 500®</td>
<td>N.D.</td>
<td>N.D.</td>
</tr>
<tr>
<td><strong>Tricalcium phosphate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ChronOS™</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td><strong>Composite</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BoneSave®</td>
<td>N.D.</td>
<td>N.D.</td>
</tr>
<tr>
<td>Calcibon®</td>
<td>N.D.</td>
<td>N.D.</td>
</tr>
<tr>
<td>Camceram®</td>
<td>N.D.</td>
<td>N.D.</td>
</tr>
<tr>
<td>ChronOS™ Inject</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>HydroSet®</td>
<td>N.D.</td>
<td>N.D.</td>
</tr>
<tr>
<td><strong>Calcium sulphate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone Plast®</td>
<td>N.D.</td>
<td>N.D.</td>
</tr>
<tr>
<td>OsteoSet®</td>
<td>N.D.</td>
<td>N.D.</td>
</tr>
<tr>
<td>Stimulan®</td>
<td>N.D.</td>
<td>N.D.</td>
</tr>
<tr>
<td><strong>Bioactive glass</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

I to VI: The highest clinical level of evidence according to Mahid et al [17] supporting use for specific indication. x: indicated by manufacturer only. N.D.: no data available.
Figure 1: Flow diagram of literature selection process

**Excluded manuscripts**

- Inadequate field of research: 70, 176, 0
- No original manuscript*: 26, 172, 9
- Language: 15, 17, 0
- No pure product used: 9, 14, 0
- Non trauma indication**: 160, 44, 0

**Eligible per database**

- PubMed: 475
- Embase: 653
- Cochrane: 10

- Omitted duplicates: -159

**Total eligible manuscripts**: 267

**Further Selection**

- Excluded based upon full-text: -67
- Additional references: +10

**Final inclusion**

218

* e.g., reviews, letters, comments, ** e.g., dental or craniomaxillofacial surgery