The Use of Coral Scaffold in Oral and Maxillofacial Surgery: A Review

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Abstract

In recent years, there has been interest on the fabrication of system using particulates or block based approach for bone tissue engineering scaffold possessing porous interconnected structures.

This article presents finding from a systematic review to describe the use of natural coral bone graft in oral and maxillofacial surgery.Literature search was conducted in the electronic database Pubmed. Using the keyword Biocoralin the initial search, we found 52 articles, after exclusion 19articles were reviewed.All the reviewed papers suggested further exploring and seeking the ideal material property that should be added to coral scaffold to improve its use.

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Keywords: Biocoral, calcium carbonate, bone graft, biodegradable, scaffold.

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Introduction

Repair of defect in oral and maxillofacial surgery caused by trauma, infection or cancer is a continuous challenge in reconstructive surgery.[1] Various grafting materials have been used in oral and maxillofacial surgery. Autogenous bone grafts are still considered the gold standard for bone reconstruction because they have the three elements for osteonenesis which are osteoconductivity, osteogenicity, and osteoinductivity. However, this kind of graft is associated with numerous limitation, including extra-surgery time, post-operative pain, hematoma formation, blood loss, nerve injury, and infection. Therefore, bone-graft substitutes represent an efficient alternative to natural tissues in the treatment of bone defect.[2,3]

There are concerns that some biomaterials may cause a foreign body reaction.[3] Tissue engineering has received increasing attention as a method for creating bioartificial tissues and organs. The spatial distributions of cells within the scaffold are one of the factors that affect the quality of tissue-engineered constructs.[2,4] Optimal bone graft performance requires a scaffold architecture that can fulfill several functions such as resorption bone in-growth or mechanical support.[1,3]

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Various biomaterial has been used in clinical or experimental dentistry.[1-5] Metals, ceramics and polymers have been predominant in fixing and replacing the major hard tissues in oral and maxillofacial surgery. Other materials being studied are self-assembled, nanofibrous, nanoparticulate that will eventually provide natural levels of biomimetic sophistication but they are technically difficult syntheses. Marine biomimetic structures offer useful advantages before the future onset of truly biomimetic artificial designs, due to their sophisticated pre-design of structure and architecture.[5]

Coral skeletons have been used as bone substitutes in surgery.[3,6] A pioneering idea for harnessing coralline materials in medicine involves an innovative process for transforming and generating high fidelity copies of marine skeletons such as coral. Coral is composed of calcium carbonate in the form of aragonite. It has achieved considerable success in bone graft application because of its large porosity and uniform pore size combined with mechanical strength.[3,4] Only a few general of corals meet the required standards of pore diameter and connectivity.[6] Further studies were carried out to assess tissue growth responses to these new implants. Now there are many published studies attesting to various levels of clinical efficacy to heal widely separated fractures and fill naturally unbridgeable bone voids caused by tumors for example.[3,7,8] Bone tissue morphogenesis has been augmented within coral skeletal frameworks by incorporating bone marrow derived stem cells with impressive outcomes.[1,4]

Even though it is difficult to define the ideal scaffold architecture for a bone graft, some scaffoldsdo perform very well in clinical application.[3,7] One typical example is coralline hydroxyapatite which is a viable optionfor bone defect. It is well known that calcium carbonate, the natural component of coral, is more soluble than hydroxyapatite.[3,5] This article presents finding from a systematic review to describe the use of natural coral bone graft in oral and maxillofacial surgery.

Materials and methods

Literature search was conducted by one author. As our aim was to scope the current use of biocoral in dentistry, we were seeking to generate a broad question, and key terms were the main focus. The question “How does the use of Biocoral scaffolds developed in oral maxillofacial surgery?” guided the search strategy. MeSH was used to obtain the correct terms for keywords. Further into this study, key search terms were identified and a Boolean search string developed. Using truncated words (in this case *) we aimed for a search that would capture all terms with the same root word. Our final string was biocoral *AND calcium carbonate*AND bone graft*AND biodegradable *AND scaffold. An initial search of Google Scholar was carried out to determine the relevance of the key terms, but google scholar was not used as the search engine in this study due to the irreplicability of this search engine.[9] To determine an appropriate time frame for the review, the Google Scholar search located biocoral in oral and maxillofacial surgery prior to 2002 so this date was chosen as appropriate for this study. Databases searched included PubMed. Inclusion and exclusion criteria, consistent with our review purpose, were developed and are outlined in Table 1. The full papers of the selected publications were obtained. Table 2 is the studies related to this review.

Criteria	Inclusion	Exclusion
Time period	Feb 2002 – Feb 2016	Any study outide the dates
Language	English	Non English
Type of article	Original article	Review
	Case report	
Study focus	Biocoral oral maxillofacial surgery	Un related with oral and maxillofacial surgery
Geographical area of interest	International studies including those with specific cultural groups	Nil
Sample	Cell line, animal, medical record, human	Nil
Type of Study	In vitro	Nil
	In vivo	
	Clinical trial	
	Retrospective study	

Table 1. Inclusion and exclusion criteria.

Results

Using the keyword *Biocoral* in the initial search, we found 52 articles, 14 of which were published in the last 10 years, and 6 articles were excluded due to irrelevance towards this review. We then continued the search using *biocoral* AND *calcium carbonate*, we found 26 articles, this time 8 articles were published in the last 10 years. We used a combination of *calcium carbonate* AND *bone graft* as keywords and found 151 articles, with 62 articles being published in the last 10 years. Afterwards, we combined the search using *calcium carbonate* AND *biodegradable* as keywords and we found 77 reports and 49 were published in the last 10 years. The combination of *calcium carbonate* AND *biodegradable* AND *scaffold* resulted in 12 articles, 10 of which were published in the last 10 years (Figure 1). Finally, we found 19 articles that were full papers. Ten articles were invitro and describe the characteristic coral as a scaffold and comparison with various material, single and combination use as composite to improve the effectiveness of coral, 5 articles were invivo describing bone formation and the healing process, 3 articles were clinical trial using biocoral describing osteogenesis process, 1 article was retrospective study using medical records to analyze postoperative complications after implantation.

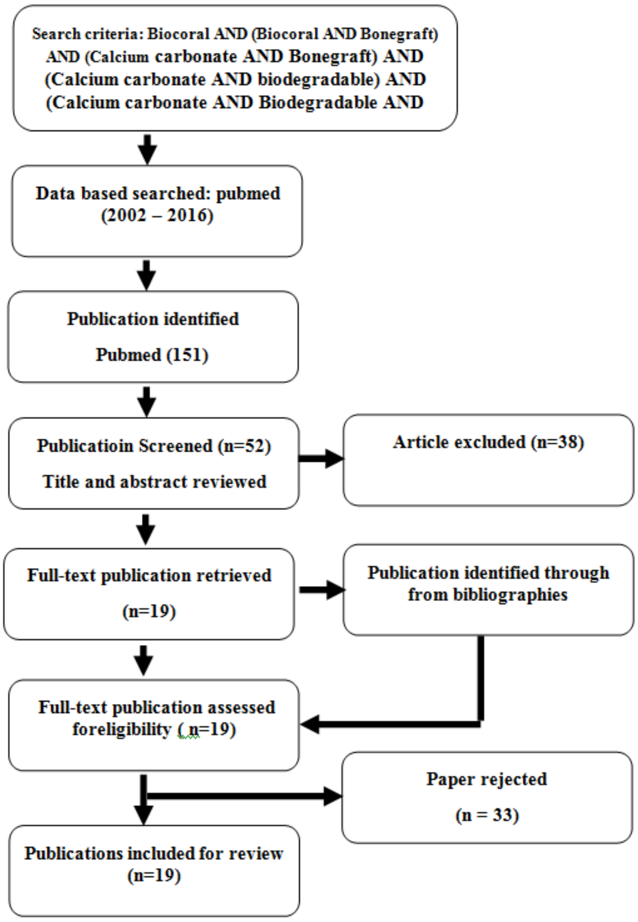

Figure 1. Flowchart of literature search and selection.

The majority of the studies (11/19) compared coral or calcium carbonate with others material and some other studies added additional material to the existing coral. Moreover stemcells were added as an additional material in three studies. Two articles presented the need of antibiotic in calcium carbonate graft. One article explained the importance of sample size and the other one said about the advanced evaluation of characteristic of coralline-derived scaffold graft using micro-CT. Further, one article presented retrospective study in the past 10 years regarding postoperative complication using coral implant compared with other material.

Numerous biomaterials have been successfully used as bone subtitutes, such as allograft, xenograft, natural and synthetic calcium-based materials, and a combination of these.[6,10-12] Recently, research on biomaterials emphasizes the creation and characterization of new material and enhancement of existing material would be degraded at the same rate as new bone is formed and would be at least osteoconductive and possibly osteoinductive.[13,14]

Discussion

The interest in natural coral exoskeletons has been increasing because natural coral exoskeletons give reduced risk of disease transmission and viral contamination compared with bovine graft.[2] Nonetheless, unconverted coral is unsuited for most long term implants because of its high dissolution rate, poor longevity and poor stability.[11] High degradation rates have also been found at low pH values (5.0-6.5), which are normally associated with infections and inflamed tissues. To overcome the limitation, corals have been converted into hydroxyapatite (coralline hydroxyapatite) by hydrothermal exchange or microwave processing, leading to products with improved resorption rates and better onsteointegration.[3] In this treatment, hydroxyapatite partially replaces aragonite while preserving the porus structure. However under certain circumstances, a decrease in structural strength may be observed. This problem can be reduced through the use of double-conversion techniques (conversion to corraline apatite followed by so-gel nanocoating).[6]

Further, It is well known that calcium carbonate, the natural component of coral, is more soluble than hydroxyapatite. By controlled conversion of the proportion of calcium carbonate in coral into hydroxyapatite, the biodegradation of the resultant coralline hydroxyapatite/calcium carbonate composition can be modified.[6,15] Another article reported that calcium carbonate was demonstrated to be clinically suitable for sinus augmentation procedures of the atrophic posterior maxilla after a 1-5 year time period, histologically biocompatible, and osteoconductive. Further studies are needed to assess the scaffold behavior with longer follow-up period and a larger sample size.[12,16]

Moreover, an in vitro study reported that bone regeneration may have different interactions with different bone replacement material tested in vitro.[2,15,17-20] Although autogenous bone was defined as gold standard, but both DFBD and Biocoral compared favorably. Since even the sterilization of DFDB cannot exclude the possibility of disease transmission, Biocoral may be considered a recommendable material.[8] Other study reported that Micro-CT technique can be used in advanced for characterization of bone tissue engineering constructs because it is noninvasive and nondestructive way, a complete, precise, and high-resolution three-dimensional analysis of their microstructural parameters.[21]

The studied materials showed both the capability of degrading and bioactive properties due to their innovative porous morphology as demonstrated by early osteogenesis.[2,6] These materials may be proposed as osteoconductive because the clearly accelerate bone defect healing and preserve alveolar bone dimensions and architecture after tooth extraction. This goal is important for clinicians to obtain good aesthetic result in both conventional and prosthetic implant rehabilitation.[12] With these in mind, commercial samples of materials currently used in dentistry were observed.[2,6,12] Regarding chemical composition, the tested samples can be divided into two groups: one comprising the hydroxyapatite-based materials and the other constituted only by Biocoral, a calcium carbonate (aragonite) material. However, even for those with similar chemical characteristics, significant differences were detected in terms of particle size, crystallinity, porosity and pore size distribution, surface, and mineral content.[3,8]

Although these morphological characteristics greatly influence the in vivo behavior of the samples, they are often not taken into consideration when the samples biological performance is evaluated. This may be responsible for the conflicting results frequently found in the literature. It is believed that the results provided for the materials investigated will be most useful to fully interpret their clinical responses.[6] Nonetheless, many important questions regarding the predictability of sinus augmentation procedures remain unanswered. However one study may confirm that different materials can be safely used, and depending on the needs and preference of the clinician, choice should be directed to one or the other. In each case, selection of the appropriate biomaterial has to be performed knowing its properties and ultimate fates, considering advantages and disadvantages, and keeping in mind that we may expect predictable result and clinical success.[10]

While Guided Tissue Regeneration promoted new bone formation, the calcium carbonate implant contributed limited, if any, osteoconductive effects.[7]

The biocompatibility and osteoconductivity of S53P4 bioactiveglass, allogeneic bone and coral-derived calcium carbonate suggest that bioactive glass S53P4 can be considered as better bone filler than coral-derived calcium carbonate, which is resorbed too quickly, thus making it less ideal material for filling cavitary defects.[14] The role of calcium carbonate in bone scaffolds is not only to provide mechanical support, but also to improve biodegradation properties.[3] The results of the recent in vitro study demonstrate the high potential of the combination of eggshell particles and hyaluronan a basic components for bone regeneration and tissue engineering. In this study the addition of hyaluronan to eggshell particles enhances the osteogene differentiation of the cells, shown by the immunhistochemical staining, especially the osteocalcin measurement. These results correspond with the finding of other studies, where beneficial effects concerning matrix mineralization, cell differentiation and osteocalcin regulation were shown.[18] Different composite materials consisting of poly-(D,L-lactide), B-tricalcium phosphate, and calcium carbonate were manufactured as candidates for degradable bone substitutes. The investigations about the bending strength indicated suitably high values for the composites materials. The critical aspects were the huge amount of swelling of the polymeric matrix and thus the reduction on the bending strength during storage in water and PBS. A swelling and thereby a volume increase, could be critical especially for use of the tri phase bone substitute compound as a 3 D scaffold with defined dimensions. This must be taken into account with respect to the composition of the compound and the scaffold design.[20]

A novel facile MCCs to be used as bone grafts were prepared under the low-temperature condition. The MCC50 possessed highest compressive strength, while MCC100 with largest amount of magnesium amount of magnesium encountered deteriorated mechanical strength. The in vitro degradation of MCCs accelerated with increasing amount of introduced magnesium. The MCCs showed excellent cytocompatibility. The rMSCs cultured on MCCs with a certain amount of magnesium (MCC50, MCC75, and MCC100) exhibited more ascendant proliferation and osteogenic differentiation compared to MCCo. Given the poor mechanical strength of MCC100, the MCC50 and MCC75 are currently considered to be optimal biomaterials as potential bone grafts.[17] Further exploration and analysis to obtain ideal materials was conducted. For example, a study has shown that automated serial optical sectioning using structured illumination FM can assess cell numbers and the 3 D distribution of hBMSCs in mineralized scaffolds. This allows for detailed analysis of the effect of different in vitro procedures used for cell seeding. The use of a fibrin matrix during seeding increases seeding efficiency and enhances both proliferation and cell survival in the central parts of the scaffolds.[4]

The results of the present study indicate that a biocoral scaffold combined with BMSCs enhanced by BMP2 can repair the critical-sized orbital defects in a canine model suggesting that this method could be a feasible approach for the clinical reconstruction of orbital bone defects.[1] Furthermore, the effects on the effects on the interaction between osteogenesis and angiogenesis were observed and substantiated by ELISA assay. Taken together, our result provide clear evidence that DPSCs differentiated into osteoblast, forming a biocomplex made of Biocoral, ECM and differentiated cells.[16]

Another study confirmed the ability of bone grafts to act as antibiotic carriers.[15,19] Bone chips mixed with HERAFILL showed efficacy against S aureus and S epderimdis. Further studies with HERAFILL as bone void-filling material are needed.[15] The susceptibility test using S. aureus show less resistance of the strain after 1 month of the elution storage. That resistance was not observed after 6 months of storage. The capacity of bone grafts to act as gentamicin carriers has been confirmed in this study. The different granules sizes did not interfere in the delivery rate of the antibiotics or in the activity against the bacteria. Storage at -80^{o}C does not interfere on the antibiotic activity.[15]

Conclusions

The existing studies are still exploring additional materials to improve the ideal characteristics of coral as a scaffold. These studies are comparing coral with other materials, and added coral with other materials or stem cell to improve its effectiveness. Various materials can be use depending on the needs and preference of the clinician. In each case, selection of the appropriate biomaterial has to perform knowing its properties and ultimate fates, considering advantages and disadvantages, and keeping in mind that we may expect predictable results and clinical success.

Declaration of Interest

The authors report no conflict of interest and the article is not funded or supported by any research grant.

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Authors	Year	Title	Journals	Aim	Sample	N	Type of Study	Technique of Measurement	Time of Experiment	Compared Material
Devecioğlu D, Tözüm TF, Sengün D, Nohutcu RM.[2]	2004	Biomaterials in periodontal regenerative surgery: effects of cryopreserved bone, commercially available coral, demineralized freeze-dried dentin, and cementum on periodontal ligament fibroblasts and osteoblasts	Journal of Biomaterial Application	To evaluate effects of different biomaterials, allogenic and alloplastic, used in periodontal surgeries to achieve regeneration have been studied in vitro on periodontal ligament (PDL) cells and MC3T3-E1 cells.	Periodontal ligament, obtained from healthy premolars, extracted from juvenile patients due to orthodontic treatment	1	In vitro	Proliferation Assay Protein Assay Initial Attachment Assay Long term Attachment Assay Mineralization Assay	15,25,30 days	cryopreserved bone allograft (CBA), coralline hydroxy-apatite (CH), demineralized freeze-dried dentin (DFDD), and cementum
Koo KT, Polimeni G, Qahash M, Kim CK, Wikesjö UM.[7]	2005	Periodontal repair in dogs: guided tissue regeneration enhances bone formation in sites implanted with a coral-derived calcium carbonate biomaterial.	Journal of Clinical Periodontology	To evaluate bone formation associated with the CI biomaterial in the presence and absence of provisions for GTR	young adult Beagle dogs	12	In vivo	Histopathologic and Histometric analysis	4weeks	CI and CI/GTR
Pretorius JA, Melsen B, Nel JC, Germishuys PJ.[8]	2005	A histomorphometric evaluation of factors influencing the healing of bony defects surrounding implants.	Intenational Journal of Oral &Maxillofacial Implants	To perform a histomorphometric study of the healing of bone defects created adjacent to titanium and hydroxyapatite (HA) -coated implants and covered with either a resorbable or a non-resorbable membrane in combination with different filler materials and to evaluate to what degree coating, membrane, and/or filler influenced the healing defects	Baboon	10	In vivo	In vivo	3, 6, 9, 12, or 18 months	semineralized freeze-dried bone (DFDB), autogenous bone, Biocora
Scarano A, Degidi M, Iezzi G, Pecora G, Piattelli M, Orsini G, Caputi S, Perrotti V, Mangano C, Piattelli A.[10]	2006	Maxillary sinus augmentation with different biomaterials: a comparative histologic and histomorphometric study in man.	Implant Dentistry	To compare different materials in maxillary sinus augmentation in man	Human	94 patient	Clinical triali	Biopsi Histologic and Histomorphometric	6 month	DFDBA (LifeNet, Virginia Beach, VA); Biocoral; Bioglass; Fisiograft (Ghimas, Bologna, Italy); PepGen P-15TM; calcium sulfate (Surgiplaster sinus; Class

										Implant, Rome, Italy); Bio-Oss; Fin granule; and hydro-xyapatite.
Nam, Su-Bong MD; Bae, Yong-Chan MD, PhD; Moon, Jae-Sul MD; Kang, Young-Seek MD.[11]	2006	Analysis of the Postoperative Outcome in 405 Cases of Orbital Fracture Using 2 Synthetic Orbital Implants	Annals of Plastic Surgery	To analyze the post-operative complications According to the location (floor / medial wall / floor and medial wall) of the orbital fracture of 405 Patients during the past 10 years and to Investigate the possible alterative of data in post-operative outcomes in change with the application of two synthetic orbital implants: porous polyethylene (Medora) and hydroxyapatite (Biocoral)	porous polyethylene (Medora) and hydroxyapatite (Biocoral).	405 medical records	Cased control study -- Retrospective	postoperative outcome after using 2 implant	10 years past	porous polyethylene (Medora) and hydroxyapatite (Biocoral)
Techno M, Fine M, Giavaresi G, Remanding L, Ambrosia L, Giordano R.[12]	2009	In vivo preclinical efficacy of a PDLLA/PGA porous copolymer for dental	Journal of Biomedical Materials Research Part B: Applied Biomaterial	To analyze surface morphology and physical–chemical properties of a copolymer of polylactic /polyglycolic acid (Fisiograft, Ghimas	minipigs	12	In vivo	(SEM), porosimetry, and rheological analysi	15, 30, 60 days	porous copolymer in SPONGE or GEL form and compared with commercial BioOss
.		application.	s	Spa, Casalecchio di Reno, Italy) by scanning electron microscopy (SEM), porosimetry, and rheological analysis.						(Geistlich Biomaterials) and Biocoral (Inoteb, France)
Figueiredo M, Henriques J, Martins G, Guerra F, Judas F, Figueiredo H.[6]	2010	Physicochemical characterization of biomaterials commonly used in dentistry as bone substitutes--comparison with human bone	Journal of Biomedical Materials Research Part B: Applied Biomaterials	To analyze the physic-chemical characterization of selected mineral-based biomaterials that are frequently used in dental applications	(BioOss1 and PepGen P-151), porcine (OsteoBiol 1), and coralline (Biocoral1) compared with human bone	4	In vitro	Analytical-grade hydroxyapatite and collagen samples were used, namely in the FTIR analysis. SEM, Laser diffraction spectrometry XRD, X-PERT	3 days	(BioOss1 and PepGen P-151), porcine (Osteo Biol1), and coralline (Biocoral1) Hunan bone
Zhu H, Schulz J, Schliephake H.[4]	2010	Human bone marrow stroma stem cell distribution in calcium carbonate scaffolds using two different seeding methods.	Clinical Oral Implants Restoration	To develop a method for the determination of the three-dimensional (3D) distribution of cells in mineralized scaffolds and to compare the effect of two different methods of cell seeding of human bone marrow stroma cells (hBMSCs) in	hBMSCs were seeded into $CaCO_{(3)}$ scaffolds by droplet seeding using culture medium with and	2	In vitro	structured illumination fluorescence microscopy (FM) with serial optical sectioning and image analysis software	2, 7, 14, and 21 days	With and without fibrin

				long-term cultures	without the addition of fibrin					
Xiao C, Zhou H, Gee S, Tang T, Hour H, Lou M, Fan X.[1]	2010	Repair of orbital wall defects usingbiocoral scaffolds combined with bone marrow stem cells enhanced by human bone morphogenetic protein-2 in a canine model	International Journal of Molecular Medicine		Autologous bone marr ow stoma c ells (BMSC s) from 16 Beagle dogs were isolated and cultured in vitro	16	In Vitro	micro-CT and histomorphometr y detection	12-24 weeks	iocoral scaffold s combined with bone marrow stem cells enhanced by human bone morphogenetic protein-2 l
Mangano C, Piano F, d'Aquino R, De Rosa A, Iezzi G, Piattelli A, Lain L, Mitsiadis T, Desiderio V, Mangano F, Papacies G, Torino V.[13]	2011	Human dental pulp stem cells hook into binocular sc affold forming an engineered biocomplPlops	Plops One	To evaluate the behavior of human Dental Pulp Stem Cells (DPSCs), as well as human osteoblasts, when challenged on a Biocoral scaffold, which is a porous natural hydroxyapatite	Biocoral Human Osteoblast (control)	2	In vitro	SEM Molecular analyses RT PCR Elisa Assays	SEM analyses , at 8, 24 & 48 h - 7, 15 & 30 days culture, morphol ogical and molecula r analyses	Human osteoblast
Fu K, Xu Q, Czernuszka J, Griffith JT, Xia Z.[3]	2013	Characterization of a biodegradable coralline hydroxyapatite/c alcium carbonate compo site and its clinical implementation.	Biomedical Materials	To characterize CHACC to assess its capacity for conductive osteogenesis and to observe its clinical performance	In vitro: human mesenchy mal stem cells. In vivo: immunodef icient mouse model Clinical trial: human	In vitro: In vivo: Cinical trial: 16 patient	In vitro In vivo Clini cal trial	Powder X ray diffraction, scanning electron microscopy, energy dispersive x ray spectroscopy	In vitro: 2 weeks In Vivo: 10 weeks Clinical trial: 18 sd 24 months	Control
Gunn JM, Rekola J, Hirvonen J, Aho AJ.[14]	2013	Comparison of the osteoconductive properties of three particulate bone fillers in a rabbit model: allograft, calcium carbonate (Biocoral®) and S53P4 bioactive glass.	Acta odontologic a Scandinavi ca	To compare the osteo-conductivity and suitability of three biomaterials used as particulate fillers; S53P4 bioactive glass, allogeneic fresh frozen bone and coral-derived calcium carbonate.	Rabbit	69 specim en from 42 knees of 21 adult rabbit	Anim al Inviv o	Host-response, osteoconductivity , bonding and filler-effect evaluated by SEM, EDXA and histology and histomorphometr y to evaluate.	3, 6, 12 and 24 weeks	S53P4 bioactive glass, allogeneic fresh frozen bone and coral-derived calcium carbonate.
Giuliani A, Meniscus A, Larsson E, Thrombi G, Lounge G, Piattelli A, Mangano F, Iezzi G, Mangano C.[21]	2014	In vivo regenerative properties of coralline-derived (binocular) scaffold grafts in human maxillary defects: demonstrative and comparative study with Beta-tricalcium phosphate and biphasic calcium phosphate by synchrotron radiation x-ray micro tomography.	Clinical implant dentistry and related research	To understand the mechanism of the binocular comparing with other material biological behavior as bone substitute using Micro CT	Human maxillary defect	12	Hum an Clini cal Trial	Micro CT	6-7 weeks	Binocular, B Top, 70%TCP/30% HA
Curacao-Huber D, Haushofer J, File M, Nobler M, Kuhn KD[15]	2014	Calcium carbonate powde r containing gentamicin for mixing with bone grafts	Orthopedic s	To evaluate the use of absorbable bone graft substitute powder as a bone void-filling material as well as an antibiotic carrier for mixing with bone graft	Bone chipsHerafi ll	1	In vitro	Bacillus subtilis Assay Susceptibility Test	7 days	Bone Chips Herafill
Carlo Mangano, Adriano Piatelli, Jamil Awad Shibli,	2014	Clinical and Histologic Evaluation of Calcium Carbonate in	Journal Periodotics Restorative Dentistry	To evaluate a clinical, histologi and histoporphometric of calcium carbonate in sinus elevation	Calcium carbonate	24 subject 68 implant	Clini cal Trial	Clinical, histologi and histomorphometr ic evaluation	6 month 1-5 years	None

Vittoria Perroti.[16]		Sinus Augmentation: A Case Series		procedures						
He F, Zhang J, Tian X, Wu S, Chen X.[17]	2015	A facile magnesium-containing calcium carbonate biomaterial as potential bone graft	Colloids and surfaces. B, Biointerfaces	To prepare magnesium containing calcium carbonate biomaterial (MCCs)	3 kinds of calcium carbonate (ACC) MCC	3	In vitro	SEM, NAVA NanoSEM 430, FEI, the Netherlands, equipped with X ray Spectometer	1, 3, 5, 7, 14, 21 days	ACC MCC
Neunzehn J, Szuwart T, Wiesmann HP.[18]	2015	Eggshells as natural calcium carbonate source in combination with hyaluronan as beneficial additives for bone graft materials - in vitro	Head & Face Medicine	To investigate the effects of eggshell granulate and calcium carbonate towards primary bovine osteoblast.	Hyaluronan, eggshells, a comninatio n of hyaluronan and eggshells and CaCo3	3	In vitro	Prolifersi: light microscopy and counted at defined position Histology and immune histochemistry	Proliferasi: 1,2,3,6, 7 day Histology and immuno histochemistry: 4 weeks	Hyaluronan, eggshells, a comnination of hyaluronan and eggshells and CaCo3
Curacao-Huber DC, Wurm A, File M, Haushofer J, Nobler M, Vogt S, Kuhn KD.[19]	2015	Antibiotic-loaded calcium carbonate/calcium sulfate granules as co-adjuvant for bone grafting	Journal of Materials Science	To evaluate Herafill granules mixed with bone chips (BCh)	Herafill mixed with bone chips from human (tissue bank)	3	In vitro	Drug release test & bacterial susceptivility using Bacillus subtilis, S. epidermidis & S. aureus	No storage 80 l month gentamicin release 1-10 days	Herafill and bone chips in different concentration
Abert J, Amella A, Weigelt S, Fischer H.[20]	2016	Degradation & swelling issues of poly-(d,l-lactide)/β-tricalcium phosphate/calcium carbonatecomposites for bone replacement	Journal of the Mechanical Behavior of Biomedical Materials	To prepare a homogenous composite material for bone replacement	PDLLA/TCP/CC in various ratio	6	In vitro	Degradation of polymer, determination of elastic constants, mechanical strength evaluation, influence of liquid environment on bending strength	2,4,8 weeks	PDLLA/TCP/CC

Table 2. Overview of studies included in the review.