Review Article

Biomimetic ceramics for periodontal regeneration in infrabony defects: A systematic review

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Abstract

Biomimetic materials are widely used in the treatment of osseous defects as an alternative to autogenous bone graft. The aim of this article was to review the literature and compare the quality of published articles on biomimetic ceramic material used for periodontal regeneration in the treatment of infrabony defects and to discuss the future direction of research. The bibliographic databases PubMed, Ebsco, and Google Scholar were searched from January 2000 to March 2014 for randomized control trials in which biomimetic ceramic graft material was compared with open flap debridement or in combination with any other regenerative material. To avoid the variability of the search terms, the thesaurus Mesh was used. The primary outcome variable assessed was clinical attachment level (CAL). The screening of eligible studies, assessment of the methodological quality of the trials, and data extraction were performed by two observers independently. Twenty-six articles were identified and included in this systematic review. The primary outcome was CAL. Out of the 26 studies, 24 showed more than 2 mm of CAL gain. The difference in CAL change between test and control groups varied from 1.2 mm to 5.88 mm with respect to different biomaterials/biomimetic materials, which was clinically and statistically significant. Meta-analysis was not done due to heterogeneity in results between studies. Overall, biomaterials were found to be more effective than open flap debridement in improving the attachment levels in intraosseous defects. Future research should aim at increasing the osteoinductive capacity of these biomimetic graft materials.

Key words: *Biomaterials, biomimetic materials, bone grafts, infrabony defects, systematic review*

INTRODUCTION

Bone grafting in dentistry is indicated in several surgical situations such as treatment of bone defects, facial clefts, re-construction of alveolar ridge, socket preservation, sinus lift, treatment of peri-implantitis, and endodontic surgeries. Autogenous grafts are used to enhance regeneration and healing of the defect site. Cancellous autograft is considered the gold standard for bone grafts, but it has its own limitations like availability, morbidity, and infection of the surgical site. This has initiated the development of several bone graft alternatives called biomaterials. While earlier the materials were designed to be bioinert, scientists have shifted their focus toward designing bioactive materials that integrate biological molecules, cells, and regenerate tissue,[1] which can offer novel methods of generating biological solutions for design and synthesis of composite materials such as bone, cartilage, cementum, periodontal ligament, skin, enamel, and dentin, re-construction of alveolar ridge, temporomandibular joint, and other joint prosthesis, new polymers for guided tissue regeneration in the treatment of bone and connective tissue defects, and growth factors to induce bone healing and developing dental and facial implants. The aim of this review is to determine and compare the quality of research articles published in the field of periodontal regeneration using biomimetic ceramic graft material with open flap debridement (OFD) or in

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combination with any other regenerative material in the treatment of infrabony defects.

HISTORY

Nature has always served as a model for inspiration, as evident in the long and rich heritage of human artifacts and technology.[2] In 1960, the process of copying from nature was regarded as a scientific discipline. Scientists have coined various names for the specific use of nature as inspiration in design (bionics, biomimetics, bio-inspiration, and biognosis). In 1969, Otto H. Schmitt, a biomedical engineer, coined the term "biomimetics" which describes an electronic feedback circuit he designed to function in a similar way to the neural networks.[3] "Biomimetics" has a Greek origin, with the words "bios" meaning life and "mimesis" meaning to copy. It is a new field that implements concepts and principles from nature in creating new materials, devices, and systems.[4]

The concept of biomimetics is vast and biomimicry finds its applications in several fields starting from aeronautics to earth sciences to medicine to zoology. In the field of medicine, biomimicry has been reported since the days of Emperor Nero in the first century AD. Nero, who was short-sighted, used an emerald to magnify things for a better vision; he got this idea from dew drops which act as a magnifying lens depending on the shape.[5] Today we have pacemakers that mimic the impulses of the sinoatrial (SA) node of the heart. Tiny serrations on the mosquito's proboscis have inspired a team of Japanese scientists to make relatively painless hypodermic needle edges.[5]

SEARCH STRATEGY

This article is an attempt to review the literature on biomimetic ceramic material used for periodontal regeneration in the treatment of infrabony defects and to discuss future direction of research. The historical and human histological data were extracted after a thorough review of the literature. A systematic search for literature reports was carried out to identify relevant studies (randomized control trials only) by using the keywords "biomaterials in treatment of infrabony defects" and "biomimetics materials in treatment of infrabony defects," and each biomimetic ceramic graft material used for treatment in infrabony defects was individually searched. The research articles were searched from 1 Jan 2000 to 30 March 2014 in PubMed, Ebsco database, and Google Scholar search engine. The hand search was limited to six periodontal journals during the years 2000 through 2014. In addition, the reference lists of all relevant articles were searched; initial screening of titles and abstract was performed and only full-text articles were included [Figure 1].

Articles on the regenerative outcome of synthetic ceramic bone replacement materials in the treatment of human infrabony defects were considered for inclusion in this review. The follow-up duration of the studies were more than 6 months and the primary outcome variable assessed was clinical attachment level (CAL). Other outcome variables assessed were probing pocket depth (PPD) and/or radiographic parameters and/or surgical re-entry measurements. The articles were restricted to English language. Exclusion criteria included non-randomized observational studies, publications providing summary statistics without variance estimation or data to permit computation, and studies without a bone replacement graft intervention alone.

QUALITY ASSESSMENT

The methodological quality for the included studies was assessed with a predetermined appraisal form focusing on the following issues: Bibliographic details, the method of randomization and blinding of patients, therapist and examiners, characteristics of the study population, frequency and course of the interventions, baseline and outcome measures, and completeness of follow-up. To achieve a discriminative objective, two reviewers (TK and JJR) independently assessed the quality of each study. Disagreements on validity assessment were resolved by consensus and discussion.

The ideal biomaterial must be compatible, resorbable, and porous to facilitate rapid vascularization and progressive replacement of newly formed tissue.[6] The majority of biomimetic materials used in regenerative medicine aim to replicate the porous architecture of cancellous bone. Research shows that the requisite pore size for ingrowth of bone is 150–500 μm and to stimulate fibrovascular growth, the pore diameter should be more than 100 μm.[7,8]

According to the European Society for Biomaterials, a biomaterial is a material intended to interface with biological systems to evaluate, treat, augment, or replace any tissue, organ, or function of the body.[9]

TYPES OF BIOMATERIALS

1. Ceramics- bioinert ceramics, bioactive ceramics, biodegradable ceramics

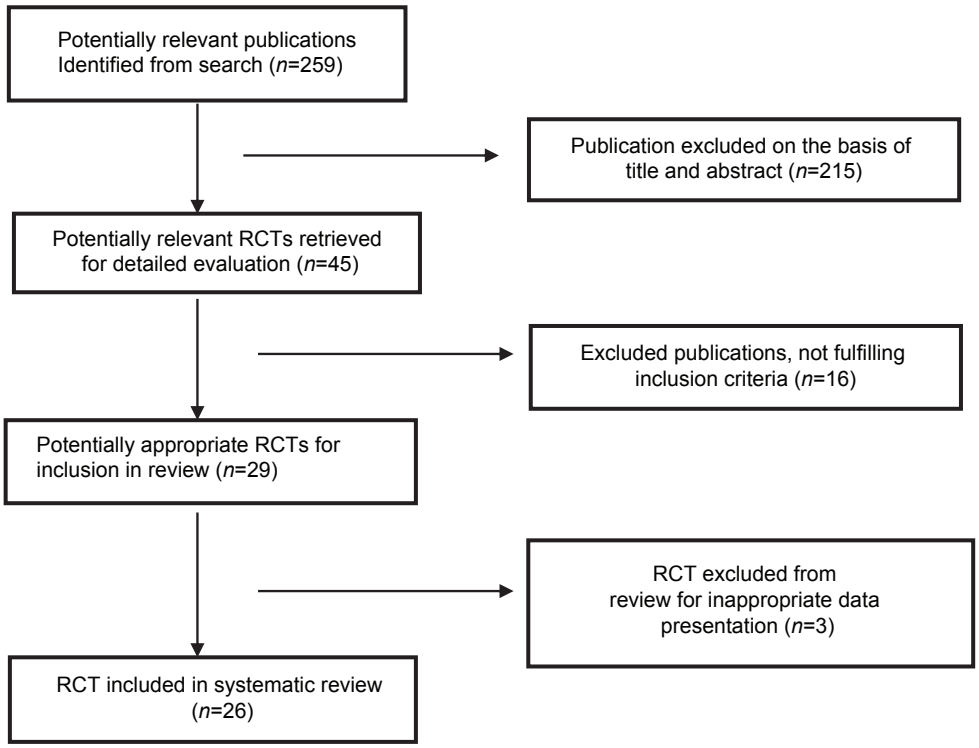

Figure 1: Flowchart for inclusion in review

2. Polymers- bioinert polymers, bioresorbable polymers
3. Metal- 316L stainless steel, commercially pure titanium alloys and titanium alloys, cobalt–chromium alloys

According to the activity of biomaterials, they could be classified as:[10]

1. Osteoconductive biomaterials which provide scaffold or framework that supports bone growth and encourages the ingrowth of surrounding bone,
2. Osteoinductive biomaterials comprising combination of growth regulatory molecules with carriers, and
3. Osteogenic biomaterials which contain osteocompetent cells.

Only synthetic biomaterials/biomimetics (of the first category, i.e. ceramics) were taken into consideration for discussion in this systematic review.

Ceramics are crystalline, inorganic, non-metallic minerals that are held together by ionic bonds and usually densified by sintering.[11]

BIOMATERIALS CLASSIFICATION

When a synthetic material is placed within the human body, the tissue reacts toward the implant in different ways depending on the material type. The mechanism of tissue interaction depends on the response of the tissue to the implant surface. In general, there are three terms by which a biomaterial may be described or classified into representing the tissues responses. These are bioinert, bioresorbable, and bioactive.

Bioinert biomaterials

The term bioinert refers to any material which has minimal interaction with its surrounding tissue when placed in the human body, e.g. stainless steel, titanium, alumina, partially stabilized zirconia, and ultra-high-molecular-weight polyethylene. Generally, a fibrous capsule might form around bioinert implants; hence, its bio-functionality relies on tissue integration through the implant.

Bioactive biomaterials

Bioactive refers to a material which upon being placed within the human body, interacts with the surrounding bone and, in some cases, even soft tissue. This occurs through a time-dependent kinetic modification of the surface that is triggered by its implantation within the living bone. An ion-exchange reaction between the bioactive implant and surrounding body fluids results in the formation of a biologically active carbonate apatite (CHAP) layer on the implant that is chemically and crystallographically equivalent to the mineral phase in bone. Examples of

these materials are synthetic hydroxyapatite (HA) and bioglass.

Bioresorbable biomaterials

Bioresorbable refers to a material which starts to dissolve upon placement within the human body and is slowly replaced by advancing tissue (such as bone). Common examples of bioresorbable materials are tricalcium phosphate (TCP), polylactic–polyglycolic acid copolymers, and gypsum.[12]

Ceramics used in periodontal regeneration are:

a. Calcium sulfate (CS)
b. Calcium phosphate
   Synthetic HA
   Biphasic calcium phosphate (BCP)
   Tricalcium phosphate (TCP)
   Calcium phosphate cement (CPC)
c. Bioactive glass (BG)
d. Ion-substituted bioceramics

RESULTS

The search resulted in the identification of 259 studies. Independent initial screening of the titles and abstracts by two reviewers (TK and JJR) resulted in further consideration of 45 randomized controlled trials for possible inclusion [Figure 1]. Of these studies, 26 articles met the defined inclusion criteria, i.e. 2 studies on calcium sulfate, 4 studies on HA, 6 studies on β-TCP, 6 studies on BCP, 2 studies on CPC, 5 studies on BG, and 1 study on composite grafts, were reviewed in this systematic review [Table 1]. All articles included have low to moderate risk of bias.

CAL has been taken as a primary outcome variable as it gives an approximate clinical measurement of loss or gain of connective tissue attachment from the root surface.[39] All the studies included showed a positive effect in relation to CAL and PPD, when compared to OFD. The difference in CAL change between test and control groups varied from 1.2 mm to 5.88 mm with respect to different biomaterials/biomimetic agents, which was clinically and statistically highly significant [Figure 2]. Only two studies showed less than 2 mm of CAL gain, which was in relation to bioactive glass and TCP [Table 1].

Each ceramic biomimetic graft material is described below.

Calcium sulfate

Calcium sulfate ($CaSO_4$) got its name plaster of Paris after a small village just north to Paris. It was used

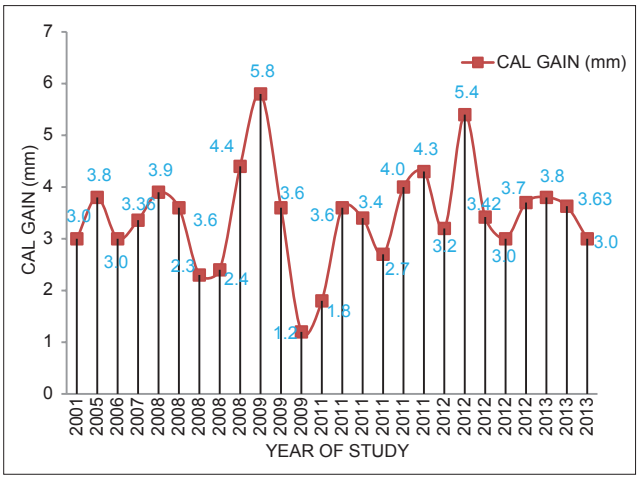

Figure 2: Plot of some of the randomized control trials (RCTs) comparing biomimetic ceramic materials in the treatment of infrabony defects, which were published between 2000 and 2014. The red square indicates the average clinical attachment level (CAL) reported

to fill bone defects caused by tuberculosis. In 1892, Dressman first reported the use of calcium sulfate in human skeletal defects to fill voids in long bones caused by tuberculous osteomyelitis.[8] It is one of the first synthetic bone grafts used as a replacement for autograft.[40]

After being placed into the bone defect, calcium sulfate undergoes degradation to calcium and sulfate ions. Calcium ions combine with phosphate ions from body fluids to form calcium phosphate, which provides an osteoconductive surface that stimulates the recruitment of osteoblasts and development of new bone in the defect. As calcium sulfate undergoes degradation in the body, there is a local decrease in pH. This pH drop results in demineralization of defect walls, thus releasing bone growth factors which stimulate the formation and development of new bone. This newly deposited material is mainly carbonated HA which is similar to apatite that is naturally present in bone. The graft material gets resorbed within 6 weeks, which is much faster than that of HA and TCP. Its degradation exceeds the rate of new bone growth into the defect; hence, to overcome this limitation, it can be used along with other graft materials.[40] Calcium sulfate is reabsorbed by a process of dissolution over a period of 5–7 weeks[41] [Table 2].

In 1997, Pecora[42] concluded that it works as a barrier membrane by excluding the growth of connective tissue and allowing bone regeneration. Calcium sulfate was also observed to possess angiogenic properties. In 2002, Strocchi *et al*.[43] reported that more blood vessels grew into the defects filled with calcium sulfate than those filled with autograft. It can effectively be used as

Table 1: Characteristics of RCT studies comparing ceramic biomaterials (biomimetic materials) in treatment of infrabony defects

S. No.	Study	Study description	Participants	Intervention	Outcomes	Conclusion (control vs. test group)
Biomimetic materials: Calcium sulfate						
2008	Paolantonio *et al.*[13]	Randomized Parallel group Three groups 12 months duration	51 individuals 41-62 years	OFD Calcium sulfate and membrane Collagen membrane	CAL, PPD, radiographic measurements, surgical re-entry	CAL gain: 2.8 mm vs. 4.4 mm vs. 5.2 mm PDR: 1.5 mm vs. 2.7 mm vs. 3.1 mm IDD: 0.7 mm vs. 2.3 mm vs. 2.4 mm No significant difference was seen between CS and CM. Both showed clinical benefits over OFD
2008	Orisini *et al.*[14]	Randomized Split mouth Two treatment groups 6, 72 months duration	12 individuals 29-62 years	Autogenous bone graft and bioresorbable membrane Autogenous bone graft and calcium sulfate	CAL, PPD (6 months, 6 years)	CAL gain: 2.6 mm vs. 2.4 mm (33% vs. 58% >2 mm) PDR: 3.3 mm vs. 4.2 mm Both groups had comparable results at 6 months and 6 years
Biomimetic materials: Hydroxyapatite						
2008	Yamamiya *et al.*[15]	Randomization Parallel group Two groups 12 months	30 patients 46-65 years	PRP, HA HCP sheets, PRP, HA HCP sheets	CAL, PPD, radiographic measurement	CAL gain: 2.7 mm vs. 3.9 mm (55% vs. 83.5% >3 mm) PDR: 4.3 mm vs. 4.8 mm Defect depth: 3.2 mm vs. 4.9 mm HCP sheets, PRP, and HA led to a significantly more favorable clinical attachment level and radiographic changes in infrabony periodontal defects
2008	Kasaj *et al.*[16]	Randomized Parallel group Two groups 6 months duration	28 individuals, 40-66 years	OFD NHA	CAL, PPD, radiographic measurements	CAL gain: 1.8 mm vs. 3.6 mm PDR: 2.6 mm vs. 3.9 mm DD: 3.6 mm vs. 4 mm Treatment of intrabony periodontal defects with NHA paste significantly improved clinical outcomes, compared to OFD
2011	Gupta *et al.*[17]	Randomization Split mouth Two treatment groups 6 months duration	15 individuals, 30 defects 30-50 years	HA HA, osteoclast inhibitor	CAL, PPD, radiographic measurements	CAL gain: 2.80 mm vs. 3.60 mm PDR: 2.47 mm vs. 3.40 mm LBG: 2.80 mm vs. 3.80 mm LBG was better in HA with osteoclast inhibitor than with HA alone
2012	Menezes *et al.*[18]	Randomized Split mouth Two treatment groups 48 months duration	60 individuals Mean: 37.75 years	PRP, saline PRP, porous HA	CAL, PPD, radiographic measurements (1-4 years)	CALgain: 3.1 mm vs. 5.4 mm (63% vs. 98% >3 mm) PDR: 4.0 mm vs. 5.8 mm DF: 2.1 mm vs. 3.2 mm Treatment with a combination of PRP and HA led to a more favorable clinical improvement in intraosseous periodontal defects after a span of 4 years
Biomimetic materials: Biphasic calcium phosphate						

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Table 1: Contd...

S. No.	Study	Study description	Participants	Intervention	Outcomes	Conclusion (control vs. test group)
2009	Stein *et al.*[19]	Randomized Parallel group Three groups 12 months duration	45 individuals 18-70 years	OFD Autogenous bone spongiosa Biphasic calcium composite	CAL, PPD, REC	CAL gain: 2.8 mm vs. 3.4 mm vs. 3.6 mm PDR: 1.6 mm vs. 2.8 mm vs. 3.0 mm BCC is equivalent to ABS, but superior to OFD
2011	Meyle *et al.*[20]	Randomized Parallel group Two groups 12 months duration Multicenter study	75 individuals 23-50 years	EMD EMD and BCP	CAL, PPD, REC, bone sounding and radiographic measurements	CAL gain: 2.8 mm vs. 2.7 mm DF: 1.9 mm vs. 1.7 mm Comparable results seen in both the groups
2012	Pietruska *et al.*[21]	Randomized Parallel group Two treatment groups 48 months duration	24 individuals 34-62 years	EMD EMD, BCP	CAL, PPD (1-4 years)	CAL gain: 3.2 mm vs. 3.2 mm PDR: 4.4 mm vs. 4.7 mm EMD+BCP did not show any advantage over the use of EMD alone
2012	Thakare *et al.*[22]	Randomized Parallel group Two groups 12 months duration	18 individuals Age: 28-50 years	β-TCP and HA rhPDGF-BB and β-TCP	CAL, PPD, REC, radiographic measurements	CAL gain: 2.06 mm vs. 3.42 mm PDR: 2.7 mm vs. 3.82 mm Bone fill: 81% vs. 54% rhPDGF-BB and β-TCP showed better clinical results than β-TCP and HA
2012	Lee *et al.*[23]	Randomized Parallel group Two groups 6 months duration	25 patients Age: 31-64 years	OFD (11) BCP (14)	CAL, PPD, REC, radiographic measurements	CAL gain: 1.4 mm vs. 3.0 mm PDR: 2.5 mm vs. 3.7 mm Defect depth: 1.4 mm vs. 2.4 mm BCP had better results than OFD in all the investigated parameters
2013	Dori *et al.*[24]	Randomized Split mouth Three groups 12, 24 months duration	34 patients 30-68 years	OFD, EMD, EMD, HA/β-TCP	CAL, PPD, radiographic measurements (12, 24 months)	CAL gain: 1.36 mm vs. 2.96 mm vs. 3.63 mm PDR: 2.37 mm vs. 3.76 mm vs. 4.25 mm DD: −0.24 mm vs. 2.62 mm vs. 3.35 mm Combination of HA/β-TCP with EMD was clinically superior to EMD alone in improving all clinical and radiographic parameters 24 months after surgical treatment in non-contained periodontal bony defects
Biomimetic materials: Tricalcium phosphate						
2005	Nevins *et al.*[25]	Randomized Parallel group Three groups 6 months duration	173 individuals, 25-75 years	β-TCP 0.3 mg/ml rhDGF-BB + β-TCP 1.0 mg/ml rhPDGF-BB + β-TCP	CAL, PPD, REC, radiographic measurements	CAL gain: 3.5 mm vs. 3.8 mm LBG: 0.9 mm vs. 2.6 mm vs. 1.5 mm Bone fill %: 18 vs. 57 vs. 34 % 0.3 mg/ml rhPDGF-BB is more effective than 1.0 mg/ml rhPDGF-BB

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Table 1: Contd...

S. No.	Study	Study description	Participants	Intervention	Outcomes	Conclusion (control vs. test group)
2011	Saini *et al.*[26]	Randomized Split mouth Two treatment groups 9 months	20 individuals, 40 defects 22-50 years	β-TCP PRP, β-TCP	CAL, PPD, radiographic measurements	CAL gain: 1.10 mm vs. 1.80 mm PDR: 2.20 mm vs. 2.80 mm LBG: 2.50 mm vs. 3.20 mm Treatment with a combination of PRP and β-TCP compared with β-TCP alone led to a significantly more favorable clinical and radiographic improvement in intraosseous periodontal defects
2011	Jayakumar *et al.*[27]	Randomized Parallel group Two groups 6 months duration Multicenter study	50 individuals 25-75 years	β-TCP rhPDGF-BB and β-TCP	CAL, PPD, REC, and radiographic measurements (3, 6 months)	CAL gain: 2.8 mm vs. 3.7 mm PDR at 6 months: 3.2 mm vs. 4.3 mm LBG: 2.8 mm vs. 3.7 mm Bone fill %: 65.6% vs. 47.5% rhPDGF-BB and β-TCP showed better clinical results than β-TCP
2012	Windisch *et al.*[28]	Randomized Parallel group Two groups 6 months duration	20 patients Age: 31-64 years	OFD rhGDF-5, β-TCP	CAL, PPD	CAL gain: 3.1 mm vs. 3.7 mm PDR: 1.7 mm vs. 3.2 mm Application of rhGDF-5/β-TCP resulted in greater (although statistically not significant) probing depth reduction and clinical attachment gain compared to the control
2013	Nevins *et al.*[29]	Randomized Parallel group Three groups 36 months duration	83 individuals 25-75 years	β-TCP 0.3 mg/ml rhDGF-BB + β-TCP 1.0 mg/ml rhPDGF-BB + β-TCP	CAL, PPD, REC, radiographic measurements	CAL gain: 3.5 mm vs. 3.8 mm LBG: 0.9 mm vs. 2.6 mm vs. 1.5 mm Bone fill %: 18 % vs. 57 % vs. 34 % 0.3 mg/ml rhPDGF-BB is more effective than 1.0 mg/ml rhPDGF-BB
2013	Leonardis *et al.*[30]	Randomized Split mouth Three groups 1, 10 years duration	22 patients 34-57 years	EMD, Bio-Oss EMD, β-TCP	CAL, PPD (1, 10 years)	CAL gain: 3.1 mm vs. 3.0 mm (64% vs. 82% ≥3 mm) PDR: 3.9 mm vs. 4.0 mm Both the groups showed stability of clinical improvement over a period of time
Biomimetic materials: Calcium phosphate cement						
2008	Shirakata *et al.*[31]	Randomized Parallel group Two groups 12 months duration	30 individuals 44-62 years	OFD Injected CPC	CAL, PPD, (3, 6, 9 months), radiographic measurements (6, 9 months)	CAL gain: 1.4 mm vs. 2.3 mm PDR: 3.3 mm vs. 3.4 mm DD: 0.3 mm vs. 1.2 mm CPC did not show any additional benefits over OFD, but radiographic measurements showed better results in relation to CPC
2009	Rajesh *et al.*[32]	Randomized Parallel group Three groups 12 months duration	60 individuals 20-45 years	OFD CPC Porous HA	CAL, PPD, (6, 12 months) Surgical re-entry in two cases	CAL gain: 2.30 mm vs. 3.5 mm vs. 5.80 mm PDR: 2.95 mm vs. 6.20 mm vs. 4.05 mm CPC is found to be better than HA ceramic granules

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Table 1: Contd...

S. No.	Study	Study description	Participants	Intervention	Outcomes	Conclusion (control vs. test group)
Biomimetic materials: Bioactive glass						
2001	Park *et al.*[33]	Randomized Parallel groups Two treatment groups 6 months duration	38 individuals 28-67 years	Control: OFD Test: Bioactive glass	CAL, PPD, REC, bone sounding	CAL gain: 1.8 mm vs. 3.0 mm PDR: 3.3 mm vs. 4.1 mm BPD: 1.3 mm vs. 2.8 mm (bone probing depth) CAL and BPD were better in BG compared to OFD
2006	Mengel *et al.*[34]	Randomized Split Two groups 5 years	16 patients 32-62 years 60 defects	BG (32) Poly (d, l-lactide-co-glycolide) membrane (28)	CAL, PPD, radiographic measurement	CAL gain: 3.0 mm vs. 3.0 mm PDR: 3.3 mm vs. 3.6 mm Defect resolution: 65% vs. 47.5% Clinical and radiological results after 5 years revealed no statistically significant differences between the two groups; long-term stability can be achieved with both materials
2007	Demir *et al.*[35]	Randomized Parallel group Two groups 9 months	29 patients 24-48 years	BG PRP, BG	CAL, PPD, surgical re-entry	CAL gain: 3.36 mm vs. 3.47 mm PDR: 3.29 mm vs. 3.60 mm IDD: 3.36 mm vs. 3.47 mm Comparable results in both the groups, PRP had no added benefit to the clinical parameters
2009	Leknes *et al.*[36]	Randomized, Split mouth, 2 groups, 6, 12 months duration,	13 individuals 41-74 years	BCF EMD	CAL, PPD (6, 12 months)	CAL gain: 1.2 mm vs. 0.6 mm PDR: 2.6 mm vs. 2.5 mm The gain in proximal attachment in treatment of infrabony defect by flap surgery with BCF was significant and twice that following treatment with EMD
2011	Yadav *et al.*[37]	Randomization Parallel group Three groups 6 months duration	22 patients 30 defects 20-49 years	Collagen membrane (10 defects) CM Autogenous bone, collagen membrane (10) Autogenous bone, BG (10)	CAL, PPD, radiographic measurements	CAL gain: 2.10 mm vs. 4.20 mm vs. 3.40 mm PDR: 2.80 mm vs. 4.60 mm vs. 4.0 mm DF: 1.06 mm vs. 3.82 mm vs. 3.09 mm Defect resolution: 26.7% vs. 57.3% vs. 46.5% Parameters were better when compared with CM, but there was no significant difference between the two test groups in any parameter
Biomimetic material: Composite graft						
2011	Kumar *et al.*[38]	Randomized Split mouth Two treatment groups 6 months duration	10 individuals 24 defects 17-35 years	OFD Composite graft (HA, TCP, BG)	CAL, PPD, REC, and volumetric analysis using CT	CAL gain: 2.7 mm vs. 4.0 mm PDR: 2.8 mm vs. 4.0 mm DD: 1.4 mm vs. 2.53 mm DV: 37.41 mm^3 vs. 62.59 mm^3 DF: 56.76% vs. 72.04% HA+TCP+BG showed better results than OFD

CAL=Clinical attachment level, PPD=Probing pocket depth, PDR=Pocket depth reduction, OFD=Open flap debridement, LBG=Linear bone growth, DD=Defect depth; DV=Defect volume, DF=Defect fill, IDD=Intrabony defect depth, CT=Computer tomography, CM=Collagen membrane, CS=Calcium sulphate, HA=Hydroxyapatite, HCP=Human cultured periosteum, TCP=Tri Calcium Phosphate, BG=Bioactive glass, EMD=Enamel matrix derivative, BCF=Bioactive Ceramic Filler, CPC=Calcium phosphate cement, rhPDGF=recombinant platelet derived growth factor, PRP=Platelet rich plasma

Table 2: Resorption rate of various graft materials

Ceramic graft material	Process of resorption	Duration
Calcium sulfate hemihydrates	Dissolution	5-7 weeks[10]
Biphasic calcium phosphate (HA + β-TCP)	Cell mediated	β-TCP resorbs faster (6-18 months); HA takes years to resorb
β-TCP	Cell mediated	6-18 months[10]
Porous HA	Cell mediated	1-2% per year[10]
Non-porous HA	Practically no resorption	-
Calcium phosphate cement	Cell mediated	Resorption and remodeling occur over ~2 years[10]
Bioactive glass	Dissolution	More than a year[11]

HA=Hydroxyapatite, β-TCP = β-Tricalcium phosphate

a drug delivery vehicle. Several drugs like Tobramycin (Beardmore *et al*. in 2005)[43] and Simvastatin (Nyan *et al*. in 2007)[43] have been delivered locally through calcium sulfate. Budhiraja showed parallel results when Demineralization Freeze Dried Bone Allograft (DFBBA) and collagen membrane was compared with DFDBA and Calcium Sulphate (CS) indicating that CS is effective as a collagen membrane as a barrier material.[44]

It is available in combination with HA or demineralized bone matrix, or as a "binder" type of material designed to be mixed with various alloplasts, allografts, or autografts to improve handling and prevent particle migration [Table 1]. Examples: Calcigen, Capset, Calmatrix, Surgiplaster

Calcium phosphate

Use of calcium phosphate ceramics was first proposed by Albee and Morrision in 1920 for biomedical applications.[45] HA is a naturally occurring mineral form of calcium phosphate that constitutes up to 70% of the dry weight of bone. HA was first identified as the mineral component of bone by De Jong in 1928.[45]

Two forms of HA are available: Natural and synthetic. Synthetic HA may be porous and non-porous. Non-porous HA does not resorb; the porous synthetic form of HA is osteoconductive and has a crystalline structure similar to the HA in bone. Porous synthesized HA is slower to resorb than the endogenous form and may stay at the site of implantation for many years[46] [Table 1]. In porous granular form, it can be used alone or with bone graft to fill voids. It is successfully used to coat metal implants to enhance their osseointegration.[47]

Microcrystalline, non-ceramic HA

Manufactured using a low-temperature precipitation process, micro-crystalline, non-ceramic HA is a readily resorbable source of bioactive calcium phosphate. By avoiding high-temperature processes, these materials do not become ceramics and maintain a chemistry that is very similar to biological apatites. The crystals are not resorbed by cell-mediated processes; rather they are dissolved into solution, providing a ready source of calcium and phosphate as well as a structural lattice which can support early bone formation.[48]

Examples**:** OsteoGen non-ceramic, microcrystalline HA powder

HA resorbs by cellular resorption during bone remodeling. Residual HA and bone growth ranges are 0–55% and 18–56%, respectively. HA coating is increasingly resorbed with time from implantation and is nearly completed at 8 years. The only demographic factor that influences the amount of bone ongrowth is age, with younger patients having higher bone ongrowth percentages than older patients. This may relate to greater initial bone stock in younger people, but can also be explained by the fact that in older patients, the resorptive component of the remodeling process is more prominent.[49]

In 2011, in a histological study, Checchi *et al*. found the percentage of new mature bone to be 49 ± 28% in the biopsy indicating the bone-forming ability and the percentage of osteoid tissue and remaining material to be 14 ± 7% indicating remodeling capacity after 6 months. It was concluded that the graft degrades in a non-homogenous manner.[50]

In 2013, Horvath *et al*.[51] in a histological study showed healing predominately characterized by epithelial downgrowth, limited formation of new cementum and connective tissue fibers with bone regeneration occurred in three out of the six biopsies. Complete resorption of the nano-HA was found in four out of the six biopsies. A few remnants of the graft particles were seen either surrounded by newly formed mineralized tissue or encapsulated in connective tissue in two out of the six biopsies.[51] HA shows better results compared to

OFD (Kasaj *et al*.) and when used in combination with other regenerative materials [Table 1].

Tricalcium phosphate (TCP)

TCP is a bioceramic that is resorbed faster than synthetic HA, but is not as strong. It exists in alpha and beta crystal forms. β-TCP has been effectively used in dental procedures and as a component of bioresorbable screws since 1981. The material has value as a bone graft extender and mineral source. The graft particles are composed of a highly porous matrix with 100–300 μm pore size. Osteoconduction is facilitated by the porous nature of the particles, with bone growth said to occur within and throughout the porous matrix. The particles are eventually resorbed and replaced by host bone in 9–12 months [Table 2].

β-TCP particles are embedded in the connective tissue, whereas the formation of a mineralized bone-like or cementum-like tissue around the particles was only occasionally observed. Stavropoulos *et al*. concluded in their study that the present data indicates that treatment of intrabony periodontal defects with β-TCP may result in considerable clinical improvement in CAL gain and PD reduction, but β-TCP does not seem to enhance the regeneration of cementum, periodontal ligament and bone.[52]

Porous β-TCP may be used as a vehicle for the delivery of drugs or biological agents. Recently, an enhanced version of β-TCP containing recombinant platelet-derived growth factor (rhPDGF-BB) has been introduced. Conceptually, this product combines the benefits of an osteoconductive scaffold with a mitogenic growth factor, allowing for precisely tailored dosage and localized delivery of a compound with proven wound healing and periodontal regenerative benefits.[53]

In 2008, Ridhway conducted a histological study to evaluate rhPDGF-BB in combination with β-TCP for the treatment of human intraosseous periodontal defects. After 6 months of minimum healing, the tooth was removed en bloc. New bone, new cementum, and new periodontal ligament had regenerated coronal to the notch placed on the root surface. New cementum formed on dentin and on old cementum. Connective tissue arrangement occurred in both parallel and perpendicular arrangements with majority of fibers aligned parallel to the root surface. Variable amounts of β-TCP particles were seen with minimal inflammatory infiltrate. Minimal amounts of newly formed bone were observed in contact with β-TCP.[53] Nevins *et al*. (2005)[25] and Jayakumar *et al*.[27] conducted a study in which they used rhPDGF-BB/β-TCP and found that implantation in intraosseous periodontal defects was safe, well tolerated, and resulted in clinically and statistically significant improvement in bone formation parameters as well as soft tissue outcomes[27] [Table 1].

Examples: Bioresorb β-TCP, CeraSorb, Vitoss porous β-TCP ceramic, GEM-21S (porous β-TCP/rhPDGF-BB)

Biphasic calcium phosphate

HA and β-TCP may be combined in different ratios into a single product known as BCP. BCP is engineered to combine the advantages of both HA and β-TCP. Straumann bone ceramic (SBC), has 40% β-TCP and 60% HA (higher the ratio of TCP, greater the resorbability).[54] The rapid dissolution of TCP provides calcium and phosphate ions as well as space for bone formation, while the slower resorbing HA maintains the scaffold until sufficient bone ingrowth has occurred[10,48] [Table 2]. The open structure of BCP with interconnected macropores (>100 μm) promotes vascular infiltration, nutritional transport, and cell colonization, while a 3-dimensional, microporous architecture (<10 μm) creates a favorable environment for adsorption of macromolecules and cell attachment.

The replacement of TCP by bone does not occur in an equal manner. There is less bone volume produced than the volume of TCP resorbed.[47] Jensen *et al*.[10] compared the percentage of new bone formation by SBC with that of autogenous bone, HA, and β-TCP separately over a 24-week period. They found that SBC was better than HA alone, but formed less bone than β-TCP and autogenous bone [Table 1].

Examples: OsSatura BCP, SBC

Calcium phosphate cement

The lack of adaptability of calcium phosphate ceramics was resolved by Brown and Chow in 1985 when they developed CPC.

CPC formulations are classified with respect to their end products. Current CPCs can be divided into two categories: (i) apatitic and (ii) brushitic cements.

This cement is a mixture of calcium phosphate powders which, on reacting with an aqueous phase, produce new calcium phosphate compounds. The consistency of the cement progresses from paste-like to solid structure by

entanglement of the setting product. This enables the cement to be molded, to adapt to bone defect borders, and permits the development of injectable preparation for minimally invasive surgery. These cements are biocompatible, degradable, and osteoconductive,[54] and management of human intrabony defects with the use of CPC shows improved clinical outcome compared to OFD[55] [Table 1].

Because of their excellent biocompatibility and non-exothermic behavior, it is possible to incorporate organic molecules in these cements, making them potential vector materials for the therapeutic agent delivery.

In two studies, novel amorphous CPC (Biobon) was implanted in human patients for the first time. After 2–12 months, 10 biopsies were obtained during the second surgical procedure. In all specimens, partial replacement by new bone was observed, while residues of the cement were still visible. Under calcified sections extensive bone formation in immediate contact with the cement without fibrous interface was observed. Polynucleated cells and superficial lacunae were indicative of resorptive activity; inflammatory quotient was absent. The new bone displayed regular trabecular and osteonatal patterns.[56]

Calcium phosphate is osteoconductive and undergoes gradual remodeling over time, mainly through a cell-mediated surface process involving osteoclasts and osteoblasts. CPC resorbs over a period of 24 months [Table 2].

Example: Biobon

Bioactive glass

Bioactive glass was discovered by Dr. L. Hench in 1969. The initial evidence of direct bond between the product and bone was given by Hench *et al*. in 1972. The unique feature of bioglass that differentiates it from other bioceramic alloplastic materials is its bioactivity. A bioactive material is defined as a material that elicits a specific response at the interface of the material, which results in formation of a bond between the tissue and that material.[57] When bioactive ceramics are implanted, they undergo surface modification, upon exposure to interstitial fluids, the pH of the local environment increases and approaches 10. A silicon-rich layer is formed on the bioactive ceramic surface, and then on top of this, a calcium phosphate–rich layer is formed from the calcium and phosphorous of the bioactive ceramic and that of the body fluids. The calcium phosphate layer is an active hydroxyl CHAP layer that serves as the bonding surface and is chemically and structurally equivalent to the mineral composition of bone. This reaction layer develops within minutes/hours of implantation (Hench *et al*. 1990),[57] and then osteogenic cells and collagen fibers from the host surgical site colonize the surface of the bioactive ceramic particles (bioactivity), becoming incorporated into the silica gel layer and eventually producing bone[58,59] [Figure 3]. Bioacive glass (BG) was approved by US Food and Drug Administration (FDA) in 1996 for use as a bone graft.

In 2000, Nevins *et al*.[60] studied the healing of intrabony defects around five teeth grafted with BG. Healing was evaluated by clinical, radiographic measurements and histological analysis. After 6 months of surgery, there was 2.7 mm probing depth reduction and clinical attachment gain of 2.2 mm. Histological analysis showed one case healing by new cementum and new connective tissue formation and the rest of the cases healing by long junctional epithelium. Bone formation was limited to the most apical borders of the defect and the particles were found to be biocompatible with minimal

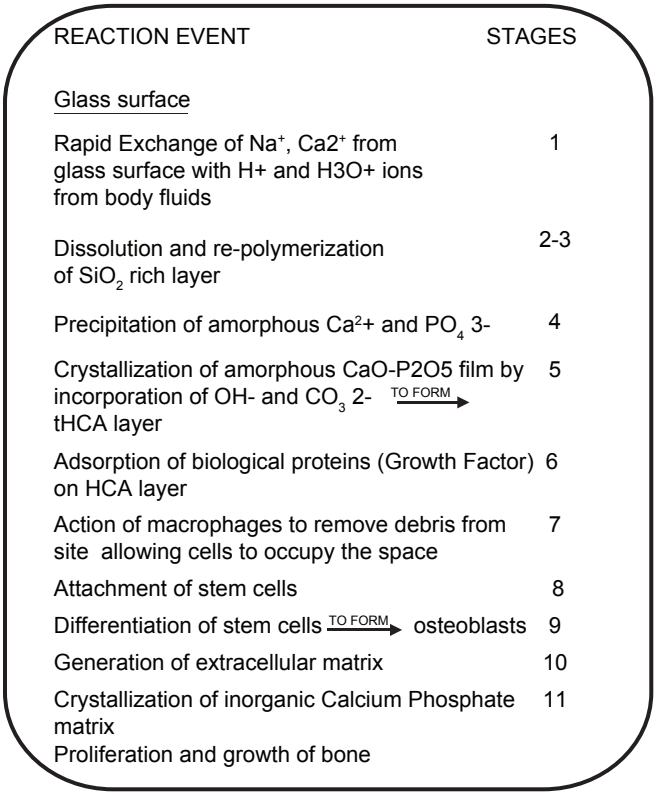

Figure 3: Sequence of reactions involved in forming a bond between bioactive glass and bone. There are 11 stages in the process of complete bonding of bioactive glass to bone. Stages 1–5 show the chemical response and stages 6–11 show the biological response between BG and bone.[58,59]

inflammatory infiltrate. The mechanism of action is through osteoconduction. Larger particles may take years [Table 2]. Bioactive glass has been used extensively in the treatment of periodontal defects.[48]

In 2012, Sohrabi *et al*. found in their meta-analysis that treatment of intrabony defects with BG imparts a significant improvement in both PD and CAL, compared to both active controls and OFD. When BG and Enamel matrix derivative (EMD) were clinically compared, it might be interpreted that BG is equally effective as EMDs in the treatment of intraosseous defects. Bioglass materials have been used extensively in periodontal regeneration with good results. The primary indication of these materials is for the repair of small, localized infrabony defects.

Examples**:** Perioglass, Novabon Putty, Biogran

FUTURE RESEARCH

Ion-substituted bioceramics

Ion substitution refers to the process wherein an ion within a substance is exchanged for another ion with the same (i.e. positive or negative) charge. Biomineralization combined with ion substitution is advantageous due to ion-substituted calcium phosphate coatings having a high similarity to the natural mineral of bone, which have beneficial effects on the anchoring of an implant to host tissue and bone regeneration.[61] There is increasing interest in developing biomaterials with carefully selected impurities to improve bioactivity. By substituting ions such as silicate, carbonate, magnesium, fluoride, and strontium, biomaterials with various compositions have emerged.

Silicon has been found in greatest concentration in immature bone. It has been proposed that silicon is involved in the initiation of calcification through an effect on the pre-osseous matrix.[62] Synthetic HA that includes trace levels of Si in its structure demonstrates markedly increased biological performance in comparison to HA.[63] The improvement in biological performance can be attributed to Si-induced changes in the material properties and also to the direct effects of Si on the physiological processes of the bone and connective tissue systems. Si substitution promotes biological activity by the transformation of the material surface to a biologically equivalent HA by increasing the solubility of the material, by generating a more electronegative surface, and by creating a finer microstructure. Release of Si complexes to the extracellular media and the presence of Si at the material surface may induce additional dose-dependent stimulatory effects on the cells of bone and cartilage tissue systems.[63]

Silicate-substituted calcium phosphate (Si-CaP) is a bioceramic in which phosphate ions have been substituted with silicate ions at a level of 0.8 wt%. Small amount of silicate seems to promote rapid apposition of immature bone, while 0.8 wt% is the optimal amount of silicate that enhances local bone bioactivity.[64]

Carbonate (CO_3^{2-}) is the most abundant (2–8 wt%) anionic substitute, and partially substitutes both in PO_4^{3-} site and OH^- site of calcium phosphate structure. The high reactivity of young bone could be related to the greater presence of carbonate compared with old bone. Carbonated calcium phosphate has shown improved solubility, increased collagen deposition and reabsorption compared with calcium phosphate.

Fluoride exists in bone and teeth of vertebrate bodies. It was reported that the substitution of fluoride for OH sites and formation of fluoride-substituted HA enhanced the acid resistance and the mechanical properties of HA bioceramics[65] and induced better biological response.[66] The superior acid resistance and the mechanical property make fluoride-substituted HA a beneficial coating on the dental implant.

Strontium is chemically and physically closely related to calcium. So, it is easily introduced as a natural substitute of calcium in HA. Strontium has been found to have the effects of increasing bone formation and reducing bone resorption, leading to a gain in bone mass and improved bone mechanical properties in normal animals and humans.[67]

Magnesium has been found in high concentrations in bone and cartilage tissue during the initial phases of osteogenesis, and causes the acceleration of the nucleation kinetics of HA and inhibits its crystallization process. In 2006, Landi *et al*. observed that Mg-substituted hydroxyapatite improved the behavior of cells in terms of adhesion, proliferation, and metabolic activity, as compared to HA.[68]

Zinc is a major trace element in bone, and has been found to play a major role in human tissue development. Zinc-substituted HA is a potential material where zinc inhibits bone resorption and has a stimulatory effect on bone formation. When zinc was substituted into the HA and TCP crystal lattices, it was found to inhibit osteoclasts and to promote bone growth.

Despite the beneficial results, the clinical applications of ion-substituted ceramics and cements are limited due to their low mechanical strength. By coating implants with ion-substituted HA, the higher mechanical strength of the metal can be combined with the properties of the ion-substituted HA. Therefore, the beneficial biological effects of the bioactive coatings makes them suitable to be applied with biomedical implants.[61]

CONCLUSIONS

Overall, specific biomaterials/biomimetics were found to be more effective than OFD in improving the attachment levels in intraosseous defects. Difference in CAL gain varied greatly with respect to different biomaterials/biomimetic agents. Due to a significant heterogeneity in results between studies in most treatment groups, general conclusions about the expected clinical benefit of graft biomaterials need to be interpreted with caution. Biomaterial-supplemented reconstructive procedures are associated with positive treatment as compared to OFD, but ceramics are used as void fillers or scaffolds and cannot be used in areas of high stress or function unless they are combined with an osteogenic or osteoinductive bone graft material.

The biological effects of the bioactive coatings makes them suitable to be applied with biomedical implants; fluoride and HA coatings are being used since a decade as implant coatings and research is ongoing for using other ions in ion-substituted ceramics. Research on stem cells and synthetic bone graft materials pertaining to regeneration is still in its infancy. A lot of research has been done on calcium phosphate ceramics and their action on stimulating bone re-growth by attracting stem cells and growth factors to promote healing and integration of grafted tissue. Soon scientists will be developing a material for bone grafts that could one day replace the "gold standard" natural bone implants.[69]

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