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Review

Combination of bone substitutes and vectors in periodontology and implantology: A systematic review

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The aim of the systematic review was to analyze the use of combination of bone substitutes and vectors in periodontology and implantology among animals models and humans. Electronic databases were searched, and additional hand search was performed. The research strategy was achieved according to the PRISMA guidelines. The including criteria were: combination of bone substitutes and vectors, *in vivo* studies, a precise number of specimens, histological and radiographic analysis, written in English. The risk of bias was evaluated for individual studies. Thirty-two articles were selected and investigated in this systematic review. The results do not show a superiority of the use of composite biomaterial in comparison with simple biomaterial but suggest the efficacity of their utilization as a carrier of bioactive agents. Future studies need to identify the suitable association of bone substitutes and vectors and explore interest in their use such as the support of growth factors.

Keywords: Combination of bone substitutes and vectors, Periodontology, Implantology, Pre-clinical study, Clinical study

INTRODUCTION

Bone grafts are used in periodontology for the treatment of intrabony and furcation defects; they are used in implantology for alveolar ridge preservation, guided bone regeneration (GBR), or sinus lift. An ideal graft material should be biocompatible, safe, non-allergenic, non-toxic, and have no risk of disease transmission. Ideally, it should provide a role of space-maintaining, and have similar resorption rate, composition and porosity to human bone[1,2]. This interconnected porosity should allow the ingrowth of blood vessels and the diffusion of bone cells and nutrients. Finally, it should have a controlled biodegradability to ensure a balance between resorption and volume maintenance during bone ingrowth and a dimensional stability to allow this adaptation in the defect[3]. Bone grafts promote bone formation under three concepts: osteoconduction (material acts like a scaffold), osteoinduction (material contains proteins which lead to proliferation and differentiation of bone cells), and osteogenesis (material containing stem cells)[4,5].

The current gold standard is still autologous graft (bone from the patient); it is the only bone graft that is osteoconductive, osteoinductive and osteogenic. This technique has several detriments, such as the necessity of a secondary operative site, which represents an augmented risk of supplementary comorbidities, or a low quantity of bone[6]. For these reasons, some alternatives have been developed. The first alternative to autologous bone is the use of allogenic graft: tissue from a human donor or cadaver. Three types of allografts exist: fresh frozen bone (FFB), freeze-dried bone allograft (FDBA), and demineralized freeze-dried bone allograft (DFDBA). The risk of transmission of bacteria, virus, or prion cannot be excluded for this type of bone substitute[7]. For these reasons, their uses are restricted, particularly in Europe[3]. The second option is xenografts: transplantation of bone tissue across species. In periodontology and implantology, deproteinized bovine bone is the most commonly used. Lastly, alloplastic bone substitutes have been developed in the form of synthetic hydroxyapatites (HA), beta-tricalcium phosphate (β-TCP), biphasic calcium phosphate (BCP), and bioglasses. HA is non-resorbable biomaterial with a low resorption rate and high space-maintaining potential contrary to β-TCP. BCP is composed of different ratios of HA and β-TCP to combine the advantages of these two families. Thus, this biomaterial can have different biodegradability and stability degrees according to the bone defect.

All of these bone substitutes are available in the form of granules or blocks, which can be difficult to manipulate and set up in some clinical situations. Therefore, combination of bone substitutes and vectors (composite biomaterials) have been elaborated; they are composed of two phases, granules of bone substitutes linked together by a vector. The vectors are polymer biomaterials, mainly represented by polyglycolic acid (PGA), hydrogel, or collagen[2].

Combination of bone substitutes and vectors are in the form of paste or injectable material. The goal of this galenic form is to allow an augmented usability for the clinician and a better stability in chirurgical sites; these materials can also be used as a support for stem cells or growth factors[8]. However, the addition of polymer between bone particles can change the property of the biomaterial and its capacities of bone neoformation.

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Nowadays, it is not yet possible to conclude at the superiority of a vector or an association vector-biomaterial. For this reason, the aims of this systematic review are to analyze relevant studies to retrieve valuable information about the interest in the use of combination of bone substitutes and vectors in periodontology and implantology and to evaluate different combinations of bone substitutes and vectors.

MATERIALS AND METHODS

The different studies concerning the use of combination of bone substitutes and vectors in periodontology and implantology on human or animal models have been collected and analyzed.

Question

Based on the PRISMA directives (Preferred Reporting Items For Systematic Reviews and Meta-Analyses)[9], a specific question has been developed with the PICO (Participant, Interventions, Control, Outcomes) method[10]: "Do combination of bone substitutes and vectors enhance clinical results in patients treated in periodontology and implantology?"

Information sources and search strategy

The search strategy was established according to the PRISMA guidelines. Original articles were searched using electronic databases (Medline and Cochrane Library), and relevant articles were screened by hand to potentially add relevant articles. A combination of Medical Subject Heading (MeSH) terms were used to identify appropriate studies: "combination of bone substitutes and vectors", "periodontology", "implantology", "pre-clinical study", "clinical study". Only English articles were included and no publication dates or publication status restriction were imposed.

Study selection and inclusion/exclusion criteria

Selection was based on the inclusion and exclusion criteria defined so as to include only the most valuable articles (Table 1).

The selection process was recorded in detail to a PRISMA 2009 flow diagram (Fig. 1).

Data collection process and data items

The following data were extracted from the included studies: 1) Biomaterial (+/− membrane); 2) Animal models: species, sex, age, weight; 3) Number of defects per group; 4) Defect type, size; 5) Treatment groups; 6) Observation period; 7) Qualification of newly formed bone; 8) Result (Tables 2 and 3).

Risk of bias in individual studies

To ascertain the risk of bias in eligible articles, their methodology was evaluated by SYRCLE's Risk of Bias tool for animal intervention studies[11], or by Risk Of Bias Non-randomized Studies of Interventions (ROBINS-I) tool[12], or by the Cochrane Collaboration's tool for human randomized trials[13].

Data synthesis

A meta-analysis was not performed; we conducted a descriptive and systematic analysis of the studies.

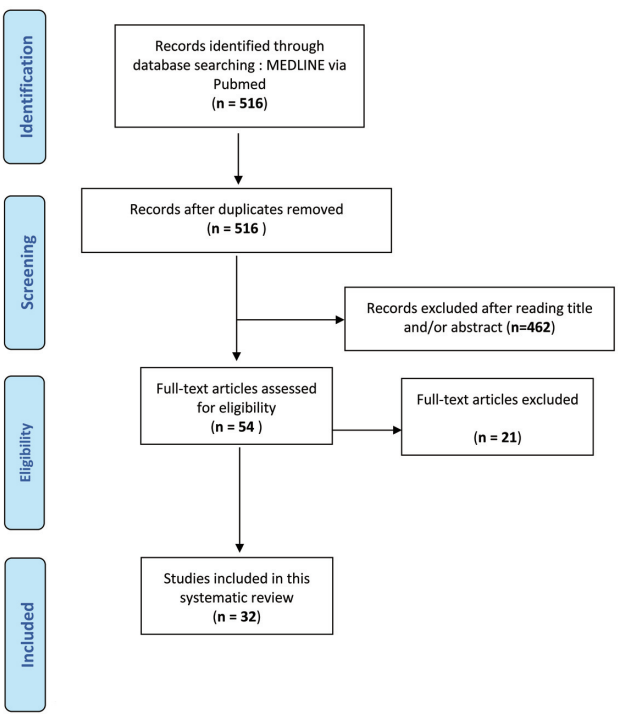

Fig. 1 PRISMA flowchart for identifying eligible studies.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Studies using combination of bones substitutes and vectors	*In vitro* studies
In vivo studies	Cases reports
Studies with the precise number of specimens	Retrospective studies
Studies with histological and/or radiographic analysis	Studies without control group
Studies written in English	Studies without statistical analysis
	Reviews

Table 2 Comparative table of pre-clinical animal studies in the use of combinations of bones substitutes and vectors

Reference	Biomaterial	Animal model, species, sex, age, weight	Numbers of defects per group	Defect type/size	Treatment groups	Observation period	Qualification of newly formed bone (NB)	Results
Okada *et al.* 2019[16]	β-TCP β-TCP+PGLA	Dogs, beagles Males 12 month-old 10 kg	6 per group	Buccal bone defect (maxillary first premolar) 4×4×5 mm	Test group: β-TCP+PGLA Control group: particulate β-TCP	12 weeks	Radiographic (micro-computed tomography) Histological Histomorphometric	Radiographic: bone volume (BV) at the test sites significantly greater than in control sites. No significant difference in bone material density (BMD). Histological and histomorphometric: Amount of connective tissue was significantly greater in the control sites. The proportions of mineralized bone area and bone marrow significantly greater at the test sites. No statistically significant intergroup differences in residual β-TCP. β-TCP + PGLA seems to be more effective than conventional β-TCP for ridge preservation.
Fukuba *et al.* 2019[18]	Gelatin/β-TCP sponges+rh-FGF (0.3%)	Dogs beagles Males 1 year old	6 per group	Saddle type bone defect 8×4 mm	a. acidic gelatin/β-TCP sponges+rh-FGF (0.3%) b. basic gelatin/β-TCP sponges+rh-FGF (0.3%)	12 weeks	Tomography analysis Histological	NB area significantly smaller in group a than in group b. NB height significantly lower in group b than in group a. Total tissue height not significantly different between the two groups.
Knabe *et al.* 2019[31]	- Si-CAOP - Si-TCP - TCP	Adults females Merino sheep 24 months	36 per group 6 per time point	Critical size defect in the left scapula (8×8 mm)	Empty defect (ED): negative control TCP: positive control Si-CAOP Si-TCP	Time points: - 2 weeks - 1 month - 3 months - 6 months - 12 months - 18 months	Histological Immunohistochemical Histomorphometric	At all the time points, defects grafted with Si-CAOP, Si-TCP or TCP exhibited a significantly higher bone area fraction than the ED. Defects grafted with Si-CAOP exhibited a significantly lower particle area fraction than defects grafted with Si-TCP and TCP. Si-CAOP displayed a better biodegradability and the greatest stimulatory effect on bone formation.
Ozawa *et al.* 2018[32]	Collagen sponge (ACS) Hydroxyapatite/ Collagen composite (HAP/Col)	Rats (F344/ Jcl) Males 10 weeks-old	10 per group	Circular grooves on each side of the cranium midsuture (5 mm ø)	a. ACS (control) b. HAP/Col	12 weeks (0, 4, 8 and 12 weeks for CT images)	Micro-computed analysis (CT) Histological	CT images: In collagen group, bone ingrowth started at 8 weeks. In HAP/Col it started at 4 weeks. At 12 weeks, the whole cap area was filled with NB. Histological: Number of osteoclasts and osteoblasts were not significantly different. CT analysis: NB area significantly wider in group b than in group a. These results suggested that application of HAP/Col increased the outgrowth of NB much more prominently than did collagen.

Table 2 continued

Leventis *et al.* 2018[14]	β-TCP+polylactic-co-glycolic acid (PGLA)+Biolinker® (N-methyl-2-pyrrolidone solution)	Landrace pigs Females 4 months-old 18 kg	Experi-mental sites : *n*=10 Control sites : *n*=4	Fresh extraction socket (ridge preservation)	Experimental group: β-TCP granules coated with PGLA mixed with Biolinker Control group: spontaneous healing	12 weeks	Histological Histomorphometric	Experimental sites showed less mean horizontal dimensional reduction of the alveolar bridge but not statistically significant. More NB in experimental group. No statistically difference regarding osteogenesis was demonstrated between the two groups.
Naenni *et al.* 2018[15]	β-TCP+PGLA	Dogs, beagles Males >1 year old 10–20 kg	Test 1: *n*=22 Test 2: *n*=22 Control: *n*=18	Fresh extraction socket (ridge preservation)	Test group 1: β-TCP+PGLA+ collagen membrane Test group 2: β-TCP+collagen membrane Control group: blood clot	4, 8 and 16 weeks T1 : pre-extraction T2 : post operation T3 : sacrifice	Dental impressions Lineal and volumetric analysis	Volumetric measurements: Buccal: T1-T3 and T1-T2: no significant statistical difference between test 1 and 2. The volume decreased was significantly lower in test 1 than in control group. Occlusal: T1-T3 and T1-T2 no statistically difference between test 1 and 2 but between test 1 and control group. Linear measurements: T1-T3: no difference between test 1 and 2 but between test 1 and control. T1-T2: the higher gain found for test 1 was not significant compared to test 2 but compared to control. Majority of volume decreased is loss the firsts weeks post-extraction. Ridge preservation procedures minimized the volume loss.
Kim *et al.* 2017[33]	Bio-Oss Collagen®	Dogs, beagles 1 to 2 years old 10 kg	6 per group	Combined endodontic-periodontic lesion	Control: no treatment Test 1: Bio-Oss Collagen graft Test 2: Bio-Oss Collagen graft+ collagen membrane	7 months	Micro-CT Histological	Vertical distance between buccal and lingual crest: no significant difference between C and T1; and between T1 and T2. Distance significantly smaller in T2 than in C. The amount of mineralized bone was significantly lower in T1 group than in C group. No difference between T1 and T2; C and T2. When grafts were used in the socket, quantity of mineralized bone tented to be less.
Benic *et al.* 2017[34]	- Porcine collagenated bone substitute block (PCBB) - Collagen membrane (CM) loaded with bone morphgenetic protein 2 (BMP2)	Dogs, beagles Males 12±3 months 8 kg	6 per group	Two surgeries: Box-shaped bone defects on extraction sites (8×4×5 mm) (1) and implant placement (2)	Block Block+CM Block-BMP2 (0.5 mg/mL; 0.2 mL) Block+CM-BMP2 (0.5 mg/mL; 0.2 mL)	20 weeks	Histological Histomorphometric	Augmented area (AA): statistically significant difference between block-BMP2 (11.8±2.9 mm^2) and block+CM-BMP2 (8.5±2.2 mm^2) New mineralized bone (NB): no statistically significant differences. Residual bone substitute (BS): only the difference between Block-BMP2 (6.1±2.2 mm^2) and Block=CM (3.4±1 mm^2) was significant. The addition of BMP2 to PCBB or CM did not render statistically significant improvement of their performance for horizontal ridge augmentation.

Table 2 continued

Joo *et al.* 2017[35]	- CBCP - CBCP loaded with rhBMP2	Males New Zealand whites rabbits 2.5–3.0 kg	5 per group	Sinus augmentation and implant placement	Control: CBCP soaked with saline Test: CBCP loaded with rhBMP-2	4 weeks	Micro-CT Histological Histomorphometric	MicroCT: The amount of newly formed bone on the apex of the implant was greater in the BMP group than in control group. The median augmented volume significantly greater in the test group. Histological and Histomorphometric: Highest point of osseointegration at the medial surface of the implant and the augmented heigh significantly greater in BMP group. Areas measurements did not differed between control and test groups.
Thoma *et al.* 2017[36]	HA/β-TCP granules Polyethylene glycol hydrogel (PEG) Arginylglycylaspartic acid (RGD)	Dogs, beagles 18 months 15 kg	6 per group	Standardized box-shaped defects (4×2×4 mm) on implant site	PEG. Synthetic bone substitute+PEG PEG-RGD. Synthetic particulate bone substitute+ PEG+RGD CM. synthetic bone substitute covered with collagen membrane Control. empty	8 weeks (n=6) And 16 weeks (n=6)	Micro-CT Histomorphometric	Percentage of regenerated area within total defect area: The treatment effects were not statistically different at 8 weeks, and significant at 16 weeks. New bone formation: Statistically significantly less bone formation was observed in group empty compared with all others group. NB formation significantly greater in CM group than in PEG. First bone-to-implant contact: Group CM statistically significantly superior to all other groups at 8 weeks. PEG and CM were statistically significantly superior compared to empty controls. Micro-CT analysis: 2 mm bellow the implant shoulder : PEG significantly higher values compared to empty and CM. PEG-RGD superior compared to empty 4 mm bellow the implant shoulder: no difference.
Hoshi *et al.* 2016[17]	Biodegradable gelatin sponges incorporating β-TCP	Dogs beagles Males 1 year old	6 per group	Saddle-type bone defect (5×10 mm)	a. Experimental group: gelatin/ β-TCP sponges+ rhFGF-2 (0.3%) b. Control group: gelatin/β-TCP sponges	8 weeks	Micro-computed tomography Histological Histomorphometric	Group a: evident large amount of NB formation continuous with host bone. Group b: NB formation limited. Total tissue height grater in group a than in group b. No statistical significant difference. Residual defect significantly smaller in group a than in group b.
Lee *et al.* 2015[23]	Autogenous bone Synthetic Bone Substitute (SBS=70% HA+30% βTCP)+Collagen Collagen membrane	Dogs, Mongrel Males 12–15 months 30 kg	5 per group (one dog excluded)	Buccal dehiscence on implant site (3 mm)	a. SBC alone (control group) b. Inner autogenous bone; outer SBC (IAB) c. Inner SBC; outer autogenous bone (OAB)	12 weeks	Radiographic Histological Histomorphometric	Radiographic analysis: total augmented volume did not differ significantly between IAB and OAB groups but was significantly lower in SBC group. Histological and histomorphometric analysis: Residual bone material and NB significantly greater in groups b and c than in group a. Median bone-to-implant contact significantly higher in group c than in group a. Median mineralized tissue area not significantly different between the three groups.

Table 2 continued

Yoshida *et al.* 2015[37]	β-TCP scaffold PLGA/β-TCP scaffold β-TCP and PLGA/ β-TCP scaffolds loaded with Fibroblast Growth Factor-2 (FGF2)	Wistar Rats		Decortication (4 mm^2) in the cranial bone	a. Control (no implantation) b. β-TCP scaffold c. β-TCP/PLGA scaffold d. β-TCP scaffold loaded with FGF-2 e. PLGA/β-TCP scaffold loaded with FGF-2	10 and 35 days	Histological Histomorphometric	10 days post-surgery: Tissue ingrowth limited to the periphery of the scaffold in groups b and c. Groups d and e : active bone formation. FGF-2 coating stimulated woven trabecular bone formation. 35 days post-surgery: PLGA- β-TCP scaffold was more effective in bone formation than uncoated scaffold. Bone formation in group e was six-fold greater that than in the control group. The open cell structure of the scaffold was adequately maintained and occupied with ingrowth tissue.
Kim *et al.* 2015[38]	- CBCP - BMP-2-loaded CBCP	Males New Zealand white rabbits 2.5-3.0 kg	4 per group One rabbit excluded in 4wBMP group.	Sinus augmentation	2wBMP 4wBMP 2wCTL 4wCTL	2 weeks (n=8) 4 weeks (n=8)	Radiographic Histological Histomorphometric	Radiographic analysis: Total augmented volume (TAV) larger in the BMP group than in CTL group both at 2 and 4 weeks. Newly formed bone (NBV) larger in BMP than in CTL at 4 weeks. No significant difference at 2 weeks. NBV and %NBV was greater in 4wBMP than in 2wBMP. Nonmineralized tissue (NMV) larger in BMP than in CTL at 2 and 4 weeks; it decrease significantly with healing in all groups. Histometric analysis: At 2 and 4 weeks : TAA and NBA larger in BMP groups than in CTL groups. NBA larger in 4wBMP group than in 2wBMP group. NMA larger in 2wBMP group than in 4wBMP group. Addition of BMP-2 to CBCP resulted in a greater initial augmented volume.
Cha *et al* 2014[39]	Bovine hydroxyapatite/ Collagen (BHC)+BMP-2	Mongrel dogs 12 months 30 kg	4 per group	Sinus elevation	a. BHC with normal saline (control) b. BHC+BMP2 0.1 mg/mL c. BHC+BMP2 0.5 mg/mL d. BHC+BMP2 1.5 mg/mL	20 weeks	Radiographic analysis Histological Histomorphometric	Radiographic: differences not statistically significant. Histomorphometric: - area and % NB significantly larger in BMP2 groups than in control group. - bone formation significantly larger in BMP2 groups - differences between BMP2 groups not significant.
Struillou *et al.* 2013[21]	- BCP - Composite hydrogel/ BCP (MBCP) - Si-HPMC	Dogs beagles 48±2 months 16±1 kg	6 per group	Dehiscence type base defects on implant site	a. no treatment b. BCP c. BCP+hydrogel d. BCP+membrane of GBR	12 weeks	Histological Histomorphometric	Significant increase in bone ingrowth values in group c and d compared with control group (a). Results no significantly different in b compared with a and between all groups with biomaterial.

Table 2 continued

Kim *et al.* 2012[22]	- BCP blocks - BCP-Collagen blocks - rh-BMP2	Adults New-Zealand white rabbits 3.0–3.5 kg	16 per group	Circular graft areas in the calvarium	a. BCP b. BCP-Collagen c. BCP/rh-BMP2 d. BCP-Collagen/rh-BMP2	8 weeks	Micro-CT Histological Histomorphometric	rhBMP-2 release assay: no statistically significant difference between BCP and BCP-Collagen blocks. The area of NB was significantly greater in the BMP-2-treated groups than in nontreated groups and greater in the BCP/rhBMP-2 group than in BCP-Collagen/BMP-2 group. Bone density was higher in group d than in group c. The degree of integration was highest in the BCP-Collagen/BMP-2 group.
Struillou *et al.* 2011[20]	Injectable composite silanized hydroxypropyl methylcellulose/BCP (Si-HPMC/BCP)	Dogs beagles 6–8 years old	Test: 4 canines+7 furcations Control: 4 canines+8 furcations	Maxillary Canines: buccal fenestration, 6mm diameter Premolars: furcation defect 6x3mm	Test: Si-HPMC/BCP Control: spontaneous healing	12 weeks	Histological Histomorphometric	Bone ingrowth more important in test group than in control group. Difference not significant. Adjunction of hydrogel did not affect new bone formation.
Hasturk *et al.* 2014[40]	Polymethylmethacrylate Polyhydroxyethylmethacrylate, and Calcium Hydroxide (PPCH) Polyanhydride (PA)	Adults minipigs 18 to 24 months old 35 kg	PPCH-PA: 16 PPCH: 16 PA: 8 No graft: 8	Immediately loaded implants placed in fresh extraction socket	a. PPCH-PA b. (positive control) PPCH c. (positive control) PA d. (negative control) no graft	12 weeks	Clinical and macroscopic Histological (SEM) EDX spectroscopy	Probing depth: no significant difference. Radiographs: no significant radiolucency along the implant. Electric mobility test device (STV): no significant difference between the groups. Only maxillary implants analyzed : STV of PPCH-PA group significantly better. No difference in the mandibule. Biomechanical testing: no statistical difference. NB well organized in the group a. Groups b and c : sites rich in marrow spaces. Group a: fewest microfissures between the implant and bone and the fewest fractures in the interface after pullout test. Group b and c: 10 µm of microfissures. Group d (control): 20 µm of microfissures.
Sato *et al.* 2009[41]	CPC : powder composed of a-tricalcium-phosphate, monocalcium phosphate monohydrate, calcium carbonate+solution of sodium phosphate	Dogs, beagles 1 year-old	6 per group	Second and third maxilla incisors extracted+ defect 7×6 mm created.	a. (experimental group): CPC b. (control group): spontaneous healing	6 months	Histological Histometrical	Clinical observation: In the CPC group, alveolar ridge enhanced compared with control group. Histological observations: NB which was in continuous with the host bone was larger in group a than in group b. No significant difference in the width of defect in both groups. Height of NB was significantlky greater in CPC group than in control group.
Barboza *et al.* 2002[28]	- Anorganic Bovine Derived Bone Matrix (ABM) - Cell binding peptide (P15) - Bioabsorbable membrane	Mongrel dogs Adults, males	Test 1: *n*=5 Test 2: *n*=5 Control: *n*=2	Class III alveolar defects and ridge augmentation	Test group 1: ABM/P15+membrane Test group 2: ABM/P15 Control group: empty	12 weeks	Clinical Histological	The total amount of bone volume showed no statistically significant augmentation in control group. In test groups 1 and 2: relevant ridge augmentation was observed. Significant bone formation was histologically observed in all test areas. The association of a membrane seemed to enhance the process of bone formation.

Table 3 Comparative table of human studies in the use of combinations of bone substitutes and vectors

Reference	Biomaterial	Animal model, sex, age, weight	Number of defects per group	Defect type/size	Treatment groups	Observation period	Qualification of newly formed bone (NB)	Results
Hala *et al.* 2019[26]	- Autogenous Bone (ABG) - ABG/Melatonin	HUMAN Female, Male 38.77±4.28 years old	26 per group	Immediate implants augmented	Control group: ABG Test group: ABG/ Melatonin	9 months	Radiographic (CBCT)	Statistically significant benefit for Test group in comparison with Control group in bone density and marginal bone loss at 6 and 9 months.
Llanos *et al.* 2019[42]	- Deproteinized bovine bone mineral (DBBM) - DBBM with 10% collagen - Collagen matrix (CM)	HUMAN Female, Male 41.9±11.9 years old	DBBM : *n*=33 DBBM-C : *n*=32	Ridge preservation and implant placement	Control group: DBBM-C+CM Test group: DBBM+CM	4 months	Radiographic (CBCT)	No significant difference between the groups. The DBBM demonstrated non inferiority to the DBBM-C group.
Lim *et al.* 2019[43]	- DBBM- C - Collagen membrane	HUMAN Female, Male 54.36±9.91 years old	Test 1 group : *n*=11 Test 2 group : *n*=10 Control : *n*=8	Alveolar Ridge Preservation and implant placement	Test group 1: DBBM-C+collagen membrane Test group 2: DBBM-C Control group: without alveolar ridge preservation (ARP)	4 months	Radiographic (CBCT) Histomorphometric	CBCT Analysis: Horizontal changes values did not differ significantly between Test 1 and Test 2. Changes were greater in the control group compared with test 1 but not with test 2. Histomorphometric: The percentage of NB not differ significantly between the groups.
Ozawa *et al.* 2018[32]	Collagen sponge (ACS) Hydroxyapatite/ Collagen composite (HAP/Col)	Rats (F344/ Jcl) Males 10 weeks-old	10 per group	Circular grooves on each side of the cranium midsuture (5 mm ø)	a. ACS (control) b. HAP/Col	12 weeks (0, 4, 8 and 12 weeks for CT images)	Micro-computed analysis (CT) Histological	CT images: In collagen group, bone ingrowth started at 8 weeks. In HAP/Col it started at 4 weeks. At 12 weeks, the whole cap area was filled with NB. Histological: Number of osteoclasts and osteoblasts were not significantly different. CT analysis: NB area significantly wider in group b than in group a. This results suggested that application of HAP/Col increased the outgrowth of NB much more prominently than did collagen.
Lim *et al.* 2017[44]	- Porcine Bone/ Cross-linked collagen - Bovine Bone/ Non-Cross-linked collagen	HUMAN Female, Male 53.83±16.22 years old	Test group: *n*=12 Control group: *n*=14	Ridge preservation	a) Test group: collagenated porcine bone b) Control group: collagenated bovine bone	4 months	Radiographic (CBCT)	The radiologic evaluation revealed the non inferiority of the test material compared to the control material.

Table 3 continued

Nart *et al.* 2017[45]	- DBBM - DBBM-C - Collagen membrane	HUMAN Female, Male 56.76 years old	DBBM: *n*=11 DBBM-C: *n*=11	Alveolar ridge preservation	Control group: DBBM+collagen membrane Test group: DBBM-C+collagen membrane	5 months	Radiographic (CBCT) Histological and histomorphometric	CBCT analysis: Height and width decreased significantly at 5 months of healing in both groups. No significant difference between the 2 groups. Histomorphometric analysis: No statistically difference were observed between groups.
Serrano Mendez *et al.* 2017[46]	- Deproteinized cancellous bovine bone xenograft embedded in a 10% collagen matrix (DBBM-C) - Demineralized freeze-dried cortical bone allograft (DFDBA) - Collagen membrane (CM)	HUMAN Female, Male 44 years old	10 per group	Alveolar ridge preservation	DBBM-C+CM (control) DFDBA+CM	6 months	Radiographic (CBCT) Histomorphometric	No statistically significant difference between the two groups. The both grafting material are suitable for the preservation of the alveolar ridge.
Scheyer *et al.* 2016[47]	- Demineralized allograft plus reconstituted (DFDBA) - Deproteinized bovine bone mineral+collagen (DBBM-C) - Crosslinked collagen membrane (RECXC) - Bilayer collagen membrane (NBCM)	HUMAN Female, Male	Control group : *n*=21 Test group : *n*=19	Alveolar ridge preservation	Control group: DFBDA+RECXC Test group: DBBM-C+NBCM	6 months	Clinical observations Histomorphometric	Horizontal changes: significantly more bony width in test group. Vertical changes: no significant difference. Histomorphometric: Percentage of NB formed was not significantly different between the two groups.
Stavropoulos *et al.* 2011[19]	- rhGDF-5/β-TCP - β-TCP/autologous bone (AB) composite	HUMAN Female, Male 53.8±12.1 years old	10 per group	Unilateral sinus augmentation and implant placement	a) rhGDF-5/ β-TCP (3 month of healing) b) rhGDF-5/ β-TCP (4 month of healing) c) β-TCP/AB (4 month of healing)	3 months 4 months	Histological Histomorphometric	No statistically significant difference between the groups regarding any of the evaluated parameters.

Table 3 continued

	- Deproteinized-bovine-bone mineral - Deproteinized-bovine-bone mineral coated with synthetic oligopeptide - Collagen membrane	Control group: n=23 Test group: n=21						
Nam *et al.* 2011[48]		HUMAN Female, Male	Alveolar ridge preservation	Control group: DBBM Test group: CBM-peptide coated DBBM	6 months	Radiographic (CBCT) Histological	Horizontal and vertical ridge changes: no statistically significant differences between control and test groups. Histological and histomorphometric analysis: Histologic analyses revealed than the test group showed a higher tendency for NB formation. No statistically significant difference.	
	- Bioabsorbable collagen wound material - Anorganic bovine-derived hydroxyapatite matrix combined with a synthetic cell-binding peptide P-15 (Putty P15)	HUMAN Female, Male 48.00±14.89 years old (test group) 49.92±14.20 years old (control group)	Test group: n=17 Control group: n=15	Alveolar ridge preservation and implant placement	Control group: Bioabsorbable collagen wound material Test group: Putty P15+bioabsorbable collagen wound material	4 months	Clinical Radiographic (CBCT) Histomorphometric	Alveolar ridge width: no statistically significant difference. Alveolar ridge height: The control group showed a mean reduction in ridge height, it appeared to remain unchanged in test group. Bone density: Mean bone density was significantly superior in the test group compared to the control group. Residual socket: Test group showed less residual socket than control group (statistically significant difference) Implant primary stability: Statistically significant difference (benefit for the test group)	
Neiva *et al.* 2008[27]								

RESULTS

Study selection

The MEDLINE literature search resulted in 516 potentially relevant articles. After the first selection step, based on the title and/or the abstract, 54 publications were included for further analysis. Based upon the full-text screening, 33 articles were included in the systematic review.

Study characteristics

The studies were ranked in a comparative table (Tables 2 and 3). The tables show a large variety of biomaterials. The review began with an analysis of the type of population, predominantly of animal species in pre-clinical studies. The majority of experimental models are dogs, used in 13 studies. The other pre-clinical studies were performed with pigs (2 studies), sheep (1 study), rabbits (3 studies), and rats (3 studies). Only 11 studies were performed with humans. A wide variety of periodontal or peri-implant defects were used in the selected studies: furcation defect (2 studies), fenestration or box-shaped defect (7 studies), alveolar ridge preservation +/− implant placement (11 studies), sinus augmentation +/− implant placement (3 studies), implant placement (3 studies), combined endodontic-periodontal lesion (1 study), scapula defect (1 study), and cranial bone defect (4 studies). The majority of pre-clinical studies used intrabony defect in contrast with clinical studies, which employed mainly alveolar ridge preservation (in 8/10 studies) and no periodontal defect.

Then, the studies were analyzed according to the type of biomaterial used. A very wide array of bone substitutes (auto-, xeno- and allografts) and vectors were employed: alloplastic materials β-TCP (7 studies) and BCP (5 studies) were the most used materials in pre-clinical studies; bovine bone matrix (DBM) and deproteinized bovine bone matrix (DBBM) (6 studies) and demineralized freeze-dried bone allograft (DFDBA) (3 studies) were mainly employed in clinical trials. Autogenous bone (2 studies), bovine hydroxyapatite or Bio-Oss (3 studies), porcine bone (2 studies), PPCH (1 study), CPC (1 study), and anorganic bone-derived matrix (1 study) were also used in the selected studies.

The vectors used in the different combination of bone substitutes and vectors was mainly collagen (6 studies), PGLA (4 studies), hydrogel (2 studies), and gelatin sponges (2 studies); melatonin, synthetic oligopeptide, P15, Si-HPMC, poly-anhydride (PA) and arginyglycylaspatic acid (RGD) were also used. Six pre-clinical studies employed growth factors in combination of bone substitutes and vectors: BMP-2 (2 studies), rh-BMP2 (2 studies), FGF2 (1 study), and rh-FGF (1 study).

Risk of bias within studies

The results of the risk of bias assessment are viewable in Fig. 2. The adapted methodology was applied for each subgroup of studies: pre-clinical animal studies (Fig. 2.a), non-randomized human trials (Fig. 2.b), and

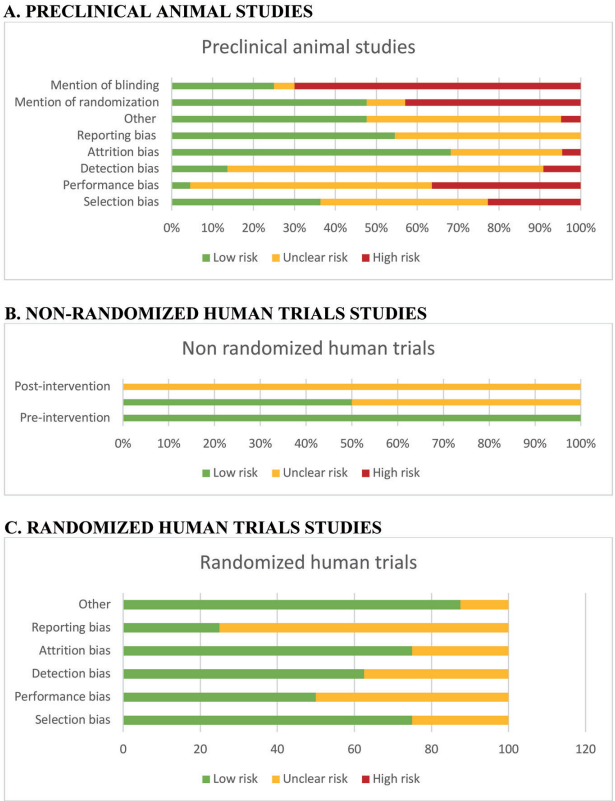

Fig. 2 Risk of bias assessment of included studies. A. Risk of bias graph for animal studies, using the SYRCLE's tool, averaged per item. B. Risk of bias graph for non-randomized human trials, using the ROBINS-I tool, averaged per item. C. Risk of bias graph for randomized human trials, using the Cochrane Collaboration's tool, averaged per item. The green, yellow and red colors depict the percentages of studies with low, unclear or high risk of bias of the total number of assessed studies.

randomized human trials (Fig. 2.c).

1. Pre-clinical studies
Only 45% and 23% of the studies mention randomization or blinding, respectively. Our data show a high score of unclear risk of bias for the performance and detection items (59% and 77%, respectively). The majority of the studies were free from selective outcome reporting (54%).

2. Non-randomized human trials
Only two studies were included in this category. Our results show that 100% of the studies were free from pre-intervention bias, and 50% were marked for unclear risk of bias for at-intervention items and 100% for post-intervention items.

3. Randomized human trials
As expected, our results did not show a high risk of bias. Regarding selection and attrition items, 75% of the studies were free from risk of bias. Our data show that 50% and 37.5% of performance and detection items, respectively, show an unclear risk of bias. Finally, 75% of the included studies were marked for an unclear risk of bias for their reporting.

Synthesis of results
For each selected study, the significant results are shown in Table 2 for pre-clinical animal models and Table 3 for human studies.

DISCUSSION

Literature searches retrieved 32 studies. After a careful analysis, our results revealed that it was not possible to perform direct head-to-head comparisons of these studies as a result of variations between studies, in terms of bone substitute, polymer vectors, the defect type and size, and the healing time. Not surprisingly, no meta-analysis of the data could be carried out.

The majority of the selected articles in this systematic review are pre-clinical animal studies (22/32 studies) with a larger panel of biomaterials and type defects tested than in clinical studies. Indeed, the selected human studies employed biomaterials exclusively in alveolar ridge preservation and sinus augmentation; none of the studies were about intrabony periodontal defect. Consequently, the use of combination of bone substitutes and vectors in periodontal defects is based only on pre-clinical studies that have a lot of risk of bias, with randomization and blinding infrequently described. This failure makes it difficult to draw conclusions from pre-clinical studies. Nevertheless, the combined analysis of the different included studies affords the retrieval of valuable information.

The combination of bone substitutes and vectors are composed of granules bound together by vectors, which can be coated with growth factors. This discussion focuses on the different combinations used in pre-clinical and clinical studies and the utilization of growth factors.

The most used bone substitute in pre-clinical studies was β-TCP, mainly in combination with PGLA, a scaffold commonly used for tissue repair. Two studies (Leventis *et al.*[14] and Naenni *et al.*[15] did not show relevant results for the use of β-TCP/PLGA combination. Okada *et al.*[16] showed that β-TCP/PLGA seems to be more effective than conventional β-TCP for alveolar ridge preservation. The results show that this injected and moldable biomaterial maintains its shape, secures the regenerative space and enlarges the osteoconductive area.

Two studies used β-TCP in gelatin sponges incorporating growth factors (rh-FGF). Hoshi *et al.*[17] showed that the combined use of rh-FGF and gelatin sponge/β-TCP is effective for alveolar ridge augmentation. Fukuba *et al.*[18] concluded that the controlled release of rh-FGF in time induces notably more alveolar bone regeneration than short-term application of this growth factor. Here, the use of a combination of bone substitutes and vectors seemed to be essential to control

the propagation of the growth factor and optimize the bone regeneration.

Only one clinical randomized trial tested β-TCP/autogenous combination and rhGDF-5 coated β-TCP[19] and concluded in the absence of significant difference.

The relevant results obtained in animal studies with β-TCP and polymer suggest that these combinations should be tested in clinical study in human models to attest their effectiveness.

BCP is used in five animal studies combined with Si-HPMC, hydrogel and collagen. Two studies of Struillou *et al.*[20,21] tested BCP with hydrogel in intrabony defects and peri-implant defects. They showed that hydrogel/BCP can promote new bone formation in large defect and implant sites, the viscosity of hydrogel, allowing for increased retention capacity and mechanical strength. Three studies employed BCP in combination with collagen (CBCP) loaded with growth factor BMP2 (bone morphogenic protein) and rh-BMP2 (recombinant human bone morphogenic protein). Two of these studies[22,23] concluded that the combination of BCP/Collagen and BMP2 was favorable for the new bone formation. It is supposed that the addition of BMP2 induced post-operative swelling at the origin of an early bone formation.

The use of BMP-2 in combination with biomaterial to promote bone regeneration has been studied in numerous pre-clinical and clinical studies[24]. This growth factor has the highest evidence of a positive effect on bone formation in comparison with other agents. However, plenty of growth factors act on the bone-healing process[25], which suggests that only one factor in a biomaterial may be insufficient to stimulate the regeneration. Future studies might be directed toward the combination of factors and the use of combination of bone substitutes and vectors like a delivery system for these bioactive agents.

Mainly randomized clinical trials were realized with DBBM or DFDBA in combination with collagen (5 studies), and one non-randomized clinical trial used synthetic oligopeptide as a vector. All these studies concluded that DBBM-Collagen is effective in the alveolar ridge preservation procedure, but no significant differences were observed with the control group.

One randomized clinical trial[26] employed autogenous bone (AB) in combination with melatonin in immediate implant placement. The result showed a significant benefit for AB/melatonin, and the author suggested that the addition of melatonin has a positive role in new bone formation around the implant and could protect and recover the gingival tissue integrity. However, only radiological analysis was performed in this study; further clinical trials with histological and histomorphometric analysis will be necessary to attest the efficacity of AB/melatonin combination in new bone formation.

One non-randomized study[27] in a human model used anorganic bovine-derived HA combined with putty P15. Cell-binding peptide was also used in one pre-clinical study[28]. The good results suggested that HA/P15 has greater compatibility with host bone than HA alone for alveolar ridge preservation.

None of the selected clinical trials studied combination of bone substitutes and vectors in periodontal defects in contrast with pre-clinical studies. Some relevant results in the use of these bone substitutes in periodontal bony defect in animal models suggested the necessity to realize these studies in human models. Particularly for the use of combination of bone substitutes and vectors as growth factors vectors, this could be interesting to promote periodontal regeneration. Indeed, a plethora of publications brings to light the valuable role of growth factors and stem cells in the bone healing process[29,24,25] and the necessity of developing sophisticated delivery systems to lead them in the defect. In that way, combination of bone substitutes and vectors may be valuable. Indeed, some studies included in this systematic review suggest this, but additional research is necessary to develop an optimal biomaterial able to support specific molecules to promote bone and periodontal system regeneration in specific clinical situations[30].

CONCLUSION

Several combinations of bone substitutes and vectors are studied with various clinical applications. The corresponding studies have heterogenous results concerning their applications in periodontology and implantology. For these reasons, a systematic approach appears essential to serve as a guide for future studies and provide data that can be generalized. The results of our systematic review indicate that combination of bone substitutes and vectors do not enhance clinical results in comparison with classical bone substitutes, but they may provide beneficial effects in combination with growth factors. The present review supports important information for the evolution of research concerning the use of growth factor in bone graft for periodontal regeneration and implantology in the future. Future studies should focus on the use of combination of bone substitutes and vectors as stem cells and bioactive molecules carrier and explore their use in complex periodontal defects to find a combination more effective than simple bone substitute.

CONFLICT OF INTEREST

None.

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