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Les biomatériaux composites de comblement osseux en Parodontologie et en Implantologie : revue systématique de la littérature

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EN CHIRURGIE DENTAIRE

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Table des matières

Introduction

Les biomatériaux de comblement osseux sont utilisés en parodontologie dans le traitement des défauts intra-osseux et des lésions inter-radiculaires de classe II ainsi qu'en implantologie lors de préservation alvéolaire pré-implantaire, de sinus lift ou de régénération osseuse guidée. Ils ont pour objectifs de stimuler la formation osseuse par croissance de l'os alvéolaire et de permettre la cicatrisation osseuse. Leur utilisation est basée sur l'existence d'un potentiel de néoformation osseuse au sein même des défauts et sur l'impossibilité d'obtenir une régénération totale sans utilisation d'un biomatériau permettant une migration des ostéoblastes à l'intérieur du caillot sanguin dans les défauts de taille critique (1) (2). Les biomatériaux de comblement osseux se doivent d'être sûrs, biocompatibles, non allergiques, non toxiques et ne doivent pas présenter de risque de transmission d'agents pathogènes. Ils ont pour objectifs de maintenir l'espace au sein du défaut pendant toutes les étapes de la cicatrisation (inflammation, prolifération, apposition et remodelage osseux), ils doivent avoir une vitesse de résorption compatible avec cette cicatrisation et leur composition, la taille de leurs particules, l'espace inter-particulaire ainsi que leur porosité doivent être proches de celle de l'os humain afin de permettre leur colonisation vasculaire, leur résorption et leur remplacement par de l'os néoformé. (3) Ils agissent sur la régénération osseuse selon trois principes : premièrement l'ostéogénèse correspond au processus de formation osseuse grâce à la présence de cellules ostéoprogénitrices au sein de la greffe; deuxièmement l'ostéoconduction est un processus de stimulation de la néoformation osseuse par des protéines conduisant à la prolifération et/ou la différenciation de cellules souches en matrice minéralisable; enfin l'ostéoconduction correspond à la propriété passive du biomatériau à recevoir la repousse osseuse par invasion vasculaire et cellulaire à partir du tissu receveur au contact de ce matériau (4).

Les greffes osseuses peuvent être classées selon plusieurs catégories: l'autogreffe, l'allogreffe, la xénogreffe et les matériaux alloplastiques (3). La greffe autogène représente le gold standard des techniques de comblement osseux, elle est ostéogène, ostéoinductrice et ostéoconductrice. Cependant elle nécessite souvent un deuxième site de prélèvement ce qui augmente le risque de complications et la morbidité, de plus la quantité d'os disponible est limitée. Pour pallier à ces difficultés, plusieurs types de substituts osseux ont été élaborés. Premièrement les biomatériaux allogènes qui sont d'origine humaine, prélevés sur cadavres et disponibles dans des banques de tissus. Ils subissent des traitements afin de réduire le risque de transmission d'agents pathogènes mais celui-ci ne peut être totalement exclu, pour cette raison ces matériaux sont très peu utilisés en Europe. Deuxièmement les biomatériaux xénogènes qui sont d'origine

animale (souvent bovine, porcine ou corallienne), ils subissent des traitements thermiques et chimiques ne faisant subsister qu'une phase minérale d'hydroxyapatite. Leur structure est proche de celle de l'os humain et ils ont une résorption lente qui leur confère un rôle mainteneur d'espace et une bonne stabilité. L'os bovin déprotéinisé est très utilisé en parodontologie et en implantologie (5). Enfin, les biomatériaux synthétiques ou alloplastiques ont été développés afin de remédier aux inconvénients des précédents matériaux à savoir leur disponibilité, leur compatibilité, le risque de transmission d'agent pathogène et leur cout. Les processus de synthèse permettent également d'obtenir différentes tailles de particules, porosités et espaces inter-particulaires afin d'obtenir un ostéomimétisme avec l'os humain. Les biomatériaux alloplastiques se composent des hydroxyapatites (HA) peu voire pas résorbables ce qui leur confère un rôle mainteneur d'espace efficient; des phosphates tricalciques en phase beta (ß-TCP) ayant une vitesse de résorption et donc une bioactivité importante mais mauvais mainteneurs d'espace; des céramiques biphasées (BCP) composées d'un mélange en proportion variable d'HA et de ß-TCP permettant de conjuguer les avantages de ces deux matériaux et des bioverres (6). Tous ces substituts osseux n'ont qu'un potentiel ostéoconducteur, c'est à dire qu'ils agissent comme un échafaudage à la néoformation osseuse et ne peuvent pas la stimuler ou l'induire eux-mêmes.

Ces biomatériaux se présentent sous la forme de granules ou de blocs, ces formes galéniques peuvent rendre leur utilisation et leur mise en place délicates dans certains défauts osseux. Pour cela, des biomatériaux composites de comblement osseux ont été développés, ils sont constitués de granules liées entre elles par un polymère vecteur tel que le collagène, l'acide hyaluronique ou l'acide polyglycolique. Ils se présentent alors sous forme de pâte ou de matériau injectable en seringue et ont pour but de faciliter leur manipulation et leur mise en place ainsi qu'augmenter la stabilité initiale du matériau. Ils pourraient également être utilisés comme support de facteurs de croissance ce qui conféreraient au matériau un potentiel ostéoinducteur ou ostéogène. Cependant, l'adjonction d'un vecteur peut modifier les propriétés des substituts osseux et donc réduire leur efficacité.

Le but de cette revue systématique de la littérature est d'évaluer l'utilisation des biomatériaux composites de comblements osseux dans des défauts parodontaux et des chirurgies implantaires afin de déterminer si ils améliorent les résultats cliniques et quelle combinaison substitus-vecteur est la plus efficiente.

Article original

COMPOSITE BONE SUBSTITUTES IN PERIODONTOLOGY AND IMPLANTOLOGY: A SYSTEMATIC REVIEW

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Declaration of interest : none

ABSTRACT:

The aim of this systematic review was to analyze the use of composite bone substitutes in periodontology and implantology from animal models and human. Electronic databases were searched and additional hand search was performed. The research strategy was achieved according to the PRISMA guidelines. The including criteria were : composite bone substitute, in vivo studies, precise number of specimens, histological and radiographic analysis and written in English. The risk of bias was evaluated for individual studies. At total of 32 articles were selected and investigated in this systematic review. The results do not show a superiority of the use of composite biomaterial in comparation with simple biomaterial but suggest the efficacity of their utilization as carrier of bioactive agents. Future studies need to identify the suitable association of biomaterial and vector and to explore the interest of the use of composite bone substitutes like support of growth factors.

INTRODUCTION:

Bone grafts are used in periodontology for the treatment of intrabony and furcation defects; and 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, have similar resorption rate, composition and porosity to human bone. (3) (7) His interconnected porosity should allow the ingrowth of blood vessels and the diffusion of bone cells and nutrients. At last, it should have a controlled biogradability to ensure a balance between resorption and volume maintaining during bone ingrowth, and a dimensional stability to allow his adaptation in the defect. (6) Bone grafts promote bone formation under three concepts : osteoconduction (material act like a scaffold), osteoinduction (material containing proteins which lead at proliferation and differentiation of bone cells) and osteogenesis (material containing stem cells). (8) (2)

The current gold standard is still autologous graft (bone from the patient himself), it is the only bone graft that is osteoconductor, osteoinductor and osteogen. This technique shows several detriments such as the necessity of a secondary operative site, which represents a augmented risk of supplementary comorbidities, or a low quantity of bone. (1) For this reasons, some alternatives have been developed. The first option to autologous bone is the use of allogenic graft : tissue from human donor or cadaver. Three types of allografts exists : 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 (10). For this reasons their uses are restricted particularly in Europe. (6) 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 (ß-TCP), biphasic calcium phosphate (BCP) and bioglasses. HA are non-resorbable biomaterials with a low resorption rate and high space maintaining potential in contrary with ß-TCP. BCP are composed by different ratio of HA and ß-TCP to combine advantages of these two families, thus this biomaterial can have different biodegradability and stability degrees according to the bone defect.

All of this bone substitutes are available in the form of granules or blocks which can be difficult to manipulate and set up in some clinic situations. Therefore composites biomaterials have been elaborated : they are composed by two phases, granules of bones substitutes linked together by

vector. The vectors are polymer biomaterials, mainly represented by polyglycolic acid (PGA), hydrogel or collagen. (7)

Composite bone substitutes are in the form of paste or injectable material. The goal of this galenic forms is to allow an augmented usability for the patrician and a better stability in chirurgical sites; this materials can also be used as a support for stem cells or growth factors (11). However, the ad of polymer between bone particles can change the property of the biomaterial and his capacities of bone neoformation. Nowadays it was not yet possible to conclude at a superiority of a vector or an association vector-biomaterial. For that reason, the aims of this systematic review are to analyzed relevant studies to retrieve valuable information about the interest of the use of composite biomaterials in periodontology and implantology and to evaluate different combinations of bone substitute and vectors.

MATERIAL AND METHODS

The different studies concerning the use of composite biomaterials 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) (12), a specific question has been developed with the PICO (Participant, Interventions, Control, Outcomes) method (13): **"Does composite biomaterials enhance clinical results in patients treated in periodontology and implantology ?**".

Information sources and search strategy:

The search strategy was established according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (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.

The following combinations of Medical Subject Heading (MeSH) terms were used to identify appropriate studies:

(« implantology » OR « dental implantology » OR « dental implant » OR « peri-implantitis » OR « peri-implant defect » OR « sinus lift » OR « sinus floor augmentation » OR « sinus floor elevation » OR « ridge preservation » OR « ridge augmentation » OR « bone augmentation »)

AND

(« periodontology » OR « periodontitis » OR « periodontal defect » OR « periodontal lesion » OR « periodontal osseous defect » OR « intra-osseous defect » OR « intrabony defect » OR « intra-bony defect » OR « angular defect » OR « bony defect » OR « osseous defect » OR "alveolar bone loss")

AND

(« guided tissue regeneration » OR « GTR » OR « periodontal regeneration » OR « bone graft » OR « bone replacement graft » OR « bone substitute » OR « osseous graft » OR « bone transplantation » OR « bone regeneration » OR « alloplastic graft » OR « alloplastic material » OR « synthetic graft » OR « composite material » OR « composite bone graft » OR « composite bone substitute » OR "osseointegration" OR "biocompatible materials" OR "injectable composite" OR "injectable biomaterial")

AND

(« composite » OR « collagen » OR « polyethylene glycol » OR "polyethylene glycol dimethacrylate" OR « hyaluronic acid » OR « IBS » OR "hydrogel" OR "hypromellose derivatives" OR OR "HPMC" OR « calcium phosphate » OR « tricalcium phosphate » OR « beta tricalcium phosphate » OR « hydroxyapatite » OR « BCP » OR "MBCP" OR « biphasic calcium phosphate » OR « biphasic calcium phosphate collagen » OR « BCPC » OR « biphasic calcium phosphate composite » OR « ceramic » OR « calcium carbonate » OR « calcium sulfate »)

AND

("human study" OR "clinical study" OR "patient" OR "human" OR "case" OR "report" OR "animals" OR "animal study" OR OR "experimental study" OR "histological study" OR "histology" OR "histomorphometrical study" OR "histomorphometry" OR "electron microscopy study" OR "biopsy" OR "block section" OR "electron" OR "microscopy")

Study selection and inclusion/exclusion criteria:

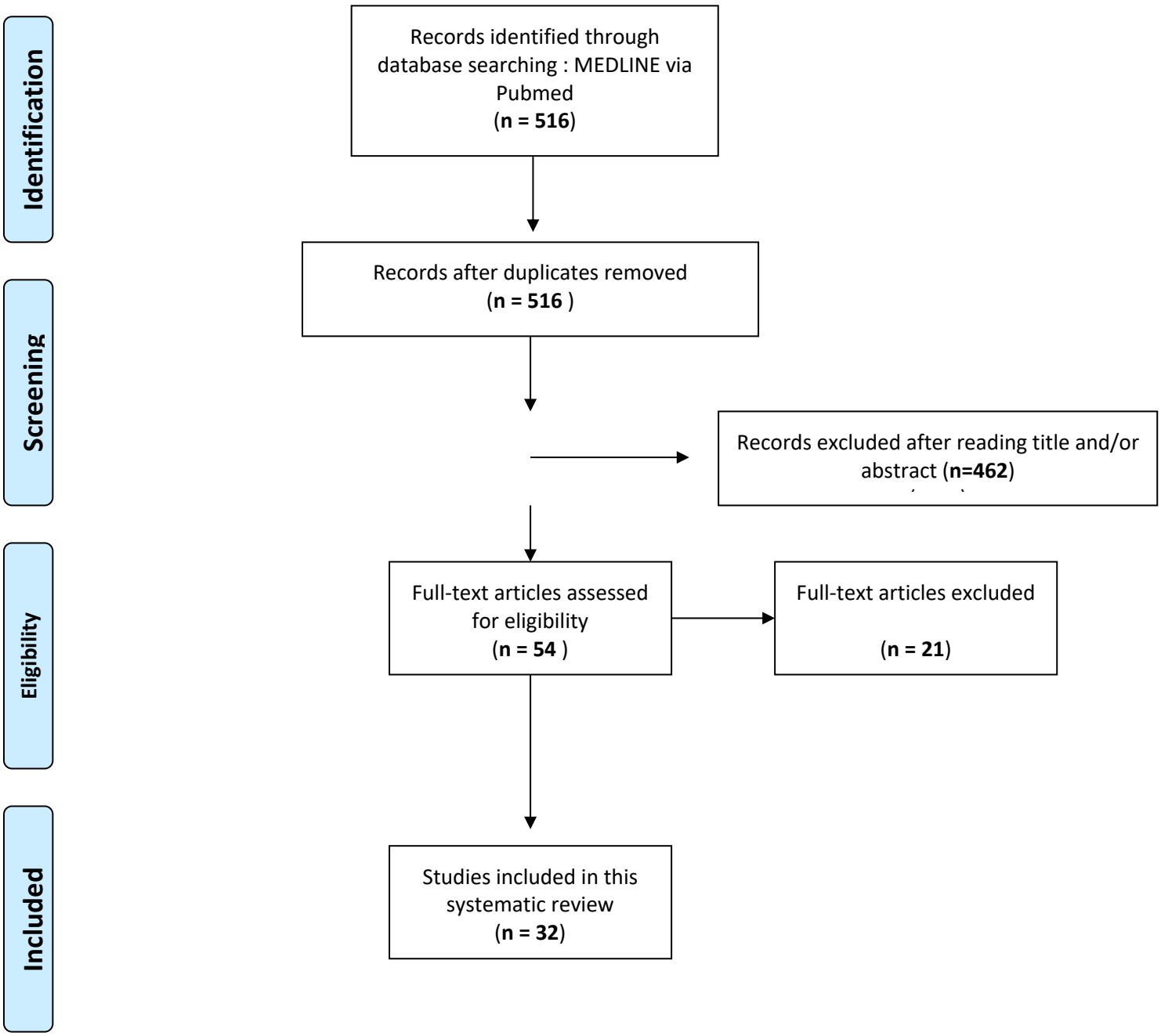
Selection was based on the inclusion and exclusion criteria defined so as to include only the most valuable articles.

Table 1. ***Inclusion and exclusion criteria***

Inclusion criteria	Exclusion criteria
Studies using composite bone susbtitute	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

The selection process was recorded in detail to a PRISMA 2009 flow diagram :

Figure 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 (**Table 2 and 3**).

Risk of bias in individual studies:

To ascertain the risk of bias in eligible articles, their methodology were evaluated be SYRCLE's Risk of Bias tool for animal intervention studies (14), or by Risk Of Bias Nonrandomized Studies of Interventions (ROBINS-I) tool (15), or by the Cochrane Collaboration's tool for human randomized trials (16).

Data synthesis:

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

RESULTS

Study selection:

The MEDLINE literature search resulted 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 full text screening 33 articles were included in the systematic review.

Study characteristics:

The studies were ranked in a comparative table (**Table 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 preclinical studies. The majority of experimental models are dogs, used in 13 studies. The other preclinical studies were performed with pigs (2 studies), sheep (1 study), rabbits (3 studies), 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 none 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 ß-TCP (7 studies) and BCP (5 studies) were the most used materials in preclinical studies, bovine bone (DBB or 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 composite biomaterials 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 used too. Six preclinical studies employed growth factors in composite biomaterials: 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 **Figure 2.** Adapted methodology was applied for each subgroup of studies: preclinical animal studies (**Figure 2.a**), non-randomized human trials (**Figure 2.b**) and randomized human trials (**Figure 2.c**).
Preclinical 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 the detection items (59% and 77% respectively). The majority of the studies were free from selective outcome reporting (54%).
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.
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 of 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 studies, the significant results are showed in **table 2** for preclinical animal models and **table 3** for human studies.

DISCUSSION

The majority of the selected articles in this systematic review are pre-clinical animal studies (22/32 studies) with a largest 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 them is about intra-bony periodontal defect. Consequently, the use of composite biomaterial in periodontal defects are based only on pre-clinical studies which have a lot of risk of bias, with randomization and blinding infrequently described. This failures makes it difficult to draw conclusions from pre-clinical studies. Nevertheless, the combined analysis of the different included studies afford to retrieve valuable information.

The composite biomaterials are composed by granules bounded together by vectors which can be coated by growth factors. This discussion focuses on the different combinations used in pre-clinical and clinical studies and on the utilization of growth factors.

The most used bone substitute in preclinical studies was **ß-TCP** mainly in combination with PGLA, a scaffold commonly used for tissue repair. Two studies (Leventis *et al.* (17) and Naenni (18)) did not showed relevant result for the use of ß-TCP/PLGA composite biomaterial. Okada et al. (19) showed that ß-TCP/PLGA seems to be more effective than conventional ß-TCP for alveolar ridge preservation. The results subjected that this injected and moldable biomaterial maintains its shape, secures the regenerative space and enlarges the osteoconductive area.

Two studies used ß-TCP in gelatin sponges incorporating growth factors (rh-FGF). Hoshi and al (20) showed that the combined use of rh-FGF and gelatin sponge/ ß-TCP is effective for alveolar ridge augmentation. Fukuba *et al.* (21) conclude 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 composite biomaterial seemed to be essential to control the propagation of the growth factor and optimized the bone regeneration.

Only one clinical randomized trial tested ß-TCP/autogenous bone composite and rhGDF-5 coated ß-TCP (22) and concluded in the absence of significant difference.

The relevant results obtained in animal studies with ß-TCP and polymer suggest that this composites biomaterials should be tested in clinical study in human models to attest their effectiveness.

BCP are used in 5 animals studies combined with **Si-HPMC, hydrogel and collagen**. Two studies of Struillou *et al.* (23,24) tested BCP with hydrogel in intrabony defects and peri-implant defects. It showed that hydrogel/BCP can promote new bone formation in large defect and implant site, the viscosity of hydrogel allowing to increased retention capacity and mechanical strength. 3 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 (25,26) conclude that the combination of BCP/Collagen and BMP2 was favorable for the new bone formation. It supposed that the addition of BMP2 induced a post-operative swelling at the origin of an early bone formation.
The use of BMP-2 in combination with biomaterial to promote bone regeneration have been studied in a lot of pre-clinical and clinical studies (27), this growth factor has the highest evidence of a positive effect on bone formation in comparation with others agents. However, plenty of growth factors act on bone healing process (28) which suggest than only one factor in a biomaterial can be insufficient to stimulate the regeneration. Future studies might be directed toward the combination of factors and the use of composite biomaterial like a delivery system for this bioactive agents.

Mainly of randomized clinical trials were realized with **DBBM** or **DFDBA** in combination with **collagen** (5 studies), one non randomized clinical trial used synthetic oligopeptide as vector. All these studies concluded that DBBM-C is effective in ARP procedure but no significant differences were observed with control group.
One randomized clinical trial (29) 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 the new bone formation around 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 composite material in new bone formation.

One non randomized study (30) in human model used **anorganic bovine derived HA combined with putty P15.** Cell binding peptide was also used in one pre-clinical study (31). The good results suggested that HA/P15 has greater compatibility with host bone than HA alone for alveolar ridge preservation.

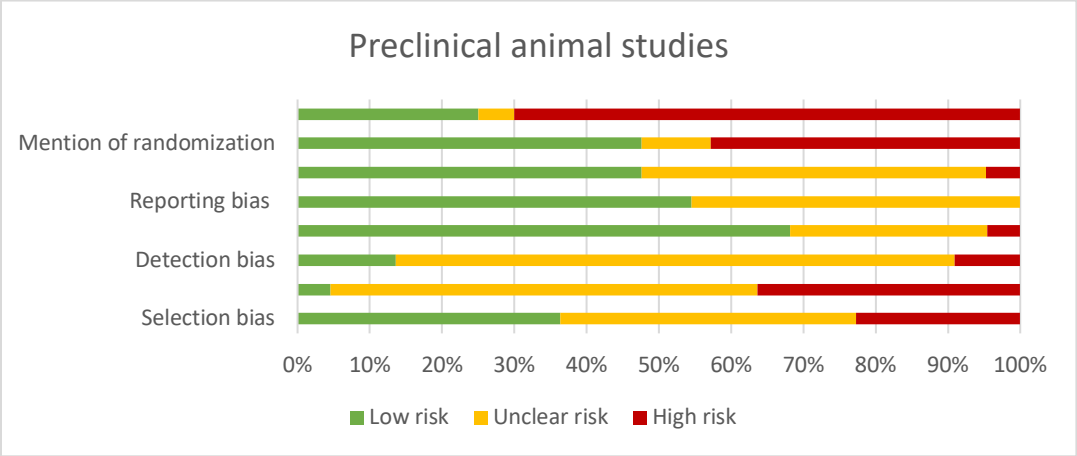
None of the selected clinical trials studied composite biomaterials in periodontal defect in contrast with pre-clinical studies. Some relevant results in the use of this bone substitutes in periodontal bony defect in animal models suggested the necessity to realize this studies in human models; in particular for the use of composite biomaterials as growth factors vectors, this could be interested to promote the periodontal regeneration. Indeed, plethora of publications bring to light the valuable role of growth factors and stem cells in the bone healing process (32), (27), (28) and the necessity of developed sophistically delivery system to lead them in the defect. In that way composite biomaterials may be valuable, indeed some studies included in this systematic review suggests this but additional research are necessary to developed an optimal biomaterial able to support specific molecule to promote bone and periodontal system regeneration in specific clinic situations. (33)

CONCLUSION

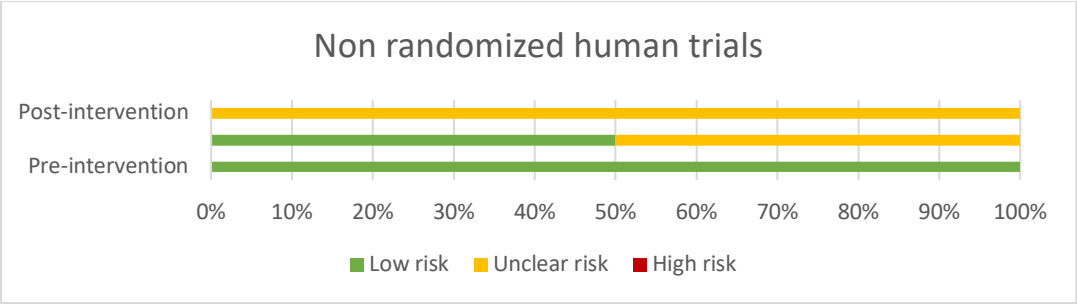
Several combinations of bone substitutes and vectors are studied with various clinical applications. The corresponding studies have heterogenous results concerning their applications in periodontology and implantology. For these reasons, a systematic approach appears essential to serve as a guide for future studies and provide data than can be generalized. The results of our systematic review indicate that composite biomaterials 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.

ANNEXES

A. PRECLINICAL ANIMAL STUDIES



B. NON-RANDOMIZED HUMAN TRIALS STUDIES



C. RANDOMIZED HUMAN TRIALS STUDIES

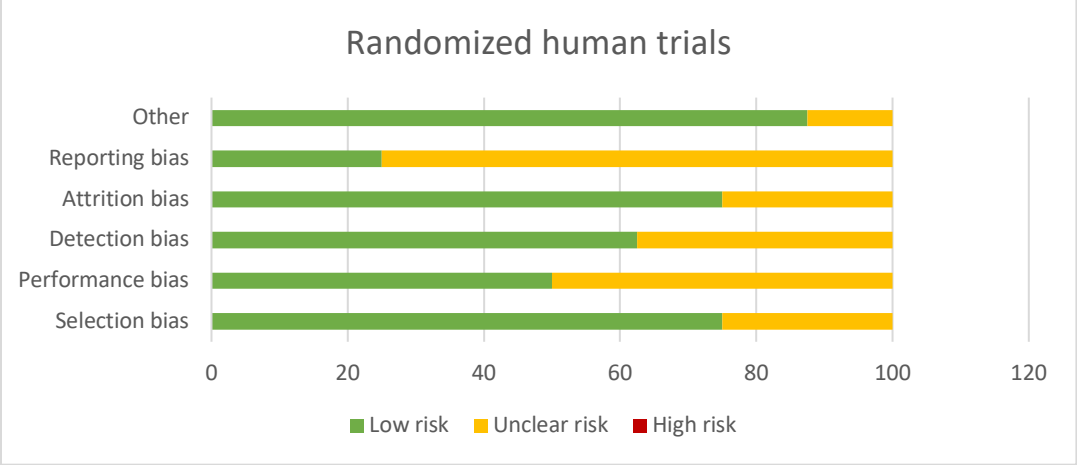


Figure 2: Risk of bias assessment of included studies.
A. Risk of bias graph for animal studies, using the SYRCLE's tool, averaged per item.
B. Risk of bias graph for non-randomized human trials, using the ROBINS-I tool, averaged per item.
C. Risk of bias graph for randomized human trials, using the 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.

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 (19)	ß-TCP ß-TCP + PGLA	Dogs, beagles Males 12 month-old 10kg	6 per group	Buccal bone defect (maxillary first premolar) 4x4x5mm	**Test group:** ß-TCP + PGLA **Control group:** particulate ß-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 ß-TCP. **ß-TCP + PGLA seems to be more effective than conventional ß-TCP for ridge preservation.**
Fukuba *et al.* 2019 (21)	Gelatin/ß-TCP sponges + rh-FGF (0,3%)	Dogs beagles Males 1 year old	6 per group	Saddle type bone defect 8x4mm	**a**. acidic gelatin/ ß-TCP sponges + rh-FGF (0,3%) **b**. basic gelatin/ ß-TCP	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.

					sponges + rh-FGF (0,3%)			Total tissue height not significantly different between the two groups.
Knabe *et al.* 2018 (34)	- 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 (8x8mm)	**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 (35)	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 (5mm 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.
Leventis *et al.* 2018 (17)	ß-TCP + polylactic-co-glycolic acid (PGLA) + Biolinker® (N-methyl-2-pyrrolidone solution)	Landrace pigs Females 4 months-old 18kg	Experimental sites : n=10 Control sites : n=4	Fresh extraction socket (ridge preservation)	**Experimental group**: ß-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.* 2017 (18)	ß-TCP + PGLA	Dogs, beagles Males > 1 year old 10-20kg	Test 1: n = 22 Test 2: n = 22 Control: n = 18	Fresh extraction socket (ridge preservation)	**Test group 1:** ß-TCP + PGLA + collagen membrane **Test group 2** : ß-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	<u>Volumetric measurements</u>: 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. <u>Linear measurements</u>:

								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 (36)	Bio-Oss Collagen ®	Dogs, beagles 1 to 2 years old 10kg	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	<u>Vertical distance between buccal and lingual crest:</u> 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 (37)	- Porcine collagenated bone substitute block (PCBB) - Collagen membrane (CM)	Dogs, beagles Males	6 per group	Two surgeries: Box-shaped bone defects on extraction	**Block** **Block + CM**	20 weeks	Histological Histomorphometric	<u>Augmented area (AA):</u> statistically significant difference between block-BMP2 (11,8 ± 2,9 mm^2) and

	loaded with bone morphgenetic protein 2 (BMP2)	12 ± 3 months 8kg		sites (8x4x5mm) (1) and implant placement (2)	**Block-BMP2** (0,5 mg/mL; 0,2mL) **Block + CM-BMP2** (0,5 mg/mL; 0,2mL)			block + CM-BMP2 (8,5 ± 2,2mm^2) New mineralized bone (NB): no statistically significant differences. Residual bone substitute (BS): only the difference between Block-BMP2 (6,1 ± 2,2mm^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.
Joo *et al.* 2017 (38)	- 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.* 2016 (39)	HA/ß-TCP granules Polyethylene glycol hydrogel (PEG) Arginylglycylaspartic acid (RGD)	Dogs, beagles 18 months 15kg	6 per group	Standardized box-shaped defects (4x2x4mm) 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	<u>Percentage of regenerated area within total defect area</u>: The treatment effects were not statistically different at 8 weeks, and significant at 16 weeks. <u>New bone formation</u>: 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. <u>First bone-to-implant contact</u>: Group CM statistically significantly superior to all other groups at 8 weeks. PEG and CM were statistically significantly superior compared to empty controls. <u>Micro-CT analysis</u>: 2mm bellow the implant shoulder : PEG significantly higher values compared to

								empty and CM. PEG-RGD superior compared to empty 4mm bellow the implant shoulder : no difference.
Hoshi *et al.* 2016 (20)	Biodegradable gelatin sponges incorporating ß-TCP	Dogs beagles Males 1 year old	6 per group	Saddle-type bone defect (5x10mm)	**a.** Experimental group : gelatin/ß-TCP sponges + rhFGF-2 (0,3%) **b.** Control group : gelatin/ß-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 (26)	Autogenous bone Synthetic Bone Substitute (SBS = 70% HA + 30% ßTCP) + Collagen Collagen membrane	Dogs, Mongrel Males 12-15 months 30kg	5 per group (one dog excluded)	Buccal dehiscence on implant site (3mm)	**a.** SBC alone (control group) **b.** Inner autogenous bone ; outer SBC (IAB) **c.** Inner SBC; outer autogenous bone (OAB)	12 weeks	Radiographic Histological Histomorphometric	<u>Radiographic analysis</u>: total augmented volume did not differ significantly between IAB and OAB groups but was significantly lower in SBC group. <u>Histological and histomorphometric analysis</u>: 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.
Yoshida *et al.* 2015 (40)	ß-TCP scaffold PLGA/ß-TCP scaffold ß-TCP and PLGA/ ß-TCP scaffolds loaded with Fibroblast Growth Factor-2 (FGF2)	Wistar Rats		Decortication ($4mm^2$) in the cranial bone	**a.** Control (no implantation) **b.** ß-TCP scaffold **c.** ß-TCP/PLGA scaffold **d.** ß-TCP scaffold loaded with FGF-2 **e.** PLGA/ ß-TCP scaffold loaded with FGF-2	10 and 35 days	Histological Histomorphometric	<u>10 days post-surgery:</u> 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. <u>35 days post-surgery</u>: PLGA- ß-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 (41)	- 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	<u>Radiographic analysis:</u> **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 (42)	Bovine hydroxyapatite/Collagen (BHC) + BMP-2	Mongrel dogs 12 months 30kg	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. (24)*	- BCP	Dogs beagles	6 per group	Dehiscence type base	**a.** no treatment	12 weeks	Histological	Significant increase in bone ingrowth values in group c

2013	- Composite hydrogel/BCP (MBCP) - Si-HPMC	48 ± 2 months 16 ± 1 kg		defects on implant site	**b.** BCP **c.** BCP + hydrogel **d.** BCP + membrane of GBR		Histomorphometric	and d compared with control group (a). Results no significantly different in b compared with a and between all groups with biomaterial.
Kim *et al*. 2012 (25)	- 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	<u>rhBMP-2 release assay:</u> 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.* (23) 2011	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.

Hastruk *et al.* 2011 (43)	Polymethylmethacrylate Polyhydroxyethylmethacrylate, and Calcium Hydroxide (PPCH) Polyanhydride (PA)	Adults minipigs 18 to 24 months old 35kg	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	<u>Probing depth</u>: no significant difference. <u>Radiographs</u>: no significant radiolucency along the implant. <u>Electric mobility test device</u> (STV): no significant difference between the groups. Only maxillary implants analyzed : STV of PPCH-PA group significantly better. No difference in the mandibule. <u>Biomechanical testing</u>: 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: 10µm of microfissures. Group d (control): 20µm of microfissures.
Sato *et al*. 2009 (44)	CPC : *powder composed of a-tricalcium-phosphate, monocalcium phosphate monohydrate, calcium*	Dogs, beagles 1 year-old	6 per group	Second and third maxilla incisors extracted +	**a.** (experimental group): CPC	6 months	Histological Histometrical	<u>Clinical observation</u>: In the CPC group, alveolar ridge enhanced compared with control group.

	carbonate + solution of sodium phosphate			defect 7x6mm created.	**b.** (control group): spontaneous healing			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 (31)	- 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 2: Comparative table of pre-clinical animal studies in the use of composite bone substitutes.

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 (29)	- 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 (45)	- 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 (46)	- 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 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 (35)	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	**a.** ACS (control) **b.** HAP/Col	12 weeks	Micro-computed analysis (CT) Histological	CT images: In collagen group, bone ingrowth started at 8 weeks. In HAP/Col it started at

				midsuture (5mm ø)		(0, 4, 8 and 12 weeks for CT images)		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 (47)	- 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.
Nart *et al.* 2017 (48)	- 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 (49)	- 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 (50)	- 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:** DBBMC + 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 (22)	- rhGDF-5/ß-TCP - ß-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/ß-TCP (3 month of healing) **b)** rhGDF-5/ß-TCP (4 month of healing)	3 months 4 months	Histological Histomorphometric	No statistically significant difference between the groups regarding any of the evaluated parameters.

					c) ß-TCP/AB (4 month of healing)			
Nam *et al.* 2011 (51)	- Deproteinized-bovine-bone mineral - Deproteinized-bovine-bone mineral coated with synthetic oligopeptide - Collagen membrane	HUMAN Female, Male	Control group: n=23 Test group: n=21	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.
Neiva *et al*. 2008 (30)	- 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)

Table 3: Comparative table of human studies in the use of composite bone substitutes.

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Discussion et conclusion

Les recherches documentaires ont permis de retrouver 32 études à inclure dans cette revue systématique. Après une analyse minutieuse, nos résultats ont révélé qu'il n'était pas possible d'effectuer des comparaisons directes de ces études en raison des variations entre elles, en termes de substitut osseux, de vecteurs polymères, du type, de la taille du défaut et de la période de cicatrisation. Aucune méta-analyse n'a donc pu être réalisée.

La majorité des articles sélectionnés dans cette revue systématique sont des études précliniques animales (22/32 études) avec un plus grand panel de biomatériaux et de types de défauts testés que dans les études cliniques. En effet, les études humaines sélectionnées ont utilisé des biomatériaux exclusivement dans la préservation de crête alvéolaire et des chirurgies d'élévation sinusienne, aucune d'entre elles ne concerne des défauts parodontaux intra-osseux. Par conséquent, l'utilisation de biomatériaux composites dans les défauts parodontaux est basée uniquement sur des études précliniques qui présentent de nombreux risques de biais, la randomisation et mise en aveugle étant rarement décrites. Ceci rend difficile de tirer des conclusions des études précliniques. Néanmoins, l'analyse combinée des différentes études incluses permet d'isoler des informations intéressantes.
Les biomatériaux composites sont composés de granules de substituts osseux liées entre eux par des vecteurs qui peuvent être chargés de facteurs de croissance par exemple. Cette discussion se concentre sur les différentes combinaisons utilisées dans les études précliniques et cliniques et sur leur utilisation comme support de facteurs de croissance.

Le substitut osseux le plus utilisé dans les études précliniques était le ß-TCP principalement en association avec le PGLA, un biomatériau couramment utilisé pour la réparation des tissus. Deux études (Leventis *et al*. (17) et Naenni *et al.* (18)) n'ont pas montré de résultat pertinent pour l'utilisation du biomatériau composite ß-TCP/PLGA. Okada *et al.* (19) ont montré que le ß-TCP / PLGA semble être plus efficace que le ß-TCP conventionnel pour la préservation de la crête alvéolaire. Les résultats indiquent que ce biomatériau injectable conserve sa forme, sécurise l'espace régénératif et agrandit la zone ostéoconductrice.
Deux études ont utilisé le ß-TCP dans des éponges de gélatine incorporant des facteurs de croissance (rh-FGF). Hoshi *et al.* (20) ont montré que l'utilisation combinée de rh-FGF et d'éponge de gélatine / ß-TCP est efficace pour l'augmentation de la crête alvéolaire. Fukuba *et al.* (21) concluent que la libération contrôlée de rh-FGF dans le temps induit notamment une

régénération osseuse alvéolaire plus importante que l'application à court terme de ce facteur de croissance. Ici, l'utilisation d'un biomatériau composite semble indispensable pour contrôler la propagation du facteur de croissance et optimiser la régénération osseuse.
Un seul essai clinique randomisé a testé le composite osseux ß-TCP / os autogène et le ß-TCP enduit de rhGDF-5 (22) et a conclu en l'absence de différence significative.
Les résultats pertinents obtenus dans les études animales avec le ß-TCP et les polymères suggèrent que ces biomatériaux composites devraient être testés en étude clinique sur des modèles humains pour attester de leur efficacité.

Les BCP sont utilisés dans 5 études animales combinées à du Si-HPMC, de l'hydrogel et du collagène. Deux études de Struillou *et al. (*23,24*)* ont testé le BCP avec l'hydrogel dans les défauts intra-osseux et les défauts péri-implantaires. Elles ont montré que l'hydrogel/BCP peut favoriser la formation de d'os néoformé dans les grands défauts et les sites implantaires, la viscosité de l'hydrogel permettant d'augmenter la capacité de rétention et la résistance mécanique. 3 études ont utilisé du BCP en combinaison avec du collagène (CBCP) chargé de facteur de croissance BMP2 (protéine morphogène osseuse) et de rh-BMP2 (protéine morphogène osseuse humaine recombinante). Deux de ces études (25,26) concluent que la combinaison BCP/collagène et BMP2 était favorable à la nouvelle formation osseuse. Elle supposait que l'ajout de BMP2 induisait une inflammation post-opératoire à l'origine d'une formation osseuse précoce.
L'utilisation de BMP-2 en combinaison avec un biomatériau pour favoriser la régénération osseuse a été étudiée dans de nombreuses études précliniques et cliniques (27), ce facteur de croissance a la plus forte preuve d'un effet positif sur la formation osseuse en comparaison avec d'autres agents. Cependant, de nombreux facteurs de croissance agissent sur le processus de cicatrisation osseuse, ce qui suggère qu'un seul facteur dans un biomatériau peut être insuffisant pour stimuler la régénération des tissus (28). Les études futures pourraient être orientées vers la combinaison de facteurs et l'utilisation de biomatériaux composites comme un système vecteur pour ces agents bioactifs.

Principalement, les essais cliniques randomisés ont été réalisés avec DBBM ou DFDBA en combinaison avec du collagène (5 études), un essai clinique non randomisé a utilisé un oligopeptide synthétique comme vecteur. Toutes ces études ont conclu que DBBM-C est efficace dans la procédure ARP mais aucune différence significative n'a été observée avec le groupe témoin.

Un essai clinique randomisé (29) a utilisé de l'os autogène (AB) en combinaison avec de la mélatonine dans la mise en place immédiate d'implant. Le résultat a montré un avantage significatif pour AB/mélatonine et l'auteur a suggéré que l'ajout de cette molécule aurait un rôle positif dans la néoformation osseuse autour de l'implant et pourrait protéger et conserver l'intégrité du tissu gingival. Cependant, seule une analyse radiologique a été réalisée dans cette étude; des essais cliniques avec analyse histologique et histomorphométrique seront nécessaires pour attester de l'efficacité du matériau composite AB/mélatonine dans la néoformation osseuse.

Une étude non randomisée sur modèle humain (30) a utilisé de l'hydroxyapatite bovine anorganique combiné avec du P15. Le peptide de liaison cellulaire a également été utilisé dans une étude préclinique (31). Les résultats satisfaisant suggèrent que HA/P15 a une plus grande compatibilité avec l'os hôte que HA seul pour la préservation de la crête alvéolaire.

Aucun des essais cliniques sélectionnés n'a étudié les biomatériaux composites dans les défauts parodontaux contrairement aux études précliniques. Certains résultats pertinents dans l'utilisation de ces substituts osseux dans les modèles osseux parodontaux chez l'animal ont suggéré la nécessité de réaliser ces études dans des modèles humains; en particulier pour l'utilisation de biomatériaux composites comme vecteurs de facteurs de croissance, cela pourrait être intéressant pour favoriser la régénération parodontale. En effet, pléthore de publications mettent en évidence le rôle précieux des facteurs de croissance et des cellules souches dans le processus de cicatrisation osseuse et la nécessité de développer un système d'administration sophistiqué pour les conduire au sein du défaut. De cette manière, les biomatériaux composites peuvent être indispensables, en effet certaines études incluses dans cette revue systématique le suggèrent, mais des recherches supplémentaires sont nécessaires pour développer un biomatériau optimal capable de transporter une molécule spécifique pour favoriser la régénération osseuse et le système parodontal.

Plusieurs combinaisons de substituts osseux et de vecteurs ont été étudiées avec diverses applications cliniques. Les études correspondantes ont des résultats hétérogènes concernant leurs applications en parodontologie et en implantologie. Pour ces raisons, une approche systématique apparaît essentielle pour servir de guide aux futures études et fournir des données généralisables. Les résultats de notre revue systématique indiquent que les biomatériaux composites n'améliorent pas les résultats cliniques par rapport aux substituts osseux classiques;

mais peuvent fournir des effets bénéfiques en combinaison avec des facteurs de croissance. La présente revue fourni des informations importantes pour l'évolution de la recherche concernant l'utilisation du facteur de croissance dans les techniques de greffe osseuse pour la régénération parodontale et l'implantologie dans le futur.

LABUSSIÈRE (Marion) – Les biomatériaux composites de comblement osseux en parodontologie et en implantologie : revue systématique de la littérature. – 52 f. ; III. ; 51 ref. ; 30cm (Thèse : Chir. Dent. ; Nantes ; 2020)

RÉSUMÉ :

Introduction : Les substituts osseux sont utilisés dans le traitement des lésions infra-osseuses et des lésions inter-radiculaire ainsi que dans les cas de préservation alvéolaire pré-implantaire, de sinus lift ou de régénération osseuse guidée. Les biomatériaux composites sont composés de granules osseuses liées entre elles par un vecteur et ont été développés afin d'améliorer la maniabilité et de facilité leur mise en place dans les défauts osseux. Le but de cette revue systématique était d'analyser l'utilisation des biomatériaux composites de comblement osseux en parodontologie et en implantologie à partir d'études pré-cliniques et cliniques.

Méthodes : La stratégie de recherche a été élaborée selon les recommandations PRISMA. Les critères d'inclusion était les suivants : études utilisant des biomatériaux composites, in vivo, analyse histologique et radiographique et rédigées en anglais. Les risques de biais ont été évalué pour chaque étude selon des protocoles adaptés. Un total de 32 articles a été inclus et analysés.

Résultats : Les résultats ne montrent pas de supériorité significative à l'utilisation de biomatériaux composites mais suggèrent l'intérêt de leur utilisation comme support de facteurs de croissance.

Conclusion : Les biomatériaux composites de comblement osseux ont montré une efficacité similaire à celle des biomatériaux classiques, suggérant que le polymère vecteur n'empêchait pas le processus de néo-formation osseuse. Leur utilisation comme vecteur de facteurs de croissance semble prometteuse et devra être étudiée dans de futures études.

RUBRIQUE DE CLASSEMENT : Odontologie – Biomatériaux

MOTS CLES MESH :

Parodontie – Periodontics
Implants dentaires – Dental implants
Matériaux biocompatibles – Biocompatibles materials
Substituts osseux – Bone substitutes
Régénération tissulaire guidée – Guided tissue regeneration
Régénération osseuse – Bone regeneration

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