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Research Article

Using Bone Substitutes for Alveolar Bone Preservation: Biological Concept, Classification, Resorption and Compared Results

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Abstract

Introduction: This systematic review was performed to study the indication of bone substitutes for guided bone regeneration during extraction, with its limitations and the properties.

Material and Methods: A thorough Pubmed and cochrane database search were performed on related keys words associated with the subject. Many titles and selected abstracts were independently screened, followed by full text evalutation of different meta-analysis, literature review and comparative clinical trial.

Results: This littérature review describes the behaviour of bone substitut concerning the host bone cells, as well as the resorption inside graft site.

The results for bone gain and preservation is analyzed for each origins and group of bone substitute.

More over, the bone preservation results is compared by littérature review of comparative study.

Conclusion: The origins and composition of each bone substitutes affects the behaviour of it inside the host bone: resorption and So, the utilisation and the choice of bone substitute during extraction time, need to be decided by the indication of bone gain (only space keeping or need to obtain vital bone) and timing before implantation.

Keywords: *Using Bone Substitutes; Alveolar Bone Preservation; Biological Concept; Classification, Resorption; Compared Results*

Introduction

The alveolar, cancellous bone surrounding the tooth must remain present in sufficient quantity and quality to carry out implant-supported rehabilitation.

Indeed, the loss of alveolar bone caused by tooth loss, often requires the practitioner to perform bone reconstruction by invasive, complex and sometimes non aesthetics techniques, and this for the only purpose of ensuring correct bone support to place the implants, and ensure their durability.

Taken in time, preservation via alveolar preservation techniques such as guided bone regeneration, ensures a sufficient volume that meets the criteria for implant success, and this without using invasive and complex techniques.

Alveolar preservation is defined as any procedure undertaken at or after extraction, with the aim of minimizing resorption of alveolar bone and maximizing bone formation [1].

Its objective is both to limit the vertical and horizontal loss of the alveolar ridge [2].

Its placement can be done at different times, especially during and after tooth extraction. However, placement during extraction surgery can limit the number of operations and reduce treatment time.

Purpose of the Study

We propose here to study the interest of bone substitutes for guided bone regeneration during extraction, with its limitations. We will see the properties of the different elements used as well as their effectiveness.

Material and Methods

This work is based on a review of the literature in the Pubmed and Cochrane database.

The keywords used for the search are

- Socket preservation
- Guided bone regeneration
- Bone resorption
- Membranes
- Bone substitutes materials
- Tooth extraction
- Dental implant
- Socket filling
- Dehiscence/fenestration.

The inclusion criteria are

- Meta analysis: High level of evidence
- Comparative analysis
- Retrospective study
- Prospective clinical trial
- Case report (low level of evidence).

The exclusion criteria are

- Article greater than 10 years except for historical study.

Number of articles included

- More than 30 articles analyzed.
- More than 20 studies included in this article.

The result is classified on different parts to facilitate reading

Results and Discussion

Generality

Definition

In 2014, Nazirkar [3] published a review of the literature in which he highlighted the advantage of different biomaterials. To facilitate the understanding of his study, he proposes a definition of the various advantages offered by biomaterials. We propose to repeat his explanations here:

- Osteoconduction is defined as the bone formation on the surface of the material, serving as a scaffold for the bone cells coming from the bone rim, which proliferate and form bone against the graft, from the wall to the center. The porosity of the biomaterial ensures the passage of new vessels and then bone cells.
- Osteoinduction is defined as the stimulation of the differentiation of undifferentiated cells from the surrounding tissue into osteogenic cells, causing the formation of a bone matrix which will secondarily mineralize. This property is only possible if the bone substitute has the necessary elements for this stimulus: growth factors. This stimulus would thus make it possible to obtain a denser bone matrix.
- Osteogenesis: viable cells in the transplant differentiate into osteoblasts and form new bone. This property implies the presence of viable cells, which is why it is only possible with an autogenous bone transplant.

Classification of biomaterials

In 2001, Bartee [4] published a review of the literature in which he guided practitioners to choose the origin of the biomaterial according to the treatment plan decided upon. He therefore proposes a classification of bone substitutes according to their rate of resorption. We resume here this classification:

- Delayed resorption material: Their density ensures slow resorption, and maintains the volume for a significant period exceeding 12 months.

- Medium resorption material: For early implantation, they increase density and preserve bone volume, allowing classic delayed implantation a few months after avulsion.
- Quickly absorbing material: They maintain the bone during healing, up to three months after the transplant. Their use allows early implantation since their replacement by newly formed bone will already be achieved.

Material's origin

Autograft

Autogenous graft is still considered the gold standard for major reconstruction. For this, it is necessary to use a block graft whose volume is chosen and then adapted to the recipient site. Oral sampling sites are the tuberosity in the maxilla, ramus and symphysis in the mandible. Particle intake is preferable for alveolar preservation.

The use of a bone collector, connected to the suction system, allows to capture (alveolectomy, implant drilling, bone plasty, etc.) to filter and recover the milled bone. Thus, bone preservation can be done, per implant or per extraction, thanks to an autogenous graft, without a second operative site. The recovered bone can be applied within the extraction socket, or on the peri-implant gap.

Allograft

Allogeneic graft uses non-vital bone from an individual of the same species. It can be «fresh frozen» (this one is not used because the risk of pathogen transmission is high) or «freezed» (washed in ethanol and frozen). Among the "freezed", we find FDBA (freezed direct bone allograft) which is mineralized and DFDBA (demineralized freezed direct bone allograft) which is demineralized.

In 2012, wood [5] compared alveolar healing in the presence of FDBA and DFDBA. It classifies 40 patients into 2 groups: 20 patients receive DFDBA filling at the time of avulsion and 20 patients receive FDBA filling. At the time of implant placement (19 weeks), a biopsy is performed. Here are the histomorphometric results.

Groupe	Vital Bone Proportion	Non Absorbed Particules Proportion
FDBA	24.63%	25.42%
DFDBA	38.42%	8.33%

Table 1

The demineralization of FDBA to DFDBA does not appear without consequences. Indeed, the proportion of vital bone is significantly higher, and the graft seems to be absorbed more quickly. Nazikar [3] explains in his review of the literature that demineralization of FDBA to FDBA (by hydrochloric acid) causes the release of osteoinductive growth factor such as BMP.

Xenograft

Xenografting uses sterilized non-vital bone collected from a different species. The organic part is removed after chemical treatment. Currently the most widely used is inorganic bovine bone.

In 2000, Yildirim [6] investigated the behaviour of Bio oss after sinus filling in humans. He performs 15 sinus floor elevations in 11 patients with this material. When the implant is placed at 8 months, he removes a bone fragment and performs his histological study. He notes direct contact between the new formed bone and the persistent particles of bio oss, but described a low osteoclastic activity around bio oss particules. The proportion of new bone formed represents 14.7% of the total volume, against 29.7% for bio oss. Thus the bovine xenograft persists beyond 8 months, and indicates a weak resorption. Bone cells seem to colonize the volume created: this material is therefore osteoconductive and slowly resorbs.

The same year, Artzi [7] investigated the same material but used it to fill 15 extraction sockets in 15 patients. The biopsy is also done, but at 9 months. Histological examination indicates an average bone filling of the alveoli of 82.3%. Persistent bioosse particles represent on average 30.8% of the alveolar volume. New formed bone represents 63.9% of the apical alveolar volume (mostly lamellar bone) versus 15.9% of cervical alveolar volume (mostly woven bone). Here again, the bio oss ensures the migration of bone cells through its porosity, but its absorption is incomplete at 9 months.

A very long-term study was carried out by Skoglund in 1997 [8], which provided alveolar filling in 6 patients, then performed biopsies at 44 months. And here again, the presence of unabsorbed particles is described. Bio oss is considered to be a slowly resorbing material, indicated for very long-term or per-implant preservation.

Synthetic bone

Synthetic or alloplastic bone substitutes are obtained by synthesis, and are exempt from any risk of potential contamination linked to the allograft or xenograft.

Calcium sulfate

In 2004, Guarnieri [9] studied the influence of calcium sulfate on healing. In 10 patients (10 sockets), it fills 5 sockets with the test biomaterial, and 5 sockets are allowed to heal simply. At 3 months, during implant placement, a biopsy is performed. The histological study indicates a total disappearance of the biomaterial, and indicates a formation of lamellar bone in the whole of the alveolus.

In 2009, Aimetti [10] studied the influence of calcium sulfate on healing. In 40 patients (40 extractions), it fills the sockets after extraction in 22 patients, and leaves 18 patients without filling as a control, before closing the site, it measures the alveolar dimensions. At 3 months, during implant placement, a biopsy is performed and clinical measures are taken. Here are the results of the study.

Groups	Vertical Résorption	Horizontal Résorption	Crestal Lamelar Bone Proportion	Apical Lamelar Bone Proportion	Trabécular Bone Proportion
Calcium sulfate	0.5mm	2.0mm	16.4%	43.6%	58.8%
control	1.2mm	3.2mm	11.4%	22.2%	47.2%

Table 2

Calcium sulfate, completely absorbed in 3 months, is a material with rapid absorption, allowing early implantation. Its appears to increase bone formation in the apical area. However, this rapid absorption makes it ineffective for alveolar preservation. Indeed, we have previously shown that maintaining space is a necessary condition for bone regeneration, and this cannot be ensured by too early resorption of the material.

Tri-calcium phosphate

In 2001, Zerbo [11] presented 2 clinical cases of the use of beta TCP in humans. The first patient receives a filling of a bone defect following a cystic ablation, the other patient receives a sinus filling. Two biopsies are performed at 8 months.

Clinical Case	Mineralized Bone Proportion	Remaining Particules Proportion
Sinus	20%	44%
cyste	34%	29%

Table 3

The beta TCP remains in a significant proportion 8 months after the transplant. We can thus classify it among the materials with average resorption.

Biphasic materials

The two-phase materials consist of tri-calcium phosphate with medium absorption (70%), and non-absorbable hydroxyapatite (30%). Thus, the majority tri-calcium phosphate ensure medium-term maintenance and will be replaced by newly formed bone, then in the very long term, hydroxyapatite persists.

In 2011, De Coster [12] studied alveolar healing in the presence of biphasic materials. In 10 patients (29 extractions), it fills 15 sockets and leaves 14 to heal spontaneous as control. Implants are placed between 6 and 24 weeks depending on patient availability (on average 22 weeks).

At the time of drilling, the author clinically indicates that the filled sites are less resistant to drilling. Some sites could not accommodate the implant due to lack of healing (5 of the 15 filled sockets).

Two of ten implants were lost within 3 months of placement. For the control sites, 13 out of 14 sockets healed normally, and 3 out of 14 implants were lost after immediate loading.

Histologically, the filled sites show less bone formation than the control site, with a predominance of unmineralized connective tissue. The author was able to perform test site biopsies at 74 weeks.

At this time, healing of the site is similar to the control site for bone formation, but a low presence of unabsorbed tissue surrounded by inflammatory infiltrate is noted.

This study indicates the resorption and difficult integration of the biomaterial, delaying the healing of the site. We regret, however, the lack of precision given by the authors regarding the exact biopsy times, and the lack of a reproducible protocol.

Osteoinductive agent

In 2001, Yuan [13] evaluated the osteoinductive potential of the BMP2 protein. He creates a hollow implant, filled with calcium phosphate, in which he adds different concentrations of Bone Morpho Protein 2 (0, 1, 10 and 40 µg). These different implants are placed in the dorsal muscle of the rabbit for 5 weeks, after which the rabbit is sacrificed for a histological study of the muscle and the implant. The implant without the presence of BMP does not indicate any bone cells within it or in the muscle environment. With 1 µg of BMP, mature lamellar bone is found in the center of the implant only. For 10 and 40 µg, the lamellar bone is present in the implant and on the external surface of the latter, without significant difference between the 2 groups. This study indicates that calcium phosphate is a reliable support to keep BMP. BMP is osteoinductive, but above a certain dose its effect does not seem to be dose-dependent.

In his review of the literature, Nazirkar [3] tells us that BMP interacts with the transmembrane serine/threonine receptor to transform mesenchymal cells into osteoblast cells. Although BMPs are known to work, other modulators can guide the healing process, such as peptide 15 and transforming growth factor.

Compared efficacity

Alveolar preservation: comparison between allogenic and synthetic bone In 2012, Toloue [14] compared the effectiveness of alveolar preservation between calcium sulphate and FDBA. In 21 patients (11 men and 10 women), it filled 13 sockets with calcium sulfate and 15 sockets with FDBA. Alveolar measurements are taken at the time of extraction. After 3 months, the site is opened, measurements taken again, and a biopsy is taken. Here are the average results.

Groups	Horizontal Résorption	Vertical Résorption	News Bone Proportion	Remaining Particule Proportion
Calcium Sulfate	-1.33mm	-0.23mm	30.9%	2.54%
FDBA	-1.03mm	-0.05mm	16.4%	16.6%

Table 4

There are no significant differences regarding the effectiveness of the 2 materials in preserving alveolar volume. However, bone formation is almost doubled with calcium sulfate compared to FDBA. Resorption at 3 months is almost terminal for calcium sulphate, unlike FDBA.

Bone formation: comparison between autogenous, synthetic and bovine bone In 2006, Jensen [15] compared the resorption of autogenous bone, bio oss and calcium triphosphate after alveolar filling. He uses 12 pigs, which he sacrifices at weeks 2, 4 and 8. In each pig, he achieves 3 mandibular defects (ramus) which he fills with a different material. The measured vital bone proportion is shown below.

Groups	2 Weeks	4 Weeks	8 Weeks
Autogenous	17.7%	39.4%	54.5%
bovin bone	5.6%	24.6%	41.6%
Beta TCP	6.3%	36.4%	57.4%

Table 5

Revascularization of the site: comparison between bovine and allogeneic bone In 1999, Tal [16] investigated the ability of the biomaterial to facilitate site revascularization. To do this, it is carrying out a clinical trial with 24 patients (aged 18 to 63) requiring extraction in the anterior sector. The extractions (42 in total) are performed in a non-traumatic technic. The socket is then filled with DFDBA or Bio oss. An epithelio-connective tissue graft is used to cover the site. The survival of the graft is examined over 3 weeks, proof of the vascularization of the site, making it possible to nourish the graft. The grafts will be classified on 3 criteria:

- Vital: if contact bleeding is present, and the attachment to the site is stable

- Not vital: the graft is lost in 2 weeks, detaches and shows a fibrin clot.
- Partially vital: the graft shows both signs of necrosis and signs of vitality.

At 1 week, 43% of transplants are vital [18], 31% partially vital [13] and 26% non-vital [11]. The results do not vary thereafter. The repartitions is as follows.

Groups	Vital Graft	Half Vital Graft	Necrosis Graft
DFDBA	57%	29%	14%
BIO OSS	29%	33%	38%

Table 6

We note that the DFDBA group presents twice as many vital grafts and more than two times less necrotic graft than the Bio oss group. The vascularization of the defect is therefore of better quality with this type of material, it thus allows better delivery of the blood vessels within the sockets.

Socket filling and immediate closure

Short-term maintenance of space.

Hemostatic sponge

In 2003, Serino [17] studied the value of hemostatic sponges in alveolar preservation. In 36 patients requiring one or more extractions, it classifies the alveoli into test groups (26 alveoli with a hemostatic sponge) and control group (simple healing). For each alveolus, a full thickness flap is lifted, the vertical dimensions of the alveolus are taken mesio-vestibular, disto-vestibular and on the full buccal surface. For the test group, a Fisiograft hemostatic sponge (polyglycolide) is inserted into the socket. The flaps are sutured non-hermetically for each socket. At 6 months, when placing the implant, the measurements are repeated and a biopsy of the site is performed. Histologically, the test and control sites are identical, and indicate mature, properly mineralized and structured bone. Dimensional variations are mentioned below.

Groups	Vertical Mesio Vestibular Variation	Buccal Vertical Variation	Vertical Disto Vestibular Variation
Sponge	-0.2mm	-0.8mm	-0.1mm
Control	-0.6mm	-1.3mm	-0.8mm

Table 7

Vertical bone resorption is significantly less when using a hemostatic sponge. This technique therefore seems to ensure alveolar preservation. The advantage of this technique consists in being able to maintain space, with a short-term absorbable material, allowing early implantation.

Calcium sulphate

In 2004, Guarnieri [9] studied the influence of maintaining the space offered by calcium sulphate on alveolar resorption. In 10 patients (10 sockets), he tested 5 sockets by filling it with calcium sulfate (hermetic flap closure), and allowed 5 sockets to heal conventionally. At 3 months, for the placement of the implant, a bone fragment 2.5mm in diameter is removed. Histological sections are made and studied.

In the test sites, there is no trace of residual material. The average trabecular bone volume in the alveolus is 58.5%. A high concentration of Ca ion is found within the alveolus, suggesting resorption of the material. In the control site, the trabecular bone volume does not exceed 46%. Thus, maintaining space increases the percentage of trabecular bone in the socket, and allows early implantation from 3 months.

In 2009, Aimetti [10] studied the impact of calcium sulfate on alveolar resorption. He selected 40 patients requiring extraction, and divided the sockets into test groups (22 sockets filled with calcium sulphate) and into a control group (18 sockets). After lifting the flap, the alveolar dimensions are measured. At 3 months, during drilling, a bone fragment is extracted, and new measurements are made. Here are the numerical and histological results.

Groups	Vertical Resorption	Horizontal Resorption	Proportion of Trabécular Bone
Calcium Sulfate	0.5mm	2mm	47.2%
Control	1.2mm	3.2mm	58.8%

Table 8

This study confirms the histological results obtained by Guarnieri, it also provides clinical elements on alveolar resorption. The vertical and horizontal resorptions are here significantly reduced.

The platelet rich fibrin (PRF)

In 2013, Girish [18] demonstrated the benefit of PRF in alveolar healing. In 22 patients requiring 38/48 avulsion, the sockets were randomly distributed into test groups (autologous PRF filling) and control (simple healing). Radiological follow-up is carried out at T0 (postoperative), 1 month, 3 months and 6 months. Here are the radiological results.

Groups	Density T0	Density 1month	Density 3month	Density 6month
PRF	383.6 pixel	385 pixels	330 pixels	325 pixels
Control	314 pixels	291 pixels	287 pixels	291 pixels

Table 9

The density within the sockets appears to be greater with the use of PRF, but no histological study indicates that it is an osteoid tissue favoring short-term alveolar conditions and no alveolar dimension can prove maintaining the initial volume. We cannot conclude on the benefit of PRF from this study.

Long-term filling

In 2009, Araùjo [19] studied the long-term preservation of the alveolus obtained by xenografting (Bio oss). In 5 dogs, it bilaterally avulses the distal root of the mandibular 3rd molar. One side is used as a test cell (filling) and the other side as a control cell. At 6 months, the dogs are sacrificed with a view to making histological sections. The study of the sections did not indicate any difference between the 2 groups regarding bone formation. However, the biomaterial is not resorbed in the test site, and forms a scaffold maintaining the initial dimensions of the alveolus, within which the bone cells are distributed. Thus, filling the socket with inorganic bovine bone maintains the initial architecture of the socket, but does not increase bone formation. Six months after the transplant in the dog, the bio oss still seems to be present without absorption.

In 2000, Artzi [7] analyzed in humans the long-term behavior of bovine bone (particle of 250 to 1000 µm). In 15 patients (9 women and 6 men) it measures the socket, before extracting the tooth and filling the site with Bio oss. After 9 months of healing, the site is opened, measured, and a bone fragment is removed. Histologically, the average alveolar bone filling is 82.3%, distributed in woven bone in the coronal zone and in lamellar bone in the apical zone. The particles of Bio oss still present are in direct contact with the bone cells. Clinically, the author indicates an average vertical bone gain of 4.64mm (ranging from 2 to 11 mm). It seems that in humans, the bovine xenograft is not completely resorbed after 9 months of healing. This long-term persistence allows a vertical bone gain varying from 2 to 11mm. Bio oss therefore appears to be effective in preserving the ridge if implant placement is delayed.

In 2008, Molly [20] compared the use of 3 different materials, and observed their behavior over the long term. In 8 patients (7 women, 1 man and an average age of 53 years) requiring more than 3 extractions, it fills the socket with bovine bone, organic coral, and a hemostatic sponge. One cell remains unfilled. An e-PTFE membrane is attached and the sites are sealed with the flap. At 6 months, a biopsy of each site allows a histological study. The unfilled socket presents a newly formed and mature bone. The alveolus having benefited from the sponge shows almost no presence of the material, and presents an unstructured fibrous tissue unrelated to the osteoid tissue. The alveolus containing the bio oss, does not show any osteoclast or gap in contact with the biomaterial, which is still present, and colonized by bone cells. The alveolus filled with bio coral shows clusters of biomaterial isolated within fibro-vascular tissue. The average histomorphometric results for the tissue distributions are as follows.

Groups	Control	Sponge	Bio Oss	Bio Corail
Vital bone proportion	29.4%	27.9%	20.7%	24%
Remaining material proportion	0	5.6%	20%	12%

Table 10

The almost terminal resorption of the sponge confirms the results of the previous section, and in the long term, it does not ensure a greater bone population than the control group. It is therefore not indicated for long-term preservation. Bio oss and bio coral do not induce bone formation, and remain present within the alveolus, so they can maintain the available volume and allow bone cells to occupy the latter.

Some authors have proposed to use the stability of the autologous fibrin network to increase the production of new formed bone.

El Moheb [21] then proposes to mix the blood plasma, separated from the red blood cells by centrifugation, with a particulate mineral phase (biomaterials with any origins). The product obtained is a dense and stable element with a biochemical bond between each particle.

He is carrying out a study on 18 patients (11 men, 7 women, average age 40 years) with partial maxillary posterior edentulous who requiring a sinus lift before implant placement.

The patients are divided into 2 groups: sinus lift with biomaterials + PRF or sinus lift with MPM.

The biopsy is performed at the time of implant drilling: 14 days postoperatively.

The histological examination aims to look for the presence of early new formed bone (woven bone).

The quantitative results are shown in the table below.

	No Bone Formation		Bone Formation	
Used Material	Number of cases	Percentage	Number of cases	Percentage
MPM	0	0%	9	100%
PRF+Bone	8	88.89%	1	11.11%

Table 11

Histologically, the MPM group shows woven bone with peripheric osteoblastic activity, while the PRF group indicates granulation tissue with no evidence of bone formation.

MPM appears to accelerate the formation of osteoid tissue using the autologous fibrin network.

Conclusion

The origin of biomaterials will determine its properties and the time of grafted integration. Depending on the treatment plan and the implantation time, the choice of biomaterial will differ.

Bone substitutes can be autogenic, allogeneic, xenogenic or synthetic. The presence of vital cells is only possible with an autogenic transplant. Biomaterials are osteoconductive but their absorption differs depending on their origin, which influences the indication. The addition or initial presence of growth factor accelerates bone formation.

Bone substitutes have different behaviors regarding bone formation, resorption and osteoinduction. There does not seem to be a perfect material, with the highest score in each observation criteria. We will say that each has advantages and disadvantages, assigning them a different clinical indication. In addition to that, it will be necessary to accept the choice of patients, who are sometimes refractory to certain origins of the biomaterial.

Depending on the length of time separating the avulsion and the placement of the implant, we will orient our preservation strategy differently. In case of early implantation, the space must be maintained by a fully resorbed material, and for this, hemostatic sponges and calcium sulfate appear to be effective. On the other hand, if implant placement is delayed, long-term maintenance must be ensured, and in this case slowly absorbing materials such as inorganic bovine bone are effective. It should be noted that their effectiveness lies in architectural maintenance but not in bone formation. Cellular selection enabled by the membrane alone allows long-term preservation of the alveolar architecture and increases bone filling during healing.s

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