

**UNIVERSITÀ DEGLI STUDI DI NAPOLI
“FEDERICO II”**



FACOLTÀ DI MEDICINA E CHIRURGIA

**Scuola di Dottorato
in Medicina Clinica e Sperimentale**

Dottorato di Ricerca in Scienze Odontostomatologiche

Coordinatore: Prof. Sandro Rengo

TESI DI DOTTORATO

“Clinical outcomes of socket preservation after tooth extraction using bovine-derived xenograft collagen and collagen membrane or deproteinized bovine bone mineral and collagen membrane compared to blood clot alone. A six-months randomized controlled clinical trial.”.

Tutor

Ch.mo Prof. PAOLO BUCCI

Candidato

Dott. Paolo Nuzzolo

XXVIII CICLO

Contents

- 1. Rationale for socket preservation 3**
 - 1.1 Phases of socket healing 4
 - 1.2 Dimensional ridge alterations after tooth loss 6
 - 1.3 Implant placement in deficient bone 7
 - 1.4 Advantages of the prevention of bone resorption 9
- 2. Materials and techniques 11**
 - 2.1 Biomaterials 11
 - 2.2 Surgical techniques 18
- 3. Outcome assessments 21**
 - 3.1 Bone height and bone width 21
 - 3.2 Histological outcomes 23
 - 3.3 Radiographic outcomes 25
 - 3.4 Implant-related outcomes 26
 - 3.6 Soft tissues 27
- 4. Cumulative results and guidelines 29**
- 5. Clinical outcomes of socket preservation after tooth extraction using bovine-derived xenograft collagen and collagen membrane or deproteinized bovine bone mineral and collagen membrane compared to blood clot alone. A six-months randomized controlled clinical trial 34**
 - 5.1 Introduction 34
 - 5.2 Materials and Methods 35
 - Experimental design 35
 - Patient population 37
 - Experimental procedures 37
 - 5.3 Results 41
 - 5.4 Discussion 42
 - 5.5 Conclusions 45
 - 5.6 Tables 46
 - 5.7 Figures 50
- 6. References 53**

1. Rationale for socket preservation

The challenge of modern implant dentistry is to achieve and maintain over the time the best functional and esthetic results, with the least invasive and most predictable treatment.

The availability of adequate bone quantity and quality is precondition to an effective anatomically- and prosthetically-driven implant placement, in terms of bucco-lingual and mesio-distal position, angulation with respect to the occlusal plane, implant length, width and number.

Bone deficiency requires pre-prosthetic reconstructive surgery, with the effect of lengthening the time of rehabilitation, increasing the morbidity and the costs for the patient.

The possibility of preventing or limiting the alveolar ridge from undergoing physiological resorption after tooth extraction has been investigated extensively, in order to avoid the need for reconstructive surgical techniques and ease the proper positioning and prosthetic loading of osteointegrated implants.

All the different procedures that take place immediately after tooth extraction and are aimed at preserving the alveolar bony architecture are referred to as “socket preservation” or “alveolar ridge preservation” techniques (Horváth et al. 2013).

In the following chapters, the different approaches to socket preservation described in the literature will be discussed and compared, in order to assess their clinical predictability and significance.

Finally, the methods and results of a randomized controlled clinical trial, comparing the use of deproteinized bovine bone mineral in a 10% porcine collagen scaffold covered with a collagen membrane versus deproteinized bovine bone mineral covered with a collagen membrane as methods for socket preservation versus control unassisted healing in a sample of 45 healthy individuals needing the extraction of one mandibular or maxillar tooth will be illustrated and discussed.

1.1 Phases of socket healing

The sequence of events that take place from tooth extraction to the later phases of socket healing have been histologically described by Cardaropoli et al. in an experimental study in the dog (Cardaropoli et al. 2003) .

The wound is first invaded by the blood clot, which is replaced in the very first days of healing by a granulation tissue with inflammatory cell infiltrate. This highly vascularized tissue is then colonized by fibroblasts that start producing a provisional fibrous matrix, which embeds a multitude of mesenchymal cells, most of which coming from the severed periodontal ligament.

Following cell differentiation, mineralized tissue starts to appear, first as immature woven bone, then as lamellar bone and bone marrow, while the periodontal ligament and the bundle bone disappear.

Meanwhile, the overlying soft tissues heal, covering the socket with a connective tissue rich in vessels and inflammatory cells, lined with epithelial cells.

The marginal part of the socket, immediately under the soft tissues, creates a bridge of hard tissue that closes the socket and, with time, undergoes a process of corticalization.

Over the newly formed cortical bone, a periosteum is established, while, apically, greater amounts of bone marrow and a limited number of trabeculae of lamellar bone appear.

The process of substitution of woven with lamellar bone, takes place over a period of about six months after the extraction, together with a process of reshaping of the ridge, which continues throughout life (Jahangiri et al. 1998).

1.2 Dimensional ridge alterations after tooth loss

Tooth extraction is always followed by a physiological bone resorption, which can reduce the original alveolar volume of 40-60% in the first 3 to 6 months after tooth loss (Atwood 1971; Cardaropoli et al. 2003; Schropp et al. 2003), in a process that can be assimilated to disuse atrophy, because the socket is a tooth-related structure.

Even though the major volumetric shrinkage occurs in the first months after extraction, such atrophy will progress over the years (Carlsson et al. 1967).

Bone remodeling affects both the horizontal and the vertical component of the residual alveolar crest, leading to a reduction in width and in height that Van der Weijden et al. estimated of 3.87 mm and 1.67 mm respectively, as weighted means from data present in the literature, after three months of healing (Van der Weijden et al. 2009). These data are in accordance with a previous study by Lekovic et al., that reported a corono-apical bone loss of 0.7-1.5 mm and vestibulo-lingual/palatal loss of 3-5mm, 6 months after tooth extraction (Lekovic et al. 1998).

After 6 months from tooth extraction 63% of original width and 22% of the original height of the socket are lost (Hämmerle et al. 2012; Tan et al. 2012).

The socket walls are covered with bundle bone, which is the outer part of the periodontal tissues and, as such, will disappear together with the tooth. This structure is usually less than (or equal to) 1 mm thick and most often is the only kind of bone that can be found on the most

coronal part of the vestibular crest. This explains the common observation that bone resorption after tooth extraction affects far more drastically the vestibular than the lingual/palatal plate.

However, after bundle bone loss, a second phase of bone resorption occurs from the outer surfaces of both bone walls, and no biological explanation has been given to this process so far (Devlin & Sloan 2002; Araújo & Lindhe 2005).

Thus, the pattern of remodeling leads to a shift of the crest towards lingual/palatal and apical, with a minor vertical bone reduction, affecting mostly the vestibular plate, and a marked horizontal shrinkage of the buccal wall in its coronal aspect, as confirmed by recent experimental models (Johnson 1969; Cardaropoli et al. 2003; Discepoli et al. 2013)

However, significant differences in the amount of bone resorption can be expected from different individuals, depending on anatomic, metabolic, functional and prosthetic factors (Carlsson & Persson 1967; Tallgren 1972; Atwood 2001).

1.3 Implant placement in deficient bone

Seibert has classified alveolar crest defects as follows:

- Class I defect, when the bone deficiency is predominantly in the horizontal dimension.
- Class II defect, when the bone deficiency is predominantly in the vertical dimension.

- Class III defect, when the bone deficiency affects both the vertical and horizontal dimensions (Seibert 1983).

Implant placement in sites where the volume and the orientation of residual bone are not ideal requires grafting and regenerative techniques to restore the altered hard tissues architecture.

For Seibert Class I defects, the anatomical limitation can be also avoided by means of short implants.

As for regenerative techniques, different approaches exist. In the case of the posterior maxilla with deficient bone height, the common treatment is the sinus lift procedure, which elevates the sinus floor either with a trans-alveolar or with a lateral window approach (Boyne & James 1980; Summers 1994). An alternative to this treatment is crestal vertical bone augmentation (Simion et al. 2004). All these alternatives imply increased morbidity and costs for the patient (Sanz et al. 2015).

Short implants have proven high survival rates and a predictability comparable to longer implants placed in regenerated bone (Thoma et al. 2015) with lesser complications and easier surgery. However, long-term evidence is lacking. Besides, mechanical and prosthetic concerns have been arisen with respect to the altered crown/implant ratio (Sanz et al. 2015).

As for the posterior resorbed mandible, vertical ridge augmentation can be carried out through different approaches: GBR, onlay bone grafts, distraction osteogenesis, inter-positional bone grafts and combinations. All of them are highly operator-sensitive, require high surgical

skills and lend themselves to post-surgical complications, with rates that range from 20% to 60% (Bianchi et al. 2008; Felice et al. 2009; Sanz et al. 2015). As well as for the posterior maxilla, an alternative to augmentation is represented by the use of short implants, with all the limitations discussed above.

The anterior regions of both maxillary and mandibular arches are less susceptible of vertical bone insufficiency, but the apical and lingual/palatal shift of the ridge after tooth extraction can impair the correct orientation of the implant and increase the prosthetic space to a point that the esthetic outcome of the restoration, and possibly its biomechanics, are compromised. Furthermore, Seibert Class II horizontal deficiencies are not a rare outcome of alveolar shrinkage after tooth loss in the esthetic zone, requiring onlay block grafting, or bone-spreading procedures.

It has been pointed out that in the frontal region regenerative procedures to correct alveolar atrophies should be planned together with soft tissues augmentation procedures in order to ensure the best esthetic outcome (Masaki et al. 2015).

1.4 Advantages of the prevention of bone resorption.

Ideally, the preservation of the alveolar bony structure would be the best, simplest and most predictable way to ensure ideal implant dimensions and position, avoiding either complex

pre-prosthetic surgery, with high morbidity and costs, or solutions of compromise, like implants of undesired length, width or position, unnaturally long restorations or pink porcelain to cover the increased prosthetic space.

Immediate or early implant placement had been suggested to preserve the alveolar anatomy (Paolantonio et al. 2001), but animal histologic and clinical studies have shown that early implantation is not responsible for any change in the healing pattern of the surrounding alveolar bone and overlying soft tissues (Araújo et al. 2005; Esposito et al. 2010; Lang et al. 2012; Schropp & Isidor 2015).

The idea of grafting the socket immediately after tooth extraction, in order to counteract the physiologic shrinkage of the hard tissues, which is the foundation of all the alveolar ridge preservation techniques, complies, at least in principle, with the criteria of ease, predictability and biological economy that inspire the modern implant therapy.

The space maintenance provided by the socket walls, the blood vessels, the stem cells and the growth factors coming from the severed periodontal ligament, the bone response to trauma, also called regional acceleratory phenomenon (Verna 2016), are all elements that increase the predictability of bone grafting. Furthermore, the surgical technique appears easier, if compared with augmentation of resorbed, irregular and atrophic alveolar ridges.

2. Materials and techniques

Alveolar ridge preservation after tooth extraction can be attempted by:

- grafting the socket with biomaterials of different origin and composition;
- sealing the socket with different kinds of plugs ;
- a combination of the two approaches.

The two main differences among all the protocols proposed are the biomaterial used and the flapped or flapless approach.

2.1 Biomaterials

The biomaterials and devices tested for socket preservation, alone or in various combinations, can be classified as follows:

- Autologous bone.

Also called autografts, autologous grafts are considered the gold standard for bone grafting,

because they provide a scaffold for tissue ingrowth (osteoconductive property), molecules

that stimulate cellular migration and differentiation (osteoinduction), and are the only type of

graft that also provides viable osteoblasts and osteoclasts for bone modeling and remodeling (osteogenesis) (Burchardt 1983; Hjørting-Hansen 2002). However, autografts require donor site-surgery and imply possible donor site- post surgical complications. Moreover, their resorption rate is quite high (Nkenke et al. 2001; Johansson et al. 2001; Schlegel et al. 2003; von Arx et al. 2005).

Donor sites can be either extra-oral or intra-oral. In the case of alveolar preservation, the volume of graft is limited and intra-oral donor sites are approached, as the mandibular chin or the ascending ramus area.

- Soft tissue grafts and substitutes.

Free gingival or connective grafts have been used to seal the socket and protect the blood clot and the graft material- when present, eliminating the need to elevate a full thickness mucoperiosteal flap to obtain a primary closure. Blood supply from the underlying socket will ensure the free graft survival (Tal 1999; Fickl et al. 2009; Jung et al. 2013).

Acellular dermal matrix (ADM), a xenogenic extracellular matrix, could also be used as soft tissue substitute, but the evidence is little, to date (Vignoletti et al. 2014).

- Homologous bone.

Bone from human cadavers can be used as a grafting material after different processing methods, mainly freezing and/or demineralizing. It is then sterilized and stored in tissue banks in the form of blocks or chips.

Depending on the type of treatment, fresh-frozen bone (FFB), freeze-dried bone (FDB) and demineralized freeze-dried bone (DFDB) can be obtained.

The release of bone morphogenetic proteins (BMPs) and the corticocancellous structure ensure osteoinductive and osteoconductive properties, respectively.

The main concerns are the risk of cross-infection and immunological reactions, although there are no reported cases in dental literature, to date (Quattlebaum et al. 1988; Yukna 1993; Keith et al. 2006).

- Xenogenic bone substitutes.

Xenografts are biomaterials of animal origin, mainly bovine, equine or porcine, which are usually chemically deproteinized, preserving the original mineral porous architecture. For this reason, their main role is that of a biological scaffold (i.e. osteoconductive property).

Deproteinized xenograft of bovine origin are the most investigated materials of this group, and are also referred to as de-proteinized bovine bone mineral (DBBM), or anorganic bovine bone grafts (ABBG). Their very slow resorption rate ensures the stability of the augmented

sites, but, on the other side, decreases the percentage of vital bone (Berglundh & Lindhe 1997; Fugazzotto 2003).

In fact, it is not clear if DBBM completely resorbs at all: graft particles have been identified in long-term specimens both in human and in experimental animals. Mordenfeld et al. provided histologic samples of sites from 20 patients who had undergone sinus lift procedure 11 years before, displaying unchanged DBBM particles integrated within the regenerated bone (Mordenfeld et al. 2010).

Another histological study in humans using DBBM granules for socket preservation provided specimens after 9 months of healing. Vital bone was predominant in the apical part of the sockets, even though its amount was limited, ranging from 26.4 to 35.1%, while in the coronal third of the sites the content was mostly connective tissue (63.9%). The graft material was present in the amount of 30% of the socket volume (Artzi et al. 2000).

On the other hand, the intimate contact of the particles of DBBM with vital bone, with minimal inflammatory cell infiltrate and without evidence of fibrous encapsulation has proven the optimal potential of integration of this biomaterial (Lee et al. 2009; Milani et al. 2016).

However, it should be noted that under the generic definition “DBBM”, different commercial products have been introduced, each one with peculiar characteristics of production, surface, dimensions and, possibly, different potential for bone regeneration.

- Membranes and GBR.

Guided bone regeneration (GBR) is a pre-prosthetic approach aimed at augmenting the bony volume by the means of barrier membranes that “guide” the healing process, creating a space in which pluripotent cells can migrate and differentiate into bone-forming cells, and isolating this space from epithelial ingrowth, that would otherwise compete with the osteoblastic progenitors, due to its faster turn over (Dahlin et al. 1988; Dahlin et al. 1989; Becker et al. 1990).

Membranes for GBR can be either resorbable or non-resorbable. The latter type is usually made of expanded polytetrafluoroethylene (e-PTFE), with or without reinforced titanium strips, and, even though the space maintaining effect is maximum, the frequent infective complication and the need for a removal surgery made them almost disappear, in favor of bio-resorbable membranes. Xenogenic porcine collagen membranes, and synthetic ones made of polyurethane, polyglactin 910, polylactic acid, polyglycolic acid, polyorthoester or polyethylene glycol, in different combinations, are all resorbable devices, which undergo enzymatic degradation when inserted in a biological system. Membrane composition, pH, temperature, the polymer crystallization degree and the cross-linking collagen structures are all factors that influence the timing of resorption. Biological compliance is generally higher with resorbable membranes, but their space maintenance is of worse quality as they tend to

collapse (Warrer et al. 1992; Sandberg et al. 1993; Hardwick et al. 1995; Zellin et al. 1995; Hämmerle & Jung 2003; Jung et al. 2006; Sanz & Vignoletti 2015).

- Alloplastic bone substitutes.

Alloplastic (or synthetic) biomaterials are a wide class that includes bioactive glass, calcium sulphate, calcium phosphate/ beta-tricalcium phosphate/phosphosilicate, polylactic acid/poligalactic acid, and hydroxyapatite. Physical, chemical and biological properties depend on the type of material and the production treatment. In particular, the resorption rate is slowest for hydroxyapatite and fastest for tricalcium phosphate (TCP), but generally alloplastic grafts resorb faster than xenografts (Govindaraj et al. 1999; Sanz & Vignoletti 2015).

- Peptides.

This category includes a set of molecules of different nature that can trigger osteogenesis. Due to their chemical and physical nature, they are most often combined to a carrier, such as collagen sponges or DBBM. The most extensively investigated, to date, are:

- Enamel matrix derivatives (EMD), that have been used in clinical treatment procedures to promote periodontal regeneration. They are xenogenic peptides of porcine origin, very similar to the human form, which are thought to have an osteoinductive role,

promoting osteogenic gene expression and cell adhesion, besides the well-known property of induction of the cementogenesis in periodontal regeneration. The role of the cells of the severed periodontal ligament, which are the main target of EMD, in the healing of the post-extractive socket has suggested the idea that such molecules could be used in socket preservation procedures (Gestrelus et al. 1997; Lekic et al. 2001; Du et al. 2005; Alkan et al. 2013).

- Bone morphogenetic protein-2 (BMP-2), that belongs to the family of transforming growth factor β (TGF β) and has osteoinductive activity, triggering the apposition of bone matrix and the differentiation of mesenchymal stem cells into osteoblasts. The two commercially available forms of this compound are produced from mammalian cell cultures or from *Escherichia coli* cultures. The second type has the advantage of lower costs but still unproven clinical reliability (Israel et al. 1996; Fiorellini et al. 2005; Bessa et al. 2008; Huh et al. 2011).

Other potentially osteoinductive peptides, such as synthetic cell-binding peptide P-15 (Fernandes et al. 2011) and collagen-binding synthetic oligopeptides (Nam et al. 2011) have been tested but the evidence is still little.

- Platelet concentrates.

Platelet concentrates are blood extracts obtained after various forms of processing of a whole blood sample, mostly through centrifugation (Bielecki & Dohan Ehrenfest 2012), with the purpose of isolating one or more components, as fibrinogen/fibrin, platelets, growth factors or leukocytes, depending on the process. Such components will stimulate wound healing and promote hard and soft tissues formation.

Depending on the methods of centrifugation, either platelet rich plasma (PRP) or platelet rich fibrin (PRF) can be obtained, being the former a liquid solution with no (or little) presence of fibrin network and the second a gel with a high-density fibrin network (Dohan Ehrenfest et al. 2014).

The release of growth factors and matrix molecules is the key to the inductive activity of these concentrates on the hard and soft tissues healing.

2.2 Surgical techniques

Given the vast amount of biomaterials available for socket preservation, the surgical technique will depend on the material of choice.

However, general guidelines for the management of the site are :

- A careful atraumatic extraction, in order to preserve the bony walls of the socket, and, mostly, the thin labial plate;

- The removal of all the granulation and inflammatory tissue that would delay the healing process and compromise the graft;
- The filling of the socket with the biomaterial or the combination of biomaterials of choice, which can be done level with the marginal bone, or in excess, to attempt not only the preservation, but also the augmentation of the site (in the case of dehiscences, for example);
- The sealing of the socket with a suture, and, possibly, with a membrane, matrix, soft tissue graft or PRF gel.

According to the manufacturer's recommendations, the evidence in the literature and the surgeon's choice, the site is then accessed for delayed implantation when a predictable bone formation can be expected, usually after 4 to 6 months.

Whether a flap should be raised or not still remains a subject of debate. The interruption of the vascular supply to the hard tissues and the reflection of the periosteum might increase the amount of bone resorption (Fickl, Zuhr, Wachtel, Bolz, et al. 2008; Engler-Hamm et al. 2011; Novaes et al. 2012), but soft tissues primary closure, that can be achieved with a muco-periosteal reflection, can protect the graft and cover a membrane, when placed (Lekovic et al. 1997; Fickl, Zuhr, Wachtel, Stappert, et al. 2008; Darby et al. 2009).

Araujo and Lindhe reported no significant difference when a flapless technique was compared to a flapped approach (Mauricio G Araújo & Lindhe 2009).

Barone et al. provided clinical, histologic and histomorphometric examinations of sockets preserved either with a flapped or a flapless approach up to three months after the procedure.

The results were controversial: while no histological difference could be detected, the flapless technique seemed to better preserve the original width of the crest and the amount of keratinized soft tissues. On the other hand, the flapped approach showed less vertical bone resorption on the buccal aspect (Barone et al. 2014).

In discordance with these observations, Vignoletti et al. , on the basis of a meta-regression analysis realized over nine randomized clinical trials, estimated that a flapped approach would favor bone width preservation (Vignoletti et al. 2012).

An alternative to seal the socket and the graft, avoiding the elevation of a flap is a plug of free soft tissue (or soft tissue substitute) graft (Tal 1999).

3. Outcome assessments

The key aspect in the evaluation of the efficacy of the different biomaterials and techniques of socket preservation is to assess what primary outcomes have been measured in clinical and pre-clinical studies and what level of clinical significance they express.

In other words, these techniques are thought to be functional to implant-supported prosthetic rehabilitations, therefore the analysis of the dimensional variations of the ridge should be related to the histologic reality and, mostly, to the accomplishment of an ideal surgical and prosthetic treatment.

3.1 Bone height and bone width

Linear intra-operative assessments are often used to estimate the amount of bone resorption.

The variation of bone crest height between the moment of the extraction and the time of the access for the placement of a delayed implant is by far the most common primary outcome taken into account in the literature to assess the validity of a procedure of socket preservation.

The measurements are made from a constant reference, such as the cement-enamel junction of

the neighboring teeth, or resin stents that allow standardized evaluations at different times.

This assessment is usually made on the vestibular side of the crest, which is the most affected by bone resorption and the most important for implant placement.

Less frequently, the horizontal shrinkage of the crest is also assessed by measuring the bucco-lingual width of different sections of the socket (i.e. mesial, central and distal) at baseline and implantation.

Most of the studies have shown lesser vertical and horizontal bone loss in sockets treated with a preservation technique (Horváth et al. 2013).

Vignoletti et al. calculated a mean greater reduction of 1.47 mm and 1.83 in height and width, respectively, for sockets left to heal spontaneously compared to preserved sites (Vignoletti et al. 2012).

Similarly, in a review by Willenbacher et al. a mean difference between test and control groups of approximately 1.31 to 1.54 mm in bucco-oral bone width and 0.91 to 1.12 mm in bone height was found (Willenbacher et al. 2015).

Jambhekar et al. stratified the results according to the biomaterial: the mean loss in bone width was found to be lowest for xenografts (1.3 mm), followed by allografts (1.63 mm), alloplasts (2.13 mm), and sockets without any socket grafting (2.79 mm). The mean loss in buccal bone height was found to be lowest for xenografts (0.57 mm) and allografts (0.58

mm), followed by alloplasts (0.77 mm) and sockets without any grafting (1.74 mm) (Jambhekar et al. 2015).

In a meta-analysis by Atieh et al. the differences in bone loss between preserved and spontaneously healed sockets were even bigger: 2.6 mm in height and 1.97 in width for xenografts; 2.2 mm in height and 1.4 mm in width for allografts (Atieh et al. 2015).

However, some randomized controlled trials reported no significant benefit ascribable to these procedures in terms of post-extractive bone height or width loss (Horváth et al. 2013; Atieh et al. 2015).

3.2 Histological outcomes

Not many human or pre-clinical studies have provided histological evidence about sockets treated with preservation procedures. The percentages of lamellar bone, woven bone, osteoid, bone marrow, connective tissue and graft particles, as well as the amount of these particles that show direct contact with bony tissue, disclose the characteristics of the graft materials and the quality of the preserved hard tissues.

In a systematic review by Jambhekar et al. alloplastic grafts were shown to ensure the highest percentage of vital bone (45,53 %), even highest than in unassisted alveolar healing. More particles of biomaterial and lesser amounts of bone could be found with the use of xenografts

(35,72%) and homologous bone (29,93%) (Jambhekar et al. 2015). These findings are in accordance with the vast amounts of vital bone found after alloplastic grafting reported by Chan et al. (Chan et al. 2013).

Barallat et al. observed that few controlled studies have provided histologic evidence that the percentage of vital bone after socket preservation procedures is higher than in untreated control sites, being most common the opposite situation instead (Barallat et al. 2014).

The clinical relevance of the qualitative composition of regenerated bone is still not clear, as slow resorption rate of the graft material might ensure the long term stability of the site; on the other hand, the presence of inert particles might depress bone response to infective agents, and accelerate bone loss in the case of a peri-implantitis.

The well-documented persistence of large amounts of bone grafts within the regenerated hard tissues might as well interfere with bone healing (Horváth et al. 2013; Morjaria et al. 2014;), but it is logical to think that each biomaterial might have a different biological behaviour.

Araújo and Lindhe studied the histological effects of DDBM in a 10% collagen matrix, in a dog model, coming to the conclusion that this material would delay socket healing, but would finally counteract the ridge physiological resorption, without altering the amounts of lamellar bone, woven bone and bone marrow and with the creation of a direct contact between the bony tissue and the graft particles (Araújo et al. 2008; Araújo et al. 2009; Maurício G Araújo & Lindhe 2009; Araújo et al. 2010).

3.3 Radiographic outcomes

Assessments of bone height changes on periapical X-rays or volumetric alterations on computed tomography (CT) have also been employed to evaluate the effects of socket preservation procedures.

Standardized periapical X-rays were taken in a study by Mardas et al. up to 32 weeks postoperatively in sites receiving either alloplastic biphasic calcium phosphate, composed of hydroxylapatite and β -tricalcium phosphate (β -TCP), and a collagen barrier membrane or DDBM and the same barrier, showing comparable changes in radiographic alveolar bone (Mardas et al. 2011).

Jung et al. used cone beam scans (CBCT) in a randomized clinical trial, coming to the conclusion that DDBM in a 10% collagen matrix, covered with a collagen membrane or with an autogenous soft-tissue graft ensures the best hard tissues preservation when compared to β -TCP and to spontaneous healing (Jung et al. 2013).

Sbordone realized a retrospective study that compared patients who had undergone socket preservation with DDBM and a resorbable collagen membrane and patients treated with extraction alone, by the means of CBCT scans realized at baseline and 6 months after. Linear, surface and volumetric alterations were measured with a dedicated software, showing that the graft would limit, but not prevent, the alveolar resorption (Sbordone et al. 2015).

3.4 Implant-related outcomes

The possibility to comply with an ideal surgical and prosthetic treatment plan, positioning implants in adequate dimensions, number and position, as well as a decrease in the need of augmentation procedures before or in conjunction with implant placement is a fundamental, and still somehow neglected, outcome variable to assess the validity of the techniques of socket preservation.

On the other hand, these criteria might be less adequate for the detection of small differences and they are clearly connected to the linear and volumetric alterations which are more often taken into account in clinical and pre-clinical studies.

Also, long-term variables as survival/success rates and marginal bone loss at preserved sites have been rarely assessed in the literature.

Even though the amount of information appears insufficient (Atieh et al. 2015; Mardas et al. 2015; Brandam et al. 2015) socket preservation techniques seem to lower the need for augmentation procedures (Horváth et al. 2013; Darby 2010; Mardas et al. 2015). A review by Willenbacher et al.

reported that in preserved sites implant placement could take place without augmentation in 90.1% of the cases while this was the case in only 79.2% of the sockets left to heal spontaneously (Willenbacher et al. 2015).

However, implant feasibility, success/survival rates and marginal bone loss don't seem to be influenced by socket preservation procedures (Mardas et al. 2015)

3.6 Soft tissues

Lately, increasing attention is being given to the health and the esthetics of the soft tissues overlying sockets treated with preservation procedures.

Vanhoutte et al. proposed a method for the evaluation of the soft tissue contour changes, consisting of taking impressions at baseline and follow-up, laser-scanning the corresponding plaster models and using an imaging software to perform measurements of the volumetric alterations. In this way, both soft and hard tissues maturation can be assessed (Vanhoutte et al. 2014).

In a comparison of spontaneous healing versus ridge preservation with corticocancellous porcine bone and a collagen membrane, Barone et al. described a better preservation of facial keratinized tissue for the test sites (Barone et al. 2013).

Roccuzzo et al. published a 10-year follow-up prospective study investigating the healing and stability of the soft tissues around implants placed in sites previously augmented with demineralized bovine bone mineral in a 10% collagen matrix. The mean recession after 10

years was found to be <1 mm and peri-implantary scores, such as bleeding on probing, proved the soft tissue to be healthy (Roccuzzo et al. 2014).

Parashis et al. measured the changes in gingival thickness and width of keratinized tissue in sites preserved with freeze-dried homologous graft and two different xenogenic collagen matrices, coming to the conclusion that both the procedures were effective in the preservation of the soft tissues and suggesting that the thickness of the buccal plate is determinant for changes in the amount and composition of the mucosal tissues (Parashis et al. 2016).

Pellegrini et al. provided histologic specimens of the soft tissues of sockets healed spontaneously and sockets grafted with DBBM and collagen membrane, arguing that the presence of a membrane causes an initial and transient modification in the healing pattern of the mucosa (Pellegrini et al. 2014).

4. Cumulative results and guidelines

A raising number of review papers and meta-analyses is being published with the aim to discuss the general validity of socket preservation procedures, summing up the abundant data coming from clinical and pre-clinical studies.

It appears quite clear that an overall advantage in terms of control of bone height and width loss can be expected from these procedures (Darby 2010; Horowitz et al. 2012; Vignoletti et al. 2012).

However, it is still controversial whether this advantage is clinically relevant, that is to say whether such hard tissues preservation improves the implant therapy feasibility and maintenance at all (Hämmerle et al. 2012; Horváth et al. 2013; Mardas et al. 2015).

Also, all the techniques and the biomaterials that have proven some efficacy, could only in part counteract the physiological shrinkage of the ridge. Some bone resorption after tooth extraction is to be expected anyways, irrespectively of the approach used to preserve the site (Byrne 2012; Wang & Lang 2012; De Buitrago et al. 2013).

Some of the authors who have been systematically reviewing the literature concluded that implant placement and survival/success rates don't seem to be drastically affected by alveolar

ridge preservation techniques (Darby 2010; Atieh et al. 2015; Mardas et al. 2015). More importantly, long-term data about the outcome of implant therapy after ridge preservation procedures are lacking (Vignoletti et al. 2012; Brandam et al. 2015).

On the other hand, these procedures seem to ensure a decrease in the need for augmentation procedures before or at the time of implant placement (Horváth et al. 2013; Willenbacher et al. 2015; Mardas et al. 2015).

No biomaterial or surgical technique has proven clear advantage over the others in terms of hard tissues preservation (Horowitz et al. 2012), even though, in some cases, a flapped approach, the application of a membrane and the usage of a xenograft or an allograft have shown to be more effective (Vignoletti et al. 2012; ; Horváth et al. 2013; Vittorini Orgeas et al.; Avila-Ortiz et al. 2014).

The 4th EAO Consensus Conference of 2015 on the therapeutic concepts and methods for improving dental implant outcome (Sanz et al. 2015) stated that socket preservation is a valid therapeutic concept because it significantly reduces the post-extraction ridge dimensional changes, increasing the possibility of complying with an ideal prosthetically-driven treatment plan and decreasing the need for augmentation procedures.

However, given all the cited concerns, the choice to either undertake a site preservation procedure or leave the socket to heal spontaneously should be done in a case-by-case attitude, considering local and general factors.

As for local factors, it should be considered that not all sockets have the same risk of bone resorption after extraction. Tooth location and reason for extraction are the main local factors: they are related to vestibular plate thickness, esthetic considerations, the degree of hard tissues impairment that have already occurred before the extraction and the presence of products of the inflammation that would contraindicate bone grafting. Also, sockets of tooth affected by periodontal disease heal slower than disease-free sites (Ahn & Shin).

A buccal bone wall thicker than 1 mm seems to better preserve the hard tissues architecture; this may also explain why the anterior segment of the arch, where the buccal plate is usually thin, is more prone to post-extractive bone resorption (Ferrus et al. 2010; Januário et al. 2011).

The number of extractions, and the presence/absence of neighboring teeth, with their periodontal tissues, might also influence the degree of bone loss (Al-Hezaimi et al. 2014).

As for general factors, treatment duration is extended when preservation is attempted, even though an evidence-based preferred time point for implant placement can't be identified .

Most importantly, cost benefit and patient expectations and preferences should be taken into account.

The EAO Consensus Conference of 2015 also advocated the need for future investigation to:

- Carry out well-designed clinical trials to compare socket preservation protocols with other implant placement protocols.

- Carry out well-designed clinical trials to compare different surgical interventions (biomaterials, sealers) for alveolar ridge preservation.
- Evaluate the outcomes of socket preservation protocols with accurate and reproducible non-invasive outcome measurements to evaluate soft and hard tissue changes.
- Evaluate the outcomes of socket preservation protocols with validated esthetic indexes, patient-reported outcome measures (PROMs) and cost benefit indicators.
- Study the healing characteristics and dynamics of the different biomaterials for socket preservation.
- Study the appropriate times for implant placement after socket preservation protocols.

To date, the published trials testing different techniques of socket preservation have a high degree of heterogeneity, being different the biomaterials, the surgical techniques and the kind of sockets tested (single/multiple, position in the mouth and number of residual bony walls), as well as the reasons for teeth extraction and the methods of evaluation. Also, the risk of bias is often moderate to high (Vignoletti et al. 2012).

Furthermore, it appears that many other less investigated local and systemic factors can affect residual ridge resorption, such as blood supply, availability of bone cells, skeletal status, bone regulatory hormones and dietary calcium (Kingsmill 1999), which makes even more complex the stratification of the risk for bone loss after tooth extraction and the consequent decision to whether attempt or not a socket preservation procedure.

The tendency for bone resorption in a post-extractive socket still remains not completely predictable: the control (i.e. untreated) sockets considered in the studies selected for the already cited meta-analysis by Vignoletti et al. displayed high degrees of variability in both vertical and horizontal bone loss, ranging from -0.3 to -3.75 mm and from -0.16 to -4.50 mm, respectively (Vignoletti et al. 2012).

Therefore, a concern for the identification of the sites with higher tendency to bone loss after tooth extraction should arise, avoiding an indiscriminate employment of socket preservation techniques in all post-extractive sites, which could easily trespass into overtreatment.

5. Clinical outcomes of socket preservation after tooth extraction using bovine-derived xenograft collagen and collagen membrane or deproteinized bovine bone mineral and collagen membrane compared to blood clot alone. A six-months randomized controlled clinical trial.

5.1 Introduction.

Several studies have demonstrated that the use of DBBM in combination with a collagen membrane as means of socket preservation promotes better results than the blood clot alone (Artzi & Nemcovsky 1998; Cardaropoli et al. 2014; Pang et al. 2014; Schneider et al. 2014; Lindhe et al. 2014) .

Recently, it was observed that the placement of bovine-derived xenograft collagen in the fresh extraction socket seemed to preserve the dimension of alveolar ridge modifying the remodeling and counteracting marginal ridge contraction that occurs after tooth removal (Araújo et al. 2009; Maurício G Araújo & Lindhe 2009; Araújo et al. 2010; Cardaropoli et al. 2012; Barone et al. 2013).

The aim of present study was to evaluate the clinical changes of fresh alveolar sockets treated with bovine-derived xenograft collagen and collagen membrane or deproteinized bovine bone mineral (DBBM) and collagen membrane compared with spontaneous healing after a period of 6-months follow-up.

5.2 Materials and Methods

Experimental design.

The study design was a randomized controlled clinical trial.

In the test sites A, bovine-derived xenograft with 10% collagen (BioOss® Collagen Geistlich Pharma AG, Wolhusen- Switzerland) was placed immediately after tooth extraction and covered with a collagen membrane (BioGide® Geistlich Pharma AG, Wolhusen- Switzerland); in the test sites B, deproteinized bovine bone mineral (BioOss® Collagen Geistlich Pharma AG, Wolhusen- Switzerland) and a collagen membrane (BioGide® Geistlich Pharma AG, Wolhusen- Switzerland) were placed; in the control sites regenerative procedures were not performed and the socket was left to heal spontaneously.

The null hypothesis was that post-extractive horizontal and vertical alveolar resorption of sockets belonging to group A, group B and control group would be similar.

The software SPSS® (Statistical Package for Social Science, IBM, Armonk, NY- USA) was used to assess the sample size, considering:

$$\alpha = 0.05$$

$$\sigma = 0.3$$

$$P = 0.8$$

The calculated sample size was of 45 patients (15 for each group).

A single fresh alveolar socket was treated in each subject. The patient was masked with respect to the experimental procedures. The fresh alveolar sockets were randomly assigned to test or control groups. The allocation was carried out using a commercially available computer software package (NCSS-PASS®, Number Cruncher Statistical Systems, Kaysville, UT- USA). Treatment allocation was performed at time of surgery after tooth extraction by opening an envelope containing the information “test A” (i.e. bovine-derived xenograft with 10% collagen and collagen membrane), “test B” (i.e. deproteinized bovine bone mineral and collagen membrane) or “control” (i.e. spontaneous healing) procedure, respectively.

The study protocol was submitted to and approved by the Ethical Committee of the “Federico II” University, Naples, Italy (protocol Nr. 25/14). Written informed consent was obtained and the study was conducted according to the principles of the Declaration of Helsinki on experimentation involving human subjects.

Patient population

In 45 subjects, a total of 45 fresh alveolar sockets were selected. The subjects were recruited from the patient pool of the Department of Periodontology, University “Federico II”, Naples, Italy.

The following inclusion criteria were applied: age ≥ 18 years; presence of one mandibular or maxillary tooth to be extracted because of endodontic failure, caries, or root fracture; integrity of extraction socket walls or presence of self-contained buccal wall dehiscences; full-mouth plaque score (FMPS) and full-mouth bleeding score (FMBS) $\leq 25\%$ at baseline; presence of at least 2 mm of keratinized tissue to allow flap management.

Subjects were excluded on the basis of presence of relevant medical conditions contraindicating surgical intervention, pregnancy or lactation, tobacco smoking, periodontal disease, or absence of neighboring teeth (mesial and distal) to the tooth that needed extraction.

Experimental procedures

Clinical parameters

At baseline, the following parameters were recorded at six sites per tooth (i.e, distobuccal, buccal, mesiobuccal, mesiolingual, lingual, distolingual): FMPS and FMBS using a manual periodontal probe (PCP-UNC 15, Hu-Friedy, Chicago, IL, USA) and a probing force of 0.3N.

Surgical procedures

After elevation of a mucoperiosteal flap extending one tooth in the mesial and distal direction, tooth extraction was performed. Granulation tissue was removed with hand instruments and the fresh alveolar socket was rinsed with sterile saline. Subjects were randomly assigned to test A, test B or control group according to randomization procedures. For the test group A, bovine-derived xenograft with 10% collagen (BioOss® Collagen Geistlich Pharma AG, Wolhusen- Switzerland) was placed into fresh alveolar sockets and covered with a collagen membrane (BioGide® Geistlich Pharma AG, Wolhusen- Switzerland), while for test group B deproteinized bovine bone mineral (BioOss® Collagen Geistlich Pharma AG, Wolhusen- Switzerland) and a collagen membrane (BioGide® Geistlich Pharma AG, Wolhusen- Switzerland) were used. The collagen membrane was left intentionally exposed to the oral cavity and non-resorbable monofilament sutures were used to stabilize the membrane. For the control group no further treatment was applied and the coagulum within the socket was left open for spontaneous healing.

Intra-surgical measurements

After tooth extraction and before randomization procedures, the following intra-surgical measurements were recorded:

- vertical distance from reference periodontal probe that connected the CEJ of the adjacent teeth and alveolar crest (CEJ-AC), measured at the mesio-distal center of the vestibular plate;

- horizontal alveolar width, measured from the outer vestibular plate to the outer lingual/palatal plate, at the mesio-distal center of the socket (WIDTH);
- thickness of buccal and lingual alveolar bone walls.

Horizontal alveolar width and thickness of alveolar walls were measured with a manual caliper, 2 mm below the top of the crest.

- In case of self-contained buccal dehiscences, height (A-B) and width (C-D) were recorded. Height was recorded as distance of the most apical point of the dehiscence from the alveolar crest. As for width, it was calculated at the top of the vestibular crest, and dehiscences were classified as “narrow” or “wide” if the C-D distance was ≤ 3 mm or > 3 mm, respectively.

Post-surgical instructions and infection control

For all groups the sutures were removed after 7 days.

Patients received ibuprofen (eg, 600 mg immediately after the surgical intervention and after 4 hours), and systemic antibiotics (eg. amoxicillin + clavulanic acid , 1g twice daily for 7 days). Patients were instructed to rinse twice daily with 0.12% chlorhexidine digluconate for the first 2 weeks.

Surgical re-entry

After 6 months of healing, a surgical reentry procedure was performed. A full-thickness flap was elevated to allow access to the bone crest. The vertical and horizontal measurements

(CEJ-AC and WIDTH) were repeated. All patients received submerged dental implants. The surgical flaps, subsequently, were sutured.

Statistical analysis

Linear variables are reported as means and standard deviations, medians and IQR (inter-quartile range) while categorical and dichotomous variables are reported as percentages.

Normality of data, according to the distribution of vertical bone levels (primary outcome variable) was assessed with Kolmogorov-Smirnov test in order to choose between parametric and non-parametric analysis.

ANOVA test was performed to assess homogeneity of groups for age, gender, FMPS and FMBS, while presence of buccal dehiscences, reasons for tooth extraction and sites location among different groups were compared with λ -test.

Inter-group comparisons for vertical and horizontal bone levels at baseline and at follow-up, as well as changes in vertical and horizontal bone levels were performed with Kruskal-Wallis and Mann-Whitney tests. A further evaluation was performed for the same parameters, using the same tests, dividing the sockets on the basis of presence or absence of buccal dehiscences and comparing the outcomes.

Intra-group comparisons between vertical and horizontal bone levels at baseline and at follow-up were performed with Wilcoxon signed-rank tests.

A p-value <0.05 was considered statistically significant for all tests.

5.3 Results

The characteristics of patient population at baseline are presented in Table 1 . A total of 45 patients who fulfilled the inclusion criteria were enrolled. No statistically significant differences ($P < 0.05$) were observed with respect to the mean age, gender, FMPS, FMBS and presence of self-contained buccal bone dehiscences between groups.

Table 2 summarizes the reasons of tooth extraction and also in this case no statistical significant differences were observed between groups ($P < 0.05$).

Table 3 shows the sites location enrolled in the study. Most of the sites included in the experimentation were located in posterior area of lower jaw, while no sites in anterior lower jaw were enrolled. No statistically significant differences between groups were found as for tooth location ($P < 0.05$).

In table 4 the findings related to the mean change at the buccal aspect within and between groups are presented. In all groups significant statistical differences were noted between baseline and surgical re-entry ($P < 0.05$), but no statistically significant differences were found between groups ($P > 0.05$).

In table 5 data of horizontal mean changes in the middle area of sockets are shown. No statistically significant differences were recorded between three experimental procedures

($P>0.05$), but statistically differences were found between baseline and 6-months surgical re-entry ($P<0.05$) within each one of the three groups.

All dehiscences were classified as “wide”, so only mean heights were considered for statistical analysis. In table 6 the intra-surgical measurements of self-contained dehiscences after tooth extraction are presented. The mean heights from bone crest were 8.29 ± 3.4 mm , 7.86 ± 2.6 mm and 6.71 ± 3.6 mm respectively for test group A, test group B and control group.

No statistically differences were noted in self-contained buccal dehiscences distribution between groups ($P>0.05$).

Table 7 summarizes intra-surgical outcomes between sites with and without self-contained buccal dehiscences in terms of vertical and horizontal mean bone changes. A statistically significant difference was recorded between groups in terms of vertical bone changes ($P<0.05$), while no significant differences were noted in terms of horizontal bone changes ($P>0.05$).

5.4 Discussion

The purpose of the present study was to evaluate the effects of two different types of bone xenograft in combination with a collagen membrane on socket remodeling after a six-months healing period and to compare these outcomes with spontaneous healing.

In apparent discordance with most of the studies that have already evaluated these materials in socket preservation procedures, our protocol showed no statistically significant difference between the two materials and between any of them and spontaneous healing as for changes in alveolar ridge height or width. This fact can be explained considering the characteristics of the fresh alveolar sockets enrolled in the study. The presence of self-contained buccal dehiscences, in many of the cases, has contributed to show no statistically significant differences between groups. Contrary to what could be expected from a socket with intact walls, after six months of healing the mean change in the distance between vestibular bone crest and the CEJ of adjacent tooth decreased. This event was more marked in the test groups, being quite similar in test A and test B group, but a slight decrease in AC-CEJ was recorded even in the sites which were not grafted, probably because of the self-contained shape of the fresh alveolar socket that would stabilize the blood clot.

In fact, a subgroup analysis showed how the decrease in AC-CEJ (i.e. the augmentation of the hard tissues) registered six months after the extraction is mainly related to the sites that displayed a self-contained buccal dehiscence after tooth extraction.

On the other hand, the sites with no dehiscence showed small changes between baseline and surgical re-entry as for bone height, irrespectively of the group, and this is the reason why no statistically significant differences could be found for subgroups with intact walls sockets.

This could be related to the fact that most tooth locations were posterior mandible or maxilla, and the vestibular plates of the fresh alveolar sockets were generally thick 1 mm or more.

Cardaropoli et al. have pointed out that, whereas preserved sockets with DDBM would undergo limited bone resorption regardless of the vestibular bone thickness, this variable is crucial to the bone loss affecting sites left to heal spontaneously (Cardaropoli et al. 2014).

As for reduction in bone width, it appeared to happen irrespectively of the graft material used or spontaneous healing or of the presence of a bone dehiscence on the vestibular plate, even though a bone dehiscence might exacerbate such reduction.

As already mentioned, previous clinical trials could find statistically significant differences between fresh alveolar sockets treated with bovine-derived xenograft collagen and collagen membrane or deproteinized bovine bone mineral (DBBM) and collagen membrane and sockets left to heal spontaneously. However, in some studies the measurements were not intra-surgical, as in the case of Cardaropoli et al. and Schenider et al., that made assessments on dental casts, in which the soft tissues component might somehow mask the underlying bony structure.

In studies conducted by Cardaropoli et al. and Barone et al. fresh alveolar sockets with self-contained buccal bone dehiscences were excluded, meanwhile Pang et al. proved statistically significant differences between DBBM and control group based on radiographic

measurements (Cardaropoli et al. 2012; Barone et al.; Schneider et al. 2014; Lindhe et al. 2014; Pang et al. 2014).

More importantly, in some trials, no unassisted healing group was tested (Mardas et al. 2011; Gholami et al. 2012; Barone et al.)

It should be noted that the absence of significance in bone height changes between groups observed in the present study should be ascribed to the stability of the control sites more than to a lack of effectiveness of the grafting materials.

5.5 Conclusions

Within the limits of this study, bovine-derived xenograft collagen and collagen membrane or deproteinized bovine bone mineral and collagen membrane are effective methods to prevent vertical bone loss after tooth extraction and to augment the ridge in presence of self-contained buccal dehiscences .

However, further studies with large samples are needed to clarify the advantage of placing graft materials in a fresh alveolar socket and covering them with a collagen membrane compared with spontaneous healing.

5.6 Tables

TAB. 1: PATIENT POPULATION

	Test Sites (A) (N=15)	Test Sites (B) (N=15)	Control Sites (N=15)	Significance
Age (Years)	43.8±15.2	43.6±14.2	38.4±13.2	0.51 NS
Gender (F/M)	8/7	5/10	10/5	0.19 NS
FMPS (%)	12.6±2.9	14.8±2.1	12.4±2.3	0.72 NS
FMBS (%)	11.9±3.6	13.5±1.7	11.9±1.3	0.56 NS
Presence of buccal dehiscence(BD)(%,Y/N)	40 (7/8)	40 (7/8)	46.7 (8/7)	0.91 NS

TAB. 2: REASONS FOR TOOTH EXTRACTION

	Test Sites (A) (N=15)	Test Sites (B) (N=15)	Control Sites (N=15)	Significance
Fractures (n; %)	2; 13.3	3; 20	2; 13.3	0.81 NS
Endodontic Reasons (n; %)	4; 26.7	6; 40	4; 26.7	
Caries (n; %)	8; 53.3	6; 40	9; 60	
Others (n; %)	1; 0.7	0; 0	0; 0	

TAB. 3: SITES LOCATION

	Test Sites (A) (N=15)	Test Sites (B) (N=15)	Control Sites (N=15)	Significance
Anterior MAX (n; %)	3; 20	2; 13,3	0; 0	0.24 NS
Posterior MAX (n; %)	7; 46.7	4; 26.7	5; 33.3	
Anterior MDB (n; %)	0; 0	0; 0	0; 0	
Posterior MDB (n; %)	5; 33.3	9; 60	10; 66.7	

TAB. 4: VERTICAL CHANGES (MEDIAN, IQR; MEAN \pm SD) AT THE BUCCAL ASPECT BETWEEN BASELINE AND RE-ENTRY AT SIX MONTHS.

		Test Sites (A) (N=15)	Test Sites (B) (N=15)	Control Sites (N=15)	Significance
Baseline	(Median; IQR)	4 .5; 6 .5	5; 6 .5	3 .5; 6 .5	0.40 NS
	(Mean \pm StdDev)	5.57 \pm 3.52	5.36 \pm 2.17	4.5 \pm 2.62	
Re-Entry	(Median; IQR)	3; 6 .5	3; 6 .5	3 .5; 6 .5	0.20 NS
	(Mean \pm StdDev)	3.29 \pm 0.73	3 \pm 1.04	3.86 \pm 1.83	
Difference	(Median; IQR)	1; 6 .5	2; 6.5	0; 6 .5	0.13 NS
	(Mean \pm StdDev)	2.29 \pm 3.81	2.36 \pm 2.37	0.64 \pm 2.27	
Significance		0.0001 S	0.001 S	0.001 S	

TAB. 5: HORIZONTAL CHANGES (MEDIAN, IQR; MEAN±SD) IN THE MESIO-DISTAL CENTER BETWEEN BASELINE AND RE-ENTRY AT SIX MONTHS.

		Test Sites (A) (N=15)	Test Sites (B) (N=15)	Control Sites (N=15)	Significance
Baseline	(Median; IQR)	10; 3	10.5; 2	10.5; 4	0.75 NS
	(Mean±StdDev)	9.24±0.31	9.58±0.24	9.76±0.38	
Re-Entry	(Median; IQR)	8; 2.5	9; 2.5	8.5; 2.75	0.47 NS
	(Mean±StdDev)	7.71±2.05	8.43±2.10	8.5±2.88	
Difference	(Median; IQR)	2; 1	1.5; 1	2; 1.75	0.35 NS
	(Mean±StdDev)	2.57±1.34	1.78±1.42	2.21±1.58	
Significance		0.001 S	0.001 S	0.001 S	

TAB. 6: MEAN VERTICAL (A-B) MEASUREMENT OF BUCCAL BONY DEHISCENCES.

		Test Sites (A) (N=7)	Test Sites (B) (N=7)	Control Sites (N=8)	Significance
Height (A-B)	(Median; IQR)	8; 4	8; 4	7; 1	0,53 NS
	(Mean±StdDev)	8.29±3.4	7.86±2.61	6.71±2.36	

TAB. 7: VERTICAL AND HORIZONTAL BONE CREST CHANGES BETWEEN FRESH ALVEOLAR SOCKETS WITH OR WITHOUT BUCCAL DEHISCENCES AFTER 6-MONTHS RE-ENTRY.

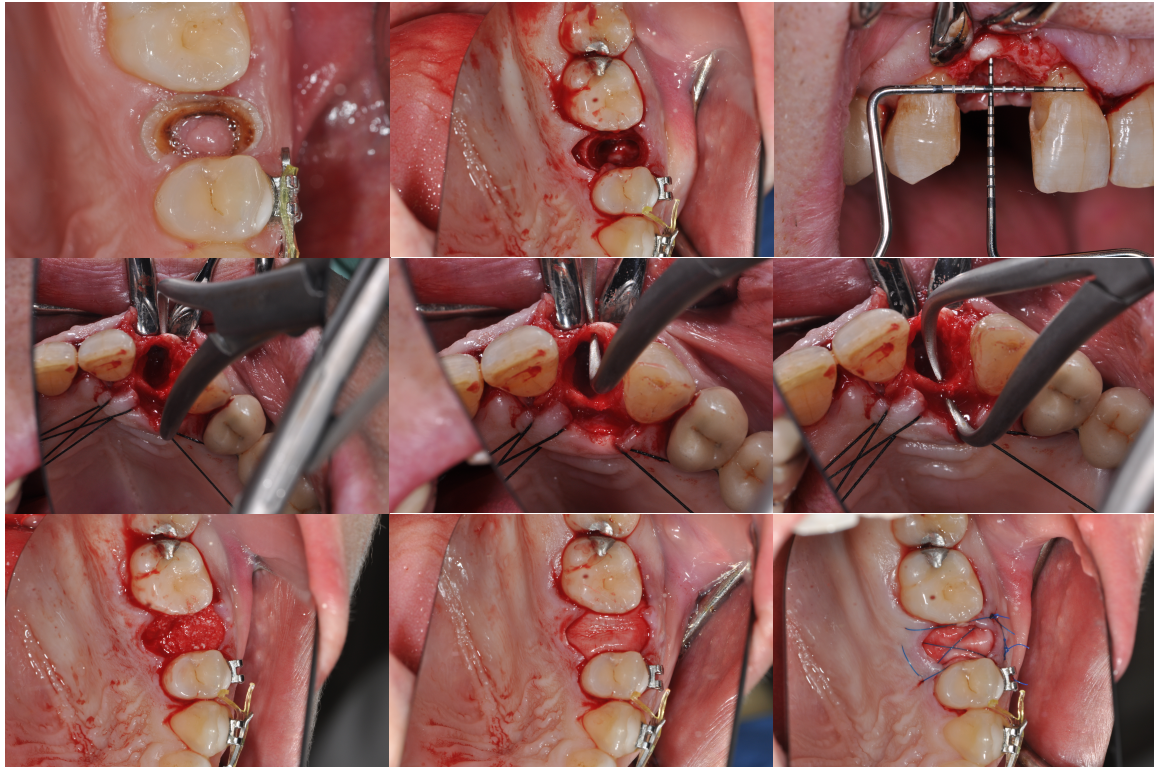
Vertical Changes										
		Fresh Alveolar Socket Without Dehiscences			Fresh Alveolar Socket With Buccal Dehiscences			Significance		
		Test Group A	Test Group B	Control Group	Test Group A	Test Group B	Control Group	Test GroupA	Test GroupB	Control Group
Baseline	(Median; IQR)	3; 1	4; 2	3; 2	8; 4	8; 4	7; 1	0.01 S	0.005 S	0.004 S
	(Mean±StDev)	3.38±0.74	4±0.93	2.88±0.99	8.29±3.4	7.86±2.61	6.71±2.36			
Re-Entry	(Median; IQR)	3; 1	3; 2	10; 5	3; 0	2; 2	5; 3	0.39 NS	0.47 NS	0.64 NS
	(Mean±StDev)	3.38±0.92	3.13±0.84	3.50±2	3±0.33	2.86±1.22	4.43±1.51			
Difference	(Median; IQR)	0; 2	1; 2	0; 2	5; 4	4; 5	2; 5	0.003 S	0.002 S	0.008 S
	(Mean±StDev)	0±1.51	0.88±1.25	-0.63±1.3	5.29±3.55	5±2.58	2.29±2.06			
Significance		0.01 S	0.01 S	0.01 S	0.01 S	0.02 S	0.02 S			

Horizontal Changes										
		Fresh Alveolar Socket Without Dehiscences			Fresh Alveolar Socket With Buccal Dehiscences			Significance		
		Test Group A	Test Group B	Control Group	Test Group A	Test Group B	Control Group	Test GroupA	Test GroupB	Control Group
Baseline	(Median; IQR)	10; 4	9.5; 3	3; 4	11; 3	11; 2	12; 4	0.81 NS	0.11 NS	0.38 NS
	(Mean±StDev)	10.38±2.13	9.75±1.83	10.63±2.45	10.29±1.6	11.14±1.35	11.14±3.53			
Re-Entry	(Median; IQR)	8; 4	8.5; 4	9; 2	8; 4	10; 2	8; 7	0.35 NS	0.16 NS	0.73 NS
	(Mean±StDev)	8.38±2.13	7.88±2.42	8.88±1.55	7.14±1.77	9.29±1.38	8.57±4.12			
Difference	(Median; IQR)	2; 0	2; 2	2; 3	3; 2	1; 2	2; 3	0.13 NS	0.77 NS	0.55 NS
	(Mean±StDev)	2±0.54	1.88±1.25	1.75±1.28	3.14±1.68	1.86±1.68	2.57±1.81			
Significance		0.01 S	0.01 S	0.01 S	0.02 S	0.02 S	0.02 S			

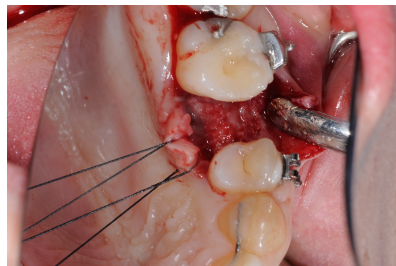
5.7 Figures

CASE FROM GROUP A (BioOss® Collagen + BioGide®)

Baseline (extraction and grafting)

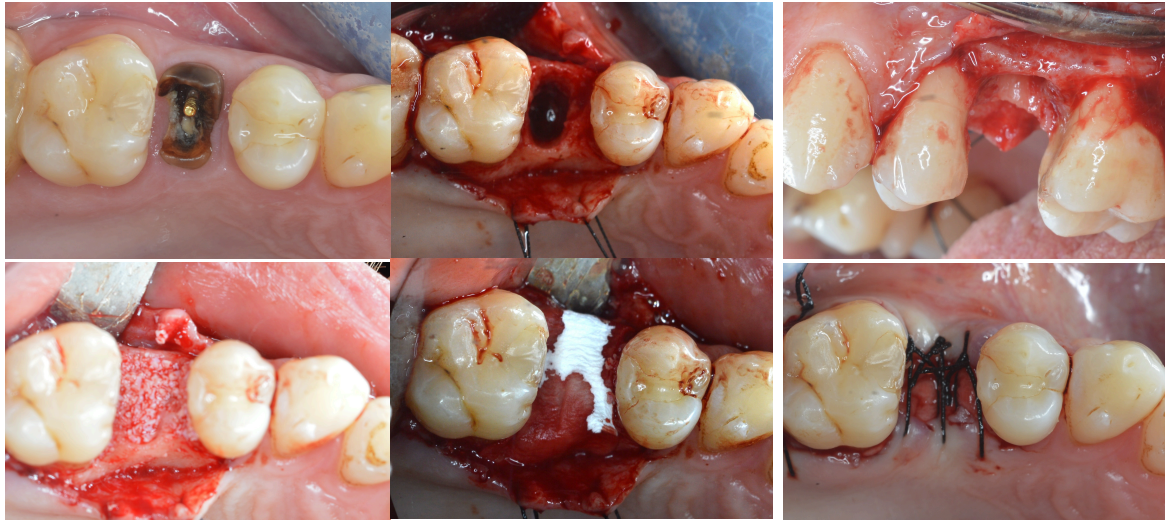


Surgical re-entry

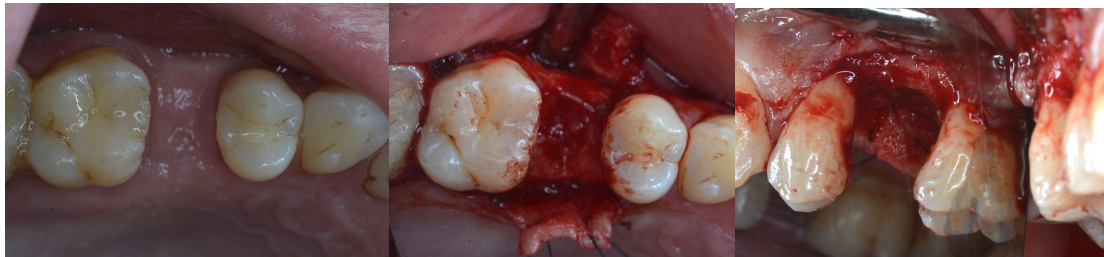


CASE FROM GROUP B (BioOss® + BioGide®)

Baseline (extraction and grafting)

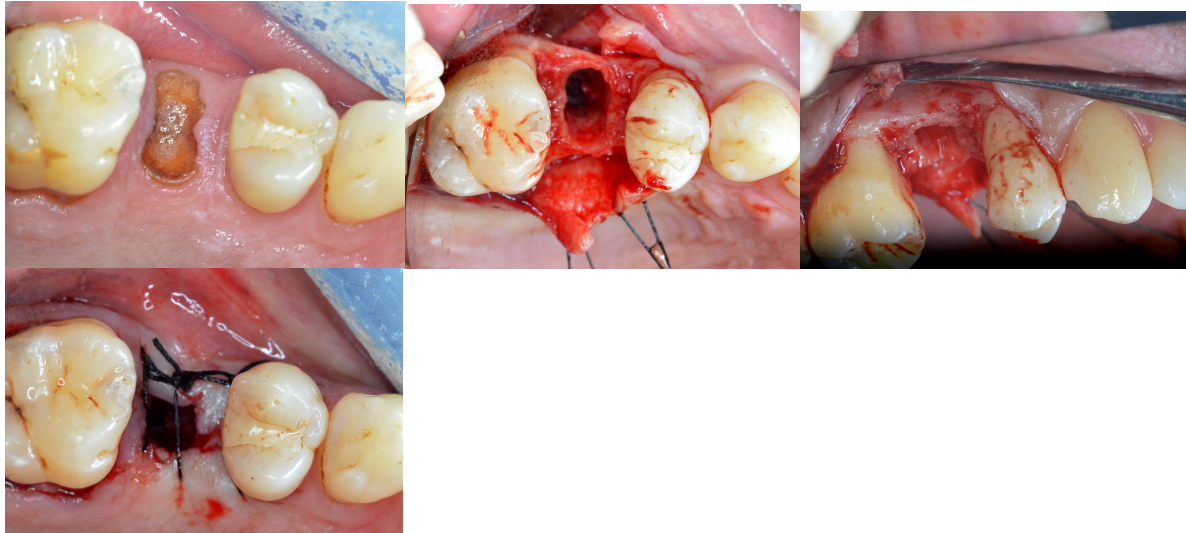


Surgical re-entry

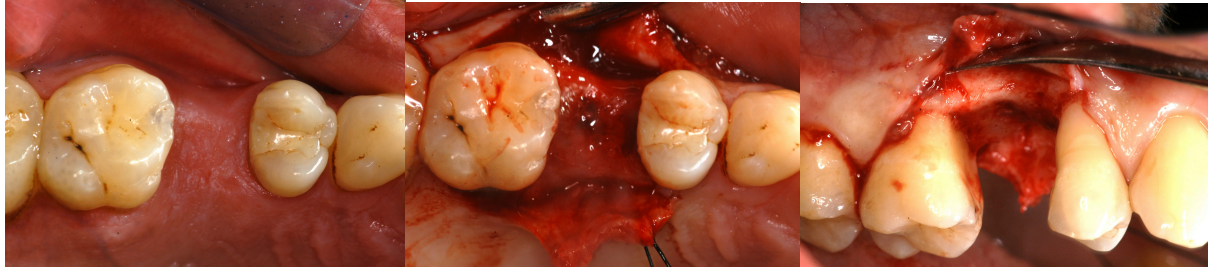


CASE FROM CONTROL GROUP

Baseline (extraction)



Surgical re-entry



6. References

- Ahn, J.-J. & Shin, H.-I., Bone tissue formation in extraction sockets from sites with advanced periodontal disease: a histomorphometric study in humans. *The International journal of oral & maxillofacial implants*, 23(6), pp.1133–8.
- Al-Hezaimi, K. et al., 2014. Microcomputed tomographic analysis of the alveolar ridge alteration around extraction sites with and without immediate implants placement: in vivo study. *Clinical implant dentistry and related research*, 16(2), pp.223–9.
- Alkan, E.A. et al., 2013. Histological comparison of healing following tooth extraction with ridge preservation using enamel matrix derivatives versus Bio-Oss Collagen: a pilot study. *International journal of oral and maxillofacial surgery*, 42(12), pp.1522–8.
- Araújo, M. et al., 2008. The influence of Bio-Oss Collagen on healing of an extraction socket: an experimental study in the dog. *The International journal of periodontics & restorative dentistry*, 28(2), pp.123–35.
- Araújo, M., Linder, E. & Lindhe, J., 2009. Effect of a xenograft on early bone formation in extraction sockets: an experimental study in dog. *Clinical oral implants research*, 20(1), pp.1–6.
- Araújo, M.G. et al., 2005. Ridge alterations following implant placement in fresh extraction sockets: an experimental study in the dog. *Journal of clinical periodontology*, 32(6), pp.645–52.
- Araújo, M.G., Liljenberg, B. & Lindhe, J., 2010. Dynamics of Bio-Oss Collagen incorporation in fresh extraction wounds: an experimental study in the dog. *Clinical oral implants research*, 21(1), pp.55–64.
- Araújo, M.G. & Lindhe, J., 2005. Dimensional ridge alterations following tooth extraction. An experimental study in the dog. *Journal of clinical periodontology*, 32(2), pp.212–8.

- Araújo, M.G. & Lindhe, J., 2009. Ridge alterations following tooth extraction with and without flap elevation: an experimental study in the dog. *Clinical oral implants research*, 20(6), pp.545–9.
- Araújo, M.G. & Lindhe, J., 2009. Ridge preservation with the use of Bio-Oss collagen: A 6-month study in the dog. *Clinical oral implants research*, 20(5), pp.433–40.
- Artzi, Z. & Nemcovsky, C.E., 1998. The application of deproteinized bovine bone mineral for ridge preservation prior to implantation. Clinical and histological observations in a case report. *Journal of periodontology*, 69(9), pp.1062–7.
- Artzi, Z., Tal, H. & Dayan, D., 2000. Porous bovine bone mineral in healing of human extraction sockets. Part 1: histomorphometric evaluations at 9 months. *Journal of periodontology*, 71(6), pp.1015–23.
- von Arx, T., Häfliger, J. & Chappuis, V., 2005. Neurosensory disturbances following bone harvesting in the symphysis: a prospective clinical study. *Clinical oral implants research*, 16(4), pp.432–9.
- Atieh, M.A. et al., 2015. Interventions for replacing missing teeth: alveolar ridge preservation techniques for dental implant site development. *The Cochrane database of systematic reviews*, 5, p.CD010176.
- Atwood, D.A., 1971. Reduction of residual ridges: a major oral disease entity. *The Journal of prosthetic dentistry*, 26(3), pp.266–79.
- Atwood, D.A., 2001. Some clinical factors related to rate of resorption of residual ridges. 1962. *The Journal of prosthetic dentistry*, 86(2), pp.119–25.
- Avila-Ortiz, G. et al., 2014. Effect of alveolar ridge preservation after tooth extraction: a systematic review and meta-analysis. *Journal of dental research*, 93(10), pp.950–8.
- Barallat, L. et al., 2014. Histomorphometric results in ridge preservation procedures comparing various graft materials in extraction sockets with nongrafted sockets in humans: a systematic review. *Implant dentistry*, 23(5), pp.539–54.

- Barone, A. et al., A prospective, randomized, controlled, multicenter evaluation of extraction socket preservation comparing two bovine xenografts: clinical and histologic outcomes. *The International journal of periodontics & restorative dentistry*, 33(6), pp.795–802.
- Barone, A. et al., 2014. Extraction socket healing in humans after ridge preservation techniques: comparison between flapless and flapped procedures in a randomized clinical trial. *Journal of periodontology*, 85(1), pp.14–23.
- Barone, A. et al., 2013. Tissue changes of extraction sockets in humans: a comparison of spontaneous healing vs. ridge preservation with secondary soft tissue healing. *Clinical oral implants research*, 24(11), pp.1231–7.
- Becker, W. et al., 1990. Bone formation at dehiscenced dental implant sites treated with implant augmentation material: a pilot study in dogs. *The International journal of periodontics & restorative dentistry*, 10(2), pp.92–101.
- Berglundh, T. & Lindhe, J., 1997. Healing around implants placed in bone defects treated with Bio-Oss. An experimental study in the dog. *Clinical oral implants research*, 8(2), pp.117–24.
- Bessa, P.C., Casal, M. & Reis, R.L., 2008. Bone morphogenetic proteins in tissue engineering: the road from the laboratory to the clinic, part I (basic concepts). *Journal of tissue engineering and regenerative medicine*, 2(1), pp.1–13.
- Bianchi, A. et al., 2008. Alveolar distraction osteogenesis versus inlay bone grafting in posterior mandibular atrophy: a prospective study. *Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics*, 105(3), pp.282–92.
- Bielecki, T. & Dohan Ehrenfest, D.M., 2012. Platelet-rich plasma (PRP) and Platelet-Rich Fibrin (PRF): surgical adjuvants, preparations for in situ regenerative medicine and tools for tissue engineering. *Current pharmaceutical biotechnology*, 13(7), pp.1121–30.
- Boyne, P.J. & James, R.A., 1980. Grafting of the maxillary sinus floor with autogenous marrow and bone. *Journal of oral surgery (American Dental Association : 1965)*, 38(8), pp.613–6.
- Brandam, L. et al., 2015. Ridge Preservation Techniques in the Anterior Esthetic Zone.

Implant dentistry, 24(6), pp.699–712.

- De Buitrago, J.G., Avila-Ortiz, G. & Elangovan, S., 2013. Quality assessment of systematic reviews on alveolar ridge preservation. *Journal of the American Dental Association (1939)*, 144(12), pp.1349–57.
- Burchardt, H., 1983. The biology of bone graft repair. *Clinical orthopaedics and related research*, (174), pp.28–42.
- Byrne, G., 2012. Socket preservation of implant sites: A critical summary of Ten Heggeler JMAG, Slot DE, Van der Weijden GA. Effect of socket preservation therapies following tooth extraction in non-molar regions in humans: a systematic review (published online ahead of p. *Journal of the American Dental Association (1939)*, 143(10), pp.1139–40.
- Cardaropoli, D. et al., Relationship between the buccal bone plate thickness and the healing of postextraction sockets with/without ridge preservation. *The International journal of periodontics & restorative dentistry*, 34(2), pp.211–7.
- Cardaropoli, D. et al., 2012. Socket preservation using bovine bone mineral and collagen membrane: a randomized controlled clinical trial with histologic analysis. *The International journal of periodontics & restorative dentistry*, 32(4), pp.421–30.
- Cardaropoli, G., Araújo, M. & Lindhe, J., 2003. Dynamics of bone tissue formation in tooth extraction sites. An experimental study in dogs. *Journal of clinical periodontology*, 30(9), pp.809–18.
- Carlsson, G.E., Bergman, B. & Hedegård, B., 1967. Changes in contour of the maxillary alveolar process under immediate dentures. A longitudinal clinical and x-ray cephalometric study covering 5 years. *Acta odontologica Scandinavica*, 25(1), pp.45–75.
- Carlsson, G.E. & Persson, G., 1967. Morphologic changes of the mandible after extraction and wearing of dentures. A longitudinal, clinical, and x-ray cephalometric study covering 5 years. *Odontologisk revy*, 18(1), pp.27–54. Available at:
- Chan, H.-L. et al., Alterations in bone quality after socket preservation with grafting materials: a systematic review. *The International journal of oral & maxillofacial implants*, 28(3), pp.710–20.
- Dahlin, C. et al., 1989. Generation of new bone around titanium implants using a membrane

- technique: an experimental study in rabbits. *The International journal of oral & maxillofacial implants*, 4(1), pp.19–25.
- Dahlin, C. et al., 1988. Healing of bone defects by guided tissue regeneration. *Plastic and reconstructive surgery*, 81(5), pp.672–6.
- Darby, I., 2010. Ridge preservation: does it actually work? *Annals of the Royal Australasian College of Dental Surgeons*, 20, pp.52–5.
- Darby, I., Chen, S.T. & Buser, D., 2009. Ridge preservation techniques for implant therapy. *The International journal of oral & maxillofacial implants*, 24 Suppl, pp.260–71.
- Devlin, H. & Sloan, P., 2002. Early bone healing events in the human extraction socket. *International journal of oral and maxillofacial surgery*, 31(6), pp.641–5.
- Discepoli, N. et al., 2013. Early healing of the alveolar process after tooth extraction: an experimental study in the beagle dog. *Journal of clinical periodontology*, 40(6), pp.638–44.
- Dohan Ehrenfest, D.M. et al., 2014. Classification of platelet concentrates (Platelet-Rich Plasma-PRP, Platelet-Rich Fibrin-PRF) for topical and infiltrative use in orthopedic and sports medicine: current consensus, clinical implications and perspectives. *Muscles, ligaments and tendons journal*, 4(1), pp.3–9.
- Du, C. et al., 2005. Apatite/amelogenin coating on titanium promotes osteogenic gene expression. *Journal of dental research*, 84(11), pp.1070–4.
- Engler-Hamm, D. et al., 2011. Ridge preservation using a composite bone graft and a bioabsorbable membrane with and without primary wound closure: a comparative clinical trial. *Journal of periodontology*, 82(3), pp.377–87.
- Esposito, M. et al., 2010. Timing of implant placement after tooth extraction: immediate, immediate-delayed or delayed implants? A Cochrane systematic review. *European journal of oral implantology*, 3(3), pp.189–205.
- Felice, P. et al., 2009. Vertical ridge augmentation of the atrophic posterior mandible with interpositional bloc grafts: bone from the iliac crest vs. bovine anorganic bone. Clinical and histological results up to one year after loading from a randomized-controlled clinical trial. *Clinical oral implants research*, 20(12), pp.1386–93.

- Fernandes, P.G. et al., 2011. Ridge preservation with acellular dermal matrix and anorganic bone matrix cell-binding peptide P-15 after tooth extraction in humans. *Journal of periodontology*, 82(1), pp.72–9.
- Ferrus, J. et al., 2010. Factors influencing ridge alterations following immediate implant placement into extraction sockets. *Clinical oral implants research*, 21(1), pp.22–9.
- Fickl, S., Zuhr, O., Wachtel, H., Stappert, C.F.J., et al., 2008. Dimensional changes of the alveolar ridge contour after different socket preservation techniques. *Journal of clinical periodontology*, 35(10), pp.906–13.
- Fickl, S. et al., 2009. Hard tissue alterations after socket preservation with additional buccal overbuilding: a study in the beagle dog. *Journal of clinical periodontology*, 36(10), pp.898–904.
- Fickl, S., Zuhr, O., Wachtel, H., Bolz, W., et al., 2008. Tissue alterations after tooth extraction with and without surgical trauma: a volumetric study in the beagle dog. *Journal of clinical periodontology*, 35(4), pp.356–63.
- Fiorellini, J.P. et al., 2005. Randomized study evaluating recombinant human bone morphogenetic protein-2 for extraction socket augmentation. *Journal of periodontology*, 76(4), pp.605–13.
- Fugazzotto, P.A., 2003. GBR using bovine bone matrix and resorbable and nonresorbable membranes. Part 1: histologic results. *The International journal of periodontics & restorative dentistry*, 23(4), pp.361–9.
- Gestrelus, S. et al., 1997. Formulation of enamel matrix derivative for surface coating. Kinetics and cell colonization. *Journal of clinical periodontology*, 24(9 Pt 2), pp.678–84.
- Gholami, G.A. et al., 2012. Clinical, histologic and histomorphometric evaluation of socket preservation using a synthetic nanocrystalline hydroxyapatite in comparison with a bovine xenograft: a randomized clinical trial. *Clinical oral implants research*, 23(10), pp.1198–204.
- Govindaraj, S., Costantino, P.D. & Friedman, C.D., 1999. Current use of bone substitutes in maxillofacial surgery. *Facial plastic surgery : FPS*, 15(1), pp.73–81.

- Hämmerle, C.H.F., Araújo, M.G. & Simion, M., 2012. Evidence-based knowledge on the biology and treatment of extraction sockets. *Clinical oral implants research*, 23 Suppl 5, pp.80–2.
- Hämmerle, C.H.F. & Jung, R.E., 2003. Bone augmentation by means of barrier membranes. *Periodontology 2000*, 33, pp.36–53.
- Hardwick, R., Hayes, B.K. & Flynn, C., 1995. Devices for dentoalveolar regeneration: an up-to-date literature review. *Journal of periodontology*, 66(6), pp.495–505.
- Hjørting-Hansen, E., 2002. Bone grafting to the jaws with special reference to reconstructive preprosthetic surgery. A historical review. *Mund-, Kiefer- und Gesichtschirurgie : MKG*, 6(1), pp.6–14.
- Horowitz, R., Holtzclaw, D. & Rosen, P.S., 2012. A review on alveolar ridge preservation following tooth extraction. *The journal of evidence-based dental practice*, 12(3 Suppl), pp.149–60.
- Horváth, A. et al., 2013. Alveolar ridge preservation. A systematic review. *Clinical oral investigations*, 17(2), pp.341–63.
- Huh, J.-B. et al., 2011. Randomized clinical trial on the efficacy of Escherichia coli-derived rhBMP-2 with β -TCP/HA in extraction socket. *The journal of advanced prosthodontics*, 3(3), pp.161–5.
- Israel, D.I. et al., 1996. Heterodimeric bone morphogenetic proteins show enhanced activity in vitro and in vivo. *Growth factors (Chur, Switzerland)*, 13(3-4), pp.291–300.
- Jahangiri, L. et al., 1998. Current perspectives in residual ridge remodeling and its clinical implications: a review. *The Journal of prosthetic dentistry*, 80(2), pp.224–37.
- Jambhekar, S., Kernen, F. & Bidra, A.S., 2015. Clinical and histologic outcomes of socket grafting after flapless tooth extraction: a systematic review of randomized controlled clinical trials. *The Journal of prosthetic dentistry*, 113(5), pp.371–82.
- Januário, A.L. et al., 2011. Dimension of the facial bone wall in the anterior maxilla: a cone-beam computed tomography study. *Clinical oral implants research*, 22(10), pp.1168–71.

- Johansson, B. et al., 2001. A clinical study of changes in the volume of bone grafts in the atrophic maxilla. *Dento maxillo facial radiology*, 30(3), pp.157–61.
- Johnson, K., 1969. A study of the dimensional changes occurring in the maxilla following closed face immediate denture treatment. *Australian dental journal*, 14(6), pp.370–6.
- Jung, R.E. et al., 2006. Evaluation of an in situ formed synthetic hydrogel as a biodegradable membrane for guided bone regeneration. *Clinical oral implants research*, 17(4), pp.426–33.
- Jung, R.E. et al., 2013. Radiographic evaluation of different techniques for ridge preservation after tooth extraction: a randomized controlled clinical trial. *Journal of clinical periodontology*, 40(1), pp.90–8.
- Keith, J.D. et al., 2006. Clinical and histologic evaluation of a mineralized block allograft: results from the developmental period (2001-2004). *The International journal of periodontics & restorative dentistry*, 26(4), pp.321–7.
- Kingsmill, V.J., 1999. Post-extraction remodeling of the adult mandible. *Critical reviews in oral biology and medicine : an official publication of the American Association of Oral Biologists*, 10(3), pp.384–404.
- Lang, N.P. et al., 2012. A systematic review on survival and success rates of implants placed immediately into fresh extraction sockets after at least 1 year. *Clinical oral implants research*, 23 Suppl 5, pp.39–66.
- Lee, D.-W. et al., Comparative histomorphometric analysis of extraction sockets healing implanted with bovine xenografts, irradiated cancellous allografts, and solvent-dehydrated allografts in humans. *The International journal of oral & maxillofacial implants*, 24(4), pp.609–15.
- Lekic, P.C. et al., 2001. Transplantation of labeled periodontal ligament cells promotes regeneration of alveolar bone. *The Anatomical record*, 262(2), pp.193–202.
- Lekovic, V. et al., 1997. A bone regenerative approach to alveolar ridge maintenance following tooth extraction. Report of 10 cases. *Journal of periodontology*, 68(6), pp.563–70.

- Lekovic, V. et al., 1998. Preservation of Alveolar Bone in Extraction Sockets Using Bioabsorbable Membranes. *Journal of Periodontology*, 69(9), pp.1044–1049.
- Lindhe, J. et al., 2014. Ridge preservation with the use of deproteinized bovine bone mineral. *Clinical oral implants research*, 25(7), pp.786–90.
- Mardas, N. et al., 2015. Does ridge preservation following tooth extraction improve implant treatment outcomes: a systematic review: Group 4: Therapeutic concepts & methods. *Clinical oral implants research*, 26 Suppl 1, pp.180–201.
- Mardas, N. et al., 2011. Radiographic alveolar bone changes following ridge preservation with two different biomaterials. *Clinical oral implants research*, 22(4), pp.416–23.
- Masaki, C. et al., 2015. Strategies for alveolar ridge reconstruction and preservation for implant therapy. *Journal of prosthodontic research*, 59(4), pp.220–8.
- Milani, S. et al., 2016. Deproteinized bovine bone remodeling pattern in alveolar socket: a clinical immunohistological evaluation. *Clinical oral implants research*, 27(3), pp.295–302.
- Mordenfeld, A. et al., 2010. Histological and histomorphometrical analyses of biopsies harvested 11 years after maxillary sinus floor augmentation with deproteinized bovine and autogenous bone. *Clinical oral implants research*, 21(9), pp.961–70.
- Morjaria, K.R., Wilson, R. & Palmer, R.M., 2014. Bone healing after tooth extraction with or without an intervention: a systematic review of randomized controlled trials. *Clinical implant dentistry and related research*, 16(1), pp.1–20.
- Nam, H.-W. et al., 2011. Enhanced ridge preservation by bone mineral bound with collagen-binding synthetic oligopeptide: a clinical and histologic study in humans. *Journal of periodontology*, 82(3), pp.471–80.
- Nkenke, E. et al., 2001. Morbidity of harvesting of chin grafts: a prospective study. *Clinical oral implants research*, 12(5), pp.495–502.
- Novaes, A.B. et al., 2012. Buccal bone plate remodeling after immediate implant placement with and without synthetic bone grafting and flapless surgery: radiographic study in

- dogs. *The Journal of oral implantology*, 38(6), pp.687–98.
- Pang, C. et al., 2014. Alveolar ridge preservation with deproteinized bovine bone graft and collagen membrane and delayed implants. *The Journal of craniofacial surgery*, 25(5), pp.1698–702.
- Paolantonio, M. et al., 2001. Immediate implantation in fresh extraction sockets. A controlled clinical and histological study in man. *Journal of periodontology*, 72(11), pp.1560–71.
- Parashis, A.O. et al., 2016. Prospective Clinical and Radiographic Study of Alveolar Ridge Preservation Combining FDBA With Two Xenogeneic Collagen Matrices. *Journal of periodontology*, pp.1–15.
- Pellegrini, G. et al., Soft tissue healing in alveolar socket preservation technique: histologic evaluations. *The International journal of periodontics & restorative dentistry*, 34(4), pp.531–9.
- Quattlebaum, J.B., Mellonig, J.T. & Hensel, N.F., 1988. Antigenicity of freeze-dried cortical bone allograft in human periodontal osseous defects. *Journal of periodontology*, 59(6), pp.394–7.
- Roccuzzo, M. et al., Long-term stability of soft tissues following alveolar ridge preservation: 10-year results of a prospective study around nonsubmerged implants. *The International journal of periodontics & restorative dentistry*, 34(6), pp.795–804.
- Sandberg, E., Dahlin, C. & Linde, A., 1993. Bone regeneration by the osteopromotion technique using bioabsorbable membranes: an experimental study in rats. *Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons*, 51(10), pp.1106–14.
- Sanz, M. et al., 2015. Therapeutic concepts and methods for improving dental implant outcomes. Summary and consensus statements. The 4th EAO Consensus Conference 2015. *Clinical oral implants research*, 26 Suppl 1, pp.202–6.
- Sanz, M. & Vignoletti, F., 2015. Key aspects on the use of bone substitutes for bone regeneration of edentulous ridges. *Dental materials : official publication of the Academy of Dental Materials*, 31(6), pp.640–7.

- Sbordone, C. et al., 2015. Retrospective volume analysis of bone remodeling after tooth extraction with and without deproteinized bovine bone mineral insertion. *Clinical oral implants research*.
- Schlegel, K.A. et al., Histologic findings in sinus augmentation with autogenous bone chips versus a bovine bone substitute. *The International journal of oral & maxillofacial implants*, 18(1), pp.53–8.
- Schneider, D. et al., 2014. Labial soft tissue volume evaluation of different techniques for ridge preservation after tooth extraction: a randomized controlled clinical trial. *Journal of clinical periodontology*, 41(6), pp.612–7.
- Schropp, L. et al., 2003. Bone healing and soft tissue contour changes following single-tooth extraction: a clinical and radiographic 12-month prospective study. *The International journal of periodontics & restorative dentistry*, 23(4), pp.313–23.
- Schropp, L. & Isidor, F., 2015. Papilla dimension and soft tissue level after early vs. delayed placement of single-tooth implants: 10-year results from a randomized controlled clinical trial. *Clinical oral implants research*, 26(3), pp.278–86.
- Seibert, J.S., Reconstruction of deformed, partially edentulous ridges, using full thickness onlay grafts. Part II. Prosthetic/periodontal interrelationships. *The Compendium of continuing education in dentistry*, 4(6), pp.549–62.
- Simion, M. et al., 2004. Long-term evaluation of osseointegrated implants placed in sites augmented with sinus floor elevation associated with vertical ridge augmentation: a retrospective study of 38 consecutive implants with 1- to 7-year follow-up. *The International journal of periodontics & restorative dentistry*, 24(3), pp.208–21.
- Summers, R.B., 1994. A new concept in maxillary implant surgery: the osteotome technique. *Compendium (Newtown, Pa.)*, 15(2), pp.152, 154–156, 158 passim; quiz 162.
- Tal, H., 1999. Autogenous masticatory mucosal grafts in extraction socket seal procedures: a comparison between sockets grafted with demineralized freeze-dried bone and deproteinized bovine bone mineral. *Clinical oral implants research*, 10(4), pp.289–96.
- Tallgren, A., 1972. The continuing reduction of the residual alveolar ridges in complete denture wearers: a mixed-longitudinal study covering 25 years. *The Journal of prosthetic*

dentistry, 27(2), pp.120–32.

Tan, W.L. et al., 2012. A systematic review of post-extraction alveolar hard and soft tissue dimensional changes in humans. *Clinical oral implants research*, 23 Suppl 5, pp.1–21.

Thoma, D.S. et al., 2015. EAO Supplement Working Group 4 - EAO CC 2015 Short implants versus sinus lifting with longer implants to restore the posterior maxilla: a systematic review. *Clinical oral implants research*, 26 Suppl 1, pp.154–69.

Vanhoutte, V. et al., 2014. A methodological approach to assessing alveolar ridge preservation procedures in humans: soft tissue profile. *Clinical oral implants research*, 25(3), pp.304–9.

Verna, C., 2016. Regional Acceleratory Phenomenon. *Frontiers of oral biology*, 18, pp.28–35.

Vignoletti, F. et al., 2012. Surgical protocols for ridge preservation after tooth extraction. A systematic review. *Clinical oral implants research*, 23 Suppl 5, pp.22–38.

Vignoletti, F., Nunez, J. & Sanz, M., 2014. Soft tissue wound healing at teeth, dental implants and the edentulous ridge when using barrier membranes, growth and differentiation factors and soft tissue substitutes. *Journal of clinical periodontology*, 41 Suppl 1, pp.S23–35.

Vittorini Orgeas, G. et al., Surgical techniques for alveolar socket preservation: a systematic review. *The International journal of oral & maxillofacial implants*, 28(4), pp.1049–61.

Wang, R.E. & Lang, N.P., 2012. Ridge preservation after tooth extraction. *Clinical oral implants research*, 23 Suppl 6, pp.147–56.

Warrer, K. et al., 1992. Guided tissue regeneration using biodegradable membranes of polylactic acid or polyurethane. *Journal of clinical periodontology*, 19(9 Pt 1), pp.633–40.

Van der Weijden, F., Dell'Acqua, F. & Slot, D.E., 2009. Alveolar bone dimensional changes of post-extraction sockets in humans: a systematic review. *Journal of clinical*

periodontology, 36(12), pp.1048–58.

Willenbacher, M. et al., 2015. The Effects of Alveolar Ridge Preservation: A Meta-Analysis. *Clinical implant dentistry and related research*.

Yukna, R.A., 1993. Synthetic bone grafts in periodontics. *Periodontology 2000*, 1(1), pp.92–9.

Zellin, G., Gritli-Linde, A. & Linde, A., 1995. Healing of mandibular defects with different biodegradable and non-biodegradable membranes: an experimental study in rats. *Biomaterials*, 16(8), pp.601–9.