case report

GUIDED BONE REGENERATION IN PATIENTS TAKING BIPHOSPHONATES: TWO CASES SERIES

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SUMMARY

Bone tissue is a specialized form of connective tissue, characterized by the mineralization of the extracellular matrix which gives the fabric considerable hardness and strength. Bone is a dynamic tis-sue that is continually renewed and reshaped throughout life.

The hypothesis is that the presence of heterologous bone in the graft reduces the possibility of post-operative bone resorption. There are different types of bone materials in dentistry. This study evaluates the different efficacy in patients receiving bisphosphonates. The radiographic examination allowed to highlight the presence of greater bone reabsorption in CASES A treated exclusively with autologous bone, compared to CASE B to which heterologous bone was also inserted. The literature is very poor, but the mix of the bone gives all the possible vantage of the two type of bone. Furthermore, the use of a membrane to cover the graft reduces the risk of reabsorption of this in the initial time and create greater stability. It is known, in fact, that the empty spaces between the graft and the recipient site can be colonized by connective tissue, which grows more rapidly than the bone.

Key words: bone tissue, bone graft, metabolic disease.

Introduction

Bone grafts are very useful in oral surgery, in order to restore the lost bone volumes following resorption. A frequent clinical feature is the atrophy of the edentulous area that does not al-low the insertion of the prosthetically guided implant. In order to allow the restoration of bone volumes and to insert the osseointegrated implant with a correct axis, it becomes necessary to restore the lost bone volumes as a result of resorption process. In dentistry different bone substitute materials are used, each with a different prerogative. The American Academy of Periodontology, has defined the term regeneration as "the reformation or reconstitution of a lost or damaged part with the result of obtaining the architecture again and the function of the tissues that have suffered loss or injury".

Tissue regeneration is a process that involves complete formation of tissue, following a trauma, differently from repair, which instead involves the formation of scar tissue, with different characteristics from the original one. After the trauma, an inflammatory response occurs, during

which an initial hematoma is produced, with red blood cells, platelets and fibrin. The cells release interleukins and growth factors, triggering the migration of lymphocytes and macrophages. These molecular signals promote the differentiation of endothelial cells, fibroblasts, chondroblasts and osteoblasts, creating a new fibrovascular tissue that replaces the initial clot. All this is all regulated by a series of complex interactions between growth factors, hormones and cytokines.

Bone must be regenerated by exploiting the biological principles of osteogenesis, osteoinduction and osteoconduction. Several techniques combine these principles with different results, due to the condition of the bone base on which we operate the changes, the surgical technique. There are several techniques used for bone regeneration, such as GBR (guided bone regeneration), which allows, through the use of resorbable or non-resorbable membranes, the filling of a defect through the guided growth of only osteogenic strains and prevents the invasion of non-osteogenic tissues that are competitive with the bone itself. There are different graft materials: autologous graft (autograft), homologous graft (transplant), heterologous graft (xeno-transplant) and alloplastic graft (1).

The autologous bone graft represents the gold standard, as it is endowed with osteogenic, osteoconductive and osteoinductive capacities; is a type of graft that contains cells and proteins such as BMP-2, BMP-7, FGF, IGF and PDGF. Furthermore, autologous bone is completely biocompatible. However, this type of graft has disadvantages, such as its limited availability, which makes it unsuitable in the case of large defects, and the need for a second surgical operation to obtain it, with a consequent increase in the risk of complications at the site level donor.

In order to avoid the morbidity associated with the harvesting of autologous bone grafts, allografts, xenografts and alloplastic grafts have been indicated. The possibility of using non-autologous material allows the elimination of a second operation (greater trauma for the patient and longer operating times), reducing postoperative morbidity, having no limitations on the amount of removable bone tissue and having greater acceptability on the part of the patient. Currently there are numerous techniques and various grafting materials that allow to obtain a regeneration of the defective alveolar process in a long-term manner, in order to optimize the insertion of implants, reaching the best final prosthetic result, both functional and aesthetic (2).

The available techniques can be divided into the following groups:

- Guided bone regeneration (GBR) through the use of membranes
- Grafting biomaterials
- Combination of graft materials and use of barrier membranes
- The use of molecular factors inducing regeneration, such as enamel matrix derivatives (EMD)
- Combination of molecular factors with grafting materials.

GBR is a surgical procedure that uses barrier membranes with or without particle bone grafts or/and bone substitutes. The main purpose in perimplant regenerative techniques is the maintenance of the space in which regeneration can take place. The so-called “space- making” effect provides the volume necessary for colonization by bone cells. Clementini et al. (3) showed that the success rate of implants placed in ridges increased by GBR varies from 61.5% to 100%; all studies, except for three, reported a success rate of over 90% (range 90-100%).

Data reported in the literature seem to show that guided bone regeneration (GBR) is a reliable surgical technique in the treatment of horizontal and/or vertical bone defects in partially edentulous patients. The implant survival rates in the areas treated with GBR range from 92.6 to 100%, without significant differences between GBR with resorbable and non-resorbable membranes

(including titanium grids) and this results are comparable to those of implants inserted in jaws that do not require of procedures to increase bone size (3).

The effect of bone graft on patients who suffering of osteoporosis is very complex, especially on patients treating with bisphosphonate. The effect of osteoporosis on the bone graft is very controversial. Especially study evaluated bone graft on osteoporotic animal and shows a major resorption due to the improvement of osteoclastic activity.

Osteoporosis is the most widespread metabolic osteopathy in the Western world, defined by the World Health Organization as "a systemic disease with multifactorial etiopathogenesis, caused by a pathological reduction in bone strength, resulting in an increase in the fragility of the skeleton and therefore of susceptibility to fractures" (Table 1).

Osteoporosis represents a serious public health problem, which affects a large number of people, of both sexes and all races, and its prevalence will increase with the aging of the population (4). In particular, it has been defined that the disease derives not only from a reduction in bone density, but also from an alteration in the quality of bone tissue. The bisphosphonates have revolutionized the treatment of osteoporosis; they represent the drugs of choice for the treatment thereof, and are also indicated for the treatment of pathologies such as multiple myeloma, Paget's disease, bone metastases and malignant hypercalcemia. The bisphosphonates help reduce bone loss mediated by osteoclasts; they are drugs with a high affinity for bone tissue, in particular for hydroxyapatite; they accumulate in the bone tissue, remaining for years, even after the drug is stopped. The target of bisphosphonates are the osteoclasts, to which they are bound by an indissoluble bond given by the amidic group they present along their chain. Once incorporated into the bone matrix, they are released during remodeling, resulting in a reduction in osteoclast activation, an increase in osteoclast apoptosis, inhibition of recruitment of osteoclastic precursors and inhibition of osteoclastic proton pump. They also determine the inhibition of the release of factors by osteoblasts, which regulate osteoclastogenesis and osteoclastic activity, such as IL-6. Finally they act by increasing protein synthesis, type 1 collagen secretion and alkaline phosphatase activity, thus favouring the differentiation and maturation of osteoblasts. They also have an antiangiogenic and anticancer effect. They present a limited bioavailability. They can be taken intravenously (zoledronate, pamidronate), intramuscularly or orally (alendronate, ibandronate and risendronate) and their elimination occurs mainly via the kidney. Adverse reactions can be represented by esophagitis, deterioration of renal activity and osteonecrosis of the jaws (ONJ) (5) (Table 2).

Major complications are associated with intravenous bisphosphonates (Bisphosphonate-related osteonecrosis of the jaws BRONJ). ONJ is a complication that causes it to be required to provide patient management that takes these drugs. It is a condition that mainly involves the jaw bones due to the rich vascularization and the high index of differentiation they present. Osteonecrosis is a disease identification as an inflammatory, infectious, necrotizing, not self-limiting, which

Table 1 - Classification of osteoporosis.

CLASSIFICATION

- PRIMARY
  - Postmenopausal Osteoporosis
  - Senile Osteoporosis
- SECONDARY

Nutritional	Malabsorption, malnutrition
Inflammatory ds	Rheumatiod ds, ankylosing spondylitis
Drug induced	Corticosteroids, excessive alcohol
Endocrine ds	Hyperparathyroidism, hypogonadism
Malignant ds	Multiple myeloma, carcinomatosis
Other	Immobilization, smoking

Table 2 - Parametres to osteoporosis.

Classification of Osteoporosis using Central DXA
World Health Organization

Classifcation	T-score (SD units)
Normal	≥ -1
Low Bone Mass (osteopenia)	< -1 and > -2.5
Osteoporosis	≤ -2.5

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presupposes the bone exposure for more than 8 weeks.

The bisphosphonates taken intravenously have a longer half-life and expose to osteonecrosis already from the first year of intake (0-10% BRONJ risk), unlike those taken orally, which present a lower risk of determining osteonecrosis (< 1%) and in particular not earlier than 3 years after the appointment (6-7).

Therefore it can be considered a risk factor for patients receiving autologous bone transplantation with simultaneous implant placement. None studies are present in literature regarding the bone graft on bisphosphonate patients. The main studies only concern reconstruction using vascularized bone grafts on the jaw already affected by BRONJ and cases of bone grafts have not been documented in the literature using GBR on patients treated with BF (8).

The aim of this study was to evaluate the possibility of correction of bone defects, by means of guided bone regeneration (GBR), comparing in particular the use of autologous bone grafts, taken from the external oblique line, and of autologous bone mixed with heterologous bone. The hypothesis is that the presence of heterologous bone in the graft reduces the possibility of postoperative bone resorption.

Materials and methods

Sample selection

Two cases of patients taking oral bisphosphonates for the treatment of osteoporosis were treated; gave consent and were informed about possible complications related to drug treatment. The medical records were collected during the first examination. Particular attention was given to medical history, drug therapy and the period of therapy. Serum CTX levels were analyzed in order to establish a risk class. The inclusion criteria were the presence of osteoporosis, serum CTX values in the range, consent to treatment, need for correction of the horizontal bone defect for subsequent implant insertion. The exclusion criteria were the high value of risk for the medication with biphosphonates (CTX < 100 pg/mL).

Preparation for the surgical phase

Two weeks before the operation, the patients received a professional oral hygiene session and everyone was given personalized instructions for maintaining home hygiene. In the same session a RX TC Cone Beam was performed. Antimicrobial prophylaxis was performed using amoxicillin and clavulanic acid (1g every 12h, 5 days before 5 days after dental treatment) and metronidazole (250mg every 12h, from 2 days before to 2 days after treatment). One of the two patients had an allergy to penicillins, for which azithromycin was used (500mg, 2h before dental treatment and one tablet a day for 5 days after surgery). The BMD was measured to assess the status of osteoporosis and serum CTX was required, which reported a value between 0.150-0.290ng/mL (low risk).

Surgical phase

CASE A

The patient presented an edentulism due to the absence of elements 2.4 and 2.5. After about two weeks from the RX TC Cone Beam, we proceeded to the surgical phase, as reported below:

- Cleansers with 0.12% chlorhexidine
- Local plexic anesthesia, obtained using 3% mepivacaine hydrochloride and epinephrine 1:100,000. The technique involved slow infiltration to ensure greater effectiveness and du-ration of the anesthetic effect. Infiltration was performed starting at the disto-vestibular level, continuing at the mesio-vestibular level and subsequently distal-palatal and mesio-palatal.
- The incision was made from the mesial portion of the 2.3 element with a short vertical discharge, in order to guarantee minimal invasiveness, and a golf club incision on the lateral portion of the mesial papilla. The intrasulcular incision was continued, again on 2.3, continuing paracrestally in area 2.4-2.5 and finally intrasulcular to element 2.6, with a horizontal discharge of the distal papilla of the same very short, so as to ensure good operative visibility, guaranteeing in any case a minimally invasive flap for the treated case (Figure 1).
- The flap was unglued at full thickness, maintaining the integrity of the periosteum. It has been used a periosteal elevator Buser for lifting the mucoperiosteal flaps, with subsequent exposure of the horizontal bone defect (Figures 2, 3).
- Bone defect was filled exclusively with autologous bone graft (Figure 4).
- The sampling took place at the level of the external oblique line. The Safescraper® TWIST was used, a bone sampling device that allowed us to obtain autologous cortical bone in a simple and minimally invasive way. In particular, the exclusive cutting performance of the blade has allowed the removal of cortical curls, while preserving the maximum cell vitality, fundamental for the integration of the graft. The removed bone, already combined with blood, was ready for placement in the defect.
- Following the positioning of the graft material, this was stabilized with a membrane (Figure 5) and its tightness was guaranteed by the use of metal pins. In particular, a Mem-Lok® membrane from BioHorizons was used, made

Figure 1
Elevation of flap.

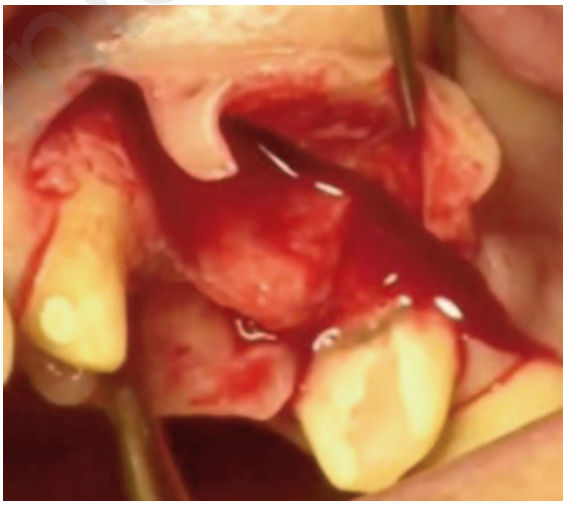

Figure 2
Mucoperiosteal flap.

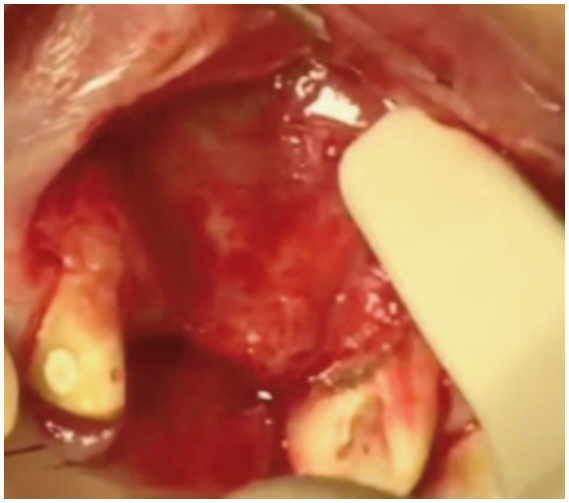

Figure 3
Bone.

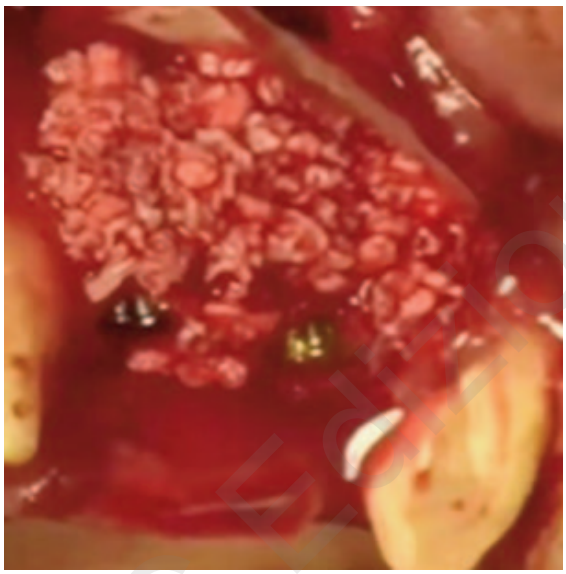

Figure 4
Autologus graft.

of purified type 1 collagen fibers.

- The approach suture was performed with detached stitches, to ensure greater tightness and healing by first intention, using a braided, coated, non-resorbable, four zero thread.

CASE B

The patient presented an edentulous site in site 4.6. Also in this case, about two weeks after the RX TC Cone Beam, the surgical phase was carried out, as reported below:

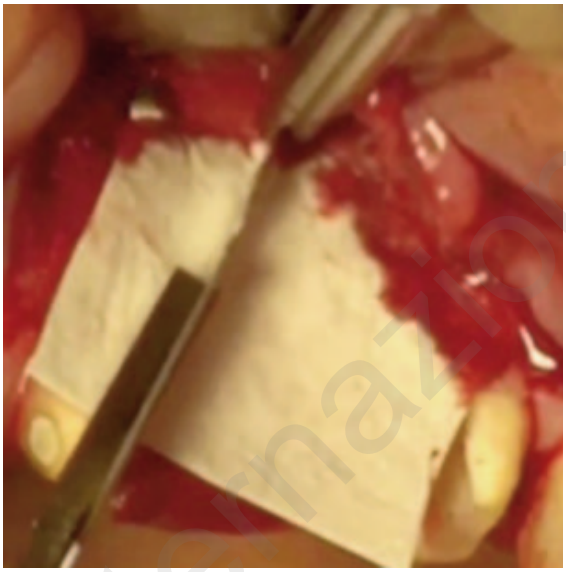

Figure 5
Membrane.

- Cleansers with 0.12% chlorhexidine
- Local anesthesia, obtained by truncating the inferior alveolar nerve, using an anesthetic without vasoconstrictor.
- The incision was performed at the intrasulcular level of element 4.7, continuing with a paracrestal incision in area 4.6 and intrasulcular at the level of 4.5; it was continued mesially, in area 4.4, with a very short, minimally invasive, golf club release incision.
- The flap was unglued at full thickness, maintaining the integrity of the periosteum. Also in this case a Buser periosteal elevator was used to lift the mucoperiosteal flaps, with subsequent exposure of the bone defect.
- The bone defect was filled with a mixed autologous bone graft, taken from the same site (external oblique line) and heterologous (80% autologous; 20% heterologous). In particular, MinerOss®, an inorganic bovine bone mineral matrix that is physically and chemically comparable to the mineral structure of human bone was used. The MinerOss®, from

BioHorizons, consists of a mixture of cortical and spongy chips, which provide an osteo-con-ductive scaffold with the aim of improving the volume of regenerated bone.
- Finally, the procedure was completed as for CASE A, with positioning of the membrane and subsequent approach suture.

Post-chirurgical phase

Patients were prescribed a CHX-based mouthwash 0.2% twice a day, until the stitches were removed after 7 days. All post-operative indications have also been provided. Patients were monitored in the following months, with radiographic control occurred 4/5 months after surgery.

Results

The radiographic examination after 4/5 months allowed to highlight the presence of a greater bone reabsorption in CASE A (Figure 6), treated exclusively with autologous bone, compared to CASE B (Figure 7), to which heterologous bone was also inserted.

Discussion

The discussion on the use of different types of materials is very controversial. In our cases we compared the post-graft resorption difference using different types of bone or only autologous or a mix between autologous and heterologous. Our study showed that the percentage of resorption, documented by radiographic control, is greater in the patient treated exclusively with autologous bone. The majority of studies such as Cassetta et al. (9), Scarano et al. (10) and Barone et al. (11) are according that during sinus augmentation the formation of bone are similar between the porcine bone and a mix of porcine bone and autologous bone. Aghadazen et al. (12) instead show the greater predicibility of bovine bone respect to autologous bone. The results show a decrease of bleeding on probing and probing depth. In contrast the study of Artese et al. (13) analysed a composition of equine bone with autologous

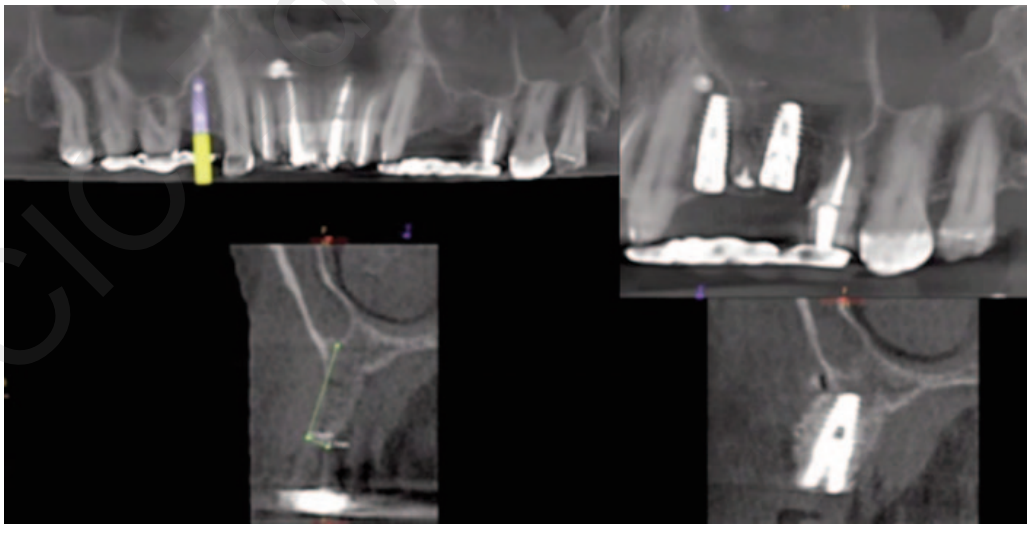

Figure 6
Post-operatory CBCT case A.

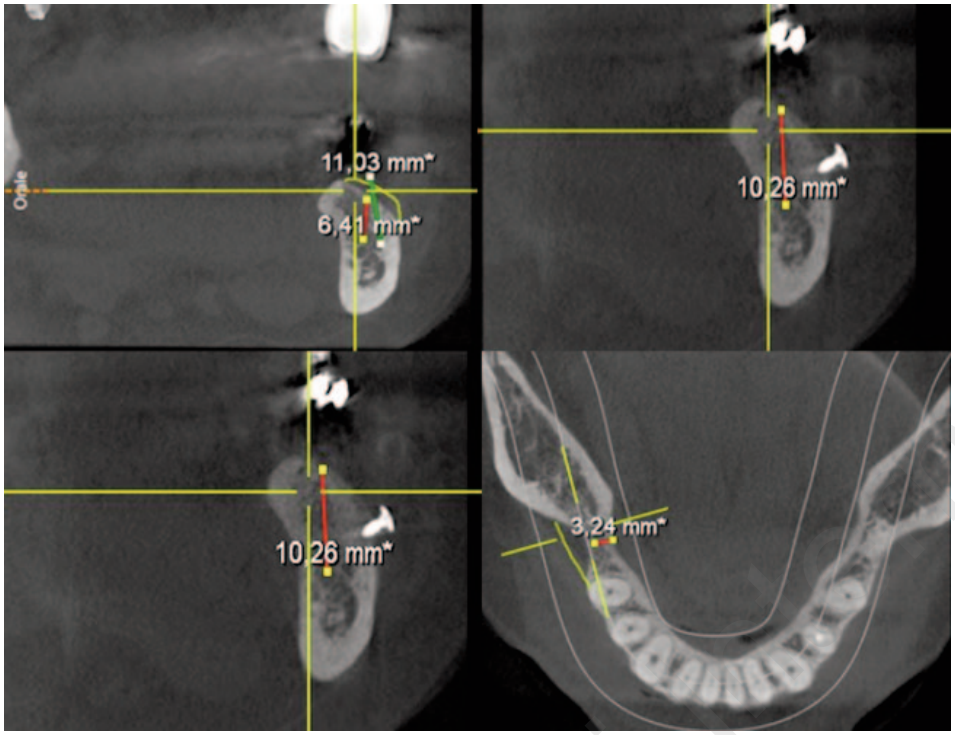

Figure 7
Post-operatory CBCT case B.

bone. The results show a greater formation of new blood vessels, then a good quality of bone. The mix of autologous and heterologous bone permit a minor surgical complication. Especially during maxillo-facial surgery the use of heterologous bone graft show a minor rates of complication and a good bone formation (14). A great part of studies according to use a mixture of the two type of bone because there are a minor rates of reabsorption. The literature is very poor, but the mix of the bone give all the possible vantage of the two type of bone as we see after. The use of autologous graft that has osteoconductive, osteogenic and osteoinductive properties plays an important role. This means that it can act as a scaffold, while promoting new bone formation thanks to bone morphogenetic proteins (BMP) and, sometimes, live cells, which can activate osteoforming and mostly angiogenesis in order to convey the cells and cytokines necessary to regulate the physiological inflammatory and immune processes. Autologous bone is still considered the "reference standard" to which all biomaterials should be compared. However, the volume of autologous bone can be lost due to its fast-term resorption and remodeling. The heterologous bone has osteoconductive properties, it acts as a scaffold on which the newly formed bone grows inside and outside the particles, thanks to the spraying of blood containing bone progenitor cells. The main advantage is that these biomaterials, if characterized by a very slow resorption rate, will keep the volume. The disadvantage lies instead in the fact that osteoconductive materials are not able to induce osteoformation independently. However, it is possible to make ideal combinations in order to minimize the disadvantages and maximize the advantages of both materials: it is possible to mix autologous particulate bone (Bone chips), which has osteoinductive and osteogenic properties, to the biomaterials, which have osteoconductive properties and the ability to maintain volume over time, thus minimizing the loss of initial bone gains. Furthermore, the use of a membrane to cover the graft reduces the risk of reabsorption of this in the initial time and

favours greater stability. It is known, in fact, that the empty spaces between the graft and the recipient site can be colonized by connective tissue, which grows more rapidly than the bone. Its interposition can be negative as it can compromise the integration of the graft in the native bone bed, eventually causing the graft loss or its remarkable reabsorption. In particular, in horizontal GBRs, resorbable collagen membranes, preferably stabilized with screws or nails, are essential to ensure the stability of the grafted material and allow safe integration. Also this study want to demonstrate if bone graft are influenced by bisphosphonate therapy. The nature of ONJs is, in summary, attributable to chronic osteomyelitis generally supported by bacteria of the oral microbial flora (Actinomyces, but also Staphylococci, Streptococci and Candida) which leads to bone necrosis, at its exposure, with little tendency to seizure. Implant treatment during bisphosphonate treatment exposes the patient to a greater risk of implant loss. Similarly, this study wants to demonstrate whether there are contraindications to the use of bone grafting materials in patients receiving BF. In the literature there are studies that use bone grafts in patients with BF it is only limited to bone grafts for the reconstruction of large bone atrophies following BRONJ. Fibular vascularized vascular grafts, iliac crest are shown to be successful and acceptable, following mandibular necrosis. However, following the risk of graft necrosis, these cases should be limited and there are different from this case series (15). Alternatively, recent histomorphomentric studies have demonstrated the effects of materials on osteoporotic patients. The result of the study is the presence of a greater reabsorption of the material in the patient suffering from this pathology (16). By contrast, very recent literature studies have shown the beneficial topical effect of BF. The study of Lozano et al. shows that porcine xenografts modified with pamindronate helped new bone formation and increased the porcine xenograft substitution/replacement after 4 and 8 weeks of healing (17). Especially the human study of Gupta suggest the potential role of the topic treatment of BF which enable the early bone resorption of bone graft and promote bone formation. However in our case obviously the patients were treated with bisphosphonates for systemic problems so this effect is not predictable as we did not present a control group that showed whether or not there are unwanted beneficial effects of systemic intake of BF, albeit due to systemic diseases (18-20). There could probably be a small contribution from the therapy taken on the prevention of graft resorption (21). However, the aim of our study was to demonstrate that this regenerative surgery can be safely performed even in patients on oral bisphosphonate therapy, showing no bone necrosis effects and we have shown, according to previously shown studies, that the material is the autologous bone mixed with heterologous (22-26). In conclusion, from the experimental study we have been able to ascertain that the obtainment of the reconstructed bone volumes is due to the presence of heterologous bone that functions as a graft stabilizer and due to the slow re-sorption associated with it.

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