Bone regeneration in dentistry

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Summary

The edentulism of the jaws and the periodontal disease represent conditions that frequently leads to disruption of the alveolar bone. The loss of the tooth and of its bone of support lead to the creation of crestal defects or situation of maxillary atrophy. The restoration of a functional condition involves the use of endosseous implants who require adequate bone volume, to deal with the masticatory load. In such situations the bone need to be regenerated, taking advantage of 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 changes, the surgical technique that we use, and finally for the bone metabolic conditions of the patient who can be in a state of systemic osteopenia or osteoporosis; these can also affect the result of jaw bone reconstruction.

KEY WORDS: osteoporosis; edentulism; guided bone regeneration.

Introduction

The loss of the tooth causes the resorption of the alveolar bone (1). As to stop the stimulus induced by the periodontal ligament, the vestibular cortical bone is subjected to resorption and the marrow component of the alveolous gradually disappeared (2-4). The consequence is the change of the morphology of the alveolar ridge, which, in limited form for number of teeth lost, configure the degree of the alveolar defect and by extension, condition of more pronounced atrophy (5). The gradual disappearance of the alveolar process involves the reduction of sagittal size and then vertical size of the jaws, as described firstly by the classifications of Cawood and Howell (6) and then by Misch and Judy (7) leading to a subversion of intermaxillary relations and functional abnormality which makes incompetent the two dental arches.
Preserving as restoring a sufficient bone volume to support the prosthetic load, and also the insertion of the dental implant as a support for prosthesis, requires the use of surgical protocols that enable the bone regeneration on the deficient sites, using the principles of osteogenesis, osteoinduction and osteoconduction.
The jaw bone will respond to these protocols in a very subjective way because of the bone site to be restored, of the operative protocol and the general bone conditions which are sometimes deficiency because of osteopenia or osteoporosis.

Aims

The different conditions of decreased bone jaw can be corrected with clinical protocols associating biological principles of bone regeneration. However, the volume of regenerated bone has to support the masticatory forces transmitted by the implant, with different results for each jaw and for patient's different metabolic conditions. These will be briefly considered.

Biological Principles

Osteogenesis, osteoinduction and osteoconduction are the biological principles that offer the possibility to regenerate lost bone volume.
The first one allows the use of autologous bone: osteoblastic cells and Haversian systems of the grafted bone fragment will be replaced by newly formed bone from the walls of the recipient bed (8).
The osteoinduction enables migrations and proliferation of connectival undifferentiated cells in the site to be regenerated. This potential differentiation is conditioned by the presence of growth factors (GF) on the site (9).
The osteoconduction is the ability of a material to operate as a scaffold to guide the tissue regeneration. The material will also partially be replaced by newly formed cells (10).
Several techniques allow the application of these principles. The results change for quantity and quality and depending on the type of principle that is used. In fact, within the jaw bone can be exploited: the repair, guided repair and regeneration.
The repair is the formation in a bone defect of a part of connective tissue formed by cells and fibroblasts, which in part will be replaced by osteoblasts that will deposit an osteoid matrix that will ossify (11). However, the volume of regenerated tissue will be lower than expected (12) for the interference of non osteocompetent cells.
The guided repair uses the principle of resorption/substitution of a osteointegrated biomaterial with new-bone. The result will depend on the features of osteoconductive grafted material and provide a tissue in which tracks of the same will long remain (13). The regeneration is limited to the implementation of undifferentiated connective cells present in the site to be regenerated by appropriate clinical solution which isolate the site (14), or to the bone formation obtained from autologous vital material inserted into the defect.

Operative protocols

Several techniques allow restoring lost alveolar bone with formation of stable bone matrix (Table 1).
Guided Bone Regeneration (GBR): it allows, through the use of resorbable or non-resorbable membrane, the filling of a defect through the guided growth of only osteogenetics strains and preventing the invasion of non-osteogenetics tissues which are competitive with the bone itself (15, 16). Among the devices used to isolate the defect, in addition to the membranes, we have also the grids that allow you to keep the space needed for bone formation avoiding the collapse of soft tissue (17). The widespread use of resorbable membranes free of mechanical consistency has meant that these defects will be filled from osseointegrative biomaterials used as support (18).
Use of growth factors (GF): this are glycoproteins with autocrine and paracrine function that grafted in the site, recruit and multiply the osteocompetent cellular strains. For the clinical use the platelet-rich plasma (PRP) (19, 20) and the platelet rich fibrin (PRF) (21) are used as autologous materials obtained from the patient's blood by centrifugation (22); we can use also bone morphogenetics proteins (BMPs) obtained by genetic engineering (OP-1). All these factors may be included alone or together with a biocompatible material acting as support (23), so that their action is prolonged for a few days.
We can distinguish between the graft materials: autologous graft (autograft), homologous graft (allograft), heterologous graft (xenograft) and alloplastic graft.
The autologous bone is the gold standard because it contains the three properties. Depending on the size of the defect is used to harvest intraoral or extraoral. The grafted material maintains the characteristics of embryological site of origin: bone density, which matures on the site reflects that principle (24).
The allograft is provided by the tissue banks in various formulations as sticks, granules or paste. This is an osteoconductive material that provides mechanical properties even in large defects (25).
The heterologous material, that has bovine or equine origin, is a non-stoichiometric apatite less resorbable, which does not resist to the traction forces and to the masticatory load (26, 27).
The alloplastic are osteointegrative materials with a different degree of resorption; they have biomechanical properties; they are partially replaced in bone remodeling based on their size and porosity (28).
The surgical procedures for the grafting materials are: the fixation of graft of sticks or bone particulate rigidly to the atrophic base or the filling of defects with bone particles. For defects of the superior alveolar process we can use the mini or large maxillary sinus lift with the crestal or lateral surgical approachor and for the sagittal deficiency of the site we can use the distraction osteogenesis.
The aim of the bone regeneration is to insert the titanium implant in its context. This alloplastic insert, whose rough and porous surface (29) allows osteointegration with the bone tissue (30, 31) and it will provide the prosthetic support solution for the clinical case.

The bone metabolism and the atrophy of the jaws

These protocols should take into consideration the patient's osseous metabolic condition. In fact, there are systematic conditions of osteopenia and osteoporosis which may also be reflected in the maxillary area (32). These diseases can be linked to regressive states (post-menopausal, senile) or secondary to osteomalacia, hyperparathyroidism, disendocrinopatie, metabolic disorders (33).
These clinical disorders include preservation of bone mass but in the marrow and in the cortical component we can note a less production of the osteoid matrix, a slow mineralization of the same, a trend accelerated remodeling with fracture of the trabeculae of less caliber (34).
The diagnosis of these conditions is not easy with the radiological diagnostic equipment as intraoral-radiograph and panoramic radiograph, even if you can get more information with Computer Tomography (CT). While the biochemical investigation is useful both in the initial assessment of patients undergoing these treatment programs, both in advanced stages of investigation for more complex cases.
There are several tests that, in case of suspected osteoporosis, you can make in the first phase or, when the information obtained from these initial biochemical investigations are not conclusive, in the second phase (Table 2) (35).
With regard to maxillary osteoporosis most of the authors agree that the skeletal osteoporosis and the maxillary osteoporosis are often associated (36) but we don't exclude situations where there are general conditions of osteoporosis, osteopenia, that don't involve the bone level of the jaws impact and on the contrary. Taguchi (76) notes the correlation between mandibular bone resorption and decreased vertebral bone density; Drage (77) by analyzing densitometry vertebrae, femurs and maxillary and comparing them, find only correlation between the mandible and the femur or vertebrae.

Discussion

Currently Oral Surgeon is in possession of numerous instruments which, using basic biological principles, allow adequate jaw bone volume rehabilitation to insert an osseointegrated implant, able to support a prosthetic restoration.
In literature, regenerative protocols techniques are associated with a high number of complications (37).
Using a GBR technique, the main complication is flap dehiscence with infection of the membrane and the grafted material. Jensen (38) records the need to second surgery to obtain sufficient bone volume in a percentage of cases ranging between 4.1% and 32%. The use of resorbable membranes and techniques of horizontal regeneration have got fewer complications (39).
In autologous bone grafts the main complication of the receiving site is always the flap dehiscence associated with graft infection (40), but in these cases we also have to consider the donor site complications. Grafts more associated to post-operative problems are those from iliac crest and chin, while the less ones are those from mandibular ramus and calvaria crest. Although calvaria graft provides an optimal bone quantity and quality, it is difficult to be accepted by patients (41, 42).
Surgeon who intends to approach to these regeneration techniques, certainly must know the implant survival rates in regenerated bone. Several systematic reviews show with GBR technique, used in vertical and/or horizontal augmentations, an implant survival rate of > 90% (43-47). These studies, however, do not consider numerous technical variables: it is then necessary to design new studies to assess factors related to the site and the individuality of the patient in considering the effectiveness and predictability of the GBR (75).
For autologous bone grafts, the implant survival rate varies between 76% and 100% (46) with worse results for iliac crest bone compared to calvaria bone or intra-oral grafts (48).
However, given the multitude of techniques and materials existing, based on our current state of knowledge and on data from the literature, we could assess that there is not scientific evidence to indicate which technique is better (37, 38).
In choosing, clinician and patient must weigh the pros and cons based on what are biological and economic costs, and priority should be given to less invasive techniques, with fewer complications and reduced treatment time (48).
Failing to reach firm conclusions, regardless of the technique used to obtain predictable results, it is essential to respect some well established principles. Among these are fundamental: stability of the grafted material, primary closure of the flap, the angiogenesis to ensure the supply of undifferentiated mesenchymal cells (49).
All the regeneration techniques are affected by the bone area in which are carried out, ensuring that clinical outcome will be different by jaws area. In fact, blood supply of the grafted material is influenced

Table 1 - Type of maxillary and mandibular defect and the bone regeneration technique.

Type of defect	Maxillary		Mandibular	
Width Reduction	Good bone density: GBR or split crest and implant at the same time	Poor bone density: GBR or split crest or graft and implant after a period of healing	Good bone density: GBR or split crest and implant at the same time	Poor bone density: GBR or split crest or graft and implant after a periodo of healing
Width and height Reduction	Three clinical situation: 1) height and width sufficient to insert an implant 2) pneumatization of maxillary sinus not associated with alveolar bone resorption: lateral or crestal sinus lift 3) pneumatization of maxillary sinus associated with aleveolar bone resorption: sinus lift and onlay graft		Two clinical situation: 1) height and width sufficient to insert a short implant 2) Regeneration (GBR, distraction osteogenesis, block graft) and after a period of healing implant insertion	

Table 2 - Different type of test to investigate osteoporosis in initial clinical phase and in the second phase.

Initial biochemical investigations	In-depth investigations
- ESR - CBC - Serum Protein Electrophoresis - Serum-calcium levels - Phosphorus - Total alkaline phosphatase - Creatinine - calciuria 24-hour	- Ionized calcium - PTH - 25-hydroxyvitamin D serum - Specific hormones (TSH, cortisoluria in 24 hours, testosterone for men) - Antibodies antiamigdala, endomysial and antitransglutaminasi - Protein immunofixation, serum and urinary - Serum tryptase, urinary N-methylhistamine - Specific markers of bone turnover and sensitive - Bone marrow aspirate - Bone biopsy

by site-specific location of the overall bone marrow, which is more sensitive to regeneration because is more vascularised than the cortical one, less disposed to metabolic exchange.
Misch and Zarb (50) have classified jaw bone density by dividing cortical and medullary quote in different portions of mandibular and maxillary bones. Therefore, bone type D1 (cortical thick) is found in symphysis region; bone type D2 (thick cortical bone and thick medullary bone) in mandibular ramus; bone type D3 (thin and porous cortical bone and thin medullary bone) across the maxillary arch; bone type D4 (thin and large trabeculae) in the tuber maxillae.
The possibility of integration of a graft material in addition to the density parameter depends on the morphology of the residual ridge. This morphology from a clinical point of view influences the depth of the vestibule, the tension of the flap and thus the stability of the material after the suture (51). The severe reabsorbed edentulous mandibular ridge has got all these characteristics in the negative, in contrast to the maxillary areas.
Nissan (52) uses to rehabilitate posterior mandibular areas the bloc grafts fixed with mini screws and protected by a membrane and shows a grafting success rate of 79.3%. Sbordone (53) shows a resorption of onlay iliac bone graft in block of 42% if placed in the anterior maxillae and 59% when placed in the posterior areas of lower jaw. Calvaria bone graft, instead, is less affected by remodeling phenomena. Smolka et al. (54) reported at one year a graft volume reduction of 19.2%.
Keith (55), in dealing with 82 defects, gets a failure rate of 71% with dehiscence and infections in the posterior lower jaw using homologous bone grafts in block. Things seem to go better in the maxilla: Ferri (56) using onlay autologous grafts reports an implant success rate of 97%, and he does not report phenomena of site infection, but complain as a major problem the graft resorption.
It could be concluded that the maxillary sites are more receptive to regenerative therapy especially when consider grafting material in block rather than in particulates, that could be explained by the lower blood supply of the atrophic mandibular edentulous ridge (57).
The porous bone while allowing a greater blood supply, promotes the regeneration techniques because it ensures a better trophism of the grafted material; at the same time being less dense it has got the worst mechanical properties and it suffers more the loads transmitted by prosthetic implant (58).
The guarantee of sufficient bone quantity and of a high bone density is a prerequisite to the biomechanical stability and implant osseointegration to maintain over time (59, 60).
A key role in maintaining bone grafted volume is played, however, by the implant: its active surface is the basis of the metabolic exchange processes with bone cells and growth factors that ensure the functioning of the bone / implant / prosthesis system.
Particularly important is the correct timing of implant surgery: in fact, drilling regenerated bone after bone grafting, to place the implant, will promote the disposal of Growth Factors behind the surface that will be in contact with the insert with a larger proportion of Bone Implant Contact (BIC) (61).

It is essential, in case we graft a biomaterial, including long waiting times until could be generated a part of mature vital bone. The type of biomaterial used affects the maturation of the regenerated tissue: in the case of autologous bone chips 3-4 months are sufficient for a 30% vital bone mineralization; in the case of alloplastic material and of homologous bone particles are needed even more times (62,78,79).
Waiting time, however, is indicative and may vary from subject to subject, and in different sites in the same subject especially in the presence of osteopenia or osteoporosis, situations in which the bone metabolism is altered and the formation of vital material will be delayed.
These diseases are not absolute contraindications for the regeneration techniques (63) and the subsequent implant therapy (64), even if they reported a higher percentage of failures and complications. Naturally, modifiable risk factors for osteoporosis should be removed, patient lifestyle should be changed and secondary forms of this disease should be treated (63).
Currently, a point of particular attention is the possibility, through systemic and / or local interventions, to promote the mineralization of regenerated bone by recruiting Vitamin D and Calcium in adequate doses, as expressed by Cooper in 1998 (65).
There are also studies on animal model showing that the administration of Bisphosphonates such as strontium ranelate, improves implant stability (66-68, 70). Let us note however that Bisphosphonates have been associated with osteonecrosis of the jaw (69) and before undertaking any therapy, surgical risks should be carefully assessed.
On the same animal model has been shown that treatment with calcitonin (71) or simvastatin (73) increases the amount of newly formed bone in defects treated with e-PTFE membranes, although statins according to the mode of administration and dosage, the effects can be void or against (74). Furthermore, Hormone Replacing Therapy seems to prevent the influence that estrogen deficiency exerts on bone healing in rats without ovary (72). But these are preliminary results in animal models that need further investigation in order to begin testing on humans *in vivo*.

Conclusion

Regenerative therapy of atrophic edentulous maxilla is configured as a real social problem because of the importance of implant-prosthetic therapy. Lack to assess the metabolic conditions of the patient and its individual parameters is certainly a source of failures.

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