# Periodontal regeneration in clinical practice

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## ABSTRACT

The regeneration or restitution of lost supporting tissue has always been considered the ideal objective of periodontal therapy. However, attempts to convert this intention into solid clinical practice can become tremendously complex, the results of which are very different from the original intention.

The aim of this article is to offer an up-to-date, general perspective on periodontal regeneration, orienting the clinician within the global strategy for oral treatment. To this end, we revise the healing process of periodontal injury, the different therapeutic approaches, the interpretation of the results, and finally, limiting factors in periodontal regeneration.

***Key words:*** *Periodontal regeneration, bone grafting, reattachment, new attachment, enamel matrix derivative.*

## RESUMEN

Siempre se ha considerado que el objetivo ideal de la terapia periodontal es la regeneración o restitución de los tejidos de soporte perdidos. Sin embargo, el intentar traducir este objetivo, en actuaciones clínicas concretas puede convertirse en una tarea tremendamente compleja y cuyos resultados disten mucho del objetivo inicial.

La intención de este artículo es ofrecer una perspectiva general y actualizada de la regeneración periodontal que permita al clínico situarla dentro de la estrategia de tratamiento oral global. Para ello se revisa: el proceso de curación de la herida periodontal, los diferentes enfoques terapéuticos, la interpretación de los resultados, y por último, los factores que limitan las indicaciones de las técnicas de regeneración periodontal.

***Palabras clave:*** *Regeneración periodontal, injertos óseos, reinserción, nueva inserción, derivados de la matriz del esmalte.*



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## INTRODUCTION

Periodontitis involves an inflammatory process, of bacterial origin, affecting the periodontal tissues and provoking the destruction of the supporting tissues to the teeth. This destructive inflammatory process is, in fact, the consequence of an inadequate interaction between the oral microflora and the host defense mechanisms. The ultimate goal of periodontal treatment seeks to preserve the teeth in relatively functional and comfortable good health, and at the same time maintaining the esthetic expectations of the patient. In order to achieve this global objective, a periodontal therapeutic strategy is needed, planned in various phases.

The first phase of treatment consists in controlling the cause of the disease, the objective being to halt the process of tissue destruction. This is denominated the Etiologic, Hygienic, or cause related phase. Through the control of the bacterial plaque and potentially periodontopathogenic flora, the modulation of the immuno-inflammatory response is sought. The procedures include educating the patient in matters of oral hygiene, the elimination of the (supragingival and subgingival) dental calculus and the contaminated radicular cementum, and the modification of those local factors that favor the accumulation of bacterial plaque. In other words, the biological objective of this phase is to achieve a smooth, clean, radicular surface, biocompatible with the periodontal tissue.

Once the cause is controlled, the correction of the consequences provoked by the disease is considered. This phase, called the Corrective or Surgical phase, centers on the treatment of the periodontal pocket and the mucogingival problems, the final objective being to re-establish a dental-gingival relationship as favorably as possible, aiming facilitate the patient's own hygienic control.

Surgical treatment can be addressed by two distinct approaches. a) The elimination of the periodontal pocket by resection, this method is founded on the concept of the irreversibility of the lesions and on the consequence of the pocket acting as a reservoir for periodontal pathogens. b) The possibility of closing the periodontal pocket by repairing the periodontal tissues is considered. These are the surgical techniques for new attachment, whose ideal objective would be the regeneration of the lost periodontal support (1).

Finally, once the cause is controlled and the consequences have been corrected, recurrence of the disease should be avoided (secondary prevention). This implies the third phase of the periodontal treatment, also called the Maintenance phase, or Periodontal Support Treatment.

Periodontal regeneration is an option within the strategy of periodontal treatment; however, we should not forget that this entails the reconstruction of the tissue lost through disease. Therefore, in order to be able to apply this treatment, previous control of the cause and the pathogeny of the destructive process, with the aim of obtaining a more favorable clinical situation is essential in order for the periodontal tissues to be able to exercise their regenerative capacity.

A good part of the knowledge currently possessed on the regenerative capacity of periodontal tissue comes from studies undertaken on the healing of periodontal wounds.

## HEALING OF THE PERIODONTAL WOUNDS

Cicatrization of surgical wounds in the skin or oral mucosa includes a series of perfectly controlled biological processes, beginning with the chemoattraction of the cells, and ending with the formation and maturation of a new extracellular matrix. This matrix is responsible for connecting the margins of the injury, supplying cells, vascularization, and finally restoring the area. Superficially, the epithelial cells migrate rapidly from the margins, covering the maturing fibrin coagulum. In a completely restored injury, the new epithelium forms a protective barrier, not significantly different in structure from the original epithelium.

The healing of periodontal wounds following flap surgery is a more complex process than that which takes place in a skin injury. In the first place, various different types of tissue, which should all coordinate with each other, participate in the cicatricial process. The two parts of the injury possess completely different characteristics; the flap of soft tissue is located over a hard tissue, the root, with an avascular surface, sometimes contaminated with bacteria and toxic materials. Furthermore, this whole process must take place in a transgingival situation, exposed to a particularly septic environment, the mouth. Therefore, the scarring process of a periodontal injury is of particular merit from the biological point of view (Figure 1).

Currently, our periodontal healing model is based on the Melcher hypothesis (2). He proposed that the nature of the attachment established between the tooth and the periodontal tissue depends on the origin of the cells (epithelial, gingival connective, alveolar bone, periodontal ligament) which repopulate the area of the injury, and that the only cells that achieve true, complete periodontal regeneration are cells originating from the periodontal ligament and perivascular bone cells (3).

The most common healing of a periodontal wound is characterized fundamentally by the epithelialization of the internal face of the flap in contact with the radicular surface, forming the so-called *long epithelial attachment*. More apically, the maturation of the connective tissue reestablishes the *connective attachment*, and, at the deepest point of the injury, it is possible to detect a certain recovery of the bone architecture and the periodontal ligament (4,5).

From the point of view of the morphologic structure and function of the tissues formed during the healing process, we can speak of the *repair* and *regeneration* phenomena. In *regeneration*, healing occurs through the restitution integra of the structure and function of the lost periodontal tissue. However, in repair, a tissue is placed that does not allow the original morphological nor functional restoration of the tissue, being considered as non-functional scarring. Thus, the long epithelial attachment is interpreted as repair, since there is no restoration of the periodontal tissular architecture, but a long epithelium that acts functionally only as a cover to the



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internal medium. Other, although less frequent possibilities for repair in humans, are the connective tissue attachment with radicular resorption, and the radicular ankylosis by bone growth and radicular resorption (Figure 2).

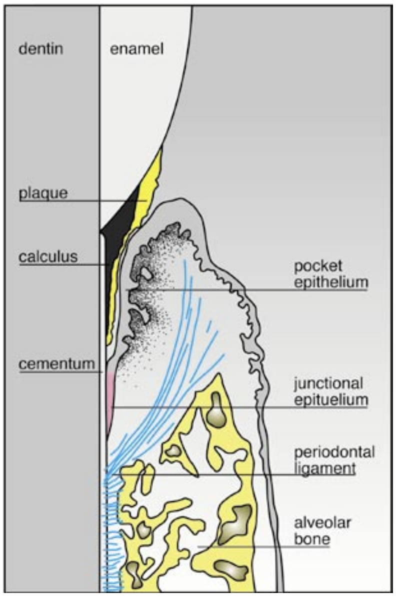


**Fig. 1.** Periodontal pocket of an infrabony defect, showing factors involved in periodontal healing.

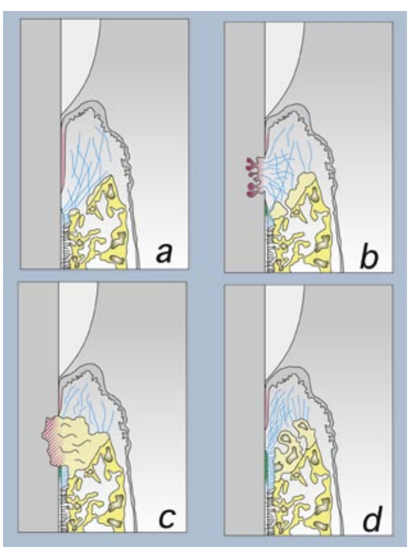


**Fig. 2**. Periodontal healing patterns according to the cell type dominant during healing: a) long epithelial attachment, b) connective attachment with radicular resorption, c) ankylosis with radicular resorption, d) partial periodontal regeneration.

Also found in the literature are the terms *reattachment* and *new attachment*. *reattachment* is the attachment between two parts of previously separated tissue, whether due to periodontal injury or to the destructive process of periodontitis. This occurs when viable ligament tissue still exists on the radicular surface, in such a way that during healing this tissue is able to unite with the periodontal fibers on the opposite side of the wound. This phenomenon may arise during the healing of the deepest areas of the periodontal pocket. On the contrary, the term *new attachment* is used when this joining of tissues (epithelial and/or connective) is produced on an area of the radicular surface previously affected by periodontitis, and where no viable periodontal tissue remained (6).

Consequently, periodontal regeneration (PR) supposes a complete recovery of the periodontal tissues in both height and function, that is, the formation of alveolar bone, a new connective attachment through collagen fibers functionally oriented on the newly formed cementum. However, when we speak of periodontal regeneration, we usually refer to the partial regeneration (in height) of the periodontia.

At the cellular level, PR is a complex process that requires coordination between the proliferation, differentiation and development of various cell types. During tooth development, the periodontal stem cells originate from the dental follicle cells, and are able to differentiate in order to form radicular cementum, periodontal ligament, and alveolar bone. Some of these stem cells remain in the periodontal ligament after the tooth has fully developed. During the healing of a periodontal wound, these stem cells, together with those located in the perivascular region of the alveolar bone, are stimulated to proliferate, migrate into the defect and differentiate to form new cementoblasts, periodontal ligament fibroblasts, and osteoblasts. This entire process should be perfectly synchronized in order to result in a new periodontal support (2).

The literature shows that the possibilities for PR are increased in infrabony pockets, also referred to as intrabony of vertical defects. It would seem that the spatial relationship established between the bone wall of the defect and the radicular surface is the fundamental factor for successful regeneration since it allows the spatial stability of the wound area during the healing period and the proximity of vascular and tissular stem cell sources.

## INTERPRETATION OF THE RESULTS

PR implies the recovery of the lost tissular architecture; therefore, the only way to verify and quantify this exactly is through histological evaluation. For ethical reasons it is not possible to apply this measurement system at the clinical level. Once animal and human experimental studies have demonstrated that a particular technique is able to achieve regeneration, other methods such as clinical measurement, intraoral radiography or surgical re-entry are accepted for the measurement of results.

Clinical measurement uses a periodontal probe in order to record the clinical attachment level, that is, the distance from the dentinoenamel junction to the point of the periodontal probe introduced into the gingival sulcus (6). Although this parameter is often used, it is an inexact measurement since it is influenced by factors such as angle, probe thickness and pressure applied, or the level of gum inflammation. Although desirable, an increase in clinical attachment level



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does not necessarily imply *new attachment* or *periodontal regeneration*. We should remember that a reduction in tissular inflammation, the formation of the long epithelial attachment, the reestablishment of the connective attachment and an increase in bone filling all achieve improvements in the clinical attachment level.

Surgical re-entry is the only clinical method that can evaluate the bone filling exactly, but for obvious reasons it cannot be used routinely. The alternative is the *bone probe* carried out under local anesthetic, and which has demonstrated a similar precision to surgical re-entry. However, neither surgical re-entry nor the bone probe can confirm that true PR has taken place. Some histological studies have demonstrated that the newly formed bone may be separated from the radicular surface by a long epithelial attachment, which would imply periodontal *repair* (5,7).

Finally, standardized radiographs supply quantitative information about the bone filling produced, but do not provide anything on the nature of the attachment between the radicular surface and the newly formed bone. As indicated by Friedman in 1958, the increase in thickness of the trabeculae that delimit the medullar spaces and the deposition on these of a dense bone layer will appear in the post-operative radiograph as coronal bone regeneration (8). For these reasons, and in spite of the spectacular radiographic images that tend to be used to endorse the regeneration, it should be taken into account that radiography, although sensitive to density, is not very specific, and so is not as reliable a method as clinical measurement or surgical re-entry (Figure 3).

In the past different methods have been attempted to obtain PR, in the following section we make a revision of the surgical techniques used, highlighting the physiological strategy on which these are based.

## PERIODONTAL REGENERATIVE THERAPY

- *Conservative therapy (debridement)*

Early studies observed that bone filling was possible with radicular scraping and planing treatment, followed by strict hygiene (9). These techniques are based on the principal that a biocompatible radicular surface and a strict hygiene control favor the development of the innate regenerative capacity of the periodontal tissue (Figure 4).

Epithelial tissue possesses the fastest growing and moving cells, being faster to arrive at, and colonize the wound than other internal tissues. With this idea in mind, it was proposed to increase by surgery the distance that the epithelial cells needed to travel, allowing the slower connective tissue to reach the radicular surface first.

Under this philosophy, we can embrace numerous surgical techniques that would include flap débridement procedures (including new attachment techniques), coronal flaps for the exclusion of epithelial tissue, and interdental denudation techniques.

The article published by Prichard in 1957 on treatment of the infrabony pocket deserves special attention (10). This is the first author to focus attention on the morphology of the bone defect, and on the importance of its careful débridement. The authors consider bone regeneration to be a real and predictable objective in treatment, provided a careful selection of cases according to the bone morphology of the defect is made.

In general, studies published where this type of surgical technique is used for PR are vague (9, 11,12). However, numerous studies have used débridement techniques as a control against other regenerative therapies. In a study published by Lang et al. (13), an average increase of 1.78mm in the clinical attachment level and 1.55mm in bone filling was calculated, highlighting the effect on both parameters of following a strict protocol for professional control of postsurgical plaque.

The information provided by these studies underlines the importance of achieving a clinical situation without inflammation and strictly controlling the bacterial plaque (periodontal health maintenance), so that the periodontal tissues can attain the ideal conditions to completely develop their regenerative capacity.

**Fig. 3.** Bone filling of two intraosseous defects treated with regenerative procedures.

**Fig. 4**. Debridement is an essential step before any regenerative technique is applied.



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- *Radicular conditioners*

The radicular surface exposed to a periodontal pocket or to the oral cavity presents bacteria, bacterial toxins or even changes in mineralization. Under these circumstances, the radicular surface is hardly an adequate substrate for the adhesion of fibrin coagulum, and its maturation remains retarded by an excess of inflammatory response. It was thought that the use of conditioners for the radicular surface helped débridement to achieve a more compatible biological substrate. On treating the radicular surface with acids, a decontaminating effect on the bacterial toxins is obtained, and furthermore, the collagen fibers of the radicular matrix become exposed, facilitating attachment and favoring the activity of the cells able to achieve regeneration. To this end, citric acid, EDTA and tetracyclines have been used as conditioners.

The results of histological studies in humans have been contradictory, and against four studies that demonstrated that following treatment with citric acid, new connective attachment, cementogenesis and the formation of new bone are possible; four other studies have no found such effect. Regarding studies that evaluate the effect at the clinical level of the use of citric acid, EDTA or tetracyclines, the results are highly variable and even contradictory. Likewise, in contrast to studies which observe an increase in clinical attachment greater than 3mm, others detect an improvement of only 0.5mm; and apart from one single study, the rest do not achieve significant differences with respect to the control group (14).

A recent systematic review of the literature, concluded that the evidence to date suggests that using these chemical agents has no significant clinical benefit for the patient with respect to the reduction in probing depth or gain in clinical attachment level (15).

- *Bone grafts and substitutes*

For almost 50 years, the attention of the investigators was focussed on bone regeneration, believing that it constituted a prerequisite for the formation of a new attachment, and that the formation of new bone would induce the formation of new cementum and periodontal ligament (16). Under this premise, different types of bone grafts and other materials have been used, which, according to their origin, have been classified as: autografts (obtained from the same patient), allograft (the same species but a different individual), xenograft (different species) and alloplastic grafts (synthetic material or foreign body graft). Depending on their action on bone, they were attributed with osteogenic, osteoinductive or osteoconductive capabilities.

The only materials demonstrated as being osteogenic, that is, having living bone cells able to create new bone, are the grafts of fresh trabecula bone from the ileac crest, and the intraoral bone graft. Autografts from the ileac crest have even demonstrated a capacity to achieve supracrestal regeneration. The disadvantages of creating a second surgical area and the possibility of provoking radicular resorption and ankylosis have limited its use in daily practice.

Autografts of intraoral bone are obtained from edentulous areas, tubera, exostosis, and from post-exodontic alveoli. Clinical studies suggest that the use of these grafts improves bone filling against conventional treatment (débridement), and that the differences in the results appear to depend on the morphology of the defect and the type of donor bone. Although some authors consider periodontal bone graft material to be the 'gold standard', its limited availability and the time required for its acquisition have stimulated the search for other materials.

In contrast to the above mentioned limitations, the allografts of lyophilized bone and demineralized lyophilized bone originating from cadaver, provide the advantage there is unlimited amount of material available, and with a minimum risk of infection. The risk of HIV transmission in any particular section of demineralized lyophilized bone, following an adequate selection and processing process, has been calculated to be 1 in 2.8 billion (17). These materials are considered osteoinductors, that is, they have the capacity to induce the formation of new bone, stimulating the maturation of the undifferentiated mesenchymal cells to preosteoblasts and osteoblast forming cells. The principal reason for demineralizing is based on studies by Urist, who suggested that the demineralization of lyophilized bone would allow the exposure of morphogenetic bone proteins, polypeptides that induce the pluripotential stem cells to differentiate into osteoblasts (18). However, it has been found that this osteoinductive capacity depends on the donor characteristics, especially the age, and the degree of demineralization, in such a way that depending on the bone bank and even the batch, the capacity to induce bone formation can vary and may even be nonexistent (Figure 5).

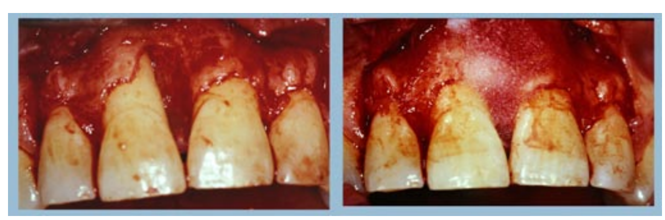

**Fig. 5.** Infraosseous defect filled with demineralized lyophilized bone.

The results of published studies indicate that following the use of bone grafts a significant bone filling can be expected against treatment by débridement, obtaining an average filling of the defect of between 60% and 65% (19). With respect to histological findings, a certain degree of regeneration has been described following the use of autografts and of demineralized lyophilized bone. In contrast, other studies have found that although formation of new cementum occurs, the ligament fibers are not functionally oriented, and even a long epithelial attachment has been observed interposed between the newly formed bone and the radicular surface (5,7).

With respect to the remaining materials, their use has been justified by their potential for *osteoconduction*, their



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chemical composition and structure endows them with the capacity to facilitate the formation of new bone from that existing in the walls of the defect, acting as a growth framework. This group includes the xenografts, taken from bone of animal origin, usually bovine, treated chemically to eliminate the organic component but maintaining a trabecular architecture similar to human bone; and all the alloplastic materials reflected in Table 1.

**Table 1.** Grafts and bone substitutes.

| **Material of bone origin** |
|---|
| *Grafts of vital bone* |
| - Autografts |
| Oral origin |
| Bone coagulum |
| Bone collected from post-exodontic alveoli, tubera, and edentulous areas. |
| Extraoral origin |
| Iliac crest |
| - Allografts |
| Freeze-dry bone |
| Fresh bone from iliac crest |
| |
| *Grafts of non-vital bone* |
| - Allografts (human origin) |
| Lyophilized bone |
| Demineralized lyophilized bone |
| - Xenografts (animal origin) |
| Anorganic bovine bone |
| |
| **Non-bone material** |
| *Organic* |
| Dentine |
| Cementum |
| Coral |
| |
| *Anorganic (alloplastic)* |
| Calcium sulphate |
| Calcium phosphates (hydroxyapatite) |
| Bioceramics |
| Polymethyl and hydroxyethyl-methacrylate polymers |
| Bioactive crystals |

In controlled clinical studies on the treatment of intrabony defects and furcation invasions, the synthetic materials have demonstrated better results at the attachment level than with débridement treatment, and similar results to those obtained with bone grafts (19). However, from the histological point of view, they act almost exclusively as filling, the material fragments appear encapsulated by the connective tissue, observing little bone filling and very limited periodontal regeneration.

- *Guided tissue regeneration*

In a study published in 1976, Melcher makes a series of reflections on graft techniques (2). According to this author, the hypothesis of Hiatt et al. was partially formed, since it was limited only to bone regeneration (16). For Melcher, the regeneration of the periodontal ligament was a fundamental question, since it is this tissue that provides continuity between the bone and cementum, and in addition contains cells that can synthesize and remodel the three tissues of mesenchymal origin that form the periodontium.

Later, studies were designed using experimental models on animals which were able to isolate the effect of each of the tissues that make up the periodontium on the process of periodontal wound healing (20). It was observed that the apical migration of the epithelium provoked the re-epithelialization of the wound and that this circumstance impeded the formation of the connective attachment. However, the re-epithelialization also had its positive effect, since it prevented radicular resorption, which was the response observed when the granulation tissue (originating in the connective gingiva or in the alveolar bone) was the first to reach the root surface. The only cells that demonstrated an ability to form a new attachment were those that originated from the periodontal ligament.

From these experimental studies the investigators obtained two fundamental conclusions: 1) The cells that repopulate the area of the wound adjacent to the root determine the type of newly formed tissue on the interface of the soft and solid tissues of the periodontium. 2) The result of healing is determined by the shape and size of the wound, that is, the distance between the various tissues that form the periphery of the wound and the root surface.

On the base of these two hypotheses, the principal of cellular exclusion of Guided Tissue Regeneration (GTR) was established. As reflected by Nyman et al., in the first study to histologically confirm the validity of GTR in humans, 'the capacity of the periodontal ligament to form a new attachment will only be demonstrated if we can prevent the bone, connective and epithelial cells from occupying that part of the wound adjacent to the radicular surface during the initial healing phases' (7). Therefore, GTR aims to isolate the periradicular bone wound from the rest of the tissues (epithelial, connective and periosteal) to aid the cells originating from the periodontal ligament to be the ones to repopulate the blood coagulum that forms below, between the alveolar bone and the radicular surface. The way in which to achieve this cellular exclusion is to interpose a physical barrier (membrane), and this surgical technique



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was denominated Guided Tissue Regeneration (GTR) (Figure 6).
Different barrier materials have been used as membranes, both non-resorbable and bioresorbable. Among the first group, methylcellulose membranes (Millipore filters), polytetrafluoroethylene (Teflon-PTFE), and expanded polytetrafluoroethylene (PTFEe) have been used. As bioresorbable membranes, a wide variety of materials have been used: collagen of both human and animal origin, lyophilized fascialata, duramadre grafts, polyglactin 910, polyglycolic acid, polylactic acid, polyorthoester, polyurethane, and polyhydroxybutirate.

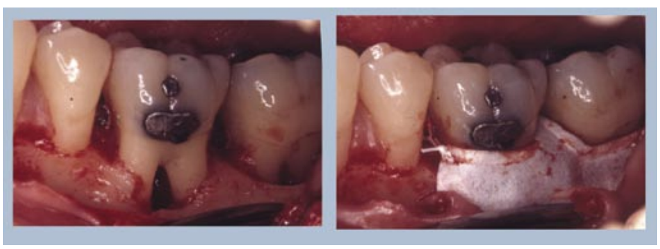

**Fig. 6.** GTR with expanded polytetrafluoroethylene (PTFEe) membrane.

- *Nonresorbable membranes*
Expanded polytetrafluoroethylene (PTFEe) membranes have been the most studied, currently being the gold standard for comparison with other PR techniques. In the literature, we find numerous studies, both histological and clinical, which illustrate the capacity of PR in bone defects and class I and II furcation invasions (21, 22). The results of clinical studies indicate that better results can be achieved with GTR techniques in bone defects than with surgical débridement, obtaining improvements in the clinical attachment level (3-6mm), in bone level (2.4-4.8mm) and significant reductions in probing depths (3.5-6mm). In the case of class I and II furcation invasions, the results clearly stand out in favor of GTR, however, in class II invasions of upper molars and class III furcation, the results find no differences with respect to conventional débridement (19).
In spite of these results, the clinical use of PR has reduced somewhat, since the technique requires follow up surgery to remove the membrane, and its effectiveness is highly sensitive to the surgical operation, which is rather complicated, as there is a high risk of exposure to infection of the membrane. Currently these types of membrane are used with reinforcing titanium strips with the aim of better preserving the space, and their use are indicated, above all, for guided bone regeneration in cases where an increase in bone crest is needed prior to the placing of dental implants.
- *Bioresorbable membranes*
For many clinicians, this type of membrane has replaced the routine use of PTFEe membranes. In general, the results published regarding the capacity for PR are very similar to those obtained with the nonresorbable membranes in relation to both the histology and the clinical parameters studied. Furthermore, the clinical management is simpler, above all because the need for follow up surgery is avoided, and there appears to be less risk of membrane exposure.
- *Mixed techniques: GTR with bone grafts*
In an attempt to improve the results of GTR a variety of surgical techniques using membranes together with bone grafts or other combinations of filling materials have been applied. In the literature, a large number of papers study many different combinations of materials and types of membranes. Probably the clearest information on the results of these techniques can be found in the systematic review carried out by Murphy in 2003 (23). This article reviews the data published on studies carried out only on humans. The conclusions indicate that in furcation defects, better results are obtained with the combination of a material to increase bone plus a membrane, but in other bone defects the results are similar between the sole use of a membrane or a combined technique.
Finally, it is worth highlighting the meta-analysis made by the Cochrane Oral Health Group (24). Their objective was to compare the efficiency of GTR in the treatment of infrabony periodontal defects, with the standard periodontal treatment of *open flap débridement*. The review made by the Cochrane group included only 11 studies that met the strict inclusion criteria. They concluded that at the clinical level, results following GTR are highly variable which questions the evidence of any worthwhile appreciable and consistent clinical benefit. On the other hand, they also show that there are no data to answer important questions such as what the adverse effects of the treatment may be, the evaluation of the patient's opinion about the treatment, or the effects of the treatment on important issues such as tooth loss.
- *New approaches in periodontal regeneration*
In recent years, investigation has centered on the application of biomedical engineering to PR, especially with the use of biomedical mediators that attempt to imitate the natural processes that occur in spontaneous regeneration. Work has been done with cellular growth factors, such as the platelet-derived growth factor (PDGF), the insulin-like growth factor (IGF), and with cellular differentiation factors, especially with bone morphogenetic proteins (BMP). The objective of these new approaches in regenerative therapy is to select and improve cellular repopulation during the periodontal healing process.
From this perspective, the enamel matrix-derived proteins (Emdogain®) have demonstrated their capacity to induce PR.
- *Enamel matrix derivative*
During root growth the epithelial Hertwig sheath deposits enamel matrix proteins on the surface of the recently formed dentin, these proteins stimulate the differentiation of the mesenchymal cells into cementoblasts to form the radicular cementum. Once the new layer of cementum is formed, the collagen fibers in the periodontal ligament become inserted into this layer. The enamel matrix derivative (EMD) is made up of an extract of proteins obtained from developing pig's teeth; the majority are amelogenins, although ameloblastin and enamelin have also been identified.



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It is supposed that the action mechanism for these proteins is effected through its stimulus of the periodontal stem cells which initiate the process that occurs during the natural development of the dental root. Studies have been carried out 'in vitro' on cells originating from the periodontal ligament, in cementoblasts and in osteoblasts, and have demonstrated that these proteins are able to stimulate their capacity for protein production and cellular proliferation (25).
Histological studies in both animals and humans have demonstrated that the EMD are able to regenerate acellular cementum and bone (26). From the clinical point of view, the principal advantages of this technique lie in the easy clinical management and in the good tolerance on the part of the gingiva during post surgical healing (Figure 7).

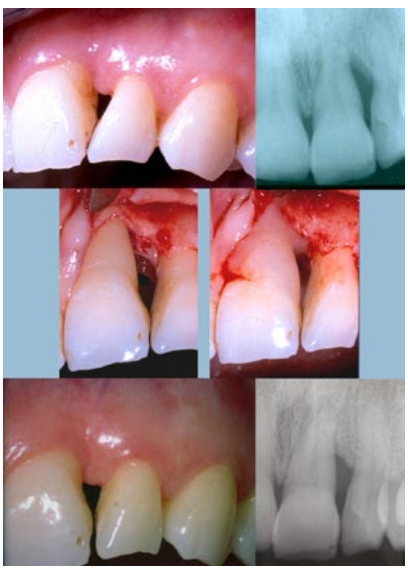

**Fig. 7.** The new techniques for periodontal regeneration allow the clinician a less complex surgical operation, and furthermore are well tolerated by the gingiva during healing. A case treated with enamel matrix derivative.

As in the case of GTR, the Cochrane Oral Health Group carried out a meta-analysis with the aim of evaluating the efficiency of the enamel matrix derivative in the treatment of intrabony defects (27). Again, the authors could only find 10 cases that met the selection criteria. The reviewers conclude that compared with surgical débridement, the enamel matrix derivative demonstrated statistically significant improvements on the attachment level (1.3mm) and in the reduction of the pocket depth (1mm), although with respect to its clinical utility these improvements are open to debate. Regarding the comparison with GTR, no significant differences could be established.
The authors emphasize the need for caution with respect to the possibility of extrapolating the review findings to a more general population since:
– The treatments were carried out by very experienced clinical dentists.
– Smokers were excluded from some trials.
– Very strict maintenance protocols were used, which are generally not applied in routine clinical situations.
– The heterogeneity of the results indicates that even within these optimum conditions the results of treatment are highly variable.
Finally, the data do not explain the cause of this variability, thus it is not possible to define the optimum patient selection, the clinical aspects of the treatment indicated, or the maintenance strategy.

## INDICATIONS AND LIMITATIONS OF PERIODONTAL REGENERATION

One of the most interesting approaches for clinical practice are 'influence diagrams', these schematize the findings of the different studies with respect to the factors implicated in the results of treatment, and serve to orientate the clinical decisions. Figure 8 shows the influence diagram for the data published on the factors related with the treatment of periodontal bone defects (28). Our intention is to transmit to the reader the complexity involved in trying to include all the different circumstances related with the results when making decisions on treatment. However, primary factors have been identified (primary line of globus, bacterial contamination, innate healing potential, local characteristics and surgical technique) whose influence on treatment of intrabony defects seems clear.
Poor control of bacterial plaque by the patient, and likewise the lack of maintenance visits, are determining factors in the results of periodontal treatment and therefore can provoke a reduction in the formation of new attachment and bone tissue (9). This statement is supported by many published studies, the authors agree in indicating that the *de novo* accumulation of plaque provokes a relapse of periodontal disease, even when a significant attachment level has been achieved by the treatment.
Given that the healing process is a structured process, any alteration in any of its steps would potentially vary the results of the treatment. The studies tend to consider diabetes and any other systemic disease that could imply an alteration in the innate healing capacity of the individual as reasons for exclusion.
In the opinion of some authors, smoking is a reason for exclusion from PR, it has been clearly demonstrated that smoking is a major risk factor, not only for the progression of periodontitis, but also in adverse results of treatment (29).
Among local factors that may influence the result of regenerative therapy, occlusion and morphology of the bone defect have been the most studied. Occlusal control and the stabilization of the tooth would be indicated in the case of hypermobile teeth which are to receive PR treatment, however, given that the effect of mobile teeth on periodontal regeneration remains undefined, the stabilization procedures used should be minimally invasive, provoking the minimum loss of dental structure (28).
The morphological characteristics of bone defects have been the most studied local factors in PR.



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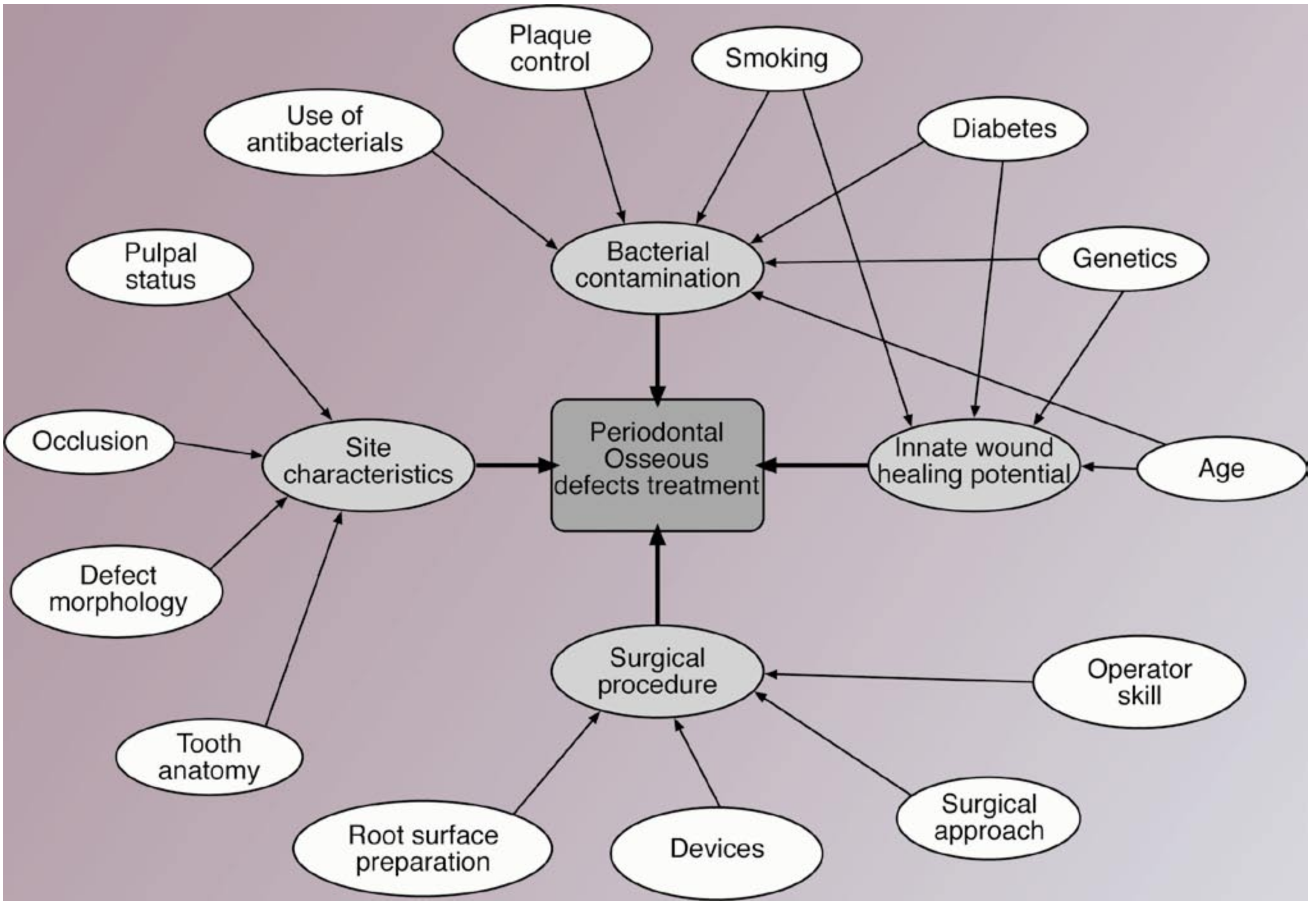


**Fig. 8.** Influence diagram for determining factors on results of treatment for periodontal bone defects (modified by Kornman & Robertson 2000).

The total depth of the defect and the angle of the bone wall with respect to the root are the variables most consistently related to the amount of bone filling obtained. As early as 1949, Goldam pointed out that one of the factors affecting the result of gingival curettage in the treatment of infrabony pockets was the type of bone defect. In such a way that the narrower the bone defect, the smaller the area to heal and the better the stability of the wound during healing; on the other hand, the wider it is then the greater the possibility of displacing the coagulum and therefore the greater the risk of secondary infection. Later, Prichard indicated that the most important diagnostic criteria in obtaining a favorable result is the presence of a 3-walled bone defect. Gottlow et al. (21), explicitly state that alveolar bone regeneration is almost totally restricted to locations where there was an angular bone defect. Studies by Cortellini (30) support the importance of this local factor, indicating that ‘the morphology of the defect plays a principal role in the healing response to GTR in intrabony defects’.

The surgical management of the tissues has also been related with the success of PR therapy. It is certainly the most difficult factor to evaluate. It is normal that when a new procedure is introduced the technique itself is considered a critical factor in the clinical results. Nevertheless, even after the technical criteria for the surgical procedure have been established, the skill of each surgeon is different, implying subjective factors that are difficult to evaluate.

## CONCLUSIONS

It is clear that as clinicians we hope that medical investigation will provide us with tangible and useful results that will reveal with certainty the effect of a procedure in any of our patients. Unfortunately, the scientific and rigorous evidence derived from procedures such as meta-analysis only reflect a degree of certainty, often narrow, about the extent of the global effect on the ‘average’ patient in the population studied. We must take into account that we are at a moment where the clinical decisions taken are beginning to be clearly determined by the predictability of the results we can offer to our patients, and likewise by cost-benefit considerations (efficiency). In this situation, and without questioning the *efficacy* of the biological principal, the available evidence on the *effectiveness* of the regenerative techniques seems to indicate that the success or otherwise is determined more by the patient than by the procedure employed.

The characteristics of the ideal patient for the application of regenerative techniques can be summarized as: a patient who has demonstrated past compliance with adequate treat-



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ment and effective plaque control techniques, non-smoker, emotionally stable, and who is prepared to undertake a commitment of time, money and energy (27, 29). Regarding the ideal clinical situation: localized bone defects (vertical, narrow, three-walled), a good clinical response to initial treatment, where PR therapy would improve the periodontal prognosis for the tooth. With respect to the PR techniques: all have their limitations, it is worth mentioning that in anterior areas or areas of high aesthetic impact it is preferable to apply techniques which respect the gingiva as much as possible.

In the last ten years, the periodontal treatment plan has been changing considerably, with the acceptance of dental implants as a valid option for the long-term replacement of teeth. For this reason, the clinician should consider the strategic value of the tooth, its long-term periodontal prognosis, and the benefit that PR would provide to the tooth. On the other hand, it is true that with the new approaches in PR therapy, the complexity involved in PR treatment is continuously reducing. Therefore, we should have confidence in the future for investigations on new PR therapies, which will, without doubt, bring new and highly useful knowledge to the clinical practice in our patients.



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