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**Regeneration**

Regeneration is one of the most important and contemporary concepts in periodontology.

The aim of periodontal treatment is to have a periodontium that is healthy and carries out normal function. The first objective or line of treatment is to stop the active disease process, which is achieved by removal of plaque and calculus deposits (the main etiological factors). The result is clean pockets which will prevent further disease progression and will even promote some gain in attachment.

However, in some cases deep pockets, mobility, furcation involvement, and recession will not be eliminated completely after non-surgical periodontal treatment. This will pose a problem regarding function, aesthetics, and mobility. Using treatment modalities such as scaling and root planning, maintenance therapy, and antimicrobial therapy, the main goal is to control the pathogenic microflora to prevent further periodontal destruction as mentioned above.

Note: In some cases, gingival recession is absent, but in reality there is underlying disease of the periodontium.

In cases with deep pockets, non-surgical therapy alone is not enough to achieve a healthy periodontium as the pockets cannot be completely eliminated. This is because deep pockets are a risk factor for further accumulation and recolonization of bacteria and plaque and further disease progression. In some patients who are compliant, attend for a dental check up every couple of months, and have very good oral hygiene, a few pockets can be maintained without plaque accumulation if the pockets are not too deep (3-4 mm in depth) and the pockets have favorable morphology.

On the other hand, deep pockets (7 or 8 mm) with underlying bone defects cannot be maintained because the depth of such pockets are impossible to clean non-surgically and this will not prevent further disease progression. Even a dentist in the clinic cannot guarantee the complete removal of all bacterial deposits from such pockets because non-surgical therapy depends on tactile sensation subgingivally.

In other words, despite successful disease management, anatomic changes resulting from past disease activity (such as bone defects) often occur and must be corrected. If they are left untreated, these defects can provide a potential harbor for the recolonization of a pathogenic microflora.

Many studies have shown that in non-surgical therapy, efficiency of cleaning pockets beyond 5 mm in depth decreases to 60-66%, and keeps decreasing continuously as you go deeper (efficiency reaches 30% at depths greater than 7 mm).

As a conclusion, in cases with persisting deep pockets, surgical procedures should be undertaken to clean the root surfaces. Surgical therapy can be divided into:

1. Open flap debridement: a flap is elevated to expose root surfaces and clean them.
2. Osseous resective surgery: this procedure involves osteotomy and osteoplasty to remove **shallow** vertical bone defects. This solution is not possible in cases with **deep** vertical defects because a lot of tissue loss will result from removing the deep defect.
3. Regeneration: this is the ideal surgical treatment modality in cases with **deep** vertical bone defects.

**Principles of regenerative medicine**

Medicine, in general, used to be prosthetic medicine. In other words, lost tissues are replaced by external tissues or prostheses regardless of the material of these external prosthetic tissues (whether they are made of metal, plastic, allogenous tissues etc.).

This era of prosthetic medicine has been changing since the 80’s and 90’s. In 1993, tissue engineering was discussed for the first time in the medical literature by Langer and Vacanti, who laid down the basics for the modern era of regenerative medicine.

Tissue replacements come in a wide range, from prostheses replacing the head of the femur in the hip joint, to dental implants, to fixed partial dentures, and removable dentures in general. Even bone grafts are, in a certain definition, replacements.

Medicine is moving from being purely prosthetic towards relatively more regenerative procedures.

Autogenous bone grafting is considered a regenerative procedure (bone graft taken from and used in the same patient). Allogenous bone grafts, xenogenous bone grafts, and synthetic bone grafts are considered replacements, with the aim that these replacements will **lead to** regeneration later on.

* **Definition of regeneration: The reproduction or reconstruction of a lost or injured part.**

**Periodontal regeneration implies the formation of new cementum with inserting collagen fibers and bone.**

* **Repair: The situation in which healing does not completely restore the architecture or the function of the lost tissue or parts.**

**Periodontal repair may include:**

1. **Formation of a long junctional epithelium**
2. **Connective tissue attachment**
3. **Ankylosis**

In other words, if bone was grafted along with other growth factors but the end result was only bone formation and ankylosis without connective tissue attachments (collagen fibers), this is considered repair not regeneration.

For a process to be considered regeneration, the tissue has to go back to the way it was anatomically and physiologically before the disease (as if the disease never took place).

In normal healthy periodontal tissues, collagen fibers are inserted **perpendicularly** to the surface of the root. In repair, there will be incomplete regeneration of bone, and as a result collagen fibers will be inserted **parallel** to the root surface along with resorption of this root surface.

**Why is regeneration not achieved in some cases?**

A space will be created in the periodontium as a result of the tissue loss. This space should be occupied by a tissue. In the area surrounding a tooth, four tissue types are available; cementum, gingiva (epithelium), connective tissue, and bone. Epithelium has the highest tendency to fill the space created by tissue loss, since it has the fastest growth rate. If epithelial growth is restricted, connective tissue will proliferate and fill the space since it has the second fastest growth rate among these four tissue types. If connective tissue growth is restricted, bone will tend to grow and fill the space. In other words, cementum is the tissue which grows at the slowest rate among the four tissue types.

Embryologically, the periodontium develops in the same sequence: epithelium is formed, followed by connective tissue fibers, then bone, and cementum is the last tissue to develop as the tooth starts to erupt. Cementum is the most specialized tissue and needs a longer time to form.

As a result of the presence of these four different tissues that are competing on the same space created by tissue loss, there are 4 possibilities to end up with (as mentioned above):

1. Formation of a long junctional epithelium
2. Connective tissue adhesion accompanied by some degree of root resorption and insertion of connective tissue fibers parallel to the root surface.
3. Root resorption and ankylosis. In this case, bone is in direct contact with the root surface.

**The first three points are considered repair.**

1. Regeneration, which involves the formation of new bone, cementum, epithelium, and connective tissues in the correct proportions.

If the regenerative procedure was not successful, repair will take place with a combination of the first three processes, meaning that in some areas there will be a long junctional epithelium, with some areas containing connective tissue adhesion, and other areas will contain bone formation and ankylosis, with regeneration seen in some other areas as well.

Note: In areas where formation of a long junctional epithelium took place, clinically a pocket cannot be detected with a probe. However, theoretically this is a weak junction.

Epithelium migrates apically with the help of the connective tissues. Once it migrates apically and produces a long junctional epithelium to occupy the defect on the root surface, it will cover the root surface and **prevent the regeneration** of the proper periodontium.

Clinically it is impossible to tell the difference between regeneration and repair by probing. Repair and regeneration can only be differentiated histologically.

The process of regeneration includes: epithelial migration and maturation which takes place first as it is the fastest, followed by connective tissue formation (collagen fibers), and then revascularization takes place. Bone resorption takes place within the first 21 days, and bone formation starts during the first 2 to 4 weeks. Bone maturation needs more than 2 years to occur. This shows that regeneration is a dynamic process and it depends on many factors. The two most important factors are:

1. The chemical stimuli that are present in the area
2. Metabolism; bone is one of the most involved tissues in the metabolism and balance of electrolytes.

**Techniques used to achieve regeneration**

1. Root conditioning procedures

Initially, it was thought that if the root surface was conditioned and cleaned this will enhance the cellular activity that is needed to achieve regeneration. The two agents that have been studied the most regarding root conditioning are **(a)** EDTA in low concentrations and **(b)** Tetracycline. It was thought that tetracycline adsorbs to the root surface and stimulates stem cells or regenerating cells to migrate to the defect site and bring about tissue regeneration. This scenario was proved in in-vitro models and in animal studies. However, in all the human studies **except one** case report, the results were negative.

In conclusion, this technique and these materials should not be used because they are not supported by evidence of success in human studies. They are only successful in in-vitro and animal studies which is not enough to advocate their use.

Often, studies may give positive results in-vitro and in animal models and higher primates (monkeys) but will give negative results in human studies.

1. Bone grafts and bone substitutes

This is the second technique which may be discussed to achieve regeneration. Bone can be grafted using bone or bone substitutes. **Any graft material other than autogenous bone is considered a bone substitute.** This is because bone is a tissue and by definition, a tissue contains vessels, cells, growth factors, and matrix (and autogenous bone is the only graft material which contains all these components). Bone grafts from allogenous sources does not contain vessels or cells; it only contains matrix and one growth factor.

1. Guided Tissue Regeneration

This concept involves the guiding of the regeneration of tissues according to their rate of turnover.

1. Biologic and biomimicry mediators

This concept was developed in the late 90’s. It involves the use of certain growth factors that will target such cellular activity which will help to induce a certain step of the regenerative process. The regenerative process has three main requirements which can be summarized into:

1. Regenerative space: the space created by the bone defect needs to be maintained. Otherwise, if the space is left as it is, it will be quickly occupied by epithelium within the first 14 days while bone starts formation at 14 days.
2. Signaling molecules: the space needs to be provided with the necessary signaling molecules. There are no less than 500 to 600 molecules that are involved directly or indirectly, in a very active manner, in the formation of bone and cementum. The same molecule may affect more than one cells type. Also, a single factor may have either a stimulating or inhibiting effect a cell depending on the stage of cell development. It is a very complex process.
3. Stem cells (progenitor cells)

The presence of regenerative space and signaling molecules only will lead to repair and not regeneration. This is because the signaling molecules alone may not be able to bring about the migration of cells from another distant site. The signaling molecules may even lead to the migration of cells that are not needed in the regenerative process. That is why stem cells in the regenerative space are necessary for regeneration.

In a case where only the regenerative space and stem cells are present without signaling molecules, the end result is also repair.

Likewise, if the regenerative space is not maintained but the site was provided with stem cells and signaling molecules, the end result will also be repair.

**In order to obtain regeneration, all three conditions need to be met.**

The objective of treatment should always be regeneration. However, due to the complexity of this process, regeneration is not always possible in most of the cases.

**Assessment of wound healing**

Wound healing can be assessed in one of the following ways:

* Probing depth
* Clinical attachment level
* Bone fill
* Histological analysis
1. Probing depth: this is not a reliable way of evaluating regeneration vs repair because it is only a clinical evaluation of the presence or absence of pockets and depth of these pockets. Whether there is a long junctional epithelium, or ankylosis, or regeneration, all three scenarios will present as attachment gain clinically and cannot be differentiated by probing.
2. Clinical attachment level: this method of assessment is more reliable than the probing depth, however it is not completely reliable. It is more reliable than probing depth assessment because probing depth relies on the level of inflammation of the gingiva at the time of probing. Clinical attachment evaluation involves the measurement of the amount of gain in attachment by evaluating the difference between the post-operative probing depth and the pre-operative probing depth (probing depth analysis only involves measuring the pocket depth post-operatively, while clinical attachment level analysis measures it both pre-operatively and post-operatively). This method is not completely reliable because tissue generation and repair cannot be differentiated from one another, the type of repair cannot be assessed, and there may be some degree of gingival recession (not only attachment gain) which may give false results.

Note: A pocket depth of 5 mm will, for example, be reduced to 3 mm after non-surgical periodontal treatment. This 2 mm decrease in probing depth if a combination of both attachment gain (1.25 mm) and gingival recession (shrinkage of inflamed gingiva by 0.75 mm).

1. Bone fill: this can be assessed by several methods;
* Surgical re-entry to the area and visually assessing bone formation
* Taking reproducible parallel technique radiographs to assess bone formation
* Anesthetizing the gingiva locally followed by bone sounding (probing the bone through the gingiva)

Bone fill does not allow the clinician to differentiate between regeneration and repair, as there is a possibility that ankylosis has occurred. Another possible scenario is the formation of a long junctional epithelium along with bone formation.

1. Histological analysis: This is the only method that can reliably be used to differentiate between regeneration and repair. It is possible to determine if the periodontal ligaments have been regenerated and if the connective tissue fibers are inserted perpendicularly to parallel to the root surface.

**Bone Grafting Materials**

Bone grafting materials can be either autogenous, allogenous, xenogenous, or alloplastic materials. These materials differ from one another in their source.

Terminology:

* Osteogenic: the graft material itself produces the new bone. The graft completely contains bone forming capacity.
* Osteoinductive: the graft material induces bone formation in an ectopic site through chemical factors. The graft contains cells for bone formation, but stimulating factors from the graft site are needed to complete the bone formation.
* Osteoconductive: the graft material acts only as a mechanical scaffold for cells to migrate and form bone. This type of bone graft only fills the space of the defect and depends on the bone forming capacity of the defect site to accomplish regeneration.

Osteogenic bone grafts are the best materials for regeneration while osteoconductive bone grafts are the least useful.

Bone substitutes should lead to regeneration but in reality they lead only to repair. This is because the environment of the periodontium is very complex.

Theoretically, bone graft materials should be resorbable. The rate of resorption should coincide with the rate of natural bone formation. However, almost all bone graft materials are not completely resorbable in the human environment, ending up in areas where the graft is resorbed and areas where it isn’t. The reason for this discrepancy in resorption is not related to the graft material itself; it is related to the difference in oxygen availability between different areas of the graft. The stem cells that attach to the bone substitute have special properties. One of their most important properties is their ability to support hypoxia for up to 7 days. Stem cells are very plastic cells and can either increase or decrease their cellular activity and need for energy and oxygen depending on the amount of oxygen available in their environment. On the other hand, oxygen from the vasculature cannot penetrate deeper than 200 microns into the graft material, and this has be shown by microscopic dynamic studies. So, in superficial areas that are close to blood vessels, the bone substitute will be resorbed and replaced by natural bone. In the deeper areas, the graft material will not be resorbed as the stem cells will die due to the persistence of hypoxia for more than 7 days. Instead, the deep site will end up with fibrous tissue formation.

An ideal regenerative material should include cells, a scaffold, and signaling molecules.

* **Autogenous bone grafts** are osteogenic because they contain cells, a scaffold, and signaling molecules. The scaffold in this case is important in maintaining the regenerative space that is needed for regeneration (as mentioned above). Sources for autogenous grafts can be either intraoral or extraoral.

Extraoral sources include flat bones such as the iliac crest. Extraoral sources have disadvantages because they are a secondary surgical site, they are associated with morbidity, and they are a limited source for bone grafts. If a bone graft is taken from an extraoral flat bone, another graft can only be taken from the same site for a second time because flat bones don’t have a high capacity for regeneration. Long bones are weight bearing bones and bone grafts are never taken from them.

Intraorally, bone grafts can be taken from edentulous ridges, maxillary tuberosities, mandibular ramus, tori and exostoses, and the anterior mandible. The disadvantage of intraoral graft materials compared to extraoral sources is that the intraoral grafts have a higher proportion of cortical bone.

Iliac bone is the best material available for bone grafts regarding physiology and biology due to its ideal structure. However, clinically it is not the best option because it is not practical to take a graft from the ilium using a secondary surgery and damaging the ilium in order to treat a vertical bone defect. Iliac bone can achieve a bone fill of up to 4 mm.

Iliac bone and DFDBA (discussed below) are the only graft materials that can achieve regeneration of periodontium in cases with horizontal bone loss (zero wall defects). However, this was only reported in two cases, in a small number of patients, with the work of one of the most skilled periodontal surgeons in the world.

* **Allogenous bone grafts** contain a scaffold and signaling molecules; they lack stem cells. They are osteoinductive and depend on the cells that are present at the site of the bone defect for regeneration. There are two types of allogenous bone grafts: DFDBA (demineralized freeze dried bone allograft) and FDBA (freeze dried bone allograft). Theoretically, the disadvantage with these allografts is the probability of disease transmission between patients. In other words, if an allograft is taken from a patient with a certain disease such as HIV or HBV, there is a possibility that this disease will be transferred to the recipient of the graft. However, this has never been reported in the literature and disease transmission has never happened in any cases clinically. So, in reality, it is a safe option. Its advantage is that its composition is hydroxyapatite which is very close to the natural bone found in humans, and it also contains BMPs (bone morphogenic proteins) which enhance the bone formation.

DFDBA (demineralized) is a better option because it is more easily resorbed and release of bone morphogenic proteins from DFDBA is easier.

The oseteoinduction of allogenous bone grafts depend on: extent of demineralization of the graft, age of the donor, and cell proliferation and alkaline phosphatase activity of the host cells (the cells that are present in the site of the bone defect). In other words, osteoinduction and formation of new bone heavily depends on the cellular activity of the host. Studies have shown that active bone gain using allogenous grafts can be maintained for up to 3 years.

DFDBA has been shown to regenerate bone in cases with horizontal bone loss.

* **Xenogenous bone grafts** are graft materials from species other than humans (*Homo sapiens*). They are osteoconductive. Xenogenous bone grafts contain only a scaffold.

The most common type is inorganic bovine bone.

The advantage of xenogenous grafts is that it is very readily avaialable.

The disadvantage of xenogenous grafts is that it does not promote regeneration in horizontal bone defects. Theoretically, xenogenous grafts should resorb. However, clinically these grafts never resorb.

Note that in implant surgeries, a benefit of bone grafts is their ability to **not** resorb. In periodontal surgery, graft resorption is important.

* **Alloplastic graft materials** are synthetic materials. Usually, alloplastic grafts may be made from many materials such as:
1. Ceramics such as hydroxyapatite and tricalcium phosphate
2. Biocompatible composite polymers
3. Bioactive glass ceramics

**Ceramics** such as hydroxyapatite are commonly used. Their resorption rate, rigidity and flexibility can be controlled by controlling the chemical and physical properties of the manufactured material. The density of these materials affects their compressive strength.

Porosity of the material affects the capacity of vascular ingrowth into the material and also affects the resorbability.

Size of particles in the material affects the resorbability; the larger the particle size, the slower the resorption rate.

Dense hydroxyapatite does not induce bone formation. What happens with this dense material is fibrous encapsulation of the graft along with the formation of a long junctional epithelium. These findings are based on clinical and animal studies.

Beta tricalcium phosphate does not induce new bone formation in a similar manner to that of hydroxyapatite. Porosity and size of particles also affects rate of resorption.

**Biocompatible composite polymers** consist of a polymer coated with calcium hydroxide. Histological studies have shown that there is no new attachment formation. However, clinically it gives similar results to that of autogenous bone. There is a difference between histological and clinical observations. The only available commercially produced biocompatible composite polymer is Bioplant.

Another alloplastic class of materials are calcium carbonates which are derived from the coral reefs. They are composed of processed natural coral skeletons. They are osteoconductive and resorbable. Their main disadvantage is that they have a very high resorption rate so their uses are limited.

**Bioactive glass ceramics** are conventional glass ceramics. They are considered bioactive because sodium particles in the ceramics will be dissoluted in the aqueous solution. This sodium will be replaced by calcium, increasing the calcium content of the glass ceramic, and this in turn will lead to adhesion of the glass ceramics with hydroxyapatite and formation of new hydroxyapatite and bone. In other words, a “silica gel layer” will be formed by dissolution of sodium, followed by the formation of a calcium phosphate layer by calcium absorption, and this calcium phosphate layer will be converted to hydroxyapatite.