BIOLOGY OF OSSEOINTEGRATION OF DENTAL IMPLANTS

* **Abdulgader Ibrahim Swaid**

Abstract

The biology of osseointegration or bone ingrowth around dental implants can be divided into five stages including wound healing and the role of fibrin which occur immediately after implant placement in response to tissue injury caused by the surgical procedure. The wound healing stage is controlled by a group of factors such as inflammatory factors and blood cells. The second stage of Osteogenesis around the dental implant is divided into two types: distant and contact osteogenesis. Osteoconduction is the third stage which involves recruitment of the osteoprogenitor cells to the surface of the dental implant. Osteoinduction occurs during the fourth stage and involves differentiation of osteoprogenitor cells induced by fibrin formation. The last stage is remodelling of bone that forms around the dental implant as result of a functional loading and stress applied on the dental implant.

* Lecturer and Head of the Department of Fixed Prosthodontics in Faculty of Dentistry, Alasmarya University, Zliten, Libya.

Email: Abdulgaderswaid@yahoo.com

1. Introduction

Dental implants are artificial metallic materials incorporated in the dental arch often in both arches to replace tooth loss and to manage lost oral components caused by various defects. The implant unit (screw or cylinder-shaped are the most typical forms) is put within a drilled space within the dentoalveolar or basal bone. In the last few decades, the replacement of the lost tooth by an implant has become the first choice for the treatment plan and was evaluated by Brånemark in the 1960s. The anchorage between the living bone and implant has been called osseointegration (Hadi et al., 2011).

Osseointegration is a direct bone to implant connection in the absence of interlocking soft tissue. Branemark defined osseointegration as a direct structural and functional connection between ordered, living bone and the surface of the implant (Branemark, 1959). To comply with the initial evaluation of osseointegration by Branemark, implants must be embedded inside hard tissue and the titanium oxide layer of the implant should become so fused with the living bone that the two become difficult to be separated without fracture. This fusion of titanium implant and bone enhances the support of a dental prosthesis (Branemark, 1959).

More recently, a tight insertion of the implant which implies that there is a high stability of the implant to the bone with which it has a direct contact means that the implant has osseointegrated. Essentially,

ISSN 2710-4478 (Online) ISSN 2710 -446× (Print)

the mechanism by which non-vital components of the implant engage inside bone which continues in all cases of force applied on the implant indicates the steps of osseointegration (Branemark, 1983).

Since Branemark's initial observations, the term osseointegration has been evaluated at many stages: clinically (Adell et al, 1981), structurally (Branemark, 1983), histologically, and ultrastructurally (Linder et al, 1983). On the other hand, plenty of studies have been done to explain the biology of the process of attachment of hard tissue to the implant surface and the effect on integration of implant materials such as surface preparations and chemical composition (Michaels et al, 1991).

2. Definition of osseointegration

The term osseointegration has been defined from diverse viewpoints (Skalak and Branemark, 1995):

2.1. From the patient viewpoint

A dental implant fixture is osseointegrated when there is no pain, inflammation or mobility in the implant that withstands a functional load and provides a stable and fixed support of prosthesis (Skalak and Branemark, 1995).

2.2. From the macroscopic and microscopic biology viewpoint

A dental implant fixture is osseointegrated when a new and reformed bone undergoes close apposition with the implant fixture so that, under the light microscope, there is no fibrous or connective tissue located between bone and fixture providing a functional connection,

which enables the carrying of functional loads without extensive deformity (Skalak and Branemark, 1995).

2.3. From the overview of the macroscopic and biomechanical

Osseointegration of a dental implant fixture in bone is defined as a lack of mobility between the implant fixture and living hard tissue under different types and degrees of functional load (Skalak and Branemark, 1995).

2.4. From the overview of the microscopic and biophysical

Osseointegration refers to a state that, under the light and electron microscopic evaluation, shows the features of tissue components within a thin area around an implant fixture surface which appears as healthy living bone. This means that there are no functionally obvious inter-positioning materials at the interface (Skalak and Branemark, 1995).

3. Evaluation of clinical application of osseointegration in dentistry

Osseointegration has been widely used in the field of dentistry for many reasons such as substituting the loss of one tooth, for the rehabilitation of multiple teeth loss in the mouth, and for the restoration of completely edentulous mouths via implant-supported

ISSN 2710-4478 (Online) ISSN 2710 -446× (Print)

fixed prosthesis or removable overdentures which connect to the implant-supported framework (Worthington, 1991).

Branemark confirmed that more than 800,000 implants had undergone osseointegration in the field of dental reconstruction worldwide between 1959 and 2001 (Adell et al, 1990).

Rather than simply replacing missing teeth, dental implants have been used to provide a connection for orthodontic, orthopaedic, and orthognathic procedures (Henry, 1999).

4. Principles of biology of osseointegration

The biology of osseointegration can be divided into various stages from the time of placing of dental implant until fusion of the implant with living bone as follows (Davies, 1998):

- Wound healing and the role of fibrin.
- Peri-implant osteogenesis.
- Osteoconduction.
- Osteoinduction.
- Peri-implant bone remodelling.
- Soft tissue integration.

4.1. Wound healing and role of fibrin:

Wound healing is a highly organised sequence of events that occurs in response to tissue injury and is mediated by various factors such as inflammatory mediators, blood cells, the extracellular matrix and parenchymal cells (Anil et al, 2011).

Healing of the bone fracture occurs in four steps: inflammation, soft and hard callus formation, and remodelling. Initially after insertion of the dental implant, blood coagulation and hematoma formation occur at the area of implantation. After that an inflammatory reaction occurs and the inflammatory cells in the hematoma such as activated leukocytes, the first line of defence in the blood, and platelets release several chemical mediators. Two mediators, thrombin and growth factors, act as chemotactic agents for various cell types that play a significant role in osseointegration (Davies, 1998., Anil et al, 2011).

Following implant insertion, the surface of the implant comes into contact with blood components from ruptured vessels at the site of implantation. Immediately, many molecules like fibrin become adhered to the implant. Fibrin is created from fibrinogen conversion and the complement and kinin systems become activated. The fibrin of the blood clot leads to recruitment of osteogenic cells to the site of healing. As fibrin can attach to any surface, this leads to recruitment of new bone to the implant surface. Formation of the thrombus and blood clotting occur in response to platelet activation (Anil et al, 2011).

Platelets store plenty of differentiation and growth factors that enhance the process of repair via a signalling action that leads to migration and differentiation of the undifferentiated mesenchymal cells at the implant surface. On the other hand, plasma contains

ISSN 2710-4478 (Online) ISSN 2710 -446× (Print)

dissolved molecules, for example glucose and amino acids, that are necessary for the tissue repair. Interactions between blood components and the implant surface cause protein adsorption like fibronectin on dental implants that enhance and accelerate bone formation.

The necrotic debris of the bone that results from the drilling process is removed by phagocyte macrophages (white blood cells after activation). The phagocytes then morphologically change and express protein receptors on the cell surface and produce cytokines and inflammatory mediators. These cytokines induce synthesis of an extracellular matrix on the surface of the implant by activation of cellular proliferation. The macrophages also secrete molecules like fibroblast growth factors and transforming growth factors. Finally, all of these complex events lead to enhancement of tissue repair as well as new blood vessel formation (Murai et al, 1996., Davies, 1998., Anil et al, 2011).

4.2. Peri-implant Osteogenesis:

This is represented by distant and contact osteogenesis that occurs around the implant which indicates the general relationship between the implant surface and hard tissue (Osborn and Newesley, 1980).

4.2.1. Distance Osteogenesis:

Refers to newly synthesised bone around implants which arise from the living bone toward the implant. The new bone surfaces become a source of bone cells which secrete new bone matrix. The osteogenesis

continues until it reaches the implant surface (Fig1A). Therefore, in distance osteogenesis, the newly formed bone is not synthesised on the implant, but the implant surfaces become surrounded by hard tissue (Davies, 1998). The trabeculae network of new bone surrounds mesenchymal cells and blood vessels that represent marrow spaces and maintain the biological fixation of the implant (Davies, 1998).

4.2.2. Contact Osteogenesis:

This is also known as "de novo bone formation". In this phenomenon, there is formation of new bone on the implant surface, but there is no bone on the implant surface at the time of implantation. Immediately after the implantation, invasion of the implant surface by a huge number of osteogenic cells occurs before the beginning of bone matrix synthesis (Fig1B). This also happens at sites of remodelling where an old bone surface becomes invaded with synthetic bone cells before synthesis of bone occurs (Davies, 1998).

The term (de novo bone formation) has been used to differentiate between contact osteogenesis and appositional growth of bone (Davies, 1998). In the latter situation the continuation of formation of new bone on the implant surface is explained by the transient anabolic behaviour of differentiated osteoblasts. Recruitment of active osteogenic cells to the area of bone matrix formation is primarily needed for de novo bone formation. These cells are called

ISSN 2710-4478 (Online) ISSN 2710 -446× (Print)

differentiating osteogenic cells and their migration called osteoconduction (Davies, 1998).

Finally, the distance and contact osseointegration lead to the line-up of bone matrix on the surface of the implant (Fig 2). The biologic importance of these various repair events is of important significance in osseointegration (Davies, 1998).

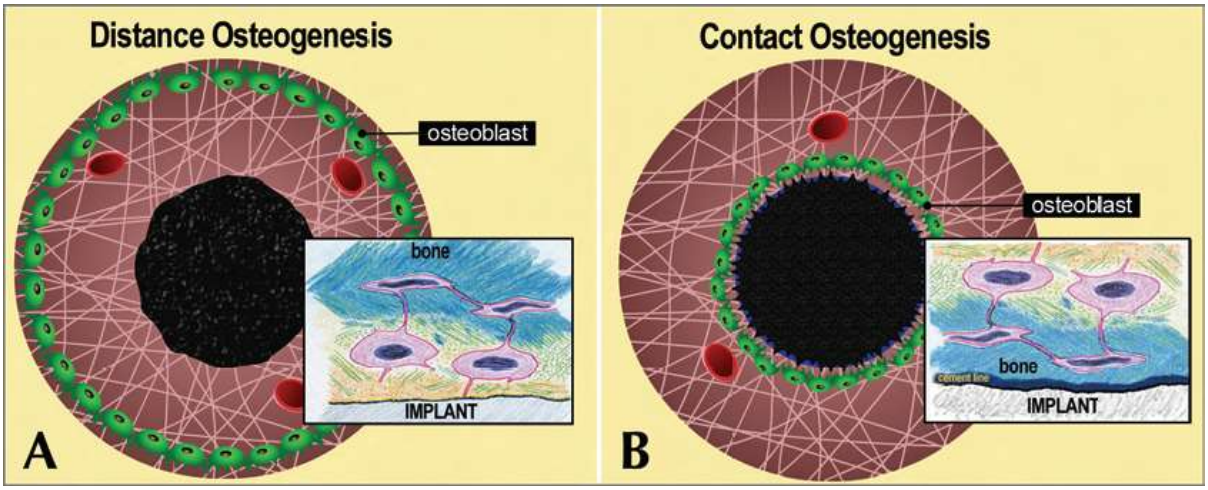

Figure 1 A: Distance osteogenesis and B: Contact osteogenesis (Davies, 2005).

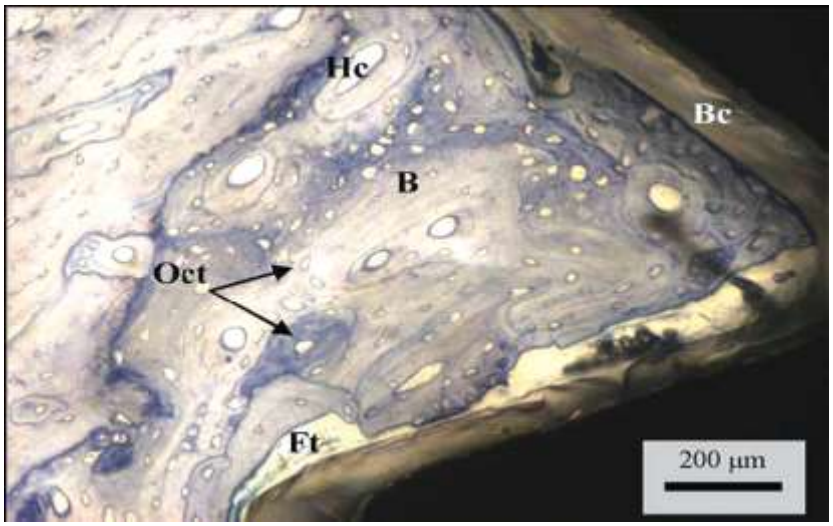

Fig. 2: Photomicrograph of osseoinegrated implant. (B) new bone. (Hc) Haversian canal. (Oct) osteocytes. (Ft) fibrous tissue. (Bc) biomimetic coating (Mavrogenis et al, 2009).

4.2.3. Factors affecting peri-implant osteogenesis

Many factors can lead to failure of peri-implant osteogenesis and are summarised as follows (Marco et al, 2005):

- Reduced number of osteogenic cells.
- Reduced function of bone-forming cells.
- High osteoclast function.
- Abnormality in bone cell reproduction.
- The response of bone cells to mechanical load.
- Inadequate vascularization of the peri-implant tissue.

4.3. Osteoconduction

As explained earlier, contact osteogenesis depends on the recruitment of the osteogenic cells that have the capability of differentiation; these cells are recruited to the surface of the implant. These cells originate from undifferentiated peri-vascular connective tissue cells at areas of new bone formation. Migration of undifferentiated peri-vascular connective tissue cells takes place as a result of fibrin formation. These cells have two actions: synthesis of connective tissue which replaces fibrin and the origin of bone formation cells. As the bone matrix

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becomes synthesised, the recruitment of osteogenic cells to the site of bone formation stops (Osborn and Newesley, 1980).

4.4. Osteoinduction

As a result of fibrin formation (discussed earlier) promoted recruitment and migration of osteogenic cells will finally lead to differentiation of these cells and the differentiation of osteogenic cells. This process is called osteoinduction. Osteogenic cells produce the matrix of trabecular bone which undergoes remodelling and is converted into lamellar bone that finally attaches to the surface of the implant (Davies, 1998).

Twenty-four hours after placement of the implant undifferentiated cells appear to move and adhere to the synthesising proteins of the bone matrix depositing a fibrillar layer on the implant (Murai et al, 1996).

4.5. Peri-implant bone remodelling

The bone that formed on the external surface of the implant undergoes remodelling due to the functional loading and stress applied to the implant. The presence of marrow spaces with accompanying osteoblassts and osteoclasts enhances the formation of mature bone around the osseointegrated implant due to the presence of undifferentiated cells adjacent to the implant. At the time of remodelling of bone surrounding the implant, new osteons appear to surround the external surface of the implant, and the long axes of

these osteons appear to be parallel to the outer surface of the implant (Franchi et al, 2005).

4.6. Soft tissue integration

Peri-implant mucosa is a term used to mean the non-hard tissue that surrounds a dental implant, and the contact area between the oral mucosa and implant contains both epithelial and connective tissue. The epithelial portion is called the barrier epithelium and is similar to the junctional epithelium that surrounds teeth (Rossie et al, 2008). A basal lamina and hemidesmosomes form fifteen days following implantation (Listgartin and Lai, 1975). The composition and type of the junctional epithelium of normal teeth differ from the barrier epithelium that surrounds implants (Carmichael et al, 1991).

The major type of connective tissue contents that come in contact with implants is collagen type 1 (Chavrier and Couble, 1999). However, this connective tissue also contains collagen type 3, 4, and 7 as well as fibronectin. On the other hand, collagen type 5 is found in an abundant amount in peri-implant tissues and collagen type 6 is observed in periodontal tissues (Romanos et al, 1995). The collagen fibre bundles of connective tissue that surround the implant are placed in various orientations (Nevins et al, 2008). Few studies have reported on the existence of perpendicularly collagen fibres connected to implant surface (Buser et al, 1992).

ISSN 2710-4478 (Online) ISSN 2710 -446× (Print)

The width of collagen fibrils in the peri-implant mucosa has been shown to be like the gingiva (Ruggeri et al, 1994). Collagen fibre bundles in the mucosa that surround the implant are arranged non-vertically, that is not parallel to the external surface of the fixture (Glauster et al, 2005). The connective tissue area near to the implant surface is similar to scar tissue which has insufficient vascular components (Schupbach and Glauser, 2007).

5. Factors affecting osseointegration

Can be divided into factors that enhance osseointegration and factors that inhibit osseointegration.

5.1. Factors that enhance osseointegration

5.1.1. Factors related to the implant

These factors include, implant design, construction and chemical composition, topography of the fixture surface, material, shape, length, diameter, and implant surface treatment and coatings (Marco et al, 2005).

The various materials, design, height, width, fixture surface management was evaluated to appear that facilitate osseointegration. When the implant is made from materials that are biologically compatible this leads to acceleration of osseointegration, as it is the essential factor to achieve constant fixation with bone-fixture contact (Anselme, 2000). Titanium is the most common material used in the construction of dental implants; because it has many advantages that make it a strong material for the implant. These advantages include excellent biocompatibility, a high resistance to rust, no harmful effect

on tissue healing, and decreased infection in the tissues surrounding the implant (Browne and Gregson, 2000). In addition to titanium, various materials can be used as a second choice – these include: tantalum, aluminium, niobium, nickel, zirconium, and hafnium (Mohammadi et al, 2001).

Alterations of metal surfaces are often used to control tissue-titanium interactions and accelerate bone fixation (Kokubo et al, 2003). At the site of implant insertion cells that synthesize proteins used in osseointegration change the surface of the fixture chemically and texturally. Continuation of these events at the implant site leads to ions being moved into tissue; these ions are excreted in the patient serum and urine (Franchi et al, 2004).

Acceptable surface properties for osseointegration include volume and interconnectedness in the status of external macro-shaped implants, external irregularities in the status of micro-shaped implant, and external chemical composition in the status of implants that are coated externally with ceramic (Park and Davies, 2000). Based on the shape of surfaces, implants are classified into irregular and painted, for example titanium embedded in hydroxyapatite, and no painted implants, for example implants blasted by sand implants etched by acids (Larsson et al, 1996).

ISSN 2710-4478 (Online) ISSN 2710 -446× (Print)

Irregular surface implants enhance osseointegration via platelets and monocytes adhesion (Park and Davies, 2000), favouring adhesion of bone forming cells to implants and subsequent division of bone forming cells (Cochran et al, 1996). In general, peri-implant bone growth is enhanced with moderately rough surfaces more than with smooth or rough surfaces (Albrektsson and Wennerberg, 2004).

5.1.2. The condition of the hard tissue network and its intrinsic recovery potential (Linder et al, 1989).

An intact bone network with little surgical injury is essential because this leads to rapid bone recovery because the storage of nutrients, bone forming cells and vessels play a significant role in the healing of bone. Also, the location of the implant affects osseointegration due to differing levels of vascularity and cellularity of the bone (Spadaro et al, 1990).

5.1.3. The mechanical status and forces applied on the implant (Soballe, 1993).

To achieve osseointegration, initial mechanical settling of the dental implant is needed, particularly when the surgical process is done in one stage. Initial mechanical settling includes firm insertion of the implant into the bone hole made by surgery with no micro-movement of the implant. Any massive movement of the implant or low implant settling leads to tensile movements, generating a flabby membrane that surrounds the implant. The membrane leads to dislocation of the implant, causing implant failure due to an infection

that impairs osseointegration (Giori et al, 1995). Initial settling is affected by the surgical method, implant design, and implantation site. An initial settling decreases implant micro-movements in the early stages of bone recovery and enhances osseointegration (Sennerby et al, 1992).

Overloading on the implant and implant micro-movements are always accompanied by unsuccessful osseointegration. The best dislocation of the implant to enhance osseointegration does not exceed 20 microns (Bragdon et al, 1996). Implant loading causes micro-movements at the bone-fixture interface but in some circumstances; mechanical loading supports bone synthesis (Turner, 1998). Osseointegration has been noticed in the presence of micro-movements up to 30 μm, but micro-movements which exceed 150 μm have been evaluated to decrease osseointegration of implants (Soballe et al, 1992). In fact, micro-movements of dental implants affect cellular division, and high micro-movements inhibit osseointegration (Leucht et al, 2007).

5.1.4. Medications such as simvastatin and bisphosphonates (Eberhardt et al, 2007).

Simvastatin is a fat decreasing medication with osteoinduction actions. Much research has reported patients receiving simvastatin having a high level of bone synthesis and high settling of the implant (Basarir et al, 2009). Bisphosphonates decrease osteoclast activity leading to

ISSN 2710-4478 (Online) ISSN 2710 -446× (Print)

reduced resorption of bone and increased bone synthesis. Recently bisphosphonates have been used to support the initial stability of implants particularly in the case of poor bone density (Eberhardt et al, 2007).

5.2. Factors that inhibit osseointegration:

5.2.1. Massive implant mobility and micro-movement (Pilliar et al, 1986)

Osseointegration has been evaluated from the perspective of movement of the dental implant inside the bone. Micro-movements must not exceed 30 μm to enhance osseointegration, on the other hand, micro-movements which exceed 150 μm has been observed to minimise or inhibit the osseointegration of the prosthesis (Soballe et al, 1992).

5.2.2. Inadequate porosity of the porous coating of the implant (Otsuki et al, 2006)

Demineralized bone matrix (DBM) was reported to favour biologic integration on porous implants. As the implant is firmly attached to the bone providing adequate fit between them, in this case, there is no need to use DBM for a porous covered implant surface (Cook et al, 2011).

Hydroxyapatite painting on the external face of dental implants supports the chance of a good matching of implant and ceramics. There are many methods of application including ion sputtering and plasma spray. Calcium phosphate ceramics provide absorption of

proteins on the surface of the fixture enhancing the aggregation of platelets and fibrin collection and accelerating implant healing (Rigo et al, 2004).

Many growth factors have been tried singly or incorporated as coverings of implants to accelerate and facilitate the osseointegration and to make the stability of the implant stronger. Among these factors are the bone morphogenetic proteins (BMPs), specifically BMP-2 and BMP-7, and growth factors such as platelet-derived growth factor (PDGF) and insulin-like growth factor (IGF). In addition, various biological materials such as collagen and fibronectin which have been tried as a coating to, mainly titanium, dental implants have the ability to facilitate bone synthesis, so promoting osseointegration (Frosch et al, 2003).

5.2.3. Radiation therapy (Kudo et al, 2001)

The influence of radiation therapy is still unclear. In general, radiation therapy appears to delay bone remodelling before and after implantation (Kudo et al, 2001).

5.2.4. Medications (Eder and Watzek, 1999., Callahan et al, 1995).

In relation to the osseointegration, warfarin administration leads to impairment of the adhesion and synthesis of bone (Callahan et al,

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1995). Heparin causes inhibition of osseointegration because it has an adverse action on collagen mainly of type II.

5.2.5. Other factors (Wong et al, 1994)

Osteoporosis appears to disrupt the osseointegration of implants, particularly those used for fixation of fracture and joint problems. Osteoporosis leads to unsuccessful implants because the texture and biology of the bone is altered. Division of bone cells appears to also be influenced by osteoporosis (D'Ippolito et al, 1999). The function of synthetic bone cells drops to a low level while the number and function of osteoclasts increases and vascularization is decreased in patients suffering osteoporosis (Augat et al, 2005).

6. Conclusion

The biology of osseointegration or bone ingrowth around dental implants can be divided into five stages including wound healing and the role of fibrin which occur immediately after implant placement in response to tissue injury caused by the surgical procedure. The wound healing stage is controlled by a group of factors such as inflammatory factors and blood cells. The second stage of Osteogenesis around the dental implant is divided into two types: distant and contact osteogenesis. Osteoconduction is the third stage which involves recruitment of the osteoprogenitor cells to the surface of the dental implant. Osteoinduction occurs during the fourth stage and involves differentiation of osteoprogenitor cells induced by fibrin formation. The last stage is remodelling of bone that forms around the dental

implant as result of a functional loading and stress applied on the dental implant.

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ISSN 2710-4478 (Online) ISSN 2710 -446× (Print)

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ISSN 2710-4478 (Online) ISSN 2710 -446× (Print)

بيولوجيا الاندماج العظمي لزارعات الأسنان

عبدالقادر إبراهيم سويعد (●)

استلم بتاريخ 2022.12.18 قبل بتاريخ 2023.01.01 نشر بتاريخ 2023.01.23

نبذة مختصرة

يمكن تقسيم بيولوجيا الاندماج العظمي أو نمو العظام حول غرسات الأسنان إلى خمسة مراحل بما في ذلك التئام الجروح و دور الفيبرين الذي يحدث مباشرة بعد وضع الزرعة السنية و التي عبارة عن برغي معدني يتكون من مادة النيكل و مغطاة بمادة التيتانيوم ، استجابة لإصابة الانسجة الناتجة عن الإجراء الجراحي.

المرحلة الأولى هي مرحلة التئام الجرح و يتم التحكم فيها من خلال مجموعة من العوامل مثل عوامل الالتهابات وخلايا الدم. في المرحلة الثانية يتم تكوين العظم حول الزرعة السنية وينقسم إلى تكون العظم البعيد والملامس للزرعة السنية.

تسمى المرحلة الثالثة بمرحلة التوصيل العظمي و التي تنطوي على تجنيد خلايا التحفيز العظمي التي تفرز المادة العظمية على سطح الزرعة السنية. خلال المرجلة الرابعة يحدث التحفيز العظمي وينطوي على تمايز وانشطار الخلايا العظمية المحفزة نتيجة تكون مادة الفيبرين.

في المرحلة الخامسة والأخيرة يحدث إعادة تشكيل العظم حول الزرعة السنية نتيجة الحمل الوظيفي والضغط المطبق على الزرعة السنية.

(●)بكالوريوس طب الأسنان و ماجستير في الاستعاضة الصناعية الثابتة للأسنان.

عضو هيأة تدريس و رئيس قسم الاستعاضة الصناعية الثابتة للأسنان بكلية طب و جراحة الفم و الأسنان الجامعة الأسمرية زليتن– ليبيا

Abdulgaderswaid@yahoo.com