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Review

Bone and soft tissue healing in dental implantology

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Abstract

The knowledge of bone and soft tissue healing can be applied to enhance the success of dental implants as the process of osseointegration depends on vascular supply at the surgical site and the primary stability of the endosseous implants. To achieve successful bone and soft tissue regeneration, factors such as systemic health of the patient, biocompatibility and characteristic of the implant surface, surgical protocol and quality and quantity of the bone at the implant site must be taken into consideration. Histomorphometric analysis can determine the microstructure of bone trabeculae, reflecting the bone density and quality. Furthermore, molecular analysis of the bone cell can provide vital information during treatment planning in dental implantology, which can help in the prediction of its success.

Keywords: Dental implant, Histomorphometry, Osteointegration, Primary stability, Bone formation

INTRODUCTION

A successful treatment in dental implantology requires the maintenance of the implant health over long periods of time such that the implant continues to improve the function of the prosthesis (Ammann P et al., 2003). Several parameters influence the integration of these endosseous implants and the maintenance of bone-implant contact and the biology of the soft tissue at the transmucosal area around the implants are also important factors for long-term health of the implant. This can be influenced by patient's overall health status, implant surface characteristics, surgical protocol and quality and quantity of the bone at the implant site (TurkyilmazI et al., 2007, 2008). The purpose of this article is to determine the factors that can effect of bone and soft tissue healing during osseointegration.

Bone-healing process (bone formation)

The remodelling process begins from quiescent stage at the bone surface with osteoclasts. The osteoblasts that are derived from mesenchymal stem cells found in the bone marrow, periosteum and soft tissues deposit osteoid and minerals forming new bone. Following which, they are encapsulated in the osteoid matrix and differentiate to osteocytes. Remaining osteoblasts continue to synthesize bone until they eventually stop and alter to quiescent stage. The linings cells completely cover the newly formed bone surface. These lining cells are highly interconnected with the osteocytes in the bone matrix through a network of canaliculi. However, the osteoclasts dig a circular tunnel and are replaced by osteoblasts, which fill the tunnel by osteon to renew bone.

Principles of bone biology and regeneration in dental implant

During insertion of dental implant, there are interruptions in the blood supply, which then activates local bone regeneration by the release of growth factors and other signalling molecules. Bone is a major source of growth factors, which are polypeptides that increase cell replication. They also have significant affect on differentiation of cell functions. Initially, growth factors were considered to act as systemic agents. Current evidence shows that they act as local regulators of cell growth. However to achieve this, they must to used in

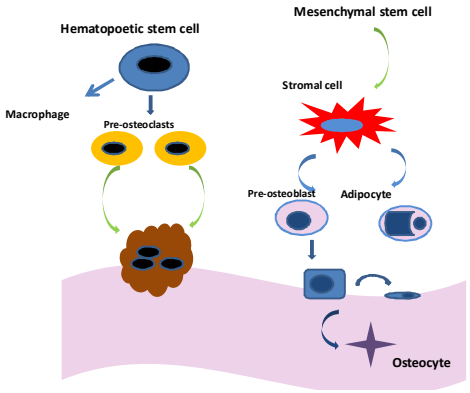

Figure 1. Bone cell lineage (Ott SM, 2010).

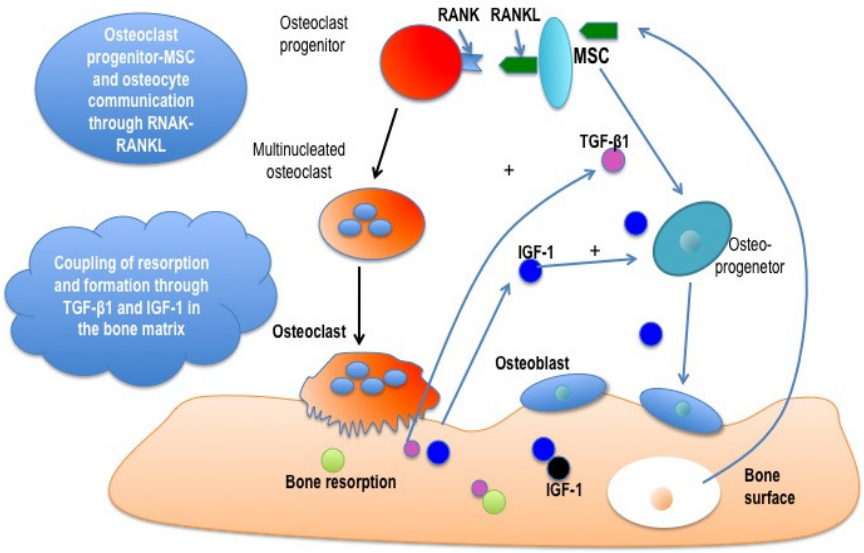

Figure 2. Bone remodeling mechanism involving in bone multicellular unit (BMU) (Adapted from Cao 2011) [Mesenchymal stem cell (MSC), Insulin-like growth factor 1 (IGF-1), Receptor activated nuclear factor κB (RANK), Receptor activated nuclear factor κB ligand (RANKL), Transforming growth factor beta (TGF-β1)]

high concentrations that can affect the entire body even when used locally (Choukroun J et al.,2013).

On cellular and molecular level, the receptor activated nuclear factor kappa-β (RANK), RANK ligand (RANKL), osteoprotegerin (OPG) and osteocalcin relate to the level of gene expression. Higher OPG values observed in denser bone types have suggested a positive association between OPG over expression and increased cortical and trabecular bone mass. An association has also been found between bone that are less dense and a reduction of RANKL. (Pereira AC et al., 2013)

Factor affecting bone regeneration in dental implantology

For the successful outcome of dental implant treatment, several characteristics of bone tissue have been identified as important factors primary stability of the implant and for vascularisation at the implant site. However, there are no consensual definition of bone quality has been reached in the literature or implemented in the clinical setting (Ribeiro-Rotta RF et al., 2007, 2011; Pereira AC et al., 2013).

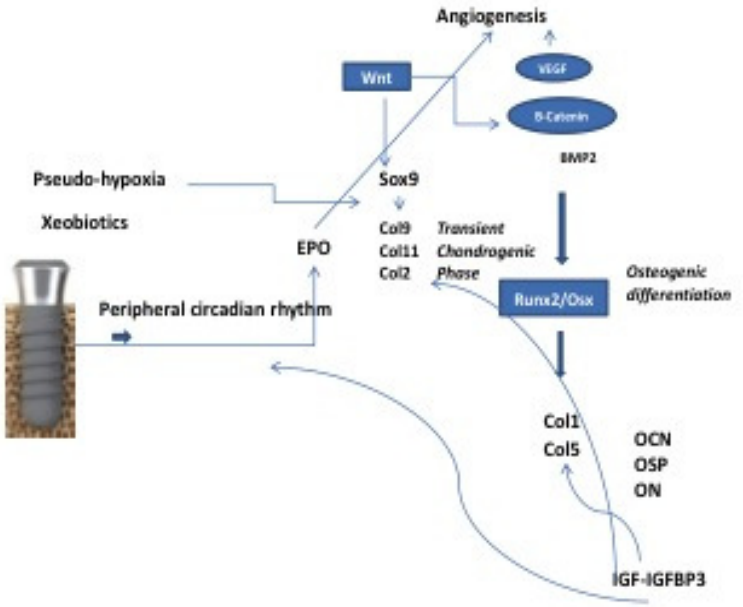

Figure 3. The osteotomy procedure used to prepare an implant placement site creates an ablative wound in the bone marrow. The proposed mechanisms may involve a thin layer of hypoxic zone due to continuous oxidization of the titanium (Ti) implant fixture, affecting the differentiation course of Mesenchymal stem cell (MSC).

The literature has shown many factors affecting bone regeneration in dental implantology (Elias CN, 2011).

1. Age, gender, alcohol and drug abuse, and smoking habits affect host defence. Underlying medical conditions such as diabetes, osteoporosis, cytostatic treatment, radiotherapy, immune defence deficiency, psychological disorders, and bruxism can also lead to early implant failures (Esposito M et al, 1998; Ekfeldt A, 2001).

2. Biocompatibility and biomechanics of the implant surface can influence proliferation, differentiation and extracellular matrix synthesis which then allows cell adhesion and cell growth. Contaminants, which are mainly alumina particles used in the sand blasting of the implant surface, can lead to cell apoptosis. The existence of metallic chips during implant insertion can compromise the osseointegration (Jayaraman M et al., 2004). The macro and micro design of the implant, including dimension, shape, holes and grooves, type and number of screw threads and surface topography, can affect the mechanical interlocking of the implant to the bone.

3. The surgical technique and the loading conditions influence the stability of the implants and the process of osseointegration. The primarily stability of the implant in bone is dependent on the mechanical interlocking design characteristics of the implant. During axial loading, forces are transmitted to the bone according to the thread design. Excessive trauma during surgery may affect the bone-to-implant interface and lead to decrease in the osseointegration (Ercoli C et al., 2004). To preserve tissue viability during implant placement, it is necessary to prepare the surgical site adequately to achieve primary bone contact (Benington IC et al., 2002; Yacker MJ et al., 1996). External or internal irrigation by cool saline with intermittent pressure on the drills, every 3 to 5 seconds, the use of new drills and an incremental drill sequence can promote osseointegration (Bakshi R et al., 1999).

Osseointegration

Osseointegration is defined as a histological structural and functional direct contact between bone and bone marrow with titanium-based implants without fibrous tissue. The osteotomy site should heal with intra-membranous ossification without cartilage tissue formation. Osseointegration of titanium implant surface is dependent upon both physical and chemical properties (Ribeiro-Rotta RF et al., 2011). The thickness of crestal bone and the surface of a load-carrying implant is critical for implant stability and is considered a prerequisite for implant loading and long-term clinical success of endosseous dental implants (Miyamoto I et al., 2005).

The Ti implant surface coat with thin titanium oxide (TiO_2) layer continues to be oxidized after surgical placement which creates a hypoxic environment that

induces chrondrogenic transcription factor SOX-9 and cartilage-related extracellular matrix (ECM) (Adesida AB et al., 2012). The peri-implant bone may be a mixture of bone and cartilage-related ECM.

Repair of bone defects

The inductions of bone formation are composed of soluble osteoinductive signals, cell response to these signals, and supportive matrix to deliver cells or molecular factors. Growth factors such as transforming growth factor (TGF) β, fibroblast growth factors (FGF), hPlatelet-derived growth factor (PDGF), vascular endothelial growth factor, insulin-like growth factors, and growth hormone have potential roles in enhancing bone repair.

Bone Morphogenetic Proteins (BMPs)

BMPs are members of the transforming growth factor (TGF) β. The function of BMPs is to induce the maturation of osteoblasts in endochondral bone formation.

Wnt

The Wnt/β-catenin signalling pathway plays a critical role in osteoblastic cell differentiation and bone formation. Wnt and BMPs have similar and overlapping effects.

hPlatelet-derived growth factor(PDGF)

The original source of PDGF is platelets, which stimulates bone DNA and protein synthesis. It can also be a systemic or a local regulator of skeletal growth. As a systemic growth factor, it can be released during platelet aggregation and have important effects in the early stages of fracture healing. As a local factor, it may interact with other hormones and growth factors. PDGF has been shown to stimulate bone resorption. Thus, it appears to have complex effects on bone remodelling.

Fibroblast growth factors(FGF)

The FGF effect is not specific for collagen, indicating that the cells affected are of an osteoblastic lineage. Although FGFs increase the number of osteoblastic cells, they have no direct stimulatory effect on the differentiated function of these cells. However, they can directly inhibit osteoblastic function.

Systemic Regulation of Bone Remodelling

The metabolic functions of the skeleton are served in large part by two major calcium-regulating hormones-parathyroid hormone (PTH) and 1,25-dihydroxy vitamin D. A third hormone, calcitonin, which can inhibit bone resorption, is important in skeletal development but it only affects calcium regulation in adult humans. It is a potent inhibitor of bone resorption and is used clinically in the treatment of osteoporosis. PTH regulates serum calcium concentration and has its greatest effect on intestinal calcium and phosphate absorption.

The fact that bone formation is not necessarily preceded by resorption can be concluded from the observation that lining cells at the bone surface can transform back to bone forming osteoblasts. The major systemic regulators consist of the parathyroid hormone, calcitriol, growth hormone, glucocorticoids, thyroid hormones and sex hormones. As the nutritional requirement for the adapting tissues are relatively high, the osteoblasts derived from peri vascular region and the pre-osteoblasts, which circulate in the blood and pass through the blood vessel wall to enter the tissue and form osteoclasts.

Periosteal growth can also play an important role in bone forming cells at different areas of the alveolar bone.

Wound-healing process

There are many factors that can interfere with the one or more phases of the wound healing process, thereby causing improper or impaired tissue repair. The wound healing mechanism consists of four highly integrated and overlapping phases- hemostasis, inflammation, proliferation, and tissue remodelling or resolution. Most chronic wounds are ulcers that are associated with ischemia, diabetes mellitus, or venous stasis disease.

Local Regulators of wound healing

Oxygenation is concerned with the blood supply and vascularization.

Infection

The inflammatory phase can lead to the prolonged elevation of pro-inflammatory cytokines, such as interleukin-1 (IL-1) and TNF. *Staphylococcus aureus*, *Pseudomonas aeruginosa* and β-hemolytic *streptococci* are commonly found bacteria at infected and clinically non-infected wounds. Endotoxins released from these bacteria can also prolong the healing.

Cellular condensation

The local specific signals can influence cellular and cell matrix interaction to start osteogenic differentiation (Einhorn TA et al., 2001).During vascular injury, trauma-induced cellular reactions can lead to inflammation.

Autocrine factors and paracrine factors

There are synthesized by many types of cells and tissues

Table1. The stages of wound healing

First stage	**Hemostasis occurs with vascular constriction and fibrin clot formation. Bleeding is controlled and the inflammatory cells migrate into the wound with sequential infiltration of neutrophils, macrophages, and lymphocytes. Then pro-inflammatory cytokines and growth factors such as transforming growth factor (TGF)-β, platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and epidermal growth factor (EGF) are released. Later, the mesenchymal cells induce cell differentiation, proliferation, and migration to the wound site. Angiogenesis, re-epithelialization and finally synthesis, cross-linking, and alignment of collagen occurs that provides strength to the healing tissue.**
Second stage	Granulation tissue replaces the clot with white blood cells and reticulo-endothelial cells associated with capillaries within 4-5 days.
Third stage	Connective tissue replaces granulation over 14-16 days.
Fourth stage	Bone formation starts from day 7 with the formation of fibrillar and poorly calcified osteoid.
Fifth stage	Epithelium regenerates on day 4. A critical function of neutrophils is the clearance of invading microbes and cellular debris in the wound area.

and may act on cells of either same class (autocrine factors) or different class (paracrine factors). The action of growth factors is still somewhat unclear. However, they effect cell replication and differentiation.

Soft- tissue healing following implant placement

Following the formation of a fibrin clot, fibroblasts migrate towards the implant surface. The epithelial and connective tissues contact the implant or abutment surface and are established within 1–2 weeks. After a healing period of at least 12 weeks, the maturation of the tissues begins. The peri-implant epithelium is similar but longer than the junctional epithelium that forms against the tooth surface. The collagen fibres run parallel and circumferentially around the implant. The presence of keratinized tissue around the implant is important for the long-term stability of the implant and should be at least 1-1.5 mm, which permits adequate cleaning. The thickness of the soft tissues to protect bone resorption should be 1.8-3.9 mm (Palacci P et al., 2008). When the soft tissue thickness around implant is less than 2mm, it is consider as a thin biotype (Albrektsson T et al., 1981).

DISCUSSION

The long-term stability of dental implant occurs by sustained maintenance of osseointegration. The strong adhesion of implant fixture can provide resistance to catabolic remodeling. Therefore, increasing reports on the loss of osseointegration after years of service may not be addressed alone by the simple infection or inflammation model. The validity and significance of the genetic networks must be carefully established for the maintenance of osseointegration.

The molecular biology can contribute to the validation of protein and growth factor. Therefore, these analyses can be useful to gather data on bone quality or the stage of healing of the jawbone for successful treatment planning in implant dentistry. (Pereira A et al., 2013)

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