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Bone Remodeling and Bone Grafting: Essentials of Synergism

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Abstract:

The majority of oral surgeries require using bone grafts due to the insufficient volume of the residual bone. To be able to make a decision on choosing a proper graft material, a surgeon should understand the whole chain of the processes which start from the graft insertion and go on. In this paper, the basic cellular and tissue mechanisms of bone formation, resorption, and remodeling are elucidated. The light is shed on the fundamentally different pathways of bone formation which occur both naturally in the course of ontogenesis and after any damage to bone has been done. Several histologic studies assessing the quality and quantity of newly formed bone when different bone grafting materials, such as autologous bone, autologous tooth, demineralized freeze-dried bone, and deproteinized bovine bone were used are included in this paper. The particles of most graft materials, except for autologous bone and tooth, to a greater extent remain unchanged within the newly formed bone matrix. This finding prompts further search for alternative materials which could completely integrate into the bone structure.

Key words: *bone tissue, osteogenesis, graft material, cell, histology*

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INTRODUCTION

A tooth with surrounding tissues (i.e., gingiva, PDL, and alveolar bone) form a complex structure with multiple interconnections. For this reason, bone, as well as other tissues, is affected to a greater or lesser extent whenever any dental surgery is performed. Oral cavity has a number of distinctive features, such as an intricate configuration of the defects and a high risk of wound infection leading to a possibility of graft rejection, making it one of the most complex surgical sites in the human body. Therefore, it is of crucial importance for an oral surgeon to know the fine modalities of bone physiology to be able to make a comprehensive treatment plan tailored for each patient. A great variety of options demands fundamentally different treatments from a clinician. Understanding the mechanisms of bone formation, resorption, and remodeling enables a clinician to make a correct choice to provide the best treatment outcomes.

Cellular and Tissue Mechanisms of Bone Remodeling

Physiological renewal of many tissues occurs via division of the cells. But mature osteocytes cannot undergo mitosis, and they die after completion of the cell cycle. However, bone is involved in the complex physiological processes of remodeling and regeneration [1]. Human bone has a unique capability to restore itself after various alterations to its original structure. Bone healing is very similar to the natural process of bone growth and maturation [2]. Sufficient blood supply and stable environment are prerequisite for fast and compete healing.

The highly coordinated process of bone remodeling demands the equilibrium between degradation of the existing bone and formation of the new bone. It is regulated by different bone cells, cytokines, and growth factors. The main cell lines involved in this process are osteoclasts, osteoblasts, osteocytes, and immune cells [3]. All these cells are joined by intercrossing regulatory mechanisms [4].

The osteoclasts, or polynucleated resorbing cells, are formed via M-CSF- and RANKL-mediated fusion of myelomonocytic predecessors in the resorption sites [4]. The RANKL/OPG (the inhibitor of RANK receptor) expression ratio determines the extent of osteoclast differentiation and, therefore, regulates their activity [5]. Lying in the resorption bays, or Howship's lacunae, osteoclasts play their part by producing enzymes and acids to remove the organic matrix and dissolve the mineral component of the residual bone respectively [3].

The osteoblasts as well as other connective tissue cell lines, e.g., chondrocytes and fibroblasts have their origin in the mesenchymal stem cells [4]. As they keep producing the bone extracellular matrix which subsequently undergoes mineralization they become surrounded by osteoid and thereby transform into osteocytes. Osteoblasts can also either transform into inactive forms covering the bone surface or die by apoptosis [7]. A number of specific osteoblast markers, e.g., alkaline phosphatase, osteonectin, osteopontin, etc. are expressed at all the stages of synthesis of specific proteins followed by hydroxyapatite secretion and deposition [4]. The crucial regulatory function of osteoblasts in bone- remodeling is well described in literature [4, 5]. It is carried out through mediating the activity of osteoclasts by PGE2, IL-6, IL-1, and RANKL.

The next type of cells worth mentioning is quiescent bone lining cells. It was long thought that BLCs play a vital role in the removal of demineralized matrix from the bone surface [6], but in 2016 Matic et al. reported BLCs to be the main source of osteoblasts and their proliferating progenitors in adults [7].

Fibroblasts are other cells originating from the mesenchymal stem cells which come to the affected site from the blood clot and induce bone regeneration. This process is regulated by various cytokines and growth factors, e.g., PDGFs, IGFs, FGFs, TGF-β, and BMPs [8-10]. The blood clot turns into granulation tissue during the first four weeks which is subsequently replaced by bundle and, finally, lamellar bone in the course of four months [11].

The growth factors of the bone-marrow microenvironment, e.g., collagen, bone morphogenetic proteins, hydroxyapatite, and glycosaminoglycans, also influence inducible osteoprogenitor cell populations, such as pericytes [12]. Pericytes appear at the periphery of bone fracture site where they surround the newly-formed vessels. They are supposed to be oligopotential with an ability of differentiating into osteoblasts [13].

In 1904 F. Jackson discovered a thin layer at the border of bone and bone marrow and coined it endosteum. It was later found that endosteum plays a major part during intensive bone formation, i.e., growth and regeneration. It was

long questioned whether it has osteogenic properties due to the dominant idea of periosteum being considered the leading factor in the process of bone formation [14]. Clinical recommendations based on this idea justified radical and minimally invasive surgical approach to the bone and periosteum respectively. Several attempts were made to evaluate the effectiveness of reparative osteogenesis in fractures, the severity of periosteal callus being the criterion. However, immobilization of bone fragments has recently been determined to be the main function of the periosteal callus. When the fragments are fixed the periosteal callus is small or even absent.

The views on the nature of reparative osteogenesis changed with the works of Fridenstein et al. [15-17] when proliferating cells capable of synthesizing fibronectin, collagen types I and III, and fibroblastic γ-globulin were discovered in the bone marrow and in the vascular canals of the diaphyseal compact bone. In fact, they are bone stem cells, since the possibility of the colony-forming fibroblastic cells capable of transforming into osteoblasts has been shown. There are no such cells in the periosteum. When appositional bone growth takes place, the inner cambial layer of the periosteum turns into bone tissue while the outer layer acquires osteogenic properties. This transformation is attributed to the direct contact of the periosteum with bone tissue expressing osteoinductive factors.

Two Types of Osteogenesis

Two major types of osteogenesis, i.e. intramembranous and chondral are distinguished depending on the preceding tissue. In case of intramembranous osteogenesis bone formation primary occurs in mesenchymal tissue whereas chondral bone formation occurs in the hyaline cartilage with its subsequent replacement [18].

The first way is intramembranous ossification when bone develops in the ossification centers and then joins with cartilage. This path is peculiar to most of the facial bones, except for the inferior nasal concha, hyoid bone, and part of the mandible. Ferretti et al. identified two types of intramembranous osteogenesis, the location and direction of movement of osteoblasts being the differential factor.

In static bone formation multi-layer laminae of osteoblasts which produce bone matrix in various directions creating primary trabeculae are identified.

As a result, they are found embedded in bone tissue at their original position [20]. The immature bone scaffold is formed as a result of the functioning of such osteoblasts which are otherwise known as mesenchymal osteoblasts [Figure 1].

When a sufficient number of primary bone islets have appeared, the next stage of intramembranous osteogenesis, i.e., dynamic bone formation, begins. At this stage the osteoblasts, referred to as surface osteoblasts [19], are polarized and aligned into one layer [Figure 2]. Hence, bone matrix is secreted in one direction, which leads to bone thickening and compaction [20].

The second way of bone tissue formation is via gradual substitution of cartilage. Endochondral ossification is typical for the bones of the skull base, the axial skeleton, and the epiphyses of tubular bones. Perichondral ossification is peculiar to the diaphyses of tubular bones respectively. It has also been repeatedly observed during fracture healing. In endochondral osteogenesis primary cartilaginous model is replaced by bone. Until recently, cartilage was thought not to play any part in creating osteogenic cells but just to be a scaffold for periosteum- and bone marrow-derived osteoblasts. Some researchers thought that cartilage cells are not directly involved in the process of osteogenesis and gradually undergo degeneration and resorption [21]. Schenk et al. discovered a phenomenon of primary bone fusion in which the bone callus is formed without preceding cartilage formation [2]. It was generally accepted that hypertrophic chondrocytes which are found in the deepest layers of cartilage undergo apoptosis. But Hinton et al. in a series of cell lineage studies in rats has found the same markers in osteoblasts adjacent to cartilage as in originally marked chondroblasts. This finding suggests that many osteoblasts are formed by direct transformation from cartilaginous cells. This process was observed in mandibular condylar cartilage as well as in fractured bones that allows one to assume that the majority of osteoblasts has developed from chondrocytes [22].

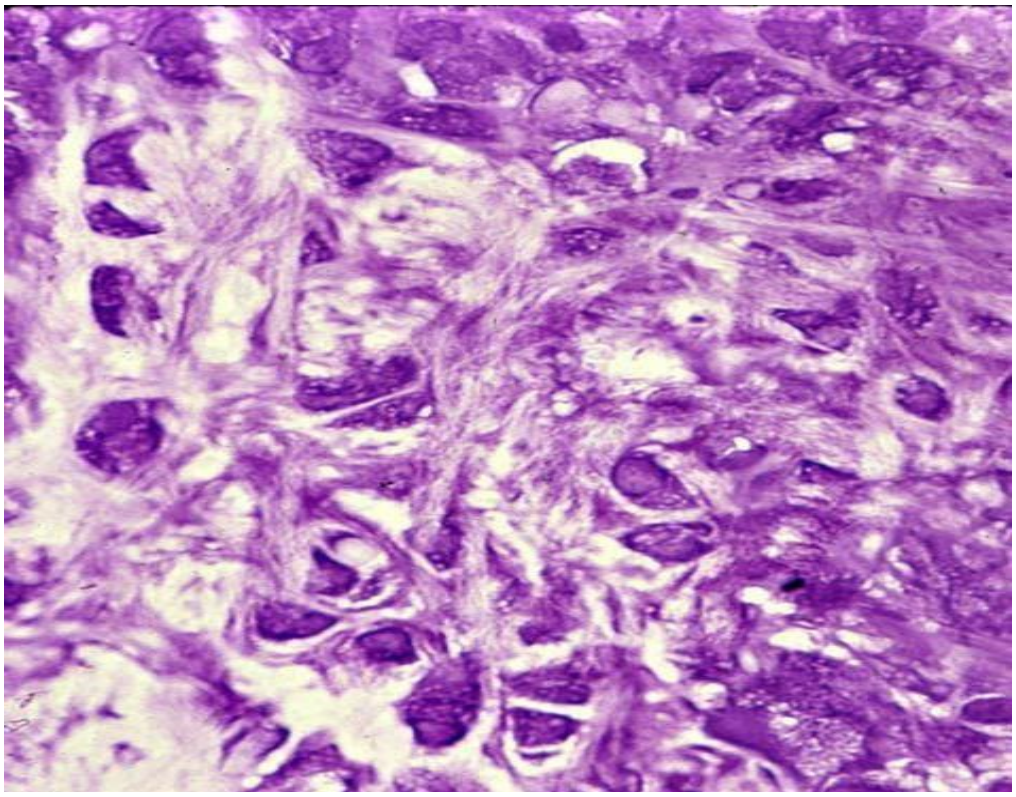

Figure 1. Mesenchymal osteoblasts surrounded by randomly orientated collagen fibers (Shapiro, 2008)

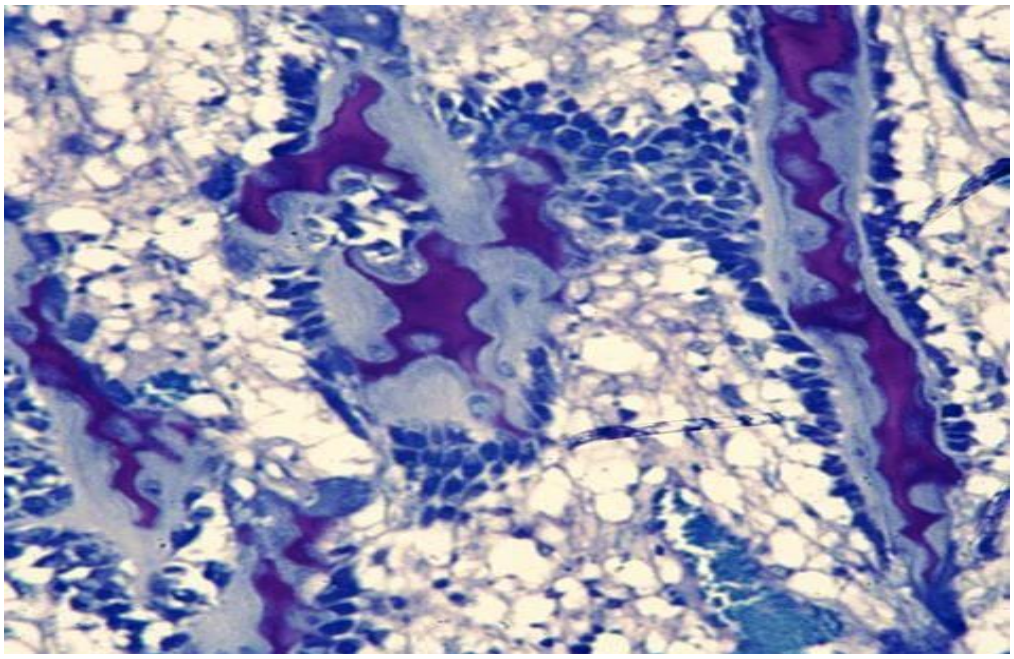

Figure 2. Surface osteoblasts aligned on the bone trabeculae (Shapiro, 2008)

Bone Repairing

Both types of osteogenesis can be observed in processes of bone repairing as well.

At the initial stage of physiological process of osteoregeneration preosteoblasts differentiate into osteoblasts. This process is similar to that taking place during antenatal osteogenesis, i.e., intramembranous osteogenesis, when primary bone is produced.

In unfavorable conditions osteoblasts differentiate into prechondroblasts and after that into chondroblasts. In this case bone formation occurs when preceding cartilage model is being replaced by bone, i.e., as it occurs in endochondral osteogenesis. The defect is filled with avascular cartilage tissue which receives nutrients via diffusion.

As the bone callus is maturating, the volume of cartilage is being gradually reduced. Mild inflammation can be detected in the areas of the newly formed bone over a long period of time. There are islets of osteocyte-free tissue in the callus that leads to the impediment of complete bone maturation. One of the negative outcomes of this type of bone regeneration is pseudoarthrosis resulting from the alteration of the prechondroblast differentiation. The microenvironment mediates the differentiation of pluripotent progenitor cells, their activity, and growth rate. The importance of the sufficient tissue oxygenation cannot be overestimated. It is also crucial to ensure the immobility of bone fragments after a comminuted fracture for achieving successful osteoregeneration. When this requirement is not met the newly formed capillaries are easily disrupted which can lead to hypoxia, fibroblast activation, and fibrous tissue invasion to the fracture gap. This process impeding bone regeneration acquires a special significance in the lower jaw where the greatest forces caused by masticatory muscle function emerge [1].

Osteogenesis and Bone Graft Materials

Bone graft materials are commonly used in dental surgery. Nowadays there is a great variety of bone graft substitutes but their classification and characteristics are out of the scope of this paper. Instead, we are discussing here their influence on bone formation and the quality of such newly formed bone.

The ideal bone graft material has not been discovered yet. It means that in each clinical case a surgeon has to choose an optimal treatment for a certain patient, the decision being based on the nature of the pathological process, the general health of the patient, and the operator's skills and experience.

Autologous bone is considered a gold standard of bone graft materials due to its excellent osteoinductive properties as well as complete compatibility with the host's tissues [23]. Nevertheless, Becker et al. discovered that some autogenous bone particles do not undergo complete resorption with subsequent bone remodeling but rather remain incorporated into vital bone as non- vital structures [Figure 3] [24].

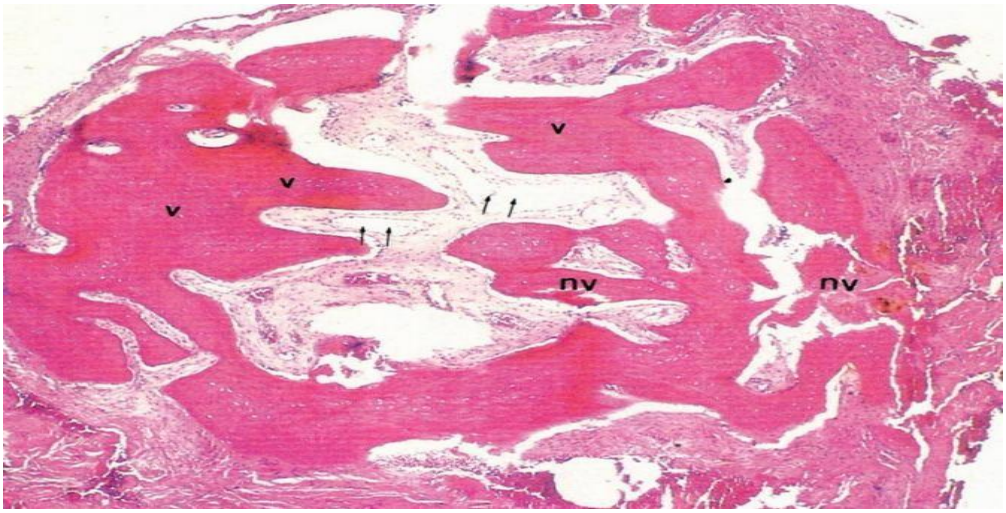

Figure 3. Non-vital (nv) bone particles in the structure of newly formed vital (v) bone (Becker et al., 1996)

Autologous extracted tooth has been proposed as another source for bone grafting. After extraction it is dehydrated, defatted, lyophilized, and sterilized with ethylene oxide. It can be processed into either powder or block form. In several studies Kim et al. showed the possibility of clinical application of this material in various bone grafting surgeries, such as sinus floor elevation, ridge splitting, GBR, etc. [25]. Its osteogenic properties have been compared with those of xenograft material in a randomized controlled trial. No significant difference has been found, so autologous extracted tooth material may present as an alternative to already existing bone graft materials [Figure 4] [26].

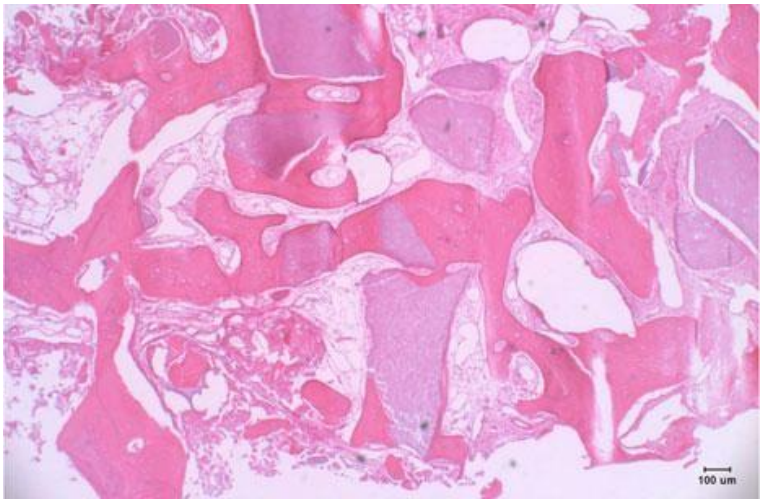

Figure 4. Newly formed bone in close contact with autologous extracted tooth graft (Kim et al., 2013)

Becker et al. compared autologous bone with DFDBA in terms of their capability to induce osteogenesis. All extraction sockets having been grafted with autogenous bone displayed histologic signs of vascular channels formation, osteocytes and primary osteons, i.e., active osteogenesis. On the other hand, no evidence of new bone formation was shown in sites grafted with DFDBA. Dead bone particles have not undergone resorption and revascularization but rather remained engulfed within the host bone [Figure 5]. Therefore, the rationale of using DFDBA is questionable because of the lack of osteoinductive activity [27].

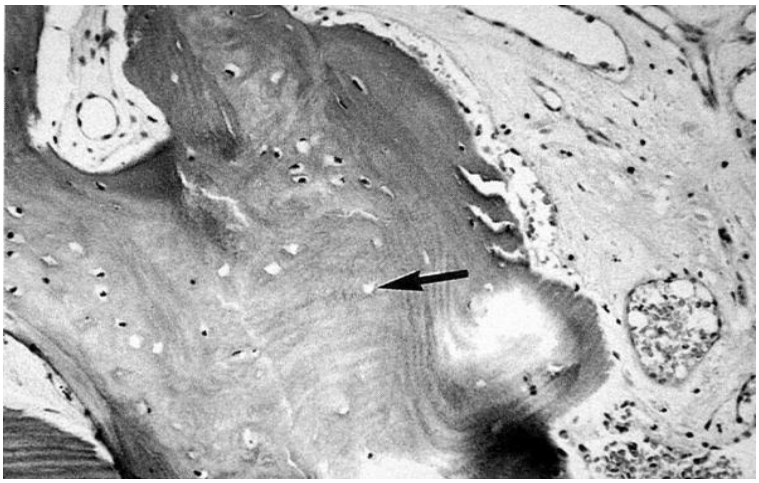

Figure 5. DFDBA graft (arrow) surrounded by vital bone. No evidence of bone cell activity around the graft at 7 months (Becker et al., 1994)

Xenograft is a commonly used particulate deproteinized bovine bone. Araújo et al. investigated its impact on bone formation in the extraction sockets. On histology, the particles were found imbedded in the connective tissue, and new trabeculae formation was delayed when compared with graft-free controls [28]. Traini et al. studied the histological structure of newly formed bone at the site of implanted xenograft nine years after maxillary sinus lift surgery and compared the results with those obtained from other human studies with lesser follow-up. The volume of xenograft particles was found to be roughly the same over the whole period. The histological investigation revealed intimate interconnection of graft material with bone [Figure 6]. The stability of implant can be due to superficial resorption of highly calcified graft particles with following ingrowth of bone which results in the formation of a dense structure [29].

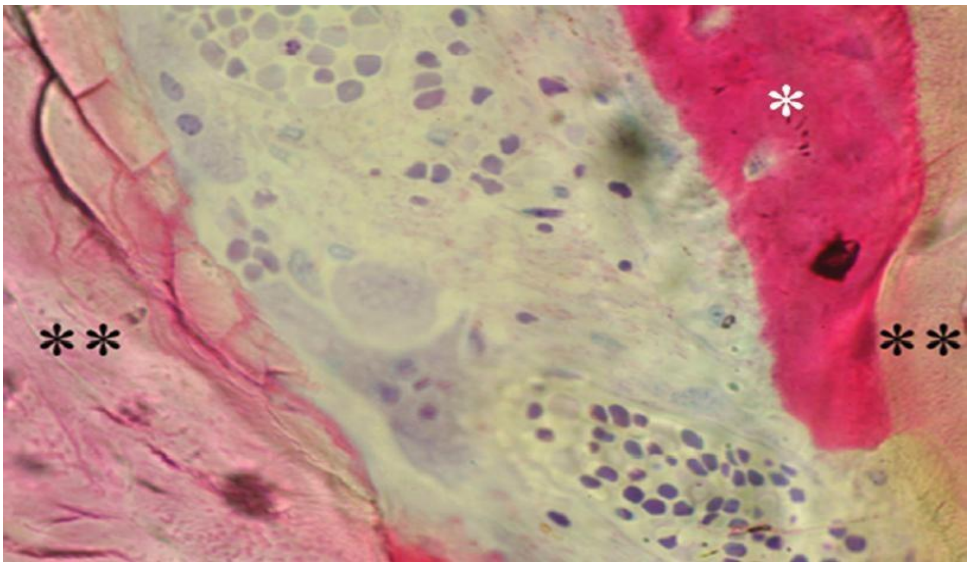

Figure 6. Intimate contact between newly formed bone (*) and xenograft (**) particles (Traini et al., 2007)

Amoian et al., suggested a scheme for a histopathologic evaluation of the new bone formation after bone grafting [Table 1]. The criteria allow analyzing various characteristics of bone and enabling clinician to make a proper judgment on the overall success of the surgery [30]

Table 1. Criteria for assessment of bone grafting surgery outcomes

Criterion	Description
inflammation and foreign body reaction	presence or absence of inflammatory cells
bone vitality	quantity of osteocytes in lacunae
quality of bone-graft interface	presence or absence of connective tissue
perfusion	number of blood vessels in 3 microscopic fields (10-fold magnification)
percentage of newly formed bone	trabecular volume, %
percentage of residual bone graft	graft volume, %
trabecular thickness	trabecular thickness, µm

CONCLUSIONS

Over the past few decades the major improvement in understanding bone physiology has been noted. Nevertheless, there are problems of bone regeneration still to be solved. Despite rather long history of bone grafting, there is still little consistency and unanimity among the researchers and clinicians in terms of the optimal surgical materials and protocols. Sometimes clinical and experimental data vary significantly, and views on different aspects of bone physiology and graft materials properties are subjected to dramatic changes. Therefore, the search for new materials capable of complete substitution of bone defects has still to be continued.

Abbreviations

BLC – bone lining cell
BMP – bone matrix protein
DFDBA – demineralized freeze-dried bone
FGF – fibroblast growth factor
GBR – guided bone regeneration
IGF – insulin-like growth factor
IL – interleukin
SF – macrophage colony-stimulating factor
OPG – osteoprotegerin
PDGF – platelet-derived growth factor
PDL – periodontal ligament
PG – prostaglandin
RANKL – receptor activator of nuclear factor kappa- B ligand
TGF-β – transforming growth factor β

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