Dental Implants and Bone Grafts: Materials and Biological Issues

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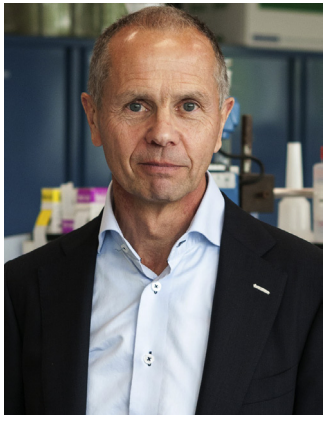

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Introduction

Healthy teeth are supported with bone tissue in the maxilla and mandible called alveolar bone, which is subjected to remodeling associated with the functional demands of mastication [1]. However, teeth loss and alveolar bony defects are common and pose a significant health problem in dental clinics. Reconstruction of alveolar bone and replacement of missing teeth using dental implants and bone grafts greatly enhances treatment success and patient satisfaction [2]. Currently, the potential market in dental implants and bone grafts is great and includes virtually every dental treatment plan in some way.

Worldwide, the market size for dental implants is estimated to reach nearly $5 billion in 2023 (BCC research report 2018–23) [3]. Dental implants show many advantages over the conventional prostheses, including high patient acceptance, natural appearance, and less requirement of maintenance. Indeed, dental implants have played a major role in oral rehabilitation in recent decades. Based on the National Center for Health Statistics, more than 90% of adults in the United States have untreated dental caries, and 69% show at least one missing tooth [4]. Moreover, more than 24% of adults aged 74 years and older are completely edentulous [4]. Also, nearly 10 million patients per year have dental injuries due to road accidents and sport injuries [3]. Therefore millions of patients need replacements for their missing teeth, hence facilitating extensive demand for dental implants. In 2016, Europe and Asia dominated the dental implant market due to an increase in the edentulous population [5]. By 2020, it has been estimated that 25% of Europeans will be older than 60 years. In addition, increased oral-care awareness in developed countries is anticipated to drive the market growth of dental implants [5].

There are many patients that require alveolar bone reconstruction prior to placement of dental implants. This is the reason for the demand and market for bone substitutes. Recently, the global market for bone substitutes was valued at more than $2.4 billion [6]. In addition, new products in a variety of shapes and sizes are providing excellent biological and clinical properties, thereby increasing the demand for bone substitutes. Bone grafts are widely used in orthopedic and maxillofacial surgeries for numerous applications. They can be categorized into natural and synthetic grafts, with natural bone grafts harvested from patients themselves or donors, and synthetic grafts being of artificial origin. Because natural bone grafts have several clinical limitations, synthetic grafts are nowadays leading the global market [6].

Interestingly, the acceptance and utilization of dental implants and bone grafts by dental practitioners are increasing. This means that the science and techniques of dental implants and bone grafts should take their rightful place in the armamentarium of the dental health professional. Therefore clinicians and

dental scientists should always gain a thorough knowledge of science related to materials and biological issues of dental implants and bone grafts.

The focus of this book is on the optimization of science and application of dental implants and bone grafts. In order to understand the principles of dental implants and bone grafts, we must first understand alveolar bone, as it part of a more specialized and complex system compared to other skeletal bone tissues. As discussed in Chapter 1, the alveolar process is a major component of the tooth-supporting apparatus and is comprised of alveolar bone proper, cortical alveolar bone, alveolar crest, and trabecular bone. The alveolar process develops along with the dentition and undergoes resorption following extraction of teeth. With the advent of dental implant-supported rehabilitation, understanding and preserving the alveolar bone has become more imperative than ever before. In order to achieve the same, knowledge about applied biology, composition, microstructure and anatomic, clinical, and radiographic features of alveolar bone is essential. Hence, the aim of Chapter 1 is to provide the reader with a thorough knowledge of alveolar bone characteristics and its applied biology in relation to dental implant therapy.

Chapters 2 and 3 highlight the clinical application and procedures of alveolar bone reconstruction as well as implant osseointegration. In particular, Chapter 2 focuses on edentulism. Whether partial or complete, toothlessness has always posed great challenges to clinicians. Among the multitude of available replacement options, dental implants have currently gained importance due to well-established and standard protocols. A systematic approach to diagnosis and treatment planning is fundamental to the success of dental implants and their long-term functionality. The success of dental implants treatment is owed to their longevity and biocompatibility. Furthermore innovative implant designs can cater to a multitude of patient needs. Thus understanding the clinical indications can be regarded as the deciding factor for the success of osseointegrated dental implants.

Bone grafts are used as scaffolds to replace the missing bone and assist in new bone formation and healing. These materials can be derived from a patient's own body (i.e., natural substitutes) or can be of a synthetic origin. Chapter 3 discusses the most commonly used bone graft materials for bone regeneration. It has been estimated that more than 2 million alveolar bone-grafting procedures are carried out yearly worldwide. Usually they involve replacing missing bone tissue with a suitable bone substitute that has the ability to trigger bone regeneration. This provides adequate tooth support and allows successful implant placement and osseointegration.

Chapter 4 explores dental implant design and surface modification as an important means to improving osseointegration. It discusses new developments in implant surface modifications that are critical for bone healing. Introduction of nanostructural features into implant surfaces accompanied by defined modification of the inorganic chemical status of the surfaces, including the release of ions, shows a great potential for addressing and improving implant osseointegration and antibacterial properties. These surfaces might be further

improved by immobilization of peptide sequences addressing both subprofiles (i.e., improved osseointegration and long-term antimicrobial properties). In many, though not all, studies the early stages of tissue regeneration and antimicrobial properties appear to be improved by organic surface modifications. However, it should be kept in mind that due to heterogeneity in study design, interstudy comparability is complicated. Therefore long-term clinical studies are still necessary to validate long-term success. Future directions could include the development of electrochemical treatments to remove biofilm contaminations from inserted implants, as it has been found that both anodic or cathodic polarization will increase pH, reduce pO_2, and generate reactive oxygen species (ROS) as well as reactive chlorine species (RCS), all of which are discussed as active agents against bacteria. Unlike conventional chairside treatment methods, here the application of a current to electrically conductive implants would result in an attack of the bacterial biofilm directly from the implant surface. For organic coatings, a promising strategy appears to be multifunctional coatings that address multiple aspects simultaneously, such as promoting bone and soft tissue regeneration as well as reducing bacterial adhesion and biofilm formation.

Chapter 5 proceeds with the science of materials related to synthetic bone grafts. This chapter describes the main characteristics and the potential of synthetic bone graft substitutes based on calcium for dental applications. It reviews aspects such as the composition, the structure, and the processing routes of the different families of materials to give the reader a general overview of the different materials. Particular attention is given to calcium phosphates due to the close chemical resemblance of these materials to the mineral phase of bone. Other families such as calcium sulfates, calcium carbonates, and calcium-containing bioactive glasses are also discussed. The chapter places particular attention on the current and novel strategies based on ion doping (to mimic mineral bone composition), surface functionalization (to mimic extracellular matrix), and additive manufacturing (to make highly porous yet mechanically stable scaffolds) in the fabrication of the next generation of materials to help accelerate tissue healing and improve bone growth at impaired sites.

Chapter 6 focuses on tissue-engineering techniques for bone grafts. In recent years, bone tissue-engineering techniques have shown great promise for generation of dental bone grafts with highly biomimetic properties. Alveolar bone tissue engineering uses a combination of scaffolds, cells, and/or bioactive factors to generate new bone tissue and, occasionally, other related and interfacial tissue types relevant to the periodontal unit. Given the highly complex environment of the periodontium in which alveolar bone resides, composite scaffold design has been instrumental in producing truly biomimetic scaffolds that can recapitulate the heterogeneous chemical, physical, and biological properties of dental bone. One important aspect of composite scaffold design has been utilizing novel material combinations and composite materials from multiple classes—including synthetic polymers, natural polymers, and ceramics—to provide a myriad of biomimetic features. Building upon this, the emergence of high-fidelity scaffold

fabrication techniques in rapid prototyping have enabled the production of complex, spatially defined architectures from these composite materials. Furthermore tissue engineers have utilized multiphasic and gradient scaffold design to directly address the heterogeneity of alveolar bone and its surrounding periodontium. Thus more biomimetic scaffolds and dental bone grafts have been produced by combining composite material selection, high-fidelity 3D scaffold fabrication, and multiphasic scaffold design. Further improvements to dental bone graft engineering can be explored through the development of more precise mechanical, physical, and biological gradients that mimic the periodontal unit.

The chapters in the second part of the book focus on the biological interaction and biocompatibility of dental implants and bone grafts. Chapter 7 highlights the importance of cellular and molecular interaction. It provides an overview of the cellular interactions and the genetic regulations at the bone-implant interface, based on experimental in vivo studies and available studies in humans. The first section discusses the current knowledge on the cellular and molecular events governing the initial cell recruitment, early inflammation, and the transition from inflammation to bone formation and remodeling during the phases of osseointegration. The modulation of these events, by different implant surfaces, and their relationship with the structural and functional development of the interface are emphasized. A subsequent section focuses on selected key biological factors potentially involved in the osteogenic differentiation of mesenchymal stem cells (MSCs) or in coupling of bone formation and remodeling at the interface. Further, the chapter discusses possible phenotypic polarizations of macrophages at the interface, in vivo. Finally, it provides some insights into possible dysregulations of the molecular activities at the interface, under selected bone-compromising conditions.

Chapter 8 reviews bone regenerative issues related to bone grafting biomaterials. Tens of millions of European citizens are partially edentulous and lack sufficient bone for placement of dental implants. This chapter reviews the different options used by oral surgeons for guided bone regeneration (GBR) prior to dental implant placement. Autologous bone grafting is the gold standard but requires a second surgery, induces pain, and the quantity is limited. Allogeneic bone from tissue banks carries the risk of immune rejection and is subjected to uncontrolled resorption. Animal-derived products such as deproteinized bovine bone are very popular in oral surgery, but there are safety concerns with the possible transmission of diseases. Synthetic bone substitutes such as calcium phosphate bioceramics are increasingly used for filling small bone defects because of their biocompatibility and osteoconductive properties. MSCs associated with calcium phosphate bioceramics have shown to induce de novo bone in preclinical and clinical studies. These cells can be easily isolated and amplified in culture from a bone marrow aspiration. When mixed with biomaterials, these cells attach on their surface and the extemporaneous mixture can be applied to atrophied alveolar bone for its regeneration. GBR membranes are essential for favoring bone regeneration while preventing fibrous tissue invasion. However,

synthetic resorbable membranes should be preferred over animal-derived products made from porcine skin for safety and ethical reasons. Furthermore these collagen membranes exhibit a rapid resorption when exposed to the proteases of the oral cavity. This chapter also presents future directions in bone regeneration, such as the use of 3D-printed personalized scaffolds and allogeneic MSCs.

Chapter 9 explores issues related to cell-based therapies in bone regeneration. Cell-based therapies hold great promise for regenerative treatment of bone defects. MSCs are most commonly used to prepare cell-based constructs for bone repair. Although preclinical and clinical evidence of successful bone healing by MSC-based constructs exists, those are far from becoming implemented as standard treatment in clinics. Considerable variation in cell-based construct preparation and study design between studies emphasize the need for a standardized manufacturing protocol and controlled trials. Furthermore the mechanism by which transplanted cells contribute to bone regeneration remains to be unraveled to further aid in developing strategies to increase bone regenerative efficacy. Additionally, in view of the impractical generation procedure of cell-based constructs with time-consuming ex vivo manipulation, directions to improve feasibility and cost-effectiveness of such cell-based constructs are increasingly being explored.

Chapter 10 extensively reviews pharmacological interventions targeting bone diseases in adjunction with bone grafting. Skeletal diseases are often difficult to treat by means of systemic pharmacological intervention due to poor drug uptake and systemic toxicity, both of which limit therapeutic efficacy. Therefore bone-targeting agents have been developed to target drugs to the skeleton. The majority of these bone-targeting agents exploit their affinity to positively charged Ca^{2+} ions that are abundantly present in the mineral phase of bone. A better understanding of bone biology provides new opportunities to develop novel bone-targeted molecular therapeutics to treat bone diseases, such as osteoporosis, osteomyelitis, osteosarcoma, and bone metastasis. This chapter illustrates the most important features of the most commonly applied bone-targeting agents. Subsequently, various strategies aimed at conjugating these bone-targeting agents to either drugs or biomaterial-based systems for local delivery are reviewed. The chapter concludes with a summary of the most promising preclinical applications of bone-targeting drug delivery systems.

Chapter 11 addresses the modern assessment methods of bone-to-biomaterials regeneration. Mainly, it focuses on the application of high-resolution X-ray imaging modalities currently available for the assessment of biomaterials and (bone) tissue engineered constructs, with a specific focus on micro-computed tomography (CT) and CT-derived techniques. It also discusses the development, applications, and limitations of both in vivo and ex vivo micro-CT imaging methods. Moreover, it describes in detail state-of-the-art X-ray imaging techniques, like X-ray phase contrast, scatter contrast, fluorescence contrast, and hybrid X-ray imaging. Finally, it presents challenging nanoresolution multimodal in vivo imaging. Such techniques are providing a simultaneous view into associated molecular, functional, and anatomical changes.

Finally, Chapter 12 aims to explore the frontiers in dental implant therapy and bone grafting and how much preclinical research efforts are needed to achieve the desired clinical translation of the science of dental implants and bone grafts. Advances in various areas of biomaterial science have been significantly contributing to bone tissue-engineering research. This chapter outlines the progress in biomaterial design for developing a biofunctional material that can accelerate therapeutic potential. It discusses various approaches inspired from native bone ECM for modification of biomaterial substrates for bone tissue-engineering applications. Significant efforts have been made to produce biomaterials with biological, compositional, and structural properties. Nevertheless, major issues remain that need to be addressed. Most of the approaches have focused on bone formation. However, considering that bone tissue has a complex structure with unique mechanical features, and bone regeneration is a multifactorial process that includes osteogenesis, angiogenesis, inflammation, and bone resorption, the biomaterial should be designed to provide multiple signals to orchestrate all these healing events. Another concern is the immunogenicity of the transplanted biomaterials. Although most synthetic polymers are biocompatible, the long-term fate of their degradation product and their effect in the body are still not well understood. Presently, most biomaterials affecting in vivo bone regeneration have been tested in small animals with mesoscale defect models. Therefore there is still a need to investigate the potential of biomaterials in larger animal models with relatively larger defect sizes that have better relevance to clinical problems associated with humans.

Rationale of book

In clinical dentistry, dental implants and bone grafts are becoming increasingly crucial. The evolution of these materials and techniques has led to an increase in successful dental treatment as well as patient satisfaction. This is because research on alveolar bone biomaterials (dental implants and bone grafts) has vastly expanded with increased understanding at the molecular and cellular level. However, knowledge of these biomaterials and biological aspects is still surprisingly limited. Thus this book presents a critical review of the science of alveolar bone biomaterials that will help to propel the continuing evolution of modern dental implants and bone grafts.

Goals of book

On completion of reading this book, dental practitioners/scientists should be able to:

- Understand the structure, function, and pathology of the alveolar bone system
- Understand the rationale and clinical indications of dental implants and alveolar bone replacements/reconstruction

- Consider the issues involved in selecting alveolar bone biomaterials (dental implants and bone grafts)
- Understand the biological basis of interactions between alveolar bone and biomaterials
- Utilize information available about the cellular and molecular basis for bone-implant regeneration in vivo and in humans
- Explore ongoing frontier research of dental implants and bone grafts within all relevant fields

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Chapter 1

Alveolar bone science: Structural characteristics and pathological changes

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Chapter outline

1.1 Introduction

Alveolar bone is a critical component of the tooth-supporting apparatus in the maxillofacial skeleton. A healthy alveolar process, comprising the alveolar bone, periodontal ligament, and cementum is required to maintain a healthy dentition [1,2]. Unlike other connective tissues, bone is a specialized connective tissue that is rigid and resilient. It is primarily responsible for supporting the soft tissue integument and protecting internal organs. The rigidity and resilience of bone are contributed by the mineralization of collagen fibers and noncollagenous proteins within the bone matrix [3,4]. Although alveolar bone is similar in microstructure and cellularity to bone in other parts of the body, the physiological and functional needs of the dental apparatus make it unique among all osseous tissues [3].

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Anatomically, alveolar bone is exclusive to the maxilla and mandible, wherein it develops occlusal to the basal bone, coinciding with the development of dentition. In principle, the alveolar bone remains as long as the teeth are in occlusion, and undergoes resorption following loss of teeth [3,5]. With the advent of dental implantology and osseointegration, contemporary dentistry has undergone a paradigm shift towards rehabilitating missing teeth with different types of dental implants [6]. Since alveolar bone is an essential element for dental implant osseointegration, knowledge regarding the techniques to preserve and reconstruct alveolar bone have gained greater predominance over the last decade [1,3,5]. Understanding the biology and characteristics of alveolar bone have therefore become an imperative part of successful implant dentistry [7].

1.2 Embryology of alveolar bone

Alveolar bone development closely follows the development of maxilla and mandible through membranous ossification. Although maxillary and mandibular development begins as early as the fourth to sixth weeks of intrauterine life, alveolar bone development does not begin until the formation of teeth [2,3]. During the fourth week of intrauterine life, embryologic development of the face, including the upper face, midface (nasomaxillary complex), and mandible, begins from five primordia. These include the frontonasal process in the midline, and the bilateral maxillary and mandibular processes surrounding the primitive mouth or stomodeum [3,8] (Fig. 1.1). Both the maxillary and mandibular processes arise from the first branchial arch. While the mandible in its entirety is formed from the mandibular process, maxillary development along with the palate is contributed in part by the maxillary and frontonasal processes [3,8,9] (Fig. 1.2).

Mandibular bone formation begins bilaterally around the inferior alveolar nerve and its terminal incisive branch, thereby forming a bony groove housing those nerves. In addition, this bony groove also houses the developing tooth germs. Medial and lateral to this groove, alveolar bone plates extend superiorly to form the body of the mandible [3]. Anteriorly, the mandibular process merges across the midline giving rise to the mandible and anatomic lower third of the face along with tongue [9]. Nevertheless the mandibular symphysis remains in fibrous union until after birth, when it is finally ossified through membranous ossification [3,9].

Contrary to mandibular alveolar process development, maxillary alveolar development is more complex owing to the simultaneous development of maxillary antrum and associated midfacial (nasal, orbital, and maxillary) structures [3,8]. However, formation of the medial and lateral maxillary alveolar bone plates, enclosing the primary tooth germs, occurs in a similar fashion to that of the mandible. With time, the tooth germs develop and are progressively separated from each other by bony partitions, giving rise to the alveolar sockets that house the teeth and their supporting structures [3,8].

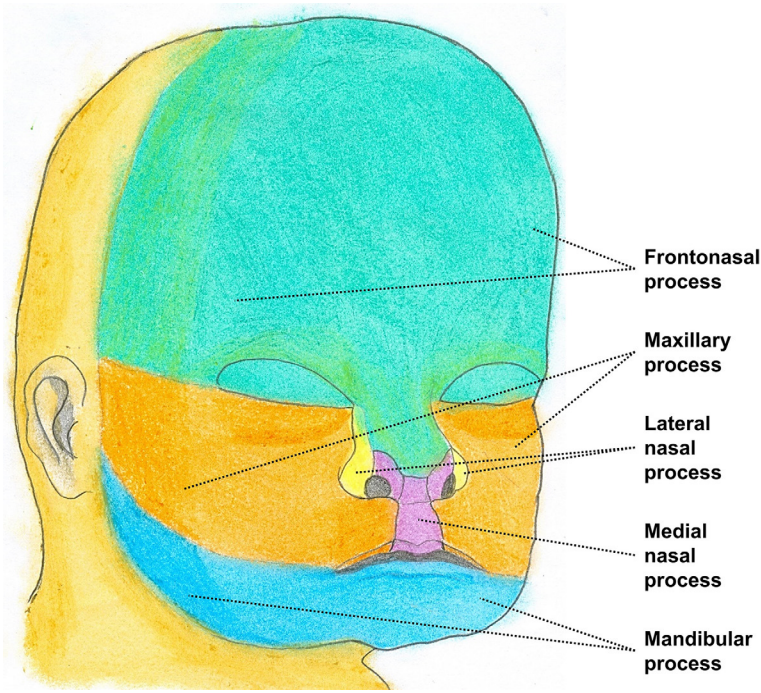

FIG. 1.1 Graphical representation of late fetal facial development in an anterior oblique view showing contributions from the different facial processes; frontonasal process *(green)*, maxillary processes *(orange)*, lateral nasal processes *(yellow)*, medial nasal processes *(purple)*, and mandibular processes *(blue)*.

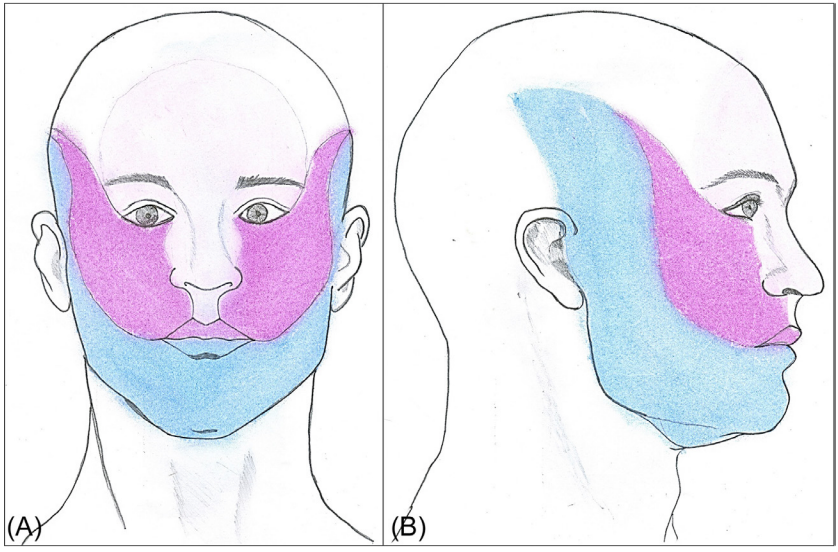

FIG. 1.2 Developmental origins of the maxillofacial skeleton in an adult (A) frontal view and (B) lateral view showing contributions from the maxillary processes *(purple)* and the mandibular processes *(blue)*.

Embryologic development of teeth is attributed to the neuroectoderm or neural crest ectomesenchyme, which underlies the stratified squamous epithelium of primitive mouth or stomodeum. Around the sixth week of intrauterine life oral ectoderm in the primitive maxilla and mandible proliferates into horseshoe-shaped bands, signifying the future dentoalveolar processes [8,10]. This primary epithelial band gives rise to a superficial vestibular lamina and a deeper dental lamina. Both of these laminae proliferate into the underlying ectomesenchyme [8,10]. While the vestibular lamina grows rapidly and degenerates to form the labial or buccal vestibule, the dental lamina undergoes localized expansions called placodes, which develop subsequently into tooth buds. Altogether, the dental lamina gives rise to 52 tooth buds, 20 for primary teeth and 32 for permanent teeth through the lingually proliferating successional lamina [11–13]. The sequence of tooth development from the dental lamina to tooth eruption is shown in Fig. 1.3.

The earliest sign of development of alveolar bone proper coincides with the developing primary dentition. Each tooth bud undergoes different stages of proliferation, differentiation, and organization to form the crown of a tooth. Once crown formation is complete, root development ensues through interaction between the dental follicular mesenchyme and the Hertwig epithelial root sheath (HERS). HERS is composed only of the outer and inner enamel epithelial layers [8,10]. Mesenchymal cells from the dental follicle undergo simultaneous differentiation into cementoblasts, fibroblasts, and osteoblasts. These cells lead to cementum deposition on the developing root surface, formation of periodontal ligament fibers, and formation of the bony socket walls, respectively [8,10].

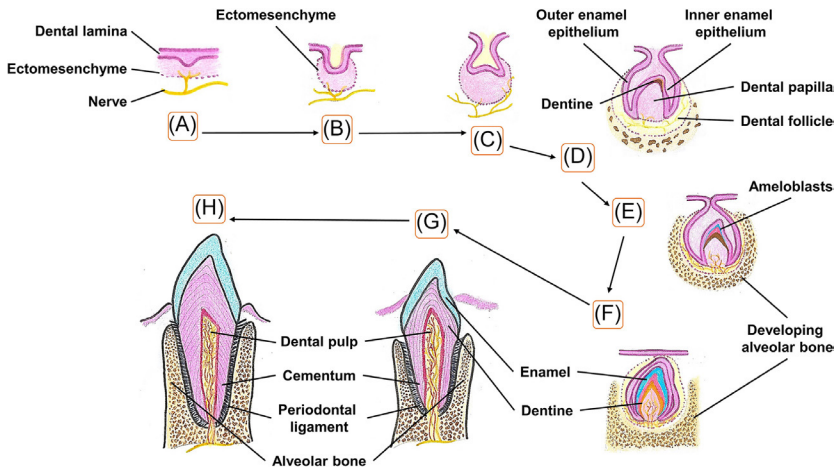

FIG. 1.3 Embryologic development of tooth and its supporting structures, showing the stages of development: (A) initiation, (B) bud stage, (C) cap stage, (D) bell stage with dentinogenesis, (E) amelogenesis, (F) development of crown and alveolar bone, (G) root formation and continued alveolar bone development, and (H) maturation of tooth and its supporting structures.

This concomitant development of the triad of periodontal tissues results in embedding of periodontal ligament fibers within both the cementum and alveolar bone proper. Periodontal ligament progressively increases in length in response to root formation and tooth eruption. Similarly, alveolar bone surrounding the tooth increases in height and continuously remodels during tooth eruption and follows the periodontal ligament [3,12]. Upon tooth eruption, a fully functional dentoalveolar process, comprising the tooth, completed root, alveolar bone, and periodontal ligament, is finally created [3,8,10]. Physiologically, alveolar bone is in a constant state of dynamism throughout life. It remodels in response to occlusal wear and tear and masticatory forces placed on the tooth, and transmitted through the periodontal ligament [3,8,10] (Figs. 1.3 and 1.4).

Similar to other anatomical sites, the two major cell types participating in the development of alveolar bone are osteoblasts and osteoclasts [4]. Osteoblasts are derived from the dental ectomesenchyme, and are responsible for the formation of bone matrix and its mineralization. After bone formation, the osteoblasts either undergo apoptosis or become osteocytes encased in a lacunae within the bone matrix or transform into bone-lining cells covering almost all quiescent bone surfaces [4]. Osteoblasts are highly active postmitotic cells containing a cytoplasm rich with secretory and synthetic organelles necessary for bone matrix deposition. Conversely, osteocytes are smaller and relatively less active cells with fewer cytoplasmic organelles. Nevertheless osteocytes have extensive cell processes that communicate with other osteocytes in the bone matrix, through canaliculi and gap junctions [4,5].

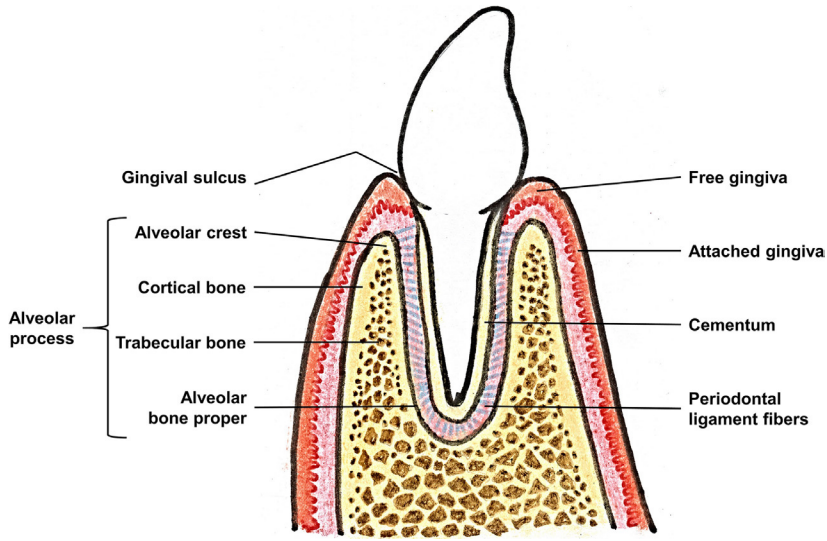

FIG. 1.4 Anatomy of the alveolar process supporting a fully erupted tooth and components of alveolar bone.

In contrast to the osteoblasts, osteoclasts are derived from hematopoietic progenitors of the monocyte macrophage system [14]. Although they originate as mononuclear cells, osteoclasts fuse during maturation to form multinuclear cells with polarized nuclei and a ruffled border. This ability of osteoclasts enables them to attach to the bone matrix and subsequently aids in bone matrix resorption. During their active phase osteoclasts exhibit numerous large and small cytoplasmic vesicles, containing cathepsin, close to the ruffled border. In addition small spherical vesicles containing plasma membrane and lysosomal enzymes, identified by a single indentation on their surfaces are also seen. These vesicles participate in osteoclastic degradation and recycling of the plasma membrane components [5,15] (Fig. 1.5).

1.3 Classification of alveolar bone

As mentioned earlier, alveolar bone is a specialized part of the mandible and maxilla that forms the primary support structure of teeth. It undergoes constant remodeling in order to accommodate to the changing morphology and physiological demands of the dental structures it contains. Alveolar bone is composed of bundle bone, formed in layers with a parallel orientation along the coronal-apical direction of a tooth [16]. Sharpey's fibers extend obliquely from the thin lamella of bone that lines the socket wall and are continuous with the fibers of periodontal ligament [16]. Within the alveolar process, alveolar bone proper lines the alveolus or tooth housing [17]. It is composed of a thin plate of cortical bone with numerous perforations (or cribriform plate) that allow the passage of blood vessels between the bone marrow spaces and periodontal ligament [17]. The coronal rim of alveolar bone forms the alveolar crest, which generally

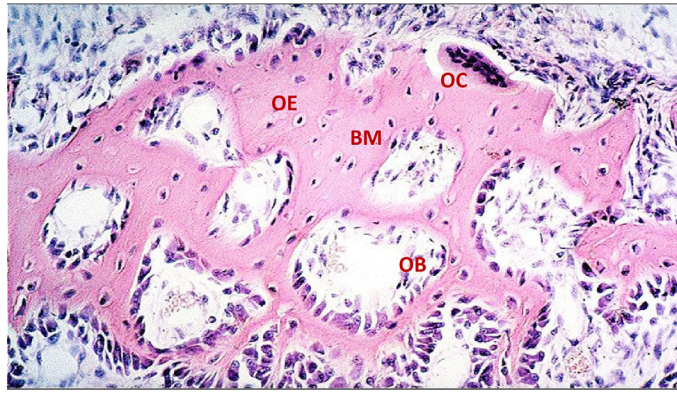

FIG. 1.5 Histological section (H and E, ×100) of bone obtained from a healing extraction socket showing, new bone formation with osteocytes (OE) entrapped in the bone matrix (BM). Islands of new bone formation by osteoblasts (OB) and remodeling through resorption by osteoclasts (OC) is also seen.