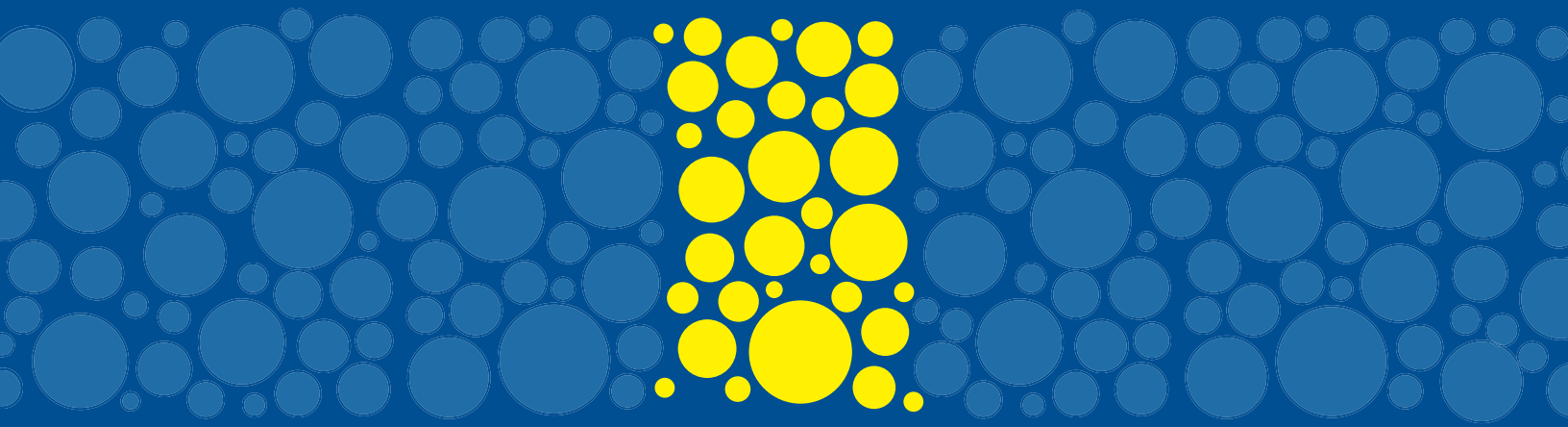
Horizontal and Vertical
BONE AUGMENTATION
for Dental Implant Therapy

EDITED BY CRAIG M. MISCH, DDS, MDS



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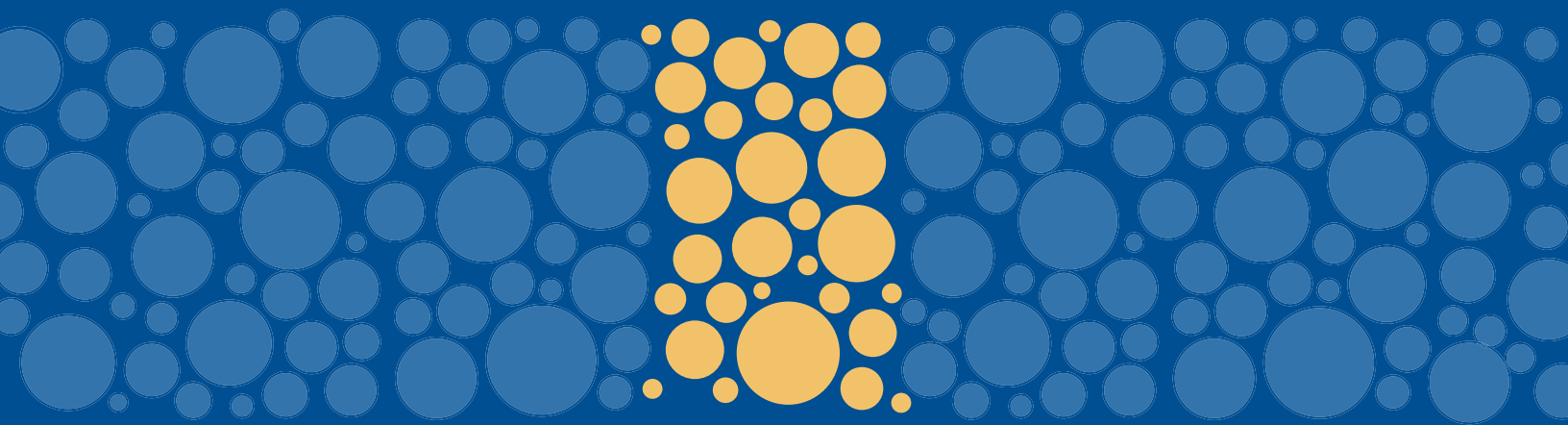

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PREFACE

The field of implant dentistry continues to evolve and improve. One constant that has not changed is the need for sufficient bone volume at the site of implant placement to facilitate osseointegration and continued bone support over time. Bone augmentation is often required to accomplish this important goal. Many books on implant dentistry reflect an author's approach to a specific clinical problem—a "this is how I do it" book. I have always had a passion for research and teaching, and my goal for this text was to explain not only how I do it but also *why* and *when* we do it.

The first six chapters provide the reader fundamental knowledge of the science of bone augmentation, and chapters 7 to 10 cover the diagnosis and planning for bone augmentation surgery. The centerpiece of the text is the Michigan Classification for horizontal and vertical bone augmentation. Dr Hom-Lay Wang and I developed the Michigan Classification to offer clinicians an evidence-based decision tree for managing different clinical situations. This classification focuses on the treatment of bone defects and deficiencies outside the bony contour. The current research on outcomes using various methods of bone augmentation and biomaterials was evaluated to construct parameters and guidelines. Finally, chapters 11 to 18 discuss the various techniques for horizontal and vertical bone augmentation.

For this text I invited the most knowledgeable clinicians and researchers in their specific areas of expertise to coauthor the chapters. As such, it reflects a collective body of work rather than one author's preference or opinion. My goal was to provide a comprehensive source of authoritative information on the topic of bone augmentation. I also wanted to establish guidelines for students, clinicians, and researchers on predictable approaches to bone regeneration for dental implant therapy.

Technology has improved our ability to diagnose, plan, and execute treatment; using CBCT, we can create a virtual patient for prosthetic guided bone augmentation. Customized scaffolds for bone regeneration can be fabricated based on the specific needs of each patient. Recombinant growth factors can be used to improve the regenerative capacity of osteoconductive biomaterials. Further advancements will undoubtedly improve outcomes. Surgeons should consider the advantages and disadvantages of each material and technique for the clinical situation and choose the approach with manageable costs, low morbidity, and the greatest chance for success. This text offers the reader a better understanding of how to accomplish these goals and improve the lives of their patients.

Acknowledgments

The first person I wish to thank is my loving wife, Katie. We have been married for over 30 years and raised three intelligent and beautiful daughters: Maggie, Angela, and Rachel. Katie and I also practice together in the same office, Misch Implant Dentistry. We have just added Maggie Misch-Haring to the team as our periodontist and her husband, Harry Haring, as another prosthodontist. Throughout our marriage, Katie has supported my professional goals and helped me achieve a successful career. I could not have done it without her. I have always had a great interest in bone regeneration and dental implant therapy; Katie knew I always wanted to write a book on this topic and that my bucket list would not be complete until this was done. I realize it has not been easy putting our lives on hold while working on this project, but she continued to be supportive, and I am exceedingly grateful.

I also want to acknowledge my brother, Carl, for encouraging my interest in dentistry and fostering my education in dental implants. We worked together in Michigan for 3 years and thereafter did our prosthodontic

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residency training at the University of Pittsburgh. Carl also inspired me to become active in professional organizations and to teach, write, and lecture.

Following my prosthodontic residency and implantology fellowship, I stayed on as faculty at the University of Pittsburgh. My program director, Dr Chester Chorazy, took a chance on accepting a prosthodontist into an oral and maxillofacial surgical residency. This opportunity was the missing piece of the puzzle in my training and professional career. Dr Chorazy was like a father to us and mentored our education and surgical training.

I also want to thank Dr Hom-Lay Wang for his continued support and friendship. Dr Wang helped immensely with writing and editing this text. Although he is extremely busy, he was always available to help. To all the coauthors in this text, I appreciate your expertise, dedication, and willingness to contribute and share your knowledge for this publication.

Last but not least, I would like to thank the Quintessence Publishing staff, including Leah Huffman (Editorial Director), Bryn Grisham (Publishing Director), and William Hartman (Executive Vice President and Director). With so many contributors, it was a challenge meeting timelines, but with dedication, persistence, and patience, our task was completed. I hope you enjoy the finished product.

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BONE VOLUME FOR DENTAL IMPLANT PLACEMENT

Craig M. Misch | *Hom-Lay Wang* | *Maggie Misch-Haring*

The replacement of missing or failing teeth with dental implants has revolutionized the field of dentistry and improved the quality of our patients' lives. High success rates and excellent predictability of dental implant therapy have been demonstrated in numerous clinical studies and a variety of indications. A number of factors important for the long-term survival and/or success of implants and implant-supported prostheses have been identified. One critical prerequisite is a sufficient volume of bone at the site of implant placement to facilitate osseointegration and continued bone support over time. In a prosthetic-driven approach to treatment, the planned prosthesis guides the number and 3D position of the implants. If the preferred implant locations have inadequate available bone, then bone augmentation may be required so that the implant can be placed in the ideal position for esthetics, prosthetic support, and long-term function.

Bone Volume

The volume of bone in the edentulous site planned for implant placement is measured in 3D in terms of width, height, and angulation.

Bone width

The minimum bone width is dependent on the preferred implant diameter and location. A minimum 2.0-mm facial bone thickness has been recommended around implants in the esthetic zone to avoid crest resorption and gingival recession.[1,2] However, this recommendation was based on 1.4-mm horizontal bone loss found around external hex connection implants[3] (Fig 1-1). Tissue-level, conical-connection, and platform-switching implants are associated with less bone resorption.[4–6] A clinical study found that the horizontal component of bone loss around platform-switching implants measured only 0.6 mm.[7] Therefore, using implant designs with a conical seal, medialized connection, or absence of a microgap, such as a tissue-level implant, may reduce the ridge width requirement to 1.0 to 1.5 mm of facial and palatal/lingual bone (Fig 1-2). In addition, the edentulous ridge typically widens apically from the crest, so vertical bone reduction may be an alternative to bone augmentation in areas where esthetics is not a concern. However, in some cases the facial and palatal/lingual cortices may show minimal divergence.

Another alternative to bone augmentation of the atrophic ridge with deficient width is to use a narrow-diameter implant (NDI; Fig 1-3). A recent systematic review and meta-analysis found that implant diameters of 3.0 to 3.5 mm showed no difference in implant survival compared to standard-diameter implants (> 3.5 mm).[8] Additional systematic reviews and meta-analyses of studies have also found that NDIs are an effective alternative to standard-diameter implants due to similar survival and success rates, marginal bone loss, and mechanical

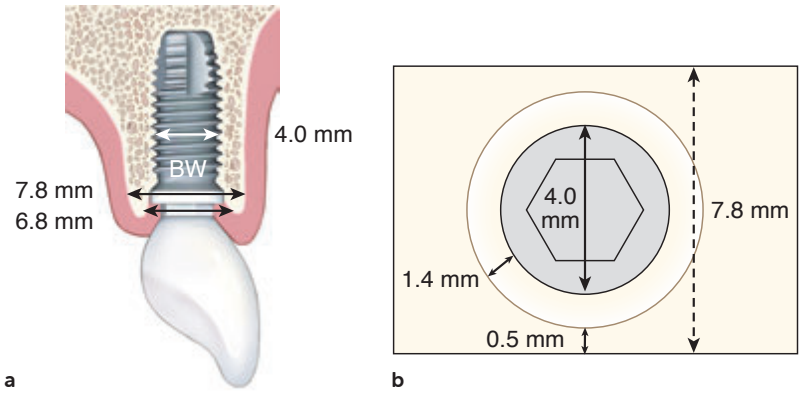

FIG 1-1 Cross-sectional *(a)* and occlusal *(b)* views of horizontal bone loss around an external hex implant. A minimum ridge width of 7.8 mm would be needed for placement of a 4.0-mm-diameter implant.

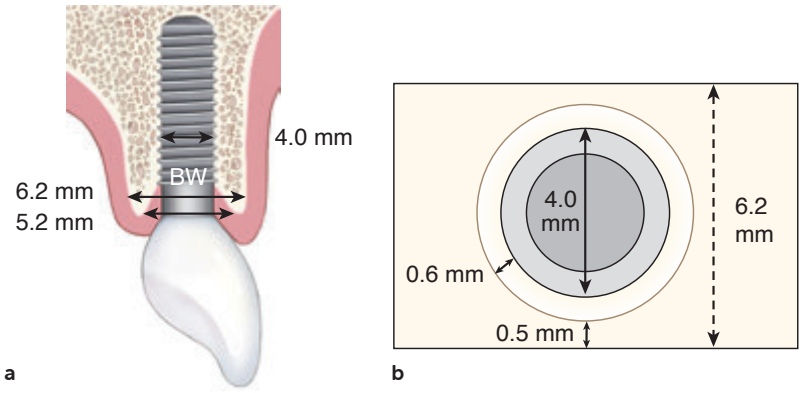

FIG 1-2 Cross-sectional *(a)* and occlusal *(b)* views of horizontal bone loss around a conical-connection implant. A minimum ridge width of 6.2 mm would be needed for placement of a 4.0-mm-diameter implant.

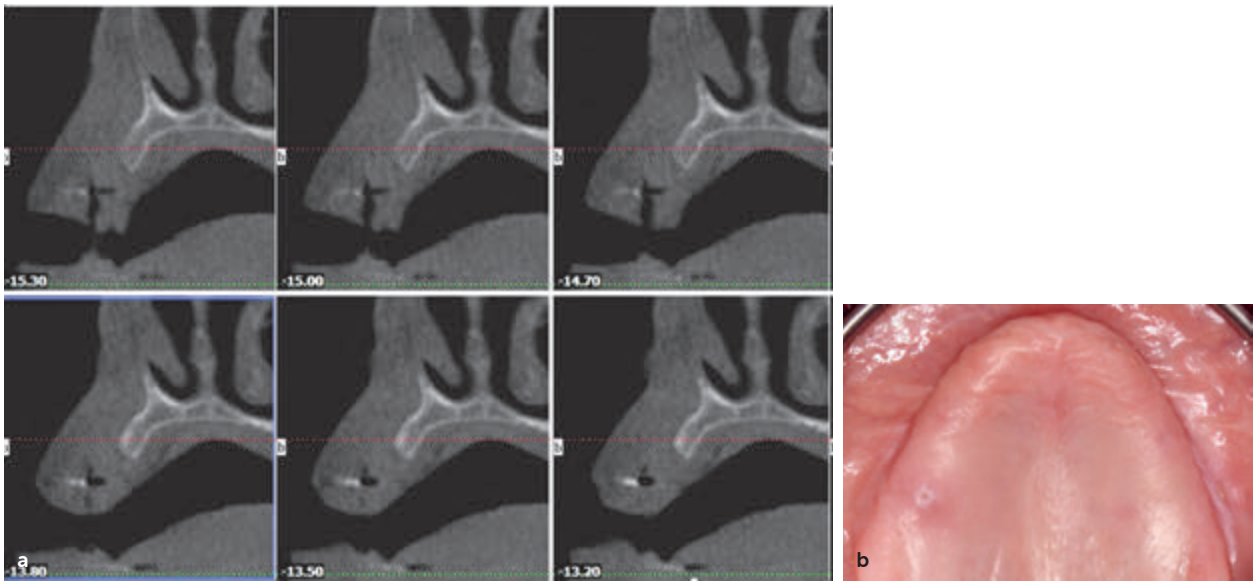

FIG 1-3 *(a)* A preoperative CT scan reveals a narrow ridge in the edentulous maxilla. *(b)* Preoperative occlusal view of the atrophic maxilla. ➜

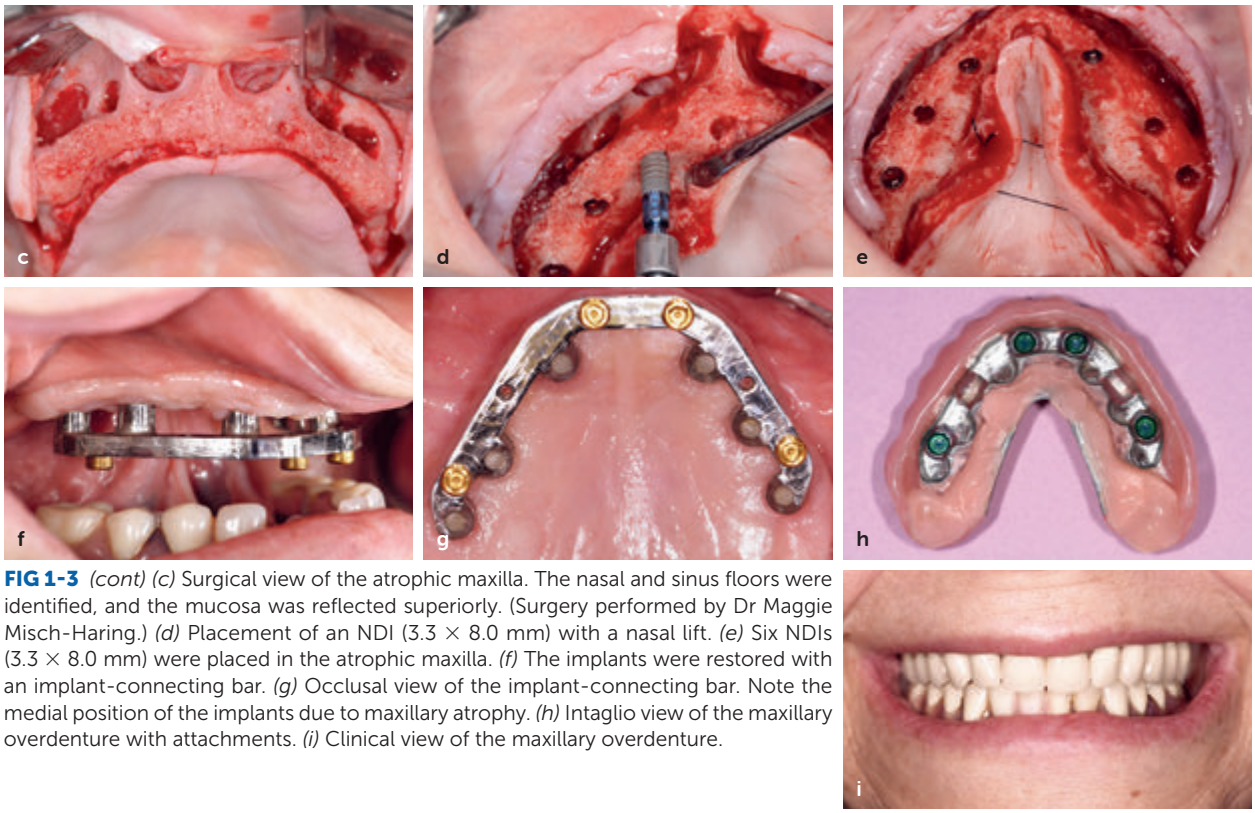

FIG 1-3 *(cont) (c)* Surgical view of the atrophic maxilla. The nasal and sinus floors were identified, and the mucosa was reflected superiorly. (Surgery performed by Dr Maggie Misch-Haring.) *(d)* Placement of an NDI (3.3 × 8.0 mm) with a nasal lift. *(e)* Six NDIs (3.3 × 8.0 mm) were placed in the atrophic maxilla. *(f)* The implants were restored with an implant-connecting bar. *(g)* Occlusal view of the implant-connecting bar. Note the medial position of the implants due to maxillary atrophy. *(h)* Intaglio view of the maxillary overdenture with attachments. *(i)* Clinical view of the maxillary overdenture.

and biologic complication rates.[9,10] Stronger metals, such as titanium-zirconium or titanium alloy, may reduce the risk of implant fracture when NDIs are used. Systematic reviews on titanium-zirconium NDIs have found implant success and survival rates to be similar to those of standard-diameter titanium implants with no increase in fractures.[11,12] However, long-term survival and data on the possible risk of technical complications with wide-platform restorations on NDIs are lacking. As such, a standard- or wide-diameter implant for single molar replacement may be prudent.

Bone height

The minimum bone height for implant placement is dependent on several factors. One consideration is the anatomical region. In the posterior maxilla, the floor of the sinus can limit the available bone height. However, the sinus floor is an anatomical boundary that can be encroached upon or manipulated via an internal or lateral sinus elevation. Many studies have shown that the survival of short implants (< 8 mm in length) is the same as that of longer implants placed into grafted sinuses.[13,14] Although there is no definitive bone dimension needed before considering sinus bone grafting, 6.0 to 8.0 mm inferior to the sinus floor appears to be sufficient (Fig 1-4). In the posterior mandible, the mandibular canal and lingual cortex can limit implant length. A common rule is to allow for at least a 2.0-mm distance from the mandibular canal for implant placement to account for potential inaccuracies in radiographic measurements, drilling depth, and implant placement.[15] As mandibular bone is usually of better quality, extra-short implants (6.0 mm in length) have been shown to be effective[16] (Fig 1-5). As such, 8.0 mm of available bone height superior to the canal is needed to place extra-short implants in the posterior mandible (Fig 1-6).

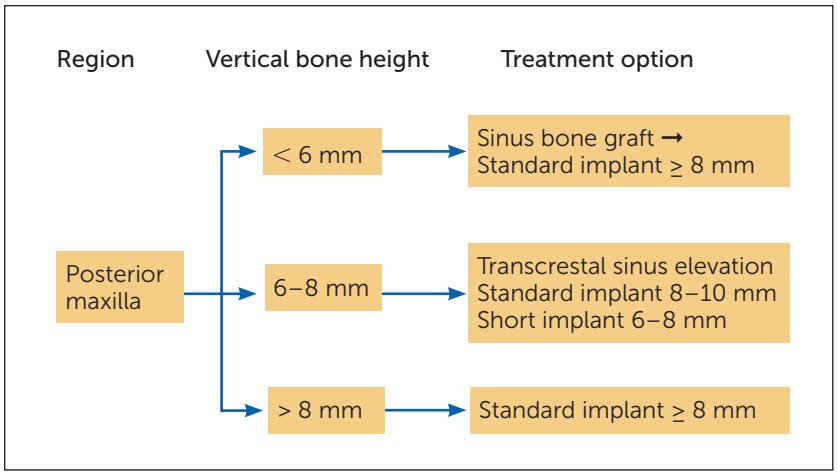

FIG 1-4 Vertical bone height requirements in the posterior maxilla.

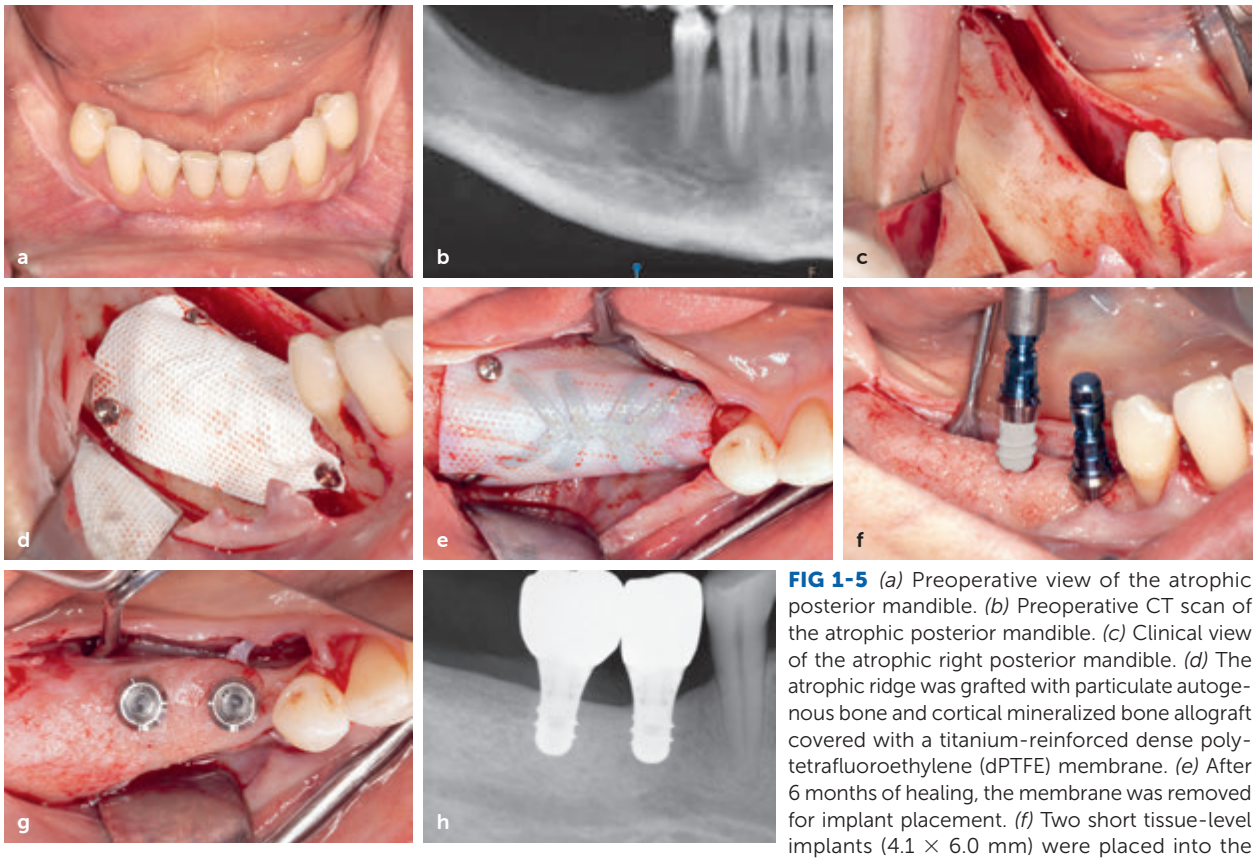

FIG 1-5 *(a)* Preoperative view of the atrophic posterior mandible. *(b)* Preoperative CT scan of the atrophic posterior mandible. *(c)* Clinical view of the atrophic right posterior mandible. *(d)* The atrophic ridge was grafted with particulate autogenous bone and cortical mineralized bone allograft covered with a titanium-reinforced dense polytetrafluoroethylene (dPTFE) membrane. *(e)* After 6 months of healing, the membrane was removed for implant placement. *(f)* Two short tissue-level implants (4.1 × 6.0 mm) were placed into the grafted mandible. *(g)* Occlusal view of the two short tissue-level implants in the right posterior mandible. *(h)* The implants were restored with individual screw-retained crowns.

The amount of bone resorption following the loss of teeth determines the crown height or prosthetic space. *Implant crown–abutment height space* is defined as the distance from the occlusal plane to the platform of the implant(s). The available restorative space will influence the type of prosthesis, material choices, and surgical techniques. It also has esthetic and biomechanical implications. In the esthetic zone, the decision needs to be made

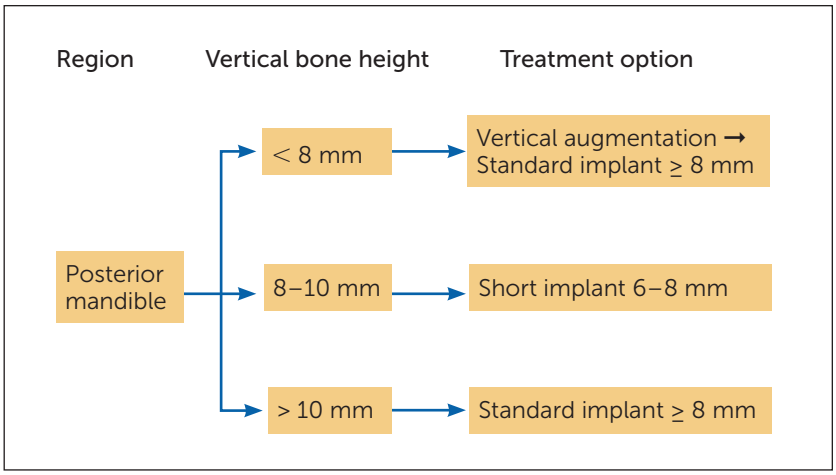

FIG 1-6 Vertical bone height requirements in the posterior mandible.

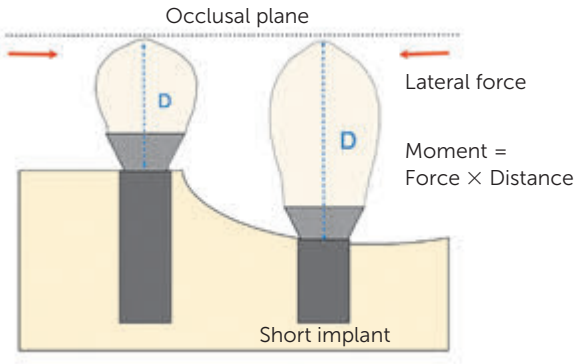

FIG 1-7 Using short implants in an atrophic ridge increases the crown–abutment height space. Placing a short implant into an atrophic ridge will result in greater crown-abutment height (D). Because moment = force × distance, a greater distance (D) will increase the moment or torque on the implant-abutment connection.

regarding whether to reconstruct a vertical bone defect in an attempt to replicate normal anatomy or to replace the missing hard and soft tissue with the prosthesis. As vertical bone augmentation is more technically difficult, a prosthetic solution may provide a more predictable and straightforward approach in some cases. When crown–abutment height space is excessive, the resultant load on the prosthetic connection increases (Fig 1-7). This can result in a greater risk of technical complications such as abutment screw loosening and component fracture. When the crown–abutment height space becomes greater, the implant crowns may be splinted to decrease the risk of mechanical complications. However, systematic reviews have found that marginal bone loss and implant survival do not appear to be influenced by the crown-to-implant ratio.[17–19]

Ridge angulation

In some cases, the angulation of the ridge in the edentulous site may not allow for the ideal implant trajectory. This problem is most often encountered in the atrophic maxilla. As the facial bone resorbs following extraction, the long axis of the ridge can become more tilted facially in line with the palatal contour (Fig 1-8). If the implant is placed in a more vertical orientation, the facial bone may be too thin or the apex may perforate the buccal cortex. This issue may be a more significant problem with single-tooth implants and small-span implant-supported partial dentures in the anterior maxilla. Bone augmentation may be needed to restore the ridge contour and allow for a better implant trajectory. An alternative approach is to place the implant at an angle within the bone and

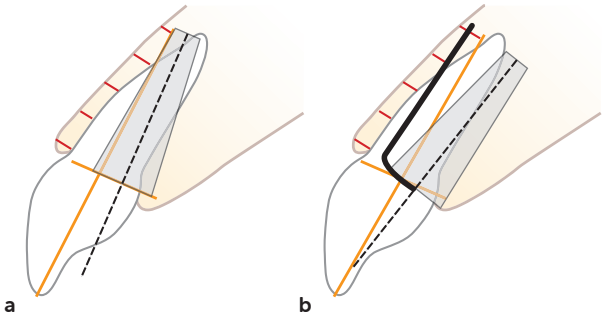

FIG 1-8 Facial bone resorption following tooth loss requires a more facial implant inclination. Note the difference between the position of an implant placed upon extraction of a maxillary incisor *(a)* versus implant placement after extraction and bone remodeling at the expense of the facial *(b, black line* represents facial contour of the resorbed ridge). The implant needs to be inclined more buccally.

use an angulated abutment to alter the path of prosthetic attachment or use an angulated screw channel. Although in the past there was concern regarding off-axis loading of dental implants, more recent studies have found no decrease in implant survival or higher marginal bone loss with tilted implants.[20]

Soft Tissue Thickness

Another important factor for stability of the peri-implant bone is vertical soft tissue thickness. Several studies have suggested that approximately 4.0 mm of supracrestal soft tissue height is required to allow the formation of a biologic seal.[21,22] A more accurate term may be *supracrestal tissue adhesion* due to horizontal fiber orientation around the dental implant.[22] Thin tissue may induce bone remodeling around the implant neck to obtain adequate biologic width.[23–26] When managing a deficient ridge with a thin phenotype, it may be necessary to plan for soft tissue as well as hard tissue augmentation.

The Consequences of Tooth Loss

Insufficient bone for dental implant placement can be a consequence of periodontitis, infection, trauma, pathology, tooth loss, jaw atrophy, congenital absence of teeth, or previous dental implant failure. Following tooth loss, the bundle bone lining the socket is rapidly resorbed. The greatest amount of alveolar bone loss occurs on the facial aspect due to the limited thickness of the buccal cortex compared to the lingual/palatal aspects of the socket walls.[27] The thickness of the facial cortex in the crestal area of teeth in the anterior maxilla has been shown to be thin (< 1 mm) in approximately 90% of patients.[28,29] Sockets that have thin facial bone are prone to more resorption following tooth loss. Although this results in more horizontal resorption, there is also loss of vertical ridge height, which has been reported to be most pronounced on the buccal aspect.[30] A CBCT study found that thin facial wall thickness (< 1 mm) was associated with significant vertical bone resorption, with a median vertical bone loss of 7.5 mm, as compared with thicker socket walls (> 1 mm), which showed vertical bone resorption of only 1.1 mm after 8 weeks of healing.[31] Human studies on alveolar bone resorption following extraction have shown horizontal bone loss of 29% to 63% and vertical bone loss of 11% to 22% after 6 months of healing.[32] These studies demonstrated rapid reductions in the first 3 to 6 months, followed by a gradual reduction in dimensions thereafter, when remodeling of the ridge begins to plateau. However, longitudinal studies have found a continued reduction of the residual ridge in patients wearing soft tissue–borne removable prostheses.[33,34]

Bone resorption following tooth loss can compromise the bone volume for implant placement and may also have a deleterious effect on the implant position. In the maxilla, there is a greater loss of facial bone initially, so the residual ridge loses width and moves in a medial direction. As a consequence, the long axis of the ridge for implant placement tilts more to the facial (see Fig 1-8). With additional resorption, there is a loss of bone height and continued palatal shift of the ridge crest (Fig 1-9a). This can compromise implant positioning as the restorations need to be facial to the ridge crest. In the mandible, the initial loss of facial bone also results in a loss of ridge width as the residual ridge moves in a medial direction. However, with continued atrophy and loss of bone height, the lingual inclination of the mandible leads to a gradual inferior and lateral shift of the ridge crest (see Fig 1-9a). In the sagittal plane, the anterior maxilla

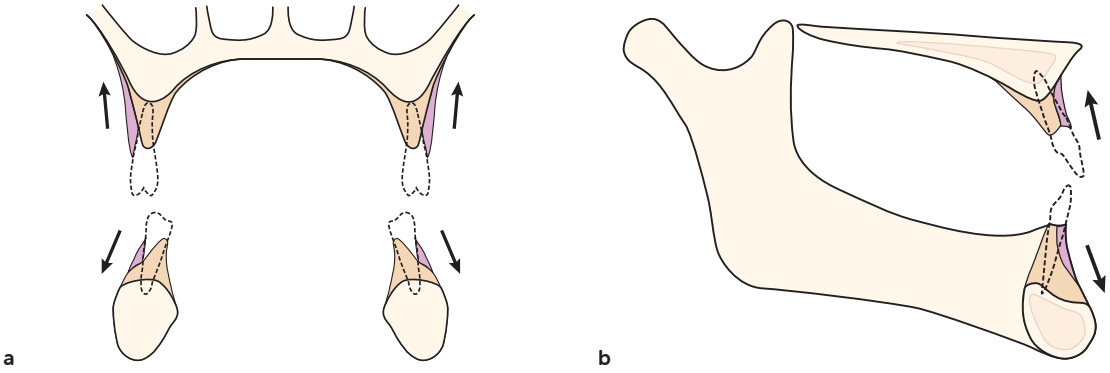

FIG 1-9 *(a)* In the posterior region, the maxilla resorbs in a medial direction. The mandible initially resorbs medially, but with vertical loss it becomes wider. *(b)* The sagittal view shows that the anterior maxilla resorbs in a palatal direction, while the anterior mandible initially resorbs medially, but with vertical loss it moves in a facial direction.

resorbs in a superior and posterior direction while the anterior mandible resorbs in an inferior and anterior direction (Fig 1-9b). In the edentulous patient who has experienced moderate to severe ridge resorption in both the maxilla and mandible, a resultant skeletal Class III relationship occurs along with a prognathic appearance. Such bone atrophy can cause compromised interarch relationships in the vertical, transverse, and sagittal planes, which may complicate dental implant placement from a functional and esthetic perspective.

Bone loss and soft tissue alterations following tooth loss in the anterior maxilla can have a significant impact on the esthetic outcome of implant-supported restorations. To restore ridge contour and provide adequate bone volume for implant placement, bone and soft tissue augmentation is often a prerequisite to achieving a satisfactory esthetic result. These cases can be especially challenging when lip mobility exposes the maxillary gingiva or vertical bone augmentation is needed.

As bone loss following tooth extraction can negatively influence bone volume for implant placement and position, esthetics, and biomechanics, it is prudent to consider measures to maintain alveolar bone. The use of alveolar ridge preservation (ARP) can minimize dimensional changes following tooth extraction to provide adequate bone volume for dental implant placement. Extraction sites treated with socket bone grafts (ARP) have been shown to have significantly less dimensional change both vertically and horizontally when compared with controls not treated with ARP procedures.[35] In conjunction with minimally traumatic tooth extraction, this may reduce the need for subsequent bone augmentation procedures or decrease the amount of bone gain required for future dental implant placement.

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2

THE SCIENCE OF BONE: FORM AND FUNCTION

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Mechanisms of Bone Growth

The pattern of human craniomaxillofacial bone growth occurs as a result of two types of bone formation, the predominant one being intramembranous (or appositional) bone growth.[1] Intramembranous bone growth generally takes place on the surfaces of the maxilla and mandible. When new bone is added on cancellous surfaces, the shape of the skeletal element does not change, but its density does. Bone accrual can also occur on buccal and lingual surfaces, and in these cases, the shape of the skeletal element changes. Appositional bone growth also occurs at midfacial sutures. For example, the premaxillary suture slants downward and backward, so as the suture's mesenchyme proliferates, the entire maxilla is displaced downward and forward.

Growth of the appendicular and axial skeletons, and select parts of the craniomaxillofacial skeleton, occurs via endochondral ossification. For example, the forward and downward growth of the mandible is propelled by endochondral ossification at the cartilage caps of the condyle.[1] Endochondral ossification is also responsible for expansion at the midpalatal suture[2] and at the sagittal suture.[3]

Cells Involved in Bone Formation

Contribution of cranial neural crest and mesoderm to craniomaxillofacial skeleton

In craniomaxillofacial (CMF) skeletogenesis, both intramembranous and endochondral ossification are accomplished by cells that arise from the cranial neural crest (for the maxilla and facial bones as well as the cranium) or cranial mesoderm (for the mandible and hyoid). Regardless of their embryonic origin, these cells are ultimately responsible for differentiating into chondroblasts and osteoblasts. The trigger for this step is not clear but is likely related to mechanical cues in the extracellular environment. Cells initiate differentiation by forming an aggregate, which distinguishes them from surrounding cells.[4]

Osteoblasts and chondroblasts

A process of condensation is associated with the upregulation of transcription factors, including Runx2[5,6] and Osterix.[7] After the aggregate or condensation has formed, cells then initiate differentiation either into chondrocytes, heralding the onset of endochondral ossification, or into osteoblasts, foreshadowing the beginning of intramembranous ossification. In the CMF skeleton, a proteoglycan-rich cartilage intermediate (*red structures* in Fig 2-1a) can be observed emerging from the immature

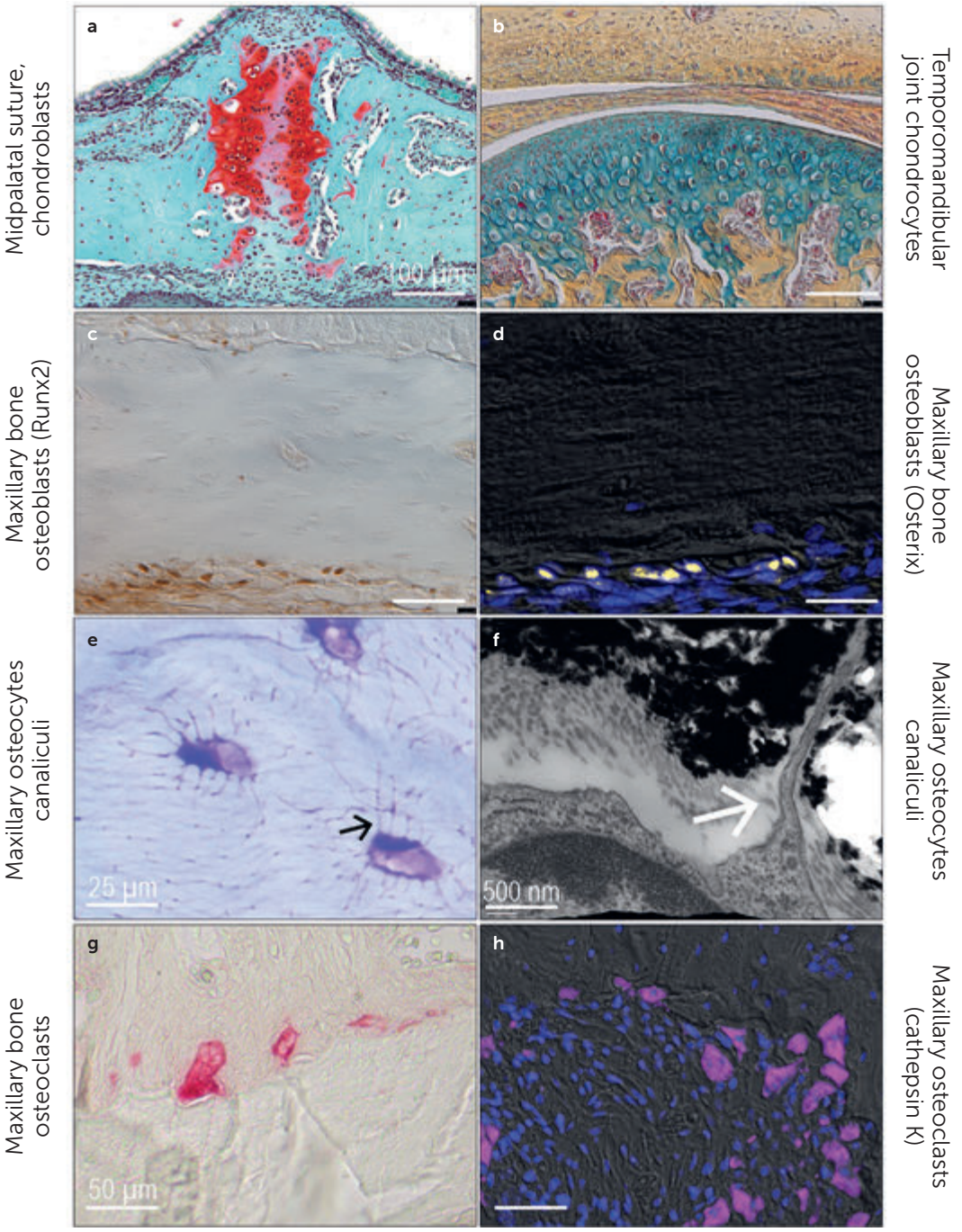

FIG 2-1 Bone development and growth. *(a)* Safranin O/fast green histology depicting appositional growth at the midpalatal suture, where chondroblasts secrete new matrix along existing surfaces, which causes the cartilage to expand and widen. *(b)* Pentachrome histology of the temporomandibular joint, whose articular surface is lined by fibrocartilage. *(c and d)* Immunostaining for the osteogenic transcription factors Runx2 and Osterix, expressed in osteoblasts that line the mineralized matrix of bone. *(e)* Van Gieson histology of mineralized bone matrix, where the dendritic morphology of osteocytes can be observed *(arrow)*. *(f)* Transmission electron microscopy of an osteocyte in its lacuna, extending a dendrite *(arrow)* within one canaliculus. *(g)* Tartrate-resistant acid phosphatase enzymatic reaction staining for multinucleated mature osteoclasts at the bone surface. *(h)* These osteoclasts are also visible in cathepsin K immunostaining. Scale bars = 100 µm *(a to d)*, 25 µm *(e)*, 500 nm *(f)*, and 50 µm *(g and h)*.

midpalatal suture. A persistent hyaline cartilage, which stains blue when using pentachrome histology (Fig 2-1b), can be observed covering the temporomandibular joint surface. In CMF periostea, the co-expression of Runx2 and Osterix signals the osteoblast maturation (Figs 2-1c and 2-1d).

Osteocytes

A subset of osteoblasts become entrapped in the collagenous matrix, and these will become some of the longest-lived cells of the body, ie, osteocytes (Fig 2-1e). Once thought to be quiescent, it is now fully realized that these nonmitotic cells are nonetheless key orchestrators of bone remodeling and mineral metabolism.[8] Osteocytes are connected to one another via dendritic processes that extend into microscopic channels (canaliculi) that penetrate the mineralized matrix (*arrows*, Figs 2-1e and 2-1f). Osteocytes play a critical role as mechanosensors via these processes, sensing not only fluid flow within the canaliculi but also sending larger molecules (receptor activator of nuclear factor kappa-B ligand [RANKL]/osteoprotegerin [OPG], fibroblast growth factor-23 [FGF-23], and sclerostin/Dkk1/Wnt) to other osteocytes and osteoblasts via the periosteocytic fluid.[9] Osteocytes direct bone homeostasis[10] and control the rate of osteoblast proliferation as well as osteoclast maturation and resorbing activity.[11]

Osteoclasts and bone resorption

Resorption occurs at the mineralized surface of bone by osteoclasts and is closely coupled to bone formation. Osteoclasts are specialized multinucleated cells that originate from the fusion of precursor cells of the monocyte/macrophage hematopoietic lineage (Fig 2-1g). When a mature osteoclast attaches to the bone surface, an anchorage mechanism involving actin filaments generates a sealing zone. The sealing zone creates a delimited compartment, and the osteoclast membrane is described as having a "ruffled" border. In the confined area of the sealing zone, the osteoclast secretes acidic hydrogen ions, which dissolve the mineral component of the bone matrix. Once the minerals have been dissolved, the osteoclast then secretes collagenase, cathepsin K, and other hydrolytic enzymes to degrade the organic component of the demineralized bone matrix (Fig 2-1h). The bone side of the sealing zone compartment is described as a "resorption bay," also known as a *Howship lacuna*.

Macrophage colony-stimulating factor (M-CSF) and RANKL are produced by osteoblasts, fibroblasts, and osteocytes and are needed to engage osteoclastic precursors to fuse and share their nuclei to form mature osteoclasts. The regulation of resorption involves OPG, which is also secreted by osteoblasts, as a decoy that binds to RANKL, thus inhibiting its ability to bind to its receptor, RANK; in this way, osteoclast maturation and bone resorption are blocked.[12]

Tissue Compartments of Bone

The periosteum

Since the first scientific demonstration of the osteogenic capacity of the periosteum by Duhamel du Monceau in 1739, when he performed the "silver ring" experiment,[13] this tissue has been under continual investigation, with the goal being to harness its bone-forming potential. Most assumptions about the periosteum's contribution to bone healing are extrapolated from experimental models of skeletal repair in long bones. For example, in several surgical orthopedic techniques, periosteal grafts have been used to treat bone fractures.[14] Periosteal grafts, however, are not employed in oral surgery. Because of their histologic similarities, it is assumed that the periosteum of long bones and craniofacial bones (Fig 2-2a) is analogous; however, this conjecture is only partially accurate. For example, in the CMF skeleton, an outer fibrous periostin-positive layer contains nerves and blood vessels (Fig 2-2b) and encases an inner (cambium) layer composed of Runx2-positive skeletal stem and osteoprogenitor cells (Fig 2-2c). Alizarin red/calcein green dye incorporation into calcifying matrix demonstrates that the CMF periosteum is the primary site of new bone formation in the CMF skeleton (Fig 2-2d).

A number of unique features distinguish the appendicular skeleton and its associated periosteum from the CMF skeleton and its periosteum. Specifically, the physical and cellular characteristics of periostea differ with anatomical location.[15] For example, the tibial periosteum is loosely attached to overlying muscle, while the maxillary periosteum is tightly adherent to overlying connective tissue.[16] Molecular, cellular, and genetic studies demonstrate that long bone periostea are more osteogenic than flat bone

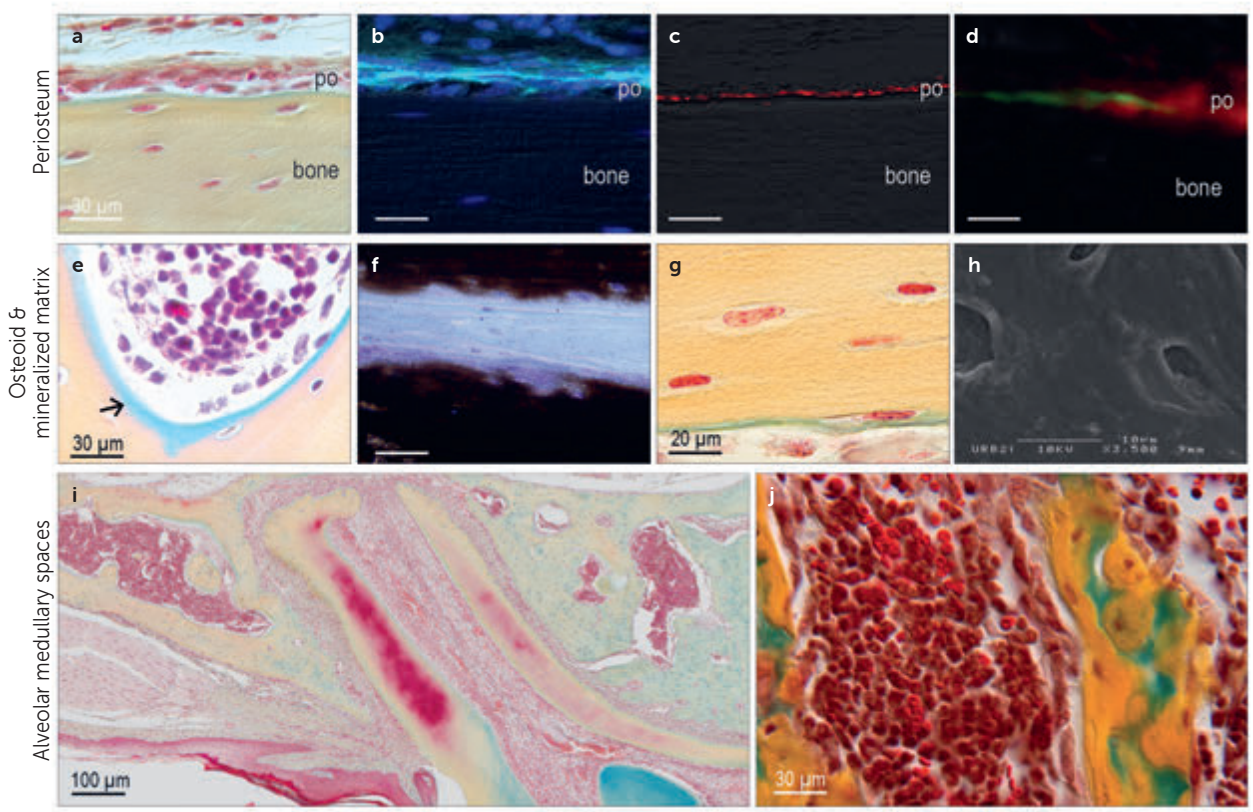

FIG 2-2 Tissue composition of bone as an organ. *(a)* Pentachrome histology depicting the periosteum membrane covering the outer surface of bone. *(b)* Periostin immunostaining showing the fibrous component of periosteum. *(c)* Runx2 immunostaining showing the layer of osteogenic cells in the periosteum. *(d)* Calcein (green)/alizarin red dye incorporation at the periosteum, revealing layers of incremental mineralization/calcification. *(e)* Pentachrome histology depicting unmineralized bone matrix *(blue, arrow)*. *(f)* This unmineralized bone matrix is also visible in toluidine blue staining, while von Kossa reaction stains for phosphate minerals/mineralized matrix. *(g)* Pentachrome histology depicting osteocytes in their lacunae within the mineralized matrix. *(h)* Scanning electron microscopy (SEM) reveals the network of interconnections between osteocytes' lacunae. *(i)* Pentachrome histology of alveolar bone harboring a dental root and large medullary spaces in the diploë. *(j)* Higher magnification of an alveolar medullary space filled with stromal tissue, blood cells, and bone trabeculae. po, periosteum. Scale bars = 30 µm *(a to f, j)*, 20 µm *(g)*, 10 µm *(h)*, and 100 µm *(i)*.

periostea,[17] but craniofacial periostea enclose cells with greater multipotency.[15]

In addition, CMF and appendicular periostea are differentially affected by anabolic agents such as bisphosphonates.[18–20] Leucht et al[15] used a lineage labeling strategy to demonstrate that craniofacial and long bone periostea contribute differently to bone repair: In long bones, periosteal stem/progenitor cells are derived from mesoderm, whereas in CMF bones, the periosteal stem/progenitor populations are derived from the neural crests.[15]

Stimulation of long bone periostea induces an osteogenic, regenerative response,[21] whereas the maxillary periosteum has a delayed, attenuated response to the same injury. Mouraret et al showed in 2014 that elevation of the appendicular periosteum through a tunneling procedure triggers an osteogenic response, whereas in the maxillary bone, tenting and space maintenance are necessary to achieve a similar vertical bone augmentation.[22]

The mineralized matrix of bone

Mature osteoblasts produce an abundant collagen-rich extracellular matrix (collagen type 1, for bone), as well as noncollagenous proteins (eg, osteopontin and bone sialoprotein), that play critical roles in directing the mineral deposition in the collagen matrix (along with the

local concentration of calcium and the ratio of phosphate/pyrophosphate). When the bone matrix is still unmineralized, it is referred to as *osteoid* (*arrow*, Fig 2-2e); as the osteoid accumulates carbonate-substituted hydroxyapatite minerals that crystalize within, on top, and between collagen fibrils, it becomes mature bone matrix and stains for von Kossa (Fig 2-2f). The mature bone matrix encases osteocytes, whose nuclei stain red in a pentachrome histology (Fig 2-2g) and whose lacunae contribute to the porosity of lamellar bone (Fig 2-2h).

The medullary cavity in CMF bones

In most CMF bones, the outer and inner dense cortical plates are separated by diploë (Fig 2-2i). This interior structure is composed of trabecular/spongy/cancellous bone without any continuous medullary cavity, as opposed to the contiguous marrow cavity in long bones. In the core of CMF bones, some islets of bone marrow are present, interwoven with cancellous bone trabeculae (Fig 2-2j). The marrow itself consists of hematopoietic cells, lymphoid tissue, stromal cells, and adipose cells surrounded by blood vessels. The bone marrow produces red and white blood cells and platelets, and it also harbors a population of skeletal and hematopoietic stem cells.

In some CMF bones, including the maxillary bones, diploë is absent, and the inner and outer layers of the bone are separated by a large air cavity (eg, the maxillary sinus) that extends through a process called *pneumatization*. This unique feature lightens the weight of the skull, and it is a shared feature of bones from birds and dinosaurs.[23]

The Structure of Bone

Bone is organized in a hierarchical manner, extending from its macroscale arrangement to its nanoscale structure. As recently confirmed with 3D imaging technologies,[24] the curved and spiral structure of bone is evident even in its nano- and macro-architecture. First observed as a ubiquitous pattern in nature,[25] the spiral pattern in biologic objects was hypothesized to confer specific adaptive functions.[26] In skeletal tissues, the spiraled mineralized extracellular matrix consists of water, carbonate-substituted hydroxyapatite crystals, and an organic component made of type 1 collagen fibrils, noncollagenous proteins, and small proteoglycans. It is the spatial arrangement of these constituents that render skeletal elements to be simultaneously pliable, strong, and lightweight. While this blueprint for skeletal architecture is partially contained within the cells' genome, there is also an epigenetic component: Skeletal tissues are responsive to mechanical forces, remodeling in reaction to both increased and decreased loads.[27] The balance between the stiffness and toughness allows bone to withstand a wide range of masticatory forces and movement against gravitational forces and protects against traumatic mechanical impact, all at a reasonable metabolic cost.

At a macroscopic level, bone extracellular matrix is organized in layers (as lamellae) and in an interconnected network (as trabeculae; Fig 2-3a). Bone that is organized in lamellae, ie, compact (cortical) bone, has limited porosity; conversely, trabecular (cancellous) bone exhibits a greater degree of porosity (Figs 2-3b and 2-3c; see Currey[28]). Typically, there is a morphologic distinction between compact (see Fig 2-3c) and cancellous bone (Fig 2-3d), and this organization is in part regulated by the rate at which osteoblasts secrete collagen. For example, osteoblasts whose rate of collagen secretion is slower give rise to lamellar bone,[12] whereas osteoblasts whose rate of collagen secretion is higher give rise to woven bone.[29,30] In the maxillary and mandibular alveolar processes, bone with a porous, woven macrostructure is called *bundle bone*, which is contained within bone that has a compact, lamellar macrostructure, ie, the buccal and lingual/palatal plates (shown in 2D and 3D in Figs 2-3e and 2-3f).

In most parts of the skeleton, woven bone is viewed as a transient tissue that is sooner or later resorbed and replaced by lamellar bone (reviewed in Shapiro and Wu[31]), but in regions of the CMF complex, woven bone persists[32]—that is, at least until teeth are lost. Then, concomitant with the edentulous state, woven porous bone is replaced by compact lamellar bone.[33] This observation clearly implicates mechanical loading as one factor influencing the macrostructure of bone in the jaws.

Mechanical forces shaping the structure of the skeleton

The rate of bone remodeling in the jaws is very high, and unlike in other bones, it remains elevated even after adolescence.[34] This high turnover in the maxilla and mandible is thought to be triggered by the constant need for repair of the microfractures inflicted by mastication

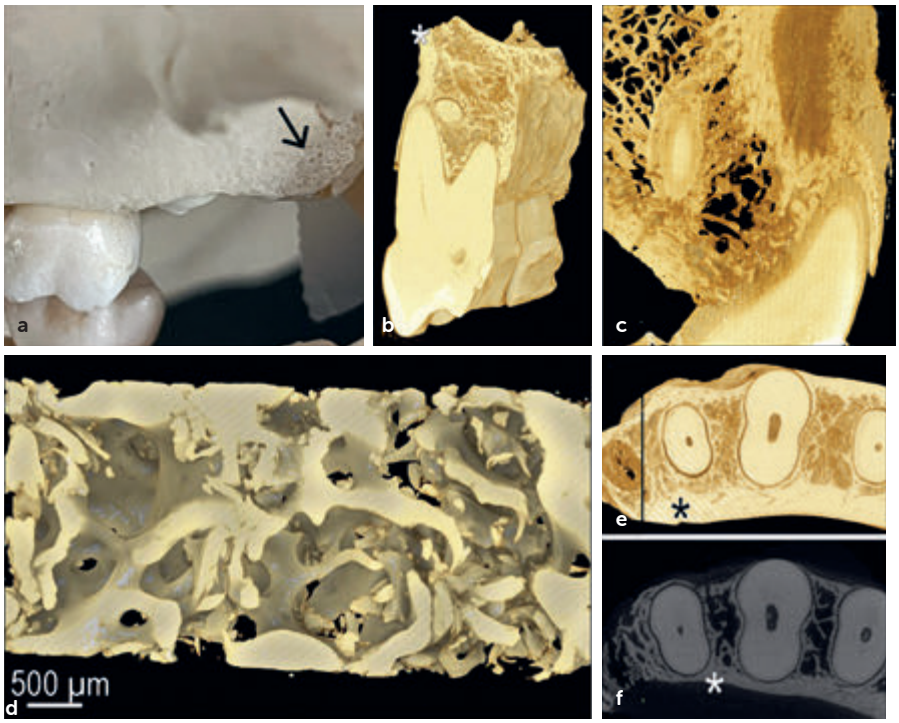

FIG 2-3 Alveolar bone structure. *(a)* Micrograph of trabecular bone *(arrow)* at the maxillary tuberosity on a dry skull. *(b to d)* Microscanning tomography 3D volume rendering of alveolar bone with dense cortical plates (asterisk in *b*) and trabecular organization of the inner diploë *(c)*, composed of cancellous bone *(d)*. *(e and f)* The dual structure of alveolar bone is also visible in the axial plane.

and occlusal loading.[35] Although the maxilla and mandible bear similar masticatory loads, the maxilla mostly transfers the strain and stress to the upper cranium; the mandible, in contrast, stands alone and absorbs all the loads. This distinctive feature impacts the morphology of the two bones: the mandible is stronger and stiffer than the maxilla. Anatomically, the maxilla has the typical structure of a bone that endures compressive loads, such as the vertebral body; it is composed of a dense network of trabeculae contained within thin cortical plates. On the other hand, the mandible resembles the shaft of a long bone, with thick cortical plates and trabeculae oriented along the bending and torsion loads.[36,37] Clinically, when tori are present in the mandible, the biggest torus develops where bending and torsion strains are maximal, typically on the side where chewing is predominant.

Masticatory loading is associated with dynamic bone remodeling,[38] and when masticatory forces are suspended (either by removing teeth or in an experimental situation, shifting to a liquid or soft diet), bone resorption predominates over bone formation, with the effect of a net loss in bone volume.[39,40] Conversely, increasing masticatory loading triggers a transient increase in bone formation and a decrease in bone resorption, resulting in a net gain of bone volume.[41] The gain in bone volume serves to reduce stresses and strains in bone back to a baseline level. This response of bone to different mechanical conditions is described by Frost in his mechanostat theory (reviewed in Frost[42]). When teeth are lost, the continuity of the jaw bones is disrupted, and the same masticatory forces can become detrimental.[43]

Transfer of periodontal mechanical loads to bone via the periodontal ligament

Functionally, the tooth-bone periodontal interface is a mechanical device, where the tooth serves as a tool to manipulate and break down food. The periodontal interface comprises two hard materials: *(1)* the bundle alveolar bone layering the bony socket of the tooth, and *(2)* the acellular cementum layering the parts of the dental root that are involved in tooth anchorage.[44] These hard tissues are separated by a fibrous periodontal ligament that serves two critical functions. The short-term function is to transmit occlusal loads (tension and pressure) to the supporting bone, while simultaneously providing protection against sudden impacts, acting as a kind of shock absorber. This short-term masticatory function is permitted by the combination of rigidity and elasticity within

the periodontium, thus mitigating concentrated, acute stresses on the surrounding bone.[41] The longer-term function of the periodontal ligament is to continually adapt to changes in loading by furnishing the cellular, sensory, and vascular elements required for tooth positioning (by natural drifting or with orthodontic treatment). This long-term positioning function is permitted by the combination of pliability and plasticity of the periodontium. In homeostasis, the periodontal ligament exhibits very low turnover,[40] but upon injury, it is capable of rapid repair and adaptation to a new mechanical condition.[39]

Transfer of peri-implant mechanical loads directly to bone

The dental implant–bone interface differs significantly from the tooth root–bone interface, from both biologic and mechanical points of view. An implant is considered osseointegrated if, under functional loading, it remains virtually immobile within the bone. There is no ligament between the implant and neighboring mineralized tissue (ie, the implant is directly connected to the bone), and this causes alterations in stress and strain distribution in the surrounding bone.[45,46] The type, frequency, and magnitude of the load, coupled with implant geometry, all have an impact on the mechanical load that is transferred from the dental implant to the surrounding bone.[47,48]

Growth and Atrophy of Bone

Maxillary and mandibular growth

There is a strong correlation between the timing, velocity, and amount of CMF bone growth with somatic (body) maturation, with one exception: Growth of the neurocranium starts soon after birth as a result of rapid perinatal expansion of the brain and reaches its adult size long before the remainder of the craniofacial skeleton. Consequently, growth and morphogenesis of each unit of the CMF skeleton should be evaluated separately. Among the units, the mandible most closely tracks with somatic bone growth.[49]

The maxillae originate as paired structures that ultimately give rise to the maxillary bones (highlighted in *blue* in Fig 2-4a); the maxilla will support the canines, premolars, and molars. The midline frontonasal prominence (highlighted in *red* in Fig 2-4a) eventually gives rise to the premaxilla, which supports the incisors.[50–52] The premaxillary and maxillary prominences, along with the lateral nasal prominences (highlighted in *yellow* in Fig 2-4a), fuse early in human development, at about the 9th week in utero (see *arrows* in Figs 2-4a to 2-4c; schematized in Fig 2-4d). The suture between the premaxilla and the maxilla proper persists into adulthood in the region adjacent to the incisive canal.

Growth of the facial prominences is not achieved in a uniform spatial manner; rather, it starts in the transverse plane, followed by the sagittal plane, and finally the vertical plane. While transverse and sagittal growth rates remain virtually stable after 24 years of age, vertical growth of the maxilla continues at a slow rate. This is due to a downward displacement of the maxilla away from the cranium as it is "pushed" by the increase in size of the eyes/orbits, the nasal cavity, and the maxillary sinuses.

As the prominences grow in size, mesenchymal cells form condensations in predetermined locations. In the maxilla, these condensations initiate intramembranous ossification, and the separate condensations corresponding to the maxilla, premaxilla, and mandible can be visualized using alizarin red/alcian blue whole-mount staining in rodent embryos (Figs 2-4e to 2-4g). The condensations initially appear as separate islands but over time begin to coalesce and give rise to bone whose shape heralds their final morphology (see Fig 2-4g).

The mandible is derived from pairs of condensations that fuse in the midline to create the symphysis, thus yielding a single, continuous prominence by the first year of life (highlighted in *green* in Figs 2-4a to 2-4d). The mandible provides insertion surfaces for the muscles of mastication and supports the mandibular dentition. These two functions are performed by the basic parts of the mandible, which include the corpus (body) and the ascending ramus (branch). The mandible follows a similar chronology as the maxilla but a different spatial pattern. For example, the amount of sagittal growth of the mandible is greater than in the maxilla during puberty. This is due to endochondral growth at the condyle and the remodeling of the ramus to accommodate the eruption of the second and third molars. Impacted mandibular third molars are thought to be a consequence of a lack of sagittal growth.

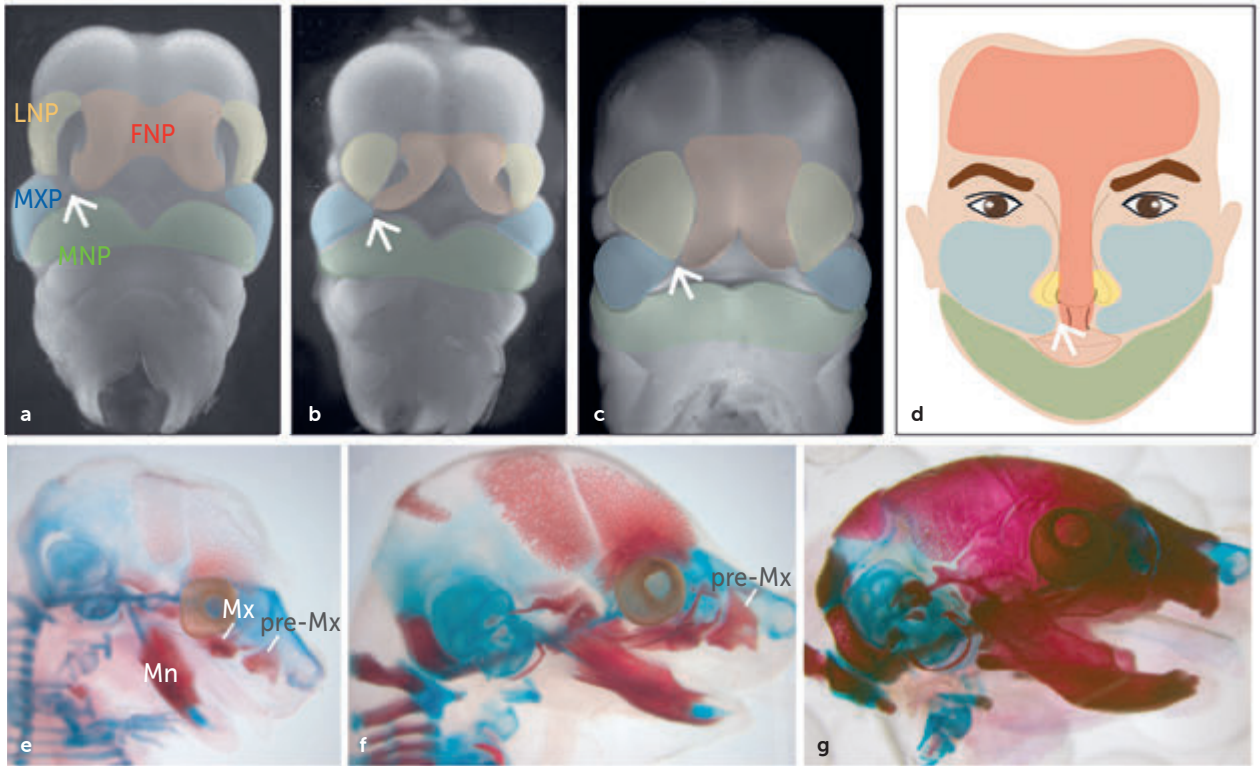

FIG 2-4 Embryonic development of the maxillofacial skeleton. *(a to c)* SEM of an embryo showing condensations of cells in prominences from an early stage *(a)*, an intermediate stage *(b)*, and a later stage *(c)*. *(d)* Eventually, the sequence of growths and merges give rise to the adult maxillofacial skeleton. *Arrow* shown for reference. *(e to g)* Whole-mount skeletal staining of mouse embryo using alcian blue and alizarin red to identify cartilage and bone, respectively, at early *(e)*, intermediate *(f)*, and late *(g)* stages of fetal development. FNP, frontonasal prominence; MXP, maxillary prominence; LNP, lateral nasal prominence; MNP, mandibular prominence; Mx, maxilla; Mn, mandible; pre-Mx, premaxilla.

Alveolar bone growth around teeth versus implants

Teeth erupt throughout life and bring along with them the surrounding alveolar bone. In cases of ankylosed teeth in young patients—or dental implants placed in any patient—localized alveolar bone growth does not occur. Around ankylosed teeth, this can result in infrapositioned (submerged) molars and incisors. This ankylosis-related malocclusion complicates subsequent prosthetic restoration and predisposes the ankylosed dentition to periodontal complications. In the esthetic region (ie, around maxillary incisors), no solution is considered optimal because extraction of the ankylosed tooth leaves behind a thin alveolar ridge, which is difficult to reconcile with bone grafting.[53,54] Surgical luxation of the ankylosed tooth is largely unsatisfactory because the tooth ultimately ankyloses again,[55] and surgical distraction of the ankylosed tooth and surrounding bone is oftentimes unstable and unpredictable, leaving behind a damaged alveolar ridge.[56]

Dental implants, like ankylosed teeth, do not passively erupt, and consequently, there is no physiologic growth of the alveolar ridge. In the case of implants, this constrained vertical growth of alveolar bone can lead to unesthetic and nonfunctional situations.[57] Coupled with the natural continuous mesial drifting of teeth and vertical growth of the surrounding bone, a relative infraocclusion or labioversion of the implant can occur, especially in patients with "long face" phenotypes.[58]

Disuse and postextraction atrophy of the alveolar ridge

The alveolar bone, its bundle bone component, and the tooth itself form a functional unit. Each unit is entirely

dependent on the presence of the tooth, as alveolar bone forms with its eruption and regresses if the tooth is extracted. Although osteoporosis[59,60] and aging[61] impact alveolar bone height, it is the loss of teeth that most significantly impacts alveolar bone resorption.[59,62] Regardless of location, tooth extraction is rapidly followed by loss of horizontal and vertical ridge dimensions. For example, 3 months after extraction, the horizontal dimension of the ridge is reduced by 30%, most pronounced at the buccal aspect, thus shifting the ridge toward the palatal/lingual aspect.[63] One year after extraction, the buccal bone continues to recede to a point where it is located below the lingual/palatal crest.[63]

The reason for rapid alveolar ridge resorption following tooth extraction is not entirely clear. A commonly employed explanation for such a radical tissue loss is disuse atrophy, that is, the removal of a tooth cancels occlusal loading and strain in the bone.[64] It must be pointed out, however, that the jaw is still in function, and loading still occurs on surrounding teeth after extraction of a single tooth.

A study conducted in dogs argues for a disuse atrophy theory to explain alveolar ridge resorption following tooth extraction. Here, the investigators suggested that once removed of its function by tooth extraction, the bundle bone that previously surrounded the tooth undergoes resorption; because the buccal wall is largely composed of bundle bone, the subsequent dimensional change is significant.[65] While this is a reasonable explanation for the loss in alveolar ridge height observed after tooth removal, it does not explain why the same nonfunctional bundle bone simultaneously and directly promotes rapid new bone formation within the socket itself.[66–68]

Relationship between tooth extraction, alveolar ridge resorption, and socket healing

The clinical literature has clearly shown that socket healing and ridge resorption are related, but precisely how the bony filling of the extraction socket curtails the erosion of the alveolar ridge is not fully understood[69–71] (reviewed in MacBeth et al[72]). In part, this is because most clinical studies that assess alveolar ridge dimensional changes (eg, Pelegrine et al[73] and Camargo et al[74]) rarely report on the extent of bony fill in the extraction socket. Nonetheless, a variety of strategies have been tested for their ability to accelerate socket repair with the hopes that this will limit the extent of alveolar ridge resorption. These strategies include autogenous bone grafting,[73] allografting,[75–77] delivery of bone morphogenetic protein 2,[78] platelet-rich fibrin,[79] and more recently, the immune modulator Maresin 1.[80] Most of these strategies show some improvement in curtailing ridge resorption (reviewed in Avila Ortiz et al[76]; only one, however, also evaluated socket repair[80]). This lack of comparative data makes it difficult to establish a cause-and-effect relationship between socket repair and ridge resorption; nevertheless, there is a general sense that if the socket repairs faster, then ridge resorption will be slowed down.

In a rodent preclinical model, socket fill and ridge resorption were both monitored simultaneously. Arioka et al found that the apical movement of the alveolar ridge proceeded until it reached the level of the bony fill in the socket; thereafter, the rate of ridge resorption slowed considerably.[59] These indirect data align with clinical observations that the most rapid period of alveolar ridge resorption occurs within the first 50 days after tooth extraction,[63,81] when the socket is still undergoing repair.[67,68]

Effects of immediate postextraction implant placement on alveolar bone height

When an implant is inserted immediately after tooth extraction, it was previously presumed to counteract ridge resorption. However, Botticelli et al and Araujo et al showed that, to some extent following tooth extraction, the alveolar process will atrophy in response to altered functional demands and that an implant cannot substitute for the tooth in terms of preservation of alveolar bone height.[65,82,83]

Incomplete Bone Repair Versus Bone Regeneration

Limited or "ad integrum" wound healing

When an organ is wounded, evolution has yielded two refined mechanisms to recover from injury: repair and regeneration. Repair is the restoration of tissue continuity, but not necessarily by the same cell type and tissue that existed prior to the injury. Regeneration, on the other

hand, fully restores both architecture and function of the injured tissues to a state that is indistinguishable from the pre-injury wound site.

Bone repair abilities

The vast majority of soft tissues heal by forming a scar tissue, which patches the wounded site but forfeits the original function of the injured organ. Soft tissues typically repair by a phenomenon called *fibrosis*, in which damaged tissues are invaded by fibroblasts that form a collagenous scar. In contrast, bone tissue bears some regenerative potential. To some extent, bone is capable of recovering from a wound to a state that is biologically and biomechanically indistinguishable from that derived from embryogenesis. The continuous process of remodeling helps integrate the newly formed bone into mature bone. These unique features of bone healing are limited, however, either by the amount of tissue that needs to be regenerated (ie, critical-sized defects) or by the location of the injured bone (ie, extrabony/vertical defects that are outside of the skeletal envelope).

In the typical fracture healing model, a series of four to six overlapping steps occur. Starting with the formation of a blood clot at the injury site, the hematoma harbors pericytes and mesenchymal cells that proliferate, differentiate, and eventually secrete a fibrotic granulation tissue. The granulation tissue becomes a provisional matrix in intramembranous bones, while in long bones, the granulation tissue turns into a cartilaginous callus. The provisional matrix (or the callus of long bones) is then rapidly mineralized, forming woven bone, which later undergoes remodeling. The processes orchestrating the biology and biomechanics of bone healing remain unelucidated for the most part. Molecular signals are as for now investigated in a reductionist manner (ie, separately and independently) although they most likely act synergistically, mimicking to some unknown extent the processes of bone embryology.

Biology underlying current regenerative therapeutic strategies

In cases where the endogenous regenerative potential is limited, a series of approaches have been developed to enhance new bone formation. These approaches fall into two general categories, involving either bone replacement grafts (autogenous, allogeneic, xenogeneic, and alloplastic) or biologic factors (growth factors, enamel matrix derivatives, and platelet-rich fibrin matrix)—or combinations of the two. Barrier membranes (resorbable or nonresorbable) have been historically considered for regenerative treatments, but their mechanism of action is solely to exclude epithelia, coupled with the fact that the material is inert and does not contribute directly to tissue regeneration. Although these biologic and physical strategies have augmented atrophic edentulous ridges and enabled implant placement, they remain sensitive to multiple factors that are related to the patient, the defect anatomy, the clinician's experience, and the procedure itself.

For example, tooth extraction typically leaves behind an osseous defect that at present can only be treated by bone grafting. The clinical use of bone grafts is covered elsewhere in this book; here, we discuss the mechanisms by which bone grafts contribute—or not—to restoration/preservation of the alveolar ridge.

In general, when the bone graft is transplanted into a skeletal defect, a critical first step is engraftment and survival of the graft.[84] This presupposes that the graft contains viable cells, which is only the case in autogenous bone grafts that are carefully managed after harvesting.[85] Allogeneic (cadaveric) and xenogeneic (from other species) grafts are devoid of viable cells; consequently, this step of engraftment and survival is not applicable.

Next, surviving cells must begin to express osteogenic proteins and then differentiate into osteoblasts that secrete a mineralized matrix and contribute directly to bone repair.[86] In the case of allografts and xenografts, the cells that populate the scaffold arise from tissues adjacent to the graft (ie, the periosteum). This step is rate-limiting in bone grafting because both cell migration and cell differentiation are passive processes.[87,88]

All of these steps occur when the graft is harvested from a young patient. When the graft is harvested from an older patient, osteogenic gene expression of engrafted cells is significantly reduced.[89] All subsequent steps, where cells differentiate into osteoblasts and secrete a mineralized matrix to heal the defect, are also reduced if the donor is elderly.[89] The cause for this age-related decline in osteogenic differentiation appears to be associated with a decline in endogenous Wnt signaling.[84,86,90–92]

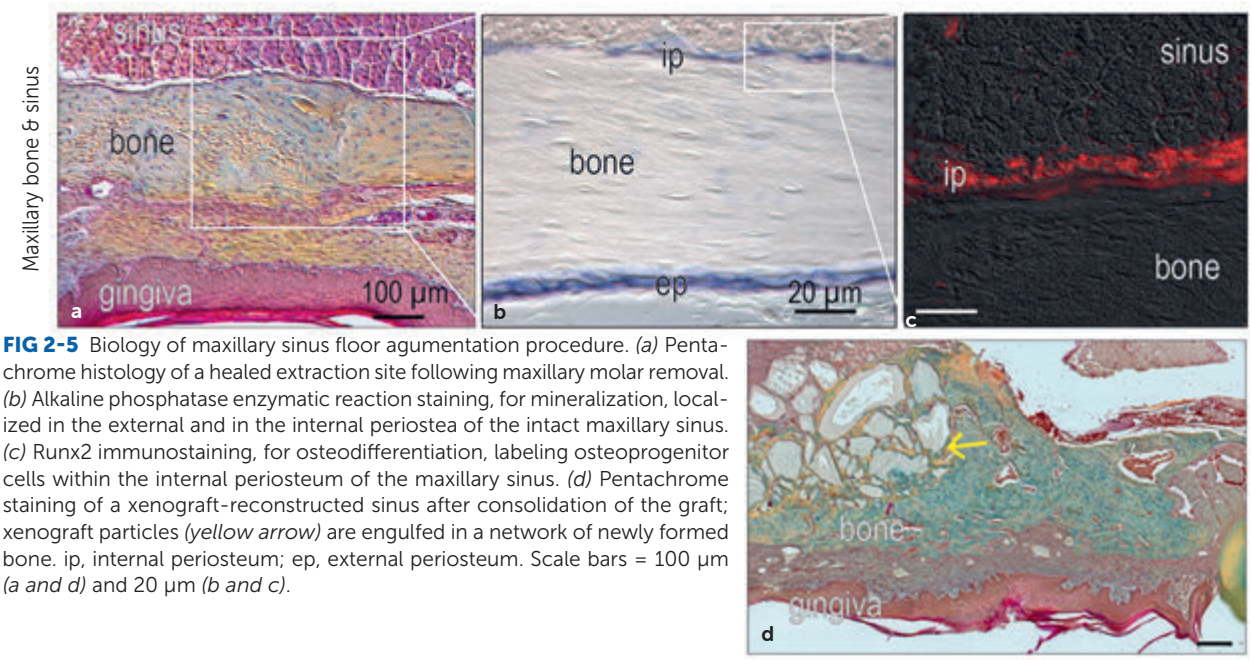

FIG 2-5 Biology of maxillary sinus floor augmentation procedure. *(a)* Pentachrome histology of a healed extraction site following maxillary molar removal. *(b)* Alkaline phosphatase enzymatic reaction staining, for mineralization, localized in the external and in the internal periostea of the intact maxillary sinus. *(c)* Runx2 immunostaining, for osteodifferentiation, labeling osteoprogenitor cells within the internal periosteum of the maxillary sinus. *(d)* Pentachrome staining of a xenograft-reconstructed sinus after consolidation of the graft; xenograft particles *(yellow arrow)* are engulfed in a network of newly formed bone. ip, internal periosteum; ep, external periosteum. Scale bars = 100 µm *(a and d)* and 20 µm *(b and c)*.

Indirect evidence also supports that when Wnt signaling is reduced, because of elevated sclerostin, the result is osteoporotic bone.[93,94]

Allogeneic and xenogeneic bone grafts do not suffer from an age-related decline in efficacy, but they are complicated by the fact that there is a documented age-related deterioration in the number and/or function of stem/osteoprogenitor cells in the host.[95–97] As previously shown (see Figs 2-1 and 2-2), osteoprogenitor cells reside in the periosteum, and this is the site of new bone formation, as shown by alkaline phosphatase activity (Figs 2-5a and 2-5b). When an allograft is placed, for example, onto the osseous floor of the maxillary sinus, then Runx2-positive osteoprogenitor cells are activated (Fig 2-5c) and eventually encase the xenograft with new bone (Fig 2-5d). Some data suggest that patients with osteoporosis[98] and osteonecrosis have fewer[99] and/or less active[100] osteoprogenitor cells compared to healthy control groups (reviewed in Hernigou et al[101]). With this age-related decline in bone-forming capacity, and the fact that they are devoid of pro-osteogenic proteins, allografts and xenografts are slower to consolidate relative to young healthy patients.[102,103] This delayed graft consolidation contributes to greater variability in clinical outcomes when allografts are used.[104]

Osseointegration: When Bone Repair Incorporates a Foreign Body

Functional ankylosis

The surgical placement of an implant consists of accessing the alveolar bone, where an osteotomy is drilled through the outer cortical layer and the diploë. Implant placement follows osteotomy drilling. Providing that a sufficient amount of mechanical stability is obtained at the time of insertion (ie, primary stability), osseointegration can ensue.

Primary stability is the result of the misfit established between the diameters of the osteotomy and the implant. The misfit enables the insertion of the implant's thread tips within the bony walls of the osteotomy canal, thus creating mechanical retention. When the misfit is excessive (ie, the implant diameter is significantly wider than the osteotomy), however, it generates excessively high strains in the peri-implant bone, causing microfractures that lead to osteocyte apoptosis; the net result is osseous destruction followed by bone resorption and early implant failure.[105] In contrast, when the misfit is insufficient, any load placed results in mobility of the implant and excessive strains in the interfacial blood clot between

the implant and surrounding bone. These high strains prevent osteogenic differentiation of progenitor cells and eventually generate early implant failure with fibrous tissue encapsulation of the implant.[106]

Essentially, osseointegration occurs in the "void" of the wells located between the tips of the threads that are inserted in bone. Following surgery, the wells initially fill with an osseous coagulum (ie, blood clot and surgical bone "debris"), which undergo the same differentiation steps as observed in bone fracture healing but in an intramembranous fashion (ie, without the use of a cartilage template).[107]

The osseous coagulum resulting from the drilling of living bone is gradually resorbed and replaced with granulation tissue. The osteotomy walls of the diploë provide cellular components for the formation of new blood vessels and the colonization of leukocytes and mesenchymal cells. The granulation tissue is replaced with collagenous tissue (provisional matrix) that is filled with noncollagenous proteins. These proteins mature until they trigger and direct mineralization of the extracellular matrix. The osteoid becomes mineralized by the nucleation and growth of mineral crystals. During the early post-implantation period, immature woven bone is rapidly formed, and tough mineralized collagen interweaves with the threads of the screw-shaped implant and chemically attaches to the metal surface by direct bonding between calcium and titanium atoms.[108] The immature woven bone located in the wells between the threads, as well as the mature bone harboring the thread tips, both will be remodeled. Eventually, these two bony compartments will be lamellar, displaying reversion and cement lines, and will be indistinguishable from one another. The then-homogenous, mature alveolar bone that fully anchors the dental implant provides secondary stability.

Mucointegration: Generating mucosal attachment

Dental roots are sealed off from the septic oral cavity by their junctional epithelium. This key component of the supracrestal tissue attachment (biologic width) directly develops from the reduced enamel epithelium, as the tooth erupts in the oral cavity. The enamel epithelium is part of the enamel organ and is secreted by ameloblasts in the early development of the tooth buds. Ameloblasts, however, degenerate as the junctional epithelium proliferates; therefore, if the junctional epithelium is lost after tooth extraction, it cannot be regenerated. Instead, when a tooth is extracted, its junctional epithelium is replaced by oral epithelium, which differs in many respects. Unlike the junctional epithelium, the oral epithelium is keratinized, has lower mitotic activity, and has no expression of laminin 5, save for cells adjacent to the basal lamina.[109]

The mucosal interface of an implant placed in a healed site derives solely from this oral epithelium. Although oral epithelium is capable of providing some degree of epithelial adhesion to the abutment surface,[110,111] its subepithelial connective fibers do not anchor in the metal surface, so the peri-implant mucosal seal inherently lacks some unique protective features of the dental supracrestal tissue. The maintenance of the peri-implant epithelium is fragile and all the more critical for preventing the initiation of peri-implant inflammatory diseases (eg, peri-implantitis).[112–118]

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