Chapter 83. Craniofacial Development
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OVERVIEW
In this chapter, we provide a brief overview of human craniofacial development. The head is one of the first structures to arise in the embryo, with morphologically distinct primordia apparent by the end of the third week of pregnancy. Here we describe key events in the development of the head and its major compartments, focusing on skeletal structures. We also consider the major congenital malformations arising from defects in head formation.

EARLY EMBRYOGENESIS
The embryo develops from conception into a trilayered disc of cells. These germ layers are called the ectoderm, mesoderm, and endoderm. Organ systems begin to form as these layers fold to create two tubes. The neural ectoderm folds dorsally to become the neural tube. The anterior end of the neural tube expands to form the brain rudiments: the prosencephalon, mesencephalon, and rhombencephalon (Fig. 1A). The endoderm folds ventrally to create the gut tube. The anterior end is the foregut, which gives rise to the majority of the oral cavity and pharynx. The brain and foregut of the early embryo are the centers around which the head is formed, and each is a source of signals that direct development of craniofacial tissues.

Many tissues of the head are formed from neural crest cells (NCCs), a pluripotential migratory cell type in the midgestation embryo. During neurulation, NCCs arise from the converging crests of the neural folds as they fuse dorsally to form the neural tube. The NCCs undergo an epithelial-to-mesenchymal transition, delaminate, and migrate through the mesoderm to populate various structures of the embryo (Fig. 1A). Cranial NCCs migrate to the head to eventually form the bulk of the facial tissues, many bones of the skull, the dental papillae of the teeth, and much of the muscular, nervous, and vascular tissue of the head and neck.

The mesoderm also contributes substantially to the early head. Paraxial mesoderm segments and condenses into somites, just lateral to the neural folds. As the trunk somites condense further, they form a series of segmented units (somites). The first seven cranial somitomeres never fully condense to form definitive somites. In all cases, these units each consist of three compartments: dermatome, myotome, and sclerotome. The dermatome contributes to the dermis of the skin. Myotomes give rise to the skeletal muscles of the body, limbs, and head. Sclerotome derivatives form the bones of the axial skeleton, including the base of the skull.1,1

PHARYNGEAL ARCHES
A large portion of the head and neck derives from the pharyngeal arches (Fig. 1B). These are five, bilaterally paired swellings formed along the pharyngeal foregut in the fourth week, as the rostral neuropore is closing. The arches are numbered 1, 2, 3, 4, and 6 by homology to the primitive gill arches of lower vertebrates. An early rostrocaudal subdivision of the first arch yields the maxillary and mandibular prominences. Each arch is composed of a mesodermal core lined with endoderm and ectoderm. Endodermal pouches and ectodermal clefts separate the arches. NCCs migrate into the arches, filling them with mesenchyme.

Each pharyngeal arch gives rise to a variety of specific structures of the head and neck (Table 1). In general, the mesodermal cores yield skeletal structures of the neck and lower head. The clefts and pouches form the epithelial linings of the many of the organs, ducts, and mucosa of the mouth and neck. The cranial neural crest differentiates into bones, cartilages, nerves, tooth rudiments, and many other craniofacial tissues.1,1

Within each arch, a cranial nerve (CN), an aortic arch artery, and an arch cartilage develops. Their derivatives are listed in Table 1. The cranial nerves innervate the structures derived from the arches in which they form. The left and right arteries of the arches undergo differential development and regression in a very complex morphogenetic progression, ultimately forming components of the aortic system. The arch cartilages form a variety of small bones and cartilages, primarily in the middle ear and neck.

NEUROCRANIUM
The bones and muscles of the skull that encase the brain comprise the neurocranium (Fig. 1C), consisting largely of the membranous bones that form the cranial vault and the cartilaginous neurocranium forming the floor of the skull. The thin, broad bones of the membranous neurocranium derive from cranial NCCs that migrate from brain regions to form the mesenchyme covering the sides and top of the brain. This mesenchyme condenses and differentiates directly into osteoblasts that secrete osteoid and form bone (intramembranous ossification). The resulting calvarial bones are separated by dense, connective tissue seams (sutures), leaving open spaces (the fontanelles). These flexible junctures accommodate deformation during birth and brain enlargement during infancy.

The cartilaginous neurocranium, or neural chondrocranium, is formed by the fusion of cartilages, composed primarily of cells from the sclerome of cranial somitomeres and occipital somites. The cartilage models then undergo endochondral ossification. Some undergo regression as membranous bone.1,2 The resulting bones comprise some of the facial bones, including the ethmoid, ethmoid, temporal, and the caudal portion of the occipital bone. These bones have complex origins: The ethmoid and sphenoid cartilages are formed from somitomeric mesoderm and NCC derivatives, whereas the caudal portion of the occipital bone is formed from the somatic sclerotomes of the first three occipital somites and the cranial half of the first cervical somite. The sensory capsules, also part of the cartilaginous neurocranium, encase the nasal passages, the eyes, and the inner ear.1,1

VISCEROCRANIUM
The viscerocranium is the skeleton of the face. These cartilages and bones form the skeletal structures of the mouth and the supporting structures of the orpharynx and trachea. The bones of the viscerocranium are also formed by either intramembranous or endochondral ossification (Fig. 1C). The membranous viscerocranium consists of the maxilla, the pala- tine bones, the zygoma, the squamous temporal bones, and the mandible. The latter is formed by ossification of NCC-derived mesenchyme that condenses around the mesodermal core of the

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mandibular prominence (Meckel’s cartilage). The endochondral (cartilaginous) viscerocranium arises from the first two arches and consists of the middle ear bones, the styloid process of the temporalis, and the hyoid bone. The laryngeal cartilages are derived mainly from arches 4 and 6.

FACIAL MORPHOGENESIS

Mesenchymal masses of NCC derivatives yield the features and structures of the face from five primary swellings: two maxillary and two mandibular prominences derived from the first arch and a single frontonasal mass derived from head mesenchyme (Fig. 2A). These are organized around the stomodeum, the future opening to the mouth. Rapid facial growth occurs from the fourth to eighth weeks. The frontonasal mass forms the bulk of tissues rostral to the stomodeum, forming structures such as the forehead. The maxillary prominences form lateral tissues, ultimately producing much of the upper face. The mandibular prominences primarily form the tissues just caudal to the stomodeum, including the chin.

The buccopharyngeal membrane, separating the stomodeum from the anterior foregut tube, ruptures at day 24 to create a broad, slit-like, embryonic mouth (the orphopharynx). This early mouth is reduced laterally by the fusion of the mandibular and maxillary prominences to form the cheeks. Nasal placodes thicken on the frontonasal mass and develop nasal pits that divide each side of the process into the medial and lateral nasal processes (Fig. 2B). The medial nasal processes grow down into the stomodeum and fuse with the maxillary processes (Fig. 2C). These medial nasal processes then expand and fuse to form the intermaxillary process, thus forming the primitive upper lip and philtrum (Fig. 2D). Proliferating mesenchyme fills in the mandibular fusion to form the lower lip.13

ORONASAL CAVITY AND PALATOGENESIS

The oronasal cavity is created as the frontonasal mass enlarges and the first arches grow together to form the stomodeum. As the nasal pits invaginate, they create the nasal passage, which grows inward toward the pharyngeal endoderm. The oronasal membrane, a layer of tissue separating the oral and nasal compartments, breaks down to form openings between the oral and nasal cavities (the primitive choana).

The oral and nasal cavities become separated by the palate, which has several components. The primary palate is a small anterior domain contributed by the medial nasal processes, whereas the secondary palate comprises most of the soft and hard tissues of the roof of the mouth (Fig. 3C). The hard (bony) portion of the palate arises as palatine shelves grow together.
Table 1. Structures Derived From Pharyngeal Arch Tissues

<table>
<thead>
<tr>
<th>Pharyngeal tissue</th>
<th>Major structures</th>
<th>Cranial nerve</th>
<th>Cartilages and bone</th>
<th>Skeletal muscles</th>
<th>Arch artery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arch 1</td>
<td>Mandibular arch, maxillary prominence</td>
<td>Trigeminal (V)</td>
<td>Palatopterygoid, maxilla, palatine, zygoma, squamous, temporal, incus</td>
<td>All muscles of mastication: masseter, temporalis, pterygoids</td>
<td>Terminal branch of maxillary artery</td>
</tr>
<tr>
<td>Pouch 1/Cleft 1</td>
<td>Linings of auditory tube and external auditory meatus and tympanic membrane</td>
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<td>Arch 2</td>
<td>Hyoid arch</td>
<td>Facial (VII)</td>
<td>Reichert, styloid, hyoid, stapes, stylohyoid ligament</td>
<td>All muscles of facial expression, Posterior digastric, stylohyoid, stapedius</td>
<td>Stapedial artery, corticotomympanic artery</td>
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<tr>
<td>Pouch 2</td>
<td>Lining of palatine tonsils</td>
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<tr>
<td>Arch 3</td>
<td></td>
<td>Glossopharyngeal (IX)</td>
<td>Hyoid</td>
<td>Stylopharyngeus</td>
<td>Common carotid artery, root of internal carotid</td>
</tr>
<tr>
<td>Pouch and Cleft 3—dorsal tissues</td>
<td>Cells of inferior parathyroid gland</td>
<td>Vagus: superior, laryngeal branch (X)</td>
<td>All laryngeal cartilages: thyroid, cricoid, arytenoids, corniculate, cuneiform, epiglottis (4 and 6)</td>
<td>Pharyngeal constrictors All soft palate muscles except tensor veli, palatini All intrinsic laryngeal muscles (4 and 6)</td>
<td>Arch of aorta, right subclavian artery, base of pulmonary arteries</td>
</tr>
<tr>
<td>—ventral tissues</td>
<td>Components of thymus gland</td>
<td>Pharyngeal Branch (X)</td>
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<td>Arch 4</td>
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<td>Pouch 4—dorsal tissues</td>
<td>Cells of superior parathyroid gland</td>
<td>Recurrent laryngeal branch (X)</td>
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<td>Ductus arteriosus, roots of definitive pulmonary arteries</td>
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<tr>
<td>—ventral tissues</td>
<td>Parafollicular cells of thymus</td>
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**FIG. 2.** Facial morphogenesis. This figure shows the progression of the facial primordia. NP, nasal pit; MD, mandible; MX, maxilla; ST, stomodeum; LNP and MNP, lateral and medial nasal processes; IMP, intermaxillary process.

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from the maxillary processes (Fig. 3A). As the secondary palate shelves grow together, they become positioned above the tongue to allow for fusion in the midline. They also fuse anteriorly to the primary palate (Fig. 3B). Fusion of the palatine shelves with each other and with the nasal septum separates the nasal cavities from the oral cavity. The posterior parts of the palatine shelves do not ossify, but fuse to form the soft palate. This is the fleshy portion of the mouth’s roof, extending posteriorly from the hard palate.

The tongue arises as a swelling from the floor of the pharynx in the fourth week. A medial and two lateral lingual buds swell and fuse to form the tongue primordium. The lateral buds outgrow the medial bud to form the oral portion of the tongue. The base of the tongue is formed with contributions from the second, third, and fourth arches.

The teeth are formed from ectodermal (oral epithelium) and mesenchymal (neural crest derived) tissues of the mandibular and maxillary prominences. Each tooth bud is composed of an ectodermal dental lamina and a basal, mesenchymal dental papilla. Their development into mature teeth is described elsewhere.

**CRANIOFACIAL BIRTH DEFECTS**

The head is most sensitive to developmental perturbations from 3 to 8 weeks of gestation, the period when most of the cranial tissues and precursors of head structures are forming. The complexity of cell types contributing to the head and their dynamic reorganizations create many opportunities for error. Depending on when and how severe the insult is, a wide range of defects can occur—ranging from minor cosmetic concerns to serious medical disasters. Significant birth defects occur in ~1 per 50 live births, a third involving craniofacial malformations. Collectively, birth defects are the leading cause of infant mortality in the Western world. In the United States, congenital malformations, deformations, and chromosomal abnormalities accounted for one-fifth of all infant deaths in 2002, as reported in the National Vital Statistics Report by the CDC. Head malformations account for many of these deaths and often lead to significant disability in those who survive infancy.

Structural anomalies of craniofacial development have a varied etiology. They can result from genetic mutation(s) or from environmental disruption of developmental pathways. Such an environmental disruption could be chemical exposure to the mother, physical stress to the pregnancy, or anything else exogenous to the embryo. Increasingly, it seems likely that many malformations might result from an unfortunate interaction between a compromising allele of some key gene and an environmental trigger, neither of which would necessarily cause a birth defect on its own. A birth defect can occur as an isolated malformation or as part of a syndrome, in which multiple defects occur in a group of organs and structures. The latter case, a syndromic association of birth defects, is likely to reflect a disruption in a key developmental process or population of precursor cells. For example, a mutation causing a defect in the migration of NCCs could cause major malformations of the face, skull, heart, and many other structures. In contrast, a mutation in a gene required for palatal fusion might result in cleft palate but no other defects. Here we describe several representative classes of craniofacial birth defects and their origins (Table 2).

**HOLOPROSENCEPHALY**

This major class of birth defects occurs because of insufficient tissue along the midline of the ventral prosencephalon and/or facial precursors. This deficiency of midline structures can show varying levels of severity. Defects can range from a single central upper incisor (Fig. 4A), to close-set eyes (hypotelorism), to either no nose (arhinia) or a single nostril (cebocephaly; Fig. 4B), or even to cyclopia, with a nose-like prosencephalic above the eye field (Fig. 4C). Alcohol consumption by pregnant females can result in midline facial dysenapties and mental retardation in the developing progeny. Unfortunately, pregnant women are normally unaware of their pregnancy during the critical period for forebrain formation, during weeks 3 and 4 of gestation. Holoprosencephalies occur in as many as 1 in 250 conceptuses and 1 in 5000–16,000 live births.

**PHARYNGEAL ARCH DEFECTS**

Arch defects often involve the tissues of the viscerocranium and are frequently caused by improper development of NCC derivatives. These defects include micrognathia (Fig. 4E), agnathia, and palatal or mandibular clefting. Mandibulofacial dysostoses are included in a large number of syndromes, including Treacher-Collins, Hallerman-Streiff, and Franceschi’s syndromes.

**TISSUE FUSION DEFECTS**

Facial fusion defects occur when the epithelia of the facial primordia fail to fuse properly, causing facial clefting. The facial cleft sequence can involve a combination of complete or incomplete, bilateral or unilateral clefting of the lip, palate, or nostril (Fig. 4D). It can also include failure of fusion of the mandibular processes or the mandible to the maxilla, causing improper lateral restriction of the mouth. These defects often cause problems in eating and breathing and require corrective plastic surgery.
FIG. 4. Examples of craniofacial birth defects. This figure shows schematic diagrams of some craniofacial defects, including (A–C) examples of holoprosencephaly (HPE) midline defects, (D) facial clefting, (E) pharyngeal arch defect, and (F) cranial synostosis. Affected tissues are shaded.
**VASCULAR DEFECTS**

A defect in vascular development or blood flow can cause a variety of craniofacial defects involving hypoplasia of head tissues. For example, hemifacial microsomia (underdevelopment of one side of the face) is caused by a unilateral insufficiency of blood supply during facial development. This can result in clefting defects caused by underdevelopment of tissues that grow together and fuse. Vascular defects are also a cause of Goldenhar syndrome.\(^{(3)}\)

**SKELETAL DYSPLASIAS**

This class of defects is caused by improper bone growth. Dysplasias that affect the head may involve cranial synostoses or premature fusion of the cranial sutures. This inhibits bone growth and puts pressure on the brain, which is forced to grow improperly and protrude where it can. Such defects include tower skull, or acrocephaly (Fig. 4F), and meningoencephalocele. Skeletal dysplasias often involve other areas of the body: limbs, digits, and vertebrae. Some of the more common are Crouzon, Pfeiffer, Saethre-Chotzen, and Apert’s syndrome.\(^{(3,8)}\)

**CONCLUSIONS**

Experimental manipulations and genetic studies in mice are identifying many of the genes and pathways that control both normal craniofacial development and its anomalies. Most of the genes to date have been intercellular signaling factors, their transducers, or their targets, highlighting the prime importance of cell interactions to normal head formation. Genetic association and expression studies in humans can test whether these candidate genes are mutated or misexpressed in human congenital malformations. Rapidly advancing genomic, embryological, and medical technologies promise to bring soon a better understanding of the basis of craniofacial development and approaches toward minimizing its defects.

**REFERENCES**


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in incisal central mammelons (rounded prominences on biting edges when incisors first erupt) and spread away, eventually delineating the whole junction between the tissues as the tooth germ grows. The expression of secretory signaling molecules varies continuously in the different cell types during tooth initiation and construction. Odontoblasts, which make dentine, are postmitotic cells that differentiate from mesenchymal cells of the dental papilla at the interface with the inner enamel epithelial cells of the enamel organ, which themselves differentiate into pre-ameloblasts. Dentine formation triggers the pre-ameloblasts to differentiate into ameloblasts, the cells that produce enamel. A bilayer of epithelial cells, the epithelial root sheath, extends from the enamel organ at the base of the developing crown to map out the dentine–cementum junction and initiate the differentiation of the odontoblasts of the root. The third tissue type, cementum, is the product of both fibroblasts and cementoblasts, which differentiate from mesenchymal cells of the dental follicle adjacent to the dentine once epithelial cells of the root sheath have moved away from the interface. In human teeth, a small amount of afibrillar cementum may form on the enamel surface close to the junction between the crown and the root if there are interruptions in the covering layer of epithelial cells once enamel formation has been completed. Within the developing tooth, a core of loose connective tissue remains and eventually forms the dental pulp.

The dental follicle, also derived from cells of the cranial neural crest, gives rise to three components of the periodontium: cementum, alveolar bone, and the intervening periodontal ligament. The tooth germs are partially enclosed by the developing alveolar bone—this is initially typical woven bone, formed by osteoblasts, with enclosed osteocytes, and is remodeled to accommodate the growing teeth by osteoclasts of hematopoietic origin. The follicle, a sac of loose connective tissue that separates the developing tooth from its bony crypt, is essential for eruption and will become the periodontal ligament on tooth eruption. This tissue contributes extrinsic collagen fibers to the cementum and alveolar bone, and its main cell type is the fibroblast (see Fig. 1 for a diagram of a mature tooth and its components).

NORMAL DENTAL STRUCTURE

Enamel

Enamel matrix is delicate when first secreted, at which time it is protected by the soft enamel organ. The mature, erupted enamel—the hardest of the hard tissues—is acellular and may contain 98% by weight or 93% by volume of an apatitic calcium phosphate of variable composition. The final strength of enamel partly derives from the dentine mold on which it grows. The junction between these tissues is ill-defined and irregular on a microscopic scale, with tongues of dentine projecting into the enamel, crystals of indeterminate provenance at the common boundary, and many fine, short enamel tubules marking where ameloblasts processes once contacted odontoblasts. Spindles, expanded continuations of dentine tubules within enamel, most likely result from the envelopment of individual ameloblasts that died as amelogenesis commenced. The extracellular proteinaceous matrix of developing enamel is secreted by ameloblasts, which are highly polarized, tall cells. Its main component is amelogenin, a tissue-specific protein rich in proline, leucine, histidine, and glutamyl residues. Other, nonacidic proteins include enamelin, tuftelin, and ameloblastin (amelin, sheathlin): this 3D protein array is thought to control crystal growth. To achieve enamel’s high degree of mineralization, much of its organic matrix is degraded by neutral metalloproteinases and serine proteases and removed, even while ameloblasts are still secretory. Enamel crystals are, even initially, very long and slender, with centers richer in carbonate; however, the net carbonate content falls as they thicken. In humans, relatively large amounts of mineral accumulate at early stages of development, and the enamel has a long postsecretory maturation period during which it becomes hard and the ameloblasts remain active. The maturation phase may last 5 years or more in human third permanent molars. In species with rapid enamel development, cyclical changes in morphology of the maturation ameloblasts are seen to coincide with episodic matrix removal. Enamel’s final composition and mechanical properties are not uniform.

The most notable feature of enamel is the organization of the crystals into enamel “prisms” about 6 μm across and up to 0.5 mm in length, demarcated by a sharp change in crystal orientation (Figs. 2 and 3). Enamel crystals grow mainly with their long c-axes nearly parallel to each other and the larger sides of their flattened hexagonal cross-sections parallel within groups. Where the rate of formation is low, as in the superficial enamel, the secretory interface is nearly flat, and there is little variation in the underlying crystal orientation. However, during most of enamel formation, the secretory (Tomes’) process of each ameloblast is lodged in a pit at the interface. Enamel matrix is released below a continuous belt of

FIG. 1. Organization of dental and periodontal tissues in the erupted tooth.

FIG. 2. External surface of cervical region of developing human permanent molar tooth, showing the morphology of the interface between ameloblasts and their calcified secretory product, the enamel. Scanning electron micrograph (SEM), field width 25 μm.
intercellular attachments so as to maintain the relatively constant shape of the interface between cells and matrix (Fig. 2).\(^{16,17}\) The interpit phase is continuous and the crystals have their long axes perpendicular to the general plane of the developing enamel surface. In human enamel, the dividing lines of the prism junctions are generally incomplete, and the interlocking prisms are described as keyhole-shaped. The concentration of the cleavage products of the enamel proteins at the discontinuities in crystal orientation increases relatively during enamel maturation. Tufts and lamellae are other regions that finally contain less mineral and higher concentrations of proteins.\(^{17}\)

As ameloblasts move away from the dentine, they travel in groups across the surface that they make. This results in de-cussion (crossing in an X fashion) of the enamel prisms, with zones of prisms with contrasting 3D courses forming the Hunter-Schreger bands. The sides of the prisms show varicosities (Fig. 3) with the same period as cross- striations in the prisms, which are thought to be caused by circadian changes in the composition of the mineral component.\(^{17}\) A prominence of the cross-striations occurs at 7- to 10-day intervals (the regular striae of Retzius), and major life events, such as birth (the neonatal line) or severe illness during enamel formation, may be recorded as conspicuous incremental lines. At the finished enamel surface, perikymata or imbrication lines are outcrops of the internal growth layers. They grade from horizontal bands displaying pits alternating with smoother regions at more in- cisoral or occlusal levels, to near the neck of the tooth, small steps at the sharp boundary between the imbricating layers.

The unerupted crown is protected from resorption by a layer of cells termed the reduced enamel epithelium, comprising remnants of mature ameloblasts. These are lost once the tooth erupts. As the tooth wears during function, the surface features of the enamel become abraded, microcracks develop particularly along development faults, and the chemistry of the mineral exposed to the oral environment changes.

**Dentine**

Dentine forms the bulk of the tooth and extends within both crown and root. It is a pale creamy yellow color, in contrast to the much whiter, harder enamel. Dentine is tough and elastic, and its prime feature is its penetration by odontoblast tubules that radiate out from the dental pulp to the periphery (Fig. 4). These, with their many side branches that remain in the tubules within the dentine, are analogous to the canaluli that house osteocyte processes in bone. The peripheral, first formed dentine is termed mantle dentine, and the inner layer is termed circumferential dentine. After differentiating from cells of the dental papilla, the odontoblasts retreat centripetally as a cone-shaped monolayer sheet, depositing a collagenous predentine matrix and leaving lengthening cell processes.\(^{18}\) The curved paths that the cell bodies take are therefore recorded in the extracellular matrix. This is similar to that of bone, comprising mainly type I collagen, acidic proteins, and proteoglycans. The predominant noncollagenous protein in dentine is the highly phosphorylated dentine phosphoprotein (phosphophoryn). This and dentine sialoprotein\(^{19}\) are cleavage products of dentine sialophosphoprotein and are formed during the maturation of predentine into dentine. Dentine matrix protein 1 and other sialic acid–rich phosphoproteins common to dentine and bone are also present. Decorin, biglycan, lumican, and fibromodulin are the main proteoglycans in predentine.\(^{20}\) The predentine matrix matures progressively, and the collagen fibrils thicken and compact and mineralize after a lag time of ~4 days.\(^{21}\)

Dentine contains ~70% mineral (wet weight). Carbonate-rich calcium phosphate (hydroxyapatite) crystals initially form in relation to submicroscopic vesicles shed by the odontoblasts in the mantle layer or at sites on collagen fibrils rich in noncollagenous proteins. Mineralization extends radially from initial nucleation sites in the matrix, possibly by a process of secondary nucleation, forming regions of dentine known as calcospherites. These may fail to fuse, leaving unmineralized interglobular dentine between them. In a second, concurrent pattern of mineralization, crystals extend along the fine type I collagen fibrils that lie in a feltwork parallel to the incremental surface. Peritubular dentine is deposited within the tubules, partially or sometimes completely occluding them. It contains a negligible amount of collagen and mineralizes to a higher degree than the surrounding bulk intertubular dentine.
Because it is harder and more wear-resistant than intertubular dentine, it stands proud on teeth worn through to dentine.

Like enamel, dentine is deposited rhythmically, leaving lines marking daily and approximately weekly increments. Major life events, such as birth (the neonatal line) and illness, or dietary deficiencies are recorded as disturbances in the structure of the tissue forming at the time. Once eruption has occurred and root formation is complete, further dentine formation occurs as slowly deposited, regular secondary dentine or, irregularly, as a response of the pulp–dentine complex to attrition or disease. Nerves pass from the dental pulp between odontoblasts and extend into the dentine tubules for variable distances. Dentine is acquisitively painful if touched or subjected to large temperature or osmotic changes.

Like any other loose connective tissue, the dental pulp shows signs of aging, which may include diffuse or local calcifications and the formation of dental stones. In the roots of human teeth, occlusion of the tubules with peritubular dentine extends coronally from the root apex; the resulting transparent dentine can be used as a guide to the age of the tooth.

**Cementum**

Cementum is a calcified connective tissue that is deposited initially on the newly mineralized dentine matrix of the root by cells derived from the dental follicle. Secretory proteins from the cells of the epithelial root sheath may be included in the first-formed matrix. Cementum is laid down centrifugally from the cement–dentine junction and is marked by incremental lines that are close together, continuous, and evenly spaced where apposition was slow and patchy and irregular otherwise. The tissue is similar to bundle (Sharpey fiber) bone in that it incorporates extrinsic collagen fibers formed by fibroblasts. These fibers may be very closely packed, comprising the whole tissue in slowly forming acellular cementum (Fig. 5), or be separated from each other by intervening intrinsic collagen fibers, of cementoblast origin, which lie in the plane of the developing root surface (Fig. 3). Where cementum is deposited very rapidly, it is cellular, containing cementocytes that resemble the osteocytes of bundle bone (Fig. 6). In heavily remodeled root apices, there may be patches of cellular cementum without extrinsic fibers. Only in cementum-containing intrinsic fibers may a well-defined region of unmineralized precementum, equivalent to osteoid, be present at the surface of the tissue. The collagen of both the extrinsic and intrinsic fibers is type I. The main non-collagenous proteins of cementum identified so far (bone sialoprotein, osteopontin, osteocalcin, and α2-HS-glycoprotein) vary in amount and distribution in the types of cementum and do not distinguish it from other calcified connective tissues.

Cementum mineralization reflects the rate of formation and the composition of the matrix. In afibrillar coronal cementum, the layer of noncollagenous proteins adsorbed on to the enamel surface mineralizes fully. At the cementum–dentine junction, collagen fibrils and non-collagenous constituents of the two tissues mingle without a regular, distinct border or osteopontin-rich hypermineralized cement line. The extrinsic fibers of slowly forming cementum mineralize completely, the advancing mineralized front across the fibers being relatively flat and defining a border between cementum and the dental sac or periodontal ligament. This type of cementum is more highly mineralized, more translucent, and paler than dentine. Where only a small proportion of intrinsic fibers exists in acellular cementum, the extrinsic fibers lead the mineralization front. As the rate of deposition of cementum increases and proportionately more intrinsic fibers are deposited, the likelihood that the extrinsic fibers will retain unmineralized cores increases. During periods of fast cellular cementogenesis, even the intrinsic fibers may retain unmineralized centers, and the mineralization front becomes irregular, with the extrinsic component lagging behind the intrinsic. This cementum type is the softest and least well mineralized of the calcified dental tissues. The mineralization front can be read to estimate the current rate of formation and the degree of mineralization of the fibers within the tissue.
successional tooth. Interspersed between resorptive bursts are appearing first and most extensively on the aspect adjacent to the deciduous tooth roots begins shortly after their completion, ap- growth drift, or changing functional forces. Resorption of de- forming to allow the tooth to move in response to eruption, surface of alveolar bone (Fig. 6) is continually resorbing and tissue.

are incorporated within cementum and bundle bone; within the alveolar bone. On either side of the ligament, its principal fibers functioning teeth are linked to each other, the gingiva, and the periodontal ligament, comprising types I and III collagen, to tooth, provides nutrition and mechanosensation, and allows months more in the deciduous teeth and up to 3 years in the a large closing cone in bone. Root completion takes formed, and the pulpal aspect of the root end (apex) resembles the dental follicle controlling eruption and root growth are unclear.(11) At emergence, the root of the tooth is not yet fully calcified tissues, enamel is destined to be exposed to an exter- nal environment. As the tooth erupts, the alveolar bone is

depleted to allow its passage, its root develops, and the crown pierces the oral mucosa that finally contributes to a tight ring seal of epithelial cells on the enamel close to the junction of crown and root. The complex molecular signaling cascades in the dental follicle controlling eruption and root growth are unclear.(11) At emergence, the root of the tooth is not yet fully formed, and the pulpal aspect of the root end (apex) resembles a large closing cone in bone. Root completion takes \(
\) months more in the deciduous teeth and up to 3 years in the permanent teeth. During root development, the follicle becomes organized into the periodontal ligament that supports the tooth, provides nutrition and mechanosensation, and allows physiological tooth movement. Through the groups of fibers of the periodontal ligament, comprising types I and III collagen, functioning teeth are linked to each other, the gingiva, and the alveolar bone. On either side of the ligament, its principal fibers are incorporated within cementum and bundle bone; within the ligament, there is constant adaptive remodeling of the soft tissue.

Cementum in permanent teeth sees little remodeling, but the surface of alveolar bone (Fig. 6) is continually resorbing and forming to allow the tooth to move in response to eruption, growth drift, or changing functional forces. Resorption of deciduous tooth roots begins shortly after their completion, appearing first and most extensively on the aspect adjacent to the successional tooth. Interspersed between resorptive bursts are occasional short periods of repair by cemento(osteo)blasts. Odontoclasts—typical osteoclasts—resorb both cementum and dentine and, in deciduous molars, a small mount of enamel.

**REFERENCES**

Chapter 85. Dental Manifestations of Disorders of Bone and Mineral Metabolism

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ORAL MANIFESTATIONS OF GENETIC SKELETAL DISORDERS

The skeleton contains two of the five mineralized tissues in the body: bone and calcified cartilage. The other three mineralized tissues, dentin, enamel, and cementum, are found in teeth. The mineral in each of these hard tissues is a biological apatite resembling calcium hydroxyapatite \( \text{Ca}_10(\text{PO}_4)_6(\text{OH})_2 \) in structure, with the most common substitutions being carbonate \( (\text{CO}_3^2-) \) for phosphate \( (\text{PO}_4^{3-}) \), and fluoride \( (\text{F}^-) \) for hydroxyl \( (\text{OH}^-) \). Therefore, disorders involving the regulation of calcium and phosphate metabolism potentially affect multiple hard tissues. In every mineralizing tissue, biomineralization occurs in a defined extracellular space. Establishing these extracellular mineralizing environments involves the synthesis and secretion of extracellular matrix proteins, the transport of ions, and matrix turnover. While each mineralizing tissue is in many ways unique, there are common elements that, when defective, lead to pathologies in multiple hard tissues. Changes in the dentition and its supporting oral structures may occur in response to disorders of mineral metabolism. The clinical presentations in these disorders may vary from mild asymptomatic changes to alterations that severely alter the form and function of craniofacial structures. In some cases, the oral phenotype may be the earliest or most obvious sign of a broader syndrome involving bone and mineral metabolism and lead to the original diagnosis. This chapter provides a concise overview of the dental manifestations of selected disorders of bone and mineral metabolism.

Osteogenesis Imperfecta, Dentinogenesis Imperfecta, and Dentin Dysplasia

Defects in either the \( \alpha1 \) or \( \alpha2 \) chain of type I collagen can cause osteogenesis imperfecta (OI). OI is associated with assortd dentin defects that are collectively designated as dentinogenesis imperfecta (DGI). In rare cases, the dentin defects are the only prominent phenotype. It has been reported that 10–50% of patients afflicted with OI also have DGI. This assessment, however, may underestimate the true prevalence because mild forms of DGI may require microscopic analysis for diagnosis. Dental abnormalities have been described in several subtypes of OI, but are most prevalent in OI types IB, IC, and IVB. The range of dental defects observed in osteogenesis imperfecta are similar to those observed in kindreds with DGI and dentin dysplasia (DD). The most abundant noncollagenous proteins in dentin are proteolytic cleavage products of a large chimeric protein known as dentin sialophosphoprotein (DSP). The intact DSP protein has never been identified in dentin, but three cleavage products spanning the entire length of DSPP have been isolated and partially characterized. Dentin sialoprotein (DSP) is a proteoglycan with both N- and O-linked glycosylations and two glycosaminoglycan attachments comprised of long chondroitin 6-sulfate chains. Dentin glycoprotein DGP is a small, phosphorylated glycoprotein. Dentin phosphoprotein (DPP) is highly phosphorylated protein, with the lowest (most acidic) isoelectric point (~1) of any known protein. DPP is thought to participate in the nucleation of hydroxyapatite crystallities on collagen. In the past few years, nine different DSPP \((4q21.3)\) mutations have been linked to inherited dentin defects in kindreds with DD-type II, DGI-type II, and DGI-type III phenotypes. No mutations in candidate genes encoding other extracellular matrix proteins, such as osteopontin, bone sialoprotein, and dentin matrix protein-1, have been identified. Like type I collagen, the DSPP gene is expressed in bone, as well as dentin. Despite this, no bony defects have been reported in any of the kindreds with dentin defects linked to DSPP mutations.

The clinical classification system most often used to categorize inherited defects of dentin was established 30 years ago, before recent discoveries concerning their genetic etiologies, and divided the phenotypes into two disease groups with five subtypes: dentinogenesis imperfecta (DGI), types I–III and dentin dysplasia (DD, types I and II), with all forms showing an autosomal dominant pattern of inheritance. Type I DGI is a collective designation for OI with DGI and has largely been abandoned in deference to the current OI classification system. An alternative designation for isolated inherited dentin defects is hereditary opalescent dentin. Type II DGI is the most prevalent inherited dentin phenotype. Clinically, the teeth of individuals with DGI are characterized by an amber-like appearance (Fig. 1). The teeth are narrower at the cervical margins and thus exhibit a bulbus or bell-shaped crown. Micro-

The authors have reported no conflicts of interest.
Osteopetrosis

The lack of appropriate bone resorption observed in osteopetrosis has several implications in the craniofacial region. The jawbones are abnormally dense at the expense of cancellous bone and these changes may affect normal tooth development. Because normal tooth eruption is dependent on resorption of alveolar bone surrounding the developing tooth germ, inadequate resorptive function in osteopetrosis may limit the eruptive mechanisms and place altered forces on the erupting teeth. Dental findings associated with osteopetrosis include congenitally absent teeth, unerupted and malformed teeth, delayed eruption, and enamel hypoplasia. There is a reduced calcium-phosphorous ratio in both enamel and dentin that may alter hydroxyapatite crystal formation and contribute to an increased caries index, as has been reported in several cases. Additionally, there are deviations in amino acid content, indicative of altered matrix composition. Perhaps the most serious dental complication of osteopetrosis is the propensity to develop osteomyelitis. Because the vascular supply to the jaws is compromised, avascular necrosis and infection after dental extractions may lead to osteomyelitis that is difficult to treat. Thus, extraction of teeth must be performed asatraumatically as possible.

Mucopolysaccharidoses

Lysoosomal storage disorders comprise >40 inherited diseases that are caused primarily by defects in genes encoding lysosomal enzymes. Among the lysoosomal storage disorders are the mucopolysaccharidoses (MPS), which are characterized by the accumulation of partially degraded glycosaminoglycans (previously called mucopolysaccharides) within lysosomes, as well as in the urine. There are 10 enzymes involved in the stepwise degradation of glycosaminoglycans, and deficiencies in these activities give rise to the MPS. There are seven MPS types: I, II, III, IV, VI, VII, and IX (types V and VIII have been retired and type IX is extremely rare). The mucopolysaccharidoses are distinguished from each other based on genetic, biochemical, and clinical analyses. Although heterogeneous, several craniofacial characteristics are similar between the different types. The oral manifestations may include a short and broad mandible with abnormal condylar development and limited temporomandibular joint function. The teeth are often peg-shaped and exhibit increased interdental spacing perhaps because of the frequently observed gingival hyperplasia and macroglossia. Some forms of MPS have abnormally thin enamel covering the clinical crowns or radiographic evidence of cystic lesions surrounding the molar teeth that contain excessive dermatan sulfate and collagen.

Mucopolysaccharidosis type IVA (Morquio A syndrome, MPS IVA) is an autosomal recessive disorder caused by deficiency of the lysosomal hydrolase, N-acetylgalactosamine 6-sulfatase (GALNS), encoded by a gene on human chromosome 16q24.3. Mucopolysaccharidosis type IVA is the only MPS associated with dental enamel malformation, although mucopolysaccharides accumulate in the developing teeth in other MPS syndromes, such as Hurler (MPS I), Hunter (MPS II), and Maroteaux-Lamy (MPS VI) syndromes. In MPS IVA, enamel malformations are a consistent feature. The enamel is dull gray in color, thin, pitted, and tends to flake off from the underlying dentin. The thin enamel layer is of normal hardness and radiodensity. MPS IVA patients often show severe bone dysplasia and dwarfism.
Cherubism

Cherubism is a rare autosomal dominant disorder that manifests as bilateral jaw enlargement primarily involving the mandible of children. The condition affects boys twice as often as girls, and the clinical symptoms generally are not present until the affected children reach 2–7 years of age. The clinical features of cherubism include painless, bilateral expansion of the posterior mandible, and upward turning of the eyes that impart the cherubic facies from which this rare developmental jaw condition gets its name. Radiographically, the lesions appear as multilocular, expansile radiolucencies that can interfere with normal tooth eruption. The histopathologic features may not help in the definitive diagnosis of cherubism because the fibrous lesion containing multinucleated giant cells may resemble giant cell granuloma and fibrous dysplasia. However, cherubism may now be more clearly distinguished from these other conditions because a mutation associated with cherubism has been identified in the c-Abl-binding protein SH3BP2. Cherubism is also a component of the Noonan-like/multiple giant cell lesion syndrome, which has additional craniofacial and skeletal abnormalities. A common problem in understanding the genetic underpinnings of craniofacial disorders such as cherubism is the genetic mutation, or genotype, does not always correlate with the phenotype. That is, a mutation in one gene may result in one of several different craniosyostoses. Therefore, with our current understanding of genetic and epigenetic events, it may be more appropriate to state that a certain gene mutation is associated with the syndromic phenotype rather than state that the gene mutation causes the specific condition.

ORAL MANIFESTATIONS OF METABOLIC BONE DISEASES

Metabolic diseases of bone are disorders of bone remodeling that characteristically involve the entire skeleton and are often manifest in the oral cavity, which can lead to the diagnosis of the underlying systemic disease. Numerous studies suggest that subclinical derangements in calcium homeostasis and bone metabolism may also contribute to a variety of dental abnormalities including alveolar ridge resorption and periodontal bone loss in predisposed individuals. The significance of this spectrum of diseases and their overall impact on oral health and dental management are likely to increase as the elderly segment of the population increases in the coming decades.

Vitamin D Deficiency

In vitamin D–resistant rickets, the primary oral abnormality is similar to dentin dysplasia. Enamel is usually reported to be normal, but in some instances may be hypoplastic. Patients also suffer from delayed tooth eruption, and radiographically, teeth often display enlarged pulp chambers. Other salient radiographic findings include decreased alveolar bone density, thinning of bone trabeculae, loss of lamina dura, and retarded tooth calcification. In familial hypophosphataemia, dental findings are often the first clinically noticeable signs of the disease and resemble those seen in rickets and osteomalacia. Patients may present with abscessed primary or permanent teeth that have no signs of dental caries. Although the enamel is reported to be normal, microbial infection of the pulp is thought to occur through invasion of dentinal tubules exposed by attrition of enamel or through enamel microfractures.

Vitamin D–dependent rickets type I is an autosomal recessive defect in vitamin D metabolism caused by mutations in the CYP27B1 gene (12q13.3-q14) encoding 25-hydroxyvitamin D-1α-hydroxylase. Decreased 1,25(OH)2 vitamin D results in teeth with yellow-brown color, pitted enamel, short roots, and a tendency to develop chronic periodontal disease (Fig. 3).

Hypophosphatasia

Hypophosphatasia is an inherited disorder caused by a defect in the alkaline phosphatase (ALPL) gene. Osteoblasts show the highest level of ALPL expression, and profound skeletal hypomineralization occurs in the severest forms of hypophosphatasia. The hard tissue that seems to be most sensitive to an ALPL defect is cementum. The classic oral presentation of hypophosphatasia is the premature loss of fully rooted primary teeth.
teeth (Fig. 4). Histological examination indicates that these teeth lack cementum on their root surface, so that the attachment apparatus fails to develop properly. The periodontal ligament fibers do not connect the alveolar bone to the root, and the teeth exfoliate prematurely. In the permanent teeth, large pulp spaces, late eruption, and delayed apical closure are often observed. Bone loss is primarily horizontal, and in the adult form of the disease, there may be widespread dental caries.

Paget’s Disease

Paget’s disease, also known as osteitis deformans, a disorder of bone remodeling,\(^{41,42}\) is characterized by the presence of irregular islands of bone with prominent internal cement lines that create a mosaic pattern. In the craniofacial bones, radiographic lesions usually progress from irregular lytic lesions to areas of sclerosis that present with a distinctive cotton-wool appearance. Involvement of the maxilla is more common than the mandible where patients often present with alveolar ridge enlargement and hypercementosis. In extreme cases, the expanding alveolar ridges can lead to the separation of teeth and poor denture adaptation in the edentulous patient. As the disease progresses, there may be extensive bone deformity with nerve compression and altered blood flow, conditions that can make tooth extraction problematic.

ORAL MANIFESTATIONS OF ACQUIRED DISORDERS

Benign Non-Odontogenic Neoplasms of the Jaws

Benign fibro-osseous lesions of the jaw are a heterogeneous group of disorders characterized by the replacement of normal trabecular bone and marrow with cellular fibrous connective tissue and a disorganized array of randomly oriented mineralized tissue. The most common group of lesions is known collectively as the cemento-osseous dysplasias,\(^{43}\) so named because they contain spherical calcifications believed to be of cemental origin and randomly oriented mineralized structures, sometimes resembling bone. In some cases, these lesions are also associated with long bone fragility (gnatho-diaphyseal dysplasia).\(^{44}\) Two other conditions included in this category are fibrous dysplasia of bone and cherubism, which are of greater clinical significance because they tend to attain a larger size and have the potential for producing greater facial disfigurement and severe malocclusion.

Among the cemento-osseous dysplasias, the most common is a condition known as periapical cemental dysplasia. This asymptomatic lesion presents radiographically as a mixed radiolucent/radiopaque lesion that involves a single mandibular quadrant in middle-aged women. It is frequently encountered below the apices of the mandibular incisors. The involved teeth are vital, and no treatment is required. Florid cemento-osseous dysplasia is a more extensive form of periapical cemental dysplasia that invariably involves multiple jaw quadrants. Fibrous dysplasia is a disorder that can affect single (monostotic) or multiple (polysyostotic) bones and can occur as part of the McCune-Albright syndrome, where it is associated with skin pigmentation and endocrinopathies. When it occurs in the absence of endocrine abnormalities it is referred to as Jaffe syndrome. The underlying cause of fibrous dysplasia and the McCune-Albright syndrome are activating mutations in the \(G\alpha\) gene, resulting in abnormal accumulation and maturation of precursor osteogenic cells to osteoblast cells and formation of sclerotic lesions in craniofacial bones.\(^{45}\) Caries prevalence in these patients is higher than in the normal population, and prevalent dental anomalies included malocclusion, tooth rotation, oligodontia, and taurodontism.\(^{46}\) Other benign expansile lesions of the jaw include the fibro-osseous tumors associated with hyperparathyroidism-jaw tumor syndrome, an autosomal dominant, multineoplasia disorder associated with primary parathyroid tumors and caused by mutation of the parafibromin gene, \(HRPT2\),\(^{47}\) and the exostoses seen in torus mandibularis that may be related to loss of function mutations in the gene for low-density lipoprotein receptor-related protein 5.\(^{48}\)

Malignant Non-Odontogenic Neoplasms of the Jaws

Osteosarcoma is the most common malignant neoplasm derived from bone cells, occurring in 1 of every 100,000 people.\(^{34}\) The peak incidence when it occurs in the jaws is \(~10\) years later than the peak incidence in the long bones. The radiographic appearance of osteosarcoma varies considerably depending on the histological type. Osteosarcomas that produce large amount of mineralized bone-like tissue will present as large areas of radiopacity within a diffuse radiolucent background. A characteristic finding in jaw lesions is widening of
the periodontal ligament in adjacent teeth. Although this finding is not unique to osteosarcoma, it is sufficiently consistent to be of diagnostic value. Occulradiographs may also reveal a sunburst pattern of radiopacity radiating from the periosteum and may be of assistance diagnostically.

**Biphosphonate-Induced Osteonecrosis of the Jaw**

Although intravenous biphosphonate therapy is the standard of care for the management of hypercalcemia of malignancy and metastatic osteolytic lesions associated with multiple myeloma and other solid tumors such as in breast, prostate, and lung cancer, recent findings point to potential complications in the jaw bones of patients undergoing this form of cancer therapy. Several groups have identified a cohort of patients that presented with exposed bone in the maxilla and mandible that resembled refractory osteomyelitis or osteoradionecrosis that is occasionally observed in patients who have received high dose radiation therapy to the jaws. In each case, patients were nonresponsive to noninvasive treatments and were receiving intravenous bisphosphonate therapy. Conservative treatment for such avascular, necrotic lesions of the jaw involves the use of antibiotic and anti-inflammatory therapy. In more severe cases, surgical intervention has been advocated, but the results have not been consistent. At this time, because of the lack of any prospective controlled data on the success rate of different treatment modalities, conservative management is strongly recommended.

**REFERENCES**


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Chapter 86. Periodontal Diseases and Bone

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INTRODUCTION

Periodontal diseases fall into two broad categories: gingivitis and periodontitis. Gingivitis is characterized by gingival inflammation. Its major etiologic factor is bacterial plaque accumulation on the teeth. The response to the plaque may be modified by systemic or genetic diseases and a myriad of drugs. One of the major features distinguishing gingivitis from periodontitis is the absence of alveolar bone loss in the former. Periodontitis is characterized by loss of soft tissue attachment to the tooth along with alveolar bone loss, resulting in decreased support of the tooth (Fig. 1).

DIAGNOSIS

Table 1 shows the terminology used to distinguish the various forms of periodontitis, according to the American Academy of Periodontology. This chapter focuses on periodontitis, because one of the hallmarks of periodontitis is alveolar bone loss. Periodontal diseases are classified by clinical syndromes, because to date there are no definitive tests for periodontitis. The current system in the United States uses rate of progression of attachment and bone loss as the key classifying factors. In Europe, the European Academy of Periodontology uses age as the primary classifying factor.

ETIOLOGY

Periodontitis is a multifactorial disease. While the bacteria in the plaque biofilm are considered the major causative agent, susceptibility of the host plays an important role. This interaction is shown in Fig. 2. There are ~500 microbiological species that have been isolated from the oral cavity. At the gingival crevice, there is a shift from a gram-positive aerobic flora in a state of health to gram-negative anaerobic or gram-negative facultative species, which have been implicated in the pathogenesis of periodontal diseases. The bacteria in biofilm were categorized into clusters. The “red cluster,” consisting of Porphyromonas gingivalis, Bacteroides forsythus, and Treponema denticola, are most often associated with inflammation and attachment loss.

The pathogenicity of the microbiological biofilm associated with disease is enabled by the virulence factors of the gram-negative and facultative species once they invade the tissue. The predominant virulence factors that play a role in host interaction are endotoxin, exotoxin, and bacterial enzymes.

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Periodontitis as a disease are arachidonic acid metabolites generated by cyclooxygenase and involved in bone loss associated with periodontal diseases. Prostaglandins, especially PGE₂, seem to be partially responsible for the mechanism of bone resorption through osteoclast stimulation.3) The exotoxins secreted by the bacteria are metabolic end products such as organic acids, amines, indole, ammonia, and sulfur compounds that produce local cytotoxic and host defense inhibitory effects. The bacterial enzymes such as collagenase, hyaluronidase, and proteinase lead to increased intracellular spaces and permeability and further enable tissue invasion.4,5)

Periodontal diseases are initiated by bacteria, and the bacteria may directly interact with the host tissues in mediating the destruction. In general, there is a well-regulated host response mediated through inflammatory cells that control the spread of bacterial infection. However, the host response itself may establish a chronic inflammatory state and may play a role in the local destruction of the supporting structures of the teeth. Mediators produced as part of the inflammatory host response that contribute to tissue destruction include proteases, cytokines, and prostaglandins. Matrix metalloproteinases are considered the primary proteases involved in periodontal tissue destruction by degradation of extracellular molecules.5) At least two pro-inflammatory cytokines, interleukin (IL)-1 and TNF, seem to have a central role in periodontal destruction. The properties of these cytokines that relate to tissue destruction involve the stimulation of bone resorption by IL-1 and induction of tissue-degrading proteases by TNF.6,7) Prostaglandins, especially PGE₂, seem to be partially responsible for the bone loss associated with periodontal diseases. Prostaglandins are arachidonic acid metabolites generated by cyclooxygenases. Cyclo-oxygenase production of PGE₂ that is associated with inflammation is upregulated by IL-1, TNF, and bacterial LPS. Clinical trials have indicated that bone loss associated with periodontitis was partially prevented by administration of inhibitors of prostaglandin synthesis.7,8)

**DIAGNOSTIC TOOLS**

The diagnostic tools used today for the diagnosis of periodontal disease are primarily based on the anatomy of the lesions. Visual inspection reveals superficial signs of gingival inflammation such as edema and redness of the tissues. Periodontal probing uses a 0.5-mm probe that is placed between the tooth root and the gingiva in the pocket or sulcus. Probing depth, the distance between the base of the pocket and the gingival margin, provides some indication of prior disease progression and alerts the practitioner to the depth of the anaerobic chamber the pocket provides for growth of gram-negative anaerobic bacteria. This measure is of importance in planning treatment because deep pockets are more difficult to clean. Probing attachment levels (or clinical attachment leads), which measure the distance from the base of the pocket to a fixed landmark such as the cemento-enamel junction, give an estimate of prior soft tissue attachment.

Radiographs are used to determine the extent of alveolar bone loss in teeth at risk. Both radiographs and probing examinations do not provide an indication of current disease activity. Rather, they represent the sum total of disease and healing that has occurred over the lifespan of the tooth. Prior studies have shown, however, that the absence of inflammation, lack of radiographic indication of bone loss, and shallow pockets are associated with a low risk of future progression.

Microbiological tests aim to detect the presence of putative periodontal pathogens in a given pocket. In many cases, cultural methods have been replaced by newer ELISA and DNA testing.9) Only cultural methods can be used to determine which antibiotics may be used to successfully treat a given bacterial infection. At present, these tests are not routinely used in the diagnosis of periodontitis but may be useful for treatment planning in aggressive or refractory disease.

Gingival crevicular fluid is a transudate of plasma. The quantity of gingival crevicular fluid is associated with inflammation. Biochemical profiles of inflammatory markers and mediators have also been studied extensively.10) Markers such as aspartate aminotransferase, β-glucuronidase, elastase, and many cytokines are elevated in periodontitis and in progressive periodontitis.

Genetic testing has become a reality for periodontal disease. Certain IL-1β polymorphisms are associated with a higher risk of periodontitis.11) Other cytokine polymorphisms are under study.

**TREATMENT**

Treatment of periodontitis is usually divided into two types: surgical and nonsurgical. While this is a helpful categorization for patients, insurance companies, and clinicians, it does not address the mechanism of each treatment modality. Therefore, treatment will be discussed in reference to Fig. 2 (treatment may be directed at the bacteria or the host).

**Treatment Directed Against the Bacteria**

This mode of treatment includes self-care, such as brushing and flossing, and professionally administered care (Table 2).
**TABLE 2. NONSURGICAL THERAPY—PERIODONTITIS**

<table>
<thead>
<tr>
<th>Category of treatment</th>
<th>Treatment</th>
<th>Strengths</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Targeted at bacteria by nonsurgical mechanical means</strong></td>
<td>Scaling and root planing—with manual instrument and ultrasonics</td>
<td>Decreases gingival inflammation by 40-60% Decreases probing depth Facilitates gain in clinical attachment level</td>
<td>Widespread</td>
</tr>
<tr>
<td><strong>Targeted at bacteria by non-surgical chemotherapy</strong></td>
<td>Chlorhexidine Triclosan co-polymer or triclosan zinc-citrate Essential oils Stabilized CPC</td>
<td>Significant reductions in gingival inflammation No evidence that there is a substantial long-term benefit for periodontitis except to control co-existing inflammation</td>
<td>Widespread</td>
</tr>
<tr>
<td><strong>Sustained release antimicrobials</strong></td>
<td>Intrapocket resorbable or nonresorbable delivery systems containing a tetracycline antibiotic, or chlorhexidine</td>
<td>When used as an adjunct to scaling and root planing, gains in clinical attachment level, and decreases in probing depth and bleeding</td>
<td>Widespread</td>
</tr>
<tr>
<td><strong>Systemic antibiotics</strong></td>
<td>Tetracyclines, metranidazole, spiromycin, clindamycin, azithromycin, ciproflocaxin and combinations such as metranidazole and amoxicillin</td>
<td>Not indicated for most adult periodontitis patients May be useful to treat aggressive destructive periodontitis</td>
<td>Widespread</td>
</tr>
</tbody>
</table>

**TABLE 3. SURGICAL PERIODONTAL THERAPY—SELECTED PROCEDURE**

<table>
<thead>
<tr>
<th>Category and goal</th>
<th>Procedures</th>
<th>Strengths</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pocket therapy</strong>—provides access to root surfaces and bony defects, reduces probing depths, facilitates plaque control and enhances restorative and cosmetic dentistry</td>
<td>Gingival flap to provide access to roots and bony defects for debridement</td>
<td>Improvement in clinical attachment level</td>
<td>Widespread</td>
</tr>
<tr>
<td><strong>Regeneration</strong>—procedures to facilitate growth of new periodontal ligament, cementum and bone over previously diseased root surfaces</td>
<td>Extraoral autogeneous bone grafts</td>
<td>High potential for bone growth</td>
<td>Limited</td>
</tr>
<tr>
<td>Intraoral autogenous grafts (i.e., maxillary tuberosity, healing extraction sites, osseous coagulum)</td>
<td></td>
<td></td>
<td>Widespread</td>
</tr>
<tr>
<td>Allografts—tissue transferred from one individual to another</td>
<td></td>
<td></td>
<td>Widespread</td>
</tr>
<tr>
<td>Freeze dried bone allograft</td>
<td>Bone fill has been reported in a high proportion of defects, but is variable Osteogenic potential may vary from vial to vial, patient differences, and clinician variability</td>
<td></td>
<td>Widespread</td>
</tr>
<tr>
<td>Alloplasts—synthetic grafts Absorbable: plaster, calcium carbonates, ceramics such as tricalcium phosphate and absorbable HA Nonabsorbable: dense HA, porous HA, bioglass</td>
<td>Improved probing depth and attachment level</td>
<td></td>
<td>Widespread</td>
</tr>
<tr>
<td><strong>Barrier membranes</strong></td>
<td>Resorbable and nonresorbable membranes</td>
<td>Improve attachment levels relative to flap surgery alone</td>
<td>Widespread</td>
</tr>
</tbody>
</table>
do not automatically kill sensitive plaque bacteria, because the gingival inflammation have been shown. Systemic antibiotics clinical attachment levels, decreases in probing depth, and as an adjunct to scaling and root planing, improvements in © 2006 American Society for Bone and Mineral Research

Formation of new bone and cementum

Growth factors

Improve bone fill and attachment

Putative collagen binding protein

Table 4. Growth Factors and Biologics

<table>
<thead>
<tr>
<th>Category and goal</th>
<th>Procedures</th>
<th>Strengths</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formation of new bone and cementum</td>
<td>Bone morphogenetic proteins</td>
<td>In experimental systems forms new cementum and bone</td>
<td>Not commercially available</td>
</tr>
<tr>
<td>Growth factors</td>
<td>Platelet derived growth factor, insulin like growth factor, transforming growth factor, fibrinogen growth factor</td>
<td>Improve healing although some studies show mixed results</td>
<td>Available from spun plasma</td>
</tr>
<tr>
<td>Improve bone fill and attachment</td>
<td>Enamel matrix proteins</td>
<td>Fill in infrabony osseous defects</td>
<td>Insulin-like factor recently approved</td>
</tr>
<tr>
<td>Putative collagen binding protein</td>
<td>Anorganic bovine-derived matrix and synthetic clone of 15 amino acid sequence of type I collagen</td>
<td>Limited trials have shown hard tissue fill</td>
<td>Cleared for marketing</td>
</tr>
</tbody>
</table>

Table 5. Nonsurgical Therapy—Periodontitis

<table>
<thead>
<tr>
<th>Category of treatment</th>
<th>Treatment</th>
<th>Strengths</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMP inhibitors low dose tetracyclines</td>
<td>Used in adult or chronic periodontitis</td>
<td>Slow the progression of attachment loss</td>
<td>Approved</td>
</tr>
<tr>
<td>Nonsteroidal inflammatory drugs</td>
<td>Used in adult or chronic periodontitis in research</td>
<td>Slow the progression of attachment loss</td>
<td>Research</td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>Used in adult or chronic periodontitis research</td>
<td>Increase bone mineral density and Slow the progression of attachment loss</td>
<td>Research</td>
</tr>
</tbody>
</table>

Targeted the host response.

Professional mechanical therapy, such as scaling and root planing, removes plaque biofilm from the tooth surface, as well as removing calculus (tartar), and it decreases endotoxin on the root surface cementum. Scaling and root planing, when performed with hand or ultrasonic instrumentation, decreases gingival inflammation, decreases probing depth, and facilitates gain in clinical attachment levels. This therapy must be distinguished from a dental prophylaxis. The goal of scaling and root planing is to remove plaque, calculus, and endotoxin as far into the periodontal pocket as possible, where a prophylaxis (conventional tooth cleaning) is more superficial. In cases of mild to moderate periodontitis, scaling and root planing may be the definitive therapy for the average patient, as well as for patients with complex medical problems or with end-stage periodontitis.

The bacteria in plaque biofilm may be controlled using chemical agents in mouth rinses, toothpastes, and intrapocket delivery systems. Both antiseptics and antibiotics are available. Antiseptics are the agent of choice for gingivitis because of the unfavorable risk to benefit ratio of antibiotics for the treatment of inflammation. At present, the gold standard antiseptic is chlorhexidine gluconate. In the United States, chlorhexidine gluconate is available in mouth rinse form. When used in a 30-s rinse, chlorhexidine gluconate reduces gingival inflammation up to 60%. Other antiseptics include triclosan copolymer or triclosan zinc-citrate, essential oils, and stabilized cetylpyridinium chloride (CPC).

Sustained release antimicrobial agents are in the form of a biofilm necessitating high doses of antimicrobial for efficacy. Tetracyclines, metronidazole, clindamycin, spiramycin, and combinations such as metronidazole and amoxicillin have been tested with mixed results. Systemic antibiotics are not indicated for gingivitis in most cases of chronic periodontitis but may be used to treat aggressive destructive periodontitis.

Surgical Techniques

Periodontal surgical therapy aims to facilitate patient plaque control through pocket reduction and improved clinical attachment (Table 3). Simple mucoperiosteal flap elevation provides access to bony defects for more thorough debridement than closed scaling and root planing may provide. The flap may be apically positioned with or without recountouring of the underlying bone. Bone grafting techniques may involve materials that are osteoconductive or osteoinductive. Alloplasts or synthetic grafts are generally osteoconductive. Autogenous bone grafts have the highest potential for bone growth. Osteoinductive materials include freeze-dried bone allografts from a tissue bank. Allografts should be tested to avoid transmission of pathogenic viruses from donor to recipient. Barrier membranes either nonresorbable or resorbable, may be used alone or in conjunction with graft materials. The goal of the barrier membrane is to exclude epithelium from the healing surgical wound, thereby promoting periodontal regeneration.

Biological agents to promote the growth of new periodontal ligament, cementum, and bone are increasingly available. These are detailed in Table 4.

Bone morphogenetic proteins have been tested in experimental systems and in limited clinical trials. Formation of bone and cementum has been shown. Other growth factors such as platelet-derived growth factor and insulin-like growth factors have also been tested. Autogenous platelet-
growth factors may be delivered using the patient’s own plasma. Most recently, the Food and Drug Administration approved a biologic including insulin-like growth factor and platelet-derived growth factor for regeneration in periodontal defects.19

Enamel matrix protein has been shown to increase bone fill in intraosseous defects.20 As well, an anorganic bovine-derived hydroxyapatite matrix cell-binding peptide (P-15) has been shown to increase bone fill in intraosseous defects.21 The patient’s own growth factors are used when a membrane is used to cover the osseous defect and blood clot, thereby promoting osseous fill.

**Therapy Directed at the Host Response**

A newer concept is therapy directed at the host response (Table 5). Low-dose tetracycline therapy has been shown to improve attachment levels in patients with periodontitis.22 This therapy is relatively long-term, and its mechanism of action is believed to be inhibition of matrix metalloproteinases. Other therapies directed at the host response are used in research. These include nonsteroidal anti-inflammatory drugs that slow the progression of alveolar bone loss.14 Bisphosphonates have also been shown to increase alveolar bone density while slowing the rate of bone loss.23

**FUTURE DIRECTIONS**

Current research is focused on eliminating pathogens and improving host response to bacteria with the aim of moderating bone and attachment loss. As well, bone grafts with allografts, alloplasts, and biologics are coming into the armamentaria for periodontal therapy with the aim of improving the predictability of fill of osseous defects.

**REFERENCES**


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Chapter 87. Oral Bone Loss and Osteoporosis
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INTRODUCTION
Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing to increased risk of fracture, with bone strength determined by both bone density and bone quality. Periodontitis is an infection-mediated process characterized by resorption of the alveolar bone as well as loss of the soft tissue attachment to the tooth and is a major cause of tooth loss and edentulosity in adults. The primary etiology of periodontal disease as a bacterial infection has been established. Several subgingival bacteria including Porphyromonas gingivalis, Prevotella intermedia, Bacteroides forsythus, Actinobacillus actinomycetemcomitans, and others are leading candidates as etiologic agents in periodontal disease. The loss of soft tissue attachment and resorption of alveolar bone as a result of bacterial infection lead to tooth loss and edentulousness, which, in turn, result in the resorption of the remaining residual ridge and continued loss of oral bone. Oral bone loss has been shown to be associated with osteoporosis and low skeletal BMD. The interaction of host infection and host susceptibility (i.e., osteoporosis) in the incidence and progression of oral bone loss and periodontal disease continues to be an area of intensive investigation, with most published studies supporting a positive association. However, many of these studies are cross-sectional in nature, include relatively small sample sizes and have inadequate control of potential confounding factors, limiting our understanding of the nature of the relationship between these common conditions.

METHODS TO ASSESS SYSTEMIC OR POSTCRANIAL BONE
Interpretation of published findings is complicated by various methods to assess both postcranial and oral bone loss. Techniques used to assess systemic BMD include single and dual photon absorptiometry (SPA and DPA), single- and dual-energy absorptiometry (SXA and DXA), QCT, radiographic absorptiometry (RA), and ultrasound (US). Systemic density can be measured at various skeletal sites, each including differing proportions of cortical and trabecular bone that may more (i.e., wrist) or less (i.e., spine) approximate that found in the oral cavity. Not all studies of oral bone loss and osteoporosis rely on some measure of BMD. Some use clinical observations, such as history of bone fracture.

METHODS TO ASSESS ORAL BONE
There are several techniques used to assess oral bone and bone loss, and all typically involve use of radiographic measures of the oral bones. The commonly used assessments of oral bone include measures of loss of alveolar crestal height (ACH), measures of resorption of the residual ridge after tooth loss (RRR), and assessment of oral BMD.

ACH is assessed using oral radiographs. In this technique, oral radiographs (bitewings) are taken in regions of the oral cavity that include intact teeth. These radiographs are typically digitized, and distance measurements are made from fixed points on the teeth (the cemento-enamel junction [CEJ]) to the top of the alveolar bone (crest) adjacent to the tooth (Fig. 1).

ACH is usually measured at two sites per tooth (mesial and distal) and is often reported as the average loss of bone height in all teeth measured in the mouth (mean ACH). The larger the mean ACH reported, the worse the bone loss surrounding the teeth. However, ACH may be reported in other ways (e.g., the number or the percent of teeth measured with ACH loss beyond a certain millimeter threshold; Fig. 1).

Cross-sectional assessments of bone height can be troublesome because ACH values can be affected by tooth loss. Teeth that have been lost because of periodontal disease no longer contribute to ACH assessments. As such, the teeth with the worst periodontal destruction (and presumably the worst oral bone) are lost, no longer contributing to average ACH measures, resulting in assessments that seem to be better than they actually are. Prospective studies are less prone to the affects of tooth loss on measures of ACH. Methods to account for periodontal related tooth loss in measures of ACH have been proposed; however, no overall consensus on methodologies to deal with this issue has been reached, and most published studies to date have not accounted for the impact of tooth loss on these ACH loss estimates.

After a tooth is lost, there is resorption or recession of the oral bone in that region. This phenomenon is called RRR. Most often the extent of RRR is described in edentulous subjects, but RRR can be described in dentate subjects that have lost one or more teeth in the region of tooth loss. RRR can be described in cross-sectional studies, but more meaningful information can be obtained in prospective studies where the rate of RRR after tooth loss or extraction is described.

Measurement of oral bone density has been assessed using a variety of techniques that include measurement of absolute bone density (DXA, DPA, QCT, RA) of oral bones and studies that approximate change in oral density over time, such as computer-assisted densitometric image analysis (CADIA). All techniques used to assess oral bone density are limited to some extent by either cost or precision. QCT provides perhaps the best assessment of oral density because it allows for assessment of density in various regions of the oral bones without obstruction by teeth; however, this technique is relatively expensive and includes relatively high exposure to radiation. Both DPA and DXA have been used to assess oral bone density; however,
positioning and reproducibility of oral density is difficult. RA has been used in several studies using bitewing radiographs taken with a calibrated step-wedge of known density in the field of X-ray. Reproducibility of this method is good when positioning aids are used.

Region of the oral bone measured varies by technique to assess oral density. Density assessments in human cadavers have shown variation across regions of the mandible by edentulation and by age and gender. QCT can measure virtually any region. RA is restricted to regions that can accessed by bitewing radiographs. DXA and DPA can measure the mandible; however, obstruction by teeth in dentate subjects makes measurement of the basal bone easier to access and reproduce than regions surrounding the teeth. Most measurements are made in the in the mandible because of easier access. Within the mandible, subregions that may be measured include molar, premolar, or incisor regions. Each region has the potential to be of different cortical thickness, which may affect density, especially techniques that are two-dimensional and sensitive to thickness differences. Most (DXA, RA) but not all (QCT) measures of oral density are two dimensional. Ability to measure oral bone density is restricted at least in part by whether or not teeth are present, with edentulous subjects being easier to measure without potential for tooth obstruction. However, edentulous subjects may have marked resorption of the residual ridge, which in turn affects the area of comparison and ultimately density. Attempts to use radiomorphometrical indices in panoramic radiographs to predict skeletal density have been largely disappointing.

Although tooth loss is the ultimate endpoint of periodontal destruction, it can also be used as a proxy measure of oral bone loss. Teeth are held in place by oral bone and surrounding soft tissue. Loss of oral bone will impact tooth stability and eventual loss. Reason for tooth loss is complex, and in addition to periodontal destruction, can include caries and trauma and is often determined by extraction practices of the dentist. There are other measures used to assess extent of periodontal disease that are not directly measures of oral bone. These include probing measures to assess loss of soft tissue attachment surrounding the teeth such as the clinical attachment level (CAL) and pocket depth (PD). Although assessment of loss of soft tissue attachment is a primary means to assess periodontal disease by dental professionals, discussion within this chapter will be limited to measures of oral bone loss. Further discussion on the relation of CAL and PD to osteoporosis can be found elsewhere. Finally, any review of evidence on the relation of oral bone loss and osteoporosis should consider both demographic makeup of the population under study (age, gender, race) and control of potential confounding variables that can vary markedly across studies and impact both the findings and interpretation.

STUDIES OF OSTEOPOROSIS, ACH, AND RRR

Most but not all studies of the relationship between osteoporosis or low skeletal BMD and ACH have shown an association. However, the studies published to date are limited in number and are largely cross-sectional in nature. Loss of ACH and RRR is more predominant in females than males and most predominant in older subjects. Presumably, the stronger consistent association found in older female subjects is associated with lower BMD in these groups. Humphries et al. showed that age was an important factor in loss of height in the residual ridge in edentulous adult mandibles in females but not in males. Ortmann et al. assessed a random sample of 459 radiographs from edentulous patients and found a significantly higher percentage of women with severe RRR than men. Older female subjects (≥55 years) were more likely to be edentulous than older males and both male and female younger subjects. Hirai et al. found skeletal osteoporosis strongly affects RRR in edentulous patients (r = −0.42, p < 0.01), as did female gender and increasing age.

Loss of ACH was assessed in 70 postmenopausal women to determine its relation to systemic BMD. Complete dental and BMD assessments (DXA) were performed, and a comprehensive medical and dental history was taken. Lower BMD of the femur was significantly correlated with worse mean ACH and was persistent after control for confounding.

In a more recent cross-sectional cohort of postmenopausal women from this same group, the relationship between osteoporosis and severity of alveolar crestal bone loss was studied. This well-controlled study of >1300 postmenopausal women showed a strong association between T score category and ACH, with those in the osteoporotic category having the worst ACH. This association was most evident in women 70 years of age or older who were over three times more likely to have moderate or severe ACH levels if they were osteoporotic. Studies of younger subjects have not found a consistent association between skeletal BMD and ACH. Elders et al. assessed the association between alveolar bone height, spinal BMD, and metacarpal cortical thickness (MCT) in 286 women 46–55 years of age, 21% of which were edentulous. The MCT and spinal BMD of dentate and edentulous subjects was not found to be different. In the dentate subjects, mean ACH was not correlated with spinal BMD, MCT, age, and years since menopause. The lack of an association may be limited by selection of relatively young subjects (46–55 years) when prevalence of osteoporosis may be low. Similarly, Ward and Mannon were unable to show a significant relationship between ACH and metacarpal BMD in a younger group (mean age, 41 years). However, “rapidity” (alveolar bone loss divided by age) was associated with the metacarpal bone index in females but not males.

Prospective studies of the association of ACH and skeletal BMD are limited. However, one small but well-designed 2-year longitudinal study in 59 postmenopausal women determined that smokers (n = 21) had a higher frequency of ACH loss and worse oral density in the crestal and subcrestal regions than nonsmokers (n = 38). A significant interaction between spinal BMD and smoking on change in alveolar BMD was found, with the nonsmoking subjects with normal spine BMD gaining oral density over time, and subjects with low BMD who smoked losing oral BMD over time.

OSTEOPOROSIS AND ORAL BONE DENSITY

Studies have found that oral bone density is correlated with systemic bone density and osteoporosis. Mandibular BMD has assessed using DPA and was found in a series of studies to be associated with total skeletal mass in osteoporotic women. Mandibular density assessed by DPA was shown to be highly accurate and precise. Using this technique, von Wowern et al. found that women had significantly lower BMC of the forearm and mandible compared with men and that, in older subjects, mandibular density varied by sex and age. Rates of BMC loss were greater over time in older women than men.

Osteoporotic women were found to have significantly lower mandibular and forearm BMC values than controls in a case-control study of 12 women with a history of osteoporotic fractures and 14 normal controls. Mandibular BMC values in osteoporotic women were 2 SD below those for young “normal” women in 92% of the osteoporotic group and in 64% of the controls, suggesting a large portion of the controls also had mandibular osteopenia.
A series of studies has been conducted to determine the relationship between osteoporosis and oral bone density and other indicators of oral health in postmenopausal women using a reproducible microdensitometry technique to determine mandibular density. In one study, 30 postmenopausal women 55–71 years of age with history of vertebral fracture taking part in a larger randomized clinical trial had significant associations between RRR and bone height and radius density. Height of the mandible was correlated with tooth loss but not with density of the forearm regions or the mandible (r = 0.21). Mandibular density was correlated with total body calcium (r = 0.89) and forearm density (r = 0.60) in edentulous women (n = 7); however, only the correlation with total body calcium was statistically significant. A significant correlation was found to exist between forearm density and oral bone density. In another study, mandibular bone mass and cortical thickness at the gonion was found to be significantly correlated with BMD of the spine (r = 0.39) and radius (r = 0.33) in 50 women, 20–90 years of age, without vertebral fractures noted at enrollment. Associations were most apparent in the older (>50 years) women. However, when spinal trabecular density was measured using QCT, only the association with cortical thickness at the gonion persisted. In 112 women 50–85 years of age with or without prevalent vertebral fracture, women with vertebral fracture had significantly lower mandibular bone mass and density. Cortical thickness at the gonion was significantly higher in the normal subjects. and others further showed that mandibular mass was correlated with all skeletal measures in osteoporotic women. The height of the edentulous ridge correlated with total body calcium and mandibular BMD. Postmortem studies in edentulous female (n = 24) and male subjects (n = 26) found the specific gravity of the mandible and radius decreased with increasing age. Females had lower densities than males, and mandibular and radius measures were highly correlated (r = 0.634, p < 0.01). BMC in 25 edentulous mandibles taken from cadavers by DPA was found to increase in male subjects with advancing age, whereas mandibular BMC of female subjects tended to decrease with advancing age. Mandibular density measured by QCT differed between partially and totally edentulous postmenopausal women who had been edentulous >12 years, suggesting years edentulous may be important when assessing the relationship between skeletal and mandibular density. Hormonal and endogenous hormone levels have been assessed in their role in BMD of oral and skeletal regions. Hormone therapy’s effect on future BMD was assessed in a prospective study of 69 women. The relationship between spinal density (DPA) and mandibular density (RA) was significantly yet moderately correlated at baseline and at an average 5-year follow-up in 28 of the subjects. Change in density in the jaw and spine were also significantly correlated. In a small study (N = 24) measuring estrogen levels (17-β-estradiol [E2]) among postmenopausal women, alveolar BMD was assessed using CADIA to measure the relative change in density in cortical and trabecular regions of posterior interproximal alveolar bone. A net gain in alveolar density was found in E2-sufficient women compared with those who were E2-deficient (p < 0.001); however, the number of sites gaining/losing density were similar. CADIA does not allow calculation of absolute density changes. In a 2-year study of the oral bone density and bone height changes in 38 nonsmoking postmenopausal women with periodontal disease, women with low BMD had higher rates of density loss and ACH loss than those with higher BMD. Estrogen deficiency was also found to be associated with greater loss of both oral BMD and ACH in women overall and for crestal region density in osteopenic women. These findings were supported by results of a 3-year double-blind randomized clinic trial of hormone therapy that revealed that both oral and postcranial BMD were increased in postmenopausal women taking oral estrogen therapy compared with placebo. In addition to the positive change in BMD, a significant increase in ACH was observed. A 28-month prospective study of the mandibular BMD (DXA), hip BMD (DXA) and ultrasound assessment of the calcaneus and hand in 18 postmenopausal edentulous women found the largest change in density occurring in the mandible with other significant loss seen in the femoral neck and Ward’s triangle. Insignificant changes were seen in the trochanteric region and in all regions assessed by US. The change in mandibular density in this study was 7.54% per year. Although small, this study provided evidence of differential loss of BMD by region. Several important questions remain regarding the correlation between systemic and oral bone density including determination of normal ranges of mandibular density by age and sex, further comparison of mandibular density in normal and osteoporotic women, assessment of longitudinal progression of mandibular bone loss, comparison of the rate of bone loss in the mandible compared with other skeletal regions, and the effects of different therapies on mandibular density compared with other skeletal sites. Further study of measurement error in various techniques to assess oral density is also needed.

OSTEOPOROSIS AND TOOTH LOSS

Numerous studies have looked at the relationship between osteoporosis and tooth loss, and most have found a positive association. A cross-sectional study of mandibular BMD in osteoporotic women found tooth loss and edentulism were significantly more common in the osteoporotic group. On average, the osteoporotic women had lost 6.9 mandibular teeth compared with 4.5 teeth in women with normal BMD (p < 0.05). In a second study, osteoporotic subjects were reported to be edentulous more often than normal subjects (20% versus 7%), although the differences were statistically insignificant. In a previously reported study of osteoporotic women, 20% of all women studied were edentulous. Taguchi et al. has studied the relation between tooth loss and oral bone density. The first study included 269 subjects, 99 men and 170 women, 3–88 years of age. In males, no relationship was seen between mandibular cortical width and tooth loss; however, in female subjects, a decrease in mandibular cortical bone width was positively correlated with tooth loss. In women past their seventh decade of life, the association was most apparent. In a cross-sectional study of 64 women 50–70 years of age, tooth loss was found to be highly correlated with prevalence of spinal fracture. A positive relationship between loss of the posterior teeth and alveolar and spinal bone density has been reported; however, no association was found between anterior teeth and density of the spine or oral cavity. A large cross-sectional study of the association of tooth loss to BMD of the spine and hip in 608 men and 874 women found skeletal BMD in male subjects correlated with self-reported tooth loss, after controlling for age, body mass index (BMI), and smoking. However, the association of tooth loss with BMD was insignificant in the females studied after controlling for the effects of age, BMI, and smoking. Overall, 24% of the men and 27% of the women were edentulous, less than expected from previous estimates from this region. No information was available on the use of hormone therapy in females. Krall et al. found a significant positive relationship between number of teeth and BMD of the spine (p < 0.05) and
radius \((p < 0.01)\) in a cross-sectional study of 329 postmenopausal women. The association persisted after control for pack-years of smoking, years since menopause, education, and body mass. A subsequent analysis of participants of one of three prospective clinical trials of calcium and vitamin D assessed the relationship between bone loss in the hip, spine, and total body and tooth loss in healthy, white, dentate, postmenopausal women. In 189 women followed, 45 had lost at least one tooth during the next 7 years. Those who had lost teeth were significantly more likely than those who retained their teeth to lose BMD in the whole body, femur, and spine (relative risk = 4.83, 1.50, and 1.45, respectively), after controlling for years since menopause, BMI, number of teeth at baseline, smoking, and intervention assignment. Interestingly, all women enrolled had relatively normal spinal BMD values at baseline (i.e., no osteoporosis); therefore, the relation of systemic bone loss to tooth loss would be predicted to be low over the 7-year study period. Of note was that one-half the women recruited reported \(\geq 400\) mg daily calcium dietary intake at baseline.

A related study of estrogen use after menopause and tooth retention in 488 women found estrogen users had more teeth than nonusers (12.5 versus 10.7, \(p = 0.046\)), and duration of estrogen use independently predicted number of remaining teeth (\(p = 0.05\)). Long-term users of estrogen had more teeth than never users (14.3 versus 10.7, \(p < 0.02\)). Estrogen use was shown to be protective for tooth loss, regardless of type of tooth or location in the mouth. Users of estrogen (1–4 years) had 1.1 more teeth than nonusers. A 3-year prospective Swedish study of 14,375 older men and women found that women with the fewest teeth at baseline (lowest tertile) had a risk of hip fracture that was twice that of the women in the highest two tertiles. The association between tooth loss and hip fracture was stronger in the men studied, with the risk of fracture 3-fold higher in men with the fewest teeth at baseline, although the absolute number of hip fractures was greatest in women. A recent 10-year prospective study found alveolar bone loss (ACH) at baseline was the strongest independent predictor of incident tooth loss in postmenopausal women. For every millimeter of ACH loss, there was a 3-fold increase in incidence of tooth loss in these older women. Not all studies have found an association between BMD and tooth loss. Klemetti et al. did not find an association with tooth loss and BMD in a group of 355 Finnish women; however, dental practices in Finland may have led to extractions for preventative purposes rather than as a result of underlying disease. One-half of all women studied had all their maxillary teeth, and 25% of women had all their mandibular teeth extracted before the age of 30, suggesting reason for tooth loss was likely not periodontal in nature.

Several studies of younger women have not shown an association between BMD and periodontal disease. Hildebolt et al. found no association between spine or femur BMD and number of remaining teeth among 135 subjects enrolled in a hormone therapy study trial. Subjects were relatively young postmenopausal women who had 10 or more teeth present and no periodontal pockets deeper than 5 mm at enrollment, limiting the ability to detect an association between BMD and tooth loss. Earnshaw et al. found no relationship between BMD and tooth number in 1365 white women 45–59 years of age, who were within 12 years of menopause. Analysis included adjustment for age, years since menopause, hormone therapy use, and center. This was a fairly large well-controlled study; however, the underlying risk of tooth loss in this relatively young population may have been too small to observe in this study. A recent prospective study of a subgroup of participants from the Study of Osteoporotic Fractures found absolute BMD and percentage change in BMD were similar in women dentate and edentulous at baseline examination. Additional studies are needed to further define this relationship in larger cohorts of women, especially prospective cohorts, where temporality can be established.

**POSSIBLE MECHANISMS AND THE BIOLOGICAL BASIS**

Based on our knowledge of osteopenia and periodontal disease and the risk factors that affect both, it is reasonable to propose the following hypothesis: periodontitis results from bacteria that produce factors that cause loss of collagenous support of the tooth, as well as loss of alveolar bone. Systemic factors can lead to loss of BMD throughout the body, including loss in the maxilla and mandible. The resulting local reduction of BMD in the jawbones could set the stage for more rapid ACH loss because a comparable challenge of bacterial bone-resorbing factors could be expected to result in greater alveolar crestal loss than in an individual with good bone mass. There are, in addition, systemic risk factors such as smoking, diabetes, diet, and hormone levels that affect systemic bone level and may also affect periodontitis. Although periodontal disease has historically been thought to be the result of a local infectious process, others have suggested that periodontal disease may be an early manifestation of generalized osteopenia.

Mechanisms by which osteoporosis or systemic bone loss may be associated with periodontal attachment loss, loss of alveolar bone height or density, and tooth loss continue to be explored. Several potential mechanisms have been proposed. First, low BMD in the oral bones may be a associated with low systemic bone. This low BMD or loss of BMD may lead to more rapid resorption of alveolar bone after insult by periodontal bacteria. With less dense oral bone to start, loss of bone surrounding the teeth may occur more rapidly. Second, systemic factors affecting bone remodeling may also modify local tissue response to periodontal infection. Persons with systemic bone loss are known to have increased systemic production of cytokines (i.e., interleukin-1, interleukin-6) that may have effects on bone throughout the body, including the bones of the oral cavity. Periodontal infection has been shown to increase local cytokine production that, in turn, increases local osteoclast activity resulting in increased bone resorption. Third, genetic factors that predispose a person to systemic bone loss also influence or predispose an individual to periodontal destruction. Last, certain lifestyle factors such as cigarette smoking and suboptimal calcium intake, among others, may put individuals at risk for development of both systemic osteopenia and oral bone loss.

Prospective study of the association between osteoporosis and oral bone loss is needed in large cohorts where temporal sequence can be established and where adequate assessment and control of confounding variables can be done. Both osteoporosis and periodontal disease are major health concerns in the United States, especially in older populations. As the population ages, the impact of both osteoporosis and periodontal disease will be more profound. Studies that improve our understanding of the mechanisms by which osteoporosis and oral bone loss are associated are needed and will be increasingly important in the prevention of morbidity and mortality related to these two very prevalent disorders in older Americans.

**REFERENCES**


