Future of bone pathology, bone grafting, and osseointegration in oral and maxillofacial surgery: how applying optical advancements can help both fields

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Abstract. In recent years, advances in technology are propelling the field of oral and maxillofacial surgery into new realms. With a relatively thin alveolar mucosa overlying the underlying bone, significant diagnostic and therapeutic advantages are present; however, there remains an enormous gap between advancements in physics, in particular optics, and oral and maxillofacial surgery. Improvements in diagnosis, classification, and treatment of the various bone pathologies are still being sought after as advancements in technology continue to progress. Combining the clinical, histological, and pathological characteristics with these advancements, patients with debilitating pathologies may have more promising treatment options and prognosis. Defects in the facial bones, particularly in the jaws, may be due to a number of reasons: pathology, trauma, infections, congenital deformities, or simply due to atrophy. Bone grafting is commonly employed to correct such defects, and allows new bone formation through tissue regeneration. Growing use of dental implants has focused attention on osseointegration and its process. Osseointegration refers to the actual process of the direct contact between bone and implant, without an intervening soft tissue layer. The theories proposed regarding this process are many, yet a clear, unified stance on the actual process and its mechanisms has not emerged. Further investigation using optical probes could provide that unifying answer. The primary goal of this manuscript is to introduce pioneers in the field of optics to the field of oral and maxillofacial surgery. With a brief introduction into the procedures and techniques, we are hopeful to bridge the ever-widening gap between the clinical science and the basic sciences. © *2013 Society of Photo-Optical Instrumentation Engineers (SPIE)* [DOI: 10.1117/1.JBO.18.5.055006]

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1 Introduction

Interest in osteology is unique among the medical sciences as it applies to every area in the human body, garnering attention in nearly every medical specialty, from neurosurgery to radiation oncology. Dentistry, specifically oral and maxillofacial surgery, is no exception. While our field is considered a specialty of dentistry, we spend a significant amount of time as a surgical specialty as well. Thus, we are heavily involved in both fields, and spend much of our energy bridging the gap between the two. While much of dentistry is focused solely in the oral cavity, our field is dedicated to the entire maxillofacial region. Trauma, cancer reconstruction, and even aesthetic procedures are just three of the areas in which our field oversees. In recent years, advances in technology are propelling the field of osteology into new realms. The study of bone physiology and pathologies has garnered sufficient attention because of the severity of such conditions. Increases in scientific advances have paved the way for unique opportunities to provide better care and more efficient therapeutic options for patients with such pathologies.

2 Bone Pathology

The densely calcified nature of bone tissue provides it with remarkable properties that allow it to resist fracture even

under the most forceful stresses. Additionally, its collagenous composition, while small, allows it to flex ever so slightly to avoid fracturing. Bone's inherent physiology is also a constantly changing and adapting process that plays a significant role in whatever role the body needs, such as maintaining and producing blood cells to replenish those lost, providing a physical barrier to vital organs, or acting as a support structure for movement. Unfortunately, like any other part of the body, bone is susceptible to a variety of diseases that can cause it to react in a dynamic fashion. The origin of many osseous diseases ranges from hereditary to infectious to idiopathic (cause unknown). Bone disease may arise in all ages, races, and genders. While all bone diseases can affect any bone in the body, we are focusing on those primarily in the maxillofacial skeleton, as those are the ones we deal with most often.

Much like other bones in the body, the maxilla (upper jaw) and mandible (lower jaw) suffer from both generalized and localized forms of skeletal pathologies. The presence of teeth adds another unique dimension to several of these diseases, making the bone more susceptible to a variety of forces and infections, and altering the response of bone to the injury. The diagnosis of bone pathologies is still based on radiographic interpretation and hard tissue biopsy evaluations by a trained specialist. The use of the terms radiolucent and radiopaque will be used to describe the various radiographic features. Radiolucent images permit the passage of radiant energy and

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appears gray to black on the exposed film. Radiopaque obstructs the passage of radiant energy and appears light or white in exposed film. While the various pathologies can often be narrowed down to a select few by the clinician, timing of treatment and appropriate management can be enhanced with advances in technology. It is important to note that it is impractical to go over all of the pathologies associated with the jaws; as such, we will describe some of the common lesions associated with the jaws and the difficulties in diagnosing and treating them. The following pathologic descriptions are from the textbook "Oral & Maxillofacial Pathology" by Neville et al.[1]

2.1 Osteogenesis Imperfecta

Osteogenesis imperfecta refers to a group of disorders related to defects in collagen maturation. Because collagen is a ubiquitous protein, the effects of this disorder are seen in a variety of structures within the body, such as the bone, dentin of teeth, sclera of the eyes, ligaments of joints, and skin. This disorder is considered to be the most common type of inherited bone disease. The defect in collagen maturation leads to bone formation with thin cortical bone with finer trabecular bone. If the area is fractured, there will be an abundance of calluses formed. Although any area of the body can be affected, we have elected to highlight those areas related to the oral cavity.

The dental alterations in osteogenesis imperfecta are rather distinct, as a blue to brown translucency occurs due to the poorly formed dentin; nevertheless, extreme bone fragility may lead to an increased incidence in fractures, particularly in the jaws. Histological evaluation reveals the presence of osteoblasts, and yet low bone matrix formation, which causes the bone to resemble immature bone. It appears the main issue is the failure of woven bone to mature into lamellar bone. There are several variations with this disorder, and depending upon the type found, the prognosis can vary from good to poor.

2.2 Idiopathic Osteosclerosis

This disorder represents a unique group of potential pathologies that are characterized radiographically by an isolated area of increased radiodensity. The origin of such findings is unknown, making it all the more mysterious. Fortunately, patients with idiopathic osteosclerosis demonstrate no remarkable symptoms. Histologically, the lesion consists of dense lamellar bone with some fibrofatty marrow, helping to distinguish it from other more dangerous pathologies.

2.3 Paget's Disease

As one of the more puzzling disorders of bone, Paget's disease still remains an important target for research. With its characteristic abnormal pattern of bone resorption and deposition, patients affected usually demonstrate a markedly weakened bone structure. It still remains one of the more common bone disorders, and varies in the bones it can affect. Pain in the affected area is the most common symptom, which can also be mistaken for arthritis as the pain occurs near the joints. When it affects the skull, there is a progressive increase in the size, leading clinicians to ask whether the patient's cap size has changed. When affecting the skull, an increase in spacing between the teeth is a common occurrence, while older patients complain that their dentures feel too tight. In the osteoblastic (deposition)

phase of this disease, patchy areas of sclerotic bone form, leading to the radiographic appearance of cotton wool.

Histologically, Paget's disease is distinguished by the presence of osteoclasts in the resorptive phase with concurrent deposition by osteoblasts. The formation of an area of osteoid matrix around the trabecular bone is also found. Additionally, the fatty bone marrow is replaced by a highly vascular fibrous connective tissue. Generally it takes clinical, radiographic, and supportive laboratory results to confirm the diagnosis of Paget's disease. Fortunately this disease is usually nonlife threatening, and patients are able to continue leading relatively normal lives with supportive therapy.

2.4 Fibrous Dysplasia

Fibrous dysplasia refers to a tumor-like formation in which the normal osseous structure is replaced by an increase in cellular fibrous connective tissue with areas of irregular bony trabeculae. The diagnosis is often clinically made, and then supported by the histopathological findings. The patient complains of a painless swelling, which has grown slowly over time. Radiographically, the trademark ground glass opacification is seen, and is due to the disorganization of poorly calcified trabecular bone. This coincides with histological findings of an irregularly shaped trabecular bone with a dispersed arranged fibrous connective tissue component (see Fig. 1). These features are key to distinguishing it from similarly characterized features; fibrous dysplasia demonstrates a more uniform pattern as compared to the random mixture of immature woven bone. As the lesion matures, the trabecular bone runs parallel to each other.

Clinical management varies as most cases cease growing after a certain time period. Patients with minimal cosmetic or functional dysfunction may elect to undergo corrective procedures; however, due to the unique physiological characteristics of this disorder, there is a chance of regrowth.

2.5 Cemento-Osseous Dyplasia

Considered by many to be the most common fibro-ossous lesion in clinical dentistry, cemento-osseous dysplasia remains a confusing disorder in terms of classification. Due to similarities, both clinically and histopathologically, with other lesions, it is often either misdiagnosed or undiagnosed. When seen on an x-ray, the lesion may be entirely radiolucent or could be densely radiopaque with a radiolucent rim. It is now commonly agreed upon that the lesion usually appears as mixed radiolucent/radiopaque in nature. Variations of this disorder are commonly encountered, including focal, periapical (below the tooth), and florid (spread throughout the jaws). Radiographically, the periapical variant resembles an inflammatory or cystic lesion, and this difference can lead to drastic changes in treatment options.

Histologically, the lesions are composed of portions of mesenchymal tissue, consisting of fibroblasts and collagen fibers with some vascular components interspersed. The fibrous connective tissue contains a mixture of osseous portions of woven bone and lamellar bone (see Fig. 2). The mineralized portion varies from site to site and lesion to lesion. Maturing lesions demonstrate increased mineralization to fibrous connective tissue ratio as time progresses. Clinically, the lesion is gritty and fragments easily when removed from the affected area, which is in contrast with similar lesions such as ossifying fibromas, which separate cleanly from the bone.
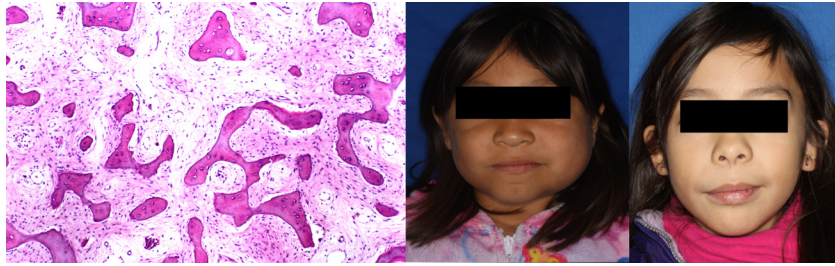
Fig. 1 Fibrous dysplasia. The characteristics curvilinear trabeculae (dark purple) of woven bone without osteoblastic rimming that arise in a background of fibrous tissue (light pink). Clinically, both patients exhibit maxillofacial swellings that appear similar. Only through histologic biopsy was it determined that the patient on the left has fibrous dysplasia, while the patient on the right has an ossifying fibroma. Thus, the treatment options vary greatly between these two clinically similar pathologies.
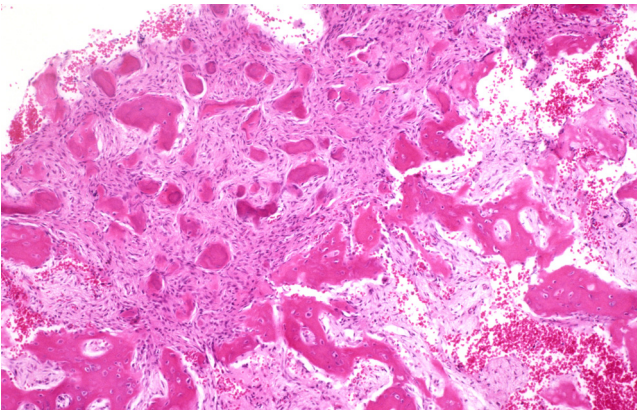

Fig. 2 Cemento-osseous dysplasia. Note the characteristic trabecular bone (dark pink) intermixed in a vascular fibrous stroma (lighter pink with dense spots).

Fortunately, this disorder does not appear to be neoplastic, and thus, does not necessitate surgical excision; however, increased sclerosis of the lesion may lead to decreased vascularity and eventual necrosis. There is a possibility for exposure of the lesion in the oral cavity, and at this point surgical intervention may be indicated.

2.6 Ossifying Fibroma

Unlike the cemento-osseous dysplasia, this disorder is considered a true neoplasm with a high growth potential. Nevertheless, the two are often confused for one another, despite their distinct differences. This neoplasm, much like cemento-osseous dysplasia, consists of a mixture of trabecular bone and cementum with fibrous connective tissue. The origin of this neoplasm still remains a mystery; it was once postulated that it was a remnant from the tooth structure. This disorder can manifest itself into a painless swelling of the involved osseous structure, leading to facial asymmetry. Radiographically, the ossifying fibroma is demonstrated as a large radiopaque lesion.

Because of its high rate of mineralization (when compared with similar disorders such as cemento-osseous dyplasia and fibrous dysplasia), the delineation between the lesion and the surrounding bone allows for a clean separation from the osseous environment. Pathologists utilize the differences in mineralization when diagnosing such disorders; ossifying fibroma demonstrates a more random pattern of ossification than fibrous dysplasia. For larger, aggressive lesions, the treatment of choice is surgical resection with bone grafting, and has a generally favorable prognosis.

2.7 Osteosarcoma

The most common type of malignancy of osseous origin is osteosarcoma; it refers to malignancy of mesenchymal cells that have the ability to produce poorly formed bone matrix. Although the frequency of this neoplasm is significantly less in the jaws than in the extraskeletal region, its discussion is necessary as its consequences are both severe and devastating. The demographics of osteosarcoma are as follows: average age is 33, equally involving the maxilla and mandible, with a slight male predilection. The most common symptoms are swelling and pain of the associated area, with increased mobility of the teeth. X-ray interpretations vary from dense sclerosis to mixed radiopaque/radiolucent to an entirely radiolucent lesion. As with many tumors of the jaws, there is marked resorption of the roots of the nearby teeth, which is demonstrated by a gradual spiking appearance. Nevertheless, the traditional sun-ray appearance often seen in osteosarcomas of the limbs is also seen in the jaws. This characteristic lesion is due to osteophytic bone production on the surface of the lesion.

Histopathologically, there is a great variety among osteosarcomas, and this is primarily due to the varying amounts of osteoid produced by the defective mesenchymal cells. Additionally, chondroid, a precursor to cartilage, can also be found within the fibrous connective tissue. This variability leads to the different types of osteosarcomas, based on what the mesenchymal cells are producing: osteoblastic (mainly osteoid), chondroblastic (mainly chondroid), and fibroblastic (mainly fibrous connective tissue). Of the three types, chondroblastic osteosarcomas comprise the majority of those found in the jaws, with some cases demonstrating lobules of cartilage with surrounding osteoid production.

When compared to osteosarcomas in the extremities, those found in the jaws have shown to be slightly less aggressive. Nevertheless, the main challenge faced by clinicians still remains incomplete surgical excision of the tumor, especially in the oral cavity. Although the current mode of therapy includes significant amounts of chemotherapy, the use of radical surgical removal remains the standard of care. Surgeons still resect well past the known margins for complete removal; however, this carefulness does not come without a cost. Many esthetic features are sacrificed, which can eventually lead to more difficult and significant rehabilitation.

2.8 Dentigerous Cyst

The jaws present a unique histological situation when compared with other areas of the body because of; the potential for epithelial-lined cysts in bone. This is due to the embryological origin of teeth and its progression. Jaw cysts that are commonly encountered are lined by epithelium, and are classified as either developmental or inflammatory. While those in the inflammatory category are often caused by infections or other outside determinants, developmental cysts appear to be the most challenging in both treatment and diagnosing, and thus, we will focus our attention on the three most commonly encountered: dentigerous cysts, ameloblastoma, and odontogenic keratocysts (OKCs).

The dentigerous cyst is the most common of all developmental cysts, and encloses the crown of an unerupted tooth and attaches just short of the root. Although the actual developmental process is unknown, some have theorized that an accumulation of fluid between the epithelial lining and the crown causes its formation. These cysts can grow to considerable size and may be associated with a painless expansion of the bone in the area. Radiographically, the area will appear as a single radiolucency associated with the crown of an unerupted tooth; the radiolucency is well demarcated. There is some subjectivity when determining whether the radiographic appearance is a dentigerous cyst or a follicle encircling the tooth, and as such dentigerous cysts cannot be diagnosed radiographically. A tissue biopsy must be performed and sent for evaluation in order to appropriately diagnose the lesion.

Histopathologically, the appearance of loosely arranged fibrous connective tissue, which contains subepithelial ground substance, along with cords of odontogenic epithelial remnants is the key feature. In some cases, the fibrous tissue contains significant amounts of collagen, and the epithelial remnants may demonstrate keratinization. Standard treatment of the cyst involves enucleation (removal of the cystic contents without cutting into it) as well as extraction of the unerupted tooth. Complete removal of the cystic contents ensures a low rate of recurrence and excellent prognosis.

2.9 Odontogenic Keratocyst

Radiographically, the dentigerous cyst can resemble an OKC, yet clinical and histological evaluation reveals a much different picture. The OKC exhibits a distinct growth pattern from the dentigerous cyst and the clinician must approach a suspected lesion appropriately. While the cyst can also be associated with swelling and pain, there is not an obvious sign of bony expansion (which is different from the dentigerous cyst), and there may be associated drainage from the area. Radiographically, the larger lesions may appear as multiple small areas of radiolucency (see Fig. 3). Also when compared to dentigerous cysts, there is not a commonly associated resorption of nearby roots; however, the diagnosis of such a disorder usually begins at the biopsy stage, and is confirmed histopathologically.

Histologic features of an OKC are distinctive and usually definitive for the lesion. The cystic lumen is oftentimes filled with a cheese-like material that is composed of a mixture of keratin and an oily-like substance known as keratinaceous debris. The surface of the lumen of the cyst appears wavy or corruagated, an appearance only demonstrated microscopically.

Much like the dentigerous cyst, the typical mode of treatment is enucleation; the complete removal is difficult because the lesion is extremely fragile, necessitating removal in several pieces. Unfortunately, the recurrence rate is rather high when compared with that of a dentigerous cyst. Nevertheless, the prognosis is rather favorable for patients.

2.10 Ameloblastoma

Ameloblastoma is one of the most common odontogenic tumors diagnosed, and its origin can be traced to its native epithelial

Fig. 3 Odontogenic keratocyst (OKC). Note the basal epithelial layer (delineated by purple spots at the base), which is composed of hyperchromatic, columnar cells. Also note the wavy appearance of the apical (top area). Note the radiolucent area on the right mandible in the panoramic radiograph. This finding is representative of the three main types of epithelial osseous cysts. Clinical photographs are unremarkable and not distinguishable between the differential diagnoses.

state. While considered to be a benign tumor, they are often slowly growing and locally invasive. Three variants exist: a conventional solid/multicystic, unicystic, and peripheral. Radiographic imaging often exhibits a soap bubble or honeycomb appearance (see Fig. 4). Many of the cases involve bony expansion, and roots near the tumor are often resorbed. While these characteristics are indicative of an ameloblastoma, definitive diagnosis requires histological evaluation via biopsy.

The histopathological features of all three variants demonstrate similarities, and for the purpose of this article, they will be discussed as one tumor. Much of the lining is composed of islands of epithelium within a mature fibrous connective tissue stroma (see Fig. 4). Also contained within this mixture are ameloblast-like cells; ameloblasts are the cells that produce and secrete the enamel on the crown of the tooth. Enamel is the hardest substance in the body, as its inorganic component comprises a higher percentage than that found in bone. In some cases, there is a degree of osseous metaplasia within the dense fibrous tissue, giving the tumor a mineralized product.

As stated earlier, the definitive diagnosis is usually made after microscopic examination of the tissue extracted in the biopsy. Ameloblastic components in the sample are the determinants on whether or not adequate tissue was excised. The traditional ameloblastoma tends to infiltrate the surrounding trabecular bone, and thus, the actual margin of the tumor may not be adequately known until it has already caused significant destruction. The conventional solid/multicystic ameloblastoma can be a devastating and potentially deadly neoplasm that spreads to vital structures. As such is the case, most surgeons elect for careful treatment and designate 1.0–1.5-cm margins past the suspected site for the areas of resection.

2.11 Roles for Raman and Other Optical Spectroscopies

Raman spectroscopy has the ability to determine the molecular composition of specific tissue (either hard or soft), which can then be classified according to its differences.[2,3] While this technique has not yet been fully applied to the pathologies described above, we believe that the subtle, yet inherent, histological and molecular differences between each disorder can be differentiated using advances in optics. This would potentially alter the diagnosis and, most likely, the timing and type of treatment. Additionally, near-infrared spectroscopy (NIRS) may be used as a way to also diagnose diseased bone, and even distinguish it from healthy bone.[4,5] While Raman spectroscopy has proven to be effective in analyzing bone excised from the native site, studies at sites other than the oral cavity have run into difficulty assessing the bone *in vivo*, as penetration through the soft tissue has proven arduous.[3] Fortunately, the mucosa overlying the hard tissue in the oral cavity offers no such resistance. There is no significantly thick connective tissue between the epithelium and bone, eliminating many of the drawbacks seen in the leg or arm, for example. This technique has also proven advantageous for analyzing such disorders as osteogenesis imperfecta and osteoporosis.[3,6] We believe the oral cavity provides the ideal environment for utilizing NIRS and/or Raman spectroscopy to analyze pathologic changes in bone.

3 Bone Grafting

Bone grafts are often necessary to restore hard tissue defects in both the mandible and maxilla. In addition to restructuring the bony sites for implants and other esthetic purposes, they can also provide structural support for prosthetic devices (such as dentures) and act as a load-bearing area for mastication. Nevertheless, in recent years, the need for bone grafts in the maxilla and mandible is generally due to stability for implant placement. Additionally, grafts can be used to restore continuity defects because of pathological reasons or traumatic injury (see Fig. 5). Regardless of the size or the cause of the defect, each one poses a unique set of circumstances that reconstructive surgical procedures must address. Modern advances in the physiologic properties of bone, protein aided regeneration, and advanced surgical techniques have provided patients with the

Fig. 4 Ameloblastoma. The central islands demonstrate a loose arrangement of epithelial cells. While the radiographic appearance is remarkably similar to that of the OKC, the histological differences are significant. Much like the OKC and dentigerous cyst, there appears to be no significant clinical appearance indicating the definitive diagnosis. Intra-oral photograph does not demonstrate anything remarkable.
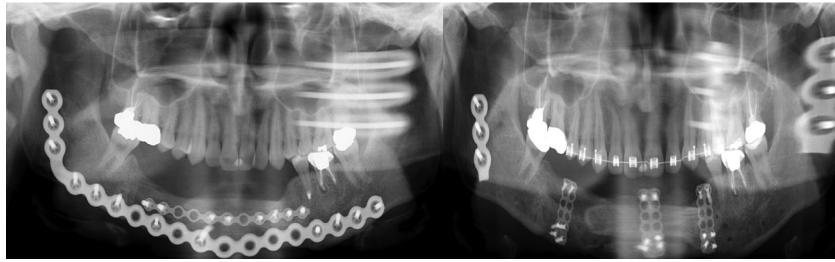
Fig. 5 Placement of an autogenous bone graft to increase the vertical dimension of the anterior mandible post-surgical resection. In this case, we used a piece of autogenous bone that was interposed between a bone cut. We also supplemented the bone graft with rhBMP-2. The photo on the left was taken preoperatively; the photo on the right was taken a few months after grafting. Note the increase in bone height.

type of care that was once unheard of. Nevertheless, challenges in such procedures still remain, and as a result, new advances are being sought to address such issues.

Unlike other connective tissue grafts used, bone grafts present a unique set of properties that provide it with advantages not usually observed with other types. The healing and subsequent new bone formation develops from tissue regeneration as opposed to tissue repair from scar formation.[7] This remarkable process results from two basic physiological actions that work together. The first phase in bone grafting involves the newly transplanted osteoblasts proliferating and forming a new osteoid matrix. The amount of matrix formed is dependent upon the amount of cells within the graft. Although a large graft may be used, the time without adequate blood to nourish it diminishes the amount of working osteoblasts, causing less osteoid to be formed than if blood had been continuously supplied. The second phase of the process involves changes to the recipient site that usually begins a few weeks after the graft has been placed. In this phase, there is significant growth in blood vessels (angiogenesis) and fibroblast proliferation, which aids in osteogenesis. The fibroblasts and other cells transform into osteoblasts, which form more osteoid matrix. Continued integration involves resorption, replacement, and remodeling of the new grafted site.

3.1 Autogenous Grafts

These types of grafts are known as self-grafts, as they are composed of tissues from the individual receiving the graft. Unlike the other types, this graft is generally free from any immune reaction seen in other grafts, making the first phase of bone grafting much less eventful. In our field, this is the most commonly used graft because the bone can be taken from any site in the body. One of the more commonly used autogenous grafts is the block graft, which are solid pieces of cortical bone with a core of cancellous bone. Many cases of bone augmentation involve the use of the iliac crest or rib, in which the entire thickness can be used. The bone pieces can be ground up into a particulate nature, and these particulate marrow and cancellous bone grafts have the ability to contain the highest concentration of cells with osteogenic potential.

As stated earlier, adequate blood supply is needed to maintain the viability of the osteogenic cells, and in the case of autogenous grafts, this is accomplished with the use of an autogenous graft still attached to its muscle. In other cases, the block bone is excised with its overlying soft tissue, as a blood vessel supplying the graft is dissected and transferred along with the graft. Once the graft has been placed in the recipient site, the accompanying vessel is attached to the surrounding vessels, maintaining the blood supply.

While autogenous grafts certainly have several key advantages—their frequent use certainly supports this—they do carry some drawbacks. Since the blood supply to the graft remains vital to its survival, the shape of the graft, as well as the soft tissue attached should not be altered or disturbed. One of the more common setbacks still remains donor site morbidity as both hard and soft tissues are removed, which may leave an unaesthetic scar.

3.2 Allogenic Grafts

One way to side step the disadvantage of donor site complications seen in autogenous grafts, an alternative method utilizes bone from a different individual of the same species. To minimize the risk of an immune reaction, many of these grafts are freeze-dried, which destroys any cells with osteogenic capability. This reduces the participation in the first phase of bone graft integration, yet the solid nature of the graft itself provides a scaffold for the second phase to occur. In this case, the host is dependent on its own metabolism to provide the cells and elements needed for proper integration.

3.3 Xenogenic Grafts

Xenogenic grafts, also called xenografts, have gained prominence in the field of oral and maxillofacial surgery for small defects, usually on the scale of a tooth socket. These are grafts that involve taking bone from one species, such as a cow or horse, and implanting them in another species. Because of this change, there is a greater chance an immune reaction against the graft, and thus a higher chance of graft failure. As a result, these grafts are often vigorously treated prior to use in order to prevent rapid rejection.

3.4 Bone Morphogenetic Proteins

Recent developments have focused on a group of cytokines to help stimulate the patient's own osteogenic pathways to form new bone. These cytokines, called bone morphogenetic proteins (BMPs), exhibit the remarkable ability to help develop and form new bone. In our field, we have focused much of our work on two BMPs, BMP-2, and BMP-7, which belong to the transforming growth factor (TGF) family of proteins. BMPs interact with their corresponding receptor on the cell surface, and via a chain of events, leads to the differentiation of osteoblasts.

With the common occurrence of continuity defects in the jaws (either maxilla or mandible) due to trauma, pathology, and any other cause, clinicians have sought ways to incorporate

the use of BMPs, specifically BMP-2. One specific variant of BMP-2, recombinant human BMP 2 (rhBMP-2) has been shown to induce bone formation in large-sized defects in many animal models.[8–11] Boyne demonstrated in a 2001 study that BMP-2 effectively induced bone regeneration in nonhuman primates, which had the same biological and biomechanical functions as native bone.[12] The bone was radiographically analyzed and found to assume the appropriate structure of its location. Herford and Boyne then attempted to observe the outcome of rhBMP-2 in 14 patients with varying mandibular continuity defects;[13] all 14 patients showed adequate and successful bone restoration in the defect sites.

With the success of rhBMP-2 established, we chose to use this particular cytokine in many of our continuity cases; rhBMP-2 helps in stimulating and recruiting chemotactic factors that eventually differentiate stem cells into preosteoblasts and functional osteoblasts.[14] While BMP-2 is sufficient by itself in stimulating this response, it does require a carrier to provide retention. At our institution, we utilize a collagen scaffold called absorbable collage sponge (ACS), which also possesses some osteoconductive properties as well. The ACS allows for the slow release of the BMP during the initial healing stage, and also helps to prevent any aberrant release of the BMP in the blood stream, which may cause systemic toxicity. The physical properties of the sponge, however, may also prove to be a drawback as its compressibility may not maintain the space needed for osseous filling of the defect. To circumvent this problem, we employ a titanium mesh plate to provide more rigid support.

When compared with conventional autograft/allograft material, BMP-2 can provide several advantages, while carrying its own disadvantages. With rhBMP-2 there is no donor site, and thus no donor site morbidity, reducing the recovery time. Additionally, rhBMP-2 also aids in soft tissue healing, which is extremely beneficial in patients with osteonecrosis. On the other hand, its increased osteogenic potential may lead to ectopic bone growth, as well as an increased chance of swelling or edema near the recipient site; rhBMP-2 is also contraindicated in patients with any allergies to bovine type I collagen. With these pros and cons still being investigated, studies have focused on comparing the abilities of both the bone grafts and BMPs to provide proper bone density for appropriate function. In our institution, preliminary radiographic findings have shown that, at the six-month mark (post-implantation), those sites with only rhBMP-2/ACS did not demonstrate the same bone density as autogenous bone;[14] however, nearly six months after dental implant placement in both sites, bone density was actually higher in the rhBMP-2/ACS than in the autograft site. The reason behind this still is under investigation, and shows that while we have learned much about the BMPs, there is much more that remains a mystery.

3.5 Complications with Grafted Site

No surgical procedure is without risks and complications, and bone grafting is certainly no exception. Many potential complications can occur, such as loosening and/or resorption of the graft, infection, and damage to the adjacent anatomical structures.[15,16] Timing also plays a role in the severity of the graft failure, as studies have shown that earlier complications affect a greater percentage of the graft.[17] Many methods have been devised to mitigate the exposure of the graft to potential pathogens, and one of these involves placing membranes, either resorbable or nonresorbable, over the grafts. Membranes can help in preventing the competing tissue from reaching the bone graft. Titanium mesh has also been utilized as a proper containment system for bone grafts, and has shown to give predictable results. Nevertheless, the membranes themselves are at risk for infection and failure as well. It is imperative that the surgeon be attentive to any signs for complications, as prompt and effective management can minimize poor outcomes and failures.

3.6 Potential Roles for Optical Spectroscopies

Recent studies have focused on the use of laser phototherapy (LPT) in aiding bone healing in defects such as fractures. The effects of near-infrared LPT have shown to demonstrate physiological stimulation of the fractured site.[18] This was proven to be effective as measured by Raman spectroscopy, which showed an increasing deposition of calcium hydroxyapatite, and by fluorescent reading, which showed a decrease in the organic components.[18] Studies have also shown that bone irradiated at the infrared (IR) wavelength demonstrates increased osteoblastic proliferation and activity and collagen deposition as well as a greater percentage of new bone formation when compared with bone that is not irradiated.[19] Low-level laser therapy (LLLT) combined with BMPs and guided tissue regeneration has also been effective in improving bone healing.[5]

4 Osseointegration

The initial definition of osseointegration was, "the apparent direct attachment or connection of vital osseous tissue to the surface of a dental implant, without intervening connective tissue."[20] Although this has been the accepted standard definition for osseointegration, it fails to specifically define the percentage of implant surface needed to be in direct contact with the bone. Some have suggested that osseointegration is a situation in which there is solid anchoring of an alloplastic material in bone that can be retained under functional loading.[21,22] Still other definitions exist, such as considering the process as an osseous scar tissue surrounding the foreign body implant.[23] It is now generally believed that any biomaterial to be used should not cause local or systemic damage, i.e., they must not be toxic, carcinogenic, allergenic, or radioactive. It is vitally imperative that many degrees of compatibility exist between the implant material and the surrounding bone for proper osseointegration to occur.

An ideal implant should elicit physiologic changes within the surrounding tissues, which include bone, connective tissue, and the overlying epithelium (see Fig. 6). The environment immediately surrounding the implant must not lead to any secondary alterations in the organism, or instability of the implanted material. From a mechanical standpoint, studies are still ongoing regarding the appropriate modulus of elasticity of a dental implant within bone, and how the mechanical compatibility can be improved. As of this moment, biocompatibility and mechanical compatibility seem to be the most important factors when considering implant placement. Immunologically, the biomaterials at a clinician's disposal are categorized into four main groups: autologous, homologous, heterologous, and alloplastic. With the exception of autologous materials, the other three represent implant materials.

As many dentists or oral surgeons will attest to, re-implantation of avulsed teeth or placement of autologous bone in a patient is a well-established and successful method of restoring lost structures. The process of re-implantation of avulsed teeth
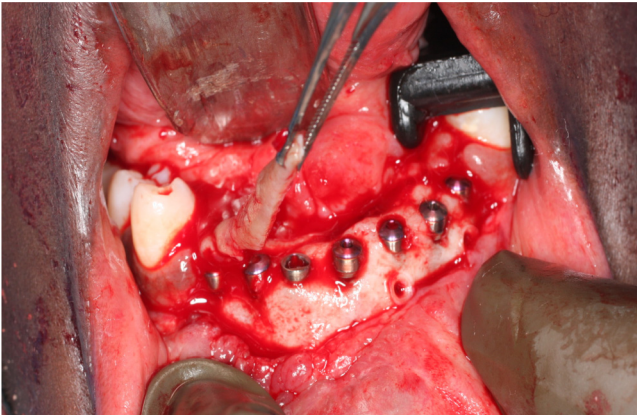
Fig. 6 Multiple anterior titanium dental implants in the anterior mandible. There is a significant period of remodeling in the entire osseointegration process. The stability of the implant during this period is crucial to success of the rehabilitation.

varies with many factors; however, the placement of autologous bone follows a more definitive course that has been well established. When first placed, autologous bone become necrotic to some degree; after some or all of the transplanted bone has been devitalized, it begins to osseointegrate, and then is replaced by new bone.[24] While this new bone formation was first observed with transplanted autologous bone, its principles have stayed through with implanted homologous and heterologous bone, which are commonly used as bone grafting materials for small osseous defects. Both materials are first osseointegrated, followed by a period of remodeling and eventual replacement with newly formed bone.

In the late 1970s, a new form of alloplastic material, titanium, was used as a means of replacing lost tooth structure.[25] While there have been many different types of metals used as dental implants, the path towards titanium metal has garnered the largest following. Titanium is either used as its pure form or as an alloy. As a non-noble metal, it is protected by a layer of titanium dioxide that forms spontaneously in air as well as in water. Fortunately, studies have demonstrated this layer to be biologically inert.[26] There have been several histologic studies that have shown sound incorporation of the titanium implants with the surrounding bone, and this allows many of the compressive and shearing forces to be transferred from the implant to the bone.[27]

There are many theories on the exact surface interaction between the titanium implant and the surrounding bone, but one hypothesis has gained attention. It is thought that the oxide layer on titanium implants is surrounded or coated by thin film of the surrounding tissue's ground substance, which consists of proteoglycans and glycsoaminoglycans. Proteoglycans are common "fillers" within biological tissue and act as binding molecules for cations and water, and glycosaminoglycans act as cell surface adhesion molecules, among other functions. Ultrastructural studies have shown that collagen fibers from the surrounding bone have been found nearly 20 to 40 μm away from this film. This filamentous bundle is eventually replaced by collagen fibers, which are connected and intertwined with the surrounding bone.[28]

It should be noted that the actual process of chemical bonding at the interface between bone and titanium is still under investigation, and may require more advanced techniques for observation. This is, in part, because of the difficulty in sectioning metal and the surrounding tissue at a layer thickness of 800 Å or less.

4.1 Histopathology

As stated earlier, following the implantation of any of the alloplastic biomaterials into bone, the healing process can occur either through bone apposition or by connective tissue encapsulation. The main determinant of proper osseointegration is the mechanical stability of the implant in the healing phase.

Before describing the process of osseointegration, it is important to discuss some of the relevant histological features of the oral cavity. The junctional epithelium is an attachment apparatus that is tightly bound to the enamel or cementum of a tooth, creating a mechanical barrier against foreign invaders within the oral cavity. While this structure spans the entire tooth, it is modified significantly when an implant replaces the lost tooth. During the placement of an implant, the host's inflammatory process begins and an increase in vascularity surrounding the tissues ensues. While the process appears similar to what occurs in the same area when invaded by a pathogenic microorganism, there are some significant differences. In pathologic inflammatory processes, exudation of more inflammatory mediators causes destruction to the normal structures (supporting fibers and alveolar bone). Osteoclastic activity also increases, and continues the destruction of the surrounding bone. In dental implant placement, the epithelial attachment becomes scar tissue that forms in the natural healing process, and does not contain the vasculature seen in the natural tooth structure. Due to the lack of vasculature seen in the scar tissue of the osseous implant bed, the area of the implant cannot mount an effective defense against infection.

The initial stages of osseous healing after implant placement are characterized by slight hemorrhaging, followed by the formation of a blood clot. The formation of this blood clot is critical for osseous healing as its attachment to the implant is increased by the interaction with the roughened surface of the implant. As the process moves further along, there is an ingrowth of capillaries that provide nutrients and cells in a hematologic medium; one of these celltypes is the preosteoblasts, which are essential in bone growth. It is during this time that the implant is recognized as a foreign body, and it begins to mount an immunologic response. It is yet to be understood, but as the bone is formed at the implant surface, the number of immunological cells at the site begins to decrease.[29] It appears that during this time period, the process of acute inflammation and wound healing are occurring simultaneously.

The timing of bone healing and filling after the initial stage just described varies with the width of the gap between the implant surface and the osseous bed. The space can usually be filled by new woven bone within two weeks. This woven bone can then be remodeled within eight weeks into lamellar bone. It is during this period where the clinician and patient must be careful not to disrupt the process. There is some debate as to the percentage of direct contact between bone and implant, with some stating 56% to 85%,[29] and others stating 46% to 82%.[25] The portion of the implant that is not covered by bone is usually filled with adipose tissue.

Defects in the cortical bone (bone found in the jaws of humans) with a diameter of approximately 0.2 mm will heal by the formation of lamellar bone. Defects between 0.3 and 0.6 mm are regenerated through the formation of trabecular bone from the fibrous or woven bone. Cells that participate

in this bony repair originate from the periosteum, endosteum, or Haversian system. Direct bridging of a small bone defect (less than 0.2 mm) occurs at a rate of 1 μm/day, and does not require a bony callus. Those defects that are significantly wider require intervening fibrous tissue and a bony callus, and bone formation occurs at a rate of 50 to 100 μm/day.

As the osseous bed of the implant is being prepared, many of the osseous blood vessels are damaged, causing the release of blood within this space. With the clotting reaction commencing, a thin and loose attachment of fibrin accumulates on both the implant and the bone. Within the next week to two weeks, this hematoma will remodel by the proliferation of new blood vessels and connective tissue. Shortly after this remodeling, new bone formation also begins, and occurs directly in the immediate surroundings of the implant. As stated earlier, this period is crucial to implant survivability, as instability of the implant may hinder cell proliferation and differentiation and subsequent bone formation. It is our experience that the development of any superfluous connective tissue within the implant's immediate environment can hinder new bone growth, and hence, mechanical stability.

After nearly one and a half months, the bony callus has been completely remodeled, and via the Haversian system, resorption canals form, helping the process continue into the formation of lamellar bone. Osteoid matrix is mineralized into the mature, calcified osseous substance of about 1 μm/day.[30]

4.2 Anatomic and Age Considerations

Tooth extraction, whether implant replacement occurs or not, leads to a remodeling of the surrounding alveolar bone. In addition to the resorption by osteoclasts, there is also bone deposition within the extraction socket itself. The timing of the resorption is crucial as well; this rate is highest in the first 12 weeks, and then slows considerably 24 weeks later. It generally takes nearly two years for the remodeling process to be complete!

While the resorption process may appear to be consistently the same in all bone, unfortunately, it is not. The process varies not only in different parts of the body, but also within the oral cavity. The average rate of resorption in the mandible is higher than in the maxilla by three to four times[31] in patients who have lost all of their teeth. While the rates vary between the maxilla and mandible, one common feature is the progressive loss of height of the alveolar bone. For patients who opt for implant placement, this can pose a significant challenge to patients and clinicians, as secure anchorage of an implant requires adequate bone quantity and density. Many of these patients are also past the age of 50, at which point osteoporosis begins to take effect. This physiologic reduction in the trabecular density, coupled with a decrease in functional osteoblasts because of hormonal insufficiencies, can make placing dental implants extremely difficult. Typical signs of these osteoporotic lesions include internal resorption, also called centrifugal osteolysis, which increases the bone marrow space and concurrent loss of trabecular bone. While the standard method of evaluating these changes has been radiographs, methods of analyzing the quality of trabecular bone through the thick cortical bone would be beneficial to both the patient and the clinician. As of now, the quality of bone is subjectively determined by the surgeon, with the initial hole drilled through the bone.

4.3 Potential Roles for Optical Spectroscopies

Studies at our institution utilizing standard Raman spectroscopy have provided us with the standard spectroscopic features for a titanium implant. It will be through further animal studies that will provide us with more answers regarding implant osseointegration and the metabolic changes associated with it. We hope to gather more information, which will significantly add to the literature regarding this technique.

While much of the discussion involving dental implants and spectroscopy has revolved around osseous changes, specifically, that which occurs directly around the implant, the surrounding soft tissues should not be ignored. Soft tissue changes surrounding the implant can also impact the success or failure of the implant, and as such optical spectroscopy may also help identify any drawbacks associated with such changes. One study demonstrated that hemodynamic alterations associated with inflammation, and thus, potential implant failure can be detected utilizing optical spectroscopy.[32] By measuring parameters such as tissue oxygenation, total hemoglobin, deoxygenated hemoglobin, and edema, a clinician can gain a better understanding of how the patient's surrounding tissues are responding to implant placement. Nogueira-Filho et al.[32] demonstrated this noninvasive method of analyzing the tissue, which may lead to newer insights on identifying and diagnosing peri-implant disease. This method may allow access to such information more rapidly, without any additional invasive procedures.

5 Conclusion

The gulf between the basic sciences, specifically between the physical sciences and the field of surgery, appears to be shrinking. However, it still remains wide between the physical sciences and maxillofacial surgery. While the reasons are numerous, it would be superfluous to enumerate them. Instead, it should be the focus of both surgeons and scientists to look toward the future in hopes of bridging this gap. The field of oral and maxillofacial surgery has an extremely wide scope, and thus, many concepts were excluded from this manuscript. The topics we chose to discuss reflect some of the more pressing issues facing surgeons in our field, which we believe can be aided by the field of optics. While we have begun to study the use of Raman Spectroscopy in osseointegration, such studies are only in their infancy. Our institution has been one of the leaders in bone physiology in the field of dentistry and oral and maxillofacial surgery, yet there are other institutions that focus on other topics. It is our goal to initiate discussions with the leaders in physics, particularly in the field of optics, with the hope that ideas can eventually lead to more collaboration between the two fields.

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