Bone Grafting

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Abstract

Successful dental implant placement for restoration of edentulous ridges depends on the quality and quantity of alveolar bone available in all spatial dimensions. There are several surgical grafting techniques used in combination with natural or synthetic materials to achieve alveolar ridge augmentation. The commonly available bone tissue replacement materials include autografts, allografts, xenografts, and alloplasts. Polymers (natural and synthetic) are widely used as barrier membrane materials in guided tissue regeneration (GTR) and guided bone regeneration (GBR) applications. However, there is no single ideal technique or graft material to choose in clinical practice currently. Treatment protocols and materials that involve less invasive and more reproducible vertical and horizontal bone augmentation procedures are actively sought. This chapter focuses on existing surgical techniques, natural tissues, and synthetic biomaterials commonly used for bone grafting in order to successfully restore edentulous ridges with implant-supported prostheses.

9.1 Preamble

Patients who become edentulous late in their lives provide unique challenges to clinicians who are to treat them and restore their dentition. These elderly patients have great difficulty in getting used to complete dentures, and when provided with the option, they seem to be more reluctant in accepting dental implants [1]. Even when such patients agree to getting dental implants placed, there are several anatomical and surgical limitations encountered. How successful dental implants ultimately are crucially depends upon the degree of osseointegration in sufficient and healthy bone [2, 3]. Dental implant osseointegration is dependent on a wound-healing response that could be less successful in older than in younger patients [4, 5]. Bone volume and quality are almost always reduced due to extended time after teeth are lost before implant placement [6, 7]. An average alveolar bone loss of 1.5–2 mm (vertical) and 40–50% (horizontal) occurs within 6 months after teeth are lost [8]. If the dentition is not restored and left

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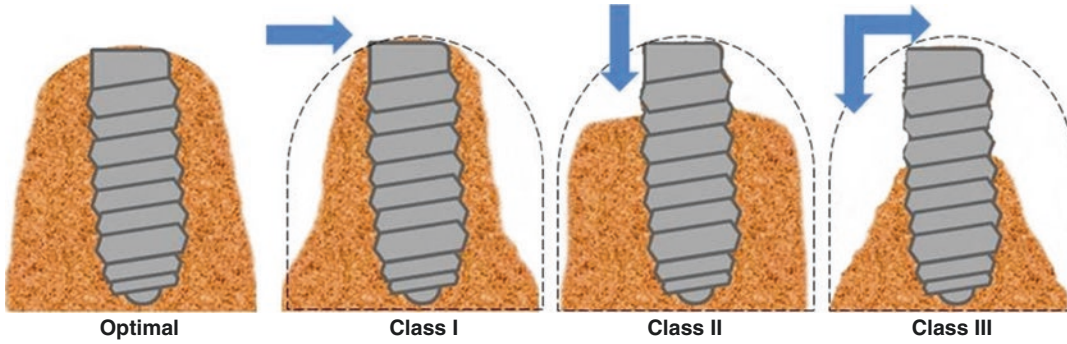

Fig. 9.1 Alveolar bone insufficiency for dental implant placement. When there is adequate alveolar ridge height and width, this allows for successful dental implant placement with optimal clinical results. In class I ridge defects, there is horizontal bone loss with adequate height leading to insufficient bone volume for successful regular diameter implant placement. In class II there is vertical bone loss with adequate width, leading to insufficient bone volume for proper placement of regular length implants. In class III there is bone loss in both vertical and horizontal dimensions not allowing placement implants in all spatial dimensions

untreated, then bone loss occurs continuously, and in the first 3 years, up to 60% of alveolar ridge volume is lost [9, 10]. This lack of sufficient bone volume, height, and quality poses extreme challenges to the final treatment outcome (Fig. 9.1) [11, 12]. A variety of bone grafting surgical techniques with and without the use of biomaterials have been explored to try successfully place dental implants in resorbed alveolar bone [13, 14]. Multiple bone grafting techniques and natural and synthetic graft materials have been tested for this purpose [14, 15], and this chapter discusses the various bone grafting techniques currently available to achieve alveolar ridge augmentation for allowing successful placement of dental implants.

9.2 Principles of Bone Regeneration and Various Grafting Techniques

Bone grafting procedures for alveolar ridge augmentation are based on biological principles of bone tissue regeneration. The osteoblasts (bone-forming cells) and osteoclasts (bone-resorbing cells) are the two basic cellular units that play a role in bone tissue formation and remodeling. The osteoblasts are derived from the mesenchymal stem cells (bone marrow stromal stem cells), while osteoclasts are derived from the hematopoietic progenitors of monocytic lineage [16]. The key factors involved in differentiation of osteoblasts are estrogen, parathyroid hormone, vitamin D3, fibroblast growth factors (FGFs), and transforming growth factor-beta (TGF-β) [17–19]. Whereas, osteoclast differentiation depends on the activation of colony-stimulating factor-1 receptor/macrophage colony-stimulating factor/CD115 (MCSF, a colony-stimulating factor receptor) and receptor activator of nuclear factor kappa-B (RANK) receptors [20], osteoblasts regulate osteoclast differentiation and activation of RANK ligand (RANKL) and its high-affinity decoy receptor, osteoprotegerin. Therefore, osteoblasts are essential to osteoclast differentiation by regulating the balance between RANKL and osteoprotegerin [21].

The presence and/or recruitment of osteoblast precursors and growth factors at sites of augmentation are essential for bone regeneration to occur. Some graft materials (cancellous autogenous grafts) and the recipient bed can provide the osteoblast precursors required [22], whereas the growth factors come from the vasculature and recipient bed. Active bone resorption and formation throughout the graft dominate the early phase of bone regeneration at grafted sites [23]. The latter phase is mainly known to be characterized by the osteoconductive processes [24]. Osteoconduction is a function of a bone graft substrate providing a three-dimensional (3D) scaffold area promoting ingrowth of host capil-

laries and osteoprogenitor cells [25]. Biomaterials that imitate natural bone chemistry and structure closely are considered ideal for cellular osteogenic differentiation. Graft macroporosity and pore interconnection have a major impact on osteoinduction potential as higher levels of porosity, appropriate pore shape, and sufficient interconnectivity are essential for ingrowth of blood vessels and bone matrix deposition [26].

During the initial first few weeks, new bone is synthesized by mature osteoblasts that are differentiated from osteoblast precursors under the influence of osteoinductors. The growth factors involved in formation of new bone act directly on osteoblast and fibroblast proliferation, mesenchymal cell differentiation, extracellular matrix deposition, and vascular proliferation [27].

Early stages of induction are influenced by the fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF) by stimulating fibroblast and osteoblast proliferation. Bone morphogenetic proteins (BMPs) affect later stages of osteoinduction such as vascular proliferation and mesenchymal cell differentiation, whereas transforming growth factor-beta (TGF-β) does not affect mesenchymal cell differentiation but acts on cellular proliferation, matrix deposition, and vascularization [14]. The various bone grafting techniques employed for alveolar ridge augmentation are discussed in subsequent sections.

9.2.1 Distraction Osteogenesis

Distraction osteogenesis (DO) is used to achieve alveolar bone volume gain in all dimensions. In DO new bone is formed by mechanical elongation of bone callus through progressive separation of two bone fragments surrounding the callus under tension [28]. This is achieved in three phases: (1) the latency phase, in which soft tissues heal after the distractor is placed surgically (this phase usually lasts about 7 days); (2) the distraction phase, in which the bone fragments are separated at a rate of 0.5–1 mm/day incrementally; and (3) the consolidation phase, where the bone formed gets mineralized and matured [29, 30]. Devices used for DO can be intraosseous or extraosseous [31]. However, devices with extraosseous distraction configuration affixed to the cortical plate are more frequently used than intraosseous devices [32, 33]. There is sufficient literature reporting the potential of DO to achieve alveolar ridge augmentation as this technique can result in significantly greater and stable bone height gain compared to other vertical augmentation techniques [34, 35]. High rate of complications is associated with DO [36, 37] with vector control being the major problem which often leads to lingual inclination of the transport segment in the mandible [38]. Although DO allows for greater alveolar bone regeneration from native bone, the sensitivity of the technique and strict anatomical requirements have limited its use in clinical practice.

9.2.2 Osteoperiosteal Flap Techniques

Vascularized segmental osteotomy performed on alveolar bone is used to accomplish the osteoperiosteal flap (OPF) technique which is based on the biologic principles of vascularization studies and understanding of Le Fort I management techniques [39]. The major blood supply of the alveolar bone is from the bone marrow and periosteum. In geriatric patients with the atrophy of the ridge, there is decreased bone marrow blood flow. In OPF technique, vascularization in bone fragments via the periosteum. Osteoperiosteal flaps through segmental osteotomies are used in combination with interpositional grafts in the gap generated by transposition of the flap in the desired position to achieve vertical ridge gain [14]. OPF combined with interpositional grafts via the osteotomy-based techniques are being used commonly for treating alveolar ridges with height deficiencies and allow for preservation of the attached gingiva and the papillae [40, 41].

9.2.3 Block Grafting Techniques

Onlay bone grafting with bone blocks was first introduced in the early 1990s and was used to

try augmenting maxillary and mandibular edentulous ridges [42]. In the classic block grafting technique, autologous bone blocks are immobilized to the recipient alveolar ridge by securing with osteosynthesis screws [43, 44]. Autologous bone grafting has been used for the treatment of severely resorbed edentulous mandible and maxilla [45, 46]. The mandibular ramus or mental region (intraoral) and the iliac crest (extraoral) are the most commonly used autologous donor sites for block grafting [47, 48]. Autogenous bone procured from the iliac crest has been used to gain ridge height, but high resorption rate before implant placement and after loading is observed [49]. This is possibly due to the low cortical-to-trabecular ratio in the graft material, endochondral versus intramembranous ossification memory, and differing osteoblast mechanosensing memory between the donor and recipient sites [14]. Other extraoral donor sites for obtaining block grafts include the tibia, ribs, and cranial vault but are not commonly used due to the high donor site morbidity associated with them [50, 51].

The mandibular ramus and the symphysis are the common sites for harvesting intraoral block grafts [52]. Although the symphysis gives greater bone volume, the morbidity is significantly higher when compared to the ramus grafts which include postoperative pain, neurosensory disturbances in the chin region, temporary mental nerve paresthesia, altered sensation in mandibular anterior teeth, and risk of mandibular fracture [53, 54]. Hence, the symphysis is used for cases that require thicker block grafts that otherwise are not possible to obtain from other intraoral donor sites. Close contact and stabilization of block grafts to the recipient bed are crucial and achieved by using osteosynthesis screws [55–57]. Revascularization and remodeling of bone can also be stimulated via inlay shaping and decortication of the recipient bed [58]. Ridge augmentation with allograft onlay blocks has demonstrated reasonable success [59], and the use of barrier membranes in combination with block grafts has been shown to improve clinical outcome [60–62].

9.2.4 Guided Bone Regeneration (GBR)

Guided bone regeneration (GBR) works on the principle of separation of particulate grafts from the surrounding tissues allowing for bone to regenerate, which naturally occurs at a rate slower than that of soft tissues [63, 64]. Since the major problem with particulate graft techniques is the high graft resorption rate and the anatomical limitations for graft containment [65], barrier membranes are commonly used in GBR technique to stabilize graft materials, to limit their resorption, and to serve as a separating barrier [64]. Local anatomy and type of bone graft tissues and materials used determine the choice of a specific membrane used for GBR. However, in some specific cases, barrier membranes are not used as the graft material can be used alone to fill the defect area [66].

Initially, the principles of GBR were applied to atrophic alveolar ridges for implant site development [67]. GBR has since been used to treat a variety of intraoral bone defect sites and is a routine technique employed in clinical practice [68]. GBR for alveolar ridge augmentation in the vertical direction is extremely technique sensitive, which limits the clinical success, and failure usually occurs due to wound dehiscence [69]. Another limitation of vertical GBR is the ability for bone generation along the long axis of applied force [14]. Barrier membranes combined with particulate and/or block grafts have resulted in more predictable clinical outcomes [70]. It has been demonstrated that there is less resorption of block grafts when used in combination with expanded polytetrafluoroethylene (ePTFE) barrier membranes [71].

Barrier membranes used alone for GBR are associated with membrane compression into the defect space by overlying soft tissues [72]. To overcome this problem, membranes made from still materials such as titanium or metal-reinforced expanded polytetrafluoroethylene (ePTFE) have been developed [73]. Treatment of complex vertical defects requires stable and stiff titanium or metal-reinforced PTFE membranes [65]. A problem associated with use of titanium

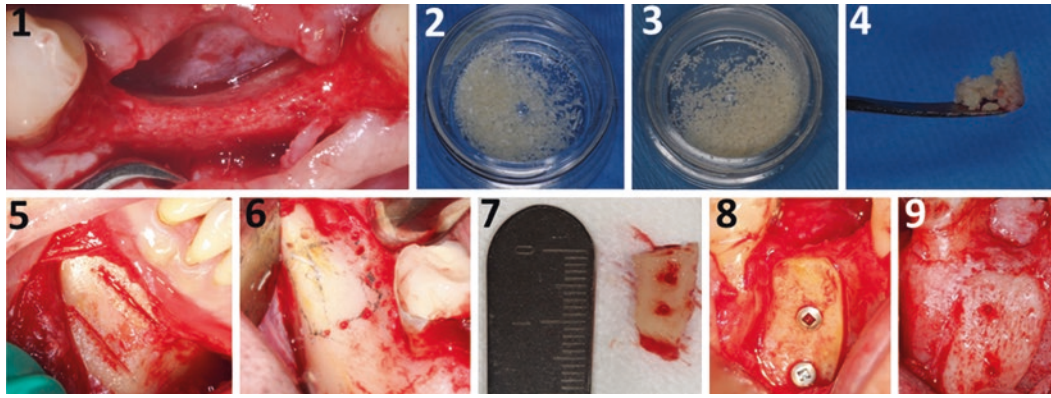

Fig. 9.2 Conventional methods of horizontal bone augmentation. Long-term edentulism can result in disuse bone atrophy resulting in residual ridge resorption of the alveolus. Areas with inadequate buccal-lingual represent a significant treatment challenge and often require horizontal bone augmentation either prior to or during implant surgery (1). Particulate demineralized freeze-dried bone allograft (DFDBA) (2) and particulate mineralized freeze-dried bone allograft (FDBA) (3) are commonly used in horizontal bone augmentation. Particulate graft materials are packed into the defect (4) and covered with biologically compatible membranes prior to achieving primary closure to allow for adequate buccal-lingual width needed for implant therapy. Alternatively, autologous block grafts harvested from the patient's chin or ramus (5, 6, 7) can be fixated to deficient areas using fixation screws (8) which allows for considerable gain in bone width following healing (9) (Periodontology Graduate Clinics, Faculty of Dentistry, University of Toronto)

membranes in GBR is the fibrous ingrowth and exposure of the membrane [74]. GBR therapy by using titanium-reinforced non-resorbable membranes in combination with dental implants has been carried out with varying levels of clinical success [74].

9.2.5 Minimally Invasive Approaches to GBR

Minimally invasive approach to perform GBR is preferred to prevent or reduce postoperative complications and graft exposure [75]. Kent et al. in the late 1970s developed a subperiosteal tunneling technique which involved a relatively small surgical incision in the alveolar ridge to elevate the periosteum and inject a low viscosity hydroxyapatite particle paste [76]. It has been observed that the hydroxyapatite particles are usually unstable and diffuse adjacently into tissues causing fibrous capsule formation which inhibits bone formation [77]. However, minimally invasive tunneling along with screw and/or barrier membrane-mediated graft stabilization can result in relatively predictable alveolar bone augmentation in vertical direction [76, 78]. Calcium phosphates such as injectable brushite cement pastes with controlled viscosity have been investigated for minimally invasive augmentation procedures [79]. Novel graft biomaterials with improved viscosity offer potential for this technique, but results are controversial with insufficient data (Fig. 9.2).

9.3 Natural Tissues and Synthetic Biomaterials Used for Bone Grafting

There are various graft options available and used for alveolar bone grafting and divided into natural transplants (autografts, allografts, and xenografts) and synthetic materials (alloplasts) (Table 9.1) [14]. These graft materials are used because they are either osteogenic, osteoinductive, or osteoconductive [80]. Most grafts undergo macrophage- or osteoclast-mediated resorption before bone deposition by osteoblasts [23, 81]. As discussed before, bone deposition is expedited by osteoinductive ability and adequate blood flow throughout the graft, providing the

Table 9.1 Available tissue and biomaterial options for alveolar bone grafting

Bone replacement graft materials
1. Human bone graft tissues
(a) Autografts
• Extraoral
• Intraoral
(b) Allografts
• Fresh and/or frozen bone
• Freeze-dried bone allograft (FDBA)
• Demineralized freeze-dried bone allograft (FDBA)
2. Nonhuman natural tissues and materials
(a) Xenografts
• Bovine hydroxyapatite
• Coralline calcium carbonate
3. Synthetic materials (alloplasts)
(a) Bioactive glasses
(b) Bioceramics
• Hydroxyapatite
• Other calcium phosphates (tricalcium phosphate, brushite, monetite)

appropriate nutrients and growth factors essential for osteoblast differentiation and function. This section discusses the various graft tissues and biomaterials used commonly for bone grafting procedures.

9.3.1 Autogenous Grafts

Autogenous bone grafts (autografts) are harvested from a site in the same individual and transplanted to another site. Although these provide the most osteogenic organic materials, donor site morbidity, increase in postsurgical recovery time, and the limited amount of graft volume that can be obtained are the disadvantages [13]. Autografts used for bone alveolar bone grafting may be of intraoral or extraoral origin. The various harvesting sites for autografts are the mandibular ramus and corpus; the tuber, spina nasalis, and crista zygomatico-alveolaris from the maxilla; and the tibia and iliac crest [82]. Although autografts of iliac origin provide optimum osteoinductive, osteoconductive, and osteogenic potential [83], there is less morbidity associated with intraoral donor sites when compared to extraoral sites [48]. Mandibular autografts are used very commonly as bone blocks, chips, and/or milled particles [48, 84]. The most common extraoral harvest site that provides relatively large amounts of autologous cortical-cancellous bone is the pelvic rim [85]. Cortical autografts have high initial strength which after about 6 months of implantation is ~50% weaker than the normal bone tissue [86]. On the other hand, cancellous autografts are mechanically weaker because of their porous architecture initially but with time gain strength [80]. Also, the cancellous autografts have been shown to revascularize sooner than cortical grafts around the fifth day postimplantation due to their spongy architecture [80]. Alveolar bone and ridge augmentation in vertical and horizontal dimensions carried out using particulate autografts with GBR has been successful for placing dental implants [87, 88]. However, block grafts outperform particulate grafts with regard to revascularization, bone remodeling, bone-to-implant contact, and bone fill potential [87].

9.3.2 Allogeneic Grafts

Graft tissues obtained from genetically nonidentical members of the same species are known as allogeneic grafts (allografts). These grafts are available in larger quantities for use and do not have the usual drawbacks of autografts. Allografts (cortical and cancellous) of various particle size ranges are used routinely for bone augmentation procedures with minimal risk of disease transmission [89–91]. Allografts are available as cortical granules, cortical chips, cortical wedges, and cancellous powder prepared as frozen, freeze-dried, mineralized, and demineralized bone tissue [92].

9.3.2.1 Fresh or Frozen Iliac Cancellous Bone and Marrow Allogeneic Grafts

Atrophic maxillary ridges when grafted with human block grafts of tibia and fresh-frozen chips show features representative of mature and compact osseous tissue surrounded by marrow

spaces [93, 94]. Fresh and/or frozen cancellous bone and marrow tissues demonstrate the highest osteoconductive and osteoinductive potential among all allografts [95, 96]. However, due to the risk of disease transmission, use of fresh or frozen iliac allografts is now obsolete.

9.3.2.2 Mineralized Freeze-Dried Bone Allogeneic Grafts (FDBA)

Freeze-dried bone allografts (FDBA) are mineralized and are used commonly for the treatment of periodontal defects with reasonable success [97–100]. The process of freeze-drying affects the immune recognition in the host by distorting the 3D presentation of the human leukocyte antigens on surface of graft particles [101, 102]. FDBA have inferior mechanical properties and osteoinductive potential when compared with fresh or frozen allografts [103]. FDBA are known to be osteoconductive and can be combined with autografts to enhance the osteogenic potential [104, 105]. Cortical FDBA have a higher volume of bone matrix, more osteoinductive potential via growth factors stored in the matrix [106]. The use of FDBA blocks for alveolar ridge grafting has demonstrated presence of vital bone with a lamellar organization [107, 108]. FDBA used in combination with resorbable barrier membranes can be used as a replacement to autogenous block grafts for ridge augmentation prior to implant placement [109].

9.3.2.3 Demineralized Freeze-Dried Bone Allogeneic Grafts (DFDBA)

Demineralized freeze-dried bone allografts (DFDBA) are used for grafting procedures alone or in combination with FDBA and/or autografts very frequently. DFDBA grafts undergo resorption quickly [110, 111] and have osteoinductive potential attributed to the morphogenetic proteins (BMPs) stored in the matrix [112]. Growth factors and differentiation factors have also been shown to be present in DFDBA preparations [113, 114]. DFDBA grafts obtained from the younger individuals have higher osteogenic potential in comparison with grafts from older individuals resulting in variation in BMP levels in different DFDBA batches [115, 116]. DFDBA has been shown to have less new bone formation in comparison to autogenous grafts used in similar grafting procedures [117].

9.3.3 Xenogeneic Grafts

Xenogeneic grafts or xenografts are tissues used for bone grafting obtained from nonhuman species. Bone xenografts were first reported in aseptic bone cavities in 1889 [118]. Xenograft materials after implantation are usually osteoconductive and show variable ability to be resorbed and replaced by new bone over time [119, 120]. The commonly used xenograft in dentistry is Bio-Oss®, which is a commercially available bovine bone processed to yield natural bone mineral without any organic component [121]. The inorganic phase of bovine bone remaining after low-heat treatment and chemical extraction of organic component mainly consists of hydroxyapatite that retains the micro- and/or macroporous structural morphology [122]. Although this heat and chemical treatment removes most of the osteogenic components from the bovine bone, it is extremely important as this eliminates any potential risk of disease transmission (bovine spongiform encephalopathy) and graft rejection [123, 124]. Bovine-derived bone particles and block grafts have been used for the treatment of human ridge augmentation procedures and intrabony defect filling [125, 126]. The advantage of using bovine bone as graft materials is the higher osteoconductive potential compared with synthetically derived materials. The major disadvantage of these grafts is the inherent brittleness and lack of toughness as they routinely are prone to failure and breakage during the screw fixation or after implantation leading to less than optimal clinical results [126, 127].

Calcium carbonate grafts are of natural coralline origin and are composed mostly of aragonite which is more than 98% calcium carbonate. Having a pore size of 100–200 μm, very similar to that is observed in cancellous bone, and relatively high porosity of ~45% allows for greater resorption and new bone formation and infiltration

within the graft area [91, 128]. Coralline calcium carbonate demonstrates high osteoconductivity since transformation to carbonate is not required like most other graft materials, allowing for new bone deposition to occur rapidly [129].

Coralline calcium carbonate has the potential for greater defect fill in periodontal regeneration applications and does not undergo fibrous encapsulation [130–132].

9.3.4 Alloplasts

Alloplastic bone grafting materials are sought after because they provide an abundant amount without the problems associated with autografts [133]. These are fabricated in various forms and with varying physicochemical properties and can be both resorbable and non-resorbable [14, 15, 134–136]. Alloplastic materials are usually osteoconductive without having any osteogenic and osteoinductive potential and have been used successfully in periodontal reconstructive applications [135]. The most routinely used alloplastic materials are hydroxyapatite (HA), tricalcium phosphates (TCP), bioactive glasses, and dicalcium phosphates [80].

Synthetic HA is available and used in various forms: porous non-resorbable, solid non-resorbable, and resorbable (non-ceramic, porous) [137]. HA is non-osteogenic and mainly functions as an osteoconductive graft material. The ability of HA to resorb is dependent upon the processing temperature. At higher temperatures the HA synthesized is very dense and non-resorbable [138]. The dense HA grafts are osteoconductive and mostly used as an inert biocompatible filler and have been shown to result in defect filling greater than flap debridement used alone [139, 140]. When processed at lower temperatures, the particulate HA produced is porous with a slow resorption rate [141]. Early implant loading studies in augmented alveolar ridges with nanostructured hydroxyapatite have shown promise [142, 143]. Also, alveolar ridge augmentation with HA granules alone [143] or in combination with autografts has shown high success rates [144].

TCP has two crystallographic forms, α-TCP and β-TCP [79], with the latter more commonly used partially resorbable filler allowing replacement with new bone formation [135]. β-TCP have been shown to be inferior when compared with allografts in terms of resorption and bone formation [145]. There is strong evidence of TCP grafts undergoing fibrous tissue encapsulation [146]. There are studies that report new bone deposition with β-TCP [146–149] and alveolar ridge augmentation in vertical and horizontal dimensions with variable results [147–149].

Bioactive glass is composed of silicon dioxide, calcium oxide, sodium oxide, and phosphorus pentoxide [150], and when implanted as bone grafting materials, the pH of the local environment increases (>10), and a silicon-rich gel is formed on the bioactive ceramic surface with the outer layer serving as a bonding surface for osteogenic cells and collagen fibers [151]. The article sizes of bioactive glasses range from 90–710 μm to 300–355 μm [150, 152], and clinical reports of alveolar ridge grafting and augmentation with bioglass show bone formation in close contact to the particles [150]. However, bioglass is non-resorption which limits the ability of bioglass to work as a bioresorptive scaffold for vertical alveolar bone augmentation.

Dicalcium phosphate (DCP) compounds have a high solubility at physiological pH, and dicalcium phosphate dihydrate (DCPD or brushite) has been tested for both vertical bone augmentation and bone defect repair as injectable cements or as preset cement granules [153–155]. Several clinical studies have demonstrated that injectable brushite cements are capable of regenerating bone in buccal dehiscence defects, atrophic ridges, and maxillary sinus floor elevation procedures [156]. The amount of vertical bone growth obtained with brushite cement granules is seen to be higher than that obtained with commercial bovine HA materials in vivo [157]. However, brushite cements undergo phase conversion to insoluble HA upon implantation and this limits their resorption [79, 158]. Dicalcium phosphate anhydrous (DCPA or monetite) resorbs at faster rates compared to brushite [159–161] and has been shown not to convert to HA [157, 158, 162].

The clinical performance of monetite granules has been compared with commercially available bovine HA and demonstrated greater resorption in vivo and bone formation in the alveolar ridge sockets [154]. Monetite bioceramic materials have been investigated for alveolar bone augmentation as 3D printed onlay blocks, and it has been shown that sufficient bone volume and height gain can be achieved for dental implant placement [155, 163].

9.4 Barrier Membranes Used in Bone Grafting Procedures

The turnover rate of soft tissues is faster than that of bone tissue formation, so using barrier membranes during bone grafting ensures that soft tissues are prevented from infiltrating and occupying the defect space where new bone is to be regenerated. If used in combination with bone grafts, then the membranes serve to stabilize the graft materials [73]. Also, the membranes also function as graft preservation devices by reducing the rate of graft resorption [64, 164]. The natural or synthetic tissues and materials the barrier membranes get fabricated from are required to be biocompatible and not evoke any immune reactions or cytotoxity once implanted [165]. If these membranes are resorbable, then ideally they should biodegrade without leaving any residues, and the degradation rate should match with the tissue regeneration rate. The mechanical properties of these membranes should be adequate to withstand the surgical placement and their function in vivo. The barrier membranes used for alveolar bone grafting can be non-resorbable or resorbable.

9.4.1 Non-resorbable Barrier Membranes

The first non-resorbable barrier membranes investigated experimentally were fabricated using cellulose acetate filters (Millipore®) [166]. Following this, commercial membranes were later produced from Teflon® which is polytetrafluoroethylene (PTFE) [167]. The function of these non-resorbable membranes is temporary as they maintain their structural integrity upon placement and are later retrieved via surgery. This second procedure for retrieval increases the risk of surgical site morbidity and renders the regenerated tissues susceptible to damage and postsurgery bacterial contamination [168]. Membrane exposure due to flap sloughing during healing is also a frequent postsurgical complication observed [169]. As evidence of resorbable membranes being effective increases, non-resorbable membranes are losing their popularity in clinical practice, and their use is being limited to specific applications [170]. Two non-resorbable barrier membranes that are commonly used are the expanded (ePTFE) and the titanium-reinforced polytetrafluoroethylene (Ti-PTFE). PTFE is a nonporous inert and biocompatible fluorocarbon polymer [171]. The ePTFE is chemically similar to PTFE and has been used in vascular surgeries for several decades [172]. ePTFE is made by subjecting PTFE to high tensile stresses which results in expansion and the formation of a porous microstructure [173]. Barrier membranes fabricated with ePTFE are highly stable in biological systems and resist breakdown by host responses. The clinical effectiveness of ePTFE barrier membranes has been studied in numerous studies [174]. There is evidence of periodontal regeneration when ePTFE membranes are used, and these membranes gained popularity and were used routinely in the past [170]. In clinical situations which require larger areas of space maintenance, Ti-PTFE can be used which are stiffer having a central portion reinforced with titanium to prevent collapse [175]. An alternative approach is using a double layer of PTFE membrane with a titanium framework interposed (Cytoplast® Ti-250) which has shown to be successful for ridge augmentation and treatment of large defects in the alveolar process [176].

9.4.2 Resorbable Barrier Membranes

Clinical studies in the early 1990s reported the successful use of resorbable membranes for GBR [177–179]. In the last few decades, research has

been focused upon development of bioresorbable barrier membranes that overcome the inherent limitations of their non-resorbable counterparts. Both natural and synthetic polymers have been investigated for this purpose with collagen and aliphatic polyesters being the mostly researched [180]. Currently, most commonly used resorbable membranes are made of collagen or by polyglycolide and/or polylactide or copolymers of them [181]. The available resorbable barrier membranes are mostly incapable in maintaining defect space on their own due to their lack of rigidity. For this reason these membranes are routinely used in combination with autogenous or synthetic bone graft substitutes [182, 183] with or without the support screws, reinforcements, and pins [184].

9.4.2.1 Natural Resorbable Barrier Membranes

Natural resorbable barrier membranes are fabricated mostly using collagen from tissues from human or animal sources. Collagen is used extensively in biomedical applications and can be acquired from animal skin, tendons, or intestines [180]. Collagen has numerous desirable biological properties such as having low immunogenicity, attracting and activating gingival fibroblast cells, and being hemostatic [185]. It has been shown that collagen membranes stimulate the fibroblast DNA synthesis [178]. Also, osteoblasts show higher levels of adherence to collagen membrane surfaces in comparison to other barrier membrane surfaces [186]. The biodegradation of commercially available collagen membranes is accomplished by endogenous collagenases into carbon dioxide and water [185]. These enzymes are produced mainly by the macrophages and polymorphonuclear leukocytes (PMNs) [23]. The degree of cross-linking of collagen fibers directly affects the rate of degradation with the relationship being inversely proportional [187].

AlloDerm® Regenerative Tissue Matrix (RTM) is a collagen Type I derived from human skin (cadavers). AlloDerm® has been shown to support tissue regeneration by allowing rapid revascularization and white cell migration. The membrane thickness ranges from 0.9 to 1.6 mm, and clinical applications include gingival augmentation, root coverage, soft tissue ridge augmentation, and soft tissue augmentation around dental implants [188]. AlloDerm GBR® RTM is manufactured utilizing the same process used for AlloDerm® RTM, and the membrane thickness ranges from 0.5 to 0.9 mm used for graft protection, containment, and flap extension to achieve adequate primary closure [189]. Paroguide® is a collagen Type I membrane enriched with chondroitin sulfate. There are reports of periodontal ligament regeneration and alveolar bone regeneration, with no signs of inflammation [182, 190]. Avitene® is a microfibrillar hemostatic collagen Type I membrane derived from bovine corium. Histological evaluation after a clinical study has shown that this membrane was not very effective and is difficult to handle during the surgery [191]. Bio-Gide® is a barrier membrane synthesized from collagen Types I and III derived from porcine skin source. Bio-Gide® has been seen to resorb in about 8 weeks with studies demonstrating their regenerative potential [192]. BioMend Extend® is fabricated from Type I collagen derived from bovine Achilles tendon. The membrane is semi-occlusive, having a pore size 0.004 μm, and resorbs in 4–8 weeks after implantation. Clinical results have revealed limited clinical effectiveness, dependent upon form and size of the defect [193]. Cytoplast RTM® is synthesized with collagen Type I derived from bovine tendon and is a multilayered membrane which takes 26–38 weeks for complete resorption. It has an organized fiber orientation providing good handling and high tensile strength [194, 195]. Collagen membrane cross-linked by diphenylphosphoryl azide is a Type I collagen membrane, derived from calf pericardium and cross-linked by diphenylphosphoryl azide. Although histology reveals significant inflammatory reaction [196], clinical studies have shown effective tissue regeneration outcomes [190]. Collistat® is another collagen Type I material which has demonstrated guided regeneration potential with the membrane completely resorbing 7 days after implantation [197].

9.4.3 Synthetic Resorbable Barrier Membranes

The most commonly used biomaterials used to fabricate barrier membranes are the poly-α-hydroxy acids, which include polylactic polyglycolic acid and their copolymers [198]. The advantage of using polyhydroxy acids are that they undergo complete hydrolysis to water and carbon dioxide, which allows for complete removal from the implantation site [195]. However, the degradation rate varies depending on the presence glycols and lactides in the constitutional makeup [199]. Resolut LT® is a barrier membrane made of glycolide and lactic copolymer and a porous network of polyglycolide fiber that completely resorbs in about 5–6 months [171, 200]. Atrisorb® is a barrier membrane that is prepared chairside during the surgical procedure because it is made up of a polylactic polymer in a flowable form, dissolved in poly-DL-lactide and a solvent. This is flowed into a cassette containing 0.9% saline for ~5 min, after which the membrane having a thickness of 600–750 μm is obtained and cut to desired shape. Studies have reported its efficacy in the treatment of periodontal defects [201], and it resorbs completely in 6–12 months [202]. Epi-Guide® is a porous three-layered and three-dimensional barrier membrane fabricated using polylactic acid polymers (D,D-L,L-polylactic acid) and is completely resorbed in 6–12 months. The three-layered construction of the membrane attracts, traps, and retains fibroblasts and epithelial cells while maintaining space around the defect. Epi-Guide® is a self-supporting barrier membrane and can be used in situations without support from bone grafting materials [182, 203]. Guidor® is a double-layered resorbable barrier membrane composed of both polylactic acid and a citric acid ester known as acetyl tributylcitrate. The external layer of the barrier membrane is designed with rectangular perforations allowing the integration of the overlying gingival flap. This surface design successfully promotes tissue integration, and only limited gingival recession after usage has been reported [181, 204]. Between the internal and external layers, internal spacers are present that create space for tissue ingrowth. The internal layer has smaller circular perforations and outer spacers for maintaining the space between the membrane and the root surface. Studies have shown this membrane to be successful in the treatment of various periodontal defects [204]. Vicryl periodontal mesh® is made up of polyglactin 910 fibers which are copolymers of glycolide and L-lactide which form a tight woven mesh [205]. This barrier membrane has been shown to start resorbing after 2 weeks of implantation and completely resorbs in about 4 weeks [206]. Mempol® is a membrane manufactured from polydioxanon (PDS) with a bilayer structure. The first layer is covered with PDS loops 200 μm long to be used on the gingival side and is completely non-permeable [207, 208].

9.5 Considerations for Bone Grafting in Older Patients

Although there are studies that demonstrate success of dental implantation in elderly patients, the major limitations of these studies are that a relatively small number of patients are involved and almost no or very few comparisons are made between groups with respect to gender, implantation site, implant type, implant length, numbers, systemic health, smoking, alveolar ridge volume and height (quality and quantity), and occlusal load considerations [5]. Although these limitations exist, still it can be concluded that the age of the patient does not seem to be the major factor in determining the prognosis of dental implants. Alveolar bone quantity and quality and the use of appropriate surgical and prosthetic techniques by a skillful team are definitely more critical to a favorable outcome. Older patients undergoing implant therapy including bone augmentation require a thorough evaluation for systemic conditions that may affect and potentially compromise bone healing and osseointegration [209]. Success of bone grafting procedures and ultimately dental implantation has been known to be affected by diabetes mellitus, postmenopausal estrogen replacement therapy, and long-term smoking

habits [5]. Additionally, patients may be using medications such as steroids and bisphosphonates that affect bone metabolism and can alter the clinical outcomes [210, 211].

Osseointegration of dental implants is crucially dependent on the bone healing response. Osteoporotic bone is characterized by a general reduction in bone quality and quantity and therefore can be expected to affect the success of dental implants in older patients. However, studies have not shown any strong evidence directly implicating osteoporosis as being a risk factor for implant failure in elderly patients [5]. There are strong reservations regarding surgical interventions in patients who have osteoporosis and are receiving long-term oral bisphosphonate therapy [212–214]. Also, it has been noted that implants placed in atrophic maxilla which has trabecular bone are at a greater risk for undergoing complications [215]. Soft tissue response in older patients is another major concern especially if oral hygiene is not maintained and deteriorates over time. Inability to remove plaque has been shown to lead to peri-mucositis and peri-implantitis [5]. Although autogenous bone grafts remain the gold standard for augmenting atrophic jaws and repairing bone defects, it has to be taken into consideration that autografting in older individuals leads to more complications and should be chosen after careful consideration. There are doubts over the bone quality available, donor site morbidity, and impaired healing response to be taken into consideration [215, 216].

9.6 Future Directions for Achieving Successful and More Predictable Bone Grafting

Currently, research on newer methodologies for bone grafting is focused on molecular, cellular, and gene therapeutics [217]. There is great potential for platelet-derived growth factor (PDGF) for use in bone regeneration [218]. Recombinant human PDGF-BB (rhPDGF-BB) and inorganic bone blocks have been investigated for bone augmentation in vertical dimensions and have shown increased vertical gain compared to controls [219]. PDGF in combination with ePTFE barrier membranes used around implants in preclinical animal models has also resulted in rapid and increased bone formation [218]. Promising results have also been observed by using collagen membranes and chitosan sponges with PDGF for achieving vertical ridge augmentation [220, 221]. Ideal dosing of PDGF and their appropriate carriers are still under research and extensive long-term studies are essential.

Separating platelet-rich plasma (PRP) from patient blood and added to the bone grafting tissues and materials is a new approach [222–224]. Initial results using this technique have shown greater volume and denser bone compared to autografts used alone for bone augmentation [225]. However, using PRP with other graft materials and its usefulness is still inconclusive [226, 227]. Bone morphogenetic proteins (BMPs) have generated a lot of interest recently and have shown promising results for intraoral applications such as sinus augmentation and alveolar ridge preservation [228–232]. The most commonly used and researched BMPs for bone regeneration applications are BMP-2 and BMP-7. BMP-2 has been approved by the FDA for clinical use in spinal fusion therapy [232, 233]. However, the dosage and carrier methods are still undergoing the regulatory approval process. Gene therapy is based on the principle of delivering to cells modified genetic material to boost their regenerative potential by increased production and concentration of differentiation factors and growth factors [234, 235]. A cellular tissue engineering approach is being investigated through which in vitro amplification of osteoblasts or osteoprogenitor cells grown on 3D constructs is carried out to increase the regenerative potential of bone [236–238]. Cell seeding of constructs with mesenchymal stem cells also has great potential to be used in the future [239, 240]. All these approaches have the potential for providing improved tissue regenerative results in alveolar ridge grafting and augmentation [235].

There are a variety of surgical techniques with various combinations of graft materials that can be utilized for achieving alveolar ridge augmen-

tation. Currently, there is no single ideal technique or graft material that exists to choose from in clinical practice, and individualized approach to ridge grafting is followed. The development of novel synthetic bone graft materials is a challenge from an engineering and biological perspective. The next generation of graft materials is expected to demonstrate improvements in implant and biological tissue interfacing based on the recent gain in knowledge. Treatment protocols that are less invasive and technique sensitive and more reproducible need to be developed and require constant revisions in light of new developments in bone regeneration therapeutics.

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