Regeneration for Implant Dentistry

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1 Guided Bone Regeneration

The concept of incorporating titanium implants into a prepared socket, that can then integrate with the surrounding bone, has revolutionised the concept of oral rehabilitation, and this has led to numerous treatment modalities for patients affected by complete or partial edentulism. Prior to implant placement, bone width and height, and the location of surrounding nerves and blood vessels must be examined, to ensure a healthy environment for osteogenesis around the implant. For rigid fixation of the implant, the dimensions of the surrounding bone are critical. In a number of conditions, these dimensions are inadequate, for example because of periodontal diseases or anatomical discrepancies. To rectify the problem, many studies have been carried out over the past three decades, although each approach has its own pros and cons.

The strategies that have been proposed include inlay/onlay bone graft techniques, distraction osteogenesis, and guided bone regeneration, with the common aim of establishing sufficient bone volume around the implant, thereby re-establishing bone integrity to sustain an adequate functional load and to regain aesthetics. Amongst all the methods that have been used to increase bone dimensions, guided bone regeneration (GBR) is the most commonly used method for the reconstruction of alveolar bone. The basic principle of this method is to selectively allow osteoprogenitor cells (stem cells) to differentiate into osteoblasts, controlling the local environment using a membrane, to promote osteogenesis under a controlled environment [1].

The ideal properties required in a barrier membrane are high biocompatibility, positive cell occlusivity, controlled space maintenance, and adequate mechanical and physical sustainability. The long term stability and success of an implant increases when GBR is used [2]. Short-term studies reveal implant placement with GBR or without GBR show similar success in bone growth around the implant (both horizontally and vertically).

GBR provides a positive support for implants to integrate at a desired site, although the major challenge here is to overcome the challenges of native bone, such as the configuration of the residual bone and the severity of bone loss in the specific individual [3]. Regaining bone dimension is possible by using advanced techniques and materials to initiate bone growth right from the molecular level. Attaining a good bone height and then maintaining the same is the more difficult part of the whole process. Any bone defect ≥4 mm normally requires the use of an autologous bone block graft to regain the lost bone height.

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Several techniques lack long-term clinical documentation, making it challenging to compare the effectiveness of individual techniques, due to the frequent combination with particulate bone and the use of non-resorbable/absorbable membranes. Clinically, it is convenient to place a resorbable membrane for GBR and secure its positive outcomes, hence many studies have focussed on the benefits of the resorbable membrane technique. Technically, non-resorbable membranes tend to give a superior outcome in regaining bone. Such non-resorbable membranes have to be removed once its purpose is served, thereby complicating the overall process with a second surgical procedure [1].

1.1 Membranes

The membrane is the most important part of the GBR technique as it holds the material in place, allows the bone to grow, prevents contamination of the site, and supports osteogenesis at the site. The membranes used for GBR can be classified as either non-resorbable or resorbable, based on their properties. Expanded-polytetrafluoroethylene (e-PTFE) membranes were the first generation technology for membranes used clinically in the GBR technique [4]. Key characteristics are low immunogenicity, resistance to enzymatic degradation by the host tissue or microbes, and a synthetic porous polymer structure.

Membranes can be reinforced with a titanium mesh to provide the necessary physical and mechanical properties to support the space, and enough flexibility to adapted over an irregular bony defect. The major disadvantage of the GBR technique is progressive soft tissue complications due to premature membrane exposure, that increases tension on the flaps and reduces vascular perfusion, eventually causing the whole system to fail [4]. Membrane exposure often leads to infection of the adjacent tissues and the need for the membrane's removal, which hampers the outcome of bone regeneration.

Alternative approaches have been proposed to manage membrane exposure, with an intention being to attain the best outcomes, although the results vary [5–7]. The most important drawback of this technique using non-resorbable membranes is the need for an additional surgical stage to remove the membrane. This additional surgery increases the morbidity and subjects the patient to further possible complications such as pain and infection. Absorbable membranes have been proposed to overcome such drawbacks.

Membranes manufactured from native collagen exhibit functional tissue integration, reduce the foreign body reaction, and increase vascularisation and biodegradation. The elimination of second-stage surgery, better cost-effectiveness, and decreased patient morbidity are the most well-known advantages of the use of collagen-based membranes [8]. In the case of a mucosal dehiscence and early exposure, the membrane induces epithelialisation and secondary wound closure. These reduce morbidity and avoid the need for any further surgical intervention.

On the other hand, the major drawback of membranes manufactured from native collagen are their poor mechanical properties, and their rapid degradation, which drives a natural loss of barrier function. In recent years, the development of multilayer collagen-based membranes (or techniques) [9, 10] has aimed to increase the life-span of these membranes, slowing their reabsorption rate, to retain the membrane in the body for a longer period to enhance bone regeneration.

Synthetic resorbable membranes can be manufactured from aliphatic polyesters such as polylactic acid, polyglycolic acid and their copolymers. These have been proposed to overcome the disadvantages of e-PTFE and collagen-based membranes [11–13]. Such new materials also offer the possibility of increasing the life-span of the membrane, improving its mechanical properties, and incorporating a drug delivery system [14]. However, the use of these membranes is frequently associated with inflammatory foreign body reactions due to their degradation products [15].

1.2 Bone Graft Substitutes

Autologous bone has been considered the gold standard for bone regeneration, due to its osteo-

genic, osteoinductive, and osteoconductive properties [16]. However, the amount of bone tissue that can be harvested intraorally at any oral site (i.e. symphysis and mandibular ramus) or extraoral site (i.e. iliac crest, calvarium) is often insufficient for treating large bone defects, especially when these are bilateral, as is usually the case. Moreover, morbidity, pain, and discomfort from the donor site, and unpredictable graft resorption are the most important limitations of the use of autogenous grafts [17, 18]. Bone grafts substitutes have been developed to augment or replace bone autografts in bone augmentation procedures. These different alternative materials include allografts, xenografts and alloplastic biomaterials [19–21].

Allografts are tissue obtained from the same species. Samples are treated to reduce their antigenicity and infectivity using freeze-drying and irradiation methods. Such products have been commercialised by licensed tissue banks, and their availability depends on a particular country's regulations, donor intents, and ethical regulations.

Xenografts are tissue obtained from a different species (e.g. bovine, equine, and swine). A different protocol is applied to generate a collagen-rich residual scaffold, by using complete or partial thermo-chemical removal of the organic material. Synthetic bone substitutes (alloplastic materials) are biomaterials synthesised from different components that are mostly inorganic in origin [22]. They are classified according to their porosity, structure, and performance. Biomaterials such as calcium phosphate, bioactive glass, tricalcium phosphate and calcium sulphate aim to replace the inorganic component of bones, to mimic its mechanical and biological properties [23].

The clinical application or combination of different materials used in bone regeneration must consider the type of bone defect, the vascular supply, and the amount of tissue to be regenerated [24]. The graft properties must include biomaterials with excellent mechanical properties, to maintain the space, and induce angiogenic growth factors to facilitate the proliferation of new blood vessels from the periphery to reach the inner core of the graft. The biomaterials ideally should have osteogenic properties, to invoke de novo bone formation [25]. To meet these requirements, it is commonplace to combine different biomaterials with various proteins and growth factors, such as platelet-rich plasma, to increase osteoinductivity of graft materials.

1.3 Bioactive Molecules

1.3.1 Bone Morphogenetic Proteins

The use of biological activate molecules that are partially responsible for regenerating bone formation was initially described by Urist [26], and subsequently named as bone morphogenetic proteins (BMPs) [27]. These constitute a large family of regulatory factors that are related to the transforming growth factor-β (TGF-β) superfamily, with the ability to initiate de novo endochondral bone formation by stimulating undifferentiated pluripotent cells to differentiate into cartilage-forming and bone-forming cells [28].

Only a small number of BMPs (BMP-2, BMP-4, BMP-6, BMP-7, and BMP-14) seem to have osteoinductive functions [29, 30]. Some current commercially available products combine a collagen matrix with a BMP (BMP-2 and BMP-7) synthesised using recombinant DNA technology. Such factors have been shown to enhance the formation of new cementum, new alveolar bone and new periodontal ligament [31]. It has also been hypothesised that lower concentrations of rhBMP-2 can boost initial chondrification, while higher concentrations are supposed to enhance osteogenesis [32].

The role of the vehicle in tailoring the delivery of BMPs has historically been underestimated. More recently, attention has focussed on improving controlled delivery systems to match the biological timing for bone tissue regeneration. The main drawback of using a collagen carrier is its rapid degradation, leading into an early boost of BMP release. This molecule has also been related to the formation of seromas, which are a sterile accumulation of serum within the tissue [33–35]. Due to the ability to predictably promote osteogenesis using BMP, there is an

ongoing need for studies to optimising dose, delivery technologies, and conditions for stimulation of bone growth [36].

1.3.2 Growth Differentiation Factor 5 (GDF-5)

This molecule is US FDA approved for periodontal regeneration, alveolar bone regeneration, and sinus augmentation. GDF-5 is a member of the TGF-β/BMP superfamily [37] that plays a critical role in mesenchymal cell differentiation and in morphogenesis of skeletal tissue. For periodontal regeneration, GDF-5 stimulates periodontal ligament cell proliferation, osteoblast differentiation (in the early stages), and extracellular matrix synthesis, by both cell types [38]. For implant site development, GDF-5 has been demonstrated in vivo to induce bone in ectopic muscle pouches, by improving mineralised tissue formation [39]. GDF-5 has been proven effective when used in high concentrations (800 μg) for sinus lift procedures. By the 12th week of the follow-up, it has shown good growth of bone with adequate density [40]. In combination with *β*-TCP, it could enhance bone formation, comparable to what happens with an autologous bone graft [41]. However, the ideal carrier and quantity to be delivered to achieve optimal bioactivity are unclear, hence the need for further research.

1.3.3 Teriparatide (Human Recombinant Parathyroid Hormone)

The US FDA has approved parathyroid hormone (PTH) to treat osteoporosis. It causes osteoblast-like behaviour, with increased osteoprotegerin expression [42]. This polypeptide (34 amino acids) has been tested in animal models, where it shows bone formation in extraction sockets, maintaining the three-dimensional aspects of alveolar bone [43]. Although PTH has shown a positive short-term effect on bone formation, the delivery route needed to maintain sufficient tissue levels needs more work to make this acceptable for patients.

1.3.4 Hemoderivates: Platelet-Fibrin (PRF), Platelet-Rich Plasma (PRP), and Leukocyte-Platelet-Rich Fibrin

Hemoderivates are preparations obtained via blood plasma fractionation through centrifugation after peripheral phlebotomy. Their empirical utilisation for improving tissue healing in a wide range of clinical applications has been reported in the literature since the early 1950s [44]. Advantages such as an autologous origin and ready availability via relatively simple chairside extraction methods have generated considerable interest in both the clinical setting and more recently in regenerative medicine (Fig. 1) [45, 46].

The action of these preparations relies on the secretion of a cocktail of proteins from the platelet-α-granules. Growth factors such as insulin-like growth factor-1 (IGF-I), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), epidermal growth factor (EGF), platelet-derived epidermal growth factor (PDGF) and fibrin matrix proteins are found in these preparations at concentrations greater than those in blood, which is why they can contribute directly to accelerating tissue regeneration [47, 48]. Hemoderivates have been clinically used as a substitute for connective tissue [49], as a graft material in sinus lifts [50] and in guided bone regeneration [51, 52]. Although the application of blood concentrates for boosting regeneration is an attractive approach, the mechanisms responsible for evoking specific biological outputs remain to be elucidated.

2 Posterior Mandible Bone Regeneration

Regeneration of bone in the posterior region of the mandible is one of the most challenging procedures, since this region has minimal blood flow, is distracted by muscle movements, and is burdened by occlusal loading. The structural fea-

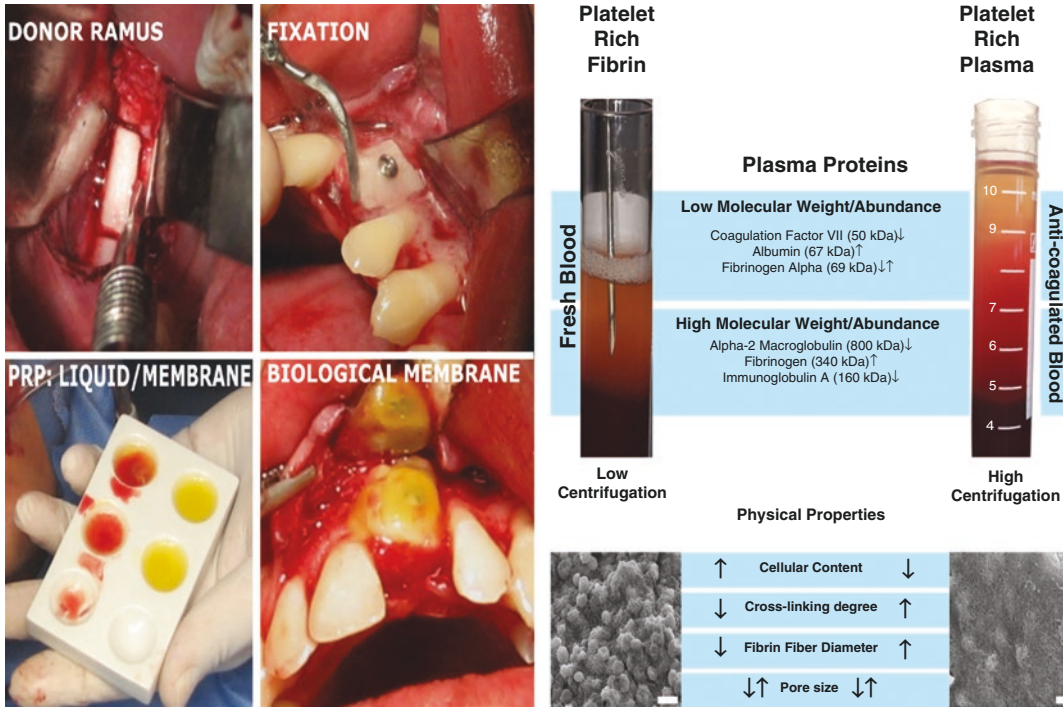

Fig. 1 (Left) An inlay bone block graft from the ascending mandibular ramus that has been fixed in the premaxilla. Platelet-rich plasma (PRP) was prepared from peripheral blood (liquid and membrane) to improve soft tissue adaptation. (Right) A general overview of fresh and anticoagulant blood protocols, protein content, and the physical properties of the fibrin network produced by centrifugation. Based on the work of author TF

tures of this region such as thicker cortical bone and the presence of the inferior alveolar foramen which serves as the entry point for nerves and blood vessels are major reasons causing failure in achieving horizontal and vertical bone regeneration. These factors influence implant placement as clinicians tend to place shorter implants and restore those with a broader crown, giving an abnormal crown to root ratio. The same region is difficult to access for oral hygiene, and implant failures compromise the whole treatment plan.

Different techniques have been proposed for vertical ridge augmentation, including block bone grafting, distraction osteogenesis and guided bone regeneration. The use of an autogenous block bone graft is still considered the 'gold standard' method, but such grafts may not be stable over long periods of follow-up, and this could compromise dental implant success. Additionally, the amount of bone tissue required frequently requires that for bilateral reconstructions an extra-oral donor site (such as the iliac crest) is used, which increases the overall morbidity of the procedure and reduces its acceptability for patients. The crucial period for an autologous bone block graft is within the first year, and after this point, the situation stabilises. As a result, clinicians are tempted to over-graft the surgical site, to compensate for the loss of hard tissue within the first year after grafting. To address these issues, the use of alternative materials has been proposed, however, a lack of evidence, especially for extended period of follow-up, limit their use.

2.1 Bone Block Grafting

In cases of severe ridge atrophy large defects (>7 mm), guided bone regeneration (GBR) or onlay/inlay bone grafts are used to re-establish volumetric posterior mandibular dimensions. However, bone blocks give outcomes that are not very predictable. This may be associated with the composition of the mandibular bone itself, when compared with the maxilla (dense trabecular bone with a thick cortical layer).

Bone microarchitecture (bone quality) is determined by the combination of factors associated with trabecular morphology and porosity. The usual primary sources for autologous bone blocks are the iliac crest, tibia, and calvarium. Intraorally, the body and the ramus of the mandible are used frequently to harvest uni-cortical blocks of living bone tissue that can be fixed into crestal and buccal bone defects. The mean gain when using bone block techniques is 3.47 ± 0.41 mm (95% CI 2.67 to 4.27 mm), regardless of the donor site [25]. Complications of the block grafting technique are sensory disorders at the donor site, especially in the mandibular symphysis region, suture dehiscence, graft exposure and graft contamination. If the bone block is not properly stabilised by titanium screws, this leads to the fibrotic encapsulation and tissue sequestration.

2.2 Distraction Osteogenesis (DO)

Distraction osteogenesis (DO) was first described in the early 1900s, and used by Ilizarov in more than 15,000 patients [53]. DO gains its regenerative capabilities by the separation of two bone segments during the bone healing process, allowing bone to grow longitudinally. Bone segment separation is achieved using a titanium distractor that is fixed in place using screws. It was not until McCarthy reported the successful application of DO in the mandible [54] that this technique was used as an alternative treatment for vertical bony defects. DO is associated with intra-operative and post-operative complications that are related primarily to the vector of distraction [55].

The DO procedure starts with a bone osteotomy and installation of the distractor. This is followed by a latency stage during which the distractor device remains static without activation, to allow osteogenic cells in the osteotomized location to proliferate. Later, the activation phase begins. The bone segment moves through a predetermined linear path (the distraction vector) towards the desired position, to fil the defect. The device is activated once or twice a day at a rate of 0.5–1 mm/day. Finally, there is a consolidation stage without any activation, to allow the bone to mature and mineralise fully. In a second surgical procedure, the distractor device is removed, and dental implants are placed. DO can provide an average gain of 6.84 ± 0.61 mm (95% CI 5.64–8.05 mm) [25]. Complications of DO include lingual vector inclination and loosening of the distractor.

2.3 Guided Bone Regeneration

Guided bone regeneration (GBR) is one of the most common methods used to reconstruct alveolar bone deficiencies [56, 57]. Since a membrane is an essential component of this technique, different materials have been used as membranes, with the goal of providing suitable mechanical and physical properties to maintain space. The membrane must be sufficiently rigid, to withstand the compression of the overlying soft tissue of the posterior mandible. Membranes can be resorbable or non-resorbable. They should also possess a degree of plasticity so they can be adapted to irregular bone defects. Membranes also need biocompatibility, and the ability to occlude the migration of cells.

Titanium mesh structures have excellent mechanical properties and are used to prevent membrane collapse, so that they provide the required level of space maintenance. These meshes can be bent, adapted, and contoured to match the surgical site. Rough cut edges of the mesh may cause mucosal irritation, leading to early exposure of the membrane with subsequent infection. Adding different biomaterials such as PTFE and collagen into the titanium

mesh can reduce such difficulties [23]. The average gain for GBR with of PTFE occlusive membranes, when used in the posterior mandible, is 3.83 ± 0.49 mm (95% CI 2.85–4.80 mm) [25]. Outcomes vary according to the type of membrane used, and the type of bone defects being treated.

Experimental GBR approaches with promising results have been reported with the inclusion of bioactive molecules such as fibrinogen [58], PRP [59] and PDGF-BB [60], or the incorporation of cell seeding strategies including MSCs [61–65] or autologous osteoblasts [66]. These results are summarised in Table 1.

3 Sinus Floor Elevation for Bone Regeneration

Dental implants offer an effective way to replace missing teeth. Adequate bone depth is essential to integrate an implant and functionalise it in the oral cavity. The available bone dimension is often compromised in the posterior region of the maxilla,

Table 1 Regenerative biomaterials for Implant Dentistry

Bio material	Group		Origin	Advantages	Disadvantages
Membranes	Natural polymer	• Collagen and extracellular matrix • Chitosan • Alginate	• Human • Bovine • Porcine	• Reduce immunogenicity • Resorbable • Tailor degradability • Carrier for drug delivery or bioactive molecules • Low complication membrane exposure	• Reduced mechanical properties • Poor space maintenance properties due to increased resorbable property • Possible cross-contamination between species
	Synthetic polymer	• Aliphatic (PCL, PLA, PGA)		• Biocompatibility • Manufacturing standardisation • Tailor mechanical properties • Bioactive molecule carries • Blend with complementary substitutes and cells • Tailor specific degradation time • 3D Printability	• Lack of self-osteoinductivity capacities • Some acidic by-products upon degradation are reported • Regulatory approvals need in some countries • Needs for long-term studies • Manufacturing cost
		• Polytetrafluoroethylene (PTFE)		• Bio inert polymer with low degradability • Selective permeable barrier • Regenerative compartmentalisation	• Non-resorbable • Complications related to early membrane exposure • Reduce mechanical properties
	Metal	• Titanium and titanium alloys • Cobalt-Chromium alloys		• Excellent mechanical properties • Reduce immunogenicity • Space maintenance • 3D Printability	• Non-resorbable biomaterials • Complication related to early exposure difficult to treat • Lack of self-osteoinductivity capacities • Need for screw fixation

(continued)

Table 1 (continued)

Bio material	Group		Origin	Advantages	Disadvantages
Alloplastic	Inorganic	• Calcium phosphate • Hydroxyapatite • Calcium sulphate • Bio-glass		• Biocompatibility • Osteoinductivity • Favourable to tailor particle size, porosity and surface modification	• Reduced mechanical properties • High solubility may hamper ions release at the longer term
Xenograft	Natural tissue	• Fresh-frozen, freeze-dried, demineralised freeze-dried bone block or particles	• Bovine • Porcine • Equine	• Biocompatibility • Osteoconductivity • Resorbable • Low immunogenicity • Availability • Favourable tailor of particle size and dimensions • CAD-CAM custom	• Possible cross-contamination between species • Regulatory issues in some countries • Variable predictability • Needs for screw fixation (blocks) • Needs for long-term studies
Allograft	Natural tissue	• Fresh-frozen, freeze-dried, demineralised freeze-dried bone block or particles	• Human	• Biocompatibility • Osteoconductivity, low osteoinductivity • Resorbable • Low immunogenicity • Favourable tailor of particle size and dimensions • CAD-CAM custom	• Possible cross-contamination • Reduced availability for insufficient donor schemes and ethical issue in some countries • Need for screw fixation (blocks)
Autologous	Live natural tissue	• Particulate. Blocks	• Patient's own tissue	• Osteoconductivity • Osteoinductivity • Osteogenic • High predictability when combined with other biomaterials • Considered the gold standard	• High morbidity and discomfort from donor site • Reduced availability: intraoral from Chin/ Mandible body (≈5 cc) • Extra-oral: Tibia(≈25 cc), Calvarias (≈30 cc), Iliac Crest (≈70 cc)

because of pneumatisation of the maxilla by the maxillary sinus. This problem increases when the duration of edentulism is longer, due to alveolar bone resorption over time once teeth are lost. Bone loss in the posterior maxilla can be treated using the patient's own bone (autogenous bone grafts), biomaterials, a combination of both, or a technique that uses a blood clot as a foundation to hold the upcoming graft, to eventually increase the bone height.

3.1 Techniques of Sinus Augmentation (Sinus Lift)

In 1980, an innovative technique to re-establish the dimensions of the posterior maxilla was described in which a buccal window was made in the posterior maxillary bone, that allowed careful elevation of the sinus epithelium, to create a space for placing particulate bone from the iliac crest [67]. After a healing period of 6 months, dental implants may be placed. The technique was subsequently described in detail by Tatum [68], including different variables within the technique such as tissue incisions, bone access, types of biomaterials used, and the combination of sinus augmentation for implant placement as a one-stage or two-stage technique. The lateral window sinus lift is now a widely used technique. It is considered reliable, especially when used with the autologous bone (≥50%).

To provide a minimally invasive approach, a one-stage technique is advised for sinus elevation. Summers [69] described the use of concave tipped osteotomes via a crestal approach, to advance a mass of bone beyond the level of the original sinus floor. This hydrostatic pressure elevates the sinus epithelium, resulting in the creation of a space that is filled with a bone graft material, with the subsequent insertion of a dental implant. This requires a minimal height of 6 mm between the floor of the sinus and the crest of the residual alveolar bone, to ensure dental implant stability. For cases with less than 6 mm of residual bone, a two-stage technique has been proposed, with the first surgery to increase bone quantity, and then dental implant placement 6 months later [70].

Although the trans-alveolar technique has many advantages, the amount of bone height that is gained is usually less when compared to the lateral window technique. Moreover, in the event of complications such sinus membrane perforation, the resolution requires the lateral window approach. Additionally, the anatomical macro and microstructural characteristics of the posterior maxillary bone make it difficult to achieve dental implant stability whenever the bone is less than 3 mm in thickness [71].

3.2 Sinus Lift Outcomes

Although the sinus lift technique is a predictable procedure for increasing the amount of bone in the posterior maxilla (>90%) [72], there is insufficient evidence whether sinus lift procedures in bone with a residual height between 4 and 9 mm are more or less successful than alternative procedures such as the placement of short implants (5–8.5 mm in length) for reducing prosthesis or implant failure [24]. Most studies comparing these techniques have focussed on complications and the amount of regenerated bone, but without taking into consideration the implications for long-term implant survival (at >10 years). Complications of sinus lifts will in turn affect the success of dental implants. The survival rate of implants placed into the sinus cavity is 95% at 52.7 months of follow-up. The more common complications are epistaxis (3.4%) and thickening of the Schneiderian membrane (14.8%) [73].

4 Bone Tissue Engineering (BTE)

In the last decade, tissue-engineered strategies have emerged as promising solutions for the reconstruction of different types of oral, maxillofacial, and periodontal tissues. The ability to offer a safe and standard technique with predictable results to partially or completely edentulous patients requiring prosthetic implant solutions is the tissue engineering chimera of the future.

Bone Tissue Engineering (BTE) involves the application of biomaterials (scaffolds), cells, and bioactive molecules (such as grown factors, hormones, and peptides), to promote regeneration of lost bone tissue. In the conventional tissue engineering paradigm, combinations of cells and bioactive molecules are seeded onto three-dimensional biomaterial scaffolds to promote an implantable ‘osteogenic’ scaffold.

The BTE concept aims to mimic natural tissue characteristics, by using a scaffold that closely substitutes for extracellular matrix, and provides structural stability, allowing for vascularisation of the site from the surrounding tissue. The new blood vessels bring in oxygen and nutrients necessary for cell proliferation. The concept promotes morphogenetic signalling, to direct cells to the most phenotypically desirable type. The scaffold is typically enriched with progenitor cells (such as MSCs), or bioactive molecules such as growth factors and peptides. Furthermore, the construct is degradable, leaving the new tissue behind.

4.1 Biomaterials

4.1.1 Osteoinductive Materials

These materials induce bone formation [74]. Natural and synthetic materials such as hydroxyapatite (HA) and calcium phosphate (CaP) have been used in a variety of forms including ceram-

ics [75], cements [76], and coatings [77]. Calcium phosphates and apatites can be derived from natural sources such as marine coral [78]. Adding such materials onto scaffolds can increase their bioactivity, to induce ectopic bone formation [79, 80].

It has been hypothesised that the biomaterial surface can absorb and present osteoinductive factors to the surrounding tissue, and can also release the calcium and phosphate ions which act on undifferentiated cells to evoke bone-cell phenotype differentiation [74]. A major drawback is poor mechanical properties, which impair their clinical application for the regeneration of sites under considerable mechanical loads (such as femur, tibia, and mandible) [81].

Bioactive glasses (BGs) are a group of silica-based osteoconductive and osteoinductive glass biomaterials containing SiO_2-CaO-P_2O_5 networks. BGs have good biocompatibility when used in bone and in soft tissue. They stimulate osteogenesis by triggering cellular proliferation and osteogenic differentiation [82]. However, their poor mechanical properties make them difficult to use clinically for large bone defects where there is significant mechanical loading.

4.1.2 Polymers

Polymers of two or more monomeric structures, such as polylactide-co-glycolide (PLGA), can show a desirable degradation rate. PLGA biomaterials form acidic by-products upon degradation, and this may result in tissue necrosis over the long term [83]. On the other hand, polycaprolactone (PCL) is a biodegradable polyester that is non-toxic and tissue compatible. It has a longer degradation time (2–3 years) and has been used widely in resorbable sutures, as well as in scaffolds for regenerative therapy and for drug delivery. It degrades by hydrolysis of its aliphatic ester linkage under physiological conditions [84]. It has recently been used for 3D printing, to produce highly porous resorbable custom 3D printed scaffolds for regeneration of large volume alveolar bone defects, with the aid of CT-scan data from the patient [85].

4.1.3 Collagen-Based Composite Scaffolds

Pure collagen scaffolds have insufficient mechanical properties to be applied as core materials for bone regeneration. Moreover, biomaterials made from pure collagen lack sufficient bioactivity to stimulate cells to infiltrate during bone formation [86]. The incorporation of a bioactive component improves the mechanical strength, bioactivity, and osteogenesis by increasing dimensional stability and the surface area for cell attachment, and has shown promising results [87].

Two methods are used widely to fabricate collagen/bioceramic composite scaffolds: an immersion method (co-precipitation) [88] and a suspension method (direct mixing) [89]. Collagen/HA composite biomaterial scaffolds have been investigated intensely, followed by β-Tricalcium Phosphate (β-TCP). These inorganic materials not only improves cellular adhesion but also accelerate cell differentiation and proliferation [90]. The ratio of collagen to the inorganic material can be altered to tailor the degradation rate of the scaffold to the clinical situation [91].

4.2 Cells

An essential requirement for the cells used in tissue engineering is that they have sufficient plasticity to be modified by the local microenvironment provided by the scaffold and the surrounding tissue. In the past, the usual approach has been to incorporate stem cells, that can then differentiate into multiple cell lineages. Mesenchymal stem cells (MSCs) are non-hematopoietic stem cells that were initially isolated from bone marrow. They have a morphology similar to fibroblasts, and can readily be found in adulty bone marrow. They can be grown in plastic culture flasks, are self-renewable, and can differentiate into osteoblasts, adipocytes, or chondrocytes in vitro [92].

The use of MSCs to repair bone defects could involve implanted cells alone injected into the site, or used in combination with a scaffold. For maxillofacial applications, MSCs are typically

derived from bone marrow concentrates and then expanded. They are used in combination with scaffolds containing β-TCP or synthetic hydroxyapatite, or with decellularized bone powders or granules, or they are embedded in hemoderivates (i.e. platelet-rich plasma/fibrin) [93–95].

A significant regulatory issue exists in many countries (especially in Europe) for the use of MSCs. From the translational point of view, a chairside strategy would be ideal for reducing the possible risks associated with cross-contamination or with immunogenicity of allogeneic cells. Even when autologous MSCs are used, the amount recovered, even from the iliac crests, is too small in most cases to accomplish the reconstruction of significant bone defects. Thus, human studies on the reconstruction of complex bone defects have proposed the different strategies of tissue engineering.

Earlier attempts have followed the guided bone regeneration approach [96–98]. From the tissue engineering perspective, these studies have demonstrated the need for space maintenance to evoke guide bone regeneration, and this necessitates the use of non-resorbable membranes to isolate the bone chamber from the surrounding soft tissue. The addition of bioactive molecules to stimulate bone regeneration can provide additional advantages over the normal processes of bone healing [99, 100]. Custom-made scaffolds and personalised bone graft substitutes can reduce operative time and increase predictability [101, 102]. Poly D, L-lactide meshes (made using a box design) have demonstrated promising results for 3D bone reconstruction in totally edentulous patients with severe resorption [103].

4.3 Protein Corona on Biomaterial Surfaces

Previous literature has focussed on the potential of nanoparticle biomaterials that that would replace the bone material to form new bone, while in recent years, the biomaterials that interact with blood and the adjacent tissue to form native bone have attracted attention [104]. After surgical implantation, biomaterials are exposed to various physiological fluids, such as blood. Many of the proteins found in blood (e.g. albumin, fibrinogen, fibronectin, vitronectin, gamma-globulins) may be bound onto the surface of the biomaterial [105].

Depending on factors such as size, surface charge, fluid composition, and physicochemical properties, the surface of the biomaterial may create a complex interface that has loosely bound proteins, and this is termed the protein corona [106]. Proteins present at high concentrations bind first and are then replaced gradually by proteins that bind with higher affinity. This is known as the Vroman effect [107].

The protein corona is responsible for further recruitment and adhesion of pro-inflammatory cells. Blood clot formation defines the provisional matrix around the biomaterial, and the type of tissue that ultimately will form on the surface [108, 109]. The variable rates of success or failure in cases reported in the literature can be explained in part by variations in the macro, micro, and physicochemical composition of materials used for guided bone regeneration and for dental implantology, as each will have a different protein corona (Fig. 2).

The incorporation of hemoderivates (i.e. PRP, PRF, L-PRF) as co-adjuvant for bone regeneration [45, 46, 110] uses blood components that have been separated by centrifugation/time, to alter the amount and type of plasma proteins, giving a specific protein corona around bone graft materials. Optimising the protein corona on the biomaterial surface provides a new way to control osseointegration of dental implants at the molecular level, and the same concept could be used in bone tissue engineering. The field is in its infancy, and a substantial amount of research must be conducted to understand how to optimise the corona for bone regeneration.

5 Peri-Implantitis

Ever since Branemark [111] introduced the concept of osseointegration, oral rehabilitation treatment planning for tooth replacement has shifted

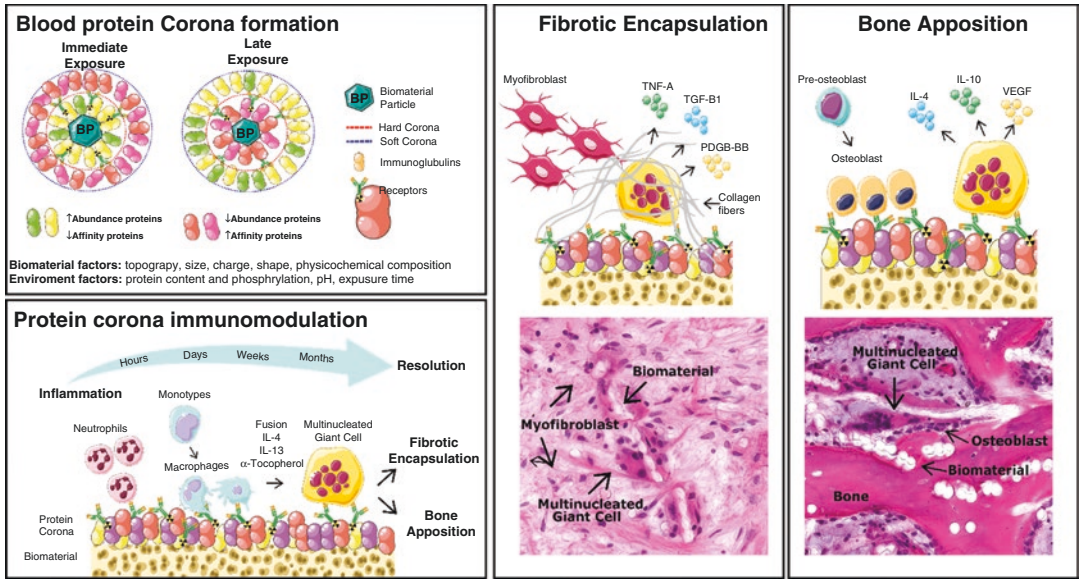

Fig. 2 Schematic representation development of blood protein corona on the surface of biomaterials, giving this surface an immune-modulatory role

from dentures that rely on undercuts and salivary cohesion for retention, to crowns, bridges or dentures that are stabilised or supported by dental implants, being held in place by special connectors. The concept of an implant-retained prosthesis has increased the outcomes that can be achieved in terms of the restoration of masticatory and phonetic functions and aesthetics in edentulous patients. The long-term success for an implant-supported or implant-stabilised prosthesis is in many patients similar to the longevity of the natural dentition, on the proviso that healthy soft tissues are maintained around the dental implants. This is a challenge because of the continuous presence of high levels of bacteria in the oral cavity, creating problems with the control of bacterial plaque. Prolonged accumulation of dental plaque biofilm leads to inflammatory conditions that hampers the long-term survival of the implants and the associated dental prostheses [112].

The first inflammatory stage is known as peri-implant mucositis. This resembles gingivitis, and inflammation is restricted to the tissues around the dental implant, but there is no loss of the adjacent bone. If not treated, in a susceptible patient this condition may progress to a more severe condition known as peri-implantitis, where bone loss occurs, and may threaten the longevity of the dental implant [113]. Although bone loss around dental implants may also be caused by overload [114], in most cases, bone loss is due to the host response to the accumulation of dental plaque, and the accompanying peri-implant inflammation [115].

The treatment of peri-implant bone defects is complex because of the topography of the implant surface as well as the three-dimensional shape of the defect. Relevant variables include the type of bone defect, its location and extent, the patient's medical background, and the quality of supportive periodontal care as well as the patient's own habits of oral hygiene. At the present time, there is no 'gold standard' treatment for peri-implantitis, and the published evidence does not suggest whether surgical or non-surgical intervention is the most effective [116].

A foundation of current treatment approaches involves decontamination of the implant surface, using hand or powered instruments. This debridement may be accompanied by, in some cases, the use of topical antimicrobial agents, or the local or systemic administration of antibiotics. Because of the complexity of the defects that are encoun-

tered, in many cases open surgical debridement is necessary. Despite this, the extent of improvement in probing attachment level (PAL) and probing pocket depth (PPD) in sites that have lost more than 50% of the supporting bone is rather limited [117]. The use of particle beams, and pulsed middle infrared lasers such as the Er: YAG laser, have attracted interest because these methods can potentially reach better into the threads of dental implants, then can traditional methods such as using plastic curettes. Reported outcomes of treatment for mechanical debridement alone vary considerably [118–120].

The treatment of peri-implant bony defects using guided bone regeneration has been reported. Such techniques include a membrane combined with a bovine-derived xenograft or with resorbable nano-crystalline hydroxyapatite. The GBR approach seems to provide greater improvement in PAL and PPD after 4 years of follow-up [121]. There are mixed results reported in terms of whether an occlusive membrane is included or not. In one study, bone regeneration associated with the inclusion or exclusion of a membrane was evaluated in 38 patients, where 29 implants were treated with a bone substitute and a membrane, while 36 implants were treated with only a bone substitute. After 1 year of follow-up, there were no statistically significant differences between the two interventions, and both therapies achieved a bone gain of around 1.5 mm [122]. Known complications include barrier membrane exposure and subsequent infection at the site [123].

Although effective at-home plaque control, regular post-operative maintenance for supportive periodontal therapy, and reduction of risk factors such as smoking are always advised to patients, these foundation for the success of surgical treatment may not always in practice be achieved. This may explain why surgical treatments based on the concept of bone regeneration may not always be effective in the long run. In response to this, resective modalities such implantoplasty have been developed, to eliminate the areas that are difficult to debride, and these seem able to cause a significant reduction in BOP and PD [124], LB it at the cost of weakening the implant fixture itself. Such approaches may only be widely acceptable in cases without strong aesthetic requirements, such as over-dentures or where hybrid prostheses are being worn.

Further studies are needed to explore the reasons for discrepancies in the outcomes of surgical treatments for bone defects around dental implants, to better explain the considerable variability that is seen clinically. A better understanding of those factors that determine the success or failure of regenerative surgical methods used in the treatment of peri-implant defects would better inform the selection of methods for specific clinical scenarios, following the principle of personalised medicine.

6 Conclusions and Future Direction

Bone and soft tissue reconstruction have been developed in parallel to dental implants in the rehabilitation of edentulous patients. It is well reported in the literature that, in many cases, there is a need to perform some kind of regenerative procedure associate with fixture placement. This is related to the preceding destruction resorption of the alveolar bone. Autologous bone is still considered the gold standard in bone regeneration due to its capacity for osteoconduction, osteoinduction and osteogenicity. A limited amount of bone volume from donor sites (either intra or extra-oral) and the morbidity at the donor site limits the applicability of autogenous bone grafting in the clinical setting. On the other hand, the use of different biomaterials and membranes for bone regeneration can give useful outcomes, and the approach can be customised to the situation of the individual site. Variability in the nature of the bone defect and in the systemic background of the patient, as well as in the particular surgical skills from operator, makes it difficult to compare success rates between different techniques.

In recent years, a better understanding of what is happening at the molecular level during bone regeneration has renewed interest in the treatment of bone defects of the jaws using regenerative approaches. At the present time, the ideal

biomaterial and technique remain to be elucidated, however many promising avenues of research are being explored, including the use of various composite scaffolds, and the use of particular blood extracts to alter the protein corona. More clinical trials are needed to compare the available techniques, to better inform the selection of different types of autogenous bone graft substitutes, and the clinical decision around whether or not to use a membrane barrier. Future research must clarify at the molecular level what are the mechanisms to induce three-dimensional reconstruction of alveolar bone.

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