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BONE REGENERATION INFLUENCE IN THE SUCCESS OF PERIIMPLANT SURGERY

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1.Introduction:

Due to its cosmetic and functional features, durability, and high success rate, dental implants continue to be a popular therapy for the rehabilitation of partially and totally edentulous arches among patients [1]. Despite the great success rate of dental implants, there will always be some cases of early or late implant failure. It's crucial to remember that the success of dental implants depends in large part on the quantity and quality of bone in the area immediately around the implant [2].Guided bone regeneration surrounding dental implants is often achieved by the use of bone grafts, either immediately following implant placement or as part of the treatment plan for periimplantitis. Implants augmented with deproteinized bovine bone mineral have shown long-term survival and substantial clinical improvements [3].

Bone grafts, bio membranes, concentrated microspheres, and topical ointments that administer antibiotics locally hold significant promise for treating the illness. Successful care of peri-implantitis and guided bone regeneration following rapid installation of dental implants can reduce the risk of implant failure by preserving connective tissue loss with the use of bone grafts and the local antibacterial impact of antibiotics [4].

Implant location, primary stability, soft tissue shape recovery, and other aspects crucial to a successful implantation restoration are all influenced by the quality and quantity of alveolar bone in the implant region in oral implantology. Secondary bone resorption and atrophy cause the alveolar ridge's breadth and height to gradually diminish following tooth loss, rendering the ridge eventually inadequate for implant placement.

For this reason, oral implantology relies heavily on successful alveolar bone repair. To repair alveolar bone defects, several therapeutic procedures exist, such as guided bone regeneration (GBR), onlay bone grafting, bone extrusion, bone splitting, and distraction osteogenesis. GBR is one of the most popular techniques for repairing alveolar bone defects now because of its ease of use, low technical sensitivity, osteogenic stability, and multidirectional osteogenesis capacity.

Based on the theory that different cell types have different migration rates, GBR technology selectively blocks epithelial cells and connective tissue cells from entering the bone defect area through a barrier membrane, letting osteoblasts preferentially enter the area to finish bone induction and regeneration. As the new bone is being formed by the osteoblasts and osteocytes, bone graft materials are inserted in the location of the bone defect to act as scaffolds.

2. Peri-implantitis

Inflammation of the surrounding soft tissue and a loss of bone of more than 0.5 mm characterize a condition known as peri-implantitis. However, there is no universal agreement on how to define mucositis; some writers characterize it as just a soft-tissue disease, while others include bone loss of less than 0.5 mm, as in peri-implantitis, in their definition [5-7].

Clinical criteria such as probing depth, blood on probing, and bone loss have been used to categorize peri-implantitis as either mild, moderate, or severe. Early implantitis is defined as a probing depth of 4 mm and 25% bone loss, whereas moderate peri-implantitis is defined as a depth of 6 mm and 25% to 50% bone loss, and advanced peri-implantitis is defined as a depth of 8 mm and 50% bone loss [8].Bone loss of 3 mm, 3-5 mm, 5 mm, and more than 50% of implant exposure were used by Javier et al. to define phases 1, 2, 3, and 4, respectively [9].

2.1. Prevalence of periimplantitis

Peri-implantitis among the dental implant patients were reported to vary between 1 and 47% [10]. A prevalence of 65% was found by Cecchinato et al. when he included soft tissue inflammation with a bone defect of less than 0.5 mm [8], whereas a prevalence of 90% was found by Fransson et al. when mucositis was classified as a bone defect of less than 0.6 mm [11].However, Marrone et al. observed only 31% even though he considered the mucositis as soft tissue inflammation with bone loss less than 2 mm [12].

A dental implant can fail due to anaerobic bacterial colonization and bacterial compounds like lipopolysaccharides from the microgap, both of which upregulate cytokines that impede bone growth and stimulate osteoclast development in otherwise healthy peri-implant cells [13,14]. Understanding the peri-implant microbiota and the process of biofilm development is crucial for developing effective therapeutic techniques to avoid microbial colonization and increase implant life.

2.2. Mechanism of microbial adherence and inflammatory pathway

Adhesion, growth, maturation, and dispersal are the stages in the formation of biofilm caused by microbial colonization. Bacteria adhere to a surface first by electrostatic attraction, and then further adhere via the release of extracellular polymers [15]. The bacteria are mechanically retained on the host due to the surface's roughness [16]. In order for different bacterial species to co-aggregate into a single colony-forming unit, certain signaling molecules must be present. As bacteria cluster together, they release a biomarker that can either encourage or thwart the development of biofilms in the host tissue. However, as the biofilm develops and produces extracellular polymers, it becomes immune to antibiotic treatment [17]. Biofilm generation and peri-implant infection are aided by bacterial communication and the inflammatory response of the host. In order to stop the first step in biofilm development—bacterial adhesion and growth—it is necessary to understand the cellular foundation of biofilm formation.

3.Guided bone regeneration (GBR)

An outer barrier membrane is used in guided bone regeneration (GBR), a type of bone transplant surgery, to prevent the infiltration of soft tissues into the grafted bone. It has been argued by some academics that GBR should be narrowly defined to only include situations when a barrier membrane is present. The term "guided bone regeneration" (GBR) is commonly used to refer to any bone transplant procedure used to treat bone deficiencies next to a dental implant [15].

For GBR to be successful, pluripotent and osteogenic cells (such as osteoblasts originating from the periosteum and/or nearby bone and/or bone marrow) must migrate to the bone defect location while cells that inhibit bone formation (such as epithelial cells and fibroblasts) are excluded [16,17].

Presumably, guided bone regeneration occurs when the osteoprogenitor cells are permitted to repopulate the bone defect location while other, non-osteogenic tissues are kept out [18].

3.1. Principles of GBR

Successful GBR, as proposed by Wang and Boyapati's PASS concept (P: primary closure; A: angiogenesis; S: space maintenance; S: stability), consists of four steps. This is a principle with which the writers agree. Wound dehiscence increases the risk of problems like infection, which can lead to the failure of a GBR, hence primary closure should be performed to avoid this. Bone repair is facilitated by an abundant blood supply at the recipient location [19].

Additionally, the bone graft and barrier membrane should be stabilized to ensure the area is protected as the bone heals [20].

It is possible to regrow bone through three distinct processes: osteogenesis, osteoinduction, and osteoconduction. Bone ossification and development can occur without any undifferentiated mesenchymal stem cells being present in the immediate area thanks to a process known as osteogenesis. Undifferentiated mesenchymal stem cells can be induced to develop into osteoblasts or chondroblasts by using growth hormones found only in healthy bone, a process known as osteoinduction. Osteoconduction is the generation of a bio-inert scaffold, or physical matrix, that can either facilitate the deposition of new bone from the surrounding bone or induce the growth of differentiated mesenchymal cells along the graft surface [21].

3.2. Necessity of Barrier Membranes

The membrane used for GBR is an essential component of the treatment. Some studies have shown that adhering to the standards of bone grafting while using a membrane has no effect on patient outcomes.

Biocompatibility, cell-occlusion capabilities, integration by the host tissues, clinical manageability, space-making ability, and acceptable mechanical and physical properties are all desirable in the membrane used for GBR treatment [22].

3.2.1. Expanded Polytetrafluoroethylene

The first generation of barrier membranes were made of non-resorbable materials, mostly expanded polytetrafluoroethylene (e-PTFE). Typically, these membranes are biocompatible and may effectively create new volume [23].

The e-PTFE membrane provides a physical barrier. Connective tissue cells like fibroblasts are kept out of the bone defect so that cells with osteogenic potential can move

in and fill it up. A second surgical procedure is required to remove non-resorbable membranes [24,25].

To promote direct bone regeneration, researchers in the field of tissue engineering are working hard to create a functional barrier membrane. Numerous research have been conducted on a variety of related issues, some of which are included below: barrier membranes; bone replacements like hydroxyapatite; growth factors/stem cells; organic/inorganic nano compositions; and nano structures [26,27].

In the years that followed, a new generation of resorbable membranes was produced and ultimately saw widespread clinical application. Recent research has focused on preparing membranes utilizing tissue engineering techniques or natural membranes to create a new generation of membranes [28].

In addition, bone grafts and replacement materials are often utilized in conjunction with membranes placed in the defect to offer structural support for the site of the defect and to encourage the host tissue's innate healing capability [29,30].

Differences in membrane characteristics and biological reactions are essential features of GBR therapy [31]. In this case, many potential approaches will entail modifying the membrane to encourage the right reactions (including predictable bone regeneration, suitable soft-tissue reactions, and effective management of microbial adherence and colonization during GBR therapy).

Additionally, a barrier may prevent mechanical disturbance and saliva contamination to the incision. A barrier membrane should be biocompatible, easy to employ, maintain space, adhere to tissue without allowing it to move, and restrict soft tissue in-growth. Both non-resorbable and resorbable barrier membranes are now available.

3.2.2. High-Density Polytetrafluoroethylene

Clinicians eventually learned that exposing e-PFTE to the oral cavity allowed microorganisms to migrate through the very porous membrane. Migration of microorganisms through the extremely porous e-PTFE membrane upon exposure is a typical issue due to the average pore size of 5 to 20 m and the diameter of pathogenic bacteria generally being less than 10 m. In 1993, the most popular Cytoplast membrane, a high-density polytetrafluoroethylene (d-PTFE) membrane, was created to solve this issue. Animal and human research have shown that d-PTFE membranes improve the success of directed tissue regeneration.

Alveolar ridge preservation, extensive bone defects, and implant implantation right after extraction are all situations when primary closure is unachievable without tension, according to Bartee [32].

Soft tissue and the established mucogingival connection can be protected by leaving exposed d-PTFE membranes. In some cases, d-PTFE membranes can speed up the healing process by eliminating the need for large releasing incisions to attain primary closure, which can disrupt the blood flow and lead to the loss of keratinized tissue [33-35].

While guided bone regenerative membranes have shown promise in treating moderate to severe osseous defects, their ability to collapse towards the defect in response to pressure from surrounding soft tissues (thereby decreasing the space required for regeneration) raises questions about the quality of the regenerated bone. A predictable and successful therapeutic strategy for regenerating and repairing a significantly inadequate alveolar ridge [36-39] is the use of titanium mesh that can preserve the space.

3.2.3. Titanium Mesh

While guided bone regenerative membranes have shown promise in treating moderate to severe osseous defects, their ability to collapse towards the defect in response to pressure from surrounding soft tissues (thereby decreasing the space required for regeneration) raises questions about the quality of the regenerated bone. A predictable and successful therapeutic strategy for regenerating and repairing a significantly inadequate alveolar ridge [40-42] is the use of titanium mesh that can preserve the space.

Titanium mesh is strong and stiff enough to facilitate osteogenesis, stable enough to keep bone graft volume intact as wounds heal, and pliable enough to reduce the compression of oral mucosa [43].

Titanium mesh, however, is not without its flaws. Titanium mesh, in contrast to absorbable membranes, cannot be resorbed by the body, necessitating a second invasive surgical procedure to remove the titanium mesh and fixation screws [44].

Furthermore, titanium mesh, unlike other absorbable and nonabsorbable barrier membranes, must be molded after surgery to adjust profile of alveolar ridge. This is a tedious, time-consuming, and technically delicate operation. When bent, sharp edges arise, which can irritate the mucosa, potentially resulting in mucosal rupture and titanium mesh exposure [45].

Mechanical qualities are mostly determined by titanium mesh's thickness and porosity. According to the results of a recent study, the amount of new bone formed beneath titanium mesh may depend on its thickness, while the ratio of bone tissue to soft tissue production may depend on its pore size [46].

Titanium mesh with a thickness of 100-200 m was shown to be optimal for reconstructing multiple bone abnormalities in a research. Rakhmatia et al. found similar results when they investigated the bone augmentation effect of titanium mesh with thicknesses of 20, 50, and 100 m in a mouse model. They concluded that using titanium mesh at 100 m can provide a more comprehensive bone regeneration impact than thinner Ti-mesh.

Mesh made of titanium is biocompatible and may be used with many tissues. Corrosion resistance and cytotoxicity are two aspects of biocompatibility that may be further broken down. Titanium's poor electrical conductivity makes it prone to electrochemical oxidation, which results in an oxide layer that is both passive and inert [47].

Multiple titanium mesh bone augmentation clinical treatments are now in use, and they may be loosely categorized as either simultaneous implantation, delayed implantation, or guided bone regeneration (GBR) with titanium mesh in conjunction with other bone augmentation methods.

Since clinical needs and digital implantation technology have evolved, tailor-made titanium mesh has emerged as a topic of study in the field of guided bone regeneration. The optimal restored alveolar ridge can be created digitally according to arch shape and predicted implant position using computer-aided design (CAD) software after a thorough preoperative examination of the patient in cross-sectional imaging and digitalized research models [48].

3.3. Bone Graft Materials

Bone grafts can be made from a variety of sources, but the most common ones are autogenous bone, allografts, xenografts, and alloplasts. One or more of these three methods of action can be found in any grafting substance. The origin and make-up of the grafts often influence the processes through which they work.

Patient-harvested autogenous bone undergoes osteogenesis, osteoinduction and

osteoconduction to generate new bone. Skeletal allografts exhibit osteoconductive and perhaps osteoinductive qualities, but they are not osteogenic. Most xenografts and alloplasts only have osteoconductive properties.

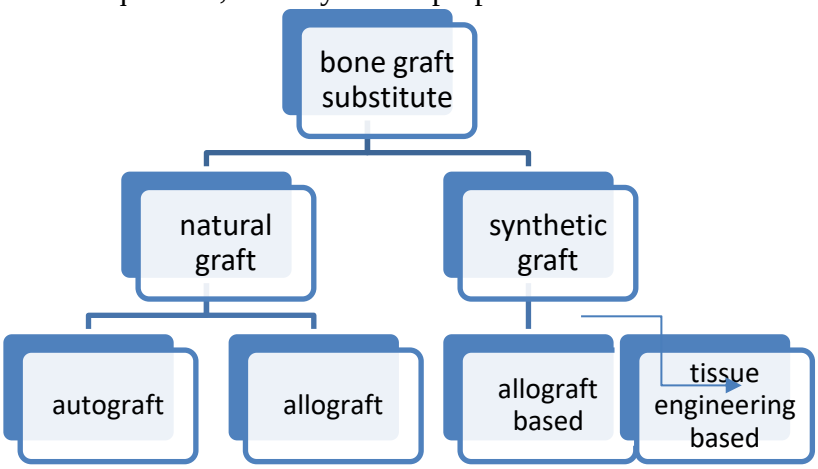

Figure 1. Classification of bone grafting substitutes.

Bone grafts are used to restore missing bone by acting as a mechanical support and encouraging osteo-regeneration [10]. Osseointegration, osteogenesis, osteoconduction, and osteoinduction are the four key biological features essential for fulfilling this function [11,14]. Osseointegration is the process by which a grafting material forms a chemical link to the surface of the bone without the presence of an intervening layer of fibrous tissue. It is the capacity of a bone grafting material to build a bioactive scaffold on which host cells can grow, known as osteoconduction. Osteogenesis is the process by which new bone is formed by osteoblasts or progenitor cells present in the grafting material.

3.3.1. bone autograft

When tissue is taken from one part of a person and transplanted to another, it is called an autograft. Normal sources of autogenous bone include the iliac crest, tibial plateau, mandibular symphysis, maxillary tuberosity, healing sites 8-12 weeks after extraction [49], ramus, tori, or exostoses [50,51].

Depending on the method used, different sized particles of autogenous bone can be generated. High-speed burs, low-speed burs, manual chisels, and bone-blending tools can all be used to harvest autogenous bone. Bone mix (obtained from cortical or cancellous bone with a trephine or rongeurs, put in an amalgam capsule, then triturated to the consistency of slushy osseous mass) has a particle size of around 210 x 105 um [52].Particle size ranges from around 300 to 500 um for grafts produced using high and low speed burs, and from 1559 x 783 um for bone chips that were hand-chiseled [52].

Because of its great osteogenicity, autogenous bone is the preferred grafting material. Success rates for bone transplantation are high because autogenous bone supplies the recipient region with proteins, bone-enhancing substrates, minerals, and essential bone cells [53- 55].

However, autogenous bone does not come without its drawbacks: Root resorption and ankylosis with fresh iliac bone graft when placed near the roots [56,57]; the difficulty of obtaining a sufficient amount of graft material, especially from intraoral sites; and the necessity of harvesting from a

secondary surgical site and the possible resultant patient morbidity.

Allografts and alloplasts were created as alternatives or complements to traditional grafting materials in response to these constraints.

3.3.2. bone allografts

In the case of allografts, tissue is transplanted from one genetically unique member of the same species into another genetically related but not identical member of the same species. Allograft bone is preferred because it reduces the severity of the host damage, may be acquired in nearly unlimited numbers, reduces blood loss, shortens the time of the procedure, and removes the need for a second incision at the donor site. Bone development after an allograft, on the other hand, often takes longer and results in less regeneration than after an autogenous transplant.

Disease transmission during grafting is a problem with allografts, however this risk is exceedingly minimal [58,59] because to careful donor screening and specimen processing.

The environment for the regeneration of critical bone is typically optimized by combining different grafting materials due to their distinct biological and mechanical qualities.

3.3.3. bone xenografts and alloplasts

Xenografts are grafts of tissue taken from a non-host species. Natural hydroxyapatite (HA) and deorganised bovine bone are two examples of xenograft materials (anorganic bone matrix or ABM). These grafts are made of inert, osteoconductive filler material that acts as a scaffold for the growth of new bone [60].

Hydroxapatite found in nature comes from the calcification of animal bones. It is extremely biocompatible to surrounding hard and soft tissues and has the same three-dimensional microstructure as genuine bone [61]. The host immune system can attack xenografts, they are fragile, and they can spread easily [62,63]. The poor resorption rate of xenografts may affect the mechanical and biological qualities of the regenerated bone and hinder the healing of the grafted location.

3.4. Phytogenic Material

Materials used as bone substitutes that are derived from plants are called "phytogenic materials," and they include Gusuibu, coral-based bone substitutes, and marine algae. There is widespread usage of the traditional Chinese herbal remedy gusuibu in China for the treatment of bone fracture and osteoarthritis [64,65,66].

Using a collagen carrier as a structural scaffold, Wong and Rabie found that new bone formation was increased by 24% across the bony defect when compared to the grafted Guisuibu alone, and by 90% when compared to an absorbable collagen sponge commonly used as a carrier for growth factors (GFs) such as BMPs to induce bone regeneration [67].

3.5. Synthetic Bone Substitute Materials

Artificial synthetic bone substitute materials are developed to precisely replicate the biological features of genuine bone in order to circumvent the possible immunogenicity and morbidity at donor locations. Nonetheless, the only synthetic properties shown by the materials that are now accessible are osteointegrative and osteoconductive.

Materials such as hydroxyapatite (HA), tricalcium phosphate (TCP), bioglass, nickel-titanium, polymethylmethacrylate (PMMA), polyglycolides, and calcium

phosphate cements come under this group [68,69].

► ***Hydroxyapatite (HA)***

HA can be employed as a bone grafting material since its chemical makeup is so similar to that of bone's inorganic component [70]. Unlike HA produced from bovine sources, synthetic HA does not have a microporous structure [8]. Due of its comparatively high Ca/P ratio and crystallinity, synthetic HA has a slower resorption rate. Its limited mechanical strength is another key issue, since it prevents HA from being employed in highly loaded areas.

► ***Tricalcium Phosphate Ceramics (β-TCP)***

A calcium phosphate substance called tricalcium phosphate (TCP) has been used for decades as a bone replacement. The lower Ca/P ratio makes for a more rapid biodegradation and absorption rate compared to HA [11]. Advantages of pure phasic -TCP include its low immunogenicity and risk of disease transmission [15,71], good resorbability compared to bovine bone grafts, and good osteoconductivity due to macroporosity that promotes fibrovascular ingrowth and osteogenic cell adhesion. It is also easy to handle and radiopaque, so healing can be monitored.

► ***Biphasic Calcium Phosphate Ceramics (HA and β-TCP Ceramics)***

Recent decades' worth of research and development have focused on creating a material that would leverage the resorbability of -TCP and the osteoconductive capability of HA [72]. Because of this discovery, biphasic calcium phosphate ceramics were developed in which -TCP and HA are frequently utilized together. Accordingly, the key advantages of employing biphasic CP ceramics are the faster and higher bone regeneration rates reported compared to the use of HA alone, and the superior mechanical characteristics than -TCP alone [73-75].

► ***Bioactive Glass***

Synthetic silicate-based ceramics called bioactive glasses (BAG) are made by coupling silicates with additional minerals such calcium, sodium, oxygen, and phosphorus [62].

Silicon ions can leak out and accumulate when implanted in the body, creating a coating of HA that promotes the adhesion of osteogenic progenitor cells. Bioglass has several beneficial characteristics, such as biocompatibility, osteoconductivity, antibacterial activity, and a porous structure that encourages vascularization [62].

4. Treatment Variations

The two main methods of guided bone regeneration in implant therapy are simultaneous guided bone regeneration at the time of implant insertion and guided bone regeneration prior to implant placement to augment the alveolar ridge or enhance ridge shape (staged approach). The best grafting method to repair an osseous defect depends on the size and nature of the lesion itself.

However, full bone regeneration on the implant surface may not be achieved even with GBR if the bone around the implant is thin. The implant should be inserted following ridge augmentation in these situations, as part of a phased strategy.

The use of an allograft material in a simultaneous approach is recommended for small abnormalities in the alveolar ridge, whereas the use of autogenous grafts in a phased method is recommended for moderate lesions in the horizontal ridge [76,77,78]. Reconstructive devices such tenting screws, mesh, and/or re-inforced membranes will be required to achieve more predictable regeneration responses in situations of severe horizontal and vertical alveolar ridge abnormalities [79, 80].

5. Future of Bone Substitute Materials in Dentistry

Although criteria for the optimum bone grafting material were established some decades ago, autografts continue to be the gold standard and the only material that exhibits all four essential biological features [68]. However, a trend away from employing these grafting materials and towards the creation of innovative synthetic bone replacements has been prompted by their limited availability and other related restrictions.

Despite extensive research and development efforts, no commercially accessible material has yet demonstrated enough biomechanical performance to fulfill this need.

The most challenging aspect of developing new materials is creating a mechanically robust, interconnected porous structure that allows for optimum osseointegration and vascularization. To make matters worse, synthetic bone replacements only have osteoconductive qualities in situations when bone growth is confined to the surface layer [68]. This lends credence to the idea that novel materials need to be meticulously designed structurally, with key biological factors like pore size, density, morphology, interconnectivity, and resorbability taken into account [78].

The paucity of study into the safety and efficacy of modern bone grafting materials is another important obstacle we confront. Since most of what we know about these more recent materials comes from anecdotal case reports or animal experiments, we should treat their accuracy with caution. In order to better understand the clinical viability and advantages of each material and bring more of them to market, more standardized preclinical and clinical research will need to be undertaken and recorded. So that we may have a deeper comprehension of the clinical viability and advantages of each substance prior to the introduction of more commercially available goods.

6. Conclusions

In dentistry, the majority of bone graft and replacement materials utilized to restore missing hard tissue components come in the form of either particle or block. Demand for cutting-edge, effective dental grafting materials is significant and rising. The primary function of current bone graft and substitution materials is to provide a framework for osteo-regenerative processes that simply need to meet the osteoconductivity requirements.

But as tissue engineering studies continue to advance, new innovations have emerged, such as various ceramic and polymeric-based bone replacements combined with growth hormones or modified with live osteogenic progenitor cells.

The price of these bone replacements is, however, a further consideration.

Clinicians need to weigh the potential benefits of these novel technologies against the greater expenses involved. As this subject continues to improve technologically, synthetic bone replacements are gradually replacing genuine bone transplants. The future of bone grafting for dental implants lies in the development of hybrid grafts that incorporate growth factors and live osteogenic cells capable of causing bone regeneration. Bone substitutes that allow for the regulated remodeling ability that is equivalent to the pace of new bone production are still in need of development, although progress has been made as noted in this review article.

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