THE ROLE OF BIOMATERIALS IN BONE REGENERATION IN ORAL AND MAXILLOFACIAL REGION

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INTRODUCTION

Bone defects occur in the maxillofacial region because of various reasons, which might be due to trauma, osseous defect following surgical resection of benign and malignant tumours, alveolar bone destruction and subsequent tooth loss because of periodontal disease. Considerable challenges are being faced by the surgeons attempting to restore the tissue to reinstate the function besides aesthetics (Smith BTet.al; 2015). The healing efficiency of a bone tissue is generally without the formation of a scar tissue under normal circumstances. Nevertheless, in complex bone fractures, like multiple comminuted fracture or in instances of more than critical size fractures can result in non-union of fracture or with defective healing(Ho-Shui-Ling et.al; 2018). The reconstructive aspect in cases of resection of large bony areas of maxillofacial region due to any tumor or congenital deficiency also results in undesirable result in case of procedures which cannot address the functional and aesthetic demand. The main objective of bone defect closure is to re-establish the lost structural integrity and restitution of the bone to withstand the mechanical stress devoid of any complications. Transplantation using autologous bone graft to bridge the defect still remains a reliable source and a promising technique with a beneficial outcome, though with some drawbacks added to it. The advantages of this technique are, lack of immunogenicity thereby preventing the risk of transmitted diseases and rejection issues to a lesser extent. The main drawbacks being, comorbidity of second surgical site, chronic pain, dysesthesia, vascular injuries, need for general anesthesia for donor site harvesting alone, inadequate graft material in cases of large defects leading to complete and successful rehabilitation (Gunzburg R; 2002, HungYW et.al, 2015).

The allogenic bone graft is the next alternative to autologous bone, but it presents with the chances of high cost, immunogenic, disease transmission, graft rejection to a larger extent and a reduction in the osteogenic ability due to the process of preservation. The drawbacks of this technique made it less favourable in spite of its unlimited availability from the donor (Chalmers, J; 1959). Another alternative to autologous and allogenic bone graft is the xenogenic bone transplant and autoclaved bone transplant (allogenic). The drawback of former being immunogenic and the latter with reduced mechanical stability made them less popular. The introduction and the rapid development of biomaterials during the latter half of the

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twentieth century concluded the search for the bone substitute to outweigh the drawbacks of auto graft and allograft (Boyan BD et al; 1998). The revolutionary growth rather than the evolutionary change in the area of bone regeneration did result in a paradigm shift in the field of biomaterials leading to a dramatic change in the treatment results even in complicated cases as large defects or even in compromised conditions.

**Terminologies**

**Biocompatibility**: refers to “the ability of a biomaterial to perform its desired function with respect to a medical therapy, without eliciting any undesirable local or systemic effects in the recipient or beneficiary of that therapy, but generating the most appropriate beneficial cellular or tissue response in that specific situation, and optimising the clinically relevant performance of that therapy” (Williams, D.F., 2008).

**Bone Substitutes**: can be defined as “a synthetic, inorganic or biologically organic combination – biomaterial which can be inserted for the treatment of a bone defect instead of autogenous or allogenous bone” (Schlickewei, W, Schlickewei, C. 2007),

**Biomaterial**: is defined as “A material intended to interface with biological systems to evaluate, treat, augment or replace any tissue, organ or function of the body. (As defined by the European society of biomaterials) (Thilakan J; 2019)

Based on Medical terminology a biomaterial is “any natural or synthetic material (which includes polymer or metal) that is intended for introduction into living tissues as part of a medical device or implant” (Ex: Artificial heart valves, TMJ - temporo mandibular Joint). In the perspective of health care biomaterial can be defined as “materials that possess some novel properties that makes them appropriate to come into immediate contact with the living tissue without eliciting an adverse immune rejection reaction.”(Thilakan J; 2019)

**Osteoinductive**: The implanted material results in a sequence of events which results in the new bone formation

**Osteoconductive**: Biomaterial acts as an osteoconductive “Guideline”. The capacity of a substance to promote the development of bony tissue(Bhat S, Kumar A; 2013)

**Osseointegration**: “A process whereby clinically asymptomatic rigid fixation of alloplastics materials is achieved, and maintained, in bone during functional loading”(Zarb G, AlbrektssonT ;1991)

**History of Biomaterials**

The introduction of biomaterial in bone replacement dates back to 1960s, and is described under three generations(Yu X;2015)

**First Generation Biomaterials**

a. They were able to replace the tissue defect exhibiting pertinent mechanical properties and with least toxicity to the host tissue.
b. They are bioinert, thereby exhibiting minimal interaction with the tissue surrounding.
c. Their ability of corrosion resistance in an aqueous environment and wear resistance.

d. They Include, Metals – Titanium and its alloys, Synthetic polymers – (Poly Methyl Metha Acrylate-PMMA and Poly Ether Ether Ketone-PEEK) and Ceramics – Ex:alumina and zirconia.

**Second Generation Biomaterials**

a. The main advantage of the second generation is their bioactive nature and few could be biodegradable.
b. They include natural polymers – collagen, Synthetic polymers, Calcium phosphates, calcium sulfates, calcium carbonates, and bioactive glasses.

**Third Generation Biomaterials**: They are designed to produce favourable biological responses by the inclusion of elements like growth factors, delivering site specific cells and various molecules to an area of regeneration by incorporating onto the second generation biomaterials based on their ability to regenerate thereby making them multifunctional.

**Classification Of Biomaterials (H. Andrzej ;2019)**

They can be classified as follows,

**Based on their source and characteristics**

a. Metal – Ex: Titanium and its alloys, Nickel Titanium alloys, tantalum, Magnesium
b. Natural – Ex: Collagen, Gelatin, Silk Fibroin, Chitosan, Alginate, Hyaluronic acid
c. Synthetic- Ex; PLA, PGA, PLGA, PCL, PVA, PPF, PU
d. Bioinert Ceramic- Zirconia, Aluminium Oxide
e. Bioactive Ceramic- Hydroxyapatite (HA), TricalciumPhosphate, Akermanite, Diopsie, Bioactive Glasses
f. Composite- Combination of two or more materials.

**Based on their dissolution property**

a. Resorbable: These materials gets disintegrated and resorbed in the tissue
b. environment after its implantation
c. Nonresorbable: They lack their ability to disintegrate and resorb.
d. Based on their interaction with the tissues,
e. Bioinert: Materials exhibiting minimal interaction with the surrounding tissues
f. Bioactive: Bonding with the tissue surrounding is encouraged
g. Biostable and Biodegradable: They disintegrate completely into the surrounding tissue over a span of time by gradually releasing their mass into it.

**Ideal Requirements Of Biomaterials For Bone Regeneration (Yu X;2015)**

1. Biocompatible
2. Bioactive /Bioreversible
3. Osteogenic
4. Osteoinductive
5. Osteoconductive
6. Osseointegrative
7. Sterilizable
8. Printable (Huawei Qu; 2019)
9. Non toxic
Bone Regeneration in Oral and Maxillofacial Region

The oral and maxillofacial region is a complex area comprising different types of hard and soft tissues, which includes oral mucosa, alveolar bone, periodontal structures, teeth, nerves, blood vessels, muscles, salivary glands, maxillary sinus, facial bones etc., Each tissue requires specialized physiochemical and biochemical factors for the successful tissue regeneration after combining with specific biomaterials, cells, surrounding environment and culture methods. Bone regeneration in the oral and maxillofacial region is of vital importance and may be due to conditions like fracture due to accidental trauma, alveolar bone loss due to periodontal diseases, minor and major surgical resection of the alveolar bone and/or facial bone in case of benign or malignant tumours, facial reconstruction in case of existing congenital anomaly.

The regenerative ability in the region of bone defect mainly depends upon the vascularization and is of utmost importance in areas of larger bone defects where bone substitutes are used. Impairment of blood supply to the regenerative part of the bone tissue due to the defect in the vascularization can result in osteonecrosis, also termed as avascular necrosis. The coupling of vascularization, osteogenesis and resorption kinetics must be in balance for the bone remodelling process to be in harmony (Fernandez de Grado.,et.al.,2018).

Periodontal Soft Tissue Reconstruction and Regeneration

The complex structure of periodontium is composed of both soft and hard tissues. Bone loss in periodontium is most commonly associated with infection and inflammation of the same and also occurs as a result of mechanical trauma. To overcome the limited availability and postoperative morbidity associated with autogenous graft harvesting techniques, alternative biomaterials have been advocated. The main advantage of such biomaterials being its unlimited availability and reduced surgical time with decreased postoperative discomfort due to the lack of a donor site. (Lisetta Lam,et.al., 2017) Different types of periodontal soft tissue biomaterials includes, Allogenic materials  e.g., Acellular dermal matrix allograft Xenogeneic materials :e.g., extracellular matrix (ECM) membrane, bilayer collagen matrix Autologous materials :e.g., platelet rich fibrin (PRF)membrane Alloplastic materials :e.g., three-dimensional (3D) printed scaffolds Tissue engineered material :e.g., living cell construct Layered scaffolds allow the development of each periodontal tissue independently, but concomitantly integrating it into a single composite construct, could be advocated for periodontal tissue engineering. The engineering challenges for this achievement include the cellular and molecular events that guide the progress of this coordinated tissue engineering construct along with particular tissue structural and functional characteristics. (Oryania-Menti Goudouri,et.al.,2017)

Dental pulp tissue engineering and regenerative endodontic therapy

Both synthetic and natural biomaterials with appropriate surface morphology and mechanical integrity have been utilized to create scaffolds for regenerative endodontic therapy. Synthetic scaffold are traditionally fabricated using rapid prototyping or 3D printers using polyactic acid or polyglycolic acid which have been shown to result in generation of pulp-like tissue after implantation. Natural scaffolds such as matrices derived from biological sources (collagen, chitosan, silk, PRP, and PRF) have also shown potential to be used as scaffolds in regenerative endodontic therapy. In particular, autogenous scaffolds involving blood clot from intracanal bleeding, PRP/PRF, and collagen have shown positive effect on the outcome of REP therapy. (Priyadarshni Bindal,et.al;2017)

Oral and Maxillofacial Defects

In addition to the minor procedures like prevention of infection at the surgical site, reduction of post-extraction socket healing time and complications, post-extraction hemostasis, reduction
of post-operative hematoma, reconstruction following cyst enucleation, tumor excision and as an adjunct to palatal wound treatment or alveolar cleft treatment, biomaterials also play an important role in restoring the fractures of the oral and maxillofacial region.

Platelet-rich fibrin can be used for the above purposes. The use of an absorbable collagen sponge (ACS) has been the primary method of delivering rhBMP-2, for use in bone augmentation, both in conjunction with tooth extraction sockets and the maxillary sinus, to permit the placement of an Osseo integrated dental implant for the rehabilitation of edentulous patients. (Aghaloo TL; 2019)

Surgical reconstruction of craniofacial bones usually involves autologous allogenic bone graft with skin flap coverings or can be with synthetic biocompatible biomaterial. In case of larger defects reinforcement can be done with titanium support. The repair of large bone defects is particularly challenging, though autologous bone grafts are supposed to be the “gold standard”. (Aileen Crawford; 2017) Bone-graft substitutes composed of synthetic or natural materials have been developed as an alternative to autologous, xenogenic, and allogenic bone grafts.

These bone graft substitutes (Fig.2) encompass a wide range of materials including collagen and collagen-hydroxyapatite (HA)-based, HA and HA-calcium orthophosphate-based composites, metals,bio glass ceramics, and cements. (Finkemeier, C.G., 2002;Giannoudis, P.V2005, Hatton, P.V,2006).The osteoinductive properties of biomaterial bone-graft substitutes are limited, though they present with good osteoconductive properties. Calcium phosphates are widely used as biomaterials for bone repair due to their biocompatibility and osteogenic potential. Though there are various available biomaterials for bone regeneration, it is still in the process of revolutionary changes to facilitate the incorporation of different materials in a single scaffold. Scaffold based regeneration with the use of an abundant variety of biomaterials, in addition to stem cell and growth factor use, has proven to efficaciously restore the microanatomy and functionality of the bone both in vivo and in vitro. Their potency in revitalizing bone provides promise and vast potential in future widespread incorporation in the defects of different maxillofacial tissues.

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Future Prospects

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