

## Bone Tissue Engineering and Bony Scaffolds

Shamaz Mohamed<sup>\*1</sup>, Bibi Halima Shamaz<sup>2</sup>

<sup>1</sup>Department of Public Health Dentistry, Amrita School of Dentistry, Kerala, India

<sup>2</sup>Amrita Centre for Nano Sciences, AIMS, Amrita University, Kerala, India

**Corresponding Author:** Shamaz Mohamed, Department of Public Health Dentistry, Amrita School of Dentistry, Kerala, India

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### Abstract

The stimulation of bone regeneration is required to treat bone loss through trauma, osteonecrosis, and tumours, which demand the need for an ideal bone substitute. Bone is composed of 65-70% hydroxyapatite (HA) and 25-30% of organic fibrous matrix (collagen), so an ideal scaffold should resemble the structural pattern (fibrous) and chemical or mechanical nature of the bone. Various bone tissue engineering techniques has been evolved and scaffolds designed to mimic the natural none and yet be safe and compatible to be efficiently used as bone tissue replacement. This review focuses on the new scaffolds and their properties used in bone tissue engineering.

**KeyWords:** Bony Tissues, Bony Scaffolds, Bone Biology, Bone engineering

### Introduction:

Bone is a vital organ playing key roles in critical functions in human physiology including protection, movement, support of other critical organs, blood production, mineral storage and homeostasis, blood pH regulation, multiple progenitor cell (mesenchymal, hemopoietic) housing, and others. Bone related problems such as osteomyelitis, trauma, and tumor cause significant damage to the skeletal structure and require replacement procedures to restore the normal morphology and function as approximating as possible [1]. In USA, there is an estimated 2, 80,000 hip fractures, 7, 00,000 vertebral, and 2, 50,000 wrist fractures occur each year. Delayed healing or non-union of fractures occurs in five percentages of all fractures, and 20 percentages of high-impact fractures. Large areas of bone loss due to trauma may exceed the body's regenerative capabilities unless surgeons intervene to bridge the skeletal defect [2]. Around 4.4 lakhs Indians get fractures every year, a figure set to hit 6 lakhs in 2020. In India, fractures constituted 7.5% of total injuries and fractures of the skull and face and lower limbs accounted for 52% and 24%, respectively [3].

### Brief insights in bone biology:

Bone tissue in the adult skeleton is arranged in two architectur-

al forms trabecular, also called cancellous or spongy bone which makes around 20% of the total skeleton and cortical or compact bone which constitutes around 80% of total skeleton. Cortical bone is almost solid, being only 10% porous, present in all stress bearing areas such as long bones (femur and tibia), short bones (wrist and ankle), and flat bones (skull vault and irregular bones). On the other side, trabecular bone presents a higher porosity, 50-90%, making its modulus and ultimate compressive strength around 20 times inferior than that of cortical bone. Trabecular bone is arranged in a sponge-like form, with a honeycomb appearance consisting of bars, of various sizes called trabeculae. It is commonly found in metaphysis of long bones, covered by cortical bone, and in the vertebral bodies. Bone matrix has two components: a mineral part constituted by hydroxyapatite (HA), which contributes with 65-70% to the matrix and an organic part, composed of glycoproteins, proteoglycans, sialoproteins, bone "gla" proteins, that comprises the remaining 25-30% of the total matrix [4]. Because of this, and from a materials science perspective, bone can be considered as a truly composite material. Few characteristic features [5] of bone can be found in Table 1.

Property	Cortical bone	Cancellous bone
Compressive strength (MPa)	100–230	2–12
Flexural, tensile strength (MPa)	50–150	10–20
Strain to failure (%)	1–3	5–7
Fracture toughness (MPam <sup>1/2</sup> )	2–12	–
Young's modulus (GPa)	7–30	0.5–0.05

**Table 1:** Mechanical properties of human bone tissues

**Treatment modalities of bony defects:**

Various treatment modalities are there for treating the bony

defect, all of which have its own advantages and disadvantages. Various properties of graft material [6] are provided in Table 2.

Property	Description
Osteoconduction	Provide a passive porous scaffold to support or direct bone formation
Osteoinduction	Induce differentiation of stem cells into osteogenic cells
Osteogenesis	Provide stem cells with osteogenic potential, which directly lay down new bone

**Table 2:** Properties of bone graft material

**Autologous (or autogenous) bone graft**

It involves utilizing bone obtained from the same individual receiving the graft. It is considered as the “gold standard” graft because it is osteogenic, osteoinductive, osteointegrative, osteoconductive and there is less risk of the graft rejection [7]. It is commonly taken in the form of trabecular bone from the patient’s iliac crest, but cortical bone can be used as well [4]. But the disadvantage of autografts is that an additional surgical site is prepared and operated, for experiencing post-operative pain and potential complications. Autografts could retain their viability for two hours when kept in normal saline [8].

**Allograft**

It involves bone taken from somebody else’s body, but from same species. The advantages include its ready availability in various shapes and sizes, avoidance of the need to sacrifice host structures and donor-site morbidity [8]. Allograft is osteointegrative and osteoconductive and may exhibit osteoinductive potential, but it is not osteogenic because it contains no live cellular component [9]. The disadvantages comprise the possibilities of immune rejection and of pathogen transmission from donor to host, and although infrequent, infections could occur in the recipient’s body [4].

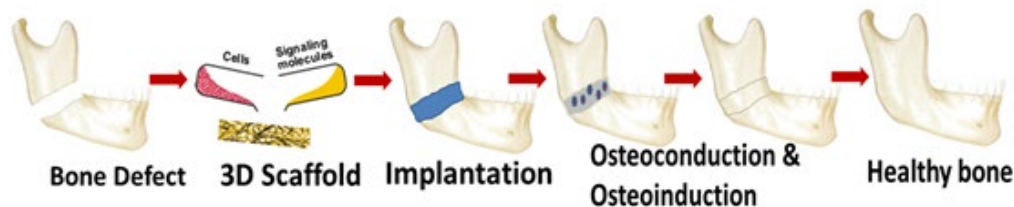
**Metals**

Metals like stainless steel and pure titanium or its alloys are used as permanent implant and provide immediate mechanical support. However, it poor overall integration with the tissue at the implantation site, and can fail because of infection or secondary due to fatigue loading [4].

Hence it is clearly seen that an adequate bone replacement is yet to be found and it is at the same time urgently needed for full recovery of the patients. A possible solution for these problems may be in bone tissue engineering.

**Bone tissue engineering**

Bone tissue engineering is a state of art and science involved in regeneration of bone with natural form and function [10]. Bone tissue engineering involves extensive use of porous 3D scaffolds to provide the appropriate extracellular environment for the regeneration of bone tissues. These scaffolds are either cultured with cells and occasionally growth factors in vitro to synthesize tissues, which can then be implanted into an injured site, or are implanted directly into the injured site using the body’s own systems, where regeneration of tissues or organs is induced in vivo [11]. This combination of cells, signals and scaffold is most often referred to as a tissue engineering triad [4]. Schematic representation of bone tissue engineering process can be seen in Figure1.



**Figure 1:** Schematic representation of bone tissue engineering

A 3D biomaterial or scaffold mimicking bone structure is needed to generate new tissue, which essentially act as a template for tissue formation in vitro or in vivo [11]. Numerous individual and combination of biomaterials are proposed using a variety of fabrication techniques to regenerate bone. Besides the choice of adequate materials, the macro and micro-structural properties of the materials are of utmost importance, which affect not only cell survival, signaling, growth, propagation, and reorganization but also their gene expression and their phenotype [4].

#### **Scaffold requirements:**

The following properties are essential for an ideal scaffold [11].

##### **Biocompatibility:**

The scaffold should be immunologically compatible, must not produce immune reaction to prevent a severe inflammatory response that might reduce healing or cause rejection by the recipient body.

##### **Biodegradability:**

The degradation rate of scaffolds must be tuned appropriately with the growth rate of the neo tissue, in such a way that by the time the injury site is totally regenerated the scaffold is totally degraded. The by-products of the degradation are also important, which should not be toxic and able to exit from the body without difficulty.

##### **Mechanical properties:**

The scaffold should have mechanical properties consistent with the anatomical recipient site into which it is to be implanted, must be strong enough to allow handling during implantation and must have the integrity to function from the time of implantation to the completion of the remodeling process. Scaffolds manufactured with good mechanical properties have disadvantage of not retaining a high porosity and thus, materials, which have demonstrated potential in vitro, have failed when implanted in vivo due to insufficient capacity for vascularization. Hence a balance between mechanical properties and porous architecture to allow cell infiltration and vascularization is important to the success of any scaffold.

##### **Scaffold architecture:**

Scaffolds should have an interconnected pore structure and high porosity to facilitate cellular penetration and adequate diffusion of nutrients / removal of waste products. Another key component is the mean pore size of the scaffold [11]. Studies suggest that micro porosity (pores < 20 micron) improves bone growth into scaffolds by increasing the surface area for protein adsorption, increasing ion solubility, and providing attachment points for osteoblasts and vascularization [12] and macro porosity (pore size >50  $\mu\text{m}$ ) enhance the osteogenic potential of the scaffold [13] The optimal macro porosity reported by many studies for the ingrowth of bone

tissue is in the range between 150 and 500  $\mu\text{m}$ . the total porous volume of the scaffold should be high enough (~80-90%) and pores should be interconnected. Porosity provides direction for fibro vascular tissue into the scaffold influencing in proper remodeling of bone [14].

Changes in macro porosity have been shown to affect the mechanical properties more than changes in micro porosity. Still, it must be balanced to have an adequate compressive strength [15].

##### **Scaffold Chemistry:**

Cells primarily interact with scaffolds via chemical groups (ligands) on the material surface. Scaffolds synthesized from natural extracellular materials (e.g. collagen) naturally possess these ligands in the form of Arg-Gly-Asp (RGD) binding sequences, whereas scaffolds made from synthetic materials may require deliberate incorporation of these ligands [16].

##### **Scaffolds in Bone tissue Engineering:**

Over the years many materials have been tested and tried in this field, which includes ceramics polymers (natural and synthetic) and composites [17-19].

##### **Bioceramics**

Hydroxyapatite (HA) and tricalcium phosphate (TCP) are the most commonly used ceramics for bone tissue engineering because they are osteoconductive and have similarity in chemical composition to bone [20]. Although these materials exhibit few favorable properties for bone tissue engineering, several disadvantages limit their clinical application. These ceramics are fragile and possess low mechanical stability. In addition, their degradation rate is not very predictable [18].

##### **Polymers**

In biomedical applications, the criteria for selecting the polymers as biomaterials are based on their material chemistry, molecular weight, solubility, shape and structure, hydrophilicity / hydrophobicity, surface energy, water absorption ability, degradation. Polymers have great design flexibility because the composition and structure can be tailored to the specific needs [18]. Biodegradability of the polymers can be modulated through molecular design [21]. Polymers can be classified as natural and synthetic.

**Natural Polymers:** Polysaccharides such as cellulose, starch, alginates, chitin / chitosan or proteins such as collagen or gelatin would be classified as natural scaffolds. The main advantages of these scaffolds are their high inherent bioactive properties and biocompatibility with the host tissue [18].

**Synthetic polymers:** Many synthetic resorbable polymers like poly lactic acid (PLA), Poly-L-lactic acid (PLLA), poly lactic co-glycolic acid (PLGA), poly ethylene glycol (PEG), poly caprolacton,

poly vinyl alcohol (PVA) have been developed to overcome the problems associated with natural polymers. Most synthetic polymers are biocompatible and degraded via chemical hydrolysis and insensitive to enzymatic processes so that their degradation does not vary from patient to patient [17].

However, the use of the natural polymers is limited due to their very low mechanical stability. Even though biodegradable synthetic polymers degrade at an appropriate rate without undesirable by-products and can be modulated by varying the ratios of the components, the increase in the local concentrations of acidic degradation products may impair cell growth on the scaffolds in vitro and induce an inflammatory response in vivo [22].

**Metals**

Over the years many metals and ceramics have been tried in medical fields and more importantly implant metals like stainless steels, cobalt based alloys, and titanium-based alloys, and typical ceramics are alumina, zirconia, calcium phosphate, and bioglass. How-

ever, metals and ceramics have two major disadvantages first, they are not biodegradable (except biodegradable bioceramics such as a-tricalcium phosphate, b-tricalcium phosphate), and second, their processability is very limited. For these reasons, polymeric materials have been increasingly received the attention from the scientific and medical communities [23]

**Hydrogels**

Hydrogels are polymeric systems with crosslinked structures capable of absorbing a considerable volume of water-based solutions. Cells are trapped within the hydrogel during the gelation process. The disadvantage of hydrogels is their poor mechanical properties. There are several scaffolds that are classified as hydrogels. These include chitosan, poly vinyl alcohol, alginate and silk fibroin, the latter being considered more suitable for bone tissue engineering due to its good biocompatibility, flexibility and mechanical stability (table 3). Alginates, which are derived from brown seaweed and approved by the FDA as wound cover, have frequently been used in tissue engineering processes [24].

Scaffold	Properties	Advantages	Disadvantages
(1) Chitosan	Chitosan, the fully/partially deacetylated form of chitin. Its wide variety of application ranging from skin, cartilage, bone and vascular grafts to substrates, mammalian cell culture. Fibrin a complex network formed by polymerization of fibrinogen in the presence of the enzyme thrombin.	Biologically renewable. Biodegradable, Biocompatible. Non-antigenic. Non-toxic. Biofunctional. Bioadhesive materials	Inducing rapid bone regeneration at initial stages. Bone formation after implanting these matrices occurs over a long period. Rapid degradation in vivo.
(2) Fibrin	Fibroin is a fibrous protein constituting the core of silk, while sericin is a glue-like protein surrounding fibroin	Induce improved cellular interaction. High biocompatibility	Difficult to maintain structural integrity.
(3) Silk fibroin	Derived from collagen Insoluble in water	Biocompatibility, Slow degradability, Excellent mechanical properties	Spider silk production very less
(4) Gelatin	Component of natural extra cellular matrix(ECM) Component of natural ECM.	Biodegradability and biocompatibility in physiological environment, Low antigenicity <sup>7</sup>	Poor mechanical properties. Brittle
(5) Collagen	Role in natural Wound healing	Biocompatible. Good cell recognition	Poor mechanical properties
(6) Hyaluronic acid	Originates from seaweed. Structurally similar to natural glycosaminoglycan	Biocompatible. Easily functionalized	Poor mechanical properties
(7) Alginate		Good cell recognition Biocompatible. Simple gelation methods	Poor mechanical properties

**Table 3:** showing characteristic features of hydrogels and natural biomaterials



## Composites:

Due to some of the unmet desired properties of individually synthesized scaffolds of single biomaterial, the researchers started manufacturing composite material made of different combinations of biomaterials making the composite gain advantageous properties of each biomaterial combined [25].

From a biological perspective, it makes sense to combine polymers and bioceramics to fabricate scaffolds for bone tissue engineering because native bone is the combination of a naturally occurring polymer and biological apatite. From the materials science point of view, a single material type does not usually provide the necessary mechanical and/or chemical properties required hence the properties of two or more materials can be combined in a composite material.

For example polymers and ceramics (and glasses) that have the ability to degrade in vivo are ideal candidates for composite scaffolds which gradually degrade while new tissue is formed. While massive release of acidic degradation from polymers can cause inflammatory reactions the basic degradation of calcium phosphate or bioactive glasses could buffer the acidic byproducts of polymers thus contributing to avoid the formation of an unfavorable environment for cells due to low pH values. Mechanically, bioceramics and glasses are stronger than polymers and play a critical role in providing mechanical stability to constructs prior to synthesis of new bone matrix by cells. However, ceramics and glasses are very fragile and prone to catastrophic failure due to their intrinsic brittleness and flaw sensitivity. The formation of composites thus capitalizes on the advantages of both material types and minimize their shortcomings [26].

There has been tried and tested combinations to tailor make the mechanical, degradation and biomechanical properties of these composites. Some of the combinations tried are synthetic-synthetic, synthetic-natural and natural-natural. However till date the result is compromise of individual properties to gain overall composite scaffold with good properties [19].

## Conclusion:

In the course of accomplishment of ideal properties of a bone substitute such as porosity, mechanical strength and cytocompatibility, many methods have been put forwarded using diverse composite materials. There is no single ideal technique or composite material, which demonstrates the fabrication of an ideal bone scaffold that mimics the properties of native bone. However bone tissue engineering field is emerging one and every day new innovations and materials are coming forth which may one day lead us to the desired novel method, technique and material to heal bone disorders.

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