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Review Article

Artificial Scaffolds for Bone Tissue Engineering

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Abstract

The disorder associated with bones has been increasing and is expected to be doubled by 2020. The bone disorders are mainly observed in population where they are suffering from obesity, age associated diseases and lack of physical activity. Now days engineered bone serves as an effective alternative to the conventionally used bone tissue grafts due to its mechanical stability and ease of availability. The engineered bones do not proceed to clinical practices due to various challenges which limit its use. Bone tissue engineering encourages regeneration of functional tissue using a biocompatible combination of different biomaterials, growth factors and cells. This review focuses on various artificial scaffold and their properties used for bone tissue regeneration and its current status. Further we discuss various approaches used for enhancing the tissue regeneration and routinely used biomaterial along with certain growth factors for mimicking its effects.

Keywords: *Bone Tissue Engineering; Scaffold; Biomaterials; Regeneration; Growth Factors*

Introduction

Tissue engineering is the discipline of science where engineering and life science are interlinked with each other and is relatively new and multidisciplinary field. It correlates medical science, material science and mechanical science with genetics. The main approach of tissue engineering is to restore the function of damaged cell or tissue by using a suitable scaffold or framework using a growth factors or promoters with the whole cell [1,2]. It uses different techniques for delivery of suitable signalling molecule to replace the damaged or non-functional cell to retain the normal physiology. The main challenge in maintaining and the normal function is its preservation and preventing cell or tissue rejection [3]. Bone tissue engineering is widely used for repairing the damage of bone occurred during trauma or injury and serve as a better option for regeneration as it uses body's own tissue and minimizes the risk of rejection.

Bone tissue engineering

It could be an approach for repairing the defects generated in the bone due to mechanical injury or the defects which arises from the birth. This field of science consists of three main components such as framework or scaffold, growth factors and cell which may be used *in vivo* or *in vitro* for regeneration [4]. It mainly focusses on stimulating the natural behavior and remolding it in its natural ways. For achieving the natural regeneration, the scaffold material should be non-toxic, inert it should improve cell adhesion and promotes the cell proliferation and differentiation [5,6]. Bone tissue engineering serves as a cost effective alternative for bone transplantation which involves blood transfusion.

Scaffold design

The framework or scaffold used in tissue engineering must incorporate the elements of mechanical, chemical and biological characteristic of the system to be studied. The current design of the scaffold mainly focusses on the biological constraints of the damaged site or the parts which gives mechanical stability. The biological environment of the bone contains the cells and various growth factors along with nutrients which promote cell growth, cell migration and cell proliferation. While the mechanical environment of bone includes the various requirements towards stability, supports and biocompatibility to promotes cell to cell interaction and cell communication. The biological and mechanical environment is useful for successful tissue or cell regeneration. Bone is an extracellular matrix which exists 5 hierarchical levels: whole bone, architecture, tissue, lamellar, and ultrastructure (Table 1).

S. No	Level	Dimension
1	Whole Bone	3 mm - 750 mm
2	Architecture	75 - 200 μm (T) 100 - 300 μm (C)
3	Tissue	20 - 75 μm (T) 20 - 100 μm (C)
4	Lamellar	1 - 20 μm (T) 3 - 20 μm (C)
5	Ultrastructure	0.06 - 0.4 μm (T) 0.06 - 0.6 μm (C)

Table 1: *Hierarchical levels of bone (where T = Trabecular Bone; C = Cortical Bone).*

The whole bone level represents overall size and shape of bone or scaffold. architectural level of bone describes the spatial distribution due to presence of microstructures. The material properties of bones represent the level 3 i.e. tissue level of bone. The lamellar level of bone composed of sheets of collagen and minerals such as calcium and phosphorus deposited by osteoblasts cells and present below the lamellar level in the hierarchy of bone [7]. Whereas the final level of bone represents ultrastructure which allows various chemical and quantum reactions [8]. These hierarchical levels of bone give over all structural changes straddling from whole bone to the quantum and chemical level which are useful while seeding the cells for bone tissue regeneration also helps in selecting suitable scaffold for bone tissue engineering [9].

Ideal features of scaffold bone tissue regeneration

It is important key factor to determine the ideal feature of scaffold chemically, biologically and commercially to fill the gap between research and clinical application [10]. An ideal scaffold used in bone tissue regeneration should allow cell growth, cell viability, cell migration and cell proliferation along with osteogenic differentiation and incorporation in host without causing adverse effects.

Moreover, it should be easy to handle and involves less invasive procedure during implantation along with cost effective and easily reproducibility techniques on large scale. The scaffold properties used in bone tissue regeneration can be classified in four types like structural, biological, composition of biomaterial and the method of fabrication use.

Biological requirements of scaffold

It should be non-toxic, non-immunogenic and biocompatible in nature. It should provide the surface for growth and regeneration of new matrix by allowing cell proliferation and differentiation [10-12]. The scaffold should be bioactive and able to interact with the tissue to enable regeneration by suitable mechanism and avoiding adverse effects as compared to conventional passive biomaterials [13].

Another feature of scaffold is, it should be biodegradable and the waste products generated after degradation should be non-toxic and easy to excrete by the body with less interaction with other organs or systems [14,15].

Moreover, it is important for a scaffold to prevent host immune response, which may be minimized by incorporating immunosuppressant or immune-modulators in suitable biomaterial used in bone tissue regeneration to minimize immune response.

Structural features

It allows mimicking the bone structure and development of new biomaterial for bone tissue regeneration. Greatest challenge in developing the scaffold material is to maintain adequate vasculature for osteointegration and this can be achieved by using suitable nanomaterial like nanofibers, nano tubes nanospheres or suitable nano composite [16-18]. The nano-biomaterials provide greatest surface area for cell adhesion and defects decreases with increase in size of crystals [19,20].

Composition

Currently used scaffold in BTE are polymers, ceramics and various composite of natural and synthetic materials. The composition of scaffold widely controls the toxicity and biocompatibility depending on from where it is derived. The naturally occurring composites are bio compatible, non-toxic, biodegradable and non-immunogenic in nature [21,22]. However, they possess certain disadvantages like low mechanical stability and the rate of degradation cannot be controlled as compared to synthetic polymers. Another polymer used in bone tissue regeneration is hydrogels, poly vinyl alcohol and gelatin due to their stability, cost effectiveness and easy method of preparation.

Types of scaffold

Three-dimensional scaffolds

Three-dimensional scaffolds in bone tissue engineering: It is responsible for guiding the cell proliferation by providing the suitable sit for cell migration and differentiation [23]. It gives mechanical support to the load bearing tissue. An ideal scaffold should be 1) porous 2) should be optimized for surface characteristics which allows cell migration, attachment and proliferation. 3) It should be non-toxic and biocompatible 4) mechanically stable 5) it should be easily fabricated and can be reproduced.

Ceramic scaffold

Extracellular matrix of bone tissue contains 30% of collagen and 70% of hydroxyapatite (HA) by weight [24]. Ceramic scaffold are biocompatible and mimics the bone tissue surface characteristics thereby provides higher proliferation and adherence to osteoblast cells as compared with other scaffolding materials [25,26]. They are widely used due to greater mechanical and compressive strength compared with polymers. Calcium phosphate ceramics (CPCs) are widely used scaffolding material in bone tissue engineering as they possess osteoinduction and osteoconduction properties which can be easily tunable to make it bioactive. Other ceramics used in BTE are tricalcium phosphate, hydroxyapatite and calcium phosphate which can either be used alone or in combination with one other [27,28].

Polymeric scaffolds for bone regeneration

These materials generally provide more controllability over other scaffolding materials such as solubility, pore size, allergic response and biocompatibility. They can be easily fabricated into various shapes due to their good mechanical characteristics and properties [29,30].

Widely used synthetic polymer and their co-polymers are poly glycolic acid, poly lactic acid and poly caprolactone. They are biodegradable and biocompatible hence widely used in various applications in bone regeneration [31] as shown in table 2.

Some of synthetic polymers shows high compressive strength but easily degraded due to the action of various enzymes crating acidic environment making adverse response on tissue [28,32].

Name of Polymer	Strength	Toxicity	Applications
Polylactic acid	High	Non Toxic	Bone tissue engineering, filler material for nasal cavity
Poly glycolic acid (PGA)	High	Non Toxic	Bone tissue engineering
Poly (lactic-co-glycolic acid) (PLGA)	Low	Immunogenicity and traces of impurities	Bone tissue engineering
Poly ε-caprolactone (PCL)	Moderate	Non Toxic	Bone tissue engineering
Polyethylene glycol (PEG)	Low	Non Toxic	Bone tissue engineering, Pharmacy, medical biology, filler material for nasal cavity
Polyurethane (PUR & PU)	Low	Non Toxic	Bone tissue engineering
Polyethylene terephthalate (PET)	High	Non Toxic	Bone tissue engineering
Chitosan	Low	Non Toxic	Carrier for drug delivery, Bone tissue engineering, Cartilage
Chitin	Low	Non Toxic	Biotech and medical applications
Alginate	Low	Non Toxic	Bone tissue engineering
Collagen (type I, type II, type III)	Low	Non Toxic	Bone tissue engineering
Poly aldehyde guluronate (PAG)	Low	Non Toxic	Bone tissue engineering
polyacrylic acid (PAA)	Low	Non Toxic	Bone tissue engineering
Polybutylene terephthalate (PBT)	Low	Non Toxic	Medicine and industry
Poly propylene fumarate (PPF	Moderate	Non Toxic	Biomedical engg and orthopedic applications
Polyvinyl alcohol (PVA)	High	Non Toxic	Permanent implants
Polyethylene terephthalate (PET)	Moderate	Non Toxic	Bone tissue engineering
Polybutylene terephthalate (PBT)	Moderate	Non Toxic	Bone tissue engineering

Table 2: *List of common polymeric scaffolds.*

Metallic scaffolds in bone tissue engineering

Metallic scaffold like iron, magnesium, magnesium rare earth metal such as magnesium calcium, iron and iron manganese alloys have been widely used as a scaffold for bone tissue engineering [33-36]. Metallic scaffolds possess higher elasticity, restorability, biocompatibility and higher biodegradability except those derived from iron and its alloys, due to their severe systemic toxicity and inflammatory response due to release of ions and metallic corrosion [37]. in animal models. Another disadvantage associated with metallic scaffolds is promotion of bone loss or resorption, poor osteo-11 integration and they acts as a permanent implant rather than scaffold [26,38,39].

Conclusion

Bone tissue engineering is the emerging field of biomedicine which undergone tremendous advances. It uses various biomaterials for tissue regeneration applications in clinical practices. Based on evidences and current development more advanced technologies are expected to explore the applications of natural as well as synthetic biomaterials in development of scaffolds. A current challenge for bone tissue engineering is to develop a scaffold which provide mechanical stability, retain the porosity and enhance cell growth with minimized immune response.

In addition, emphasis should be placed on developing new scaffold with improved physical properties which mimic the action of tissue and facilitating its regeneration. Therefore, variety of scaffolds derived from various materials is used in current practices which give support, cell adhesion, cell proliferation and its migration.

Conflict of Interest

Authors declares no financial interest or any conflict of interest exists.

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