EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 12
Issue: 7
Year: 2025

THE ROLE OF POLYMERS IN BONE TISSUE ENGINEERING - A REVIEW

Nithya M.[1] and Dr. S. Angelina Glorita Parimala*[2]

[1]Research Scholar, A.D.M College for Women (Autonomous), Nagapattinam – 611 001. Affiliated to Bharathidasan University.
[2]Associate Professor of Zoology, A.D.M College for Women (Autonomous), Nagapattinam – 611 001. Affiliated to Bharathidasan University.

***Corresponding Author: Dr. S. Angelina Glorita Parimala**
Associate Professor of Zoology, A.D.M College for Women (Autonomous), Nagapattinam - 611 001. Affiliated to Bharathidasan University. **Email id:**

Article Received on 02/05/2025 **Article Revised on 22/05/2025** **Article Published on 12/06/2025**

ABSTRACT
The rise of scaffold-based polymeric tissue regeneration has been driven by the properties of biodegradable polymers. These biodegradable polymers offer mechanical support and promote tissue regeneration. They also influence cellular populations, enhancing regeneration. Growth and morphogenetic factors can influence cellular migration and differentiation. Biodegradable polymers are attractive biomaterials for scaffold development due to their flexibility in chemistry and ability to produce biocompatible degradation products. This paper reviews approaches to polymeric scaffold-based bone tissue regeneration, highlighting the roles of natural polymers and scaffold design challenges. The functions of natural polymers and the difficulties in designing scaffolds are highlighted in this review of methods for polymeric scaffold-based bone tissue regeneration.

KEYWORDS: Scaffold, Regeneration, Polymer, Influence, Bone.

1. INTRODUCTION

Bone engineering has evolved steadily since the introduction of the concept of "tissue engineering". Biomaterials are used as basic materials for scaffolds which play an important role in bone regeneration (Bose *et al.,* 2012). Bone is employed in the body by supporting mechanical stress and maintaining ionic balance. Trauma or diseases such as tumours and osteoporosis can cause bone damage and regeneration of bone takes a long time. In this case, finding other effective ways to reverse bone regeneration seems essential (Yunus *et al.*, 2015, Bilezikian *et al.*, 2002).

Bio Scaffolds showed promising results in bone regeneration because of their, biocompatibility, non-immunogenicity, and the degree of deterioration long enough to allow mechanical support during bone formation. In addition, collagen is a natural polymer that enhances structural stability, and a high level of biocompatibility and induces the proliferation of new cells (Addad *et al.*, 2011, Atala *et al.*, 2002).

Bone is an essential and multifunctional organ. While providing weight-bearing sustainment and assisting locomotion, the 206 bones in the adult human body (Clarke *et al.,* 2008). Bone repair and regeneration can be enhanced through implantation of biocompatible and biodegradable scaffolds with similar mechanical properties to bone and controlled degradation properties commensurate with endogenous regeneration and remodeling in situ (Groeneveld *et al.*, 1999).

Additionally, scaffolds can also serve as delivery vehicles for transplanted cells, growth factors or even gene therapy, to further enhance the regeneration process. A popular modality is to expand progenitor cells in vitro and seed them onto biodegradable scaffolds in combination with growth factors that stimulate osteogenic differentiation, followed by implantation into the site of the bone defect. However, the major challenges faced with this approach are the risks of pathogenic transmission, possible immunological rejection depending on the cell source and overriding costs. A better strategy may before scaffolds to induce endogenous osteoblasts and their progenitors in situ, as well as work synergistically with growth factors for subsequent bone regeneration (Liu *et al.*, 2006).

In the field of dentistry, bone deterioration is one of the health issues that frequently arise. Bone deterioration may result from infection, necrosis, trauma, neoplastic illness, or periodontal disease (Ghassemi *et al.*, 2018, Funda *et al.*, 2020). Although bones may be reconstructed, major fractures need surgery to promote recovery. In this instance, a strategy for creating a 3D scaffold was used. The scaffold facilitates the

development of stem cells into new bone by combining them with growth factors and stem cells to replace damaged tissue (Oryan *et al.*, 2017, Wilerth *et al.*, 2019).

To promote stem cell attachment, the scaffold serves as a microenvironment. Furthermore, it could encourage the growth of cells that might lead to the development of bone. Biocompatible, biodegradable, osteoconductive, having adequate porosity, and having acceptable mechanical qualities are some of the parameters for the perfect scaffold (Ghassemi *et al.*, 2018, Black *et al.*, 2015). The inherent qualities and the combination of the material's physical and chemical characteristics establish the scaffold's characteristics (Wilerth *et al.*, 2019).

Tissue engineering aims to create new organs and repair existing ones. This is accomplished by bone tissue engineering, which uses stem cells and polymers to build a framework for bone restoration and healing (Fig. 1) (Murphy *et al.*, 2013, Abazari *et al.*, 2020). Because they multiply and develop into osteo-like cells, stem cells, such as mesenchymal stem cells (MSCs) and induced pluripotent stem cells (iPSCs), offer enormous promise in bone tissue engineering (Hosseini *et al.*, 2019, Tahmasebi *et al.*, 2020, mirazaei *et al., 2019*). Moreover, polymers are used in tissue engineering to build a tissue framework.

Millions of people worldwide suffer from osteoporosis, fractures/injuries and various orthopaedic problems that are commonly treated with medical or surgical procedures, including partial or complete replacement of diseased tissue (LeGeros *et al.*, 2002). These polymeric scaffolds will be promising biomaterials to regenerate fractured bone for use in bone tissue engineering applications (Goodman *et al.*, 1998, Schatten *et al.*, 2005). X-ray diffraction (XRD), a scanning electron microscope energy dispersive X-ray (SEM-EDX), and Fourier transform infrared spectroscopy (FTIR) were used to analyse the features. Furthermore, an investigation of the swelling ratio and the water content percentage (WCP) was conducted. Making the perfect scaffold requires careful consideration of its composition (Oryan *et al.*, 2017).

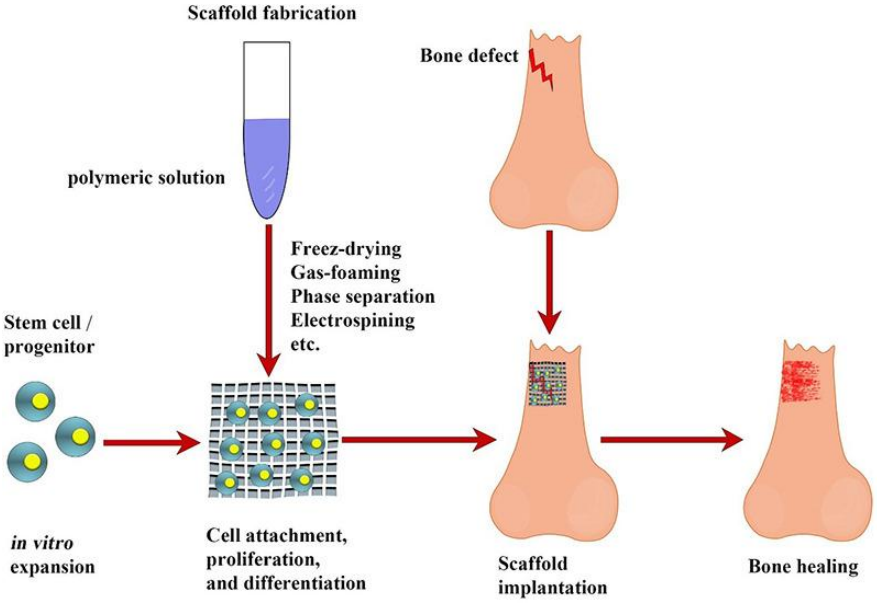

Figure 1: An overview of bone tissue engineering using polymeric scaffolds fabricated through natural polymers. Stem cells are seeded on the scaffolds, proliferated and differentiated into osteo-like cells. The scaffold is implanted into the site of the bone defect to repair the tissue and restore its function.

2. CONCEPT AND RECENT ADVANCES IN BONE REGENERATIVE ENGINEERING

A biomimetic scaffold that serves as a structural guide for tissue regeneration is excellent for scaffold-based bone regenerative engineering (Laurencin *et al.*, 2012, Amini *et al.*, 2012, Matassi *et al.*, 2011). Biodegradable polymers are essential substrates for tissue formation in this method (Laurencin *et al.*, 2012, Matassi *et al.*, 2011, Ogueri *et al.*, 2017). This method's primary goal is to offer a versatile toolkit for bone grafting and the regeneration of intricate organs and tissues (Piskin *et al.*, 1995, Sabir *et al.*, 2009). Clinical translation, physics, developmental biology, stem cell science, and sophisticated materials science and engineering are all included in this toolkit (Laurencin *et al.*, 2012,). In a perfect world, sophisticated material science and engineering would guarantee a suitable scaffold with the proper geometry and architecture (Laurencin *et al.*, 2012,)

In a perfect world, the scaffold would modulate cellular activity by giving chemical and biological signals with precise spatial and temporal control, while simultaneously offering sufficient initial mechanical support, structural integrity, and dimensional stability (Deng *et al.*, 2011). Drawing on insights from developmental biology and morphogenesis, the use of bioactive compounds to promote bone healing and tissue regeneration can be a significant component of bone

tissue regeneration (Laurencin *et al.*, 2012, Lanza *et al.*, 2011, Amini *et al.*, 2012). In terms of complicated tissue regeneration and tissue induction, growth is crucial (Laurencin *et al.*, 2012,). Bone repair and tissue regeneration may benefit from mechanical simulation (Matassi *et al.*, 2011). It is now known that stem cells play a significant role in tissue regeneration (Tuan *et al.*, 2012, Bianco *et al.*, 2011, Chamberlain *et al.*, 2007).

Because stem cells may divide and differentiate into a wide variety of cell types, they are now being studied for the repair and regeneration of cartilage, bone, ligament, tendon, and muscle tissue (Yang *et al.*, 2007). Additionally, they have the ability to release bioactive molecules that aid in cell migration and proliferation, including cytokines, chemokines, and growth factors (Pipino *et al., 2015*). There are significant opportunities to bring findings to the bedside through clinical and translational studies in stem cell utilisation. Since polymeric biomaterials provide precise tunability in terms of mechanical, biocompatible, and degradable qualities, they continue to play a significant role in novel and creative methods to tissue regeneration (Matassi *et al.*, 2011).

3. NATURAL POLYMERS IN BONE TISSUE ENGINEERING

Bone tissue engineering has so far made use of a variety of natural polymers. These polymers are represented by their fundamental structures.

3.1 Collagen

Thirty percent of the body's protein weight is made up of collagen. Type I collagen, which makes about 90% of all collagens, is extensively distributed in the extracellular matrix (ECM) of natural tissues such as dentine, bone, skin, tendon, pancreas, and cartilage (Kadler *et al.*, 2021, Abazari *et al.*, 2020, Mansour *et al.*,2018). Two α 1, three polypeptide chains, and one collagen structure (Fratzl *et al.*, 2008). The chemical makeup of the α α 2 that makes up the triple-helix 2 chain varies throughout collagen types (Maria *et al.*, 2019). In a recurring Gly-Pro-Hyp triplet, the polypeptides are abundant in glycine (Gly), proline (Pro), and 4-hydroxyproline (Hyp) (Fratzl *et al.*, 2008).

The chemical makeup of the α α 2 that makes up the triple-helix 2 chain varies throughout collagen types (Maria *et al.*, 2019). In a recurring Gly-Pro-Hyp triplet, the polypeptides are abundant in glycine (Gly), proline (Pro), and 4-hydroxyproline (Hyp) (Fratzl *et al.*, 2008). Procollagen is a triple-helix structure made up of the three polypeptide chains. Mature collagen is produced when metalloproteinase enzymes split the N- and C-terminal of the helix (Mouw *et al.*,2014).

These collagens self-assemble to form microfibrils that range in size from 3 to 5 nm. Ultimately, a three-dimensional collagen fibre is formed by the microfibrils self-assembling (Orgel *et al.*, 2006, Olszta *et al.*, 2007). Environmental variables such as temperature, ionic strength, and pH have a significant impact on the production of collagen fibres from monomers (Fratzl *et al.*, 2008, Kadler *et al.*, 1996).
In vitro fibrillogenesis should be supported by these variables. The properties of collagen make it a perfect biomaterial for tissue engineering (Abazari *et al.*, 2020, Mansour *et al.*, 2018).

All vertebrates' natural tissue contains large amounts of it. It is lowly antigenic and highly biocompatible. To enhance its qualities, it might be readily processed and mixed with other biomaterials (Ferreira *et al.*, 2012). The human body's metalloproteinases break it down (Liu *et al.*, 2015). The polypeptide backbone of collagen contains functional groups that may be linked to genes, growth factors, and biological substances that provide therapeutic benefits (Ferreira *et al.*, 2012, Pawelec *et al.*, 2016).

The main natural sources of collagen are horse, pig, bovine, and ovine (Albu *et al.*, 2011). Decellularized collagen matrix and isolated collagen molecules are the two methods by which collagen may be separated and used (Chattopadhyay *et al.*, 2014). Nonetheless, there is a significant chance of infectious disorders as a result of pathogen transmission. Another source of collagen is the production of recombinant collagen protein (RCP) in insects, yeast, and mammals.In this instance, the molecular weight and amino acid content of RCP may be regulated. They have a minimal risk of disease transmission and may be generated in huge quantities (Olsen *et al.*, 2003). However, RCP has a low propensity to form fibrils because it does not include hydroxy proline residues (Ramshaw *et al.*, 2016). Osteoblasts produce type I collagen, which is widely distributed in the extracellular matrix of bones.

Osteoblasts produce type I collagen, which is widely distributed in the extracellular matrix of bones. In matrix mineralisation, it plays a significant role (Tomoaia *et al.*, 2015). Consequently, the usage of collagen products may enhance osteoblast activity and the biological integration of cells with surrounding tissues (Maria *et al.*, 2019). Numerous research conducted both in vitro and in vivo have demonstrated the potential of collagen-based scaffolds in bone engineering. Collagen scaffolds enhanced matrix mineralisation, increased the activity of the osteogenic enzyme alkaline phosphatase (ALP), and enhanced the maintenance and function of cultured osteoblasts in vitro (Aravamudhan *et al.*, 2013).

The scaffolds that were implanted shown significantly osteogenic qualities in crucial bone defects in vivo (Miguel *et al.*, 2013). It would be simple to mix collagen with other biomaterials. Collagen and hydroxyapatite (HAp) have been demonstrated to enhance MSC development into osteoblasts. In a sizable patient population, collagen-HAp has also demonstrated osteochondral tissue regeneration. In an animal model,

the use of collagen scaffold loaded with dexamethasone enhanced the ectopic bone repair upon subcutaneous implantation and encouraged the osteogenic differentiation of MSCs in vitro (Chen *et al.*, 2018). Letic-Gavrilovic et al. shown that a collagen/hydroxyapatite (Col/HAp) composite that delivers nerve growth factor β (NGF β) improves the ingrowth of new bone in rats (Letic cavrilovic *et al.*, 2003).

Viruses can also be incorporated into the collagen matrix. After 4 and 8 weeks of implantation, Zhang et al. demonstrated that adding adenoviruses that produce PDGF-B and bone morphogenetic protein 7 (BMP-7) to chitosan/collagen scaffolds enhances bone growth in animal models (Zhang *et al.*, 2009). These investigations demonstrated collagen's enormous potential for bone repair. Collagen is one of the natural polymers of interest for bone tissue regeneration and repair in clinical trial investigations. A collagen sponge scaffold was employed by Jager et al. for individuals with bone deficits. All of the patients had new bone development visible in their radiographic pictures. However, it was shown that two patients (out of twelve) did not cure their bones (Agar *et al.*, 2011). Numerous clinical trials have employed porous collagen scaffolds, with encouraging outcomes in terms of the production of new bone. However, there have been reports of a number of problems, including haematoma, inflammation, hardware failure, wound discharges, and more (Agar *et al.*, 2011, Govender *et al.*, 2002, Calori *et al.*, 2008).

4. DESIGN OF SCAFFOLDS FOR BONE TISSUE ENGINEERING

Using scaffolds in a damaged tissue niche and the principles of BTE, the healing process is induced by eliciting certain biological responses from the surrounding environment (Figure 2). According to (Porter *et al.*, 2009), these concepts are used in a variety of techniques, including as stem cell transplantation, medication and growth factor administration, gene therapy, and acellular scaffold engineering.

BTE scaffolds serve the following purposes: (i) temporarily supporting the affected area mechanically and filling in the gaps of bone defects; (ii) encouraging circulating precursor cell adherence and growth and permitting ECM deposition onto the scaffold surface (osteoconduction); (iii) stimulating vessels and bone in-growth into the porous scaffold; (iv) enhancing osteogenic differentiation through molecular signalling and the formation of new bone tissue (osteoinduction); (v) promoting cell activity to support the integration with native tissue (osteointegration); and (vi) administering medications or bioactive molecules to speed up the healing process (Daculsi *et al.*, 2013).

The scaffolds should ideally fulfil certain crucial requirements in order to perform these roles. In addition to being osteoconductive, osteoinductive, biocompatible, and bioactive, they should also retain their mechanical integrity during the healing process, while their rate of degradation should ensure that the required mechanical support is maintained until the regeneration process is finished. Furthermore, if the internal architecture's structural interconnection displays a pore width of at least 100µm, the implanted graft may have excellent cell penetration and vascularization ingrowth (Wagoner Johnson *et al.*, 2011).

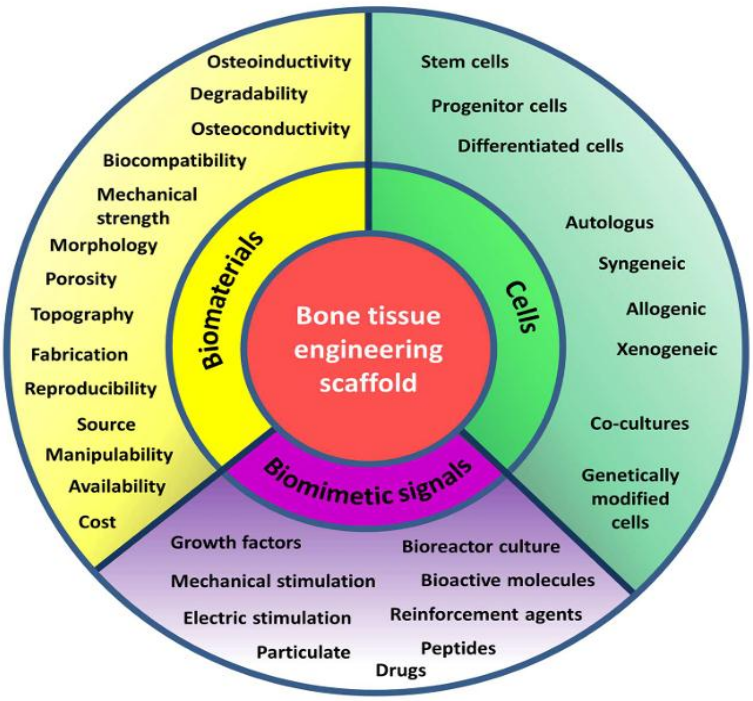

Figure 2: Principles of bone tissue engineering.

The size and form of holes should facilitate cell mobility, the diffusion of nutrients and growth stimulants, and the simple removal of cell waste. Interestingly, it has been shown that the topography and rigidity of three-dimensional (3D) microenvironments can cause adult SCs, like MSCs, to commit towards an osteogenic lineage. This is in line with the observation that regenerative cells specifically respond to the mechanical properties of the extracellular matrix (Discher *et al.,* 2009).

Because they are reliant on traction pressures, matrix stiffness can alter the adhesion ligand arrangement and integrin binding organisation, which in turn initiates osteogenic commitment (Huebsch *et al.*, 2010). In order to create transplantable grafts with optimal biological characteristics and increased regeneration capacity, it has become popular to adjust the physical characteristics of adhesion substrates (Moosazadeh Moghaddam *et al.*, 2019). However, further understanding is still needed to fully understand the nature and scope of the biophysical events that underlie the ECM-mediated cellular destiny control. Additionally, the chemistry of the scaffold surface should permit functionalisation with substances that promote the formation of the new osteoid matrix.

As a result, there should be a large number of readily available chemical groups for conjugation with bioactive factors, enabling the use of straightforward coupling procedures based on either covalent or non-covalent interactions. According to Liu and Ma *et al., (*2004), Wang *et al*., (2018), and Cui *et al.*, (2019), the material properties should also enable the implementation of techniques for the intelligent, regulated, and sustained release of the biomolecules. As a result, choosing the right polymer is essential to scaffold design.

5. CHALLENGES IN FABRICATING SCAFFOLDS FOR BONE TISSUE ENGINEERING

A number of requirements should ideally be met by the scaffolds and materials used in bone tissue engineering, most notably strong biocompatibility, which is a necessary need for any materials (including possible degradation products) used in tissue engineering.

5.1 Porosity, pore size, interconnectivity and microstructure

It is not required for scaffold subtilised in bone tissue engineering to precisely replicate the microstructure of autologous bone grafts, which have long been considered the gold standard to which other alternatives are compared. Other materials will react differently in vivo and hence encounter diverse microenvironments due to their differing surface tensions and rates of degradation. It is commonly known that increased bone ingrowth occurs in vivo when porosity, pore size, and interconnectivity are higher. Good tissue migration, nutrition transport, and capillary vascular development are thought to be supported by pores bigger than 300 µm (Karageorgiou *et al.,* 2005), whereas interconnections need to be larger than 100 µm. In osteogenesis, the microstructure is crucial (Habibovic *et al.,* 2005).

5.2 Mechanical properties and integration with host bone tissue

Both the scaffolds' mechanical characteristics and the regenerated osseous tissue that results from them must be able to withstand the strain of daily activities. Mechanical thresholds are provided by in vivo research on how daily activities affect bone formation. The mechanical characteristics of bones under sub failure and failure situations are far higher than those that bone substitutes would probably experience following surgery (Butler *et al.*, 2000). Both macroscopic and microscopic mechanical characteristics are significant (Liebschner *et al.,* 2004). Functionality, which can be further reinforced by the inclusion of ceramics, depends on the integration of scaffolds and regenerated bone inside host tissue in addition to mechanical characteristics (Maguet *et al.*, 2004).

5.3 Controlled degradation

In order to allow the mechanical properties of newly regenerated bone tissue to gradually compensate for the loss of mechanical support from the original scaffold, scaffolds must degrade in a controlled manner as bone regeneration and subsequent remodelling occur over a period of several months (Hutmather *et al.,* 2000). However, the majority of recent studies focus more on the scaffolds' microstructure and initial mechanical characteristics, paying less attention to their rate of deterioration (Hollister *et al.,* 2002).

5.4 Retaining/enhancing osteoinductive properties of inductive/growth factors

Osteoinduction is the term used to describe the process by which scaffolds should ideally aid in bone rebuilding. However, this depends on a number of variables that manifest at various times, as well as the temporal expression of genes that are indicative of osteoblastic differentiation (Hollinger *et al.,* 2004). The effects of scaffolds with various components and microstructures on osteogenic cell development and proliferation have been the subject of much investigation. Octa calcium phosphate (OCP), beta tricalcium phosphate (beta-TCP), hydroxyapatite, and other calcium phosphates make up scaffolds. These scaffolds display varying osteoinductive potencies when combined with varying doses of human bone morphogenetic protein. The scaffold osteoinductivity is also influenced by the scaffold microstructure, or porosity (Wildemann *et al.,* 2007).

To ensure that growth factors can target the required cells and maintain release for suitable durations in vivo, several growth factor delivery devices have been developed (Chen *et al.,* 2003). The regulated release of growth factors has shown some promise (Lee *et*

al.,2000), but research on this topic is still in its early stages. Before being added to the polymeric scaffold, osteoinductive factors can be recombinantly synthesised or isolated and purified from cortical bone in humans and animals.

Another strategy is to provide plasmid DNA encoding the factors, however genetic alteration raises a number of safety issues. There have also been reports of the controlled release of dual growth factors, such as VEGF-165 and PDGF-BB, which have different kinetics and effects (Richardson *et al.*, 2001). In a different research, two growth factors transforming growth factor β3 (TGF-β3) and bone morphogenetic protein-2 (BMP2) were administered in order to produce a synergistic effect because they are ineffective when taken alone (Simmons *et al.*, 2004).

5.5 Compatibility with other technology platforms and biomaterials

A mix of many technological platforms would likely be needed for bone tissue creation, as no single technique can adequately induce bone regeneration. Scaffold compatibility with biomaterials and other technological platforms is therefore crucial. It is also important that scaffolds have sufficient flexibility to be used as carriers or vehicles for gene therapy, protein delivery and cell seeding.

5.6 Customized design

There are clear variations in the composition and mechanical characteristics of bone tissue depending on the specimen's location, gender, race, and age. Additionally, various therapeutic modalities have varying effects on the repair and regeneration processes, and even within a single person, regeneration is not uniform. Adapting scaffolds to the biodata of a specific patient might be advantageous.

6. CONCLUSION

The goal of current research is to attract osteogenic cells to move onto scaffolds and then induce their proliferation and differentiation. Preventing fibroblast migration and proliferation, the primary cause of fracture non-union, is another crucial aspect of scaffold design. Scaffolds may be helpful in vascular, neurone, and hyaline cartilage regeneration in addition to bone tissue engineering. Expanding our knowledge of material science and cell chemotaxis will be essential to future advancements. There are four possible approaches: (a) using a chemical or growth factor concentration gradient to repel fibroblasts; (b) adding chemical groups to prevent fibroblasts from attaching to scaffolds; (c) selectively inhibiting fibroblast growth so that other cell types will overwhelm them; and (d) minimising non-specific cell adhesion to scaffolds while maximising the specificity of cell adhesion via incorporated peptides. Because alginate and polyethylene glycol (PEG) have low native cell adhesion, they are frequently used as synthetic extracellular matrix (ECM) (Schatten *et al.*, 2005).

7. REFERENCES

1. A. Aravamudhan, D.M. Ramos, J. Nip, M.D. Harmon, R. James, M. Deng, et al., Cellulose and collagen derived micro-nano structured scaffolds for bone tissue engineering, J. Biomed. Nanotechnol, 2013; 9(4): 719–731.
2. A. Letic-Gavrilovic, A. Piattelli, K. Abe, Nerve growth factor β(NGF β) delivery via a collagen/hydroxyapatite (Col/HAp) composite and its effects on new bone ingrowth, J. Mater. Sci. Mater. Med., 2003; 14(2): 95–102.
3. A. Mirzaei, A.S. Moghadam, M.F. Abazari, F. Nejati, S. Torabinejad, M. Kaabi, et al., Comparison of osteogenic differentiation potential of induced pluripotent stem cells on 2D and 3D polyvinylidene fluoride scaffolds, J. Cell. Physiol, 2019; 234(10): 17854–17862.
4. A. Tahmasebi, S.E. Enderami, E. Saburi, M. Islami, S. Yaslianifard, J.A. Mahabadi, et al., Micro-RNA-incorporated electrospun nanofibers improve osteogenicdifferentiation of human-induced pluripotent stem cells, J. Biomed. Mater. Res. A., 2020; 108(2): 377–386.
5. A.M. Ferreira, P. Gentile, V. Chiono, G. Ciardelli, Collagen for bone tissue regeneration, Acta Biomater, 2012; 8(9): 3191–3200.
6. Addad, S., Exposito, J. Y., Faye, C., Ricard-Blum, S., and Lethias, C. Isolation, characterization, and biological evaluation of jellyfish collagen for use in biomedical applications. Mar. Drugs, 2011; 9: 967–983. Doi: 10.3390/md9060967.
7. Amini AR, Laurencin CT, Nukavarapu SP. Bone tissue engineering: recent advances and challenges. Crit Rev Biomed Eng., 2012; 40(5).
8. Atala, A.L. and Lanza, R.P. Methods of Tissue Engineering (San Diego, CA: Academic), 2002.
9. Bianco P, Riminucci M, Gronthos S, Robey PG. Bone marrow stromal stem cells: nature, biology, and potential applications. Stem Cells., 2001; 19(3): 180–92.
10. Bilezikian, J.P., Raisz, L. G. and Rodan, G. A. 2002. Principles of Bone Biology (San Diego, CA: Academic).
11. Black, C. R. M., Goriainov, V., Gibbs, D., Kanczler, J., Tare, R. S., & Oreffo, R. O. C. Bone tissue engineering. Current Molecular Biology Report, 2015; 1(3): 132–140.
12. Bose, S., Roy, M., Bandyopadhyay, A. Recent advances in bone tissue engineering scaffolds. Trends Biotechnology, 2012; 30(10): 546-554.
13. Butler D L, Goldstein S A and Guilak F.J. Biomech. Eng., 2000; 122: 570.
14. C.M. Murphy, F.J. O'Brien, D.G. Little, A. Schindeler, Cell-scaffold Interactions in the Bone Tissue Engineering Triad, 2013.
15. Chamberlain G, Fox J, Ashton B, Middleton J. Concise review: Mesenchymalstemcells:their

phenotype, differentiation capacity, immunological features, and potential for homing. Stem Cells., 2007; 25(11): 2739–49.
16. Chen R R and Mooney D J. Pharma. Res., 2003; 20: 1103.
17. Clarke, B. Normal bone anatomy and physiology. Clin. J. Am. Soc. Nephrol, 2008.
18. Cui, Y., Zhu, T., Li, D., Li, Z., Leng, Y., Ji, X., et al. Bisphosphonate functionalized scaffolds for enhanced bone regeneration. Adv. Healthc. Mater, 2019; 8: ce1901073. doi: 10.1002/adhm.201901073
19. D. Liu, M. Nikoo, G. Boran, P. Zhou, J.M. Regenstein, Collagen and gelatin, Annu. Rev. Food Sci. Technol, 2015; 6: 527–557.
20. D. Olsen, C. Yang, M. Bodo, R. Chang, S. Leigh, J. Baez, et al., Recombinant collagen and gelatin for drug delivery, Adv. Drug Deliv. Rev., 2003; 55(12): 1547–1567.
21. Daculsi, G., Fellah, B. H., Miramond, T., and Durand, M. Osteoconduction, osteogenicity, osteoinduction, what are the fundamental properties for a smart bone substitutes. IRBM, 34: 346–348. doi: 10.1016/j.irbm.2013.07.001
22. Deng M, Kumbar SG, Nair LS, Weikel AL, Allcock HR, Laurencin CT. Biomimetic structures: biological implications of dipeptide-substituted polyphosphazene–polyester blend nanofiber matrices for load-bearing bone regeneration. Adv Funct Mater, 2011; 21(14): 2641–51.
23. Discher, D. E., Mooney, D. J., and Zandstra, P. W. Growth factors, matrices, and forces combine and control stem cells. Science, 2009; 324: 1673–1677. doi: 10.1126/science.1171643
24. F.B. Miguel, AdAB Júnior, F.L. de Paula, I.C. Barreto, G. Goissis, F.P. Rosa, Regeneration of critical bone defects with anionic collagen matrix as scaffolds, J. Mater. Sci. Mater. Med., 2013; 24(11): 2567–2575.
25. F.R. Maia, V.M. Correlo, J.M. Oliveira, R.L. Reis, Natural Origin Materials for Bone Tissue Engineering: Properties, Processing, and Performance. Principles of Regenerative Medicine, Elsevier, 2019; 535–558.
26. F.S. Hosseini, S.E. Enderami, A. Hadian, M.F. Abazari, A. Ardeshirylajimi, E. Saburi, et al., Efficient osteogenic differentiation of the dental pulp stem cells on β-glycerophosphate loaded polycaprolactone/polyethylene oxide blend nanofibers, J. Cell. Physiol, 2019; 234(8): 13951–13958.
27. Funda, G., Taschieri, S., Bruno, G. A., Grecchi, E., Paolo, S., Girolamo, D., & Fabbro, M. D. Nanotechnology scaffolds for alveolar bone regeneration. Materials (Basel), 2020; 13(1): 1–20.
28. G. Calori, L. Tagliabue, L. Gala, M. d'Imporzano, G. Peretti, W. Albisetti, Application of rhBMP-7 and platelet-rich plasma in the treatment of long bone non-unions: a prospective randomised clinical study on 120 patients, Injury, 2008; 39(12): 1391–1402.
29. G. Tomoaia, R.-D. Pasca, On the collagen mineralization. A review, Clujul Medical, 2015; 88(1): 15.
30. Ghassemi, T., Shahroodi, A., Ebrahimzadeh, M. H., Mousavian, A., Movaffagh, J., & Moradi, A. Current concepts in scaffolding for bone tissue engineering. Archives of Bone and Joint Surgery, 2018; 6(2): 90–99.
31. Goodman, S, B., et al., Clin. Orthop. Relat. Res., 1998; 348: 42.
32. Groeneveld E H, van den Bergh J P, Holzmann P, ten Bruggenkate C M, Tuinzing D B and Burger E H J. Biomed. Mater. Res., 1999; 48: 393.
33. Habibovic P, Yuan H, van der Valk C M, Meijer G, van Blitterswijk C A and de Groot K. Biomaterials, 2005; 26: 3565.
34. Hollinger J O, Einhorn T A, Doll B and Sfeir C 2004 Bone Tissue Engineering (New York: CRC Press).
35. Hollister S J, Maddox R D and Taboas J M. Biomaterials, 2002; 23: 4095.
36. Huebsch, N., Arany, P. R., Mao, A. S., Shvartsman, D., Ali, O. A., Bencherif, S. A., et al. Harnessing traction-mediated manipulation of the cell/matrix interface to control stem-cell fate. Nat Mater, 2010; 9: 518–526. doi: 10.1038/nmat2732
37. Hutmacher D W. Biomaterials, 2000; 21: 2529.
38. J.A. Ramshaw, Biomedical applications of collagens, J Biomed Mater Res B Appl Biomater, 2016; 104(4): 665–675.
39. J.P. Orgel, T.C. Irving, A. Miller, T.J. Wess, Microfibrillar structure of type I collagen in situ, Proc. Natl. Acad. Sci., 2006; 103(24): 9001–9005.
40. K. Pawelec, S. Best, R. Cameron, Collagen: a network for regenerative medicine, J. Mater. Chem. B., 2016; 4(40): 6484–6496.
41. K.E. Kadler, C. Baldock, J. Bella, R.P. Boot-Handford, Collagens at a glance, J. Cell Sci., 2007; 120(12): 1955–1958 579. L. Guo et al. Journal of Controlled Release, 2021; 338: 571–582.
42. K.E. Kadler, D.F. Holmes, J.A. Trotter, J.A. Chapman, Collagen fibril formation, Biochem. J., 1996; 316(1): 1–11.
43. Karageorgiou V and Kaplan D 2005 Biomaterials, 26: 5474.
44. Lanza R, Langer R, Vacanti JP. Principles of tissue engineering. Academic, 2011.
45. Laurencin CT, Khan Y. Regenerative engineering. In: American Association for the advancement of science, 2012.
46. Lee K Y, Peters M C, Anderson K W and Mooney D J. Nature, 2000; 408: 998.
47. LeGeros, R, Z. Clin. Orthop. Relat. Res., 2002; 395: 81.
48. Liebschner M A. Biomaterials, 2004; 25: 1697.
49. Liu H, Kemeny D M, Heng B C, Ouyang H W, Melendez A J and Cao T J. Immunol, 2006; 176: 2864.
50. Liu, X., and Ma, P. X. Polymeric scaffolds for bone tissue engineering. Ann. Biomed. Eng., 2004; 32:

477–486. doi: 10.1023/b:abme.0000017544.36001.8e
51. M. J¨ ager, M. Herten, U. Fochtmann, J. Fischer, P. Hernigou, C. Zilkens, et al., Bridging the gap: bone marrow aspiration concentrate reduces autologous bone grafting in osseous defects, J. Orthop. Res., 2011; 29(2): 173–180.
52. M.F. Abazari, F. Soleimanifar, M. Amini Faskhodi, R.N. Mansour, J. Amini Mahabadi, S. Sadeghi, et al., Improved osteogenic differentiation of human induced pluripotent stem cells cultured on polyvinylidene fluoride/collagen/ platelet-rich plasma composite nanofibers, J. Cell. Physiol, 2020; 235(2): 1155–1164.
53. M.F. Abazari, F. Soleimanifar, M. Amini Faskhodi, R.N. Mansour, J. Amini Mahabadi, S. Sadeghi, et al., Improved osteogenic differentiation of human induced pluripotent stem cells cultured on polyvinylidene fluoride/collagen/ platelet-rich plasma composite nanofibers, J. Cell. Physiol, 2020; 235(2): 1155–1164.
54. M.G. Albu, I. Titorencu, M.V. Ghica, Collagen-based Drug Delivery Systems for Tissue Engineering: Chapter, 2011.
55. M.J. Olszta, X. Cheng, S.S. Jee, R. Kumar, Y.-Y. Kim, M.J. Kaufman, et al., Bone structure and formation: a new perspective, Mater. Sci. Eng. R. Rep., 2007; 58(3–5): 77–116.
56. Maquet V, Boccaccini A R, Pravata L, Notingher I and Jerome R. Biomaterials, 2004; 25: 4185.
57. Matassi F, Nistri L, Paez DC, Innocenti M. New biomaterials for bone regeneration. Clin Cases Miner Bone Metab, 2011; 8(1): 21.
58. Moosazadeh Moghaddam, M., Bonakdar, S., Shokrgozar, M. A., Zaminy, A., Vali, H., and Faghihi, S. Engineered substrates with imprinted cell like topographies induce direct differentiation of adipose-derived mesenchymal stem cells into Schwann cells. Artif. Cells Nanomed. Biotechnol, 2019; 47: 1022–1035. doi: 10.1080/21691401.2019.1586718
59. Ogueri KS, Ivirico JLE, Nair LS, Allcock HR, Laurencin CT. Biodegradable polyphosphazene-based blends for regenerative engineering. Regen Eng Transl Med., 2017; 1–17.
60. Oryan, A., & Sahvieh, S. Effectiveness of chitosan scaffold in skin, bone and cartilage healing. International Journal of Biology Macromolecule, 2017; 104: 1003–1011.
61. P. Fratzl, Collagen: structure and mechanics, an introduction, Springer, Collagen, 2008, pp. 1–13. J.K. Mouw, G. Ou, V.M. Weaver, Extracellular matrix assembly: a multiscale deconstruction, Nat. Rev. Mol. Cell Biol., 2014; 15(12): 771–785.
62. Pipino C, Pandolfi A. Osteogenic differentiation of amniotic fluid mesenchymal stromal cells and their bone regeneration potential. World J Stem Cells., 2015; 7(4): 681.
63. Piskin E. Biodegradable polymers as biomaterials. J Biomater Sci Polym Ed., 1995; 6(9): 775–95.
64. Porter, J. R., Ruckh, T. T., and Popat, K. C. Bone tissue engineering: a review in bone biomimetics and drug delivery strategies. Biotechnol. Prog., 2009; 25: 1539–1560. doi: 10.1002/btpr.246
65. R.N. Mansour, F. Soleimanifar, M.F. Abazari, S. Torabinejad, A. Ardeshirylajimi, P. Ghoraeian, et al., Collagen coated electrospun polyethersulfon nanofibers improved insulin producing cells differentiation potential of human induced pluripotent stem cells, Artif. Cells Nanomed. Biotechnol, 2018; 46(3): S734- S9.
66. Richardson T P, Peters M C, Ennett A B and Mooney D J., 2001; Nature Biotechnol, 19: 1029.
67. S. Chattopadhyay, R.T. Raines, Collagen-based biomaterials for wound healing, Biopolymers, 2014; 101(8): 821–833.
68. S. Govender, C. Csimma, H.K. Genant, A. Valentin-Opran, Y. Amit, R. Arbel, et al., Recombinant human bone morphogenetic protein-2 for treatment of open tibial fractures: a prospective, controlled, randomized study of four hundred and fifty patients, JBJS, 2002; 84(12): 2123–2134.
69. Sabir MI, Xu X, Li L. A review on biodegradable polymeric materials for bone tissue engineering applications. J Mater Sci., 2009; 44(21): 5713–24.
70. Schatten G 2005 Current Topics in Developmental Biology (Singapore: Elsevier Academic Press)
71. Schatten, G. 2005. Current Topics in Developmental Biology (Singapore: Elsevier Academic Press).
72. Simmons C A, Alsberg E, Hsiong S, Kim W J and Mooney D J., 2004; Bone 35: 562.
73. Tuan RS, Boland G, Tuli R. Adult mesenchymal stem cells and cell-based tissue engineering. Arthritis Res Ther., 2002; 5(1): 32.
74. Wagoner Johnson, A. J., and Herschler, B. A. A review of the mechanical behavior of CaP and CaP/polymer composites for applications in bone replacement and repair. Acta Biomater, 2011; 7: 16–30. doi: 10.1016/j.actbio.2010.07.012
75. Wang, Q., Huang, Y., and Qian, Z. Nanostructured surface modification to bone implants for bone regeneration. J. Biomed. Nanotechnol, 2018; 14: 628–648. doi: 10.1166/jbn.2018.2516
76. Wildemann B, Kadow-Romacker A, Haas N P and Schmidmaier G. J. Biomed. Mater. Res., 2007; 81: 437.
77. Willerth, S. M., & Sakiyama-Elbert S. E. Combining stem cells and biomaterial scaffolds for constructing tissues and cell delivery. Stem Journal, 2019; 1(1): 1–25.
78. Y. Chen, N. Kawazoe, G. Chen, Preparation of dexamethasone-loaded biphasic calcium phosphate nanoparticles/collagen porous composite scaffolds for bone tissue engineering, Acta Biomater, 2018; 67: 341–353.
79. Y. Zhang, B. Shi, C. Li, Y. Wang, Y. Chen, W. Zhang, et al., The synergetic bone- forming effects of combinations of growth factors expressed by adenovirus vectors on chitosan/collagen scaffolds, J. Control. Release., 2009; 136(3): 172–178.

80. Yang G, Rothrauff BB, Tuan RS. Tendon and ligament regenera tion and repair: clinical relevance and developmental paradigm. Birth Defects Res C Embryo Today, 2013; 99(3): 203–22.
81. Yunus, B.R., Sampath Kumar, T.S., Doble, M. Design of bio composite materials for bone tissue regeneration, Mater. Sci. Eng. C Mater. Biol. Appl., 2015; 57: 452.