A Review of 3D Polymeric Scaffolds for Bone Tissue Engineering: Principles, Fabrication Techniques, Immunomodulatory Roles, and Challenges

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***Abstract*—The bone tissue engineering has been shown as a promising approach to address the shortcomings of the traditional bone grafting methods in management of large and critical-size bone defects. Three-dimensional (3D) polymeric scaffolds are central in this and a range of other techniques since they offer a temporary structural framework to support cell adhesion, cell proliferation and osteogenic differentiation and replicate the native extracellular matrix. This is an overview of the principles that are entailed in the design of 3D polymeric scaffolds; biocompatibility, biodegradability, porosity, mechanical properties, bioactivity and Oste conductivity. The most frequently employed natural and synthetic polymers and polymer-based composite systems are addressed in terms of their benefits and drawbacks in terms of the application in bone regeneration. Besides that, key fabrication strategies including standard methods and sophisticated additive fabrication methods are outlined in relation to their capability of regulating scaffold structure and biological functioning.**

***Index Terms*— Adhesion, Biocompatibility, Fabrication, Grafting, Oste conductivity.**

I. INTRODUCTION

1.1 Background and Clinical Need for Bone Regeneration

Bone is a highly specialized dynamic connective tissue which offers mechanical support to the body, which protects the vital organs, facilitates body movement and plays a critical role in mineral homeostasis. Even though bone has anatural healing and remodelling capacity following injury, the natural regenerative capacity is insufficient in situations where the damage is too large. Big defects induced by trauma, disease or surgery do not easily heal fully resulting in the permanent loss of functionality. Thus, bone regeneration has become one of the most active fields of regenerative medicine and tissue engineering, to restore the structural integrity and the biological functionality of damaged bone. The clinical demands in bone regeneration are growing because of the rise in the occurrence of complicated fractures, traumatic injuries, bone loss after tumor resection, chronic infections and skeletal defects. In most of those conditions, the area and magnitude of the defect are bigger than the inherent healing capability of the body, and thus it takes longer to heal or fails to heal. Even though the use of conventional therapies like bone grafting is common, it is reported to have a few limitations such as the inadequate source of donor materials, susceptibility to infections, donor-site morbidity, and unreliable clinical results. In addition, the increasing age issue and increased prevalence of bone associated disorders are further increasing the need to come up with effective and safe regenerative solutions. Therefore, innovative bone regeneration approaches are clinically necessary to enhance faster healing, mechanical strength, decrease complications as well as increase the overall quality of life of patients

1.2 Limitations of Conventional Bone Grafting Approaches

Conventional bone grafts, including autografts and allografts, suffer from several important limitations that restrict their widespread and long- term clinical use. Autografts, although considered the gold standard, require an additional surgical procedure for graft harvesting, which increases operative time, blood loss, postoperative pain and the risk of donor-site morbidity and infection. Moreover, the quantity of available autologous bone is limited, making it unsuitable for treating large or critical-sized defects. Allografts, on the other hand, carry the risk of immune rejection and

disease transmission and often show reduced biological activity due to processing and sterilization procedures. Both graft types may exhibit unpredictable integration with the host tissue and insufficient vascularization, leading to delayed healing or graft failure. These limitations highlight the need for advanced and more reliable bone regeneration approaches.

1.3 Role of Three-Dimensional Polymeric Scaffolds in Bone Tissue Engineering

Three-dimensional polymeric scaffolds play a crucial role in bone tissue engineering by providing a temporary structural framework that mimics the native extracellular matrix and supports new tissue formation. These scaffolds facilitate cell attachment, proliferation and differentiation, while maintaining an interconnected porous architecture that allows nutrient diffusion, waste removal and vascular ingrowth. In addition, polymeric scaffolds can be engineered with suitable mechanical strength and controlled degradation rates so that they gradually transfer load to the newly formed bone during healing. Their surface properties and composition can also be tailored to enhance osteogenic responses and to deliver bioactive molecules such as growth factors in a sustained manner. Thus, 3D polymeric scaffolds serve as an essential platform for guiding organized bone regeneration and improving functional recovery in large or critical-sized bone defects.

II. OBJECTIVES

This review aims at the in-depth overview of the basic principles of the design of three-dimensional polymeric scaffolds to regenerate bone tissue, critically review the key methods of major fabrication methodologies and its impact on the structure, mechanical and biological properties, and examine the immunomodulatory action of such scaffold in the modulation of host immune response and macrophage polarization during bone tissue regeneration. Moreover, the review is expected to identify recent developments in scaffold-based approaches to promote osteogenesis, angiogenesis, and functional bone repair using surface modification and bioactive factors addition and to discuss the limitations associated with mechanical mismatch, vascularization, infection control, scalability, and regulatory problems. Lastly, this review aims to discover new trends and future studies to enhance the clinical translation and long-term therapeutic efficacy of 3D polymeric scaffolds to bone tissue engineering.

III. PRINCIPLES OF 3D POLYMERIC SCAFFOLDS DESIGN

3.1 Biocompatibility and biodegradability

Basic design requirements in biodegradation and biocompatibility of 3D polymeric scaffolds in bone tissue engineering are basic design elements. Biocompatibility of the scaffold means that the scaffold does not induce any unwanted immune or inflammatory reactions and can support cell adhesion, cell proliferation and osteogenic differentiation in the implantation site. The biocompatible scaffold must also be able to blend well with the surrounding tissue, and encourage normal biological processes without leaving any toxic by-products. Biodegradability is also a factor in this, because the scaffold should degrade slowly in vivo in a rate comparable to that of new bone generation, and thus no secondary surgery is needed to remove it. The degradation end products should not be toxic and should be readily metabolized or excreted by the body. The ideal ratio of biocompatibility and controlled biodegradation allows the scaffold to provide the organism with a temporary mechanical support and gradually be replaced by newly formed functional bone tissue [2].

3.2 Porosity and mechanical characteristics

Porosity is a design parameter of critical importance to 3D polymeric scaffolds because it determines directly cell infiltration, nutrient and oxygen diffusion, wastes and vascularization of the regenerating tissue. Porous network an interlacing porous structure allows equal distribution of cells across the scaffold and facilitates effective bone growth across the scaffold. Nonetheless, porosity tends to rise, which means that there is a decrease in mechanical strength. Hence, there should be an ideal balance in between high porosity and adequate structural integrity. The mechanical properties of the scaffold must also be optimally adjusted to the mechanical properties of the native bone at the implantation location, which will give temporary load-bearing advantages as well as the structural stability of the scaffold during the initial phases of healing. Simultaneously, the scaffold must

be able to gradually transfer mechanical loads to the newly developed tissue as it deteriorates promoting appropriate bone remodelling and functional regeneration [5].

3.3 Bioactivity and Osteoconductivity

The characteristics of 3D polymeric scaffolds required in effective bone regeneration are osteoconductivity and bioactivity. Osteoconductivity is a term that is used to describe how a scaffold enhances the attachment, migration and proliferation of osteogenic cells on its surface and through its porosity structure which leads to the formation of new bone. A very high osteoconductivity scaffold has a good microenvironment which supports the organization and deposition of cells. Bioactivity further increases the process as it allows certain contact between the scaffold and the adjacent biological tissue, including adsorption of proteins and induction of osteogenic signaling pathways. Polymeric scaffolds can also be designed to facilitate cell differentiation and fast-track mineralized tissue growth by using the right choice of materials and surface reformulation, which increases adhesion to the bone of the host and provides a better regeneration process [7].

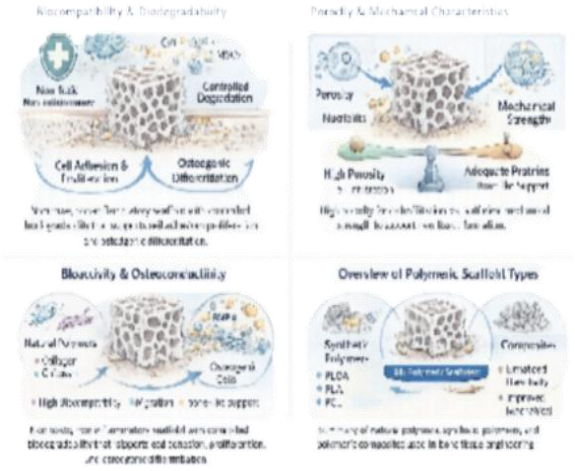

Fig 3.1-Functional characteristics of 3D polymeric scaffolds

IV. ORGANIZATIONAL MATERIALS 3D POLYMERIC SCAFFOLDS.

4.1 Natural polymers (collagen, chitosan, gelatin)

The natural polymers have become popular in bone tissue engineering due to their high biological compatibility and close resemblance to the native extracellular matrix. The first structural protein found in the natural bone is collagen which inherently contains cell-recognition sites contributing to the cell adhesion, proliferation as well as osteogenic differentiation. It has a natural bioactivity that facilitates the early integration of tissues and the promotion of cellular communication [6]. Nevertheless, collagen-based scaffolds are usually weak and highly degradable, and thus cannot support load bearing bone unless reinforced or cross-linked. Chitosan is a polysaccharide that is a degradation product of chitin which is biocompatible, has weak antibacterial effects and structural resemblance to glycosaminoglycans present in bone matrix. It facilitates cell adhesion and may be digested to three-dimensional porous structures. However, it has a low mechanical stability which is not osteoinductive, it needs to be modified or combined with other materials to enhance better performance in bone renovation. Gelatin is a denaturated variant of collagen containing numerous bioactive sequences, which cause cell adhesion and cell proliferation. It is very processable, cost-effective enough and can be used to make hydrogels and porous scaffolds.

Gelatin scaffolds however decay quickly in physiological conditions and are not mechanically sound enough to be used in load bearing bone defects or as a component of composite systems. On the whole, natural polymers are primarily appreciated due to their bioactivity and compatibility with cells, whereas they tend to need reinforcement to satisfy mechanical requirements of the bone tissue engineering [1].

4.2 Synthetic polymers (PCL, PLA, PLGA)

Synthetic polymers are widely used in preparation of bone scaffolds because of their controlled composition, reproducible properties and controllable degradation characteristics. Polycaprolactone (PCL) is a material which is tough, highly flexible with high processing ability, especially in 3D printing and electrospinning. It has a low degradation rate which can support the structures of the bone in the long run. Nonetheless, this hydrophobic property and low cell recognition points are able to decrease the first cell adhesion, which requires modification or incorporation of bioactive-based surfaces. PLA is stiffer and stronger than many natural polymers and

can be broken down to lactic acid by hydrolysis. Its degradation rate is adjustable through the change of molecular weight as well as processing conditions. Though the PLA is a good mechanical support, the acids degradation products can lead to local inflammation and affect the cell activity in an adverse way unless it is managed. Poly (lactic-co- glycolic acid) (PLGA) is a polymer that is a combination of lactic and glycolic acid, which allows the rate of degradation to be accurately tuned by varying the ratio of the two monomers. PLGA facilitates the delivery of drugs and growth factors and is common in the controlled release system. Although versatile, PLGA does not have an intrinsic osteoconductivity quality and in most cases, surface modification or addition of bioactive fillers are necessary to increase bone-forming responses. Synthetic polymers in general are better in mechanical reliability and design flexibility although they do not have inbuilt biological signals needed to regenerate bones easily [8].

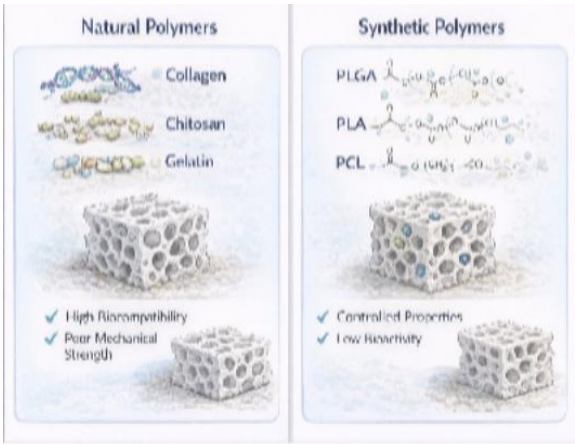

Fig 4.1 - Natural vs Synthetic Polymers Used in Bone Tissue Engineering

4.3 Polymeric composites (Polymer-ceramic and polymer-nanoparticle systems)

Polymeric composite scaffolds have become one of the successful methods to address the shortcoming of natural polymers and synthetic polymers. Bioactive ceramics, like calcium phosphate or hydroxyapatite will be added to polymer matrices in polymer-ceramic composite to enhance osteoconductivity and mechanical strength. The mineral deposition is increased and the bond between the scaffold and the native bone tissue is strengthened by the ceramic phase, whereas the polymer phase makes it flexible, tough, and processable. Such synergistic compounds allow the scaffold to approach more closely what natural bone is all about in terms of its hierarchical structure [11]. Polymer- nanoparticle system also boosts the capabilities of the scaffolds with the inclusion of nanoscale fillers of bioactive glass, nanohydroxyapatite or metallic nanoparticles. These nanoparticles drastically enhance surface roughness and surface area that enhances the process of protein adsorption and cell-material interactions. They give nanoscale cues as well which are very similar to the natural bone microenvironment thus stimulating the osteogenic differentiation and faster mineralization. In addition to this, composite scaffolds enable individual modulation of mechanical behaviour, degradation behaviour and biological behaviour. Polymeric composites can also be individualized to site-specific bone defects by optimizing the nature and concentration of fillers and provide a more clinically relevant answer to bone regeneration that requires large and critical-size bone defects [5].

V. FABRICATION TECHNIQUES

5.1 Traditional (freeze-drying, solvent casting, electrospinning) techniques.

Traditional fabrication processes have been extensively utilized in the manufacturing polymeric scaffolds due to its simplicity, low cost and well-established processing procedures. One method that is frequently used is freeze-drying where a polymer solution is frozen, followed by the sublimation of the solvent to produce a highly porous three-dimensional structure. The approach allows the creation of interconnected pores which are conducive to the infiltration of cells and transport of nutrients. Nonetheless, fine regulation of pore size, pore geometry and mechanical homogeneity is a difficult task, which could interfere with the reproducibility of the scaffold operation. The solvent casting method entails the process of dissolving the polymer in a proper solvent, then letting the solution dry by evaporation when it is poured into a mold. The addition of porosity will normally be through the use of particulate leaching agents like salt. This method is straightforward and it is easy to control the general shape and thickness of scaffolds. However, it is restricted due to incomplete solvent removal, lack of interconnectivity of pores and control of the internal

architecture, limiting its use in complex bone defect repair. Fibrous scaffolds are made by the process of electrospinning which is capable of closely resembling the nanofibrous structure of the native extracellular matrix. The mats that are formed as a result enable a high surface-volume ratio that promotes cell attachment and multiplication. Although these benefits exist, the scaffolds produced by electrospinning are mostly characterized by small pore sizes which do not allow deep penetration of cells and vascularization and thus do not lend themselves to use as an independent structure in large 3D bone regeneration [13].

5.2 Superspecialized technologies (3D printing, bioprinting).

The development of advanced fabrication methods has received considerable interest because of the capability of the precise control of scaffold architecture and spatial organization. Three-dimensional printing allows the scaffolds to be produced in a layer-by-layer construction of the scaffold with a predetermined pore size, shape and relationship to interconnectivity according to the digital model. This enables the making of custom-made scaffolds that conform to the anatomical configuration of bone defects. Moreover, mechanical properties and internal architecture may be customized through the control of printing parameter, and this method makes the technique very appropriate in load bearing bone applications. Bioprinting is another step forward but it uses living cells, growth factors and biomaterials as an ingredient in the printing process. This method enables spatial localization of several cell types in the same construct and is very similar to the cellular structure of native bone tissue. It is also possible to print biologically functional scaffolds with the use of bioprinting to facilitate early tissue maturation and vascularization. Nevertheless, preservation of cell viability during printing, as well as attaining adequate mechanical strength are significant technical issues [18].

5.3 Comparison of techniques

Traditional techniques of fabrication are cheap and technically easy, which is why they can be used in preliminary studies and extensive screening of materials. Nevertheless, these methods provide a poor degree of control over internal architecture, interconnection and spatial distribution of bioactive components in the structure. Consequently, porous structures formed by traditional techniques could have a unpredictable biological functionality and lack mechanical stability to be applied in complex clinical settings. Conversely, state-of-the-art fabrication methods, including three-dimensional printing and bioprinting, have better control of the geometry of the scaffolds, reproducibility and customization. They permit making complex defect-specific constructions with customized mechanical and biological characteristics. Advanced techniques need more cost of equipment though, specialized skills and more rigid conditions of processing, but have more potential of translating polymeric scaffolds into clinically relevant and patient specific bone regeneration therapies[12].

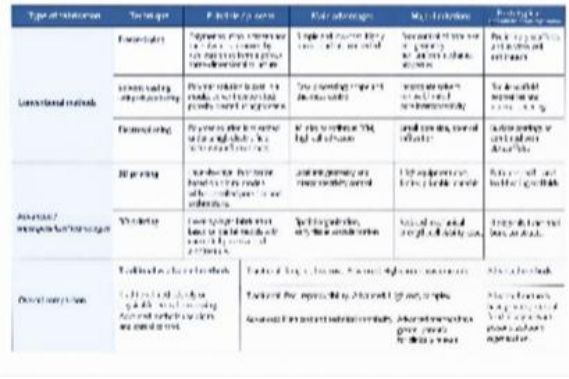

Fig 5.1- Fabrication methods of polymeric scaffolds for bone tissue engineering

VI. IMMUNOMODULATORY EFFECT IN BONE REGENERATION.

6.1 Host immune response

The success or failure of bone regeneration after implantation of scaffolds is dependent on the host immune reaction.

The presence of a foreign material and an injury immediately after implantation provokes an acute inflammatory response in the form of the attraction of immune cells neutrophils, monocytes and macrophages. Not only is this early inflammatory process inescapable but also critical to the beginning of tissue repair as cytokine and growth factors are released by immune cells which govern angiogenesis, cell recruitment and osteogenic differentiation. But once the inflammatory process is overstimulated or

sustained, it may prevent osteoblast and slow down the process of vascularization and eventually inhibit the formation of the new bone.Hence, balanced immune response is very important, whereby the initial inflammatory response facilitates tissue remodelling, and is later dissolved in order to enable successful bone repair [5].

6.2 Macrophage polarization (M1/M2)

Macrophages are the key controllers of the bone healing microenvironment among immune cells. Macrophages are able to assume various functional phenotypes after scaffold damage or implantation of scaffolds based on local biochemical and physical signal transduction. M1 phenotype, which is classically activated, is linked to the release of pro-inflammatory cytokines and reactive species that are required to protect against pathogens and clear the debris in the initial stages of healing. Conversely, the M2 phenotype which is activated alternatively is linked to anti-inflammatory signaling, tissue repair and regeneration. M2 macrophages also stimulate angiogenesis, mesenchymal stem cell recruitment and osteogenic differentiation by the release of pro-healing growth factors. Effective bone regeneration necessitates a well co- ordinated shift between the first stage of inflammatory transition to the second regenerative stages which is M1 to M2. Loss of this phenotypic change can lead to persistent inflammation, fibrosis and defective bone incorporation [14][17]. Immune modulation in form of scaffolds. The new generation of scaffolds is more concerned with the active control of the local immune microenvironment to support bone regeneration. Immune cell behavior and macrophage phenotype can all be affected by scaffold composition, surface chemistry, topography and mechanical properties. With the choice of polymers and the integration of bioactive factors, it is possible to design scaffolds so that the excessive inflammatory reaction is not stimulated, and a shift to a regenerative macrophage profile is maintained. Moreover, surface modification techniques e.g. incorporation of functional groups or biomimetic surfaces augment protein adsorption and control immune cell adhesion and activation. Localized and sustained immune regulation is also facilitated by the controlled release of anti-inflammatory agents and pro-regenerative cytokines of the polymeric scaffolds. By these means, scaffold-based immune modification seeks to establish a positive healing environment that can facilitate angiogenesis, osteogenic differentiation and stable bone integration, which can in turn enhance the overall bone regeneration therapy [9].

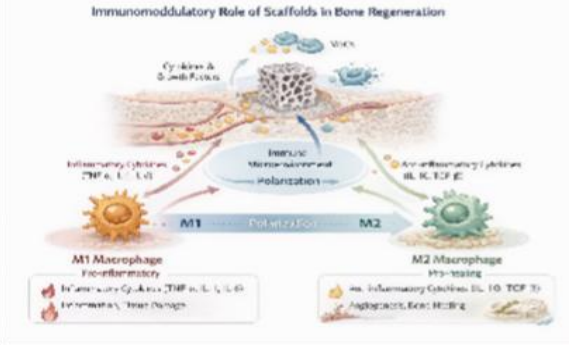

Fig 6.1-Immunomodulatory role of scaffolds in bone regeneration

VII. THE MEASURES TO IMPROVE OSTEOGENESIS AND ANTIMICROBIAL ACTION.

7.1 The incorporation of growth factor and stem cell.

Growth factor and stem cell introduction into 3D polymeric scaffolds are a popular approach used to promote osteogenesis and bone healing. Cell migration, proliferation and differentiation is regulated by osteogenic growth factors which are important in the initiation and maintenance of bone formation. These biological signals produce a localized microenvironment when delivered directly into the scaffolds to recruit endogenous progenitor cells and induce their differentiation into osteoblasts. Nevertheless, the immediate delivery of growth factors usually has a high rate of diffusion and low biological half-life. Thus, polymeric scaffolds are often designed to act as a delivery vehicle that allows sustained and spatially controlled release, and thus maintains effective local concentrations over a long period. Moreover, stem cells especially mesenchymal stem cells lead to a further increase in regenerative capability, as they offer a direct source of cells to build bone. Under optimal biochemical and mechanical signals, these cells are capable of attaching themselves to the scaffold surface and growing in its porous network and developing osteogenic lineages. The concomitant arrangement of stem cell and Oste inductive factors in a single scaffold produces a synergistic effect that results in the increase of the

matrix deposition, augmented mineralization and accelerated functional incorporation with the host bone. However, there is the crucial matter of preserving cell viability at fabrication and implantation, and ensuring sufficient cell-material interactions and this is a critical design consideration [10].

7.2 Surface modification

Surface modification is also a good strategy that enables the enhancement of osteogenic performance of polymeric scaffolds without changing their bulk mechanical properties. Cell behavior is largely regulated by the properties of surfaces, surface chemistry, roughness and wettability can be used to regulate protein adsorption, cell adhesion and subsequent differentiation. Functional groups or bioactive coating of the scaffold surface promotes interactions between cells and the scaffold, leading to a higher degree of cell adhesion and activation of cellular signaling. Micro- and nanoscale surface topographies are especially advantageous, because they resemble natural structure of bone, which is hierarchical, and they give physical signals leading to cell morphology and cytoskeletal organization. These topographical patterns have been demonstrated to induce osteogenic differentiation through Mechan transduction pathways enabled by the topographical patterns. More so, surface coagulation of peptides or Oste inductive molecules enables localized cell activity to be stimulated that enhances early bone formation and integration of the scaffold in the long term. Therefore, surface modification is a flexible and manageable approach to the increase of Oste conductivity and bioactivity of polymeric scaffolds [6].

7.3 Antimicrobial agents and drug release control

Some of them are post-implantation infection which is still a significant clinical problem in the bone regeneration that can cause implant failure or delayed healing and further surgeries. One way to solve this problem is by designing polymeric scaffolds to have intrinsic or incorporated antimicrobial functionality. The scaffold matrix can be loaded with antimicrobial agents like antibiotics, metallic nanoparticles or antimicrobial polymers to prevent the bacterial adhesion and biofilm formation on the scaffold surface. The use of controlled drug release systems is also quite beneficial, because it allows localized and extended delivery of antimicrobial agents at the defect site. This specific methodology requires a low level of systemic drug dosages and the elimination of side effects. Besides the antimicrobial agents, polymeric scaffolds can be designed to release osteogenic and anti-inflammatory factors at the same time which in combination will promote bone regeneration and inhibit infection and excessive inflammation. Combination of controlled release modalities in polymeric scaffolds thus gives a multifunctional scaffold which increases osteogenesis, antimicrobial colonization and boosts general efficiency of bone tissue engineering applications.

VIII. CHALLENGES AND FUTURE FORECASTS.

8.1 Mechanical mismatch

One of the largest problems of the clinical use of 3D polymeric scaffolds is mechanical mismatch between the scaffold and the native bone tissue. The structural complexity of natural bone is also discovered to be hierarchical and region-specific mechanical properties and most polymeric scaffolds are lower in stiffness and strength. The outcome of this misfit can be an insufficient load carrying capacity, structural instability or stress shielding at the site of defect particularly in big or load bearing bones. Although to improve the mechanical performance, there is a possibility to strengthen polymers with ceramics or fibers, it is difficult to offer an ideal balance of mechanical strength and porosity and degradability. Future scaffold designs need to be interested in building mechanically graded or biomimetic designs that more effectively resemble the heterogeneous mechanical activity of native bone and are stable throughout the healing process [16].

8.2 Vascularization

The large bone defects and critical-sized defects have the major limitation of being inadequately vascularized. Adequate blood supply is highly essential to bone regeneration process because it provides oxygen, nutrients and osteoprogenitor cells and removes metabolic waste. The conventional scaffolds are often incapable of facilitating rapid and extensive vascular infiltration such that the growth of tissue and complete regeneration of the interior regions of the scaffolds are slow. Although the

migration of cells can be accomplished by using highly porous structures, effective vascular networks cannot be generated by them alone. It is believed that the future directions will be scaffold structures that induce the formation of directed vessel-growth, addition of angiogenic molecules as well as co- culture or co-delivery of endothelial and osteogenic cell types to form stable and functional vasculature in engineered bone structures [20].

8.3 Infection control

One of the most dangerous complications that have been witnessed with bone implants and tissue-engineered scaffolds is infection. Biofilm formation and adhesion of bacteria to the surface of the scaffold can have a severe impact on the osteogenesis and cause the failure of the implants, prolonged hospitalization and re-hospitalization. In spite of the fact that it has been proved that the local delivery of antimicrobial agents by the help of polymeric scaffolds has some perspectives, long-term and controlled antimicrobial protection is impossible without the emergence of cytotoxicity or bacterial resistance. Second, the high concentration of antimicrobial agents may make a negative contribution to the bone regenerative cells of the host. Future researchers should therefore strive to develop multifunctional scaffolds that can support osteogenesis, regulate inflammation and provide long-term antimicrobial protection of the inflammation in a safe and controlled manner. Issues of regulatory and clinical translation. The fact that the 3D polymeric scaffolds have not been successfully translated into the normal clinical practice is despite the tremendous successes achieved in the laboratory and preclinical work. One of the largest barriers is the lack of the standard methods of fabrication and quality control that can be repeated with other platforms of manufacture. The content of the materials, the architecture of the scaffold, and the biological performance is different and thus making it hard to produce large-scale and perform regulations [12]. In addition, the long-term safety and in vivo stability and performance of multifunctional complex scaffolds are supposed to be widely established. Better still, regulatory pathways in highly developed scaffolds such as cells, growth factors or drug delivery systems are extremely difficult to navigate because they entail a conglomeration of both medical device, biologics and pharmaceutical characteristics. Three aspects of work in the future should be scalable production, standardization of testing procedures and the timely consideration of regulatory aspects when developing scaffolds in order to make the transition into clinical practice of scaffolding with the use of polymers faster and to enable more or more people to use the technologies of bone regeneration [11].

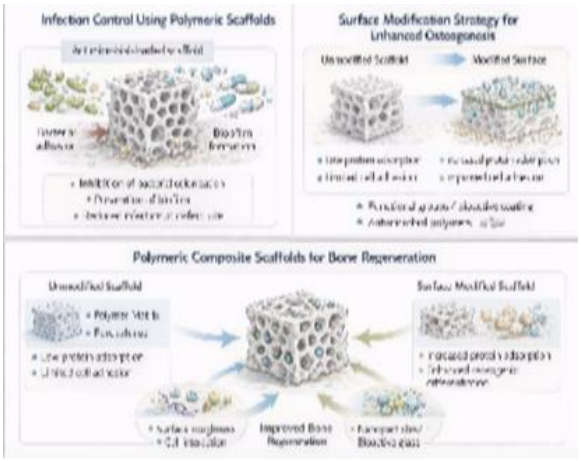

Fig 8.1-Enhancement strategies for polymeric scaffolds

VI. CONCLUSION

In conclusion, three-dimensional polymeric scaffolds represent a promising and versatile platform for bone tissue engineering due to their tunable physicochemical properties, controllable architecture and ability to mimic the native extracellular matrix. This review highlights that rational scaffold design, appropriate fabrication techniques and emerging immunomodulatory strategies are critical for achieving effective cell–material interactions, balanced inflammatory responses and enhanced osteogenesis. Although significant progress has been made in improving scaffold functionality through surface modification and bioactive incorporation, major challenges such as mechanical mismatch, limited vascularization, infection risk and difficulties in large-scale manufacturing and clinical translation remain. Future research should therefore focus on developing multifunctional, immuno-instructive and clinically scalable scaffold systems that can better integrate with host tissues and promote long-term functional bone regeneration, ultimately accelerating the translation of 3D polymeric scaffolds into routine clinical practice [13].

REFERENCES

[1] F. J. O'Brien, "Biomaterials and scaffolds for tissue engineering," Materials Today, vol. 14, no. 3, pp. 88–95, 2011.

[2] S. Bose, M. Roy, and A. Bandyopadhyay, "Recent advances in bone tissue engineering scaffolds," Trends in Biotechnology, vol. 30, no. 10, pp. 546–554, 2012.

[3] [3] S. J. Hollister, "Porous scaffold design for tissue engineering," Nature Materials, vol. 4, pp. 518–524, 2005.

[4] C. M. Murphy and F. J. O'Brien, "Understanding the effect of mean pore size on cell activity in collagen–glycosaminoglycan scaffolds," Cell Adhesion & Migration, vol. 4, no. 3, pp. 377–381, 2010.

[5] V. Karageorgiou and D. Kaplan, "Porosity of 3D biomaterial scaffolds and osteogenesis," Biomaterials, vol. 26, pp. 5474–5491, 2005.

[6] D. W. Hutmacher, "Scaffolds in tissue engineering bone and cartilage," Biomaterials, vol. 21, pp. 2529–2543, 2000.

[7] K. Rezwan, Q. Z. Chen, J. J. Blaker, and A. R. Boccaccini, "Biodegradable and bioactive porous polymer/inorganic composite scaffolds for bone tissue engineering," Biomaterials, vol. 27, pp. 3413–3431, 2006.

[8] M. M. Stevens, "Biomaterials for bone tissue engineering," Materials Today, vol. 11, no. 5, pp. 18–25, 2008.

[9] E. S. Place, N. D. Evans, and M. M. Stevens, "Complexity in biomaterials for tissue engineering," Nature Materials, vol. 8, pp. 457–470, 2009.

[10] M. A. Woodruff and D. W. Hutmacher, "The return of a forgotten polymer Polycaprolactone in the 21st century," Progress in Polymer Science, vol. 35, pp. 1217–1256, 2010.

[11] M. Dash et al., "Chitosan A versatile semi-synthetic polymer in biomedical applications," Progress in Polymer Science, vol. 36, pp. 981–1014, 2011.

[12] T. Ghassemi et al., "Current concepts in scaffold-based bone tissue engineering," Journal of Biomedical Materials Research Part A, vol. 106, no. 2, pp. 443–455, 2018.

[13] G. Turnbull et al., "3D bioactive composite scaffolds for bone tissue engineering," Bioactive Materials, vol. 3, pp. 278–314, 2018.

[14] S. V. Murphy and A. Atala, "3D bioprinting of tissues and organs," Nature Biotechnology, vol. 32, pp. 773–785, 2014.

[15] A. A. Zadpoor and J. Malda, "Additive manufacturing of biomaterials, tissues, and organs," Annals of Biomedical Engineering, vol. 45, pp. 1–11, 2017.

[16] Z. Chen, A. Bachhuka, F. Wei, X. Wang, G. Liu, and K. Vasilev, "Nanotopography-based strategies for regulating macrophage behaviour," Advanced Materials, vol. 29, p. 1603367, 2017.

[17] Q. Chen and G. A. Thouas, "Metallic implant biomaterials," Materials Science and Engineering R, vol. 87, pp. 1–57, 2015.

[18] K. L. Spiller and T. J. Koh, "Macrophage-based therapeutic strategies in regenerative medicine," Advanced Drug Delivery Reviews, vol. 122, pp. 74–83, 2017.

[19] O. Veiseh et al., "Size- and shape-dependent foreign body immune response to materials implanted in rodents and non-human primates," Nature Materials, vol. 14, pp. 643–651, 2015.

[20] D. Campoccia, L. Montanaro, and C. R. Arciola, "A review of the biomaterials technologies for infection-resistant surfaces," Biomaterials, vol. 34, pp. 8533–8554, 2013.