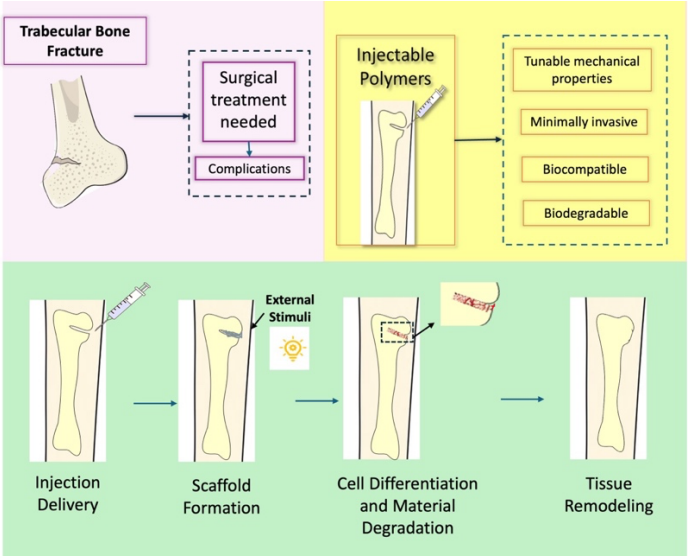

Injectable Biomaterials for Trabecular Bone Regeneration: Current Strategies and Future Directions

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Abstract

Injectable biomaterials have emerged as a promising solution for bone repair, offering tunable mechanical properties, minimally invasive delivery, and excellent biocompatibility. This work comprehensively explores the trabecular bone physiology, its intrinsic healing mechanism, and conventional surgical and non-surgical methods for bone fracture management. Furthermore, it provides a detailed discussion on injectable polymeric biomaterials, including their classification, advantages, biomedical applications and their role in bone scaffolding. Special attention is given to the emerging field of 4D materials, which exhibit responsiveness to external stimuli like light, temperature, and pH, offering significant potential in tissue engineering. Finally, some examples of clinical studies assessing the efficacy of injectable polymers in bone repair are presented, providing insights into future advancements in biomaterials for trabecular bone repair.

Key words:

Spongy bone; Trabecular bone; Cancellous bone; Bone repair; Injectable Polymers; 4D materials

1. Introduction

Bone defects usually result from trauma, or falls, and distal epiphysis fracture of forearm is the most common injury encountered among others [1]. Thus, the restoration of bone integrity remains a critical challenge in orthopedic and reconstructive medicine. Special attention is needed for trabecular bone repair while it is more active in remodeling, and which leads to lower mineralization (newly formed bone has lower mineralization than the older one). It is important to note that trabecular bone balance (the amount of new bone minus old bone resorbed) is mildly negative in adult life, which explains trabecular thinning with aging and thus higher fragility and susceptibility to fracture. Conventional therapies involve many non-surgical methods in case of simple fractures, but with more severe fractures, surgical attention is required. Traditional surgical methods involve bone substitutes like autografts or allografts and metal implants [2]. These methods have many limitations like immune rejection, causing infection and inflammation at insertion site, instability of fracture, limited availability etc. [2,3]. These challenges highlight the need for better materials and minimally invasive approaches that can reduce complications and improve patient outcomes.

Injectable biomaterials have emerged as a promising solution, offering targeted delivery to defect sites while minimizing surgical trauma, thus enhancing healing efficiency and reducing the risk of adverse reactions. These materials conform to complex bone shapes, stabilizing irregular defects with minimum surgical intervention. Different materials can be combined to gain specific properties suitable for bone stabilization An ideal injectable materials should be a composite system leading to the scaffold formation directly at the defect site, supporting bone regeneration. These systems should be tailored to meet specific clinical needs, such as mechanical strength, biological activity, and degradation rate which matches the rate of new trabecular bone growth. Moreover, the gradual breakdown of the material helps prevent the weakening of surrounding bone. These properties should make them a versatile tool in bone tissue engineering. Further, a new advancement in development of 4D materials is the most enlightening topic in bone tissue engineering nowadays [4]. These materials should respond to external stimuli, which enable their easy application and handling of a material and ensure stable fixation in bone defects.

This review paper aims to provide a comprehensive overview of the current state of the art on injectable polymers for trabecular bone repair, highlighting their properties, advantages, and applications. It will also discuss the challenges and future directions in the development of these materials, emphasizing their potential to revolutionize the treatment of bone injuries and defects.

2. Bone Physiology

2.1. Structure and Composition of Bone

Bone is a biological material composed of bone tissue, bone marrow, blood vessels, nerves, lymph, and periosteum (***Figure 1***). Bone tissue contains five cell types, which include bone mesenchymal stem cells, preosteoblasts, osteoblasts, osteoclasts, and osteocytes (***Figure 2***). Bone marrow mesenchymal stem cells (MSCs) are multipotent cells which migrate to sites of injury and can differentiate into mesodermal cells such as osteoblasts, adipose cells, cartilage cells or skeletal muscle cells. MSCs redound to damaged tissue repair and have the capacity of suppressing the local immune response. Preosteoblasts are precursor cells to osteoblasts; both of these cells are important for bone formation, such as regulating mineralization and expression of functional proteins. Osteoclasts allow for a constant bone remodeling by secreting acid and proteolytic enzymes to dissolve the mineral and organic matrix components of bone. Osteocytes, which are produced as a result of osteoblasts being trapped in a bone matrix, are responsible for

generating syncytial networks, supporting bone structure and metabolism. These cells are involved in various stages of bone formation and maintenance.

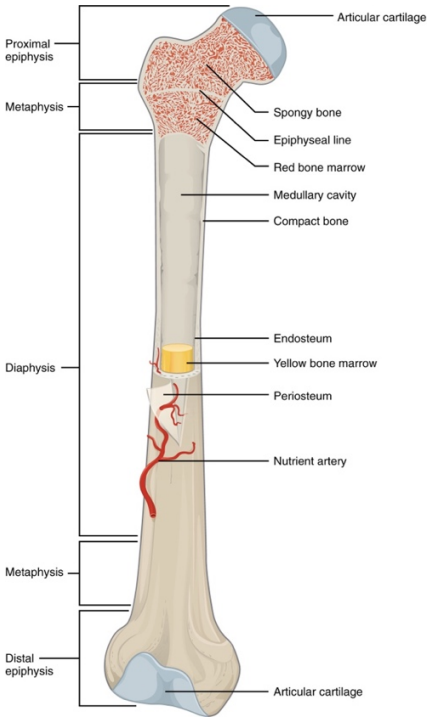

Figure 1 Long bone structure and anatomical sections [5]. Reproduced with permission from OpenStax.org

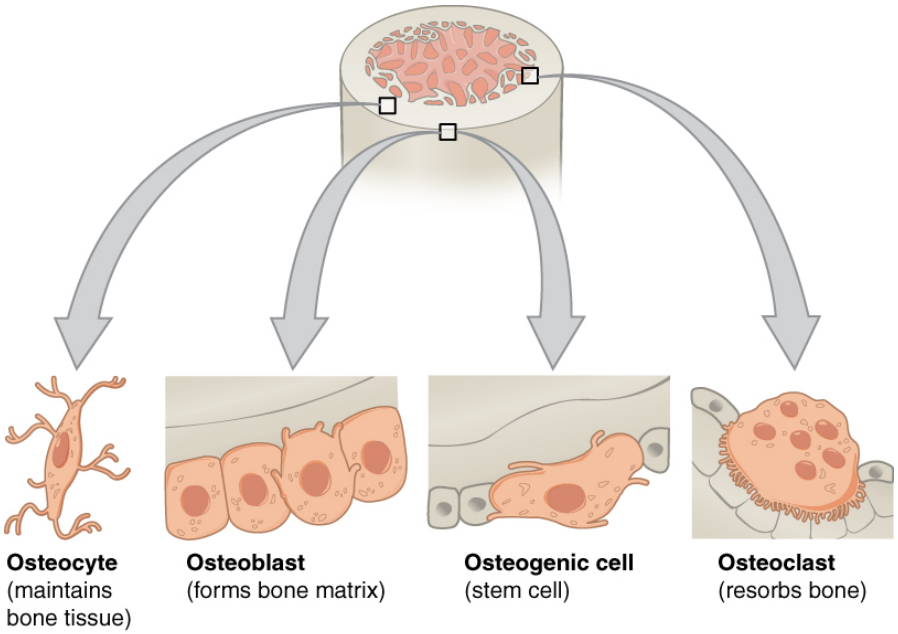

Figure 2 Cell types found within bone tissue [5]. Reproduced with permission from OpenStax.org

Bone has a hierarchical structure and can be viewed as a natural composite material containing organic and inorganic phases, where water accounts for around 25% of the mass of the bone. At a nanoscale level it is composed mainly of type I collagen fibers which account for about 90% of bone's organic matter; collagen is a protein which is responsible for bone's ductility and absorbing energy. Collagen fibers/molecules are tightly packed with a consistent gap of approximately 35 nm between them, which facilitates the formation of crystallization nuclei. The inorganic component of the composite are small hydroxyapatite (HA) crystals, which account for about 65% of dry bone weight and provide the stiffness and structural strength. Mineral crystals have a plate shape and align with the longitudinal direction of collagen fibers (***Figure 3***). These plate shaped crystals vary in thickness from 2 to 7 nm, width from 10 to 80 nm, and length from 15 to 200 nm. This arrangement is responsible for the anisotropic properties (varying, depending on the direction of measurement) of bone such as higher values of stiffness and strength in that direction. Further up the structural hierarchy, these mineralized collagen fibrils (measuring 0.5 – 1 μm) organize parallel to each other to form larger fibers. Depending on the bone's developmental stage and its mechanical requirements, these fibers can be arranged in a lamellar (layered) or woven pattern. Woven bone, which appears in the early stages of bone formation,

has a less organized structure and is typically replaced by the more structured lamellar bone as the bone matures [6].

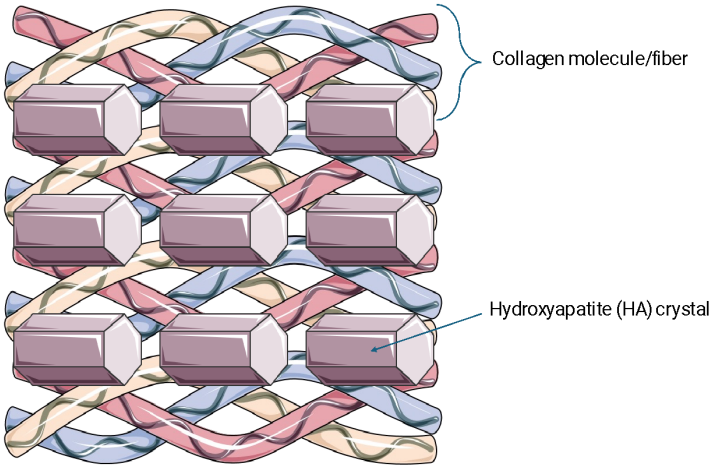

Figure 3 Arrangement of the HA crystals aligned in the longitudinal direction of collagen fibers

Bone can be categorized into two primary types: cortical (compact) bone and trabecular (spongy, cancellous) bone. Cortical bone, found in the outer shell of all bones, is a dense tissue that accounts for around 80% of bone tissue mass. It is composed of tightly packed layers of lamellae arranged around central blood vessel (Haversian canal) forming a structure called an osteon. Each osteon is cylindrical, about 200 to 300 micrometers in diameter, and aligned parallel to the bone's length. The gaps between osteons are filled with a substance known as the cement line, which is approximately 1 to 5 micrometers thick and results from the ongoing process of bone remodeling [7]. Cortical bone demonstrates density of around 1800-2000 kg/m^3 and porosity of less than 6%. These properties provide cortical bone tissue with a resistance to compression and torsion, which are significant in supporting and securing the internal bone structure.

The other bone tissue type is the trabecular bone (***Figure 4***) otherwise known as spongy or cancellous bone. Generally spongy bone exists at the end of the long bone (protected by a shell of a cortical bone named periosteum) and bone cavity or in the middle of the laminar bones. It can be divided into four forms based on the structure of trabecular networks: (i) a mesh structure formed by small rods; (ii) a structure where part of those rods is replaced by small plates; (iii) a structure where somewhat aligned plates, can be few millimeters long and lastly (iv) trabecular tissue formed entirely out of plates. In trabecular bone, lamellae are aligned with the long axis of

the trabeculae, which form a network of rods and plates with a thickness ranging from 100 to 300 μm and length of 1mm. The distances between individual trabeculae range from 0.5 to 1.5 mm or more [8].

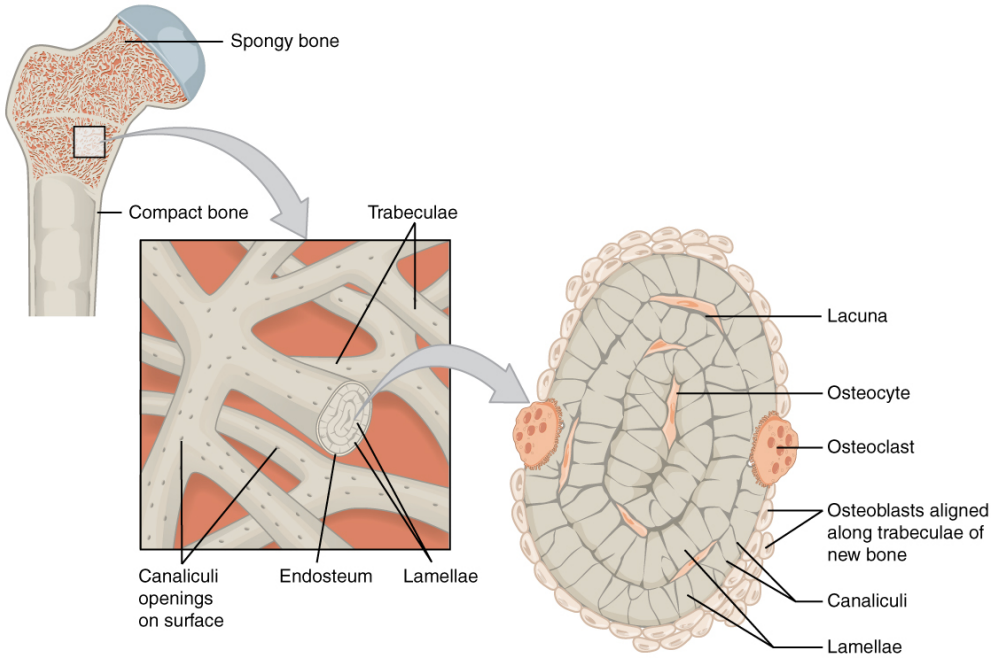

Figure 4. Trabecular (spongy) bone structure composed of trabeculae that contain the osteocytes [5]. Reproduced with permission from OpenStax.org

2.2. Natural Bone Healing Process

Bone remodeling is responsible for preserving bone's mechanical strength by replacing damaged tissue with healthy one as well as calcium and phosphate homeostasis. Trabecular bone is more active in remodeling which leads to lower mineralization (newly formed bone has lower mineralization than the older one). Trabecular bone demonstrates 26% volume per year turnover rate, which is significant in comparison to the 3% for cortical bone [9]. This indicates that trabecular bone plays a particularly significant role in mineral metabolism, as newly formed bone due to its lower mineral content is able to better exchange ions with intracellular fluid. Cortical and trabecular bone follow the same bone remodeling mechanism, with bone remodeling units in trabecular bone equivalent to cortical bone remodeling units divided into half longitudinally. It is important to note that trabecular bone balance is mildly negative in adult life, which explains trabecular thinning with aging [10]. Blood marrow is present in the medullary cavity of the long bone

and all trabecular bone which serves as a scaffold. Trabecular bone equals around 20% of bone tissue mass, has a porosity of around 80% (due to which, the surface area of trabecular tissue is 10 times larger than that of cortical bone) and has a density equal to 1820 kg/m^3. Above mentioned properties allow the trabecular tissue for energy absorption, load transfer, and metabolic activities such as bone cell metabolism and bone marrow erythropoiesis.

2.2.1 Trabecular Bone Healing

Healing of a trabecular bone must be viewed with great attention, considering its nature is surprisingly disparate from shaft healing process in cortical bone [11121314151617]. From a biomechanical perspective, the fractures of distal bones usually take place in fall injuries with protective arm movement [18] and is located in the distal upper or lower extremities. They may be a result of common commuting accidents such as bike falls, stair falls, or the recently emerging number of electric scooter accidents [19]. This type of injury is highly complex and poses a significant risk of complication [20].

Trabecular bone is believed to heal mainly through inter-trabecular (otherwise known as intermembranous) bone formation. This process is characterized by direct bone formation occurring freely in the metaphyseal marrow. In some cases, mechanical instability may lead to cartilage formation as well as an external callus, which otherwise is rather unspecific to healing of trabecular bone tissue. The fractured fragments need to be anatomically correct to each other and remain within a very close distance [1621]. The inter-trabecular healing process starts with a hematoma consisting of blood and marrow cells (***Figure 5***). Blood vessels directly neighboring the fracture site undergo rupture and release blood into the fracture, allowing immune cells to access the site. It is followed by inflammation, which causes the hematoma to coagulate[21].

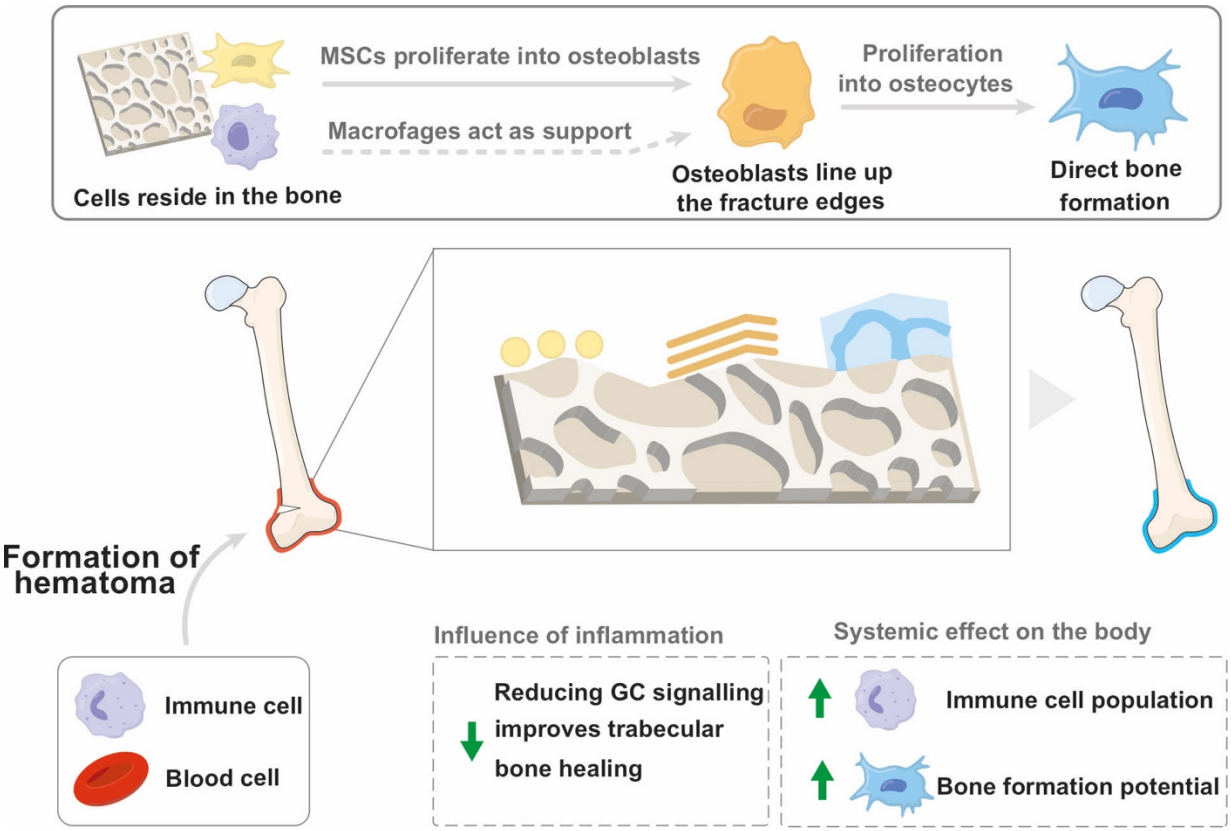

Figure 5 General scheme of bone healing process. MSC – mesenchymal stem cells, GC – glucocorticoids.

Next, the mesenchymal stem cells (MSCs) proliferate at three days from the injury [2216]. If the bone is mechanically stable, the mesenchymal cells proliferate directly into osteoblasts lining the trabeculae directly to the fracture[16] and osteocytes, forming bone in an instant manner [23]. Simultaneously, macrophages known as “osteomacs” play a crucial role in supporting the osteoblasts, substantially enhancing direct ossification event [24]. In cases of mechanical instability of the fracture a cartilage and an external callus may appear, which are otherwise unusual[2225]. Hematomas in the gap are completely replaced by loose connective tissue and all trabeculae in the area of the gap become lined with osteoid seams [16]. Cell condensations that form osteoid become woven bone. Woven bone is remodeled into lamellar bone through resorption and synthesis[26]. Lamellar and woven bone formation were observed to establish a contact between the two trabeculae on the sides of the fracture [16].

The role of local stem cells is considered decisive for the outcome of this healing process [1112]. The metaphyseal marrow possesses a high number of MSCs, which present a higher degree of interaction with immune cells and an elevated division, and a higher ratio of following an osteogenic fate compared to diaphyseal MSCs [1113]. In the diaphysis on the other hand, recruitment of mesenchymal progenitor cells is necessary for optimal bone formation, as local diaphyseal MSCs are not enough in number and activity to effectively support bone regeneration. Additional stem cells are recruited from bone marrow of distant bones and from surrounding soft tissue to proliferate into osteogenic cells.

Trabeculae in vicinity to the fracture in trabecular bone increase in thickness, with around a 5-fold increase in bone formation and a subsequent 5-fold increase in resorption, in the end giving no net increase in bone volume. This is referred to as "formation and resorption coupling" and is not observable in the fracture itself. There, the direct bone formation is an overwhelmingly dominant process [11].

Fast healing response in inter-trabecular healing can be attributed to osteoid forming simultaneously throughout the entire volume of the injured tissue. Regeneration may resolve in as little as four weeks if the distance between two fractured parts is minimal [2216], as response to trauma extends only as far as 2 millimeters from the fracture (***Figure 6***). The depth of bone necrosis reaches up to 100 micrometers [16].

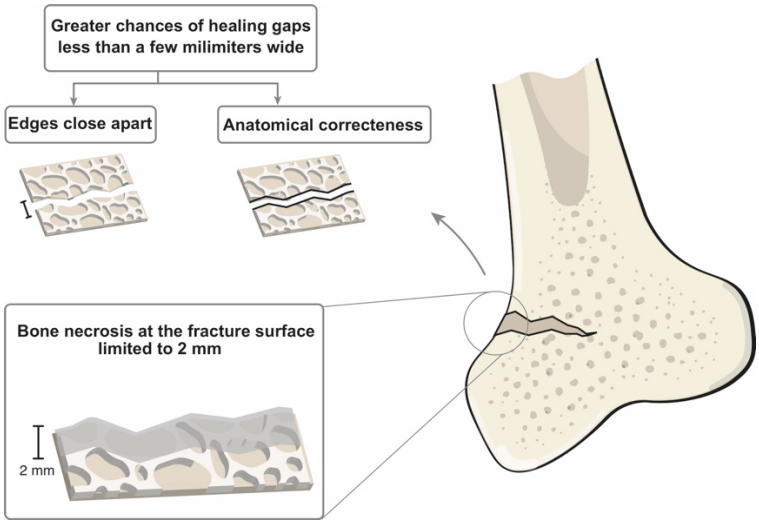

Figure 6 Spatial effects in trabecular bone healing

Contrary to shaft fractures where healing may reach substantial gaps, filling of a defect in trabecular bone can be severely delayed or ceased at all if the gap width is well over few millimeters [2221]. This is why this healing mechanism only partially observed in cortical bone healing while being the major healing process for trabecular bone.

2.2.2 Influence of Macrophages on Bone Healing

Macrophages are one of the leading cells in response to the trauma and support in healing of all bone types [26]. Their depletion leads to an increase of membranous bone formation in the periosteum and decrease in the intertrabecular space, which suggests a deeper influence on the healing process. They fulfill an important role in onset and resolution of inflammation. Two primary macrophage types are involved in this process: the inflammatory M1 macrophages, which predominantly respond to infections, and the anabolic M2 macrophages, which are critical for tissue regeneration [11 26].

Looking at the cancellous bone, macrophages do not have a clearly defined role in healing, however their interactions with osteoblasts suggest an indirect yet significant impact. Those interacting macrophages labeled as osteomacs reside in bone lining tissues in a subsurface anatomic location (within three cells of the bone surface). In sites of bone remodeling, they form an organized “canopy” structure around the osteoblasts, enhancing mineralization and performing “maintenance” of mature osteoblasts. Osteomacs are recognized for their role in anabolic bone modeling, specifically associated with sites of intramembranous ossification [11 24].

2.2.3 Intramembranous versus Endochondral Ossification

Intramembranous ossification and endochondral ossification are the two main processes for bone regeneration, both fulfilling the same need albeit following different approaches. Generally, intermembranous ossification is known as the primary healing process, and endochondral ossification is the secondary healing process of a bone and is a more commonly known one [2728].

Intramembranous ossification is the dominant healing mechanism for porous parts of the bone, a dominant structure in the metaphysis. Contrary to cortical healing, it is characterized by the direct conversion of mesenchymal cells into bone tissue [11 23]. Most of the MSCs are readily

available by residing in the trabecular bone. The gap between fractured elements must be minimal in size and anatomically correct [21]. Compared to cortical healing, cartilage formation with an external callus is usually only observable in case of mechanical instability as a result of engaging the periosteum in the healing process, while the instability is mostly thought about in the form of cyclic deformation. From a medical perspective, such cyclic deformation phenomena is even believed to be beneficial for optimal bone formation in cancellous bone [11].

For cortical bone in the diaphyseal part, the main healing process is endochondral ossification, characterized by healing processes taking place mostly on the fracture surfaces [28]. The process is known for an indirect conversion of cells into bone tissue and it is divided into five subsequent phases, involving the presence of cartilaginous intermediate for upcoming bone tissue. In the first phase, most of the MSCs are recruited. In contrast to direct bone healing, inflammation is key for this step, as the stem cells are not readily available in the local tissue. Those cells then enter a path of chondrogenic differentiation [23] which can be additionally promoted by mechanical instability at the fracture site [11 2627][28]. After forming a callus the chondrocytes halt their dividing and begin increasing massively in volume becoming so called "hypertrophic chondrocytes". At this point the fate of the chondrocytes is debated, whether they conclude their life cycle by apoptosis or undergo trans-differentiation into osteogenic cells [2327], however remaining cells surrounding the cartilage differentiate into osteoblasts, which begin replacing the cartilage with bone tissue trough mineralization of the matrix [2326].

2.2.4 Systemic Effect in Trabecular Bone Healing

The systemic effect of local trauma in trabecular bone is observed as a global increase in bone formation potential and an elevated immune cell population, in the marrow of distant bones unrelated to the injury[24]. Injuries have been shown to influence the expression of some immune cell markers in correlation with recovery outcome, for example, glucocorticoids (GCs) may be more or less imperative for healthy bone growth depending on the bone type [29]. According to studies, a biomechanically stable bone healing in metaphysis remains unaffected by disruptions of osteoblast GC signaling, contrary to fractures in the diaphysis [11 3031].

Furthermore, it has been found that a therapy based on GCs paired with other anti-inflammatory drugs may actually increase healing quality of metaphyseal fractures for patients with upregulated inflammatory response, but only if sufficient lymphocytes were present, aggregating osteoblast and osteocyte apoptosis, resulting in increased mechanical properties of the regenerated bone [11].

This may be explained through biological differences between said bone fragments. Cortical bone healing depends on stem cells from distant sources, making inflammation a critical factor, in contrast to metaphyseal bone healing, which utilizes local abundance of stem cells, contributing to its independence from an inflammatory response [2627]. In consequence, a decreased signaling in inflammatory response hinders the cortical bone healing in diaphysis, due to insufficient MSC migration to the fracture. On the contrary, a decreased signaling is neutral or even beneficial for the trabecular healing in metaphysis, where the migration of MSCs is largely irrelevant for the process flow [11 31]. The differences in cancellous and cortical bone healing are summarized in **Table 1**.

Table 1 Comparison of cancellous and cortical bone healing.

Intramembranous ossification/direct bone healing	**Endochondral ossification/indirect bone healing**
Primary bone healing	Secondary bone healing
Cancellous bone tissue (porous parts of the bone – dominant in metaphysis and epiphysis)	Cortical bone tissue (dominant in the diaphysis)
Direct conversion of mesenchymal stem cells into bone tissue	Indirect conversion, MSCs enter chondrogenic differentiation path
Local abundance of MSCs	Dependent on “recruitment” of MSCs
Small distance and anatomical correctness between fractured fragments	Larger distances between fragments
Cartilage formation is rare	Cartilage formation with an external callus is characteristic
Independent of inflammatory response/ benefits from a reduced inflammation	Highly dependent on inflammatory response

2.2.5 Summary of Trabecular Bone Healing

The healing of trabecular bone tissue is a complex and not yet completely understood phenomenon, however, many studies already indicate its differences compared to the healing of cortical bone tissue, and the need of establishing specific medical approaches.

Many factors come into consideration, mainly the mechanism of the healing itself, which can be characterized by its fast pace, or the abundance of locally residing cells that support the bone remodeling. Additionally, the process is strictly limited in distance thus requiring a great attention to anatomical compatibility between bone fragments in the fracture site. Another effect to consider is the positive impact of reduced inflammatory response. These factors are characteristic of fractures in metaphyseal and epiphyseal regions of the bone, which emphasizes the contrast to fractures in the diaphysis. Thus developing compatible treatment methods and novel materials, is a major contributing factor to progress in medical practice regarding this category of fractures. However, various stabilizing methods for fractured bones are employed to ensure the proper alignment and support during this natural healing process. Some of these common methods are mentioned below.

3. Stabilization Methods for Fractured Bones

Our body inherent a remarkable ability to heal fracture by itself but the optimal outcomes rely on a critical factor of stabilization which involves the fracture reduction and its subsequent immobilization to ensure that the reduction is maintained [32]. Some conventional methods for stabilization of fractured bone are depicted in ***Figure 7*** and will be discussed in the following sections.

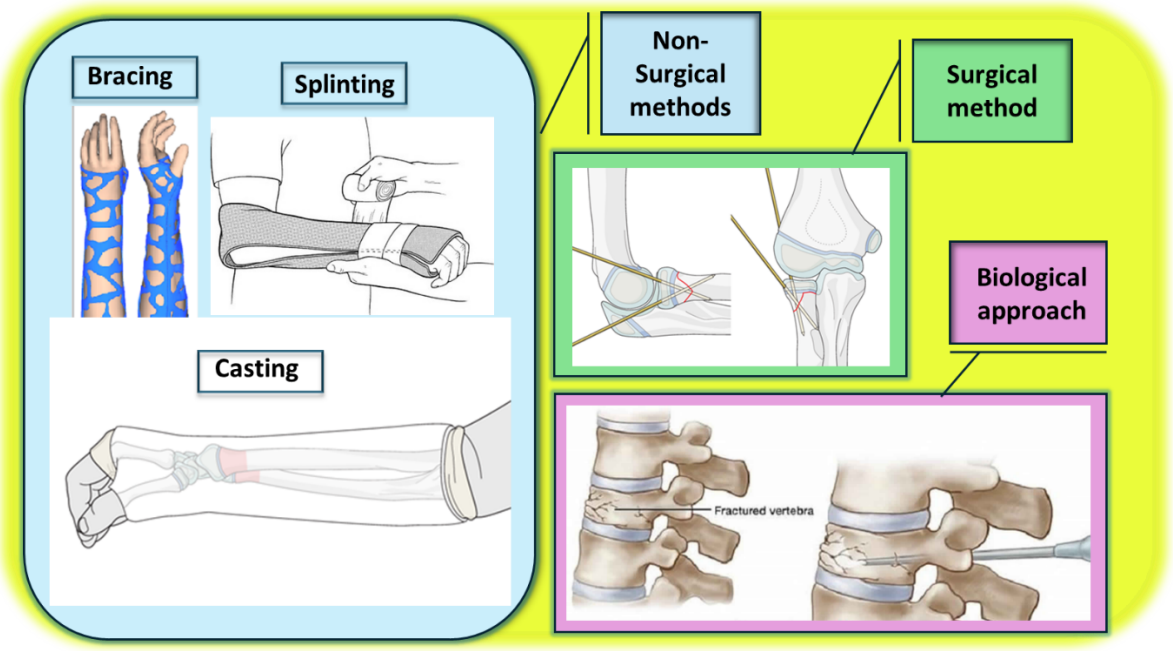

Figure 7 Different methods for stabilization of fractured bone

3.1. Non-Surgical Methods

In some cases like non-weight bearing bones or closed fractures, non-surgical methods for stabilization can be used which relies on immobilization of fracture achieved through casting, splinting and bracing [33]. In casting, the fractured bone and surrounding structure is encased by casting materials, typically plaster and fiber glass, which restrict the movement and promotes proper alignment. Whereas, splints offer a more temporary and adaptable form of immobilization, often used for initial fracture management or in situations where some degree of joint motion is desirable. Braces, on the other hand, provide a less rigid form of support, allowing for controlled movement while still promoting stability. Somehow, this strategy can lead to malunion when significant bone displacement is present because it may struggle to achieve and maintain proper alignment [33,34]. Immobilization can also lead to muscle stiffness and weakness, particularly with prolonged casting. In case of open fractures, surgical interventions are needed to clean the wound and address bone contamination [35].

3.2. Surgical Methods

Surgical methods are usually implied for complex, and load bearing bone fractures. It usually involves metal stabilizing elements like rods, plates, screws and wires. Among these elements, Kirschner wires has been proven to be a cheap and minimally invasive technique for stabilizing bone fragments [36]. This method has been commonly used to treat bone fractures, especially comminuted or unstable fractures (***Figure 7***) [36,37]. It involves usually less soft tissue disruption as compared to screws and plates, but it provides less stable fixation of trabecular bone and wires can also be loosened. Metal stabilizing elements often comes up with the infection at their insertion site and needs to be removed after bone healing [38,39]. These cannot be helpful if the fracture is complicated and results in multiple bone fragments [40].

3.3. Biological Approach

Modern stabilization methods increasingly incorporate biological techniques to enhance fracture healing. Bone grafts, including autografts and allografts, are often used to fill gaps or support bone regeneration in severe fractures. Some calcium based bioceramics are used as bone cement because they comprises most part of the natural bone structure [41]. However, most commonly used bone cement is based on poly(methyl methacrylate)(PMMA) which is strong, shows acceptable biocompatibility and can easily be cured but its rigidity leads to brittleness and also cause stress shielding where bone weakens around the implant [40]. This triggered a strong need for alternative materials which can be resorbed in the body getting replaced by natural bone tissue and promote self-healing process of bone [40,41]. Recently, more advancement has been introduced in stabilizing bone fracture by using biomimetic materials. These materials are designed in a way to mimic the natural bone structure and functions. For example, hydroxyapatite and tricalcium phosphate (TCP) are widely used in bone repair as their composition resembles the mineral component of bone. Mostly, HA or TCP are used as a coating on metal implants to enhance their integration with bone [2]. Some metal alloys like magnesium and titanium have also been used in bone scaffolds due to their excellent biocompatibility and mechanical properties. These scaffolds can be customized to fit the specific requirements of the bone defect and promote better osseointegration [2,42]. Moreover, bioactive glass (bioglass) is one of the most studied

material used in bone grafts substitutes and implants coating. It is capable of bonding to bone and soft tissues, and releases ions that stimulates bone formation [2]. Furthermore, other materials like injectable polymers are currently at forefront of research to be used as a good replacement for bone repair. These materials facilitate bone regeneration by providing tunable mechanical strength and degradation, enhancing biological healing and cell growth, while reducing surgical complications.

4. Injectable Polymers

Injectable polymers have emerged as a versatile and promising class of materials with great potential across various biomedical fields. Their ability to be injected into the body and subsequently crosslink *in situ* offers unique advantages for applications ranging from drug delivery and tissue regeneration [35], [36] to cell encapsulation and cosmetic procedures [37], [38].

4.1. Types of Injectable Polymers

Injectable polymers are categorized into different types depending on their properties. They encompass hydrogels, non-hydrogels and the hybrids; which are combining properties of different components. On one side, hydrogels with their ability to absorb high water content, mimic the cell environment and are mostly used in the applications as drug delivery [43]. However, they may lack the mechanical strength required for the load bearing trabecular bone defect and find it difficult to maintain the shape in defect cavity [44]. On the other hand, non-hydrogel elastomers have good mechanical strength and mimic the behavior of load bearing trabecular bone. They provide good conformability to the defect site and some of their degradation rate allows them to be replaced by newly formed bone [44]. However, some synthetic materials need to be designed carefully to fulfill biocompatibility concerns. Therefore, a promising approach is to construct hybrid materials that combine the diverse characteristics of the individual components and exhibit tailor-made properties. Moreover, they can also make a 3D structure, known as scaffold, to facilitate bone regeneration by giving a template on which bone tissue can grow [45]. **Table 2** highlights some examples of natural and synthetic polymers, and their copolymers/blends, each with their unique properties tailored for specific medical applications.

Natural polymers are usually biocompatible and biodegradable, making them suitable for wound healing and tissue engineering. On the other hand, synthetic polymers possess good mechanical properties and controlled degradation, critical for bone repair and drug delivery. However, composites and blends possess combined properties of both.

Table 1 Summary of the common injectable materials based on natural and synthetic polymers, and composite/blends.

	Name	**Properties**	**Applications**	**References**
Natural Polymers	Collagen	Biocompatible Biodegradable Bioactive High tensile strength	Tissue engineering Bioprinting Wound healing Facial volumization	[46,47]
	Fibrin	Viscoelastic Bioactive Fast resorption rate Hemostatic Low mechanical strength (long-term)	Wound healing Therapeutic delivery	[48,49]
	Elastin	High elasticity Biocompatible Cellular interactions	Drug delivery Tissue engineering	[50]
Synthetic Polymers	Silicones	Biocompatible Hydrophobic Chemical stability	Drug delivery Cosmetic fillers Breast implants	[44,51]
	Polyurethanes	Biocompatible Tunable mechanical properties Durable	Tissue engineering Drug delivery Medical implants and devices	[52–54]
	Poly(lactic acid) (PLA)	Biodegradable Biocompatible Tunable mechanical properties	Bone repair Tissue regeneration Drug delivery Medical implants and devices	[55–57]
	Poly(glycolic acid) (PGA)	Biodegradable Biocompatible Good tensile strength Hydrophilic	Bone tissue engineering Cartilage regeneration Drug delivery	[58,59]
	Poly(ε-caprolactone)	Thermoresponsive Biocompatible Biodegradable	Tissue Engineering Drug delivery Biosensors	[60]

		Promote osteogenesis Shape memory effect		
Copolymers and blends	HA-PEG copolymers	Biocompatible Viscoelastic Tunable	Drug delivery Tissue engineering Ophthalmic applications	[61]
	Chitosan-collagen blends	Mucoadhesive Structural support Biocompatible	Drug delivery Tissue regeneration in mucosal membranes	[62]
	PLA-Polycaprolactone blends	Tunable degradation property	Long-term tissue regeneration applications	[63]

4.2. Advantages and Characteristics of Injectable Polymers

In biomedical research, injectable polymers offer great advantages over most conventional solutions, particularly in the application for bone repair. Their unique properties like minimal invasion [64] have reduced the risk of complications associated with the most common surgical methods, which may cause painful surgery, instability of fractures, infections, and tissue damage [6566,67]. These polymers usually undergo self-assembly upon injection and can be formulated to flow and fill any irregular defects, providing conformability and improved stability to the bone structure instead of rigid implants [68 69]. Many injectable polymers are biocompatible which ensure their safe use in the body, promoting cell adhesion, proliferation, and differentiation for improved bone formation [70]. Some injectable polymers are also biodegradable which allow them to be used in the application for bone regeneration as the implant is resorbed by the body to form new bone tissue in its place [71]. They can also serve as a therapeutic drug delivery system as they can encapsulate and carry drugs to the targeted site to promote bone regeneration and osteogenesis [71]. However, the characteristics of injectable polymers influence their use in different applications.

A clear aspect of understanding the functionalities of injectable polymers lies in the properties of both, polymer precursors and resulting polymer network. The main characteristics of polymer precursors include viscosity which determines its flowability and ability to fill complex bone defects; reactivity, which influences the polymerization kinetics and curing time; and

solubility, which affects its compatibility with biological environments. Additionally, the monomer should also possess biocompatibility and low toxicity to ensure safety during and after administration in the body. Viscosity of the polymer precursor is crucial as optimal shear-thinning properties are desirable to ensure polymer injectability through a syringe or catheter while maintaining its structural integrity and localization at injection site, i.e. self-healing. Previously, Uman *et. al*, Samimi Gharaie *et. al*, Zandi *et. al* and Bertsch *et. al* studied the high shear-thinning properties among the polymers which bind or crosslink through physical interactions (electrostatic interaction, hydrophobic interactions, ionic interactions, hydrogen bonding etc.) and dynamic covalent bonding (e.g. Schiff base, reversible Diels-Alder, disulfide bonds, and oxime chemistry) [72–75]. Later on, Chandel *et. al* synthesized the polymer precursors with strong shear-thinning properties composed of diazirine-modified hyaluronic acid (HA-DAZ) and dendritic polyethyleneimine (DPEI) which crosslinks under UV light through amide linkage and other physical interactions [76]. Moreover, the resulting polymer network must possess good mechanical strength to prevent stress shielding and promote the remodeling of new bone tissue; degradation rate, which should be tailored to match the rate of new bone formation to avoid premature resorption or prolonged presence; and porosity, which could facilitates cell infiltration, nutrient diffusion, and vascularization. These properties are tunable and can be controlled easily by the appropriate selection of monomer type and their combination [77].

A recent approach comes up with the idea of injectable polymers as 4D materials combining the minimally invasive delivery with advanced healing capabilities. These materials can respond to physiological stimuli, leading to controlled and time-dependent transformations that enhance bone healing. Mainly, acrylate-based compounds have been used as bone grafts due to their high mechanical strength and good biocompatibility as mentioned previously. These compounds are light-sensitive and crosslink on exposure to specific wavelength for a specific range of time. However, polymerization method using chemical or thermal initiators is usually slow and also, non-degradable diluents make it inefficient for clinical usage. That's why, photocrosslinking has been evolved as a solution which is a single paste formulation and have control over setting reaction by exposing it to specific wavelength of light in a short range of time [78]. This process involves free radical polymerization mechanism and is more energy efficient,

faster and easier to handle [79]. However, these polymers responding to physiological stimulus like temperature and pH, including light, have been used in bone regeneration. **Table 3** provides some examples of such injectable polymers used as 4D materials for bone repair.

Table 2. Selected examples of injectable systems sensitive to different external stimuli

External Stimulus	**Injectable Polymer based materials**	**Physiological Studies**
light	Gelatine methacrylate (GelMA)	Lim et al. [80] found that visible light-crosslinked gelatin hydrogels exhibit enhanced mechanical properties and improved light penetration depth, making them suitable for creating injectable, light-responsive polymer systems. Their study demonstrated that these hydrogels support cell viability and functionality, which is critical for bone repair applications where precise spatial and temporal control of material properties is needed [81].
	Poly(ethylene glycol) dimethacrylate (PEGDMA)	Unagolla *et al.* [82] prepared PEGDMA-based 3D printed light-sensitive scaffold which showed enhanced mechanical strength similar to trabecular bone. Their *in vivo* and *in vitro* studies proved good biocompatibility and bioactivity and also enhanced adhesion and osteogenic differentiation.
pH	Chitosan (CS)-based hydrogel	King *et al.* [83] found out that CS based hydrogels have shear thinning and self-healing properties facilitating minimally invasive injection. These hydrogels are designed to support bone healing by subsequent gelation, transitioning from solution at lower pH to a gel at physiological pH
	Poly(ethylene glycol)-modified alendronate (PEG-ALN)	Matsui *et al.* [84] founds that PEG-ALN responds to acidic pH and selectively accumulates at fracture site promoting bone healing. It has the potential to be a versatile treatment for intractable fractures as, it induces bone formation and inhibits bone resorption at inflammatory phase.

temperature	Polyurethane (PU)-based composites	Park *et al.* [85] found that polyurethane-silica hybrids are tough and biodegradable and ideal for injectable, thermosensitive bone repair applications. This material had demonstrated excellent mechanical strength, biodegradability, and biocompatibility, supporting cell adhesion and osteogenic differentiation.

4.3. Mechanism of Action of Injectable Polymers in Bone Repair

The injectable polymers work through a multi-step process that mimics the natural bone healing process. They offer a minimally invasive technique for bone repair, in which material is injected into the defect site and works by forming a supportive scaffold for cell growth. Afterward, polymer degrades timely to be replaced by new forming bone tissue. Additionally, certain polymers could transfer growth factors for improved healing and encourage cell growth on their surface, a process known as osteoconduction. In certain cases, they even promote vascularization, the formation of new blood vessels, which supplies essential nutrients for a successful repair. This mechanism is shown in **Figure 8** and explained in details with following steps:

4.3.1. Delivery

The injectable polymer solution, usually precursor formulation, is injected into the defect site by using injection tools. This solution conforms defect site and crosslink upon injection, enhancing control over scaffold formation [86]. A recent breakthrough in biomaterial research has been introduced, exploring stimuli responsive materials that gel upon some physical stimuli like light, temperature, pH, chemical signals, enzymes, or mechanical stress [81,87]. This *in situ* gelation method involves triggering gel formation within the body using external factors, e.g. light sensitive polymers are injected and it crosslinks within the body on exposure to specific light wavelength enabling precise, localized gelation. This method can enhance the control over conformation and scaffold behavior [81].

4.3.2. Scaffold Formation

The injected solution undergoes self-assembly or curing reaction to crosslink the polymer forming a 3D scaffold. The scaffold is designed to resemble natural trabecular bone extracellular matrix that can provide mechanical support and have interconnecting microporosity which gives a favorable environment for cell attachment, migration, proliferation, and differentiation [86]. It allows the mass transport of oxygen, nutrients, and cellular infiltration throughout the scaffold [88]. Nowadays, 4D bioprinting is extensively used to produce channels in the scaffold, using sacrificial polymers, for vascularization and mass transfer [89]. Mainly, gelatin and agarose are used to fill the cavities which can then be degraded using external stimuli like heating in this case [90].

4.3.3. Cell Recruitment and Differentiation

After the scaffold is formed, its gradual degradation occurs, allowing the formation of new bone forming cells. The optimal scaffold must degrade and resorb in line with the formation of new osteoblast cells otherwise this approach may fail if scaffold degrade at a faster rate than tissue regeneration [91]. The recruited cells differentiate into mature osteoblasts under the influence of internal cues within the scaffold and signaling from surrounding tissues. The osteoblasts then replace degrading polymer and deposit new bone matrix within scaffold pores. Certain growth factors like bone morphogenic proteins (BMPs), platelet-derived growth factors and stem cells induced in scaffold promotes bone formation and healing process[67,86,92,93]. Nowadays, the use of physical cues (light, magnetic signal, mechanic signal, electric signal, morphology, and heat) as short acting growth factors is enlightened instead of expensive other regulators, to achieve efficient bone regeneration [4].

4.3.4. Polymer Degradation and Tissue Remodeling

As previously mentioned, polymer is designed to degrade at the rate gradually transferring mechanical support from itself to the new forming bone tissues. Eventually, the polymer starts degrading and create space of infiltrating cells such as osteoblasts, mesenchymal stem cells, and endothelial cells, which are essential for bone formation and vascularization. So, the polymer is designed to resorb in the body after the regeneration of bone by natural metabolic processes[67]. It is crucial that the degrading products of polymers must be non-toxic which can help to minimize

any side effects, however it can also influence the local microenvironment, promoting osteogenesis (bone formation) and angiogenesis (blood vessel formation). Over time, polymer degrades, and new tissues start to form within the defect site changing its mechanical properties and ultimately replacing the polymer with healthy bone tissue allowing them to bear loads, which is critical for proper remodeling [91].

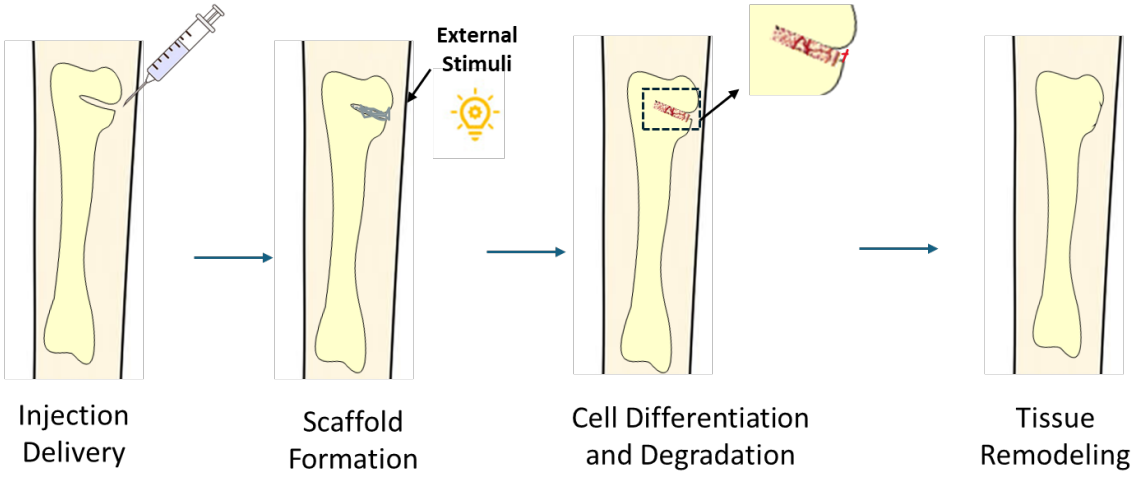

Figure 8 Schematic of mechanism of injectable polymer based bone repair

5. Clinical Studies on Injectable Polymers for Bone Repair

Injectable polymers being an advanced research has been studied now clinically in many applications. For example, Jiang *et al.* [94] developed an injectable polymer-based material for irregular bone defects, using bone marrow stromal cells (BMSCs) encapsulated in mechanically reinforced hydrogel microspheres. Sodium alginate, being a biocompatible material, has low mechanical strength and cell viability to support bone regeneration. In this study, the microspheres were prepared from sodium alginate reinforced with xonotlite ($Ca_6Si_6O_{17}(OH)_2$, CSH) nanowires, which provide good mechanical strength and promote bone growth along with BMSCs. The *in vitro* and *in vivo* studies on femoral condyles of rats, gave a promising approach for bone regeneration in this method [94]. Zhou et al. [95] presented a promising new therapeutic strategy for intervertebral disc degeneration (IVDD) using immune-defensive microspheres. These microspheres target the inflammatory cascade, a key driver of IVDD progression, offering

a potential breakthrough compared to current treatments that primarily focus on pain management. The developed microspheres have shown potential to effectively entrap inflammatory factors and promote biomechanical properties along with the regeneration of nucleus pulposus, the disc's jelly like center. However, these microspheres are more likely focused on short term effects and still need to be tested on animal models for *in vitro* studies [95]. Injectable polymers have also been used in dentistry as bioadhesive sealants. He *et al.* [96] prepared injectable biocompatible sealants for post-extraction bleeding and alveolar bone regeneration in dental surgery. They used tetra poly(ethylene glycol) (PEG) hydrogel, composed of tetra-armed PEG succinimidyl succinate and tetra-armed PEG amine, which easily crosslinked on injection and form *in situ* hydrogel. In their studies, they made comparisons with gelatin sponge, usually used for wound extraction, which in contrast showed poor performance in hemostasis, wound healing, and bone regeneration. On the other hand, tetra-PEG hydrogel had shown efficient results in hemorrhage control, good biocompatibility, better adhesion, rapid gelation, good mechanical strength, and appropriate degradation rate. The *in vivo* study on the rat tooth extraction model also proved that this material is even suitable for patients having anticoagulant drugs [96].

6. Conclusions and Future Trends

In this article, some advancements in injectable polymers mainly in bone repair has been highlighted. They offer significant advantages like minimal invasiveness, conformability to irregular bone defects, and also bioactivity through the incorporation of growth factors. As discussed previously, their properties can also be tailored to mimic the porosity and mechanical strength of trabecular bone as a temporary scaffold. Regardless of these facts, the highly porous structure of trabecular bone makes it still very challenging to possess good mechanical strength in load bearing regions.

Hydrogels mimicking the extracellular matrix in the body have been very commonly used in tissue engineering because of their high porosity and excellent biocompatibility, but their big challenge is to provide sufficient mechanical support and create isotropic network structure. They also show weak tissue adhesion and lacking bone conductivity[97]. Some innovations like incorporation of bioactive fillers, such as calcium phosphate nanoparticles or ceramic materials,

have been made to address the issue of immediate mechanical strength [98] and the incorporation of human mesenchymal stem cells (HMSCs) have enhanced *in situ* bone regeneration [99] [100]. However, hydrogels still lack the necessary mechanical support for load bearing areas in case of trabecular bone.

Therefore, a promising direction can be development of injectable materials prepared by photocuring using various precursors (***Figure 9***). Injectable polymers, such as UV-cured elastomers can provide good mechanical properties and controlled degradation rate due to incorporation of liable functional groups sensitive to enzymes or hydrolytic cleavage. However, they are less porous compared to hydrogels thus requiring further modification for porosity induction. Furthermore, their high viscosity can be a challenge. Therefore, a promising approach is to combine the best features of hydrogels and elastomers, creating hybrid systems like supramolecular networks that balance mechanical strength, bioactivity, and controlled degradation for optimal trabecular bone repair. Continuous research in this field is essential to further optimize these materials and enhance bone regeneration outcomes.

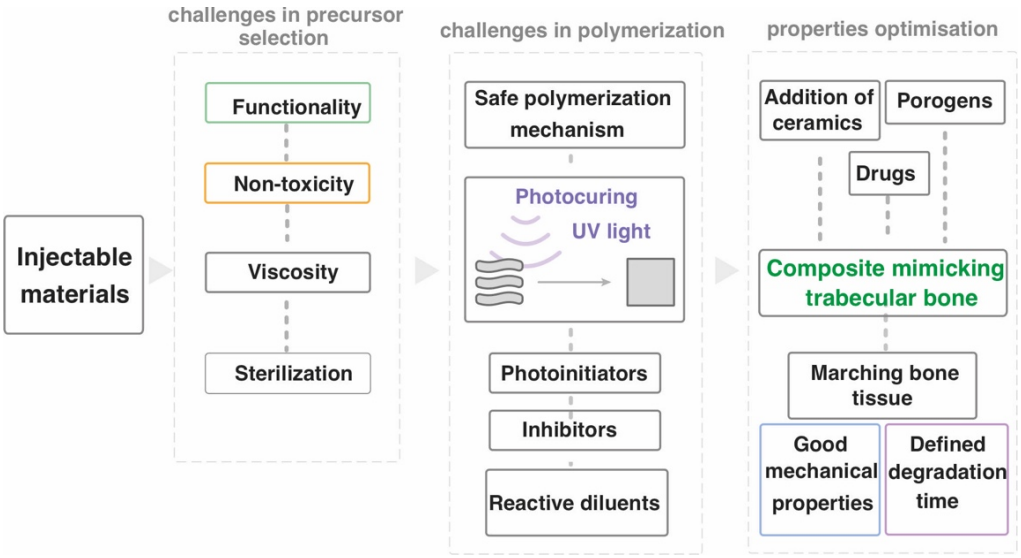

Figure 9 Challenges in injectable materials development for bone tissue repair.

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The manuscript was written through contributions of all the authors. All the authors have given approval to the final version of the manuscript.

Notes

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