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Review Article

Recent Progress in Stimuli-Responsive Hydrogels Application for Bone Regeneration

Hamza Abu Owida and Feras Alnaimat

Medical Engineering Department, Faculty of Engineering, Al-Ahliyya Amman University, Amman 19328, Jordan

Correspondence should be addressed to Hamza Abu Owida; h.abuowida@ammanu.edu.jo

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Bone defects have recently surfaced as an important topic to discuss in orthopedic clinics, and as a result, they have captured the attention of the biomedical community as well as the general public. Because of their unique characteristics, such as high water content, softness, flexibility, and biocompatibility, hydrogels are gaining more and more traction in the field of tissue regeneration research within the medical industry. Intelligent biomaterials, like hydrogels, are much better than their predecessors because they can respond to new stimuli on multiple levels, such as the physical, chemical, and biological. Because they are sensitive to different outside cues, like shape in three dimensions and conditions between solid and liquid phases, they show certain traits. This indicates that they have the capability of developing into a more efficient material in the future, which would make them better suited to facilitate the localized repair of bone lesions. This article takes a look at hydrogels that alter their shape in response to the environment they are in. Some of the topics covered in this article include the classification of these materials, the concepts that underlie their synthesis, and the current state of research in this potentially fruitful field. This research was conducted with the intention of finding novel ways to treat severe bone defects.

1. Introduction

Large bone deficiencies are typically the result of trauma, congenital abnormalities, and tissue removal due to cancer [1, 2]. These defects can be either small or large, and they always require an efficient and secure treatment to restore bone tissue. Bone grafting has traditionally been the therapy of choice for bone abnormalities [3]. The restricted availability of autologous bone grafts [3], high treatment costs [4], danger of immunological rejection [5], difficulties in bone handling technologies [6], and the possibility of infection and consequences [7] have all contributed to the limited success of bone transplantation [3–7]. The current state of the art in treating bone defects is inadequate to provide adequate care for patients [8]. Tissue engineering is an interdisciplinary study of how to repair and regenerate injured or diseased tissues using artificial or naturally occurring biological materials. When attempting to repair damaged tissue, the standard approach in tissue engineering is to employ stem cells to produce new cells [9, 10]. In this situation, distinct scaffolds serve as anchoring points. Successful bone tissue regeneration requires the identification of a scaffold that can act as a temporary replacement for the injured tissue, adjust its biological processes to match those of the host tissue, have adequate porosity, and allow for the passage of a sufficient quantity of individual cells. Furthermore, the scaffold needs to decay naturally within the host tissue [11–13]. The proposed biomaterial needs to be compatible with the host's tissue while also reducing the risk of an adverse immunological response. As an added bonus, the scaffold should be able to contain and regulate the release of medicines or proteins [14, 15], all while providing appropriate mechanical strength to the bone defect site [16].

It is commonly recognized that osteocytes, osteoblasts, and osteoclasts, collectively referred to as fundamental multicellular units, make up the process of bone defect repair [17]. Bone marrow stromal cells (BMUS) stimulate bone resorption and repair by directly acting on the periosteum, trabecular surface, and cortical bone [18]. The extracellular matrix (ECM) and cellular milieu are important for BMUS

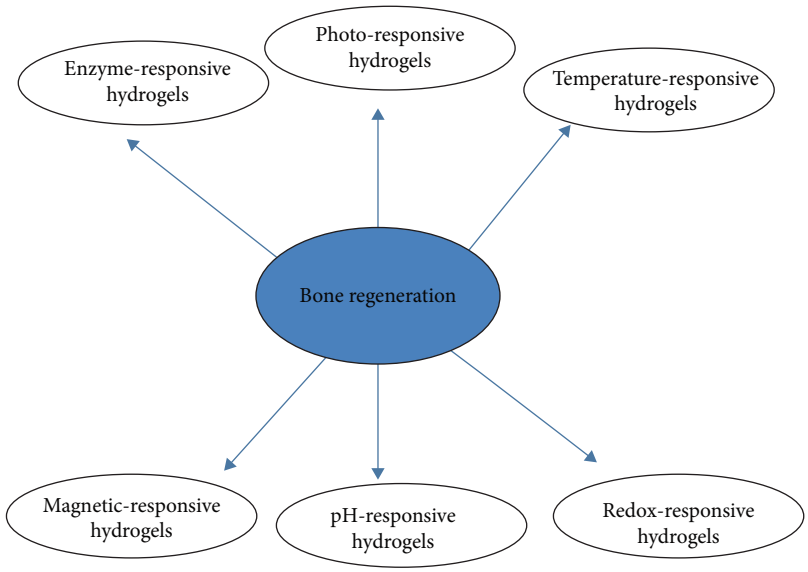

Figure 1: A schematic representation of various smart hydrogels for bone regeneration.

adherence, proliferation, and differentiation [19]. The ECM is a complex network of proteins organized in configurations that are very particular to each kind of tissue [20]. In terms of mechanics, the skeleton's ECM is found in the bones. Calcified bone tissue provides rigidity to the biomaterial, while flexibility is provided by the organic components of the extra ECM [15]. In addition to a substantial type I collagen-rich organic ECM, the calcified ECM is mostly hydroxyapatite-calcium phosphate (HAP). ECM networks govern osteoclastogenesis, osteoblast cell differentiation and proliferation, and osteocyte activity [21]. When it comes to intracellular signaling, tissue development, influencing matrix synthesis, and organizing matrix mineralization for bone remodeling, the ECM has a more vital and active function than previously appreciated. In addition, the ECM can exert its activities and functions through binding to external growth factors, ligands and receptors on cells, and proteases [22, 23].

Hydrogels are adequate scaffolds for mononuclear cells, attachment, development, growth, migration, and differentiation due to their hydrophilic nature, 3D assembly, and equivalent ECM constituents [24]. Hydrogels are amenable to simple chemical alterations and are tailored to exhibit a desirable deterioration pattern and structural stability. Hydrogels can be employed as essentially functional composites to reproduce the dynamics of natural environments [25]. Consequently, hydrogel scaffolds have seen extensive usage in the medical field of tissue repair [26] due to their distinctive qualities, including a high water content, softness, flexibility, and biocompatibility for cell adhesion, proliferation, and differentiation [27–29]. There are three main types of hydrogels, synthetic and natural hydrogels, both of which are classified by the origin of their gel components. First, synthetic polymers make up the bulk of the classic polymer hydrogel's ingredient list [30]. One of the main reasons they have not been more widely used is because their synthesis is complicated, they require a lot of energy, they're expensive, they slow down the bone regeneration process, and their elastic modulus does not change to suit the needs of the microtissue environment [30, 31]. Furthermore, standard hydrogel molding cannot accurately fill uneven fault sections, and its efficacy is both static and patient-dependent, making it unsuitable for the remediation of big, complex bone injuries. Due to these flaws, its use in repairing bone abnormalities is severely restricted. However, biocompatibility, biodegradability, nontoxicity, and acclimatization make natural hydrogels desirable. These natural polymer hydrogels can be manufactured on a large scale after undergoing extensive purification, fermentation, and other procedures while retaining their original biocompatibility and high biodegradation performance [30, 32]. To harness the advantages offered by natural and synthetic hydrogels, researchers have sought to integrate natural biopolymers with synthetic polymers. Hybrid hydrogels, alternatively referred to as semisynthetic or seminatural hydrogels, are widely favored due to their ability to combine the advantageous characteristics of both natural and synthetic polymers. The hydrogel possesses the ability to exhibit both mechanical and biological activity due to its composition, which encompasses both synthetic polymer material and natural protein components [30, 33].

Physically responsive hydrogels, chemically responsive hydrogels, and biochemically responsive hydrogels are the three primary classifications of hydrogels based on the nature of the stimuli they are able to respond to Fan et al. [34]. Since Wichterle's seminal article [32] was published in 1960, hydrogel has been included in bone injury restoration and has progressed from an inactive hydrogel to a sophisticated, changeable, and regulated "smart" gel with responsive features. Due to its responsiveness to physical, chemical, and biochemical stimuli (Figure 1), its capacity to convert its shape, produce injectability, and demonstrate soul remodeling and shape memory attributes, it is becoming an increasingly popular scaffold material in bone tissue repair. In order to make hydrogels that react to stimuli, polymer molecular chains can be engineered. The swelling and degrading

behavior of hydrogels can be controlled by varying the hydrogels' response to external environmental stimulation [35]. The ability of stimulus-responsive hydrogels to gel and degrade in response to their environment has broad applications in bone tissue repair. Hydrogel degradation allows cells to proliferate, differentiate, and secrete ECM at a steady rate, leading to the development of new tissue and, ultimately, functional bone restoration [36].

This review will begin by introducing the concept of classifying and designing smart hydrogels in response to various environmental stimuli and will then go on to discuss relevant examples of research progress using these stimuli-responsive hydrogels, with a primary focus on, but not exclusive to, bone repair applications.

1.1. Temperature-Responsive Hydrogels. Temperature-responsive hydrogels, also known as temperature-sensitive hydrogels, have the ability to undergo physical and chemical transformations from a sol state to a gel state, depending on the deviation in temperature from the ambient room temperature [36]. Hydrogels with a temperature response have hydrophilic and hydrophobic groups, as well as a shift in the process qualities that trigger at a critical solution temperature, which may lead to a shift in affinity to the solvent. The lowest critical dissolution temperature (LCST) or the highest critical dissolution temperature [37] is the temperature at which the swelling-contraction state transition occurs, also known as the sol–gel state transition. Poly *N*-isopropyl acrylamide and its derivatives are the most widely utilized LCST temperature-sensitive hydrogels for bone healing. The LCST of temperature-sensitive nanogels made from NIPAAm increases from 32 to 37°C when additional hydrophilic acrylamide (AAm) is added to the mixture. Using radical polymerization, Yoshimatsu et al. [38] produced poly(NIPAAm-*co*-AAm) copolymers and generated nanogels that ranged in size from 50 to 450 nm, and their volume phase transition temperature was between 37 and 43°C. Controlling the LCST and tissue heating processes of the nanogels allowed for targeted gel administration in animal tests using a near-infrared fluorophore. Nanogels with a temperature-sensitive coating can also be loaded with anticancer medicines. This nanogel may be used to specifically treat cancerous tumors and bone defects. As a type of bone regenerative medication, temperature-responsive hydrogel technology has been used to release various growth factors. Cell proliferation, migration, recruitment, and angiogenesis are all stimulated, and cell differentiation is modulated once growth factors have been covalently bound to injectable hydrogels.

To treat Paget's disease, postmenopausal osteoporosis, and osteoporosis caused by glucocorticoids, Nafee et al. [39] described the use of a temperature-responsive chitosan/-glycerophosphate (GP) hydrogel to efficiently distribute bone resorption inhibitors and suppress the osteoclast action. The BCS III bone resorption inhibitor alendronate (ALN) was encapsulated in a chitosan/-GP hydrogel, which exhibited temperature-reversible gelation behavior and ensured controlled ALN release over 45–65 days, resulting in a reduced inflammatory response and accelerated proliferation and maturation of the granulation tissue. Analysis at 21 days following hydrogel injection validated the system's biodegradability and biocompatibility.

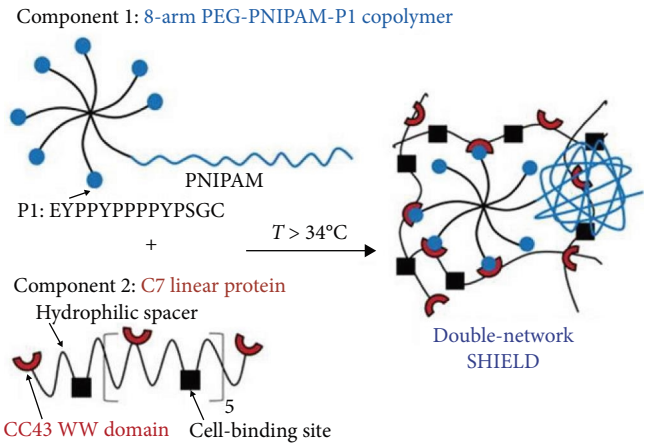

FIGURE 2: Schematic and material properties of injectable shear-thinning hydrogel (SHIELD). Component 1 is an eight-arm PEG with one arm attached to PNIPAAM and 7 to proline-rich peptide domains. Component 2 is a C7 linear protein copolymer with CC43 WW and RGD cell-binding domains.

Also typical of the LCST category of hydrogels are copolymers of polyethylene glycol (PEG) and polycaprolactone (PCL). Injectable PEG-PCL-PEG hydrogel was examined by Ni et al. [40] as a thermally induced material for bone tissue engineering with reversibility recovery during transformation from sol to gel upon addition of heat. The use of this hydrogel to repair bone tissue abnormalities had the benefits of being both noninvasive and anatomically correct. Fu et al. [41] synthesized a hydrogel by combining collagen and HAP in a poly(ethylene glycol)-poly(*ε*-caprolactone)-poly(ethylene glycol) PEG-PCL-PEG copolymer; the hydrogel's biocompatibility and increased biomimetic microstructure made it a highly effective treatment for bone defects. To facilitate the direct injection of transplanted stem cells such as human adipose stem cells and human bone marrow mesenchymal stem cells (BM-MSCs), Cai et al. [42] created a dual network hydrogel (SHIELD). When peptides are molecularly identified with one another, they can form a weak network that cushions the injection process and protects cells from shear stress (Figure 2). Increased hydrophobic contact between PNIPAAm polymer chains at SHIELD LCST (34°C) bolstered the network structure and increased the cell retention duration, creating a milieu favorable to cell proliferation, differentiation, and bone healing. Polyacrylic acid, gelatin, and so forth are examples of conventional temperature-sensitive materials. However, their limited usage in bone repair can be attributed to their high solid-state temperature, which is not friendly to implanting materials into the body or promoting bone formation.

1.2. Redox-Responsive Hydrogels. When their constituent molecules are reduced or oxidized, redox-responsive hydrogels exhibit a reaction. Hydrogels with redox properties grow as a result of redox reactions that occur through incomplete

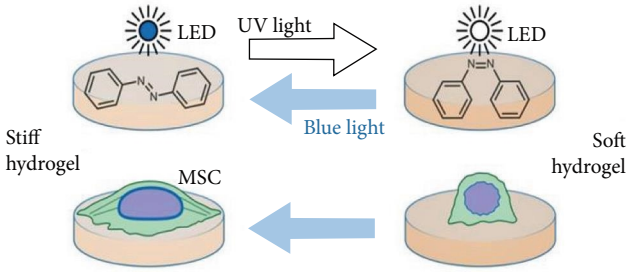

FIGURE 3: Schematic of steps to fabricate photo-responsive hydrogels with photoswitchable of cellular responses to matrix stiffening.

subunits in the polymer backbone, leading to an influx of counterions to neutralize the newly produced charges [43]. Variations in mechanical characteristics are a direct outcome of the metal ion's redox reactivity. Because they may be switched between two oxidation states—trivalent and divalent—iron ions are seen as a viable crosslinker for use in biomedical applications, granting hydrogels redox responsiveness and the ability to tune their mechanical properties. This makes up for the fact that simple hydrocoagulation and support have no mechanical qualities. For their new redox hydrogel, Papanikolaou and Pantopoulos [44] aimed to create a material that could alternate between soft (0.06 MPa) and hard (2.1 MPa) states by introducing divalent and trivalent iron ions. Hydrogel hardness modulation by a redox reaction has been shown to improve bone regeneration [45–47] because of the extensive research into the correlation relationship between metallic ions and material strength characteristics. The connection between metal ions and biomineralization has the potential to become a hot topic, but further study is needed.

1.3. Photo-Responsive Hydrogels. As a distant stimulus, light can offer temporal and spatial precision [48]. Hydrogels that can change color in response to light have a polymer network and photochromic groups. There are a variety of light conditions in which these groups break apart, undergo isomerization, or form dimers [49]. There are two types of photo-responsive hydrogels, those in which nitrobenzyl is covalently attached to the hydrogel and those in which it is suspended in a network (Irgacure 2959, phenyl-2,4,6-lithium, eosin Y, and so forth) [50–54]. In the case of the first type of hydrogels, the photochromic molecules absorb the light and transmit it to the chromophores, which in turn convert it into a chemical signal [55]. The size and mechanics of a hydrogel formed from copolymerizing sequentially bifunctional polymers with a photocatalyst of azobenzene can be modulated by exposing it to light; the light-sensitive groups in the polyacrylamide undergo light fracture, isomerization, and light dimer formation depending on the intensity of the incident radiation [56]. For instance, Lee et al. [57] photo-induced Azo-polymer—polyacrylamide hydrogel varied in stiffness with the wavelength of visible light, degraded at a rate that matched the period required for bone production, and had its biocompatibility confirmed. Cellular shape changes throughout time revealed that cells responded to increased substrate stiffness by spreading out and becoming more "squashed" in shape (Figure 3). Hydrogels like these offer a novel tool for bone tissue engineering research on mechanotransduction transcription factors and bioactivities.

Cellular mechanosignaling hypothesises that bone flaws at different sites play a role in the body's reaction to dynamical variations in rigidity. When light hits the second form of hydrogel, photoinitiators polymerize or isomerize, leading to changes in the conformation of macromolecular chain molecules and the swelling volume. Slowly preparing a hydrogel composed of methyl methacrylate and hyaluronan was described by Khetan et al. [51], who used dithiothreitol to initiate gelation of the hydrogel composed of methyl methacrylate and hyaluronan. After being swollen by Irgacure 2959's photoinitiator, the initialized hydrogel stiffened due to free radical polymerization of the residual methacrylate group. In this way, the photoreactivity of hydrogels could be used to control their physical or chemical properties. The management of photo-responsive hydrogels was enhanced by the fact that the photoreaction fraction was sensitive to particular wavelengths of light (including visible, ultraviolet, and infrared).

1.4. Enzyme-Responsive Hydrogels. In order to promote the creation or destruction of the hydrogel network, enzyme-responsive hydrogels often comprise enzyme-responsive polypeptides. Matrix metalloproteinase (MMP) [58], phosphatase, and tyrosinase [59] are all examples of naturally occurring enzymes that are either present in the organism or are abnormally strongly expressed in the lesion, and are frequently used in the construction of enzyme-responsive hydrogels. Enzyme-responsive hydrogels, used as cell and protein transporters in tissue engineering, can catalyze the disintegration of the hydrogel scaffold to promote the release of cell growth factors or to create an environment for cell proliferation and differentiation. To control the release of growth factors and stem cell differentiation, Anjum et al. [60] developed a dual-responsive hydrogel based on the ECM sugar 695 aminoglycan. Hydrogel was formed by crosslinking chondroitin sulfate (CS) with eight-arm PEG (PEG-Gln) modified by glutamine polypeptide. CS was functionalized with an MMP-sensitive glutamine transaminase factor XIII (FXIIIa)-specific lysine polypeptide sequence (TG-MMP-Lys). The hydrogel's cell adhesion capacity might be enhanced by using the cell adhesion polypeptide as a model ligand (TG-RGD-Lys). Bone marrow mesenchymal stem cells (BMSCs) were able to sustain cell viability, realize proliferation, and migrate after being encapsulated with bone morphogenetic protein (BMP-2) and hydrogels, and the released BMP-2 was able to stimulate osteogenic differentiation of the BMSCs. Because of this, a CS-PEG composite hydrogel may easily incorporate the molecular tools required to induce distinct tissues to mimic the characteristics of the extracellular environment, allowing for precise regulation of cell differentiation and tissue regeneration.

1.5. pH-Responsive Hydrogels. In chemical stimulus-responsive hydrogels, pH has received the greatest attention. The polymer hydrogels are equipped with an intelligent reaction to pH solutions due to the abundance of acidic or alkaline groups present in the hydrogels, which allow them to rapidly protonate or deprotonate the environment. Changing the proportions

of the precursor's molecules and aspartic acid can affect a hydrogel's gel lifetime and mechanical strength [61].

The polymer backbone and ion side groups in pH-sensitive hydrogels are responsible for the conversion via proton absorption and release in response to variations in pH [62]. pH-sensitive hydrogels show greater repulsive forces, ionic group identity, and volume variation at pKa or pKb. Two types of pH-responsive hydrogels exist, known as anionic and cationic, respectively, based on the charge characteristics of the charged groups they contain. Negatively charged groups can be found in anionic hydrogels, such as carboxylic acid, sulfonic acid, and so forth [63]. If the hydrogel's pH is exceeds the pKa value, the charged groups will cause it to swell. Just like a cationic hydrogel, a noncationic hydrogel will undergo a transformation when exposed to low pH (pH > pKb). In addition, some academics have mentioned that a weak polymeric electrolyte should be employed to produce the pH-sensitive hydrogels in order to mimic the natural ECM. To fine-tune the ionic strength in a weakly polymerized electrolyte and produce the desired mechanical properties, one needs to make small adjustments to the pH [64]. By including weak electrolytes at their hydrophobic ends, the pH of the pH-responsive hydrogels may be adjusted as desired [65]. Triblock copolymers were produced by Yoshikawa et al. [66] from pH-sensitive poly(2-(diisopropylamino)ethyl methacrylate) and poly(2-(methacryloyloxy)ethyl phosphorylcholine). Hydrogels with a Young's modulus of 1.4–40 kPa were easily changeable by changing the pH of the solution within a restricted medically relevant range. To alleviate the complicated pressures induced by a wide variety of bone abnormalities, hydrogels that are able to mimic the natural environment well under such conditions have several potential applications. It was shown by Rogina et al. [67] that a chitosan-HAP hydrogel could be formed using $NaHCO_3$ as a gelling agent and that the hydrogel would change its composition depending on the pH of the surrounding solution. Within 4 min, the chitosan-HAP-based hydrogel could gel with the right amount of $NaHCO_3$, showing promise as a cell transporter for cell proliferation and differentiation. Synthetic thiol-functionalized histamine was produced, then Lundberg et al. [68] used it to make a hydrogel that changed its pH depending on its environment. Hydrogels' biocompatibility in various cell lines and their enhanced hardness during the pH 5.0–8.0 range both point to potential uses in the repair of major bone lesions.

1.6. Magnetic Field-Responsive Hydrogels. Hydrogels that respond structurally and functionally to an external magnetic field are typically made up of a matrix hydrogel and magnetic components, allowing for the remote regulation of physical, biochemical, and mechanical properties. The composition, concentration, size, and homogeneity of the magnetic particles in the hydrogel determine its behavior in response to a magnetic field. The hydrogel's form is rapidly altered when exposed to a magnetic field because magnetic particles congregate, the hydrogel network contracts, and the solvent is "crowded out" [69]. Hydrogels incorporating magnetic nanoparticles have been the focus of recent research for their potential utility in bone mending. Iqbal et al. [70] produced magnetically modified Fe_2O_3 nanoparticles (m-nHAP) and then mixed them into a polyvinyl alcohol (PVA) solution to create an m-nHAP/PVA hydrogel. PVA's high mechanical characteristics, moderate biodegradability, and great biocompatibility made it a prime candidate for use in bone healing. As the amount of m-nHAP in the hydrogel grew, the pores within it grew in size, allowing for easier nutrient exchange and leading to much higher levels of osteoblast adhesion and proliferation. To improve protein adsorption, Mahdavinia et al. [71] recombined chitosan and magnetic Fe_3O_4 to create magnetically sensitive gel microspheres. Researchers frozen and thawed the mixing solution multiple times before obtaining the final gel sample after first fixing the Fe_3O_4 in place in an inorganic thickening liquid. Since the magnetic material was incorporated into the gel microspheres, the results demonstrated a maximum adsorption capacity of 240.5 mg/g.

Also crosslinked magnetic nanoparticles with chitosan after mixing Fe_3O_4 with carrageenan on site [72]. Significant effects on the hydrogel's multiple properties were observed after magnetic particles were introduced into a carrageenan/chitosan complex, with results indicating that the gel's water absorption and encapsulation rate towards the model drug both increased as the magnetic particle content did. A further uncharted territory is the union of xanthan gum with chitosan. With the help of glucuronic acid, they can self-assemble into a magnetically sensitive polyelectrolyte hydrogel [73]. Fibroblast proliferation and adhesion capability on the gel were found to be greatly increased in the presence of an external magnetic field. The mechanical strength and rheological energy of the gel can be greatly enhanced by the incorporation of magnetic nanoparticles (increased energy storage modulus). So, this magnetically responsive hydrogel may find use in treating bone defects.

Hydrogels need to have anisotropy for use in tissue engineering, and magnetic materials have been suggested as potential agents to accomplish this. Due to their magnetic properties, magnetic nanoparticles can be used as magneto-mechanical remote actuators to manipulate the activity of cells contained within hydrogels. There may be a variety of benefits to bone tissue engineering techniques that benefit from the integration of magnetic materials and the subsequent application of magnetic fields. Anisotropic magnetically responsive scaffolding materials can be designed with the help of magnetic nanoparticles, which first give biomaterials the visual anisotropy found in real bone tissues. Magnets at the interaction between cells and polymer composites can trigger specific receptors, increasing cellular activity and encouraging bone production and matrix incorporation [74–76]. Overall, magnetic hydrogels with anisotropic structures not only provide a controlled environment for cell function but also an ordered 3D template in which the intricate architectural characteristics of original tissues can be recreated. Therefore, there are specialized approaches to the research and production of magnetically sensitive hydrogels with the necessary architectural features to accurately replicate various anisotropic tissues [77]. Hydrogels loaded with supersaturated medications that respond to magnetic fields may be attached

to injured bodily tissue for regulated, localized discharge to promote bone healing. Magnetic nanoparticles from hydrogel-based scaffold breakdown may be hazardous. Tendons and tendon-to-bone interfaces are just two examples of additional tissues that can have their main physicochemical properties mimicked using these stimulus-responsive hydrogels. Echave et al. [78] created a multiphasic hydrogel system based on gelatin, each phase of which has its own unique composition and microstructure. Bone and tendon-like structures were created by incorporating HAP particles or cellulose nanocrystals (CNC) into an enzymatically crosslinked gelatin network, respectively. Mineralized particles added stiffness to the hydrogels created, and the magnetic alignment of CNC led to the development of anisotropic structures. Human adipose-derived stem cells had their biological commitment to the tendon-to-bone interface evaluated, and the results showed aligned cell growth and increased synthesis and deposition of tenascin in the anisotropic phase, indicating the potential versatility offered by the gelatin-transglutaminase.

2. Conclusions and Outlooks

As a novel category of intelligent biomaterials, hydrogels that may react to a variety of external physical, chemical, and biological stimuli, such as light, temperature, pressure, electric field, and magnetic field, are now under development. Emerging scaffold materials, controlled stimulus-sensitive hydrogels are widely employed for bone injury healing in tissue repair due to their advantageous combination of extreme hydrophilicity, good biocompatibility, and responsiveness to external stimuli.

In recent years, a considerable body of literature has emerged, comprising numerous studies on hydrogel scaffolds. These studies have primarily concentrated on exploring the potential of chemical or physical stimuli to facilitate the regeneration of damaged bone tissue and their application in the biomedical field. Hydrogels exhibit a range of desirable properties such as flexibility, adaptability, responsiveness to stimuli, and a soft structural nature, rendering them very versatile materials suitable for diverse medical applications. Conversely, the remarkably elevated water content, porous characteristics, and smooth texture have a closer resemblance to real tissue compared to any other available biomaterials. The notable resemblance seen between hydrogels and other materials presents several opportunities for possible uses within the realm of biomedicine. Hydrogels possess a notable presence in our daily utilitarian artifacts, yet, their complete range of prospective uses remains unrealized. Hydrogels have demonstrated significant involvement in the wound healing process, alongside their utilization in the advancement of contact lenses, tissue engineering, and diverse hygiene goods. However, there has been a lack of comprehensive research on commercially accessible hydrogels in the domains of tissue engineering and drug delivery. Over time, numerous devices and scaffolds pertaining to drug delivery have been developed, assessed, and in certain cases, obtained patents. However, it is worth noting that only a limited proportion of these innovations have successfully reached the commercial market. This examination primarily focuses on the study of hydrogel-based biomaterials and their applications in various fields such as wound healing, tissue engineering, cosmetics, medicine administration, and contact lens manufacture [30].

The hydrogel scaffolds were fabricated using a range of physical and chemical triggers. These substances performed admirably in the treatment of bone problems. In the case of an injury that needs quick attention, for instance, a novel hydrogel synthesized via light activation under mild conditions could be used. The exceptional compatibility of a robust hydrogel with a double crosslinking network with hard bone tissue is not the only benefit of this material. The injectability of thermally responsive hydrogels also makes them a promising candidate for use in the minimally invasive surgical treatment of bone problems. Numerous studies and applications of smart techniques have resulted in the development of novel hydrogels amenable to application in bone tissue formation, with consideration given to a wide variety of trigger scenarios. Biodegradable and biocompatible hydrogels can be designed and manufactured with the help of new polymers, easing biocompatibility worries. To repair small hole defects after microfracture surgery, injectable hydrogels made of polymers with thermally responsive chains have been produced. In order to achieve desirable therapeutic outcomes for certain bone diseases, drug-loaded devices are constructed using a variety of delivery types.

In the present review, the authors aim to focus on the potential of hydrogels, which are chemically or physically stimulated, to facilitate the regeneration of bone tissue that has been injured. This review specifically focuses on the classification, design principles, and research advancements of stimulus-responsive hydrogels. These hydrogels are based on different types of external environmental stimuli and their advantages and disadvantages are discussed. The objective of this review is to present novel concepts and methodologies for the repair of complex bone defects.

The field of tissue engineering has provided important strides in bone over the past few decades; however, there is still a way to go before we attain native-like bone tissue. Artificially produced healthy tissue and organ replacements have the ability to significantly alter medical practice. Particularly, the following three points still require extra attention. For tissue-engineered scaffolds, it is possible to create hydrogels with biocompatible composition and stimulus response. The hydrogel can optimize its reaction by selecting the most suitable strategy, taking into account the specifics of its surrounding environment. Further research into precision fabrication and individualized medicine treatments for unique difficulties will allow for the engineering of biomaterials with exact structures and specialized functionalities.

In the foreseeable future, there remain numerous unresolved challenges in hydrogel design that must be addressed to effectively meet therapeutic requirements. Numerous hydrogel variants have been investigated in animal models, although the translation of these findings into practical applications in the human model remains limited.

Table 1: The benefits and drawbacks of different types of responsive hydrogels in bone regeneration.

Stimuli-responsive hydrogels types	Benefits	Drawbacks	Reference
Temperature-responsive hydrogels	Capability of injection; heightened specificity with reduced toxicity; support and sustain' health while decreasing the financial burden of their treatment	Unsatisfactory reactivity; little dissimilarity between diseased and healthy tissues	[37, 39, 40]
Redox-responsive hydrogels	Bone healing facilitated by redox-responsive drug release; the correlation between metal ions and mechanical properties of hydrogels	As the differentiation between diseased and healthy tissues is so slight, their use is constrained	[31, 42, 79]
Photo-responsive hydrogels	Very little risk of adverse effects on humans spatial and temporal regulation of medication release independent of physical contact with the lesion	Due to the inability of ultraviolet or visible light to permeate tissue, their use is restricted to in vitro systems and superficial skin treatments	[31, 53, 56]
Enzyme-responsive hydrogels	Cell proliferation and differentiation are facilitated by the release of biofactors, which are caused by structural changes and rapid breakdown in response to certain enzymes	Weak peptides activity and low half-life limit the long-term use	[31, 59, 60]
pH-responsive hydrogels	A problematic tissue, such as one with inflammation, infection, or cancer, will have a pH that is different from that of a healthy tissue	It's possible that unfavorable tissue reactions could arise from clinically predicting pH value at sick regions	[62–64]
Magnetic-responsive hydrogels	Targeted treatment is possible through the use of magnetic fields in the environment to guide the transport of drugs in a diseased state in a certain direction	In some cases, living organisms could be harmed by the magnetic nanoparticles' potential toxicity	[69, 71, 72]

To ascertain the suitable osteogenic index, hydrogel materials are commonly introduced into the subcutaneous tissue. Nevertheless, this approach lacks the ability to accurately represent the specific microenvironment of a bone lesion. The combined influence of the uncertain degradation rate in vivo and the interaction between vehicles and bioactive molecules will collectively influence the dynamics of drug release, consequently affecting the overall therapeutic effectiveness. One of the primary obstacles that must be surmounted before the utilization of hydrogels in therapeutic contexts pertains to their limited capacity for convenient storage.

Hydrogels that possess a water component are prone to structural damage during the processes of storage and transportation, potentially resulting in the subsequent release of the enclosed medication. Despite the existence of numerous bioactive hydrogel systems designed for bone tissue regeneration, the development of an affordable, adaptable, and easily manipulable approach for creating commercially viable hydrogels remains elusive. In this particular context, it is expected that a comprehensive comprehension of physical and chemical processes is necessary for the effective utilization of regenerative materials pertaining to bone regeneration. This understanding is crucial for the right development of hydrogels. Significantly, doing research on the fundamental principles governing material-biological interactions can provide valuable inspiration for enhancing biomimetic hydrogels, hence facilitating the integration between materials and organisms.

To conclude, the main factor and greatest challenge in the field of bone lesion restoration will be the development of the hydrogel matrix with appropriate degradation efficiency, mechanical characteristics, and capillary bioactivity; for instance, the creation of extremely sensitive hydrogels that can be governed by using extremely weak external cues after implantation to prevent the potential of harmful effects or threats with some useable but detrimental native implants. Since the changing microenvironment after biomaterial implantation has a significant effect on bone development, it is important to track the body's material changes in real time. It is anticipated that as bone tissue engineering advances, stimulus-responsive hydrogels will rapidly develop to provide additional solutions for the therapeutic treatment of bone abnormalities and comprehend a change in medical consequences. The benefits and drawbacks of different types of responsive hydrogels are outlined in Table 1.

Data Availability

The data that support the findings of this study are available on request from the corresponding author.

Conflicts of Interest

The authors declare that they have no conflicts of interest to report regarding the present work.

Authors' Contributions

Hamza Abu Owida devised the project, the main conceptual ideas, and the proof outline. Feras Alnaimat drafted the manuscript with formal analysis and designed the figures. Hamza Abu Owida and Feras Alnaimat have read and agreed to the guidelines of the journal.

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