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REVIEW
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3D bioprinted hydrogel systems for mesenchymal stem cell delivery in chronic wound healing: emerging strategies and clinical potential

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Abstract

The healing of chronic wounds, particularly diabetic ulcers and burns, remains a complex clinical challenge due to prolonged inflammation, excessive oxidative stress, and disruptions in the normal interaction between cells and the extracellular matrix. Mesenchymal stem cells (MSCs), particularly those isolated from adipose tissue, demonstrate significant therapeutic potential due to their immunomodulatory, anti-inflammatory, and angiogenic properties. However, their direct injection into a wound is ineffective due to low cell survival in the inflammatory environment and rapid washout.

The aim *of this narrative review is to summarize current advances in optimizing the delivery of MSCs to chronic wounds, specifically to evaluate the use of hydrogel scaffolds and 3D bioprinting technologies to ensure cell viability and maximize their regenerative potential.*

Materials and methods. *The narrative review is based on an analysis of in vitro and in vivo research results. The use of hydrogels based on natural polymers (alginate, collagen, hyaluronic acid) as scaffolds for MSCs isolated from adipose tissue was evaluated. The application of 3D bioprinting technologies was also considered for the creation of three-dimensional biocompatible structures.*

Results. *The analysis revealed that 3D polymer networks effectively mimic the extracellular matrix and protect cells from the effects of reactive oxygen species. The application of encapsulated MSCs in a hydrogel matrix ensures a stable and sustained release of bioactive substances. A clear tendency towards a significant acceleration of epithelialization processes, stimulation of angiogenesis, and increased collagen deposition in the wound was observed compared to direct cell delivery methods.*

Conclusions. *The utilization of hydrogels and 3D bioprinting technologies for the encapsulation of MSCs is a promising strategy that overcomes the problem of low cell viability. Such scaffolds support cell proliferation and differentiation, facilitating rapid and complete tissue regeneration with minimal scarring.*

Keywords*: chronic wounds; mesenchymal stem cells; hydrogels; 3D bioprinting; regenerative medicine*

Introduction

Pathophysiology of wounds: diabetic wounds and burns

Wound healing is a complex dynamic process involving various cellular and biochemical processes, including dermal collagen remodeling and scar formation, which are

two important aspects of tissue repair [1]. The process consists of several key stages, namely inflammation, proliferation, matrix formation, and remodeling, which are regulated by various cells, growth factors, and cytokines, which in turn play an important role in each of these phases. There is a natural mechanism for healing simple wounds; however, chronic wounds caused by diabetes, burns, or cancer rarely heal on their own [2, 3].

Diabetic wounds (DWs) are a common complication of diabetes, affecting approximately 25 % of patients and often leading to lower limb amputation, which creates a significant economic and psychological burden [4, 5]. Unlike normal healing, DWs are characterized by a chronic delay in the inflammatory phase due to elevated levels of reactive oxygen species (ROS), cellular dysfunction in the wound microenvironment, and impaired immune function. ROS induce the expression of extracellular matrix (ECM) degradation enzymes, which break down the ECM, thereby hindering the normal interaction between the matrix and cells necessary for wound healing. In addition, the balance between collagen production and degradation is disrupted, further impairing the wound healing process [2, 4].

Burn injuries also represent a significant clinical problem. According to the World Health Organization (WHO), approximately 11 million people suffer burns each year, making them one of the most common types of injury [6]. Unlike mechanical injuries, burns are dynamic and can progress over time, primarily due to apoptosis and as a result of complex, interrelated pathophysiological mechanisms, such as prolonged excessive inflammation, oxidative stress, and impaired tissue perfusion. The pathophysiology of a burn includes a coagulation zone (irreversible damage) and a stasis zone, which is initially viable and potentially salvageable but is in a state of ischemia. Immediate therapy is aimed at saving this specific zone to prevent the wound from deepening due to apoptosis, excessive inflammation, and oxidative stress. New interventions are needed to reduce inflammation and promote wound healing with minimal scarring [7].

To address these issues, new treatment methods are needed that aim to reduce inflammation and promote wound healing with minimal scarring. Therefore, the objective of this review is to identify effective methods for optimizing the delivery of mesenchymal stem cells to the wound microenvironment to ensure their survival and the realization of their regenerative potential. In particular, this review evaluates the use of hydrogels based on natural polymers and 3D bioprinting technologies as promising cell therapy strategies for the treatment of chronic wounds.

Materials and methods

This study is structured as a narrative review. The aim was to summarize current advances in the development of hydrogel scaffolds, as well as in the application of 3D-bioprinted structures for the delivery of mesenchymal stem cells in the treatment of chronic wounds. We used the PubMed and Scopus databases to find relevant literature. To access the full texts of the articles and broaden the scope of our search, we used the platforms of individual publishers, such as ScienceDirect and SpringerLink. We primarily analyzed articles published in recent years to reflect current trends in this field. We formulated the search query using the following terms and their combinations: “mesenchymal stem cells,” “AD-MSCs,” “hydrogels,” “3D bioprinting,” “chronic wounds,” “diabetic ulcers,” and “burns.” We included English-language peer-reviewed articles that presented original results from in vitro and in vivo studies, as well as review articles on related topics.

Mesenchymal stem cells: characteristics and mechanisms of action

Mesenchymal stem cells (MSCs) are multipotent progenitor cells capable of differentiating into osteoblastic, chondrocytic, and adipocytic cell lines [8, 9] (Fig. 1). According to the standards of the International Society for Cell Therapy (ISCT), MSCs must express the cluster of differentiation (CD) markers CD73, CD90, and CD105 and must not

express CD14, CD19, CD34, CD45, CD11b, and human antigen DR (HLA-DR). They can be obtained from various sources: bone marrow (BM-MSCs), adipose tissue (AD-MSCs), and the umbilical cord [3, 8, 9, 10].

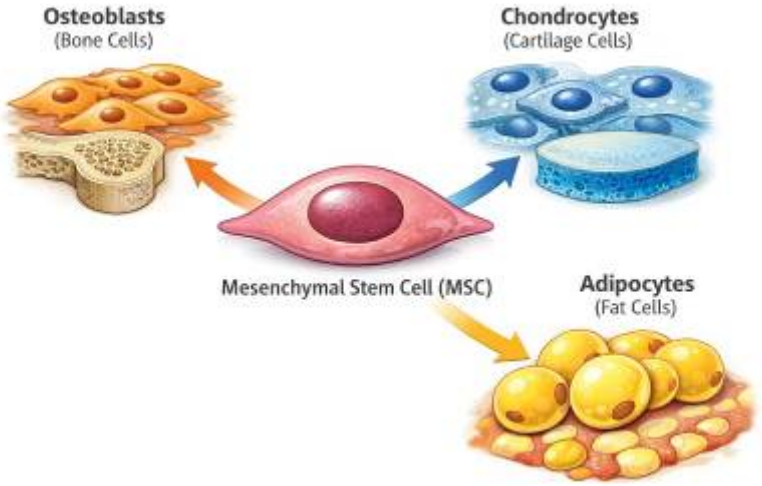

Fig. 1. *Differentiation of mesenchymal stem cells (MSCs) into osteoblasts, chondrocytes, and adipocytes.*

AD-MSCs derived from subcutaneous adipose tissue are particularly interesting because their harvesting is less invasive (e.g., via liposuction) compared to the isolation of stem cells from bone marrow , they are available in large quantities, have the ability to proliferate rapidly, and do not raise ethical concerns [1, 10, 11]. This specific type of cell possesses immunosuppressive, anti-inflammatory, and angiogenic properties due to the paracrine release of soluble mediators. They have a limited replication lifespan, which reduces the risk of malignancy compared to embryonic stem cells and induced pluripotent stem cells (iPSCs) [10]. According to the study by Zampar et al. [12], it was shown that among the proposed sources, the back area provided the highest concentration of AD-MSCs. Studies show that AD-MSCs are genetically more stable in long-term culture and less immunogenic compared to BM-MSCs, while their wound-healing efficacy is equivalent [11]. It is important to note that AD-MSCs do not change with the donor's age, and a small volume of adipose tissue contains a high concentration of these cells; they do not elicit an immune response and do not cause a "graft-versus-host" reaction [13].

Mesenchymal stem cells are involved in all phases of the wound healing process, regulating the inflammatory response and reducing the severity of scarring due to their immunomodulatory properties. The primary therapeutic effect of MSCs is mediated primarily through paracrine mechanisms, specifically the secretion of a wide range of cytokines, chemokines, and growth factors [3, 8]. It has been established that MSCs produce over 30 biologically active molecules, including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), hepatocyte growth (HGF), interleukins (IL) such as IL-6, and IL-10; the last of which plays an important role in suppressing excessive collagen formation, inhibiting neutrophil migration to the site of injury, and reducing the production of reactive oxygen species.

Thus, MSCs not only modulate inflammation, fibrosis, and scarring processes but also stimulate angiogenesis and granulation tissue formation, exhibit antimicrobial properties, and contribute to ROS neutralization by binding free radicals. In addition, these cells reduce levels of pro-inflammatory cytokines, particularly IL-1 and tumor necrosis factor alpha (TNF-α), which helps regulate the inflammatory process, and also enhance the migration of fibroblasts

and keratinocytes [8, 10, 14].

Exosomes derived from MSCs also demonstrate significant therapeutic potential, including the ability to reduce scarring and accelerate wound healing. Preliminary studies of their use in atopic dermatitis have shown a reduction in symptom severity, associated with decreased expression of pro-inflammatory cytokine mRNAs (IL-4, IL-23, IL-31, and TNF-α) in *in vivo* experimental models. Furthermore, following subcutaneous administration of exosomes derived from AD-MSCs in an oxazolone-induced dermatitis model, reduced levels of IL-5, IL-13, TNF-α, interferon gamma (IFN-γ), and IL-17 were observed [10, 15].

Intravenous administration of AD-MSC exosomes into a mouse skin model demonstrated the ability to remodel the extracellular matrix by altering the ratio of collagens or transforming growth factors (TGF). AD-MSC-derived nanovesicles increase the production of collagen I and III, particularly during the early stages of wound healing. Furthermore, other extracellular vesicles derived from MSCs possess properties that prevent scar formation [10].

Hydrogels as delivery systems for cell therapy

Despite the significant therapeutic potential of stem cells, their direct administration (via injections or sprays) is often associated with limited efficacy. This is due to low cell survival in the inflammatory microenvironment of the wound, their rapid washout from the site of injury, as well as potential additional traumatic effects on tissues and the lack of adequate cell adhesion to extracellular matrix components.

In particular, under conditions of hyperglycemia associated with diabetes, diabetic wounds form a chronic inflammatory microenvironment accompanied by the accumulation of glycosylation end products. Such conditions are unfavorable for stem cell survival and simultaneously promote the degradation of growth factors secreted by effector cells, which collectively leads to a reduction in the therapeutic efficacy of cell therapy.

Therefore, the delivery strategy must be optimized to ensure cell viability, paracrine function, and differentiation. This is why cell delivery using hydrogels and bioscaffolds has recently become highly sought after [2, 8].

To overcome the limitations associated with effective cell delivery, hydrogels – three-dimensional polymer networks with a high water content, whose properties are similar to those of the extracellular matrix are widely used. Hydrogels provide an optimal moist microenvironment, facilitate gas exchange, protect cells from ROS, and serve as a scaffold that supports uniform cell distribution, proliferation, and differentiation. Therefore, increasing attention is being paid to the use of hydrogels as bio-inks for three-dimensional (3D) printing in tissue engineering. Bioprinting involves the fabrication of complex structures from multiple types of materials, cells, and bioactive compounds [2, 9, 13, 14].

Biomaterials used to create hydrogels are broadly classified into natural (including alginate, collagen, hyaluronic acid, gelatin, and silk fibroin) and synthetic (polyethylene glycol, polylactic acid, and polycaprolactone) (Fig. 2). Natural polymers are characterized by high biocompatibility and biodegradability, whereas synthetic materials allow for more precise control of mechanical and physicochemical properties; however, they may be inferior in terms of biological activity or exhibit potential cytotoxicity [9, 13, 16, 17].

One of the most common natural materials used in hydrogel-based tissue engineering and for the transdermal delivery of active ingredients is alginate. It is a highly biocompatible hydrogel whose physical properties can potentially be adapted to guide 3D cell growth and differentiation both *in vitro* and *in vivo*. Alginate is a natural polysaccharide derived from brown algae, widely used due to its availability, low toxicity, and ability to gel in the presence of divalent cations (primarily Ca^{2+}) [9, 16, 18, 19]. This polysaccharide provides an inert environment, has controlled porosity, and structural similarity to the ECM [19]. The mechanical properties of alginate and the rate of substance release can be adjusted by varying

its molecular weight and the type of cross-linking agent [18]. Since alginate cannot promote cell proliferation and differentiation, current research is primarily focused on composites of alginate and other biological materials. When mixed with other materials, the optimal alginate concentration range is considered to be between 1 % and 5 %. At alginate concentrations below 1 %, the solution exhibits high fluidity and good miscibility; however, after bioprinting, low shape accuracy and insufficient structural stability of the gel are observed. Conversely, at concentrations above 5 %, an increase in the system's viscosity is observed, which complicates its use as a bio-ink for extrusion printing and negatively affects cell viability [17].

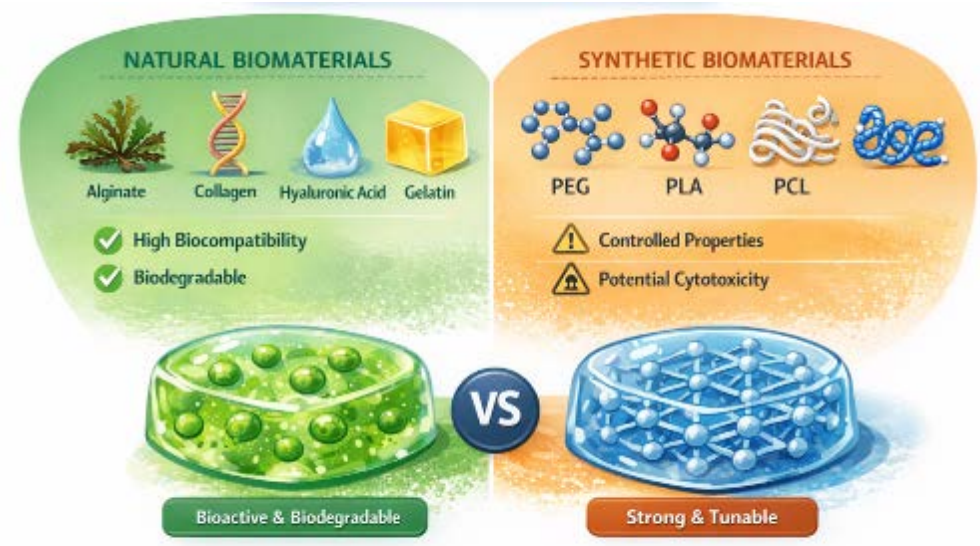

Fig. 2. *Classification of biomaterials used for hydrogel fabrication.*

Collagen is the primary protein of the ECM, which ensures its excellent biocompatibility and performs structural and functional roles, promoting cell migration and proliferation. The most widely used collagens in tissue engineering are fibril-forming collagens, specifically types I, II, III, IV, and V.

It should be noted that type I collagen is considered one of the key biomaterials in tissue engineering, as it accounts for up to 90 % of the protein component of connective tissue. At the same time, hydrogels based on pure collagen are often characterized by insufficient mechanical properties, which limits their practical application.

Combining collagen with alginate in a composite hydrogel (CAC) allows for the integration of the advantages of both components: alginate provides the necessary structural integrity and hydration of the system, while collagen enhances biological activity and supports cell adhesion, proliferation, and function [9, 16, 19, 20]. This combination also allows for the adjustment of the scaffold stiffness, which influences stem cell differentiation [19]. In an *in vitro* study, Zhou et al. [21] demonstrated the efficacy of sodium alginate and collagen in preventing MSC apoptosis. In another study, Zhang et al. [22] used a sodium alginate/collagen hydrogel in combination with Umbilical cord-derived mesenchymal stem cells (UC-MSCs) for wound healing, and their results demonstrated the efficacy of this combination in promoting wound healing, collagen deposition, enhanced angiogenesis, and reduced inflammation at the wound site [13].

Hyaluronic acid (HA) is a natural polysaccharide that plays a key role in regulating inflammation, as it acts as a signaling molecule that controls cell adhesion, migration, and proliferation. In practice it is used in the form of its sodium salt. Low-molecular-weight HA (150-250 kDa) promotes wound healing and exhibits angiogenic properties, whereas high-

molecular-weight HA can inhibit cell proliferation and migration [4, 13, 16]. HA is known for its hydrophilicity due to numerous carboxyl groups that form hydrogen bonds with water molecules. This property allows 1 g of HA to bind up to 6 liters of water, making it an ideal component for hydrogels. HA is an ideal bio-ink due to its viscosity, but it often requires chemical modification or blending with other substances to improve stability and rheological properties [9, 13, 16]. For example, Eke et al. [23] cross-linked methacrylated gelatin (GelMA) and methacrylated hyaluronic acid (HAMA), which in turn increased the hydrogel's efficacy and improved the performance of ADSCs. A study by Pak et al. [4] also showed that catechol-modified hyaluronic acid hydrogel (HA-CA), in addition to tissue adhesion, provides better survival and efficacy of stem cells than hyaluronic acid hydrogel.

3D bioprinting technologies for the production of therapeutic products for wound treatment

3D bioprinting enables the creation of biocompatible structures with complex geometries that precisely match the shape of the wound through the layer-by-layer deposition of cells and biomolecules [2, 9, 16]. The main bioprinting methods include extrusion (the most common due to its scalability and ability to work with viscous materials), laser, droplet, and stereolithography printing. The extrusion method is considered the most optimal, as it allows the use of bio-inks with high viscosity (up to 600 kPa·s) and a sufficiently high cell concentration (10^8 cells/mL) (Fig. 3) Depending on the viscosity of the bio-ink, the cell concentration within it, and the nozzle size, cell viability after printing can range from 40 % to 95 % [16].

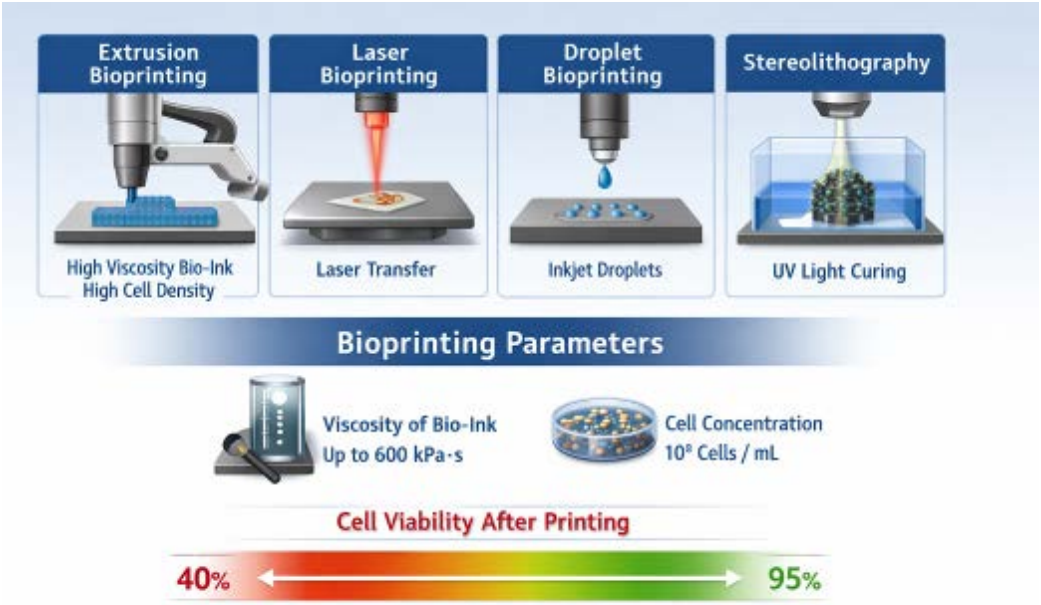

Fig. 3. *Overview of main bioprinting techniques and key process parameters.*

The fabrication of three-dimensional matrices involves the use of specialized materials, bio-inks, which are typically cell-laden hydrogels. Such systems must provide an optimal microenvironment for cell viability, which necessitates a number of requirements, including proper printability, mechanical stability, biocompatibility, biodegradability, non-toxicity, and the ability to rapidly stabilize or cross-link during or immediately after the printing process.

A key physicochemical parameter of bio-inks is their viscosity, which increases with rising polymer concentration and molecular weight. Increased viscosity promotes the

formation of stable layers during extrusion; however, it can also complicate the printing process due to the risk of nozzle clogging and interruptions in material flow. In this context, the phenomenon of shear thinning plays an important role, as it reduces the material's viscosity under shear stress during extrusion. At the same time, excessive shear stresses can negatively affect the viability of encapsulated cells, which requires careful optimization of bioprinting process parameters.

Therefore, the main challenge for researchers is to overcome the "biofabrication window" paradigm - finding the ideal balance between optimal printability of the material and maximum viability of the encapsulated cells. In addition, the gelation time of the hydrogel is extremely important for print reliability and should be as short as possible [9, 16]. Studies have also shown that optimizing printing conditions, such as the use of tapered needles, pre-crosslinking, and others, allows for the maintenance of high cell viability (> 85 %) [18].

Therapeutic efficacy and translational potential

Numerous *in vitro* and *in vivo* studies demonstrate the high therapeutic efficacy of the combined use of hydrogels, stem cells, and bioprinting technologies. The application of hydrogels containing MSCs demonstrates significant advantages in the treatment of complex wounds. In animal models (mice, rats, pigs), the use of AD-MSCs within hydrogel scaffolds accelerated epithelialization, increased collagen deposition, and improved wound healing. The results of relevant studies are presented in Table 1.

Table 1. *Analysis of current approaches to the production of scaffolds using encapsulated MSCs.*

Cell type	Composition of the hydrogel	Key result	Sourse
AD-MSCs	Bilayer scaffold: polycaprolactone (PCL)/gelatin nanofibers (top layer) + alginate/collagen hydrogel (bottom layer)	Enhanced re-epithelialization, robust angiogenesis, and collagen remodeling at 14 and 21 days; minimized inflammation; optimal collagen organization in the wound compared to the control	Lashkari et al. (2023) [14]
hUC-MSCs	Sodium alginate + type I collagen	Decreased expression of NLRP3-associated proteins; accelerated wound healing; increased expression of VEGF and TGF-β1; effective inhibition of cell proliferation *in vivo*; decreased levels of TNF-α and IL-1β	Zhang et al. (2021) [22]
AD-MSCs	Alginate + pullulan + hyaluronic acid	Excellent cell adhesion and migration through the pores of the scaffold were observed *in vitro*; the use of the hydrogel with cells accelerated wound healing, resulting in better re-epithelialization and well-developed granulation tissue at 7 and 14 days compared to the other groups	Khandan-Nasab et al. (2023) [24]
AD-MSCs	10 % methacrylated gelatin (GelMA) + the antioxidant curcumin	Curcumin blocked the AGEs/AGER/NF-κB p65 pathway, reducing ROS production and apoptosis in ADSCs. Diabetic wound healing was significantly improved; active formation of CD31+ cells was observed	Xia et al. (2022) [25]

hUC-MSCs	Sodium alginate + recombinant type III collagen	Promoted tissue regeneration and increased fertility, and regulated the mesenchymal-epithelial transition (MET) in endometrial stromal cells (ESCs); the hydrogel demonstrated therapeutic efficacy in terms of endometrial thickness, glandular regeneration, and angiogenesis; it helped maintain the hormonal response	Shuai et al. (2023) [20]
MSCs-derived exosomes	Carboxymethylchitosan + bioactive glass + TiO_2 nanoparticles	Strong antibacterial activity; stimulation of VEGF-A production; cytokine modulation (increased IL-10, decreased TNF-α) in diabetic and burn models in mice	Shang et al. (2024) [15]
AD-MSCs	A patch based on hyaluronic acid functionalized with catechol groups	The size of the diabetic wound was significantly smaller in the HA-CA + ADSC group (8% ± 2%) compared to the control group (16% ± 5%). In mice treated with HA-CA + ADSC, epidermal regeneration and restoration of skin thickness occurred; CD31-positive vessels were detected. mRNA and protein levels of VEGF, insulin like growth factor 1 and 2 (IGF-1, FGF-2), and ANG-1 were the highest among all groups	Pak et al. (2021) [4]

These studies have shown that hydrogel in combination with various materials can promote wound healing and protect stem cells during this process [13].

Findings and clinical applications

The clinical efficacy of MSC-based therapy for wound treatment is increasingly supported by data from human clinical trials. A systematic review conducted by Rangatchew et al. analyzed 42 studies on acute thermal burns, identifying three specific human clinical trials that confirmed the safety and efficacy of allogeneic MSC therapy. These trials demonstrated that MSC administration leads to a significant acceleration of re-epithelialization and a reduction in systemic markers of inflammation without reports of side effects [7].

To further confirm the clinical efficacy of these treatment methods, an increasing amount of data from human clinical trials (summarized in recent pharmacological reviews [8]) indicates the successful application of various types of MSCs for the treatment of chronic, non-healing skin wounds. Studies using MSCs derived from bone marrow, umbilical cord and adipose tissue for the treatment of diabetic foot ulcers and other chronic ulcers demonstrate optimal results. These human studies show that local administration of MSCs by various methods, whether by injection or topical application, leads to a significant reduction in ulcer size, accelerated complete wound healing, and enhanced granulation tissue formation compared to standard treatment.

Despite the success of cell therapies in clinical settings, the transition to 3D-bioprinted constructs made of MSCs and hydrogel still presents a significant gap in translating research from preclinical trials to clinical practice. Because three-dimensional systems combine living cells with biomaterials, they are classified under strict regulatory requirements as advanced therapy medicinal products. A key challenge lies in demonstrating that, despite the mechanical stress during printing, MSCs retain their initial therapeutic efficacy and paracrine activity over the long term. A specific critical aspect is the ability of the bioprinted system to

maintain stable homeostasis, particularly to regulate acidity levels both within the hydrogel and directly in the wound, which is crucial for cell survival in an aggressive microenvironment. Furthermore, since most promising strategies rely on the use of autologous cell lines, a serious standardization issue arises. The need for individual material collection for each patient complicates the development of universal protocols and the expansion of technology. Thus, future research should focus on establishing reliable methods for validating the stability and functionality of such personalized systems before their implementation in widespread clinical practice.

Conclusions

Based on analysis conducted in this narrative review, it can be concluded that mesenchymal stem cells are a promising tool for the treatment of chronic wounds due to their immunomodulatory, proangiogenic, and regenerative properties, which are primarily mediated through paracrine mechanisms. At the same time, the effectiveness of their direct application is limited by low cell viability, insufficient retention in the injury site, and an unfavorable inflammatory microenvironment, especially in cases of diabetic lesions.

Hydrogel delivery systems significantly enhance the therapeutic potential of MSCs by providing a biomimetic extracellular environment, improving cell viability, and promoting their localized action. Composite hydrogels, particularly those based on alginate and collagen, demonstrate particular efficacy, combining mechanical stability with high biological activity.

The integration of hydrogels with 3D bioprinting technologies opens up opportunities for creating structured cellular constructs with controlled architecture. At the same time, a key challenge remains the optimization of bio-ink properties, particularly viscosity and shear thinning, to ensure proper printability without compromising cell viability.

Despite significant progress, issues regarding the standardization of bio-ink composition, monitoring of cell behavior post-bioprinting, and confirmation of the long-term efficacy and safety of such approaches in clinical practice remain relevant. Although clinical trials have already confirmed the safety and efficacy of MSC suspensions in patients, the transition to using 3D-bioprinted matrices in clinical trials requires the development of standardized protocols. Future efforts should focus on ensuring cell functionality after printing and maintaining stable homeostasis, particularly pH regulation, to fully realize the clinical potential of personalized treatments.

Overall, the combination of MSCs, hydrogel systems, and 3D bioprinting holds significant potential for the advancement of regenerative medicine in the treatment of chronic wounds and requires further translational and clinical research.

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CONFLICT OF INTEREST STATEMENT. *The authors declare that they have no conflicts of interest related to the research, authorship, and/or publication of this article.*

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References

1. Zhou Z, Chen Y, Chai M, Tao R, Lei Y, Jia Y, et al. Adipose extracellular matrix promotes skin wound healing by inducing the differentiation of adipose-derived stem cells into fibroblasts. Int J Mol Med. 2019; 43(2):890-900. https://doi.org/10.3892/ijmm.2018.4006
2. Huang JN, Cao H, Liang KY, Cui LP, Li Y. Combination therapy of hydrogel and stem cells for diabetic wound healing. World J Diabetes. 2022; 13(11):949-61. https://doi.org/10.4239/wjd.v13.i11.949
3. Kwon JW, Savitri C, An B, Yang SW, Park K. Mesenchymal stem cell-derived secretomes-enriched alginate/ extracellular matrix hydrogel patch accelerates skin wound healing. Biomater Res. 2023; 27(1):107. https://doi.org/10.1186/s40824-023-00446-y
4. Pak CS, Heo CY, Shin J, Moon SY, Cho SW, Kang HJ. Effects of a Catechol-Functionalized Hyaluronic Acid Patch Combined with Human Adipose-Derived Stem Cells in Diabetic Wound Healing. Int J Mol Sci. 2021; 22(5):2632. https://doi.org/10.3390/ijms22052632
5. Burgess JL, Wyant WA, Abdo Abujamra B, Kirsner RS, Jozic I. Diabetic Wound-Healing Science. Medicina. 2021; 57(10):1072. https://doi.org/10.3390/medicina57101072
6. Radzikowska-Büchner E, Łopuszyńska I, Flieger W, Tobiasz M, Maciejewski R, Flieger J. An Overview of Recent Developments in the Management of Burn Injuries. Int J Mol Sci. 2023; 24(22):16357. https://doi.org/10.3390/ijms242216357
7. Rangatchew F, Vester-Glowinski P, Rasmussen BS, Haastrup E, Munthe-Fog L, Talman ML, et al. Mesenchymal stem cell therapy of acute thermal burns: A systematic review of the effect on inflammation and wound healing. Burns. 2020. https://doi.org/10.1016/j.burns.2020.04.012
8. Kucharzewski M, Rojczyk E, Wilemska-Kucharzewska K, Wilk R, Hudecki J, Los MJ. Novel trends in application of stem cells in skin wound healing. Eur J Pharmacol. 2019; 843:307-15. https://doi.org/10.1016/j.ejphar.2018.12.012
9. Deptuła M, Zawrzykraj M, Sawicka J, Banach-Kopeć A, Tylingo R, Pikuła M. Application of 3D- printed hydrogels in wound healing and regenerative medicine. Biomed Amp Pharmacother. 2023; 167:115416. https://doi.org/10.1016/j.biopha.2023.115416
10. Czerwiec K, Zawrzykraj M, Deptuła M, Skoniecka A, Tymińska A, Zieliński J, et al. Adipose-Derived Mesenchymal Stromal Cells in Basic Research and Clinical Applications. Int J Mol Sci. 2023; 24(4):3888. https://doi.org/10.3390/ijms24043888
11. Guo J, Hu H, Gorecka J, Bai H, He H, Assi R, et al. Adipose-derived mesenchymal stem cells accelerate diabetic wound healing in a similar fashion as bone marrow-derived cells. Am J Physiol Cell Physiol. 2018; 315(6):C885-C896. https://doi.org/10.1152/ajpcell.00120.2018
12. Zampar AG, Farina Junior JA, Orellana MD, Caruso SR, Fernandes TR, Gomes R, et al. Analysis of Adipose-Derived Stem Cells from Different Donor Areas and Their Influence on Fibroblasts In Vitro. Aesthet Plast Surg. 2020; 44(3):971-8. https://doi.org/10.1007/s00266-019-01586-0

13. Sukmana BI, Margiana R, Almajidi YQ, Almalki SG, Hjazi A, Shahab S, et al. Supporting wound healing by mesenchymal stem cells (MSCs) therapy in combination with scaffold, hydrogel, and matrix; state of the art. Pathol Res Pract. 2023:154575. https://doi.org/10.1016/j.prp.2023.154575
14. Lashkari M, Rahmani M, Yousefpoor Y, Ahmadi-Zeidabadi M, Faridi-Majidi R, Ameri Z, et al. Cell-based wound dressing: Bilayered PCL/gelatin nanofibers-alginate/collagen hydrogel scaffold loaded with mesenchymal stem cells. Int J Biol Macromol. 2023:124099. https://doi.org/10.1016/j.ijbiomac.2023.124099
15. Shang S, Zhuang K, Chen J, Zhang M, Jiang S, Li W. A bioactive composite hydrogel dressing that promotes healing of both acute and chronic diabetic skin wounds. Bioact Mater. 2024; 34:298-310. https://doi.org/10.1016/j.bioactmat.2023.12.026
16. Antezana PE, Municoy S, Álvarez-Echazú MI, Santo-Orihuela PL, Catalano PN, Al-Tel TH, et al. The 3D Bioprinted Scaffolds for Wound Healing. Pharmaceutics. 2022; 14(2):464. https://doi.org/10.3390/pharmaceutics14020464
17. Fang W, Yang M, Wang L, Li W, Liu M, Jin Y, et al. Hydrogels for 3D bioprinting in tissue engineering and regenerative medicine: Current progress and challenges. Int J Bioprinting. 2023. https://doi.org/10.18063/ijb.759
18. Freeman FE, Kelly DJ. Tuning Alginate Bioink Stiffness and Composition for Controlled Growth Factor Delivery and to Spatially Direct MSC Fate within Bioprinted Tissues. Sci Rep. 2017; 7(1). https://doi.org/10.1038/s41598-017-17286-1
19. Hu T, Lo AC. Collagen–Alginate Composite Hydrogel: Application in Tissue Engineering and Biomedical Sciences. Polymers. 2021; 13(11):1852. https://doi.org/10.3390/polym13111852
20. Shuai Q, Liang Y, Xu X, Halbiyat Z, Wang X, Cheng J, et al. Sodium alginate hydrogel integrated with type III collagen and mesenchymal stem cell to promote endometrium regeneration and fertility restoration. Int J Biol Macromol. 2023:127314. https://doi.org/10.1016/j.ijbiomac.2023.127314
21. Zhou J, Zhang K, Ma S, Liu T, Yao M, Li J, et al. Preparing an injectable hydrogel with sodium alginate and Type I collagen to create better MSCs growth microenvironment. E Polym. 2019; 19(1):87-91. https://doi.org/10.1515/epoly-2019-0011
22. Zhang Z, Li Z, Li Y, Wang Y, Yao M, Zhang K, et al. Sodium alginate/collagen hydrogel loaded with human umbilical cord mesenchymal stem cells promotes wound healing and skin remodeling. Cell Tissue Res. 2020. https://doi.org/10.1007/s00441-020-03321-7
23. Eke G, Mangir N, Hasirci N, MacNeil S, Hasirci V. Development of a UV crosslinked biodegradable hydrogel containing adipose derived stem cells to promote vascularization for skin wounds and tissue engineering. Biomaterials. 2017; 129:188-98. https://doi.org/10.1016/j.biomaterials.2017.03.021
24. Khandan-Nasab N, Mahdipour E, Askarian S, Kalantari MR, Ramezanian N, Oskuee RK. Design and characterization of adipose-derived mesenchymal stem cell loaded alginate/pullulan/hyaluronic acid hydrogel scaffold for wound healing applications. Int J Biol Macromol. 2023:124556. https://doi.org/10.1016/j.ijbiomac.2023.124556
25. Xia S, Weng T, Jin R, Yang M, Yu M, Zhang W, et al. Curcumin-incorporated 3D bioprinting gelatin methacryloyl hydrogel reduces reactive oxygen species-induced adipose-derived stem cell apoptosis and improves implanting survival in diabetic wounds. Burn Amp. 2022; 10:tkac001. https://doi.org/10.1093/burnst/tkac001