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Tendon and bone healing: Integrating physiology, autografts, and regenerative strategies

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Abstract

Tendon and bone injuries are crucial components of the locomotor system. They can be damaged easily, and they require a long time rest for healing. Sometimes the healing process could be no existed due to the limited regenerative capacity and slow healing, so there are significant clinical challenges remaining. Although they appear structurally simple, their hierarchical organization, cellular heterogeneity, and tightly regulated healing phases reveal a complex biological system that is highly sensitive to mechanical and molecular disturbances. Recent advances in bioengineering have introduced scaffold-based and exosome-based strategies as promising approaches to improve tendon healing outcomes. In aspects of bone healing, although already used technological approaches exist, the American Food and Drug Administration approved developments are highlighted in recent years. This review integrates current knowledge on tendon and bone physiology, the autograft approach, and emerging bioengineering strategies. Thus, the new approaches are how far from the clinics.

Keywords: Tendon healing, bone healing, bioengineering, tendon injuries, autograft, bioprinting, exosomes

1. Tendon Structure

Tendons, which link muscle to bone, have a hierarchical structure that is intimately connected to the muscles' structure to which they are attached. Tendons are predominantly composed of water and various extracellular matrix elements; notably, water constitutes the most significant proportion of the total tendon mass. The collagen exists as a vertical line, and each layer is coated with the non-collagen extracellular matrix that includes proteoglycans and glycoproteins. This encapsulated structure is composed of tenocytes, the primary cellular component of tendons, and is localized within two distinct regions of the tendon tissue. Also, tenocytes regenerate the extracellular matrix in the tendon, even though at a low level. Two types of tenocytes differ in shape and size, but information about their phenotypes remains limited.^{1,2} Although tenocytes are traditionally described as a uniform cell population, recent studies have revealed significant cellular heterogeneity within tendon tissue. Distinct tenocyte subpopulations differ in morphology, gene expression profiles, and functional roles, including matrix synthesis, mechanosensing, and tissue maintenance. In addition to mature tenocytes, tendon-derived progenitor or stem-like cells have been identified, primarily localized within the endotenon and epitendon regions (Figure 1).³⁻⁵

This variability in cells is becoming acknowledged as a crucial factor in healing. Resident tenocytes and tendon

progenitor cells contribute to intrinsic repair mechanisms that improve matrix organization. In contrast, extrinsic fibroblast-like cells originating from surrounding tissues are more frequently linked to fibrotic scar formation. Understanding the spatial distribution and functional specialization of these cellular niches is therefore critical for designing strategies aimed at scarless tendon regeneration.

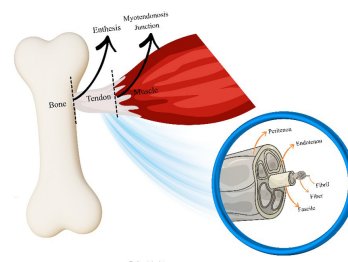


Figure 1. Schematic representation of tendon tissue structure.

While the gross anatomy of tendons appears straightforward, their microscopic and molecular organization reveals significant complexity. The tendon's structural physiology is divided into intrinsic and extrinsic systems. While the inherent system encompasses the cellular and fibrillar elements of the collagen core, the extrinsic system is formed by synovial-like tissues. These tissues are organized into distinct layers namely the endotenon, epitendon, and paratenon ordered from the internal

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to the external aspects of the tendon (Figure 2). The system provides contacts with other systems and also covers the intrinsic component. While both components contribute to tendon healing, further elucidation is required to fully understand the specific roles and interactions of the intrinsic and extrinsic pathways.^{1,2}

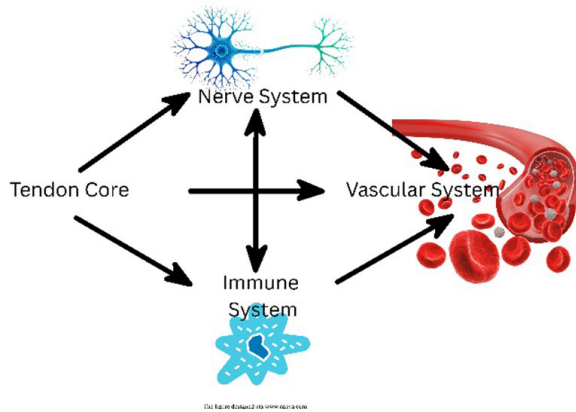


Figure 2. The schematic represents the tendon core and other systems.

2. Bone Structure

The bone tissue is one of the largest organs in the body, and there are six main functions including supportive, protective, storage, locomotion, endocrine regulation and hematopoiesis. Although the main part occurs the inorganic molecules, it has structural organic compounds like collagen, osteocalcin, osteonectin, osteopontin, and bone sialoprotein. All these components compose bone matrix. In addition, the matrix, bone tissue has four types of cells that osteoblasts, osteocytes, lining cells and osteoclast. Among them, osteoclasts that originated from hematopoietic stem cells are different from the others that are derived from same stem cells. Its main role is efficient resorption, so it contributes to remodeling processes. Moreover, it secretes proton for acidity of environment so dissolve the mineralized bone matrix if needed minerals. Osteoblast is the other type of cell in bone. Duty of osteoblast is to produce the osteoid that is known as unmineralized part of matrix. It takes a role phosphate mechanism with osteoclast. Following the bone-forming phase, osteoblasts can trans-

form osteocytes and lining cells. Osteocytes are hidden in the matrix of mineralized bone, and their morphology is changed so communicating other cells and transporting the nutritional compounds. It contributes to resorption of bone as called osteositik osteoliz. The last cell type is line cell that occurs differentiation of osteoblast. They usually been silent and prevent osteoblast-matrix connection.⁶⁻⁸

3. Healing Processes

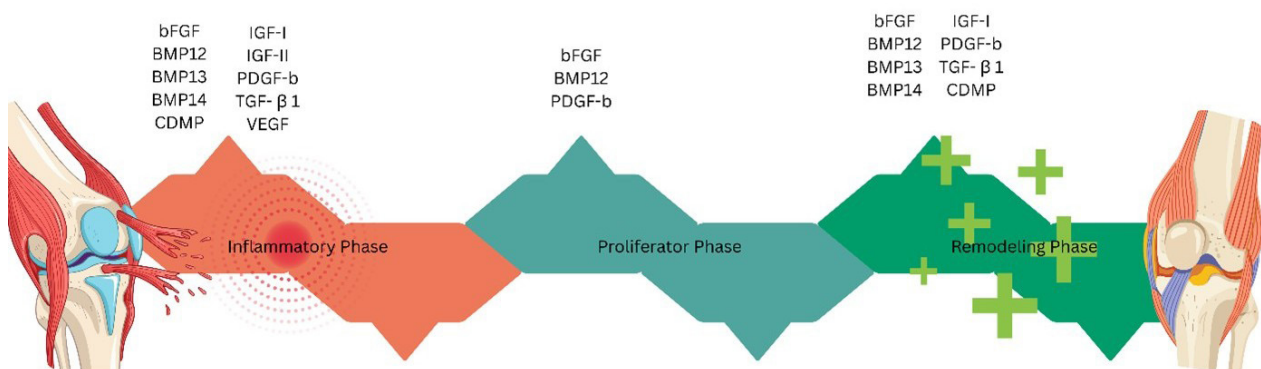
3.1. Tendon Healing

Tendon damage is categorized as acute and chronic injury. Acute injuries occur after a sudden event and affect healthy tendons. The traumatic injury type could be a total or partial rupture, and surgical treatment is generally the first treatment option. Following that, rehabilitation and supplementary treatment methods promote tendon recovery. It's well known that the tissue does not recover as healthy as before, regardless of the medical approaches, operative procedures, and rehabilitation in the pursuit of a cure.⁹

Chronic tendon injuries, commonly referred to as tendinopathy, are often caused by repetitive daily activities. Their symptoms are functional losses, pain, and swelling due to cumulative microtrauma.^{2,10,11} Activity restriction and drug treatment are applied for pain control, and then rehabilitation is recommended for recovery.⁹

External and internal reasons, including age, gender, obesity, imbalanced loading, and genetics, trigger both types of damage. Existing one or more predisposing factors become more vulnerable to the tendons³. Despite the robust structure of tendons, millions of people still suffer from tendon injuries.^{12,13}

The cellular process involved in tendon healing comprises three interconnected and overlapping stages: the inflammatory, proliferative, and remodeling phases (Figure 3). Each healing stage exhibits a distinct timeframe, depending on variables such as tendon location, injury type, and the clinical management approach (Table 1). Moreover, cells that contribute to the healing process are changed. In adult tissues, the inflammatory phase is frequently exaggerated, characterized by prolonged infiltration of neutrophils and profibrotic macrophages¹⁴. This inflammatory imbalance biases the healing respon-



The figure designed via www.canva.com.

Figure 3. Tendon healing stages and responsible cytokines.

se toward fibrosis rather than regeneration. During the proliferative phase, fibroblasts rapidly deposit type III collagen in a disorganized arrangement. Although this matrix restores initial continuity, it lacks the tensile strength and alignment of native type I collagen. The extrinsic component is repaired by circulating or neighboring tissue cells. On the other hand, the tendon cells that produce tendon parenchyma, epitenon, or endotenon play a central role in the recovery of the internal components.^{14,15}

Scar formation that impairs tendon quality results from a disordered healing process. It occurs due to unorganized extracellular matrix formation caused by extrinsic components. Following injury, the extracellular matrix diminishes and, together with disturbed mucosal integrity and a lack of blood supply, impairs healing. They lead to increased apoptosis and metabolic stress, so the signaling pathways in progenitor cells change. Therefore, scar formation is a side effect. It is reported that tenocyte morphology is abnormal in scar tissue and that matrix components are reduced near the cells. Furthermore, an overabundance of Type III collagen relative to healthy tissue can lead to fibrotic changes, resulting in increased tissue stiffness and significant functional limitations in range of motion. Scarring leads to a significant

loss of tendon mobility, as the tendon becomes unable to slide effectively within the sheath; this is especially critical in the context of hand flexor injuries. When scar formation involves the tendon sheath, surgical procedures may be needed.^{2,15} Therefore, novel strategies are crucial for scarless healing in tendons¹⁷.

3.2. Bone Healing

Bone tissue has various roles including locomotor, protection, minerals storage, and hemopoiesis. Due to protects soft tissues, it easily affects traumatic process.¹⁸ Bone healing is complex process that consists of interwoven three stages known as inflammatory, repair and remodeling (Figure 4).^{19,20} In the first stages continue few days, the main aim regulates area that damages due to bone integrity loss. To this, secreting molecules induces inflammatory cells and fibroblasts comes into the area, so granulation tissue formation existed. Moreover, various molecules trigger both vascularity and migration of mesenchymal cells²¹ In the second phase starts average 1- week post-fracture, vascular buds' growth leads to callus formation known as woven bone. It happens intramembranous, that done hard callus directly, or endochondral, that hard callus following the soft callus, ossifications. The process proceeds weeks

Table 1. Temporal progression of tendon healing and corresponding biological and clinical characteristics¹⁶

Healing stage	Approximate time frame	Dominant biological events	Typical clinical management
Early inflammatory stage	First 0–7 days	<ul style="list-style-type: none"> Formation of a provisional hematoma Accumulation of innate immune cells Local release of inflammatory mediators and growth factors 	<ul style="list-style-type: none"> Temporary protection or immobilization when required Symptom-oriented anti-inflammatory treatment
Cellular proliferative stage	~1–6 weeks	<ul style="list-style-type: none"> Expansion of fibroblasts and resident tenocytes Production of provisional extracellular matrix Predominance of type III collagen with gradual maturation toward type I collagen 	<ul style="list-style-type: none"> Carefully controlled mobilization Early-stage, supervised rehabilitation
Matrix remodeling stage	≥6 weeks to 12 months or longer	<ul style="list-style-type: none"> Reorganization of collagen fibers in response to mechanical loading Progressive replacement with aligned type I collagen Incremental improvement in tensile and functional properties 	<ul style="list-style-type: none"> Stepwise increase in mechanical load Functional and task-specific rehabilitation programs

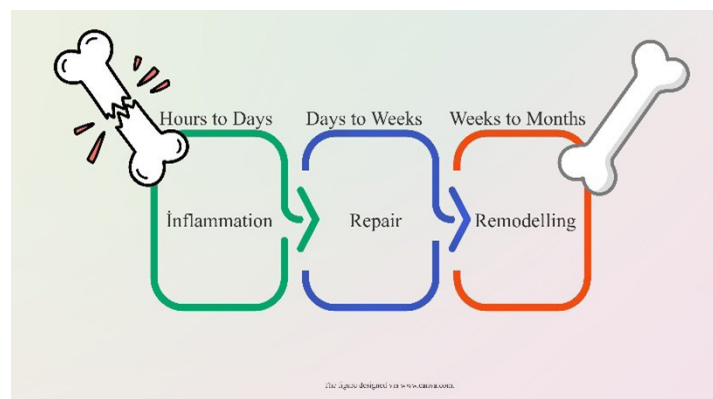


Figure 4. Bone healing phases

and the first two weeks is critical for healing. Lastly, remodeling phase that heals is completed extends over months to years, so bone recovers to original capacity as soon as possible. Osteoblasts and osteoclasts mainly contribute to the process and provide a metabolic balance for construction and destruction.^{21–23}

5. Approaches for Tendon Healing

5.1. Tendon Autografts

Tendon autografts have used until 1900s and it is still a widely used approach. Following the surgery, graft necrosis, revascularization, cell repopulation and remodeling are consist in the area and completed to process is nearly two years. Although it preferred flexor tendons' healing, it can use extensor groups. Palmaris longus, fascia lata and other all tendons could be using autograft, but every tendon has different characteristics, so it's chosen to depend on the surgeon.^{24–26} Moreover, tendon autografts give a concern about donor-site complications including tendon truncation during harvest, variable sizes and lengths of grafts and mobility.^{27–29} Due to the disadvantages, the studies is continued for tendon healing.

5.2. New Approaches to Tendon Healing

Bioengineering is advancing rapidly, thereby contributing to tissue healing. Tendon healing is unquestionably a crucial topic in bioengineering. The primary objective of targeted therapies and scaffolds is to support cellular activity and promote regenerative healing.³⁰

5.2.1. Scaffolds-Based Approaches

Scaffolds are rapidly developing materials in tendon healing that are used not only for scaffolding but also for drug delivery. Various materials are used to produce products, but unfortunately, there is no gold-standard material for scarless healing. Poly(lactide-co-glycolide) (PLGA), silk protein, polyethylene terephthalate (PET), polycaprolactone (PCL), and polylactic acid (PLA) are the most preferred materials for researchers. To ensure satisfactory outcomes, an ideal scaffold for tendon repair and regeneration must meet several strict requirements. Firstly, the scaffold needs to be biocompatible to prevent an unfavorable immunological reaction after implantation. Secondly, its structure should be degradable at the same time as tissue healing. Beyond biocom-

patibility, biodegradability, and mechanical robustness, the ability of materials to support the microenvironment, promote cellular activity, and induce extracellular matrix secretion is critical for optimal tissue regeneration.^{16,31,32} In this regard, scaffolds produce structures similar to tendons, and extracellular matrix supportive molecules, including ions or growth factors, are loaded into them. Furthermore, each technique offers distinct advantages regarding scaffold morphology, mechanical properties, and their subsequent biological interactions with host tissues (Table 2).¹⁶

Among them, 3D bioprinting technology has been highlighted in recent years for its ability to mimic tendon structure and size. With this approach, it's possible to incorporate both biomaterials and bioactive substances to design a scaffold tailored to the individual. Moreover, 3D bioprinting provides a sophisticated platform that brings together three primary components essential for tissue engineering. Firstly, smart bio-inks commonly produce synthetic and natural polymers. Smart bio-inks provide drug release, proliferation, and differentiation. In addition, it has a commonly non-immunogenic structure and regulates dynamic cross-linking.

On the other hand, bio-inks made from natural polymers have low loading capacity, and synthetic polymer bio-inks do not fully heal. To address these reasons, generally channeling the mixture of both types of polymers^{33,34}. Secondly, the 4D Bioprinting application, with a more dynamic structure that changes after printing, is one of the newest forms of 3D bioprinting. The core content is the approach to the type of scaffold, which has mechanical adaptability and response programming, thereby allowing size, shape, or functionality to be changed in response to the environment or stimuli.^{33,35} Last but not least, an artificial intelligence (AI)-designed approach is highlighted as technological developments advance. AI plays a pivotal role in determining the scaffold's and material's structure. Also, it contributes to optimizing the model and print path, so the biomaterial becomes of higher quality and better suited to the injury areas.^{33,34}

5.2.2. Exosome-Based Approaches

Exosomes are secreted vesicles from cells that act as a small cargo packet for the cell. They are approximately 30-150 nm, with a similar mother cell topology, so their function changes based on cell type. Moreover, exoso-

Table 2. Bioengineering strategies for tendon and tendon-bone repair

Technology	Material / Loading	Clinical Target	Primary Benefit	References
3D-Printed PCL Scaffold	PCL + bFGF + BMSCs	Rotator Cuff Tears	Immunomodulation & Osteogenesis	³⁶
Multiscale Scaffold	Biomimetic Polymers	Tendon Body	Hierarchical cell alignment	³⁷
Synergistic Biofilter	Bio-active Tubes	Flexor Tendons	Prevention of adhesions	³⁸
Muscle-to-Bone Trifecta	Hierarchical Interfaces	Entezis (Interface)	Functional integration	³⁹
Patient-Specific Grafts	MRI-driven 3D Bioprinting	Motion-active joints	Anatomical fit & early mobilization	³³

mes are used as delivery systems called smart exosomes. Their smarts come from 4 main modification categories (Table 3). These modifications could alter the content so that exosomes can serve as a drug delivery system. Other options include surface modification or covering the packet, which can protect and/or target them in the body. The modifications not only involve changing but also purification to collect varying amounts of exosomes in a small volume of liquid. Consequently, exosome-based bioengineering approaches are emerging as new treatment approaches.^{40–42}

In tendon healing, exosome applications are attractive after their identification. Exosomes have biological structures and consist of various molecules, including proteins, miRNAs, siRNAs, and growth factors, which support the healing process and are accepted as adjuvant therapy due to their properties. Exosomes have various benefits on tendon healing that summarize three main categories: (1) modulation of inflammation, (2) induced angiogenesis, and (3) regulating cellular processes. Furthermore, exosomes have been reported to exhibit negligible immunogenicity and minimal adverse effects, establishing them as a highly promising and secure therapeutic modality for tendon regeneration. Thus, exosomes derived from Bone marrow-derived MSCs (BM-MSCs) and adipose-derived MSCs (AD-MSCs) are extensively researched in chronic tendon damage.⁴² Similarly, a systematic review by Zou et al.⁹ reports that

human and rat MSCs are the most commonly used sources of exosomes. Furthermore, research indicates that direct injection and biomaterial-mediated implantation are the most prevalent delivery methods for facilitating tendon regeneration. Based on this information, exosomes are a promising approach for tendon recovery. In particular, their application does not require any surgical procedure, so they have more advantages than the scaffold-based approach. On the other hand, it is still inadequate as the main option⁹.

5.2.3. Advantages and Disadvantages of Biomaterials for Scarless Healing

Although tendon-healing treatments accelerate healing, preventing scar formation remains difficult. The evidence presented indicates that despite their respective advantages—as summarized in Table 4 neither scaffold nor exosome-based approaches have yet achieved definitive scarless tendon healing. For this reason, recent studies focus on combining them for theranostic approaches. Loading molecules in scaffolds is commonly used for scarless healing. Furthermore, in vitro and in vivo studies have demonstrated the synergistic effects of bioactive tubes on scarless tendon regeneration³⁸. In parallel, specific proteins have been developed to further facilitate the scarless healing process⁴³. Recently, the focus of research has shifted from conventional repair toward achieving complete scarless regeneration;

Table 3. Smart exosomes have four main categories and features⁴²

Main Category	Definition	Specific Methods and Features
Inherent Qualities	Exosomes possess intrinsic biological properties that make them ideal delivery vehicles.	<ul style="list-style-type: none"> • Safety: Immunocompatible, non-toxic, and non-mutagenic. • Targeting (Homing): Ability to reach target cells without artificial scaffolds. • Intercellular Communication: Natural capacity to mediate cell–cell communication and deliver cargo directly into the cytoplasm.
Parent Cell Modification	Manipulation of the exosome-secreting source cell to enhance exosome content or production efficiency.	<ul style="list-style-type: none"> • Genetic Manipulation: Modification of the donor cell genome • Environmental Modulation: Adjustment of oxygen levels or nutrient conditions. • Priming: Pre-stimulation of cells using inflammatory cytokines. • Culture Systems: Expansion of cells in three-dimensional scaffolds or hydrogel-based systems.
Direct Modification	Engineering of exosome surfaces or structures after isolation.	<ul style="list-style-type: none"> • Hybridization: Functionalization with aptamers or targeting ligands. • Conjugation: Covalent attachment of polymers to the exosome surface. • Fusion: Combination with liposomes to enhance cargo-loading capacity.
Cargo Loading	Techniques used to introduce therapeutic agents or biomolecules into exosomes after isolation.	<ul style="list-style-type: none"> • Incubation: Passive loading through co-incubation with drug solutions • Electroporation: Transient pore formation using electrical pulses. • Other Methods: Sonication, saponin-mediated permeabilization, and freeze–thaw cycles.

however, these advancements currently remain limited to pre-clinical in vitro and in vivo models.

6. Approaches for Bone Healing

6.1. Bone Autografts

Autografts were introduced to the medical world in the 20th century. It became popular to be really short time due to the safest and most cost-effective procedure.⁴⁴ Autograft is identified as taken bone and transported to other body parts in the same person. The procedure is cost-effective and is suitable for tissue transfer. Also, it supports osteogenesis with the content of mesenchymal stem cells and growth factors, so it provides growth to growing new bone⁴⁵ Although the positive sides,

it has some disadvantages. First of all, the donor areas are limited to areas such as the calcaneus and distal tibia.^{46,47} Moreover, another surgery is required at the same time. Another difficulty with autografts is that it is hard to develop grafts suited to certain defects (Table 5). Although the disadvantages are still accepted, a gold standard for bone healing, especially post-traumatic situations^{45,48} and current studies are focusing on a new approach that alternative for autografts.⁴⁷

6.2. New Approaches

Compared to the tendon approach, it seems that the bone area is more ready for the clinical process. Synthetic grafts, including bone cements and calcium phospho-

Table 4. Comparison of biomaterial approaches

Feature	Exosome-Based Approaches	Scaffold-Based Approaches
Primary mechanism	Modulation of intercellular signaling via transfer of miRNAs, proteins, and lipids	Provision of mechanical support and structural guidance
Mechanical contribution	None	Significant
Inflammation regulation	Potent anti-inflammatory and immunomodulatory effects	Indirect and material-dependent
Impact on scarless healing	Actively promote scarless healing by suppressing profibrotic signaling (e.g., TGF- β pathways) and enhancing regenerative remodeling.	Indirectly influence scarless healing; non-biomimetic or stiff scaffolds may promote fibrotic repair, whereas aligned and compliant scaffolds support scar-minimized remodeling.
Collagen organization	Promotes organized collagen I deposition with reduced collagen III dominance	Highly dependent on fiber alignment, stiffness, and degradation profile
Suitability for acute tendon injury	Highly suitable; effectively modulates early inflammation and prevents excessive fibrotic cascade.	Limited as a stand-alone approach; may be used when early mechanical stabilization is required.
Suitability for chronic tendon injury	Limited when used alone due to established fibrosis and altered tissue architecture	Highly suitable; provides structural replacement and mechanical guidance in degenerated tissue.
Cellular response	Enhances tenocyte proliferation and matrix synthesis	Promotes cell adhesion, alignment, and mechanotransduction
Biological specificity	High (source-dependent)	Moderate
Mode of application	Local injection, hydrogel delivery, or scaffold immobilization	Surgical implantation
Standardization and reproducibility	Challenging	Relatively easier
Stage of clinical translation	Emerging	More advanced
Effectiveness as a stand-alone strategy	Limited	Limited
Optimal role across injury stages	Acute-phase biological reprogramming toward regenerative, scarless healing	Structural and mechanical restoration in chronic or severe tendon defects

Table 5. Advantages and disadvantages of bone autografts

Advantages	Disadvantages
<ul style="list-style-type: none"> • Safe • Cost effectiveness • Same person • Provide osteogenesis • Regulates microenvironment 	<ul style="list-style-type: none"> • Another surgery required • Limited donor area • Hard to arrange to defect area

Table 6. FDA-approved processes some bone graft approaches (*: for different indications) ⁴⁹

Growth factor/bioactive molecules name	Approved Years
Infuse (BMP-2) device	2002-2004-2007*
OP-1 (BMP-7) Device	2001-2004*
Augment (PDGF-BB)	2015
GEM 21S (PDGF-BB)	2005
iFactor (P-15)	2015

te cements, have been used in clinics for almost 100 years to contribute to bone healing with osteoconductive effects. Although they already use clinics, they cannot consist of growth factors so initial healing effects are limited. Thus, some molecules and supportive approaches bone tissue engineering cover the last century in terms of osteoinductive, osteoconductive, and biodegradable. It is reported that one of the 3D-bioprinted scaffolds has a phase 2 study, and also, there are some growth factors and bioactive approved by the Food and Drug Administration (FDA) ^{6,49}

Conclusion

Tendons have a complex structure, and several factors influence their healing. Bioengineering represents an innovative strategy in tendon repair by recapitulating developmental biological processes to facilitate functional regeneration. Scaffold-based approaches include 3D bioprinting and dynamic systems, which are commonly used for acute tendon injuries and support healing by providing mechanical support, structural guidance, and promoting the progression of healing. Exosome-based approaches derived from natural or supporting technologies are practical for both types of tendon damage due to their easy application. However, both methods have limited effects for tendon healing, so scarless tendon healing remains behind.

Although autografts are the gold standard for bone healing, there are some limitations. Primarily, it is hard to overcome a slight donor area. Due to this reason, new applications are still required.

An aim of enhancing tendon and bone healing strategies is no longer a distant goal with the advancing technology. On the other hand, experimental procedures are required for using clinicals in routine procedures.

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Ethical approval

This study does not require approval from the Ethics Committee for Animal Experiments.

Conflict of interest

There is no conflict of interest between the authors

Author contribution

All authors contributed equally and were involved in all stages of the manuscript.

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