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Review

Known data on applied regenerative medicine in tendon healing

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Abstract:
Tendons and ligaments are important structures in the musculoskeletal system. Ligaments connect various bones and provide stability in complex movements of joints in the knee. Tendon is made of dense connective tissue and transmits the force of contraction from muscle to bone. They are injured due to direct trauma in sports or roadside accidents. Tendon healing after repair is often poor due to the formation of fibro vascular scar tissues with low mechanical property. Regenerative techniques such as PRP (platelet-rich plasma), stem cells, scaffolds, gene therapy, cell sheets, and scaffolds help augment repair and regenerate tissue in this context. Therefore, it is of interest to document known data (repair process, tissue regeneration, mechanical strength, and clinical outcome) on applied regenerative medicine in tendon healing.

Keywords: Tendon, ligament, ACL, PRP, stem cells, scaffolds, gene therapy

Background:
Tendon and ligament injuries are quite prevalent in the world. 33 million musculoskeletal impairments are recorded every year where about 50% are linked to tendons and ligaments in USA **[1]**. Walker *et al.* (2012) showed a loss of $27 million per annum due to sick leave for lateral epicondylitis (inflammation of an epicondyle) in the UK **[2]**. Conditions causing pain and reduced function of tendons are often referred as tendinopathy **[3]**. Effective strategy for the management of tendon injuries is limited **[4]**. Scleraxis (Scx) is a sclerotome marker and it is expressed in both tendon progenitor cells and mature tenocytes **[5]**. Fibroblast growth factor 8 (FGF8), secreted by the myotome, is partly responsible for inducing Scx

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expression through the Ets transcription factors *Pea3* and *Erm* **[6]**. Growth and differentiation factors (GDF), members of the bone morphogenetic protein (BMP) family, are additional regulators of tendon development **[7].** Tendons are enveloped by a layer of connective tissue known as endotenon that comprises of blood vessels, lymphatics, and nerves, to form larger structural units called fascicles, which are surrounded by another connective tissue layer called epitenon **[8].** Type I Collagen is the fibril-forming collagen in tendons and co-polymerizes with collagen type V **[9].** The type II transmembrane glycoproteins Tenomodulin (TNMD) is a marker for primed tenocytes and it is positively regulated by Scleraxis **[10].** The natural healing process of tendons is extremely slow due to the hypo cellular and hypo vascular nature of tendon structure **[11] w**ith three stages: (a) inflammation, (b) repair and (c) remodelling [12] as shown in **Figure 2**. The inflammatory stage remains for 2 days followed by the repair and remodelling phase, which takes almost one year **[13, 14]**. The role of various growth factors in the healing process of tendons **[15]**. There are various growth factors like insulin-like growth factor-I (IGF-I), TGF-β, bFGF, platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), BMP, and connective tissue growth factor (CTGF) which are particularly up-regulated following a tendon injury and are active at various stages of the healing process **[16-19]**. The current management plan for flexor tendon injuries including the post-operative plan to prevent re-rupture and hypertrophy of tendon is known **[20]**. However, a meta-analysis found rate of re-operation of 6%, re-rupture of 4%, and adhesion formation of 4% **[21]**. Achilles tendinopathy accounts for 40 to 50 % of sports injuries in young athletes [22]. Histo pathological studies have proved extensive degenerative changes in ruptured TA **[23]**. A failure rate of 5%-95% is observed for chronic tears in rotator cuff of shoulder joints **[24].** The formation of fibro vascular scar tissue in place of a tough fibro collagenous band **[25]** due to the presence of anti-adhesive protein lubricin in synovial fluid **[26]** is seen in such cases. Therefore, it is of interest to document known data (repair process, tissue regeneration, mechanical strength, and clinical outcome) on applied regenerative medicine in tendon healing.

Methodology:

The methodology for data collection is illustrated in **Figure 1.**

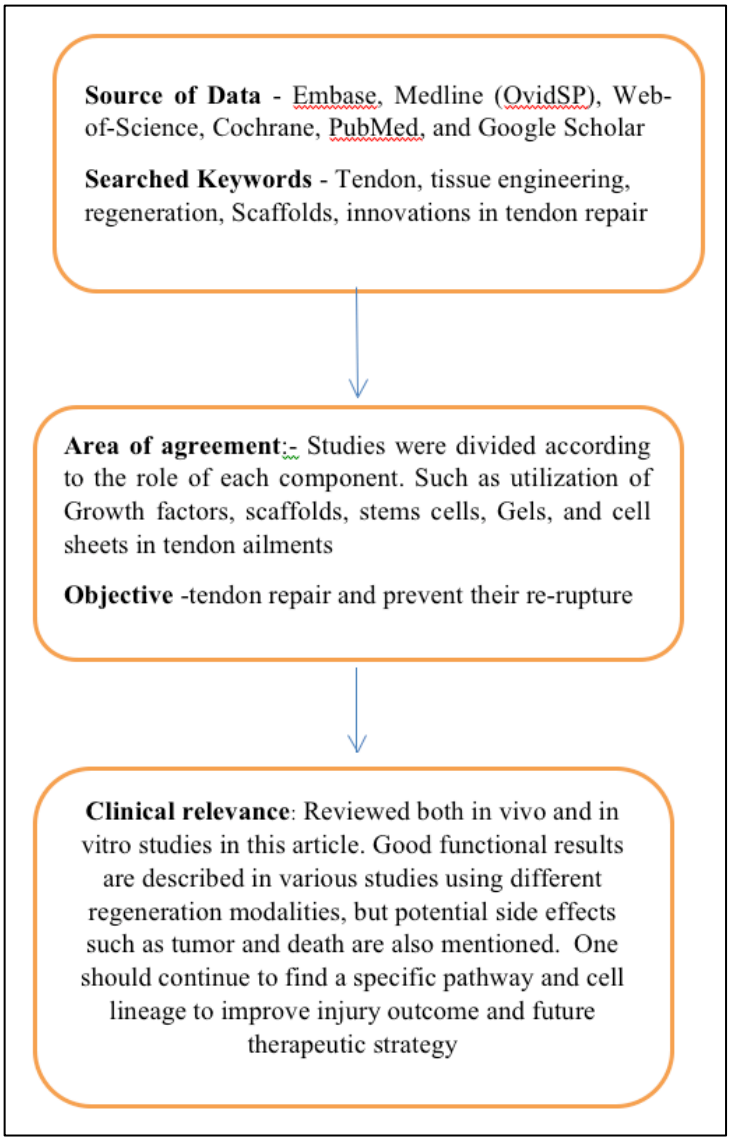

Figure 1: Methodology flowchart for data collection is shown

Discussion:

Methods for tendon repair and regeneration:

Current treatments for tendon repair and augmentation include biological grafts (e.g. auto grafts, allo grafts, and xeno grafts), prosthesis and tissue engineering. The biological grafts have several shortcomings as they induce donor site morbidity (auto graft) and

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tissue rejection (allograft). However, permanent prosthesis lack material durability causing mechanical malfunctions. Tendon tissue engineering (TTE) represents a most promising approach due to interdisciplinary engineering strategies. It aims to promote full tendon regeneration, rather than physically replacing tendons with partially functionalized foreign substitutes. TTE typically involves scaffolds, stem cells, gels, culture sheets, and gene therapy. TTE scaffolds can enhance tendogenesis by promoting cell proliferation, increasing matrix production, and organizing the matrix into functional tendon tissues. Moreover, tendogenesis can be facilitated through many strategies such as cellular hybridization, surface modification, growth factor cure, mechanical stimulation, and contact guidance.

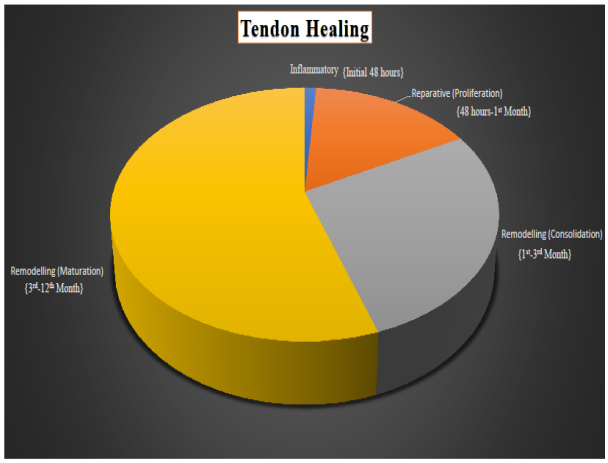

Figure 2: Stages in tendon healing is shown

Growth factors:

Tendon injuries stimulates the increased expression of growth factors particularly in the early phases of healing. The growth factors that have shown a significant impact in tendon healing are bFGF, BMP-12, -13, -14, CTGF (connective tissue growth factor), IGF-1, PDGF, TGFβ, and VEGF. The role of these growth factors in tendon repair is extensively investigated **[27-36]**. The role of PRP (platelet-rich plasma derivative) has been analyzed in the field of orthopedics over a decade in human (**Table 1**). PRP is the plasma section of autologous blood containing a large concentration of platelets and growth factors such as platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), insulin-like growth factor-I (IGF-I), fibroblastic growth factor (FGF), and hepatocyte growth factor (HGF) **[37]**. Most of these factors promote neo-vascularization, tenocyte proliferation, and increase extracellular matrix production. PRP is prepared from autologous blood and it is inherently safe. PRP are present in physiological proportions with a natural balance of proliferative and inhibitory agents **[38]**. PRP preparation is made simple using advanced preparation devices. These technological advances have allowed PRP treatments to move from operating rooms to outpatient offices produced easily and safely in 15–30 minutes **[39-45]** (**Table 2**).

Scaffolds:

The histological changes that are typical of the healed tendon are poor alterations in fiber structure, arrangement, vascularity, cellular morphology, and cellular proliferation. Scaffolds are placed into the defect zone to provide mechanical support and guide endogenous cells to improve matrix production and organization. Metcalf *et al.* described the use of porcine small intestinal submucosa (SIS) in 12 patients who underwent arthroscopic repair of massive chronic rotator cuff tears using Restore SIS as an augmentation device **[46]**. Postoperative magnetic resonance imaging (MRI) scans showed significant thickening of the cuff tendon with the incorporation of the SIS graft in 11 patients. However, worsening of symptoms in some patients due to SIS is also reported **[47]**.

Acellular human dermal matrix **[48]**, collagens repair patch **[49]**, and polyfilamentous carbon composites **[50]** are various other alternative therapies giving promising results in human trials. Zimmer (USA) and De Tissue Science Laboratories, DePuy supply collagen repair patches for commercial purposes. The material is purified and cross-linked to collagenase degradation. Other therapies such as Type I collagen sponge **[51]** OFM (ovine fore stomach matrix **[52]**), fresh autograft fascia lata **[53]**, PGA sheet **[54]** and polylactic acid patches **[55]** give good results in animal models. The findings of these studies are compelling and indicate the need for a long-term evaluation to verify the overall effectiveness of this augmentation method (**Table 3**).

Tendon gene therapy:

Gene therapy is the utilization of therapeutic nucleic acids into patient's cells to treat a disease condition. Tashjian *et al.* identified an SNP within the estrogen-related receptor beta *(*ESRRB*)* gene that appears to promote increased susceptibility to re-tears after a rotator cuff repair **[56]**. The molecular therapeutics and targeted gene therapies are the new frontiers in the treatment of rotator cuff disease **[57]**. Robertson *et al* found an increase in *MMP1* and *MMP9* gene expression in the patients with rerupture, compared to the

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group that displayed good healing **[58]**. The antibiotic doxycycline is an inhibitor of MMPs. Pasternak *et al* found that rat Achilles tendons repaired with doxycycline-coated sutures resulted in improved suture-holding capacity compared to a control group with uncoated sutures **[59]**. Current tissue engineering strategies using synthetic biomaterial scaffolds have yet to yield tendon substitutes. The appeal of these engineered scaffolds is that they can potentially be impregnated with growth factors or genes for targeted and timed-release at the site of implantation to improve healing. We reviewed 9 studies (**Table 4**) for the effect of various genes (rAAV-Gdf5, BMP-12, BMP-14 and PDGF) on tendon healing, strength, and movement [60-69]. This data is promising for further consideration.

Stem cells:

Pluripotent stem cells carry great potential for cell therapy and tissue engineering. The use of embryonic stem cells (ESCs), adult mesenchymal stem cells (MSCs) tendon derived stem cells (TDSs), and Human skeletal muscle progenitor (SMP) cell to regenerate functional tendons and ligaments [70-79] (**Table 5**) is of interest. Various sources of MSCs have been investigated for their impacts on tendon repair. Embryonic stem cells (ESCs) have unlimited proliferation capacity and it can be induced into all types of somatic cells for tissue repair. However, there is a risk of teratoma formation. There are two promising cell types, namely bone marrow mesenchymal stem cells (BM-MSCs) and adipose-derived mesenchymal stem cells (AD-MSCs). They are well characterized and simple for *in vitro* proliferation. Interestingly, most of the preclinical animal studies concluded that MSC delivery can lead to increased cell proliferation, but these cells often differentiated towards osteoblasts or adipocytes within the tendon area, suggesting their inherent preference to commit to the original lineage of the tissue from which they were isolated **[80].** The isolation of the native to the tendon-tenocytes, tendon stem/progenitor cells, or tendon-derived fibroblasts is relevant to the context **[81].** MSCs have self-renewal and multilineage differentiation potential. BMSCs have shown immense collagen production after seeding on polylactide/glycolide (PLGA) suture material. Lee *et al.* **[77]** used Allogeneic adipose-derived mesenchymal stem cells in lateral epicondylosis and found tendon defect significantly reduced in 6 weeks. Ilic *et al.* studied mesenchymal stromal cells (MSCs) from the human placenta. They were injected directly into the site of tendon damage using ultrasound guidance in the treatment of chronic refractory tendinopathy and observed that there is significant improvement in tendon repair. Hernigou *et al.* **[79]** showed the role of crest bone marrow-derived mesenchymal stem cells (MSCs) in rotator cuff injury to prevent further damage.

Gel and cell sheets:

Tendon repair and minor defects can be augmented with hydrogels with stem cells or direct cell sheets (**Table 6**). The tendon hydrogel promotes host cell infiltration, supporting its biocompatible properties and sustained the viability and proliferation of donor, adipose-derived stem cells (ASCs). The tendon hydrogel's thermo-property under physiologic temperature enhances its applicability *in vivo*. The gel polymerized and formed the shape of the defect at 37 degree Celsius. Hydrogel is a promising biomaterial for guided tissue regeneration. Degen *et al.* [**82**] showed rotator cuff repair augmentation with purified human MSCs with hydrogels in rat models. It was observed that there is improved early histologic appearance and biomechanical strength of the tendon at 2 weeks as described elsewhere **[83-86].** Cell-cultured sheets derived from adipose stem cells, ACL, rotator cuff, and tendon stem cells were also used in this context despite increased cost [**87-91**].

Amniotic membrane:

The epithelial and mesenchymal cells of amnion contain various regulatory mediators like Epidermal growth factor, Keratinocyte growth factor, a hepatocyte growth factor that results in the promotion of cellular proliferation, differentiation, epithelialization, inhibition of fibrosis, immune rejection, inflammation, and bacterial invasion (**Table 7**) [**92**]. The presence of platelet-derived growth factor (PDGF) and vascular endothelial-derived growth factor (VEGF) is suggestive of a pro-angiogenic role [**93**]. It is known that amniotic epithelial and mesenchymal cells lack HLA class A, B, DR, and co-stimulatory molecules CD-40, CD-80, and CD-86 making it non-immunogenic **[94]**. The effects of human amniotic fluid on peritendinous adhesion formation and tendon healing after flexor tendon surgery in rabbits are shown **[95]**. Amniotic membrane in flexor tendon repair has reduced adhesion [**96**]. Properties of the amniotic membrane for potential use in tissue engineering are available [**97**]. Flexor tendon repair using allograft amniotic membrane is also shown [**98, 99**].

Conclusion:

Known data (repair process, tissue regeneration, mechanical strength, and clinical outcome) on applied regenerative medicine in tendon healing is documented in this review**.** Information on the use of applied regenerative technologies such as the use of growth factors, scaffolds, gene therapy, stem cells, gel and cell sheets and amniotic membrane in tendon healing is gleaned from known literature to enrich our knowledge in this context. Caveats and limitations on known data including clinical trials, evidence based research information and FDA reveiws were found to be useful for further consideration [**100-104**].

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Conflict of Interest:
There is no conflict of interest in this article.

Ethical approval:
The Ethical committee of MMMCH at Kumarhatti Solan approved the review material.

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Table 1: Role of platelet rich plasma in tendon regeneration

S. No	Current Strategies	Materials used for study	Study Model	Result Outcome	References
1.	PRP	Platelet rich concentrate with human tenocyte	*In vitro*	In vivo use of PRP in tendon injuries might accelerate the catabolic demarcation of traumatically injured tendon matrices and promote angiogenesis and formation of a fibrovascular callus.	Marieke de Mos *et al.* 2008
2.	PRP	Platelet rich plasma with human tenocyte	*In vivo*	These findings suggest that PRP might be used as a useful biological tool for regenerative healing of rotator cuff tears by enhancing the proliferation and matrix synthesis of tenocytes from tendons with degenerative tears.	Chris Hyunchul Jo 2012
3.	PRP	Leucocyte rich Platelet rich plasma	*In vitro*	This study demonstrated that PRP enhanced the tendon healing and promoted the recruitment of MPs to the injured tissue. The subtypes of MPs were different depends on the types of PRPs, suggesting that leukocytes in PRP influence the effect of PRP therapy.	Hirofumi Nishio *et al.* 2020
4.	PRP	Autologous PRP in rotator cuff tendon cells	*In vitro*	PRP is a source of growth factors such involved with tendon-bone healing. PRP had an anabolic effect on the human rotator cuff tenocytes of the same individual in vitro by means of cell proliferation and absolute, but not relative collagen I synthesis. These results encourage further studies on clinical outcomes with more comparable standards in terms of preparation and application methods.	Stephan Pauly *et al.* 2012
5.	PRP	Allogenic PRP gel	*In vitro*	The results of this study suggest that the local application of PRP could enhance the tissue-healing process both directly through action on localized cells and indirectly through the recruitment of reparative cells through the blood flow. Further investigations will be needed to confirm the mechanisms of PRP in tissue-healing processes with the development of this experimental model.	Yohei Kobayashi *et al.* 2020
6.	PRP	PRP combined with recombinant human type 1 collagen	*In vitro*	STR/PRP is a safe treatment that effectively induces clinically significant improvements in elbow symptoms and general well being as well as objective measures of strength and imaging of the common extensor tendon within 6 months of treatment of elbow tendinopathy recalcitrant to standard treatments.	Uri Farkash *et al.* 2019

Table 2: Role of growth factors in tendon regeneration

S. No	Current Strategies	Materials used for study	Study Model	Result outcome	References
1.	Growth factors	Rabbit platelet-rich plasma (PRP)	Rabbit; patellar tendon; full-thickness surgical defect; PRP with the gel form were placed in the defect; analysis at 1, 2, 3 and 4 wks.	Stronger and more extensive expression of TGF-b1 was showed at 1 and 2 wks by immunohistochemistry.	Lyras *et al.*
2.	Growth factors	Basic fibroblast growth factors	Rat; Achilles tendon; surgical defect; analysis at 12 weeks	Biomechanical properties were not significantly improved.	Kraus *et al.*
3.	Growth factors	Bone morphogenetic Protein 12 (BMP 12)	Dog; flexor digitorum profundus tendon; surgical transection; 5 mm depth, 2.5 mm width; scaffold with adipose derived stromal cells and BMP 12 were placed in the transection; analysis at 28 days.	Tensile properties showed no significantly difference; Proteomics analysis showed amplification of Inflammation, stress response and matrix degradation	Gelberman *et al.*
4.	Growth factors	Bone morphogenetic Protein 2 (BMP 2)	Rabit: First, recombinant human bone morphogenetic protein-2 (rhBMP-2) was injected into the flexor digitorum communis tendon in the rabbit hind limb to induce ectopic ossicle formation. In a second step, the resultant tendon/ossicle complex was then surgically transferred onto the surface of the rabbit tibia to generate a stable tendon-bone junction.	Enthesis like tissue had been successfully formed at 4 weeks and this tissue was shown functionally competent for mechanical repairing	Hashimoto G *et al.*
5.	Growth factors	Insulin growth factor -1 (IGF-1)	Rabit: the effects of recombinant human insulinlike growth factor (rhIGF-I), insulin and fetal calf serum	The E_{max} of stimulation of proteoglycan and collagen synthesis by rhIGF-I were two times that of FCS, and	Abrahamsson SO *et al.*

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			(FCS) on the synthesis of proteoglycan, collagen, and non-collagen protein and cell proliferation were investigated in short-term explants cultures of the deep flexor tendon	the E_{max} of cell proliferation by FCS was twice that of rhIGF-I. Growth factors thus have the ability to stimulate matrix synthesis and cell proliferation in rabbit flexor tendon.	
6.	Growth factors	Platelet-derived growth factor (PDGF)	Rat: Platelet-derived growth factor isoform B at various dosages (0, 10, 100, or 1000 ng) was delivered into the gap wound in patellar tendons via microsyringe injection on Day 3 or Day 7 after injury. Tendon specimens were harvested on Day 14 for measurement of cell proliferation, pyridinoline content, and mechanical properties.	Supplementation of platelet-derived growth factor isoform B at Day 7 benefits the mechanical properties and maturation of healing tendons.	Chan BP *et al.*
7.	Growth factors	Transforming growth factor (TGF)	Rabit: 30 female rabbits were divided into three groups, after a 3 mm wide and 10 mm long tendon substance was resected from the central portion in the patellar tendon. In Group I, 5-ng TGF-beta1 dissolved in 0.1-ml saline was injected into the resected portion in the patellar tendon. In Group II, only 0.1-ml saline was injected into the resected portion. In Group III, nothing was injected. All animals were sacrificed at 6 weeks after surgery	The tangent modulus and the tensile strength of Group I (with TGF Beta) were significantly greater than those of Groups II and III,	Anaguchi Y *et al.*
8.	Growth factors	Transforming growth factor B 1,B2, B3	Sheep: infraspinatus repair model to evaluate the effect of osteoinductive growth factors (bone morphogenetic protein [BMP] 2, transforming growth factor [TGF] β_1, TGF-β_2, TGF-β_3, and fibroblast growth factor) and on tendon-to-bone healing.	These molecules improve formation of new bone and fibrocartilage at the healing tendon attachment site, resulting in improved load to failure	Rodeo SA *et al.*
9.	Growth factors	Vascular endothelial growth factor (VEGF)	Canine: the temporal accumulation of VEGF mRNA at the repair site of an in vivo canine intrasynovial flexor tendon repair	Significant accumulation of VEGF mRNA occurred at the flexor tendon repair site at 7 days post-operatively, with peak levels seen at post-operative days 7 and 10. Levels returned to baseline by day 14. Local VEGF mRNA accumulation at the repair site temporally precedes and is spatially distinct from the vascular ingrowth itself, which has been shown to occur maximally at day 17.	Boyer MI
10.	Growth factors	Autologous conditioned serum (ACS)	Rat: the Achilles tendons of 80 Sprague Dawley rats were transected and sutured back together. Ten rats from each group (ACS group, n = 40; control group, n = 40) were euthanized at 1, 2, 4, and 8 weeks postoperatively for biomechanical (n = 7) and histologic (n = 3) testing.	The ACS-treated tendons were thicker, had more type I collagen, and an accelerated recovery of tendon stiffness and histologic maturity of the repair tissue	Majewski *et al.*

Table 3: Role of scaffolds in tendon regeneration

S. No	Current Strategies	Materials used for study	Study Model	Result Outcome	References
1.	Biomaterials (Biological scaffolds)	Type I collagen sponge	Rat; Achilles tendon; surgical transection; analysis at 1, 2 and 4 wks.	Defects receiving collagen sponges showed improved healing, with significantly stronger and less stiff tendons than control tendons. No inflammatory reaction due to the collagen sponge was found histologically.	Müller *et al.*
2.	Biomaterials	Ovine forestomach matrix (OFM) scaffold	Rat; rotator cuff, surgical transection; OFM scaffolds (5 mm × 10 mm) were overlaid longitudinally on the superficial aspect of the tendon-bone insertion; analysis at 6 days and 12 wks	Improved healing quality was shown by histological analysis, no evidence of excessive inflammatory response, no biomechanical advantage of augmentation	Street *et al.*
3.	Biomaterials	Porcine small intestinal submucosa (SIS)	Human- 2-year followup of 12 patients who underwent arthroscopic repair of massive chronic rotator cuff tears using Restore SIS as an augmentation device.	Postoperative magnetic resonance imaging (MRI) scans showed significant thickening of the cuff tendon with the incorporation of the SIS graft in 11 patients.	Metcalf *et al.*
4.	Biomaterials	Collagen Repair Patch (single layer porcine skin xenograft)	Human- evaluated 10 patients with extensive rotator cuff tear treated with Zimmer Collagen Patch	All patients experienced significant pain relief and improvement in abduction power and range of motion. Ultrasound imaging at the final follow up identified intact grafts in eight and disrupted grafts in two patients	Badhe *et al.*
5.	Biomaterials	Acellular dermal	Human-11 patients with acute tendon ruptures	At 20 months, there were no reruptures or recurrent pain;	Lee Dk *et*

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		matrix (ACM)	were followed up for 20 to 31 months with ACM	the average return-to-activity time was 11.8 + 0.75 weeks. Significant increase in strength and stiffness of Achilles tendon repair augmented	*al.*
6.	Biomaterials	Fresh autograft fascia lata	Rabbit- in supraspinatus injury model fresh autograft fascia lata as an interpositional graft	At the fascia-bone junction, chondrocytes started to appear at 2 weeks after surgery, and increased rapidly in number and columnar organization. By 8 weeks, remodelling of direct insertion with fibrocartilage was almost complete	Sano *et al.*
7.	Synthetic Scaffolds	Polyglycolic acid (PGA) sheet	Rabbit: polyglycolic acid (PGA) sheet to augment rotator cuff repairs of infraspinatus tendons	Histological improvement in fibrocartilage layering but only a slight improvement in tensile strength	Yokoya *et al.*
8.	Biomaterials	Synthetic ECM	Rabbit- in infraspinatus tendons the 10-mm defect was covered with chitin, a biodegradable polymer, sutured into the bone trough, and attached to the free end of the infraspinatus tendon. The contralateral shoulder was left untreated as a control.	The tendon-to-bone junctions covered with chitin fabric demonstrated greater cell number, better collagen fiber alignment, and greater mechanical strength than the tendon-to-bone junctions left free as control	
9.	Biomaterials	Polylactic acid patches	Dog- The superior 2.3 of each infraspinatus tendon was removed from the rotator cuff and then repaired in both shoulders. In one shoulder, a woven poly-L-lactide device was placed over the repair. In the other shoulder, the repair was left unaugmented.	The augmented rotator cuff repair resulted in fewer tendon retractions, greater strength, and increased stiffness when compared to the contralateral untreated rotator cuff repairs	Derwin *et al.*
10.	Biomaterials	Polymer filamentous carbon composites	Human- implant composed of filamentous uniaxially aligned carbon fibres coated with an absorbable polymer in 48 patients with a rupture of Achilles tendon.	The early strength of this repair was provided by the composite implant and by the rapid ingrowth and attachment of new tissue. All patients demonstrated continuous improvement during the first post-operative year, and a high level of function throughout the second year. Both repair of chronic and acute injury greatly improved	Parsons *et al.*

Table 4: Role of Gene therapy in tendon regeneration

S. No	Current Strategies	Materials used for study	Study Model	Result Outcome	References
	Gene therapy				
1.	*In vivo*	BMP-14/GDF-5 with AAV	Mouse, flexor tendon: recombinant adeno-associated virus (rAAV)-loaded tendon allografts mediate efficient transduction of adjacent soft tissues, with expression peaking at 7 days	The rAAV-Gdf5 vector significantly accelerates wound healing in an in vitro fibroblast scratch model and, when loaded onto freeze-dried FDL tendon allografts, improves the meta tarso phalangeal (MTP) joint flexion to a significantly greater extent than the rAAV-lacZ controls do.	Basile P *et al.*
2.		BMP-14/GDF-5 Adenovirus	Rat Achilles: the histological and biomechanical effects of adenovirus-mediated transgene expression of bone morphogenetic protein-14 (BMP-14) on healing in a rat Achilles tendon laceration model	Tendons transduced with BMP-14 exhibited less visible gapping, a greater number of neotenocytes at the site of healing, and 70% greater tensile strength	Bolt P *et al.*
3.		BMP-12/GDF-7 Adenovirus	Chick, flexor tendon: the effect of BMP-12 gene transfer on tendon cells.	Adenovirus mediated in vitro BMP-12 gene transfer into chicken tendon cells increased type I collagen synthesis. It resulted in a two-fold increase of tensile strength and stiffness of repaired tendons, indicating improved tendon healing in vivo	Lou J *et al.*
4.		PDGF-B Liposome	Rat, patellar tendon: he early biological effect of in vivo introduction of the PDGF-B gene on the healing of ligaments, a HVJ-liposome suspension containing platelet-derived growth factor (PDGF)-B cDNA was injected directly into the injured patellar ligament	PDGF-B gene transfer caused the enhanced expression of PDGF in healing ligament up to 4 weeks after transfection, leading to an initial promotion of angiogenesis and subsequent enhanced collagen deposition in the wound. Enhanced and accelerated matrix synthesis in the PDGF-B gene introduced healing ligament	Nakamura N *et al.*
5.		BFGF with AAV	Chick, flexor tendon: In Group 1, a total of 2 x 10(9) particles of adeno-associated viral	The ultimate strength of repaired tendons that had been treated with adeno-associated	Tang JB *et al.*

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			vector harboring the basic fibroblast growth factor gene were injected into both ends of the cut tendon. In Group 2, the same amount of adeno-associated viral vector carrying the luciferase gene was injected. In Group 3 (the non-injection control group), the tendons were sutured without any injection.	viral vector-basic fibroblast growth factor was significantly greater than that of tendons that had been treated with the sham vector or simple repair both during the early healing period four weeks, and a later period of eight weeks	
	Ex vivo				
7.		TGFβ, VEGF Adenovirus	Rabbit, Achilles: Bone Marrow-Derived Mesenchymal Stem Cells (BMSCs) were transduced with adenovirus carrying human TGF-beta1 cDNA (Ad-TGF-beta1), human VEGF(165) cDNA (Ad-VEGF(165)), or both (PIRES-TGF-beta1/VEGF(165)) Viruses, no cDNA (Ad-GFP), and the BMSCs without gene transfer and the intact tendon were used as control. Biomechanical features were measured at 1, 2, 4, and 8 weeks after surgery	The TGF-beta1 and TGF beta 1/VEGF (165) co-expression groups exhibited improved parameters compared with other groups. Treatment with TGF-beta1 cDNA-transduced BMSCs grafts is a promising therapy for acceleration and improvement of tendon healing, leading to quicker recovery and improved biomechanical properties of Achilles tendons.	Hou Y *et al.*
8.		Scleraxis with Adenovirus	Rat, superspinatus: Thirty animals received MSCs in a fibrin glue carrier, and 30 received Ad-Scx-transduced MSCs. Animals were sacrificed at 2 weeks and 4 weeks and evaluated for the presence of fibrocartilage and collagen fiber organization at the insertion. Biomechanical testing was performed to determine the structural and material properties of the repaired tissue	There were no differences between the Scx and MSC groups in terms of histologic appearance at 2 weeks. However, the Scx group had higher ultimate stress-to-failure and stiffness) compared with the MSC group.	Gulotta LV *et al.*
9.		BMP-12/GDF-7 Adenovirus	Rat, Achilles: Biopsies of autologous skeletal muscle were transduced with a type-five, first-generation adenovirus carrying the human BMP-12 cDNA (Ad.BMP-12) and surgically implanted around experimentally transected Achilles tendons in a rat model. The effect of gene transfer on healing was evaluated by mechanical and histological testing after 1, 2, 4 and 8 weeks	Reatment with BMP-12 cDNA-transduced muscle grafts thus produced a promising acceleration and improvement of tendon healing, particularly influencing early tissue regeneration, leading to quicker recovery and improved biomechanical properties of the Achilles tendon.	Majewski M *et al.*
10.		SMAD8, BMP-2 Liposome	Rat, Achilles:: A biologically active Smad8 variant was transfected into an MSC line that coexpressed the osteogenic gene bone morphogenetic protein 2 (BMP2). he engineered cells demonstrated the morphological characteristics and gene expression profile of tendon cells both in vitro and in vivo	A novel mechanism in which Smad8 inhibits the osteogenic pathway in MSCs known to be induced by BMP2 while promoting tendon differentiation.	Hoffmann A *et al.*
11.		PDGF-Band Retrovirus	Rat, rotator cuff: Adult male Sprague-Dawley RTFs were isolated, cultured, and transduced with genes for either IGF-1 or PDGF- by retroviral vectors. After selection and expansion, the transduced RTFs were seeded onto a polymer scaffold and further cultured	Adult male Sprague-Dawley RTFs were isolated, cultured, and transduced with genes for either IGF-1 or PDGF- by retroviral vectors. After selection and expansion, the transduced RTFs were seeded onto a polymer scaffold and further cultured it was found that there improvement in healing in tendon	Uggen JC *et al.*

Table 5: Role of stem cells in tendon regeneration

S. No	Current Strategies	Materials used for study	Study Model	Result Outcome	References
1.	Stem cells	Human	Rat; Achilles tendon; surgical transection	Implantation of hMSC-Scx, in contrast to hMSC and empty	Hsieh *et al.*

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	mesenchymal stem cells (hMSC) and scleraxis (hMSC-Scx) - programmed tendon progenitors	3 mm; 3D cell pellet transplantation; analysis at 16 weeks.	defect, results in smaller diameters, negligible ectopic calcification and advanced cellular organisation and matrix maturation in the injured tendons.	
2.	Human induced pluripotent stem cells (iPSC)-derived neural crest stem cells (iPSC-NCSCs)	Rat; patellar tendon; standardized full-thickness window defect (1*4 mm); defect filled with fibrin gel with iPSCNCSCs; analysis at 1, 2 and 4 weeks	Superior repair performance in macroscopical observation; significantly enhancement in histological and mechanical examinations.	Xu *et al.*
3.	Rat bone marrow mesenchymal (BMSC) and tendon derived stem cells	Rat; Achilles tendon; surgical transection 5 mm; TDSCs or BMSCs were injected; analysis at 1, 2 and 4 wks.	TDSCs showed better biomechanical properties and higher tendency in Col-I/III gene expression level during wks 1 and 2. Immunofluorescent assay revealed higher expression of Tenascin-C in TDSCs at week 1.	Al-ani *et al.*
4.	Horse amniotic membrane-derived mesenchymal cells (AMCs)	Horse: the immunomodulatory characteristics of AMCs and of their conditioned medium (AMC-CM) in vitro, and studied the potential therapeutic effect of AMC-CM in thirteen different spontaneous horse tendon and ligament injuries in vivo.	AMCs are capable of inhibiting peripheral blood mononuclear cell (PBMC) proliferation after allogenic stimulation either when cocultured in cell-to-cell contact and Clinical outcomes were favorable and the significantly lower rate (15.38%) of reinjuries observed compared to untreated animals	
5.	Human skeletal muscle progenitor (SMP) cell	Mouse: The SMP population was quantified, isolated, and assayed in culture for its ability to proliferate and fuse in vitro and in vivo. Cells from all cuff states were able to fuse robustly in culture and engraft when injected into injured mouse muscle	SMPs are capable of contributing to muscle hypertrophy and regeneration regardless of tear severit	Gretchen A Meyer *et al.*
6.	Tendon-derived stem cells (TDSC)	Rat; patellar tendon; surgical window defect, 1 mm in width; TDSC-fibrin constructs transplantation; analysis at 2, 4 and 8 wks.	The treated TDSCs accelerated and enhanced the quality of tendon repair compared with untreated TDSCs up to week 8, which was better than that in the controls up to week 16 as shown by histology, ultrasound imaging and biomechanical testing.	Lue *et al.*
7.	Mesenchymal stem cells (MSCs)	Rabbit; they were divided into 6 groups (three treatments with two time points each) evaluated at either 14 or 28 days after surgery: cross section of the Achilles tendon (CSAT); CSAT + Suture; and CSAT + MSC.	Comparison between the two time points within the same group showed a statistically significant decrease in the inflammatory process and an increase in the structural organization of collagen in the CSAT and CSAT + MSC groups MSC transplantation is a good alternative for treatment of Achilles tendon ruptures	Vieira MH *et al.*
8.	Allogeneic adipose-derived mesenchymal stem cells	Human: lateral epicondylosisllo-ASCs mixed with fibrin glue were injected into the hypoechoic common extensor tendon lesions all evaluated at 6, 12, 26, and 52	Tendon defects also significantly decreased through this period. Allo-ASC therapy was thus safe and effective in improving elbow pain, performance, and structural defects for 52 weeks.	Lee *et al.*
9.	Mesenchymal stromal cells (MSCs) from Human placenta	Human:MSCs were injected directly into the site of tendon damage using ultrasound guidance in the treatment of chronic refractory tendinopathy.	Clinical trials using both allogeneic and autologous cells demonstrated MSCs to be safe.	Ilic N *et al.*
10.	Iliac crest bone marrow-derived mesenchymal stem cells (MSCs).	Human: forty-five patients in the study group received concentrated bone marrow-derived MSCs as an adjunct to single-row rotator cuff repair at the time of arthroscopy. The average number of MSCs returned to the patient was 51,000 ± 25,000.	Forty-five (100 %) of the 45 repairs with MSC augmentation had healed by six months, versus 30 (67 %) of the 45 repairs without MSC treatment by six months. Bone marrow concentrate (BMC) injection also prevented further ruptures	Hernigou P *et al.*

Table 6: Role of gels and cell sheets in tendon regeneration

S.No	Current strategies	Materials used for study	Study Model	Result outcome	References
	Hydrogel				
1.		Hydrogel with Fibrin	Rat: Fifty-two athymic rats underwent unilateral detachment and transosseous repair of the supraspinatus tendon	Rotator cuff repair augmentation with purified human MSCs improved early histologic appearance and	Degen RM *et al.*

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		BMSCs	augmented with either fibrin glue (control group) or fibrin glue with 10^6 human MSCs (experimental group) applied at the repair site.	biomechanical strength of the repair at 2 weeks, although the effects dissipated by 4 weeks with no significant differences between groups.	
2.		Fibrin TSPCs	Rat: Green fluorescent protein-TDSCs (GFP-TDSCs) were pre-treated with or without CTGF and ascorbic acid for 2 weeks before transplantation. The patellar tendons of rats were injured and divided into three groups: fibrin glue-only group (control group), untreated and treated TDSC group. The rats were followed up until week 16.	The transplantation of TDSCs promoted tendon repair up to week 16, with CTGF and ascorbic acid pre-treatment showing the best results up to week 8. Pre-treatment of TDSCs with CTGF and ascorbic acid may be used to further enhance the rate and quality of tendon repair after injury	Lui *et al.*
3.		Tendon ECM ADSCs	Rat:Using 55 Wistar rats, a full-thickness defect was created within the midsubstanceof each Achilles tendon supplementation of a biocompatible tendon hydrogel with platelet-rich plasma (PRP) and adipose-derived stem cells (ASCs) would augment the tendon healing process	PRP and ASCs are easily accessible bioactive products that have potentiating effects on tendon hydrogel. Augmentation with these two factors encourages earlier mechanical strength and functional restoration. Thus, biochemically, tendon hydrogel augmented with PRP and/or ASCs, serves as a promising therapeutic modality for augmenting the tendon healing process after injury.	Chiou GJ *et al.*
4.		MSC with collegen gel	Rabbit: in Achilles tendon mesenchymal stem cells were suspended in a collagen gel delivery vehicle; then implanted into a 1-cm-long gap defect	Delivering mesenchymal stem cell-contracted, organized collagen implants to large tendon defects can significantly improve the biomechanics, structure, and probably the function of the tendon after injury.	Young *et al.*
	Cell Sheets				
5.		Rabbit ADSCs sheet	Rabbit: In vitro ADSCs were cultured in 6-well culture plates until 100% confluence. Confluent cells were then Cultured in expansion medium supplemented with 50 mg/ml ascorbic acid for 3 weeks to facilitate cell sheet formation.	Cell sheets were cultured over 3 weeks, and cell metabolic activity, cell sheet thickness, and early differentiation gene expression were analyzed. One week-old cell sheets displayed upregulation of early differentiation gene markers (Runx and Sox9). Cell sheet thickness and cell metabolic activity increased in the second and third week	Neo *et al.*
6.		Human ACLderived CD34 + cell sheet	Rat ACL injury model: Cells were plated in temperature-responsive culture dishes at 37 °C for 17 h, and then incubated at 20 °C for 20 min, and afterwards the cell sheets detached spontaneously	ACL-derived CD34+ cell sheet improved the ACL repair which was judged by histological assessment at week 2 and biomechanical evaluation at week 8 in a rat ACL injury model	Mifune *et al.*
7.		Human rotator cuff derived cell sheet	Rat rotator cuff injury model: Cells were cultured on 24-well temperature responsive culture dishes at 37 °C for 17 h. Then, the plates were placed at room temperature for 20 min, and the cell sheets detached from the wells spontaneously	The cell sheets transplanted to the infra spinatus injury site induced angiogenesis and Col synthesis, and improved tendon-bone junction repair at 4 and 8 weeks postoperation.	Harada *et al.*
8.		Rat TSPC GFP-labelled sheet	Rat ACL injury Model: Cells were plated in normal culture dishes in low-glucose medium. After 100% confluence, cell sheet was detached by rinsing with saline.	The TSPC sheet radiographically, histologically and biomechanically improved ACL healing in a rat model at week 2, 6 and 12 postoperatively. GFP-labelled TSPCs were detected at the graftbone tunnel interface and in the intra-articular graft midsubstance in all samples at week 2.	Lui *et al.*
9.		Rat TSPC sheet	Rat Achilles tendon injury model: TSPC sheets were prepared by plating on temperature-responsive culture dishes. Cells were cultured for 3 days and then induced for cell sheet formation by treating with 25 mM as corbic acid in complete culture medium at 37 °C. After 9 days, monolayer cell sheets were obtained by reducing the temperature from 37 °C to 20 °C for 20 min	TSPC sheet grafting into Achilles tendon defect significantly improved the histological features and Col content both at 2 and 4 weeks postsurgery, indicating that TSPC sheets can speed up tendon remodelling in the early stages of the healing process	Komatsu *et al.*

Table 7: Role of amniotic membrane in tendon regeneration

S. No	Current Strategies	Materials used for study	Study Model	Result Outcome	References
1.	Human amniotic fluid	Peritendinous adhesion formation and tendon healing in long flexor tendon of digits	Rabbits	Least adhesion and the best healing were observed in tendons treated with sheath repair and HAF application. Tendons treated with HAF had significantly higher tensile load values.	Ozgenel GY *et al.* (2001)
2.	Amniotic membrane	Flexot tendon injury in zone II	Chickens	Significantly reduced the amount of adhesion. No amniotic membrane remanants at 3 months	Demirkan F *et al.* (2002)
3.	An anisotropic collagen-glycosaminoglycan (CG) scaffold biomaterial, incorporating	Mechanical strength and growth factors	*In vitro*		Hortenisious (2018)

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	amniotic membrane (AM)-derived matrix				
4.	Amniotic membrane	Ten patients of flexor tendon injury	Human	Unfavourable results	Leppanen OV *et al.* (2017)
5.	Amniotic membrane	19 patients of flexor tendon injury	Human	Quicker function and better tendon healing	Saket Parkash *et al.* (2020)

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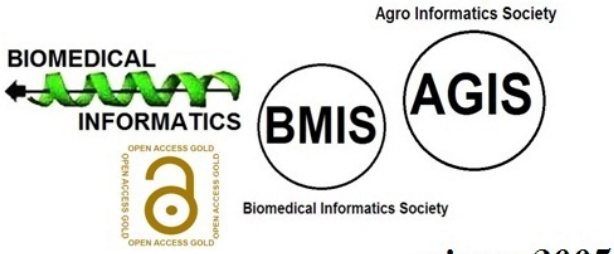

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