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Original Article

Effects of Acellular Dermal Matrix and Epidermal Growth Factor on Tendon Healing and Functional Recovery: An Experimental Rat Model Study

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ABSTRACT

Objective: Although flexor tendon injuries are relatively uncommon, they pose significant challenges due to postoperative complications such as adhesion formation and tendon ruptures, potentially resulting in substantial functional impairment. Contemporary research efforts increasingly focus on optimizing surgical outcomes by targeting the biochemical and cellular mechanisms underlying tendon healing. This study aimed to investigate the effects of acellular dermal matrix (ADM) and epidermal growth factor (EGF) on tendon healing, biomechanical strength, and functional recovery in a rat Achilles tendon repair model.

Methods: Thirty-three male Sprague-Dawley rats were randomly allocated into three groups: Group 1 (primary repair only), Group 2 (repair with ADM wrapping), and Group 3 (repair with ADM wrapping combined with local EGF injection). At six weeks postoperatively, functional recovery was assessed using the modified Achilles Functional Index (AFI), while biomechanical testing evaluated tensile strength. Histopathological analysis was performed to assess vascularization, fibroblast proliferation, inflammatory infiltration, and collagen deposition.

Results: Group 3 exhibited significantly greater tensile strength compared to Group 1 ($p<0.008$), alongside markedly increased collagen deposition ($p=0.007$). Functional assessment revealed that AFI scores in Group 3 approximated those of healthy controls, suggesting superior restoration of tendon function. While no significant differences were observed among groups regarding vascularization, inflammatory infiltration or fibroblast activity, ADM usage was associated with enhanced fibroblast proliferation and improved collagen organization.

Conclusion: The combination of ADM and EGF significantly improved tendon biomechanical strength and functional recovery in this experimental model. ADM provided a supportive scaffold for cellular integration, whereas EGF augmented collagen synthesis and promoted tissue regeneration. These findings highlight the potential of combined ADM and EGF therapy as a promising approach for enhancing tendon healing.

INTRODUCTION

The hand plays a crucial role in many aspects of our lives, not only due to its high tactile sensitivity but also its superior motor skills. Tendons play a critical role in the development of these motor skills. In hand trauma, particularly in flexor tendon injuries, despite an incidence rate of 4.83 per 100,000 annually, the treatment process and associated morbidities impose a significant burden on individuals, society, and the healthcare system.[1] Although well-defined surgical treatment principles exist for flexor tendon injuries, postoperative complications such as adhesions and ruptures, which are frequently encountered, may lead to functional loss. Therefore, the search for new protocols that optimize postoperative healing and restore functionality continues. This pursuit has increasingly directed researchers' attention toward the cellular and biochemical aspects of tendon healing.[2]

It is known that many factors, primarily growth factors, play a role in the tendon healing process. Collagen, which constitutes the majority of healthy tendon structure and whose production increases in response to tendon injury, is also present in MatriDerm®, an acellular dermal ma-

trix (ADM) used in acute and chronic wound healing.[3,4] Several studies in the literature have reported successful outcomes in the use of different tissue scaffolds either by wrapping the repair site or filling the tendon defect during tendon repair.[5] However, there are only a limited number of studies evaluating the histological and biomechanical effects of Epidermal Growth Factor (EGF) in combination with different tissue scaffolds on tendon healing. To date, no study has specifically assessed the effects of ADM combined with EGF on tendon healing.

In this study, tendon healing, strength, and functional outcomes were evaluated using ADM and EGF following Achilles tendon repair in rats. Thus, our study aims to develop a protocol to improve surgical outcomes in tendon injuries.

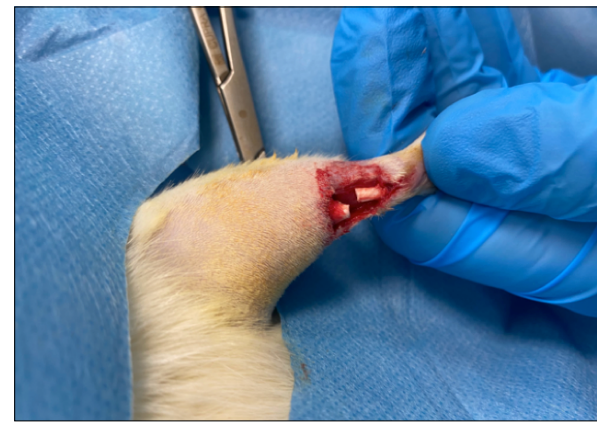

Figure 1. Complete transection of the Achilles tendon.

MATERIALS AND METHODS

Approval for the present study was obtained from the Ethics Committee for Animal Experiments (Approval No: 2022/07-12; Date: 05/07/2022). All experimental procedures were conducted in strict accordance with the institutional guidelines for the care and use of laboratory animals. A total of 33 male Sprague Dawley rats, aged 8 to 12 weeks and weighing between 350 and 450 grams, were utilized. Animals were housed individually in standard cages under controlled environmental conditions (22°C room temperature; 12-hour light/dark cycle). All rats had free access to standard pellet diet and tap water throughout the study period. Subjects were randomly allocated into three experimental groups as follows: Group 1 underwent primary tendon repair only; Group 2 underwent tendon repair followed by application of an acellular dermal matrix (ADM) around the repair site; and Group 3 underwent tendon repair combined with ADM application and local injection of Epidermal Growth Factor (EGF) at the tendon ends and repair site. At the end of the sixth postoperative week, all animals underwent physiological evaluation, after which tendon specimens were harvested for histopathological and biomechanical analyses. Sample size determination was guided by a priori power analysis, indicating that inclusion of 5 to 8 rats per group would be sufficient to detect statistically significant differences. Accordingly, six rats per group were allocated for histopathological evaluation, and five rats per group were allocated for biomechanical tensile strength testing.

Surgical Technique

Thirty minutes prior to surgery, 15 mg/kg Cefazolin sodium was administered subcutaneously for prophylaxis. Anesthesia was induced via intraperitoneal injection of 80 mg/kg ketamine and 7 mg/kg xylazine, with depth assessed by toe and skin pinch responses. All procedures were performed by a single surgeon under standard sterile conditions. For analgesia, 2 mg/kg meloxicam was given postoperatively, followed by 1 mg/kg on postoperative days 1 and 2. The right lower limbs were shaved, placed prone, and prepped with 10% polyvinylpyrrolidone-iodine (Batticon®).

In Group 1, a 3 cm vertical incision was made over the right Achilles tendon. Following dissection, the tendon was transected 2 cm proximal to its calcaneal insertion and repaired using the modified Kessler technique with 5/0 polypropylene sutures, plus epitendinous sutures with 6/0 polypropylene. The skin was closed and re-disinfected. In Group 2, the same repair was performed and wrapped with a 1 mm acellular dermal matrix (ADM; MatriDerm®). In Group 3, ADM coverage was followed by local injection of 25 µg/kg EGF (Heberprot-P) into the repair site and tendon ends.

All animals resumed unrestricted activity postoperatively. On day 42, euthanasia was performed using CO_2. Re-exploration showed intact repairs with complete ADM absorption in Groups 2 and 3. Tendons were excised en bloc from the musculotendinous junction to proximal calcaneus. In each group, 6 specimens were allocated for histology and 5 for biomechanical testing (Fig. 1).

Acellular Dermal Matrices (ADM) and Matriderm®

Biological matrices were initially used in stress urinary incontinence and pelvic floor reconstruction surgery, later expanding into applications such as abdominal wall and hernia repair.[6] In recent years, acellular dermal matrices (ADMs) derived from human cadaveric, bovine, and porcine dermis, intestinal submucosa, and bladder tissue have been widely used in burn surgery, breast reconstruction, and various tissue defect repairs.[6] Additionally, ADMs have been applied in Achilles tendon and rotator cuff repairs.[6]

When implanted into recipient tissue, ADMs undergo matrix remodeling following inflammatory cell infiltration, leading to increased collagen and elastin production, followed by revascularization. ADMs serve as a scaffold to support tissue growth.[7] MatriDerm® is a bovine-derived ADM containing type I, III, and V collagen and elastin, acting as a scaffold for skin regeneration and modulating scar tissue formation.[8] Tendon structure primarily consists of type I collagen, proteoglycans, glycosaminoglycans,

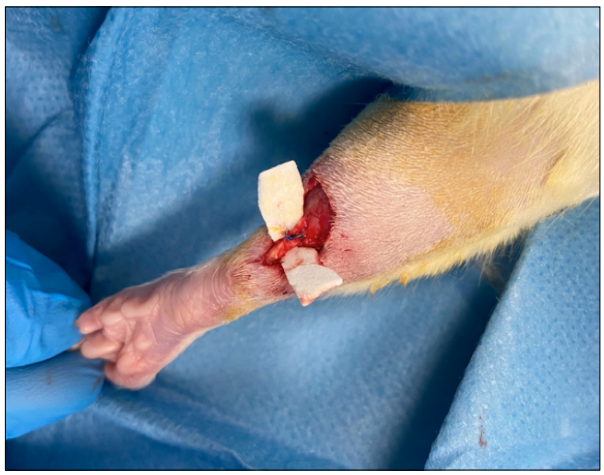

Figure 2. Wrapping of the repair site with acellular dermal matrix.

and elastin. During tendon healing, the synthesis of these components increases, particularly in the inflammatory and proliferative phases.[9] MatriDerm® is hypothesized to support tendon healing by providing extracellular matrix (ECM) proteins and serving as a scaffold for inflammatory cells and fibroblasts during the healing process. In this study, MatriDerm® was expected to regulate healing by providing essential ECM proteins during tendon repair and serving as a scaffold for cellular activity (Fig. 2).

Epidermal Growth Factor (EGF)

EGF is a polypeptide synthesized by fibroblasts and macrophages, with increased concentrations during the inflammatory phase of wound healing, where it plays a crucial role in epidermal maturation and proliferation.[10] In addition to inducing keratinocyte proliferation and migration, EGF stimulates fibroblast migration and is responsible for granulation tissue formation.[11] Understanding its effects on wound healing has led to the development of various EGF-containing products. One such product, recombinant human epidermal growth factor, has been successfully used topically and via intralesional injection for diabetic foot ulcers.[12] EGF also enhances collagen production by promoting fibroblast proliferation and migration, significantly contributing to tendon healing.[13] Following tendon repair, EGF concentrations increase in the local environment.[14] When applied exogenously, EGF significantly increases the number of tenocytes, DNA content, and collagen production (Fig. 3).[15]

Walking Test

The plantar surfaces of the rats' feet were stained with black ink, and the animals were then allowed to walk on a flat white surface. Footprints were recorded and photographed according to their numbering to evaluate walking function on the preoperative day and on postoperative day 42. The study was terminated at week 6, which corresponds to the remodeling phase, considering that the proliferative phase—during which the majority of collagen, proteoglycans, and other extracellular matrix (ECM) components required for tendon healing are synthesized—was expected to be completed.[4,16] Functional evaluation was performed using the Modified Achilles Functional Index (AFI).[17] In both the non-operated (N) and operated (O) limbs, the following parameters were measured from each footprint: Print length (PL), distance between intermediary toes (IT; i.e., between the second and fourth digits), and total toe spreading (TS; i.e., between the first and fifth digits). For each rat, the average of three footprints from the left and three from the right foot was calculated and included in the analysis (Fig. 4).

The following formulas were used to compute the print length factor (PLF), toe spread factor (TSF), and intermediary toe spread factor (ITF), respectively:

Print Length Factor (PLF): (NPL-OPL) / OPL

Toe Spread Factor (TSF): (OTS-NTS) / NTS

Intermediary Toe Spread Factor (ITF): (OIT-NIT) / NIT

Subsequently, the Achilles Functional Index was calculated using the following equation based on the derived factors:

$$AFI=(74\times PLF)+(161\times TSF)+(48\times ITF)-5$$

Figure 3. Injection of epidermal growth factor into the repair site wrapped with acellular dermal matrix.

Figure 4. Walking of rats with ink-stained soles on a white surface.

Biomechanical Evaluation

The biomechanical analysis was conducted at the Mechanical Engineering Application Laboratory. The Achilles tendon was excised en bloc from the distal calcaneus to the proximal myotendinous junction. The harvested tendon was mounted onto a universal testing machine (Instron®, Model 3382A) by securing both ends with clamps. Using the Instron Bluehill software, the tensile test was programmed to apply a constant elongation rate of 5 mm/min. Throughout the test, real-time data including force (N), elongation (mm), and time (s) were recorded. Force–elongation curves were obtained as a function of time. Peak values of force and elongation, along with the corresponding time points at which these peaks occurred, were documented in Newtons, millimeters, and seconds, respectively (Fig. 5).

Histopathological Evaluation

Following fixation in 10% formaldehyde, the tissue samples were decalcified using 10% nitric acid. Subsequent tissue processing was performed automatically using the Leica ASP300 tissue processor. Processed tissues were embedded in paraffin blocks, which were subsequently cooled. Sections with a thickness of 3–5 µm were obtained using a microtome (Leica RM2125RT) and mounted on microscope slides. To remove residual paraffin, the slides were incubated in a drying oven and immersed in xylene. Histological staining and coverslipping were carried out using automated devices (Tissue-Tek Prisma® Plus and Tissue-Tek Film®). The stained sections were examined under a light microscope (Olympus BX53). Microscopic fields adjacent to the tendon repair site were evaluated by a blinded pathologist using a semi-quantitative scoring system. The following histological parameters were assessed: Vascularization, fibroblast density, inflammatory cell infiltration, and collagen deposition. Each parameter was scored on a four-point scale based on intensity (0: None, 1: Mild, 2: Moderate, 3: Severe)

Statistical Analysis

All analyses were performed using statistical software packages. Categorical variables were presented as frequencies and percentages. For continuous variables, descriptive statistics including mean, standard deviation, median, minimum, and maximum values were calculated. Normality of data distribution was assessed using the Shapiro-Wilk test. As the continuous variables were not normally distributed, comparisons between two independent groups were performed using the Mann–Whitney U test, while comparisons among more than two groups were conducted using the Kruskal–Wallis test. For comparisons of histopathological findings between groups, the Pearson Chi-Square test and Fisher's Exact test were employed as appropriate. The correlation between tensile strength and the Achilles Functional Index was evaluated using the Spearman correlation test. A p-value of less than 0.05 was considered statistically significant.

Figure 5. Placement of the dissected Achilles tendon into the tension testing device.

RESULTS

Functional Evaluation

The TSF (Toe Spread Factor) values of Group 3 were found to be significantly higher than those of Group 1 ($p<0.001$) and Group 2 ($p=0.034$). Additionally, Group 2 exhibited significantly higher TSF values compared to Group 1 ($p=0.008$). In contrast, no statistically significant differences were observed among the groups in terms of PLF (Print Length Factor) ($p=0.527$) and ITF (Intermediary Toe Spread Factor) ($p=0.279$) median values. The Achilles Functional Index (AFI) values of Group 1 were significantly lower than those of Group 2 ($p=0.013$) and Group 3 ($p<0.001$). The difference in AFI values between Group 2 and Group 3 did not reach statistical significance but showed borderline significance ($p=0.056$). When compared to the healthy population, the AFI values of both Group 1 and Group 2 were found to be significantly lower ($p=0.001$).However, no statistically significant difference was found between Group 3 and the healthy population ($p=0.054$) (Table 1; Table 2).

Biomechanical Evaluation

Following functional assessment, the repaired Achilles tendons were dissected in all groups, and biomechanical tensile testing was conducted. No statistically significant differences were found between Group 1 and Group 2 ($p=0.056$) or between Group 2 and Group 3 ($p=0.151$). However, the tensile strength in Group 1 was found to be significantly lower than in Group 3 ($p<0.008$). No statistically significant correlation was observed between tensile strength and Achilles Functional Index (AFI) values (Spearman's rho=0.489, $p=0.06$) (Table 3).

Table 1. Comparison of AFI values between groups

Group (n=11)	Median	Minimum	Maximum	Comparison	p-value
Group 1	-27.278	-42.699	-7.440	Group 1 vs Group 2	0.013
Group 2	-14.296	-38.775	1.258	Group 1 vs Group 3	<0.001
Group 3	-6.052	-14.487	4.823	Group 2 vs Group 3	0.056

Note. p<0.05 is considered statistically significant. AFI: Achilles Functional Index.

Table 2. Comparison of AFI values with healthy controls

Group	Median	Minimum	Maximum	Comparison	p-value
Group 1 (n=11)	-27.278	-42.699	-7.44	Group 1 vs Healthy Group	0.001
Group 2 (n=11)	-14.296	-38.775	1.258	Group 2 vs Healthy Group	0.001
Group 3 (n=11)	-6.052	-14.487	4.823	Group 3 vs Healthy Group	0.054
Healthy Group (n=20)	2.223	-13.432	12.2		

Note: p<0.05 is considered statistically significant. AFI: Achilles Functional Index.

Table 3. Comparison of tensile strength values between groups

Group	Median	Minimum	Maximum	Comparison	p-value
Group 1	4629829.00	3815041.00	5401762.00	Group 1 vs Group 2	0.056
Group 2	5541081.00	4930054.00	6129739.00	Group 1 vs Group 3	<0.008
Group 3	5955242.00	5423209.00	6555269.00	Group 2 vs Group 3	0.151

Note. p<0.05 is considered statistically significant.

Table 4. Comparison of collagen deposition among the groups

Group (N=6)	None	Mild	Moderate	Severe	Comparison	p-value
Group 1	0 (0%)	2 (33.3%)	4 (66.7%)	0 (0%)	Group 1 vs Group 2	0.931
Group 2	0 (0%)	3 (50%)	1 (16.7%)	2 (33.3%)	Group 1 vs Group 3	0.007
Group 3	0 (0%)	0 (0%)	1 (16.7%)	5 (83.3%)	Group 2 vs Group 3	0.071

Note: p<0.05 is considered statistically significant.

Histopathological Evaluation

After functional evaluation, six tendons from each group were subjected to histopathological examination. There were no statistically significant differences between groups in terms of inflammatory cell infiltration (p=1), neovascularization (p= 0.645), or fibroblastic activity (p=0.576). However, comparison of collagen deposition revealed that specimens from Group 3 exhibited significantly more intense collagen accumulation compared to group 1 (p=0.007). whereas no significant differences were found between Group 1 and Group 2 (p=0.931) or between Group 2 and Group 3 (p=0.071). MatriDerm® appeared to be largely degraded in histological sections. In Groups 2 and 3, only one section from each group showed limited residual non-degraded material, surrounded by foreign body-type multinucleated giant cells (Table 4).

DISCUSSION

It is well-established that several growth factors—including transforming growth factor-beta (TGF-β), fibroblast growth factor (FGF), vascular endothelial growth factor

(VEGF), platelet-derived growth factor (PDGF), and epidermal growth factor (EGF)—modulate tendon healing at various stages through distinct cellular mechanisms. [18] Although numerous clinical and experimental studies have investigated the role of EGF in wound healing, granulation tissue formation, and epithelialization, data on its effect on tendon healing remain limited. Gauger et al.[19] demonstrated that EGF increases tenocyte numbers in a dose-dependent manner but has only a limited effect on collagen synthesis. Tsubone et al.[14] reported increased levels of EGF, IGF, and bFGF around the site of inflammation following flexor tendon repair. Similarly, Duffy et al.[20] found elevated EGF concentrations around injured tendons. Franklin et al.[15] showed that exogenous EGF injection into rat Achilles tendons enhanced cell counts, DNA content, and collagen deposition. EGF has been shown to enhance fibroblast proliferation, migration, and collagen production, all of which are essential components of tendon healing.[13,21]

In our study, the tensile strength in the EGF group was significantly higher than in the repair-only group ($p<0.008$). These findings suggest that the increased local concentration of EGF following its administration may contribute to enhanced tensile strength. Zhao et al.[22] showed that the use of a collagen membrane improved tensile test outcomes at postoperative weeks 4 and 8 in rat Achilles tendon repairs. Likewise, a clinical study using human ADM for Achilles tendon repair reported no cases of re-rupture after a 20-month follow-up, implying a supportive role of ADM in tendon regeneration.[23]

MatriDerm®, which contains high levels of type I collagen and elastin, is believed to support tendon healing by providing essential extracellular matrix (ECM) proteins. Moreover, it may act as a scaffold for inflammatory cells during the early phase and for fibroblasts during the proliferative phase, thereby regulating tissue regeneration. Although no statistically significant difference in tensile strength was found between the MatriDerm® group and the repair-only group, the former demonstrated a higher mean tensile strength.

In our study, tendon samples were evaluated on postoperative day 42, corresponding to the remodeling phase.[16] The absence of marked inflammation in any group likely reflects the reduced cellular density at the repair site and progression to the remodeling phase. The lack of significant differences in inflammatory infiltration among groups suggests that neither EGF nor MatriDerm® triggered prolonged inflammation.

Previous studies have reported various tissue responses to dermal matrix applications. For instance, porcine intestinal submucosa has been associated with severe inflammatory reactions due to residual DNA and cellular components, while cross-linked equine pericardium matrices have shown poor integration and foreign body reactions. [24,25] Unlike these, MatriDerm® used in our study is not chemically cross-linked-a feature known to promote faster tissue integration.[19] Histopathological analysis revealed near-complete degradation of MatriDerm®; only one specimen in each of Groups 2 and 3 displayed limited residual material surrounded by foreign body-type giant cells. These findings indicate that MatriDerm® is rapidly degraded and integrated into the tissue without eliciting significant inflammation. Additionally, the absence of cellular and DNA residues likely reduces its immunogenic potential.

Although there were no statistically significant differences in fibroblastic activity among groups, half of the specimens in Groups 2 and 3 exhibited pronounced fibroblastic activity, while only one specimen in Group 1 showed similar findings. Furthermore, all specimens with low fibroblastic activity were observed in Group 1. These results suggest that MatriDerm® may stimulate fibroblastic activity, although the addition of EGF did not appear to further enhance this effect.

It is known that dermal matrices facilitate fibroblast colonization.[26] The slightly elevated fibroblastic activity observed in the MatriDerm® groups supports this concept. Despite literature reports that EGF enhances fibroblast proliferation and migration,[13,20,21] our study did not reveal a significant impact of EGF on fibroblastic activity. This may be due to the single-dose administration of EGF during surgery and the lack of repeated dosing during later stages of healing, resulting in insufficient local concentration—especially during the proliferative phase when fibroblastic activity peaks.

During the inflammatory phase of tendon healing, type III collagen is produced by tenocytes and fibroblasts.[3] This synthesis peaks during the proliferative phase and transitions to type I collagen during the remodeling phase. [16] The deposited collagen constitutes the structural framework of the repaired tendon, contributing to tensile strength and stiffness.[27] Franklin et al.[15] found that 15 days of EGF injection into injured rat Achilles tendons increased collagen content. Similarly, the EGF group in our study showed more collagen accumulation compared to repair only group. The higher tensile strength observed in this group supports the notion that increased collagen content positively affects tendon strength.

The Achilles Functional Index (AFI), developed by Murrel et al.,[17] is a validated scale for assessing tendon function. Among its most sensitive parameters are intermediary toe spread and total toe spread distances. In our study, no significant differences were noted in intermediary toe spread or print length factors, whereas total toe spread was significantly higher in the MatriDerm®+EGF group compared to the other groups, and also higher in the MatriDerm® group compared to the repair-only group. The AFI scores in the repair-only group were significantly lower than those in the other groups.

When compared with healthy controls, only the repair-only and MatriDerm® groups had significantly lower AFI scores, whereas the MatriDerm®+EGF group did not differ significantly from healthy rats. Studies in the literature investigating dermal matrices and growth factors for

tendon repair have reported similar findings. For example, Gabler et al.[28] found significantly lower AFI scores on postoperative day 28 in rats treated with bovine or porcine-derived dermal matrices. Although no prior study has evaluated EGF in terms of AFI scores, a study by Kurtz et al.[29] demonstrated that IGF application in transected rat Achilles tendons significantly improved AFI scores starting from day 1.[29] Our results suggest that EGF exhibits similar effects to IGF, as the AFI scores in the EGF group closely approximated those of healthy controls, indicating its potential to enhance tendon function and healing outcomes.

Although a strong correlation between AFI and tensile strength was previously reported by Best et al.,[30] our study did not find a statistically significant association. Nevertheless, the group with the highest tensile strength also had the highest AFI scores, supporting a potential relationship.

In our study, EGF was administered as a single intraoperative dose. Although co-application with MatriDerm® was intended to maintain local concentration, sustained release through repeated injections was not provided. This may have limited the efficacy of EGF, particularly during the late inflammatory and proliferative phases. Additionally, different healing stages (acute, subacute, chronic) were not assessed, as the study focused only on day 42 postoperatively. Future studies with extended follow-up may better elucidate the long-term effects of EGF and ADM.

In conclusion, EGF demonstrated a significant capacity to enhance tendon tensile strength, with corresponding improvements in functional outcomes. When combined with dermal matrix, which also increased tendon strength, EGF yielded statistically significant improvements in walking function. Future studies optimizing EGF dosage and administration schedules, along with long-term evaluation, may yield further insights into its therapeutic potential across the stages of tendon healing.

Conclusion

Although previous studies have explored the effects of various scaffolds and epidermal growth factor (EGF) on tendon healing, they have generally lacked assessments of tendon functionality. To our knowledge, no prior study has evaluated the combined use of MatriDerm® and EGF with the aim of enhancing tendon strength following repair.

Our findings demonstrate that this combination supports tendon regeneration and contributes to improvements in both tensile strength and functional outcomes. These results provide valuable contributions to the existing body of literature and offer a promising foundation for future investigations aimed at optimizing tendon healing protocols.

Ethics Committee Approval

The study was approved by the Yeditepe University Animal Experiments Local Hospital Ethics Committee (Date: 05.07.2022, Decision No: 2022/07-12).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: C.A., C.C.; Design: C.A., C.C.; Supervision: C.A., C.C.; Fundings: C.A., C.C.; Materials: C.A., C.C.; Data collection &/or processing: C.A.; Analysis and/or interpretation: C.A.; Literature search: C.A.; Writing: C.A.; Critical review: C.A., C.C.

Conflict of Interest

None declared.

REFERENCES

1. Kwan TD, El Haj AJ. Multifactorial tendon tissue engineering strategies. In: Tendon Regeneration. Academic Press; 2015. p. 281–320. [CrossRef]
2. Dy CJ, Hernandez-Soria A, Ma Y, Roberts TR, Daluiski A. Complications after flexor tendon repair: A systematic review and meta-analysis. J Hand Surg Am 2012;37:543–51. [CrossRef]
3. Oakes BW. Tissue healing and repair: tendons and ligaments. In: Rehabilitation of Sports Injuries: Scientific Basis. 2003. p. 28–98. [CrossRef]
4. Garner WL, McDonald JA, Koo M, Kuhn C 3rd, Weeks PM. Identification of the collagen-producing cells in healing flexor tendons. Plast Reconstr Surg 1989;83:875–9. [CrossRef]
5. Barber FA, Herbert MA, Boothby MH. Ultimate tensile failure loads of a human dermal allograft rotator cuff augmentation. Arthroscopy 2008;24:20–4. [CrossRef]
6. Anaim AA. Use of a non-crosslinked porcine dermal matrix in repair of the achilles and other tendons of the foot. Foot Ankle Spec 2018;1:1938640017751189. [CrossRef]
7. Petrie K, Cox CT, Becker BC, MacKay BJ. Clinical applications of acellular dermal matrices: A review. Scars Burn Heal 2022;8:20595131211038313. [CrossRef]
8. Cervelli V, Brinci L, Spallone D, Tati E, Palla L, Lucarini L, et al. The use of MatriDerm® and skin grafting in post-traumatic wounds. Int Wound J 2011;8:400–5. [CrossRef]
9. Kannus P. Structure of the tendon connective tissue. Scand J Med Sci Sports 2000;10:312–20. [CrossRef]
10. Cohen S. Isolation of a mouse submaxillary gland protein accelerating incisor eruption and eyelid opening in the new-born animal. J Biol Chem 1962;237:1555–62. [CrossRef]
11. Hardwicke J, Schmaljohann D, Boyce D, Thomas D. Epidermal growth factor therapy and wound healing--Past, present and future perspectives. Surgeon 2008;6:172–7. [CrossRef]
12. Yang Q, Zhang Y, Yin H, Lu Y. Topical recombinant human epidermal growth factor for diabetic foot ulcers: A meta-analysis of randomized controlled clinical trials. Ann Vasc Surg 2020;62:442–51. [CrossRef]
13. Carpenter G, Cohen S. Human epidermal growth factor and the proliferation of human fibroblasts. J Cell Physiol 1976;88:227–37. [CrossRef]
14. Tsubone T, Moran SL, Amadio PC, Zhao C, An KN. Expression of growth factors in canine flexor tendon after laceration in vivo. Ann Plast Surg 2004;53:393–7. [CrossRef]
15. Franklin TJ, Gregory H, Morris WP. Acceleration of wound healing by recombinant human urogastrone (epidermal growth factor). J Lab

Clin Med 1986;108:103–8.
16. Liu SH, Yang RS, al-Shaikh R, Lane JM. Collagen in tendon, ligament, and bone healing. A current review. Clin Orthop Relat Res 1995;318:265–78.
17. Murrell GA, Lilly EG, Davies H, Best TM, Goldner RD, Seaber AV. The Achilles Functional Index. J Orthop Res 1992;10:398–404. [CrossRef]
18. Almekinders LC, Banes AJ. The use of growth factors in the management of tendinopathies. In: Tendon Injuries: Basic Science and Clinical Medicine. London: Springer London; 2005. p. 298–303. [CrossRef]
19. Gauger A, Robertson C, Greenlee TK Jr, Riederer-Henderson MA. A low-serum medium for tendon cells: Effects of growth factors on tendon cell growth and collagen production. In Vitro Cell Dev Biol 1985;21:291–6. [CrossRef]
20. Duffy FJ Jr, Seiler JG, Gelberman RH, Hergrueter CA. Growth factors and canine flexor tendon healing: Initial studies in uninjured and repair models. J Hand Surg Am 1995;20:645–9. [CrossRef]
21. Mehta V, Mass D. The use of growth factors on tendon injuries. J Hand Ther 2005;18:87–92. [CrossRef]
22. Zhao H, Guan HG, Gu J, Luo ZP, Zhang W, Chen B, et al. Collagen membrane alleviates peritendinous adhesion in the rat Achilles tendon injury model. Chin Med J (Engl) 2013;126:729–33. [CrossRef]
23. Lee DK. Achilles tendon repair with acellular tissue graft augmentation in neglected ruptures. J Foot Ankle Surg 2007;46:451–5. [CrossRef]
24. Zheng MH, Chen J, Kirilak Y, Willers C, Xu J, Wood D. Porcine small intestine submucosa (SIS) is not an acellular collagenous matrix and contains porcine DNA: Possible implications in human implantation. J Biomed Mater Res B Appl Biomater 2005;73:61–7. [CrossRef]
25. DeCarbo WT, Feldner BM, Hyer CF. Inflammatory reaction to implanted equine pericardium xenograft. J Foot Ankle Surg 2010;49:155–8. [CrossRef]
26. Molnar JA, DeFranzo AJ, Hadaegh A, Morykwas MJ, Shen P, Argenta LC. Acceleration of Integra incorporation in complex tissue defects with subatmospheric pressure. Plast Reconstr Surg 2004;113:1339–46. [CrossRef]
27. James R, Kesturu G, Balian G, Chhabra AB. Tendon: Biology, biomechanics, repair, growth factors, and evolving treatment options. J Hand Surg Am 2008;33:102–12. [CrossRef]
28. Gabler C, Saß JO, Gierschner S, Lindner T, Bader R, Tischer T. In vivo evaluation of different collagen scaffolds in an Achilles tendon defect model. Biomed Res Int 2018;2018:6432742. [CrossRef]
29. Kurtz CA, Loebig TG, Anderson DD, DeMeo PJ, Campbell PG. Insulin-like growth factor I accelerates functional recovery from Achilles tendon injury in a rat model. Am J Sports Med 1999;27:363–9. [CrossRef]
30. Best TM, Collins A, Lilly EG, Seaber AV, Goldner R, Murrell GA. Achilles tendon healing: A correlation between functional and mechanical performance in the rat. J Orthop Res 1993;11:897–906. [CrossRef]

Aşil Tendonu Onarılan Sıçanlarda Aselüler Dermal Matriks ve Rekombinant Epidermal Büyüme Faktörü Uygulamasının Tendon İyileşmesi ve Yürüme Fonksiyonuna Etkisi

Amaç: Fleksör tendon yaralanmaları nispeten nadir görülmekle birlikte, adezyon ve tendon rüptürleri gibi postoperatif komplikasyonlara bağlı olarak ciddi fonksiyonel kayıplara yol açabilmektedir. Günümüzde araştırmalar, tendon iyileşmesinin biyokimyasal ve hücresel mekanizmalarını hedef alarak cerrahi sonuçların iyileştirilmesine odaklanmaktadır. Bu çalışmanın amacı, aselüler dermal matriks (ADM) ve epidermal büyüme faktörünün (EGF) tendon iyileşmesi, biyomekanik dayanıklılığı ve fonksiyonel iyileşme üzerindeki etkilerini sıçan Aşil tendonu onarım modeli kullanarak araştırmaktır.

Gereç ve Yöntem: Otuz üç adet erkek Sprague-Dawley cinsi sıçan rastgele üç gruba ayrıldı: Grup 1 (sadece primer onarım), Grup 2 (ADM ile sarılarak onarım) ve Grup 3 (ADM ile sarılarak onarım + EGF enjeksiyonu) olarak planlandı. Postoperatif altıncı haftada yürüme testi ile modifiye Aşil Fonksiyonel İndeksi (AFI) ile fonksiyonel iyileşme değerlendirilmesi sonrası sıçanlar sakrifiye edilerek biyomekanik testler ile tendonun gerilme kuvveti ölçüldü. Onarılan tendonda yapılan histopatolojik analizlerde vaskülarizasyon, fibroblast proliferasyonu, inflamatuvar infiltrasyon ve kollajen depozisyonu incelendi. Gruplar birbirleri arasında ve sağlıklı kontrol grubu ile karşılaştırıldı.

Bulgular: Grup 3'te tendon gerim kuvveti Grup 1'e kıyasla anlamlı olarak daha yüksek bulundu ($p<0.008$) bunun yanında kollajen depozisyonunda Grup 1'e kıyasla belirgin şekilde artış izlendi ($p=0.007$). AFI skorları açısından, Grup 3'ün değerleri sağlıklı kontrol grubuna en yakın sonuçları gösterdi. İnflamatuvar infiltrasyon, vaskülarizasyon ve fibroblast aktivitesi açısından gruplar arasında anlamlı bir fark bulunmazken, ADM kullanımının fibroblast proliferasyonu ve kollajen organizasyonu üzerinde olumlu etkisi olduğu gözlendi.

Sonuç: Bu deneysel modelde, ADM ve EGF kombinasyonu, tendonun biyomekanik dayanıklılığı ile fonksiyonel iyileşmeyi anlamlı ölçüde artırmıştır. ADM, hücresel entegrasyon için destekleyici bir iskelet sağlarken, EGF kollajen sentezini artırmış ve doku rejenerasyonunu teşvik etmiştir. Bu bulgular, ADM ve EGF kombinasyonunun tendon iyileşmesini güçlendirmek için umut verici bir yaklaşım olabileceğini göstermektedir.

Anahtar Sözcükler: Aselüler dermal matriks; Aşil fonksiyonel indeksi; epidermal büyüme faktörü; tendon iyileşmesi; tendon onarımı.