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Article

Histopathological Study of the Effect of Xenogeneic Platelet-Rich Fibrin on Achilles Tendon Healing in Rabbit

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ABSTRACT

Tendon is a mechanical bridge that transforms the force generated by muscle contraction into movement. This tissue is well known for its low cellularity and vascularity; therefore, any tendon damage is characterized by a slow and inefficient healing process resulting in mechanically, structurally, and functionally inferior tissue. The current study aimed to evaluate the effect of the regenerative capacity of xenogeneic platelet-rich fibrin on the acceleration of Achilles tendon healing in rabbits. 24 adult rabbits weighing (1.5-2) kg were used in this study. The animals were divided equally into three groups: A-PRF group, in which the tendon defect was treated with xenogeneic Advance-platelet rich fibrin; L-PRF group, which used xenogeneic for tendon defect treatment; and control groups treated with normal saline. Clinical investigation of the rabbits during the experiment period revealed improvement of lameness and disappearance of swelling and redness at the operation site in the A-PRF and L-PRF groups compared to the control group at the same period. Histopathological examination revealed a good tendon healing process in the A-PRF group characterized by a highly organized Achilles tendon and lightly stained collagen fibers arranged in parallel. At the same time, these are less evident in the L-PRF group. In conclusion, this study suggests that xenogeneic Advanced platelet-rich fibrin treatment can be useful as a biomaterial for accelerating Achilles tendon healing in rabbits and this biomaterial.

Keywords: Xenogeneic platelet-rich fibrin; Rabbit Achilles tendon; tendon healing; Advanced platelet-rich fibrin; Iraq.

INTRODUCTION

Tendons are collagen structures that transmit traction from muscles to bones. Tendon tissue has low blood supply, cell turnover, and metabolism. Healing from tendon injuries is protracted and often results in the formation of lower scars or residual lesions. The high rate of tendon damage is due to the gradual wear of the tendon tissue due to overuse. These injuries usually occur during exercise, sports, or daily activities with weight bearing and high mechanical stress. Recently, large and small animals have been used to tackle tendon healing. For example, the rabbit

Achilles tendon has the same biochemical advantages as the flexor tendon of the human hand [1]. Sheep have also been used as an animal model for experimental studies of superficial finger flexor tendon healing [2]. Although recent therapeutic strategies based on biomaterials have shown potential for tendon healing, future research should aim to find the best combination of biomaterials and regeneration factors ideal for tendon repair [3]. Laser treatment has been used to treat the Achilles tendon in rabbits and has shown a wavelength-dependent effect on tendon healing [4]. Platelet-rich concentrations are regenerative biomaterials most widely applied in various clinical scenarios like healing therapies, ophthalmology, orthopedics, and wound healing [5]. Platelet-rich plasma can also be used with mesenchymal stem cells to treat growth plate defects in sheep [6]. Platelet-rich fibrin (PRF) is the second generation of platelet concentration with huge potential in many fields of medicine, such as wound healing, esthetic medicine and surgery [7]. PRF can be used as a beneficial adjuvant to promote the healing process for a range of chronic tendons, muscles, bones, and other soft tissue [injuries 8]. It is a cytokine delivery vehicle promoting cell viability proliferation, differentiation and extracellular matrix synthesis. Recently, we investigated the effect of platelet-rich fibrin (PRF) on the healing and regeneration of rabbit Achilles tendon.

MATERIALS AND METHODS

Animals

The present study was conducted after approval from the University of Basrah -Faculty of Veterinary Medicine Research Committee, and all animal procedures were conducted according to guidelines provided by the Faculty of Veterinary Medicine, University of Basrah. Twenty-four adult rabbits (both sexes) weighing (1.5-2) kg were used in this study. The animals were acclimatized for seven days before surgery and divided into three groups as follows: - Control group (treated with normal saline), L-PRF group (treated with Leukocyte -platelet-rich fibrin), and A-PRF group (treated with Advance-platelet rich fibrin). The animal anesthetic protocol was accomplished by intramuscular injection of a combination of ketamine HCL 10 mg/kg and xylazine 3 mg /kg, and for maintaining anesthesia, only one-third of the ketamine dose can be used [9].

Surgical procedure

The right hind limb was prepared surgically by shaving and cleaned with iodine. Exposure of the Achilles tendon was achieved by a midline skin, subcutis and fascia incision at about 1cm distal to the gastrocnemius muscle 1cm above the calcaneus (Figure 1A). After Achilles tendon exposure, stay sutures were placed on both proximal and distal end of the tendon to mark the proposed tendon defect (Figure 1B). A core lesion defect was created by perforating the Achilles tendon using a needle gauge 16 inches (Figure 1C). In the control group, the tendon defect was treated locally (Figure 1D) using normal saline, while in the L-PRF group, the tendon defect was locally treated with leukocyte-platelet-rich fibrin. In the A-PRF group, advanced platelet-rich fibrin treated the tendon defect locally. The skin was closed routinely.

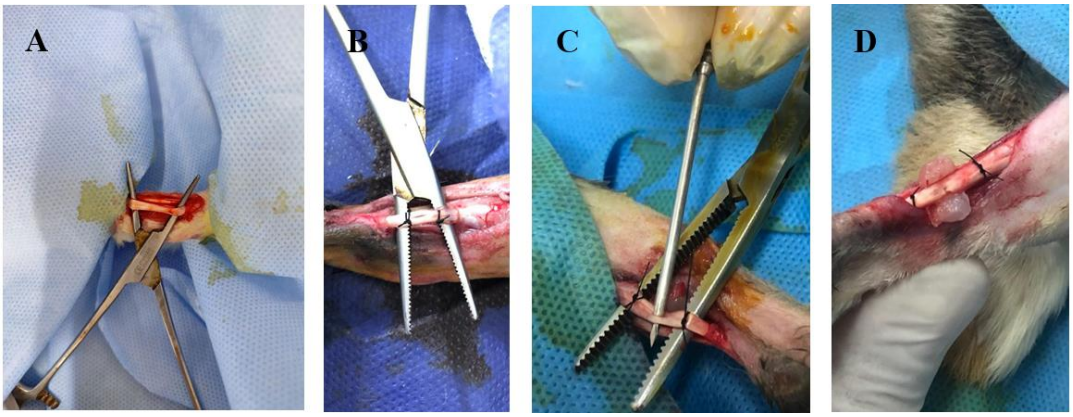

Figure 1. The surgical procedure involved (A) Exposure of Achilles tendons, (B) Stay suture, (C) Core lesion, and (D) Treated locally by PRF.

Preparation of L-PRF and A-PRF

Leukocyte platelet-rich fibrin (L-PRF) was prepared by collecting 10 ml of peripheral blood sample from the goat jugular vein. The blood sample was collected without anticoagulant in a special PRF tube (Figure 2) and immediately subjected to centrifugation at 2,700 rpm (around 400 g) for 12 min. The obtained PRF is called L-PRF [11].

Figure 2. PRF tube

Advance-platelet-rich fibrin was prepared the same way as L-PRF preparation, but the centrifugal force was 1500 rpm for 14 minutes [12].

Clinical observation

All animals were evaluated clinically during the study. The rabbits were observed daily for gait, lameness, body temperature, and local signs of inflammation at the operative site and weight bearing. The scoring system of lameness was documented (Table 1).

Criteria / Score	0	1	2	3
Standing	Continuous weight-bearing	Intermittent weight-bearing	Completely non-weight-bearing	N/A
Gait with movement	Continuous weight-bearing	Intermittent weight-bearing	Toe touches Non-weight bearing	Non weighs bearing
Swelling	None	Mild	Obvious	N/A
Pain on palpation of the operated limb	None	Mild (occasional vocalization)	Moderate (frequent vocalization)	Severe (vociferous vocalization withdraws limb, bites, struggles)
Behavior	Normal cage exploration food and water consumption, animal calm in cage	Minimal exploration, food and water consumption	No cage exploration, hunched posture, or movement when stimulated anorexic for 24 hours	No cage exploration, hunched posture, piloerection, no movement, anorexic, increased respiratory or labored breathing
Body temperature	Normal	>39.4ºC and a lameness score of 5; or 40ºC	> 40ºC for 24 hours post-treatment (analgesia) and anorexic	> 40ºC for 48 hours post-treatment (analgesia) and anorexic
Appearance of incision	Clean, no chewing, no redness	Mild chewing, redness, suture intact	Severe chewing, incision open	Incision infected (redness, swelling, purulent drainage)

Table 1. Pain scale for rabbits after femoral orthopedic surgery.

Histopathological evaluation

Tendon samples were collected from all groups after 7, 14, 30, and 60 days post-operatively. The samples were fixed in 10% neutral buffered formalin, cleared through a gradient of alcohols, embedded in paraffin, sectioned, stained using Hematoxylin and Eosin, and visualized under a light microscope at X10 and X40.

RESULTS

Clinical examination of the animals revealed swelling, redness, and pain at the operation site, and these signs disappeared in all experimental animals after one week postoperatively. Clinically, all animal groups showed the same degree of lameness characterized by the disability of the affected limb to the point where movement is impaired. However, lameness gradually improved in the APRF group at the end of the third week and showed normal weight-bearing compared to L-PRF and control groups (Figure 3, Table 2).

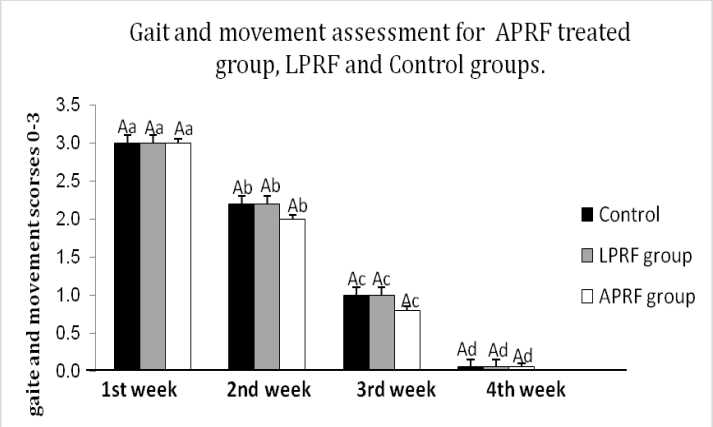

Figure 3. The clinical study showed the gait and movement for control, LPRF, and APRF groups during different periods (7, 14, 21 and 28 days post-surgery). ABC Different letters among groups indicate significant differences (P< 0.05). Abc Different letters within the group indicate significant differences (P<0.05).

7 days	14 days	21 days
3.00± 0.00 ^{Aa}	2.20±0.20 ^{Ab}	1.00±0.00 ^{Ac}
3.00± 0.00 ^{Aa}	2.20±0.20 ^{Ab}	1.00±0.00 ^{Ac}
3.00± 0.00 ^{Aa}	2.00±0.00 ^{Ab}	0.80±0.20 ^{Ac}

Table 2. Results of gait and movement scores for control, LPRF, and APRF groups during different periods (7, 14, 21 and 28 days post-surgery).

Different letters within each column indicate significant differences (P<0.05). Abc Different letters within each row indicate significant differences (P<0.05); Values are means and standard errors (M±SE)

After one week, the histological examination of group APRF shows necrosis, disorganization of collagen fibers, and heavily stained collagen fibers (Figure 4). The repopulation of the evacuated cavity of the Achilles tendon and early collagen bundle accumulation were notified after two weeks (Figure 5). Furthermore, the greater density of collagen fibers and orderly aligned fibers were indicated in APRF-treated rabbits compared to the control group after one month. Moreover, the junction between tendon sites was notified in APRF-treated rabbits during this period (Figure 6). In comparison, the A-PRF group for two months revealed a very highly organized Achilles tendon and lightly stained collagen fibers arranged in parallel (Figure 7). At the same time, the LPRF group showed necrosis, destruction, and disorganization of the Achilles tendon collagen fibers after one week of injury induction. (Figure 8). After two weeks, the changes included densely eosinophilic staining fibers, disorganization of collagen fibers, and the presence of a zone of adhesion to the surrounding tissue. The same pathological findings include necrosis and disorganization of collagen fibers. (Figure 9). were notified after one month of treatment, as well as to the presence of a zone of adhesion to the surrounding tissue and the formation of a junction between tendon sites (Figure 10). Furthermore, the LPRF group after two months revealed angiofibroblastic hyperplasia, the tendon fibers are invaded by fibroblasts and atypical vascular granulation tissue, and the adjacent tissue becomes degenerative, hypercellular and micro-fragmented and some inflammatory cells and extravasated RBCs are seen (Figure 11). In the control group, one week, necrosis, destruction, disorganization of collagen fibers, and the presence of a zone of adhesion to the surrounding tissue (Figure 12). Two weeks revealed increased cellularity and the fibers are slightly deteriorated (Figure 13).

The same changes were indicated in one month, with increased cellularity and slightly deteriorated fibers (Figure 14). Two months shows necrosis, destruction, and disorganization of collagen fibers (Figure 15).

DISCUSSION

Tendon tissue is known for its slow subsequent recovery Injury due to inadequate blood supply and low metabolic rate of tendon tissue 13. Tendon healing is a multi-step process that is affected by many factors. Inflammation, proliferation, and remodeling are the stages it goes through 14. This process does not form the usual surgical structure. Instead, it produces scar tissue of lower quality than normal tendons. As a result, the repaired tendon does not function properly and is at risk of re-damage 15. Tissue engineering approaches to repair and enhance tendon healing include using growth factors, stem cell-based therapies, biological and decellularized tissues, natural and synthetic biomaterials, or a combination of these strategies 16. Concentrated platelets can provide 6-8 times the hyperphysiological dose of growth factor, which is the basic mechanism that stimulates wound healing 17.

Growth factors released from platelets stimulate the need and differentiation of mesenchymal stem cells and other target cells involved in the healing process 7. The use of platelet-rich plasma mesenchymal stem cells is effective in promoting the regeneration of frozen allograft tendons 18. This study evaluates the effectiveness of heterologous leukocyte-platelet-rich fibrin (L PRF) and highly platelet-rich fibrin (A-PRF) in promoting healing of the Achilles tendon and the tendon regeneration process in rabbits. We hypothesize that topical application of A-PRF and L-PRF to iatrogenic Achilles tendon defects promotes and accelerates the tendon healing process and growth factors (PDGF, TGF-ß1, IGF-1, etc.). It can promote tendon regeneration through release. It stimulates tendon formation by regulating cell proliferation, inflammation, angiogenesis and extracellular matrix (ECM) deposition.

This is the first study to use goat PRF as a heterologous PRF to accelerate and regenerate healing of the Achilles tendon in rabbits. Heterologous PRF can behave similarly to autologous and allogeneic morphology in treating scars on rabbit skin 19. In 2020, we prepared platelet-rich plasma (PRP) from eight EDTA tubes from patients with high platelet concentrations at the Institute of Clinical Pathology, University Hospital UFMG. They applied this heterologous PRP to a skin incision in the back of a rabbit. They found no significant reduction in scar contraction, side effects, or observed changes in healing time, and therefore no evidence of impaired wound healing process. Heterogeneous or homologous PRP is induced. Dog-derived PRF was used to treat serious cat wounds, inducing healthy angiogenic granulation tissue causing epithelialization rather than rejection, necrosis, or infection. Clinical observations from the current study showed that lameness in rabbits treated with A-PRF was used 3 weeks after surgery. This result is consistent with 20 showing that a platelet-derived product, a self-protein solution, reduced pain and lameness compared to client-owned dog saline. Garbin and Olver 21 showed that the degree of lameness in horses from clients with natural osteoarthritis improved significantly after treatment with leukocyte-rich platelet products without adverse effects. Platelet-rich plasma is lame in horses when treatment between single lesions of superficial finger flexor tendon (SDF) disorders with PRP and PRP treatment may increase the number of horses returning to previous performance levels. It has the effect of improving 22.

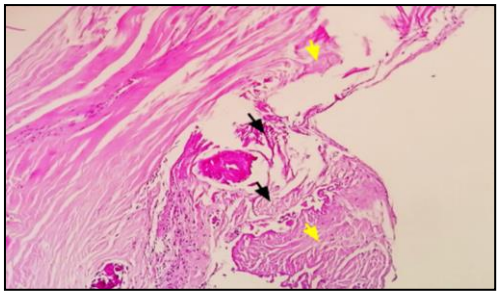

Figure 4. APRF-one week Section of Achilles tendon shows necrosis (black arrows) and disorganization (yellow arrows) of collagen fibers. H&E, 100X

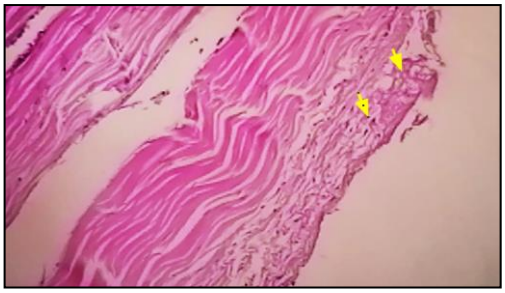

Figure 5. APRF-two week Section of Achilles tendon shows repopulation of the evacuated cavity and early collagen bundles (yellow arrows). H&E, 100X

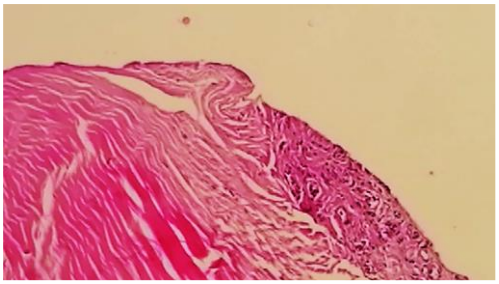

Figure 6. APRF-one Month Section of Achilles tendon shows greater density of collagen fibers. H&E, 100X.

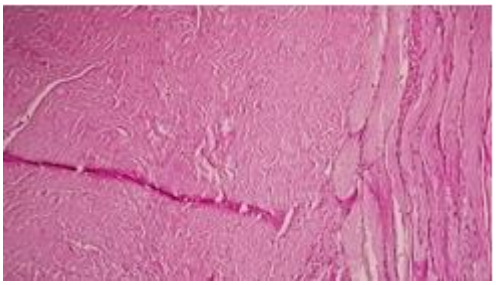

Figure 7. APRF-two Month Section of Achilles tendon showing very highly organized and lightly stained collagen fibers arranged in parallel. H&E, 100X.

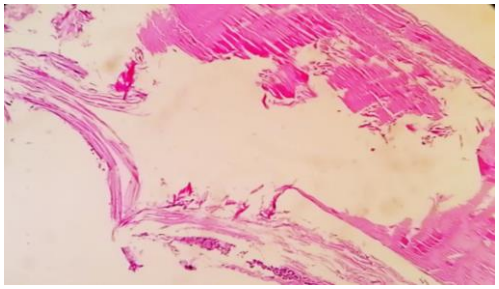

Figure 8. LPRF-one week Section of Achilles tendon shows necrosis, destruction, and disorganization of collagen fibers. H&E, 40X

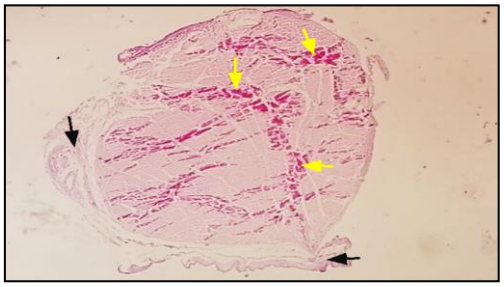

Figure 9. LPRF-two-week. Transverse section of Achilles tendon shows densely eosinophilic staining fibers (yellow arrows), disorganization of collagen fibers, and an adhesion zone surrounding the tissue (black arrows). H&E, 40X

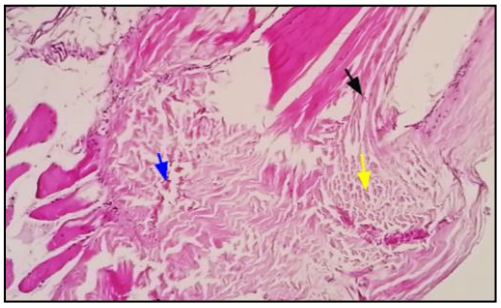

Figure 10. LPRF-on two month. Section of Achilles tendon shows necrosis (blue arrow), disorganization of collagen fibers (yellow arrow), and a junction between tendon sites notified (black arrow). H&E. 400X

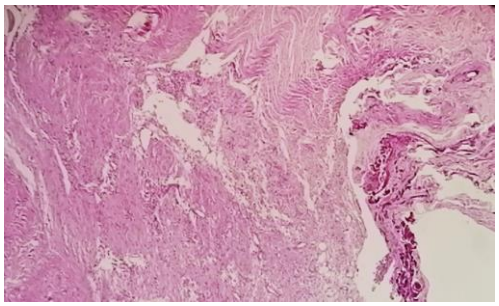

Figure 11. LPRF-two month-. angiofibroblastic hyperplasia, fibroblasts and atypical vascular granulation tissue invade the tendon fibers, and the adjacent tissue becomes degenerative, hypercellular, and microfragmented. H&E,

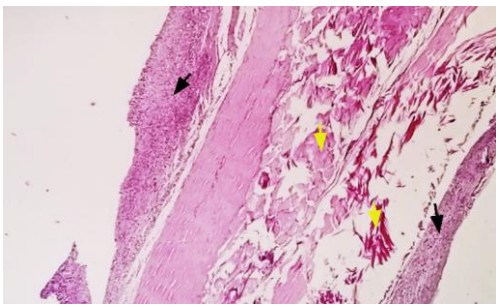

Figure 12. control one week. Section of Achilles tendon shows necrosis (yellow arrows), destruction, disorganization of collagen fibers, and a zone of adhesion to the surrounding tissue (black arrows). H&E, 40X

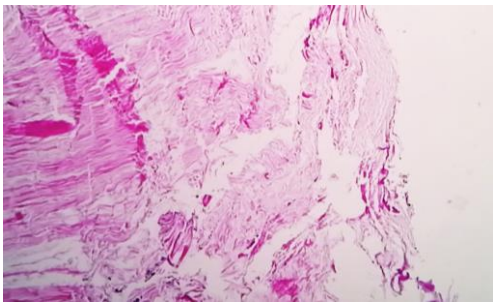

Figure 13. control two weeks. Section of Achilles tendon shows necrosis, destruction, and disorganization of collagen fibers. H&E, 40X

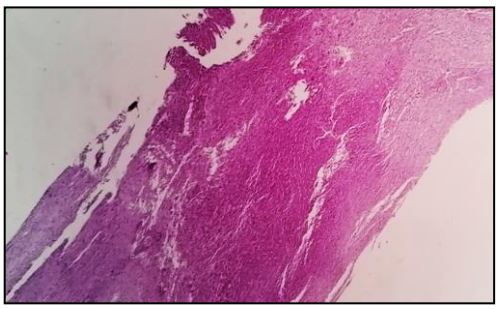

Figure 14. control one month .Section of Achilles tendon shows increased cellularity and the fibers are slightly deteriorated. H&E, 40X

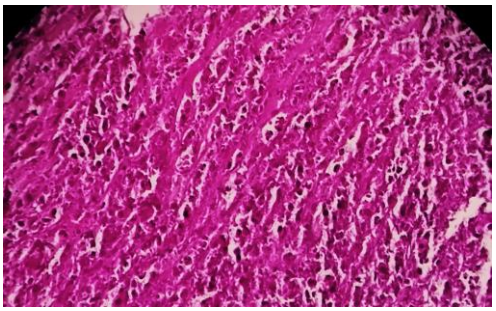

Figure 15. control two month. Section of Achilles tendon shows increased cellularity and the fibers are slightly deteriorated. H&E, 400X

The present histopathological results indicated that the local application of advanced -platelet-rich fibrin as xenogenic biomaterial on Achilles tendon defect induced in the rabbit produced new tendon tissue characterized by a very highly organized Achilles tendon and lightly stained collagen fibers arranged in parallel when compared with the L-PRF group. These results are because A-PRF is richer in the total number of neutrophils, lymphocytes, and platelets than L-PRF [11]. Secondly, the total amount of released growth factors (TGF-ß1, VEGF, PDGF, EGF, and IGF1) is markedly higher in A-PRF compared with L-PRF [23]. The growth factors that play an important role in the tendon healing process include platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), transforming growth factor-beta (TGF-beta), and insulin-like growth factor (IGF) [24]. The scientific rationale behind using PRF-based products is related to the intrinsic nature of the entrapped platelets, acting as a reservoir of many GFs; they accelerate the healing process, controlling pain and inflammation [25].

Our histopathological results agree with several studies evaluating the efficacy of platelet-rich fibrin to accelerate healing and regenerate tendon tissue. The bioactive PRF can promote tendon tissue healing, tenocyte viability, and tenogenic phenotype differentiation when administered to Achilles tendon defect. Also, physiologically active PRF may effectively promote the healing of tendon-bone grafts by inducing the formation of a transitional tendon-bone healing zone consisting of fibrocartilage and bone [26]. Combining tendon surgery and self-application of growth factor-rich formulations (PRGF) may offer new opportunities to improve tendon healing and functional recovery [27]. Our results are comparable to those of [28].

We investigated the effectiveness of PRP and PRF to repair the Achilles tendon in rats. They suggest that PRF promotes and accelerates Achilles tendon regeneration. The ability of PRF to regenerate and accelerate the healing of the Achilles tendon has been demonstrated by Senga et al. [29]. They conclude that PRF can promote and accelerate the healing of Achilles tendon defects, restore athletic performance and exert biomechanical properties.

CONCLUSIONS

The results of the present study showed that platelet-rich fibrin can provide tendon regeneration and have the ability to accelerate the tendon healing process. Xenogenic PRF can be used as an alternative biomaterial to autogenic platelet-rich fibrin in the treatment of tendon defects with promising results. Further studies are recommended to investigate Xenogenic PRF's effect on other tendon disorders, especially those that occur in the sports field. Xenogenic PRF can be used as alternative biomaterials to fasten tendon healing.

Author Contributions: Conceptualization, S.S.A.A. and A.A.I.A.; methodology, S.S.A.A. and R.M.N.A.; software, S.S.A.A.; validation, S.S.A.A., A.A.I.A. and R.M.N.A.; formal analysis, S.S.A.A.; investigation, S.S.A.A.; resources, S.S.A.A.; data curation, R.M.N.A.; writing-original draft preparation, S.S.A.A.; writing—review and editing, S.S.A.A.; visualization, A.A.I.A.; supervision, A.A.I.A.; project administration, S.S.A.A. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Scientific Ethics Committee of the Department of Veterinary Surgery and Obstetrics, University of Basrah, Basrah, Iraq.

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Conflicts of Interest: The authors declare no conflict of interest.

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