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Original Article
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Comparison of the effects of platelet-rich fibrin and platelet-rich plasma on experimental tendon injury in rabbits[1]

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ABSTRACT.- Akyol ET, Ceylan C, Erol M, Usta M, Karaman M, Ilhan F, Atik A. **Comparison of the effects of platelet-rich fibrin and platelet-rich plasma on experimental tendon injury in rabbits**. *Pesquisa Veterinária Brasileira 46:e07765, 2026.* Department of Surgery, Faculty of Veterinary Medicine, Balıkesir University, 10145, Balıkesir, Turkey. E-mail: etakyol@balikesir.edu.tr

This study aimed to compare the early-phase histopathological and immunohistochemical effects of platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) following their application in the inflammatory phase of experimentally induced calcaneal tendon injuries in a rabbit model. A complete calcaneal tenotomy was performed and repaired using the modified Kessler technique. In the PRP group, 0.5–1 ml of non-activated liquid PRP was injected into the paratenon. In the PRF group, a PRF membrane was wrapped around the tenotomy site. The Control group received sutures only. On the 14th postoperative day, tendon tissue samples were collected for analysis. Healing was assessed via histopathology (HE, Masson's trichrome) and immunohistochemistry for key growth factors (TGF-β, VEGF, FGF-β) and inflammatory markers (iNOS, nitrotyrosine). Histopathological evaluation revealed that both PRP and PRF groups exhibited superior healing compared to the Control group, characterized by reduced inflammatory cell infiltration, less edema, and a more organized, parallel arrangement of newly synthesized collagen fibers. Compared to controls, both treatment groups showed significantly increased expression of the pro-regenerative FGF-β and decreased expression of TGF-β and VEGF. Furthermore, levels of iNOS and nitrotyrosine were markedly lower in the PRP and PRF groups. Both PRP and PRF demonstrated comparable and significant efficacy in enhancing the quality of early tendon repair. Their therapeutic effect appears to be multifactorial, created by a pro-regenerative and anti-inflammatory microenvironment that favorably modulates growth factor expression and reduces inflammatory tissue damage. These findings support the use of both preparations as effective strategies to promote healing in acute tendon injuries.

INDEX TERMS: Calcaneal tendon, platelet-rich plasma, PRP, platelet-rich fibrin, PRF, tendon healing, growth factors, rabbit.

RESUMO.- [**Comparação dos efeitos de fibrina rica em plaquetas e plasma rico em plaquetas em lesão experimental de tendões em coelhos.**] Este estudo teve como objetivo comparar os efeitos histopatológicos e imunohistoquímicos de fase inicial do plasma rico em plaquetas (PRP) e fibrina rica em plaquetas (PRF) após a sua aplicação na fase inflamatória de lesões do tendão calcâneo, induzida experimentalmente em um coelho. Uma tenotomia completa do calcâneo foi realizada e reparada através da técnica de Kessler modificada. No grupo PRP, foram injetados 0,5–1 ml de PRP líquido não ativado no espaço do paratendão. No grupo PRF, uma membrana de PRF foi enrolada em torno do local da tenotomia. O Grupo controle recebeu apenas suturas. No 14º dia pós-operatório, os tecidos tendinosos foram recolhidos para análise. A cicatrização foi avaliada por histopatologia (HE, tricrômico de Masson) e imunohistoquímica para fatores de crescimento chave (TGF-β, VEGF, FGF-β) e marcadores inflamatórios (iNOS, nitrotirosina). A avaliação

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histopatológica revelou que ambos os grupos, PRP e PRF, apresentaram uma cicatrização superior em comparação com o Grupo controle, caracterizada por uma menor infiltração de células inflamatórias, menos edema e um arranjo paralelo mais organizado das fibras de colágeno recém-sintetizadas. Em comparação com os controles, ambos os grupos de tratamento apresentaram uma expressão significativamente aumentada do pró-regenerador FGF-β e uma expressão diminuída de TGF-β e VEGF. Além disso, os níveis de iNOS e nitrotirosina foram significativamente mais baixos nos grupos PRP e PRF. Tanto o PRP como o PRF demonstraram uma eficácia comparável e significativa na melhoria da qualidade da reparação precoce do tendão. O seu efeito terapêutico parece ser multifatorial, envolvendo a criação de um microambiente pró-regenerador e anti-inflamatório, modulando favoravelmente a expressão do fator de crescimento e reduzindo os danos inflamatórios nos tecidos. Estes achados corroboram a utilização de ambas as preparações como estratégias eficazes para promover a cicatrização em lesões agudas do tendão.

TERMOS DE INDEXAÇÃO: Tendão de Aquiles, plasma rico em plaquetas, PRP, fibrina rica em plaquetas, PRF, cicatrização do tendão, factores de crescimento, coelho.

INTRODUCTION

Tendon injuries remain a subject of significant research interest due to their prolonged healing periods, the altered biological and biomechanical properties of newly formed tissue, and the subsequent limitations in functional recovery (Twaddle & Poon 2007, Leong et al. 2020). In addition to conventional treatment methods, which often result in suboptimal healing, the pursuit of strategies that promote faster and more robust tendon regeneration has led researchers to explore tissue engineering approaches. Platelets, given their key function in hemostasis, play a crucial role in these mechanisms, which aim to accelerate tendon and other tissue repair processes (Sunitha Raja & Munirathnam Naidu 2008). Growth factors released by platelets following tendon injury are closely involved in regulating the repair response (Wang & Li 2023). Platelet-rich fibrin (PRF) and platelet-rich plasma (PRP) have been widely utilized for this purpose.

PRP is derived from autologous blood, ensuring a high safety profile (Xie et al. 2012). Unlike exogenously administered growth factors used in varying concentrations, PRP contains growth factors in physiological proportions, maintaining a natural balance between proliferative and inhibitory agents (Marx 2001). Moreover, the development of commercial PRP preparation systems in recent years has significantly simplified its clinical application (Yuan et al. 2012). Both *in vitro* and *in vivo* studies have demonstrated that PRP enhances tendon healing by increasing collagen gene expression, stimulating angiogenesis, promoting cell migration, differentiation, and proliferation, and enhancing extracellular matrix production (De Mos et al. 2008, Kajikawa et al. 2008, Zhang & Wang 2010). However, some studies have failed to demonstrate a clear clinical superiority of PRP over conventional treatments (De Jonge et al. 2011, Schepull et al. 2011). PRF, on the other hand, is an autologous platelet concentrate embedded within a natural fibrin matrix, without the addition of exogenous agents, and has shown high efficacy for tissue repair (Choukroun et al. 2006, Dohan et al. 2006). Due to its structural characteristics, PRF plays a pivotal role in the early phases of angiogenesis, subsequently promoting enhanced collagen synthesis, vascular development, and fibroblast proliferation (Modarressi 2013). Consequently, PRF has been proposed as a strategy to enhance the cellular response to tendon injuries and improve the overall quality of tissue repair (Sánchez et al. 2007).

Transforming growth factor β (TGF-β) is significantly upregulated following tendon injury and is active in nearly all stages, including inflammation (Molloy et al. 2003). TGF-β1, which is particularly active during the early inflammatory phase, plays a key role in the chemotaxis of macrophages and fibroblasts to the wound site and may also act as a suppressor of excessive inflammation (Amento & Beck 1991). Its various roles include regulating cellular migration and proliferation, mediating fibronectin-binding interactions, and enhancing the synthesis of related proteins, such as collagen (Molloy et al. 2003). TGF-β is expressed in the early stages of tendon repair and promotes collagen deposition and tendon healing. However, increased TGF-β can enhance local tissue adhesion (Durgam & Stewart 2017). Given its multifaceted and critical role in tendon healing, determining appropriate dosages for therapeutic applications is crucial (Wang & Li 2023).

Vascular endothelial growth factor (VEGF) is produced at its highest levels after the inflammatory phase. As a potent stimulator of angiogenesis, it is essential for tendon repair by providing oxygen, growth factors, and the necessary building blocks for collagen synthesis (Molloy et al. 2003). Following an acute tendon injury, endogenous VEGF levels typically increase for a period, peaking at around 7-14 days depending on the model, and subsequently decrease (Stange et al. 2015). Tendon healing may proceed more slowly than in other connective tissues because it has lower vascular and cellular components. Angiogenic activation is critical in promoting key biological events for the tendon healing process. The application of exogenous VEGF can induce regional angiogenesis and enhance tissue healing (Zhang et al. 2003).

Basic fibroblast growth factor (FGF-β) is a mitogenic factor that plays a crucial role in wound healing, cell proliferation (including endothelial cells, fibroblasts, and tenocytes) and tissue repair (Hsu & Chang 2004). Active throughout all stages of the healing process, FGF-β can significantly accelerate tendon healing, enhance angiogenesis, and promote cell proliferation and collagen synthesis. Furthermore, improving collagen fiber orientation in repaired tendons can increase biomechanical strength and reduce adhesion (Oryan & Moshiri 2014, Najafbeygi et al. 2017, Zhou et al. 2021).

In addition to these growth factors, nitric oxide (NO) is a free radical that also plays a significant role in various cellular processes and tissue healing. NO is synthesized from L-arginine by the nitric oxide synthase (NOS) family of enzymes (Murrell et al. 1997, Bokhari & Murrell 2012). A marked increase in NOS activity is observed following both animal and human tendon injuries. The increase is typically observed on day 7 post-injury, before returning to basal levels by day 14 (Lin et al. 2001). Immunohistochemical studies suggest that NOS activity is localized within the injured tendon tissue and is thought to be expressed by the cells that constitute the healing tissue. In animal models, inhibition of NOS activity with inhibitors has led to significant impairment of calcaneal tendon healing, manifested as decreased tendon cross-sectional

area and load-bearing capacity (Murrell et al. 1997). NO has been shown to significantly affect cellular adhesion, a critical process during tendon repair, resulting in injured tendons with better material and mechanical properties (Murrell et al. 1997, Molloy et al. 2006, Bokhari & Murrell 2012).

Tendon healing and regeneration occur in three overlapping stages specific to tendons (Voleti et al. 2012). These phases are the inflammatory phase, which lasts for approximately 48 hours; the proliferative phase, lasting 7–21 days; and the remodeling phase, which can begin months after the initial injury and extend for more than 12 months. In the inflammatory phase, macrophages clear necrotic tissue. The proliferative phase is characterized by the production of new, less durable tendon tissue, and during this stage, tenocytes primarily proliferate in the epitenon. The remodeling phase involves the alignment of the extracellular matrix; however, the regenerated tissue has a scar-like appearance and possesses biomechanically inferior strength compared to the original, healthy tendon (Chartier et al. 2021)

The present study aimed to compare the histopathological and immunohistochemical effects of PRP and PRF during the proliferation phase of healing, following their application in the inflammatory phase of experimentally induced calcaneal tendon injuries in a rabbit model.

MATERIALS AND METHODS

Ethical approval. This study was conducted with the approval of the Erciyes University Animal Experiments Local Ethics Committee (EUHADYEK, Approval No: 17/015), and care was taken to minimize the number of animals used.

A total of 30 New Zealand rabbits (*Oryctolagus cuniculus*) of varying weights (1.5–3 kg) and ages (1–3 years), including 15 females and 15 males, were included. The rabbits were randomly divided into three equal groups of 10 animals each (five males and five females per group). The experimental groups were designated as the control (Group A), the PRP (Group B), and the PRF (Group C). For all animals, intravenous catheters were placed in the ear veins to facilitate drug administration when necessary and to collect blood samples for PRP and PRF preparation. Before the surgical procedure, 5 ml of blood was collected from the PRP group and 8 ml from the PRF group for the preparation of the respective products.

Preparation of PRP. PRP was prepared using a commercial PRP kit (a commercially standardized preparation system that aims to achieve consistent results by following a specific protocol) (EasyPRP® Kit 10, Neotec Biotechnology, Turkey). Initially, 0.5 ml of sodium citrate (PPS Natrium Citricum 3.13%, MediPac, Germany) was added to the 10 ml syringe included in the kit as an anticoagulant. Subsequently, 4.5 ml of blood drawn from each rabbit was added to the syringe, resulting in a total volume of 5 ml. The lower chamber of the syringe was attached, and the mixture of blood and anticoagulant was gently agitated to ensure proper mixing. The syringe was centrifuged at 1200 G for 5 min. After the first centrifugation, the red blood cells that had settled in the lower chamber were discarded along with the chamber itself, and a stopper was affixed to the syringe. The second centrifugation was performed at 1200 G for 10 min. Following this process, three distinct layers were visible in the syringe: platelet-poor plasma (PPP), PRP and the buffy coat layer above the sedimented cells. To extract the PRP, the stopper was removed, and the kit-provided 3 ml Luer-lock application syringe was attached. The PRP layer, along with the buffy coat, was aspirated into the application syringe, and the PRP was then ready for use (Dernek et al. 2017, Celik et al. 2024).

Preparation of PRF. Blood samples collected in anticoagulant-free tubes were centrifuged immediately at 400 G for 10 min (Dohan et al. 2006). This process resulted in the formation of three distinct layers: red blood cells at the bottom, a fibrin clot (PRF) in the middle, and PPP at the top. The fibrin clot was carefully extracted and placed on a piece of sterile gauze. Light pressure was applied to compress and flatten the clot, preparing it for use (Fig. 1-3).

Surgical procedure. Anesthesia was induced in all groups with 0.3 mg/kg bw IM medetomidine HCl (Domitor, Pfizer, Germany) and 30 mg/kg bw IM ketamine HCl (Alfamine, Alfasan, Netherlands), followed by maintenance with 4% sevoflurane (Sevorane, AbbVie, USA) in oxygen.

Surgical preparation was performed on the right calcaneal tendon. A skin incision was made, and the subcutaneous connective tissue

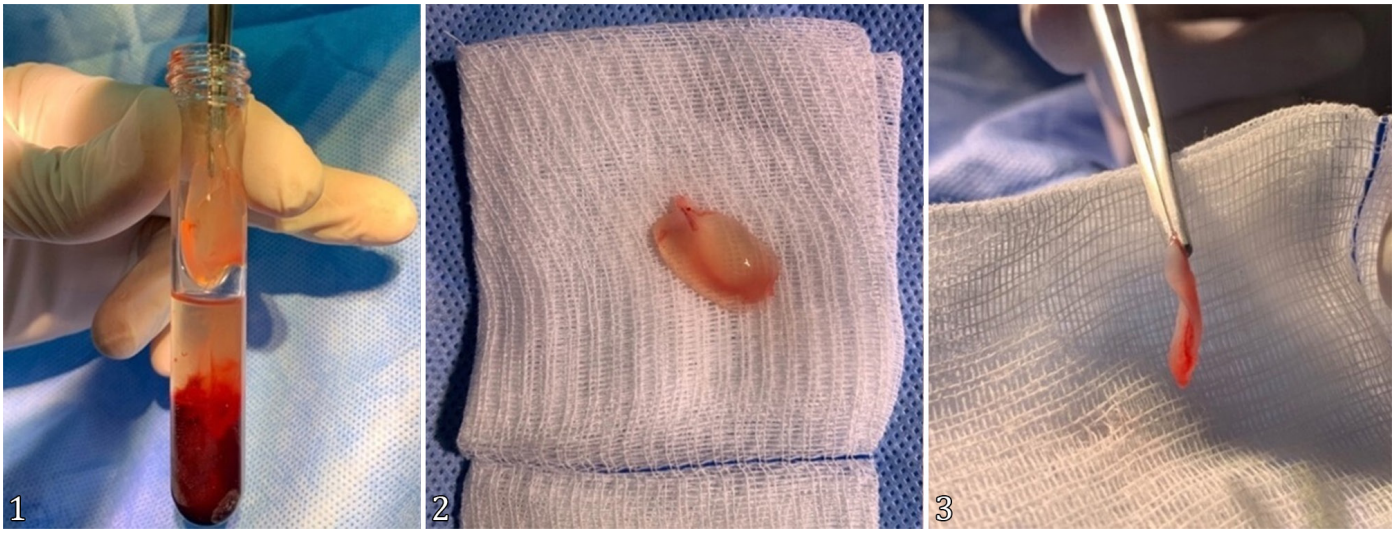

Fig. 1-3. Key steps in the preparation of the platelet-rich fibrin (PRF) membrane. (**1**) The natural fibrin clot formed in the tube after a single centrifugation. (**2**) The extracted clot on sterile gauze before compression. (**3**) The final, compressed PRF membrane, ready for surgical application.

and paratenon membrane were dissected to access the calcaneal tendon. The calcaneal tendon complex (including the medial and lateral gastrocnemius tendons) was identified and then completely sliced perpendicularly to the length of the tendon, approximately 2.0 cm above the calcaneus (Meier Bürgisser et al. 2016). The tendon ends were sutured using the modified Kessler technique (Kleinert et al. 1981). In Group B, 0.5–1 ml of non-activated liquid PRP was injected into the space between the tendon and the paratenon. In Group C, the fibrin clot was wrapped around the tendon, covering the tenotomy site. The surgical site was routinely sutured with 3-0 absorbable multifilament suture material (Vicryl, Ethicon®, USA).

After the surgery, 11,000 IU/kg bw IM penicillin (Ieciline, IE Ulagay, Turkey) was administered as a prophylactic antibiotic for five days. Postoperative analgesia was provided for three days using meloxicam (Maxicam, Sanovel, Turkey) at a dose of 0.3 mg/kg BW SC. A protective bandage was placed over the surgical site and maintained for seven days.

On the 14th postoperative day, a second planned surgical procedure was performed. Using the same surgical approach, a tissue sample from the previous tenotomy site was excised for analysis. Following sample collection, the tendon ends were re-sutured using the modified Kessler technique to ensure structural continuity. The surgical site was closed routinely, and the animals were recovered under the same postoperative care protocols, as they were kept alive for subsequent studies.

Histopathological and immunohistochemical evaluation. The excised tendon tissues were fixed in 10% neutral buffered formalin, routinely processed, and embedded in paraffin. Five-micron-thick sections were prepared using a microtome (RM2245, Leica, Germany) and stained with hematoxylin-eosin (HE) and Masson's trichrome for histopathological evaluation. Tendon healing was assessed using a light microscope (Eclipse Ni, Nikon, Japan).

Immunohistochemical (IHC) staining was performed using the avidin-biotin-immunoperoxidase complex method to evaluate factors influencing fibroblast activity and collagen production during the healing process. Five-micron-thick sections from tendon samples were mounted onto poly-L-lysine-coated slides and dried overnight in an incubator. After deparaffinization, the sections were washed three times in phosphate-buffered saline (PBS) with 5-minute intervals between washes and incubated with 0.001% trypsin at 37 °C for 30 min to expose antigenic epitopes. The sections were then rewashed in PBS and incubated in a 3% hydrogen peroxide-methanol solution for 20 min to block endogenous peroxidase activity. After further PBS washes, the sections were incubated at room temperature for 30 min with non-immune goat serum to prevent non-specific binding. Without additional washing, the sections were incubated with primary antibodies for 1 h at 37 °C. The targeted antibodies included inducible nitric oxide synthase (iNOS, 1:100, ThermoFisher, PA5-16855), nitrotyrosine (AB5411, 1:500, Millipore, USA), βFGF (rabbit polyclonal; 1:200, AB8880, Abcam, Cambridge, UK), VEGF (mouse monoclonal; 1:200, Abcam, AB1316, Cambridge, UK), and TGF-β1 (AB190503, 1:200, Abcam).

After primary antibody incubation, the sections were washed three times in PBS and incubated with a biotin-conjugated secondary antibody (Streptavidin Peroxidase, Katalog No: TS-125-HR, Thermo) for 30 min. This was followed by treatment with peroxidase-labeled streptavidin for 30 min. The sections were rewashed in PBS and developed using a DAB (3,3'-diaminobenzidine tetrahydrochloride-H_2O_2) solution as the chromogen. After rinsing in distilled water, counterstaining was performed with Mayer's hematoxylin. The tissue samples were examined under a light microscope, and representative micrographs were captured using a digital camera integrated into the light microscope (Eclipse Ni, Nikon, Japan). Image analysis was performed using Fiji (version 2.12.0), a digital pathology software. For each antibody and case, five distinct fields captured at 200× magnification were evaluated. The proportion of immunopositive regions relative to the total tissue area in each image was calculated as a percentage, and the mean value across the five images was considered the final score for that subject and antibody.

The Bonar scoring system was used to assess histopathological healing quantitatively. According to this system, each tendon specimen was evaluated based on four main histological parameters: tenocyte morphology, ground substance deposition, neovascularization, and collagen fiber organization. Each parameter was graded from 0 (normal tendon structure) to 3 (most severe pathological appearance) (Zabrzyński et al. 2021) (Table 1).

All histopathological and immunohistochemical evaluations were performed by a pathologist blinded to the treatment groups.

Statistical analyses. All data obtained from the histopathological and immunohistochemical analyses were statistically analyzed using GraphPad Prism software (version 9.5.0). The Kruskal-Wallis test, a nonparametric method, was applied for the comparison of Bonar scores among the groups. The expression levels of TGF-β, FGF-β, VEGF, iNOS, and nitrotyrosine in tendon tissues were analyzed using the nonparametric Kruskal-Wallis test, followed by Dunn's multiple comparisons test. A p-value of < 0.05 was considered statistically significant.

RESULTS

Tendon tissues were histopathologically evaluated for hemorrhage, edema, inflammatory cell infiltration, fibroblast morphology, collagen, and vascularization. In the Control group, all animals exhibited edema, hyperemia, and inflammatory cell infiltration predominantly composed of macrophages, with hemorrhage observed in three cases. In all cases within this Control group,

Table 1. Histopathological scoring of tendon healing based on the Bonar score*

Parameter	Score 0 (Normal)	Score 1 (Mild)	Score 2 (Moderate)	Score 3 (Severe)
Tenocyte morphology	Normal spindle-shaped cells	Mild rounding	Predominantly rounded cells	Large, rounded, irregular cells
Ground substance accumulation	None	Mild increase	Moderate increase	Marked increase, mucoid degeneration
Neovascularization	None	Few new vessels	Moderate density of vessel formation	Marked and chaotic new vascular network
Collagen organization	Parallel, organized collagen fibers	Mild disorganization	Marked disorganization and separation	Chaotic arrangement, markedly disrupted collagen structure

* Zabrzyński et al. (2021).

connective tissue cells with various morphological characteristics and orientations were identified. The majority of these cells consisted of large, prominent fibroblasts with large nuclei, while a smaller proportion displayed spindle-like morphology (tenocytes/fibroblasts). In all cases, numerous newly formed blood vessels with narrow or wide lumens were observed, with dilated vessels noted to have opened into the circulation (Fig. 4-6). Masson's trichrome staining revealed irregularly arranged collagen fibres of varying thickness and orientation in the Control group (Fig. 7-9).

When the study groups were evaluated in terms of histopathological assessment criteria, no significant differences were observed between the PRP and PRF groups (Fig. 10). However, compared with the Control group, both degenerative changes and inflammatory findings were less pronounced. In contrast, regenerative changes were more prominent in the PRP and PRF groups. Hemorrhage was not observed in either treatment group, and the severity and extent of hyperemia, edema, and inflammatory cell infiltration were notably reduced compared to the Control group. Most connective tissue cells in these groups were spindle-shaped, arranged in a parallel and organized manner. Newly formed blood vessels in the tenotomy region were predominantly dilated with wide walls. Masson's trichrome staining showed that the collagen fibers in both groups were regularly arranged and oriented in parallel.

Quantitative analysis and intergroup statistical comparison of TGF-β, VEGF, FGF-β, iNOS, and nitrotyrosine immunoreactivity levels in tendon tissues are summarized in Figure 10. Microscopic images of these stainings are presented in Figure 11-25. In the study groups, TGF-β and VEGF immunoreactions were similar but showed lower intensity and severity than in the Control group. TGF-β immunostaining was prominent in macrophages and was also detected in the cytoplasm of fibroblasts and other inflammatory cells. VEGF immunoreactivity was primarily noted in vascular endothelial cells, as well as in macrophages and fibroblasts. While FGF-β demonstrated moderate immunoreactivity in the Control group, both study groups showed intense immunostaining. FGF-β immunostaining occurred mainly in the cytoplasm of fibroblasts and to a lesser extent in macrophages. iNOS and nitrotyrosine immunostaining were intense in the Control group but moderate in the study groups. Both iNOS and nitrotyrosine immunostaining were predominantly localized in the cytoplasm of macrophages, neutrophils, fibroblasts, and vascular endothelial cells.

DISCUSSION

PRP and PRF were administered at the time of acute calcaneal tendon injury, during the inflammatory phase of healing, and evaluations were made on day 14, representing the proliferative phase. Therefore, the histopathological and immunohistochemical findings can be interpreted as a result of these biomaterials modulating the early inflammatory phase rather than directly affecting the proliferative phase. Tendon healing is a process comprised of closely interconnected and overlapping phases, and the nature and duration of the inflammatory phase play a critical role in determining the quality of the subsequent proliferative phase (Jiang et al.

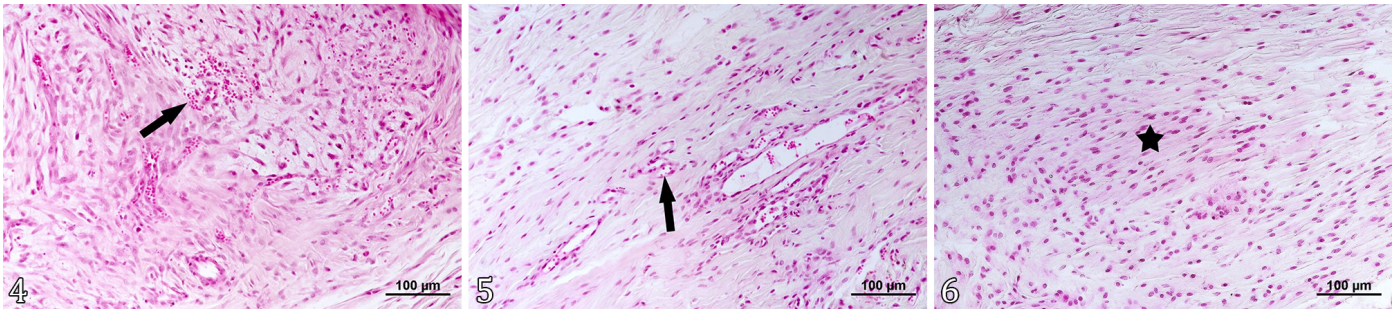

Fig. 4-6. (**4**) Hemorrhage (arrow), hyperemia, edema, and macrophage-rich inflammatory cell infiltration in control groups. (**5**) In the platelet-rich plasma (PRP) group, neovascularization (arrow), a small number of macrophage infiltrations, edema, fibroblasts with large nuclei, a few spindle-like fibroblasts, and irregular connective tissue formation. (**6**) In the platelet-rich fibrin (PRF) group, a small number of macrophages, spindle-like fibroblasts, and organized collagen structures (star). HE, obj. 20x.

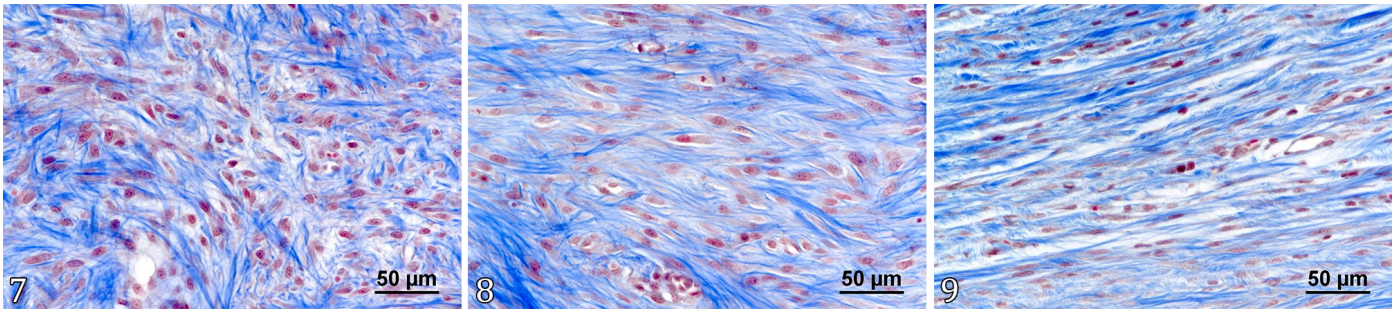

Fig. 7-9. (**7**) Irregular collagen formation with varying orientations in the control group. (**8**) Large-nucleated fibroblasts and organized collagen structures in the platelet-rich plasma (PRP) group. (**9**) Spindle-like fibroblasts and organized collagen extensions in the platelet-rich fibrin (PRF) group. Masson's trichrome, obj. 40x.

2024). The aim of the present study was to demonstrate how this early intervention affected histopathological outcomes during the proliferative phase.

Previous studies have reported that PRF supports tissue healing by promoting more organized collagen fibers and reducing vascularity in the healing process of calcaneal

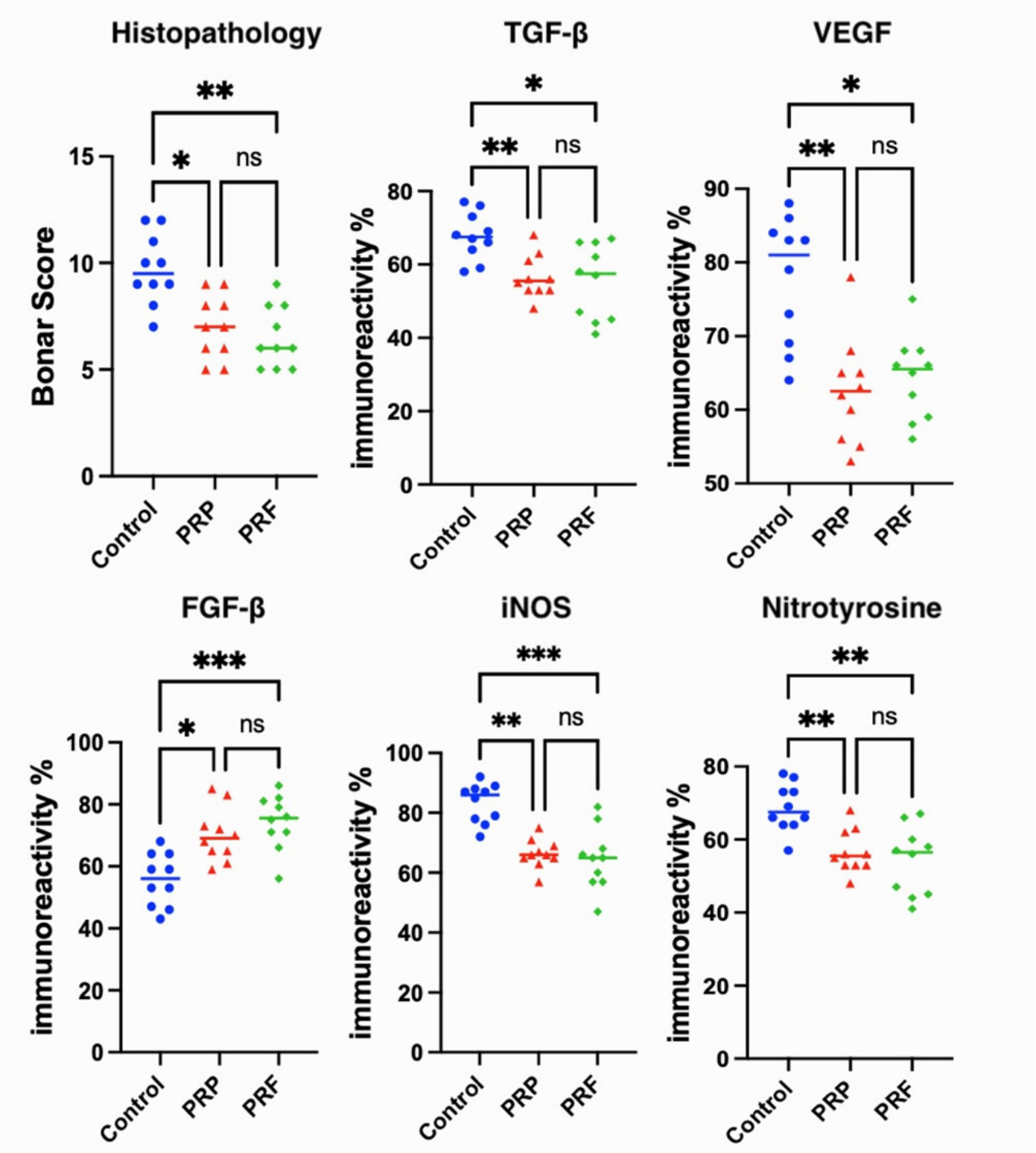

Fig. 10. Comparison of Bonar scores and immunohistochemical expression levels (TGF-β, VEGF, FGF-β, iNOS, and nitrotyrosine) in rabbit tendon tissues. Statistical significance was determined using the Kruskal-Wallis test followed by Dunn's post-hoc test. ns = no significant difference, $p < 0.05$, *$p < 0.001$, **$p < 0.0001$, ***$p < 0.0001$.

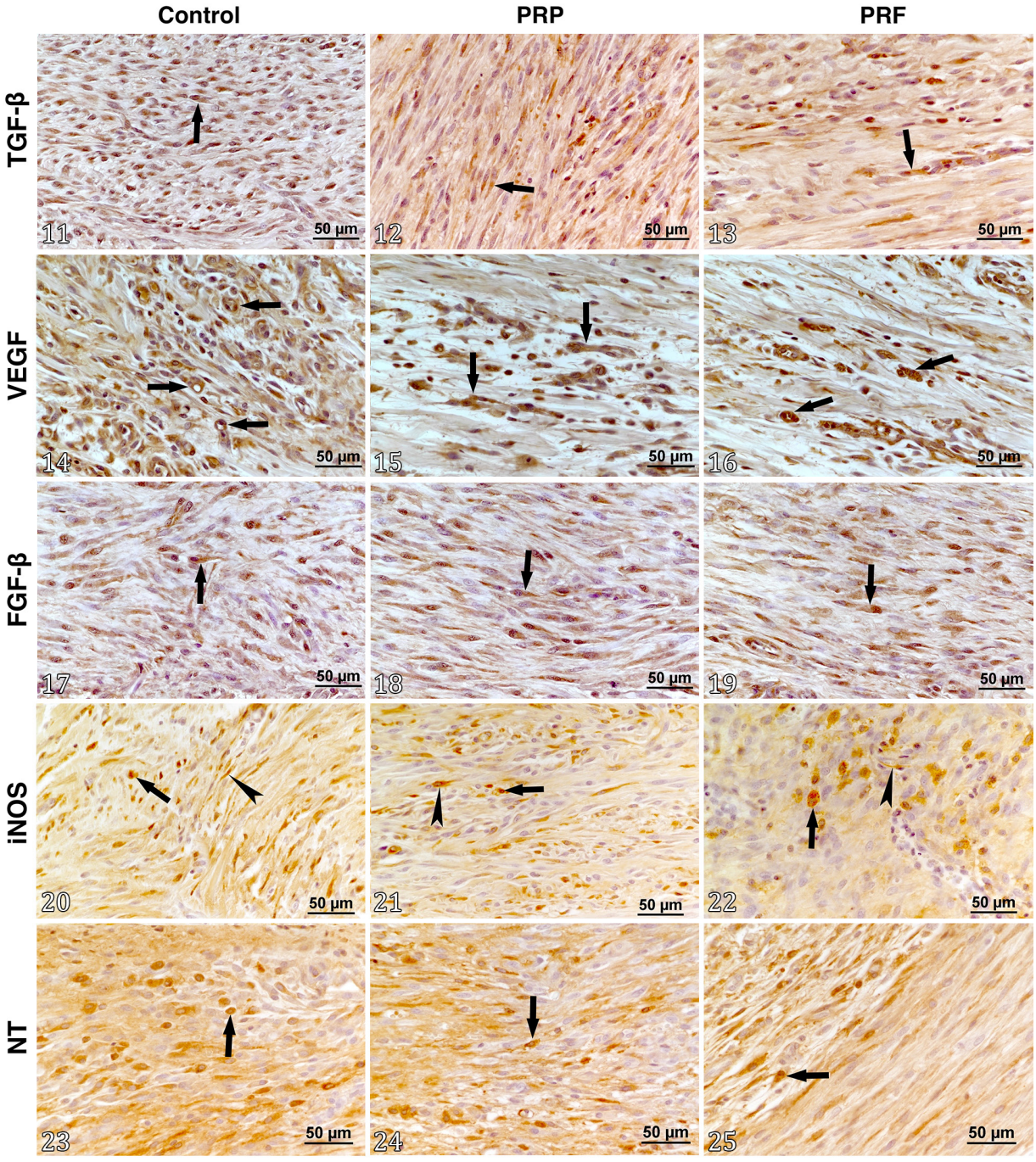

Fig. 11-25. Comparative immunohistochemical (IHC) analysis of growth factors and inflammatory markers in healing tendon tissues. (**11-13**) Transforming growth factor β (TGF-β) expression. (**11**) Intense intracytoplasmic immunoreactivity in macrophages and fibroblasts in the control group (arrow). Both the (**12**) PRP and (**13**) PRF groups exhibited moderate positive immunoreactivity localized within the cytoplasm of fibroblasts (arrow) and a small number of macrophages. (**14-16**) Vascular endothelial growth factor (VEGF) expression. (**14**) Intense intracytoplasmic positive immunoreactivity in vascular endothelium (arrows), macrophages, and fibroblasts in the control group. Moderate positive immunoreactivity in the cytoplasm of vascular endothelium, fibroblasts, and a small number of macrophages in the (**15**) PRP and (**16**) PRF groups. (**17-19**) Basic fibroblast growth factor (FGF-β) expression. (**17**) Moderate positive intracytoplasmic immunoreactivity in fibroblasts (arrows) in the control group. Intense positive intracytoplasmic immunoreactivity in fibroblasts and a small number of macrophages in the (**18**) PRP and (**19**) PRF groups. (**20-22**) Inducible nitric oxide synthase (iNOS) expression. (**20**) Intense positive intracytoplasmic immunoreactivity in fibroblasts (arrowhead) and macrophages (arrow) in the control group. Moderate positive intracytoplasmic immunoreactivity in fibroblasts (arrowhead) and a small number of macrophages (arrowhead) in the (**21**) PRP and (**22**) PRF groups. (**23-25**) Nitrotyrosine (NT) expression. (**23**) Intense positive intracytoplasmic immunoreactivity in macrophages (arrow) in the control group. Moderate positive intracytoplasmic immunoreactivity in a small number of macrophages (arrow) in the (**24**) PRP and (**25**) PRF groups. IHC, obj. 40x.

tendon injuries in rabbits (Wong et al. 2020). Additionally, although collagen fibrils exhibited similar density and were irregularly distributed, PRF administration resulted in decreased inflammatory cell infiltration. In a study comparing the efficacy of PRP and PRF in calcaneal tendon healing, it was reported that on the 14th day, the PRP group exhibited comparable cellularity, active granulation tissue, and extensive hemorrhagic areas (Dietrich et al. 2015). In contrast, the PRF group demonstrated increased vascularization, reduced inflammatory cell infiltration, and an absence of granuloma formation (Dietrich et al. 2015). However, a study found no statistically significant difference in healing between the PRP and control groups (Şen et al. 2016). Although previous research has yielded both positive and negative findings regarding the effects of PRP and PRF on tendon healing, and their overall efficacy remains a subject of debate, the findings of the present study suggest that these treatments may provide greater benefits than the Control group.

Furthermore, when PRP and PRF were compared, their effects on growth factors and the inflammatory response appeared similar. Unlike PRF, PRP is typically prepared with the addition of thrombin. PRP is often exogenously activated to produce a rapid release of growth factors, while PRF's natural fibrin matrix is thought to provide a more sustained, slow release. In the present study, the PRP was not activated with exogenous agents like thrombin or calcium chloride before application. Instead, the liquid PRP was injected into the tenotomy site, where it would have been activated *in vivo* by contact with native tissue collagen. This physiological activation process results in a more gradual in situ formation of a fibrin gel and a more sustained release of growth factors, closely mimicking the release profile of PRF, which may explain their comparable effects on growth factors and the inflammatory response.

All growth factors are tightly regulated following tendon injuries and play a crucial role at multiple stages of the healing process (James et al. 2008, Alsousou et al. 2009). Among these, TGF-β is a key molecule that regulates various biological processes, including cell proliferation, migration, differentiation, apoptosis, extracellular matrix deposition, and tendon healing (Hou et al. 2009). However, excessive levels of TGF-β have been reported to contribute to tendon adhesions, which can significantly impair the range of motion (Chan et al. 1997). To counteract these effects, neutralizing TGF-β antibodies to mitigate the influence of TGF-β on tendon healing could result in approximately a twofold improvement in the range of motion in treated animals (Chang et al. 2000). Similarly, researchers demonstrated that PRP administration increased tendon strength and stiffness by approximately 30% within the first week post-injury (Aspenberg & Virchenko 2004). PRP enhanced the activation of circulating cells and stimulated an immune response that promoted collagen production in the early stages of tendon healing (Kajikawa et al. 2008). In the present study, TGF-β levels were lower in the PRP and PRF groups than in the Control group, while collagen levels were increased. This suggests that PRP and PRF applications may contribute to reducing tendon adhesions and promoting more structured tendon healing. However, additional studies are required to determine the optimal TGF-β levels that support the formation of a functionally superior tendon structure while minimizing excessive scar formation, which could negatively impact mechanical strength.

VEGF plays a complex, dual role in tendon repair, and its effects are highly context-dependent. In the early inflammatory phase, VEGF is crucial for initiating angiogenesis, a process essential for supplying oxygen, nutrients, and reparative cells to the injury site. However, the nature of this angiogenic response is critical for the outcome. While optimal VEGF levels promote a healthy, organized vascular network that supports regeneration, excessive or prolonged VEGF expression can be detrimental. Overexpression can lead to the formation of a disorganized, hypervascular scar-like tissue, contributing to fibrosis and ultimately compromising the tendon's mechanical strength (Sahin et al. 2012, Liu et al. 2021). In the context of the present study, findings at day 14 (the proliferative phase), the intense VEGF expression observed in the Control group likely represents a sustained, unregulated angiogenic signal that risks promoting a weaker, fibrotic repair.

In contrast, the moderated VEGF levels in the PRP and PRF groups suggest a beneficial modulation of this process. These treatments do not inhibit the necessary angiogenesis but rather appear to temper the response, guiding it away from a pathological, scar-forming pathway. This controlled regulation is interpreted as a beneficial effect, preventing the hypervascularization associated with tendon fragility (Nakamura et al. 2008) and instead fostering an environment conducive to the formation of more organized, functional tendon tissue. Therefore, the ability of PRP and PRF to optimize the angiogenic response appears to be a key mechanism by which they improve the quality of tendon healing.

FGF-β is another crucial growth factor involved in tendon healing, as it stimulates collagen production, promotes tendon development, enhances tenocyte proliferation, and facilitates tendon tissue differentiation in the early stages of injury. Additionally, it promotes extracellular matrix secretion while inhibiting matrix degradation by increasing the expression of tissue inhibitors of metalloproteinases (Tang et al. 2016) In an *in vivo* study utilizing a calcaneal tendon defect model, FGF-β was shown to enhance tendon regeneration by promoting organized collagen morphology and reducing scar formation, thereby improving the tensile strength of the tendon (Jayasree et al. 2019). While TGF-β plays a significant role in tendinogenesis, it has been shown to impede or slow down this process under certain conditions. Notably, FGF-β may counteract TGF-β's inhibitory effect, thereby facilitating a more effective tendinogenic response (Hyun et al. 2017). In the present study, FGF-β expression was significantly higher in the PRP and PRF groups compared to the Control group. Additionally, the reduction in TGF-β levels may indicate a more pronounced role for FGF-β, which could accelerate the healing process by promoting the differentiation of tendon cells in a more structured and functionally efficient manner.

The role of NO in tendon healing is complex and bimodal, which is essential for interpreting the present study findings in the context of the existing literature. At physiological concentrations, typically produced by constitutive nitric oxide synthase isoforms (eNOS and nNOS), NO is beneficial, promoting collagen synthesis and modulating cellular activity (Bokhari & Murrell 2012). Seminal work by researchers highlighted this pro-regenerative role, demonstrating that providing an exogenous NO source enhances tendon repair, while inhibiting NOS impairs it (Murrell et al. 1997, Murrell 2007). This underscores the necessity of a basal level of NO

for effective healing. However, during a robust inflammatory response, a different isoform, inducible NOS (iNOS), is highly expressed in cells like macrophages, producing large, cytotoxic bursts of NO. This excess NO reacts with superoxide radicals to form peroxynitrite, a potent oxidant that damages tissue by nitrating tyrosine residues in proteins, thereby forming nitrotyrosine. Consequently, nitrotyrosine should not be viewed as a marker of beneficial NO signaling, but rather as a hallmark of pathological nitrosative stress. The intense expression of iNOS and nitrotyrosine in the Control group indicates severe, uncontrolled inflammation and associated nitrosative tissue damage.

In contrast, the moderate levels observed in the PRP and PRF groups do not suggest healing impairment. Instead, they indicate a beneficial modulation of the inflammatory cascade. By reducing excessive inflammation, PRP and PRF likely limit pathological iNOS overexpression, thereby mitigating collateral tissue damage from nitrosative stress while allowing the beneficial effects of physiological NO to proceed. Therefore, the results are consistent with the literature, emphasizing that while physiological NO is beneficial, controlling the excessive, iNOS-driven nitrosative stress during the inflammatory phase is crucial for achieving higher-quality tendon repair.

A significant challenge in the clinical application and research of both PRP and PRF is the variability in their final composition, which stems from differences in preparation protocols, device specifications, and centrifugation forces, ultimately leading to inconsistent efficacy (De Vos et al. 2010, Schepull et al. 2011, Dhurat & Sukesh 2014). Various conventional preparation protocols yield platelet concentration factors ranging from 2.27 to 7.4 times baseline levels. To mitigate this inconsistency and ensure a standardized product for the present study, a commercial kit was used. However, the therapeutic effect is not solely dependent on achieving the highest possible platelet count. The efficacy of these treatments is multifactorial, relying on a synergistic combination of multiple growth factors secreted from platelet granules, as well as the concentration and subtypes of leukocytes, which also play a critical role (Dernek et al. 2017). This may explain why similar clinical results can sometimes be obtained from kits that yield different platelet concentrations. While a standardized approach is a strength, it is important to acknowledge the limitations of the study. A primary limitation is the lack of a quantitative analysis of platelet or leukocyte concentrations in PRP and PRF preparations. Direct measurement would have provided a more definitive confirmation of the product composition. However, the use of a standardized commercial system provides much greater consistency and reproducibility compared to manual or non-standardized protocols. Additionally, the present study focused on early histopathological and immunohistochemical changes at day 14; it did not include long-term follow-up or biomechanical testing to assess the functional quality of the healed tendon. Future studies should incorporate these analyses to evaluate the clinical potential of these treatments fully.

CONCLUSION

Platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) applications significantly enhance the quality of early-phase tendon healing, showing comparable efficacy. Their contribution extends beyond merely modulating inflammation; they were found to orchestrate a pro-regenerative environment through several key mechanisms actively. The sustained release of growth factors, evidenced by increased fibroblast growth factor (FGF-β) expression, directly stimulates tenocyte proliferation and guides more organized extracellular matrix remodeling, leading to structurally superior collagen fiber alignment. Furthermore, PRP and PRF create a more favorable healing environment by moderating the expression of factors linked to fibrosis and disorganized repair, such as transforming growth factor β (TGF-β) and vascular endothelial growth factor (VEGF), while simultaneously mitigating tissue damage from nitrosative stress. PRP and PRF accelerate and improve early tendon repair by promoting crucial cellular and matrix-level processes essential for functional tissue regeneration. Future long-term studies with biomechanical analysis are warranted to confirm that these early histological benefits translate into superior mechanical strength.

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