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Review

Neovascularization in Meniscus and Tendon Pathology as a Potential Mechanism in Regenerative Therapies: Special Reference to Platelet-Rich Plasma Treatment

Dawid Szwedowski [1,*,†], Łukasz Jaworski [2,3,†], Wioleta Szwedowska [4], Przemysław Pękala [5] and Maciej Gagat [6]

1 Orthopedic Arthroscopic Surgery International (O.A.S.I.) Bioresearch Foundation, 20-133 Milan, Italy
2 Private Center of Surgery, 87-100 Torun, Poland; lukaszmjaworski@gmail.com
3 Department of Orthopaedics, Orvit Clinic, Citomed Healthcare Center, 87-100 Torun, Poland
4 Family Medicine Clinic Sadowa, 87-100 Torun, Poland; fiolka_slesinska@o2.pl
5 Faculty of Medicine and Health Sciences, Andrzej Frycz Modrzewski Krakow University, 30-705 Kraków, Poland; pekala.pa@gmail.com
6 Department of Histology and Embryology, Faculty of Medicine, Nicolaus Copernicus University in Torun, Collegium Medicum in Bydgoszcz, 85-067 Bydgoszcz, Poland; mgagat@cm.umk.pl
* Correspondence: dszwedow@yahoo.com
† These authors contribute equally to this work.

Abstract: Neovascularization is a complex, multistep process that includes the activation of endothelial cells, degradation of the basement membrane surrounding the blood vessel, formation of tip cells, the sprouting, migration and proliferation of endothelial cells into the interstitial space, and then the generation of space in the matrix to allow for the formation of a new, proper lumen of a newly formed blood vessel. Abundant neovascularization can be found in tendinous tissue obtained from asymptomatic athletes or the meniscus early after the injury. The concept of neovascularization in musculoskeletal system disorders seems to be mainly associated with pain and poor clinical outcomes. On the one hand, this phenomenon allows for tissue regeneration, but on the other, it is present during the degeneration process in connective tissue. Establishing the current concept on neovascularization is also needed. A narrative review of the current literature was conducted using databases including Embase, PubMed and Cochrane. This review aims to investigate the exact role of the neovascularization process in tendon and meniscus lesions and its role as a potential target in clinics, specifically in platelet-rich plasma (PRP) therapy. The stabilization of the neovessels required to achieve the healed tissue, together with the standardization of the PRP injections, can offer an alternative future therapeutic approach for the treatment of tendinopathy and meniscal injuries.

Keywords: tendon; tendinopathy; meniscal tear; PRP; orthobiology

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1. Introduction

Neovascularization is the natural formation of new blood vessels that serve as collateral circulation in response to poor local perfusion. Abundant neovascularization can be found in tendinous tissue obtained from asymptomatic athletes or the meniscus early after the injury [1]. The neovascularization process is crucial in the connective tissue healing process. During the regeneration, in the formation phase, intensive neovascularization is observed [2]. However, the neovascularization process is also typical for osteoarthritis, retinopathy, inflammation, tumors as well as tendon and meniscus pathology [3,4]. The concept of neovascularization in musculoskeletal system disorders seems to be associated mainly with pain and poor clinical outcomes [5]. On the one hand, this phenomenon allows for tissue regeneration, but on the other, it is present during the degeneration process in connective tissue. Establishing the current concept on neovascularization is also needed.

Hence, this review aims to investigate the exact role of the neovascularization process in musculoskeletal, sport-related pathologies, such as tendinopathies and meniscus lesions. In addition, the role of platelet-rich plasma (PRP) therapy as a potential target in a clinical therapy was analyzed.

2. Neovascularization in Tendon Disorders and Its Therapeutic Potential

Tendons are structures responsible for the distribution of force generated by muscles. They are designed to contribute to human body movements, stabilize joints, and absorb the shocks [6–8]. The special properties of tendinous tissue allow for the high load toleration, which results mainly from the organized structure often described as "synthetic climbing rope" [7]. This unique construction of the tendon allows for the spreading of stress and decreases the risk of rupture [7,9]. Tendinous tissue is classified as dense regular connective tissue formed and supported by specialized fibroblasts called tendon cells (tenocytes). The extracellular matrix (ECM), abundant with densely packed and regularly arranged collagen fibrils, forms a scaffold for tenocytes, capillary vessels, nerve endings, and creates an environment for metabolic reactions [10,11]. Tendons are metabolically active structures, and like other tissues, they require a blood supply. However, its vascular perfusion is relatively weak compared to other types of connective tissue, such as muscles [2,12]. In healthy tendons, vascularization is extremely limited, with a small number of capillaries localized between bundles of collagen. These capillaries arise mainly from the musculotendinous junction, osteotendinous junction, and connective tissue sheath [2].

There is a group of tendons that contain specific hypovascular regions that lead to poor regeneration and predispose the tendons to pathology [4,6,7,13–19]. Moreover, these specific tendons are usually exposed to increased forces with various vectors of action, e.g., the rotator cuff tendons, the long head of the biceps tendon, Achilles tendon, posterior tibialis tendon, patellar tendon, gluteal tendons, and the tibialis anterior tendon.

The excessive load acting on tendinous tissue from these certain regions, in the presence of risk factors, may lead to the development of pathology—tendinopathy, which manifests microscopically as a degenerative process. The etiopathogenesis of tendinopathy indicates hypoxia and an anaerobic environment within degenerated tendinous tissue lesions [20]. These specific conditions activate the metabolic pathways to save tissue from hypoxia, and the abundant expansion of newly formed capillaries followed by the chaotic production of ECM components is observed [21–23] (Figure 1).

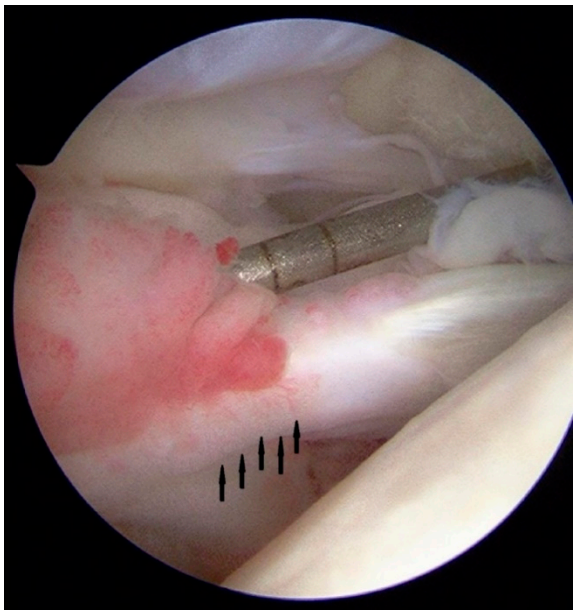

Figure 1. Arthroscopic view of the long head of the biceps brachii muscle tendon. The neovessels in the proximal part of tendon are seen (arrows) in the patient with symptomatic tendinopathy.

In the 1990s, blood flow in symptomatic tendons assessed by ultrasound (US) and power Doppler modality was described by Newman et al. [24]. Hypothetically, the concomitant nerve ending ingrowth that accompanies new vessel formation is thought to be responsible for pain. Neurovascular ingrowth in painful areas of tendons has been described in a few studies [12,25–27]. Moreover, it was supported by the detection of several sensory neurotransmitters within and around the tendons using microdialysis [28]. Additionally, Alfredson and Öhberg presented US-guided techniques to reduce neovascularization by injecting the sclerosants in the most abundant regions of neovascularization [29]. On the other hand, some recent studies revealed that neovascularization in tendon disorders has a mythological status and does not necessarily correspond to the clinical outcome [5,18,20,21,30,31]. Various authors clearly showed that there is no connection between neoangiogenesis and pain [19,30,31]. Neovascularization was also found in Achilles tendons among asymptomatic athletes [1]. Most of the studies which presented the negative impact of neovascularization were related to the Achilles tendon, but more recent research showed that neovessels are detected in 29% of asymptomatic athletes, and in 100% of subjects after strenuous exercise [1,29,32–34].

The question arises as to whether the neovascularization found in these studies reflected a physiological or a pathological response. This is especially interesting considering a surprising phenomenon observed in the tendinous tissue of smokers. It indicates that cigarette smoking inhibits the neovascularization process [21,35]. Although neovascularization in smokers was deeply reduced, it did not correlate with the clinical outcomes. It clearly shows that microscopic evaluation of the new vessel formation may not be fully comparable with clinical parameters of patients. Fearon et al. suggested that the complete lack of vascularity in the obtained pathological tendons, as well as the excessive expansion of new capillaries, should be graded as extreme pathology in the histopathological score—the Bonar scoring system [36].

Tendinous tissue after the injury requires the regeneration process, which consists of three main phases, while the most intensive neoangiogenesis is observed in the formation phase [2]. Tendons in response to hypoxia secrete angiogenic growth factors that induce the growth of neovessels [20,37,38]. However, in tendinopathy, we can observe that this mechanism fails, which results in an impaired delivery of oxygen and nutrients, which are required for tissue regeneration.

The ECM regulates the topology and elongation of vessels, using the proteases to form the area for new capillaries [39]. Interestingly, some authors observed that angiogenesis is significantly reduced in the areas of the tendinous tissue with the increased production and aggregation of non-collagenous ECM (glucosaminoglicans and mucopolisacharides) [21,40]. Koehler et al. using a 3D angiogenesis model showed that glycosaminoglycan accumulation impaired the biological activity of vascular endothelial growth factor (VEGF) [41]. Cheng et al. also revealed that non-collagenous components of the ECM inhibit VEGF receptor signaling [42]. VEGF, the major role of which is related to the stimulation of the angiogenesis process, is elevated after the inflammatory phase, during the formation and remodeling phases [7]. Studies in cancer biology or retinopathy revealed that hypoxia-induced newly formed capillaries are hyperpermeable and characterized by impaired perfusion [20,37]. In turn, in tendinopathy, the immaturity of vessels may be responsible for persisting hypoxia within regions of neovascularity [20,37].

From a clinical research perspective, neovascularization can be defined in different ways. The summarized definitions and clinical implications are presented in Table 1.

Table 1. Different approaches to the neovascularization phenomenon in tendon and meniscus studies.

Author	The Definition of Neovascularization	Clinical Implications
Xu et al. [10]	Tendinopathic tendons often have infiltrations of vascular and small blood vessels.	Authors concluded that pathological alterations changes are consistent with tendon degeneration. It can be recognized as an attempt of tissue regeneration.
Lewis et al. [23]	Neovascularity associated with tendinopathy is characterized by the formation of microvascular networks, in and around tendon tissue. Moreover, it may be associated with neural tissue ingrowth.	Authors concluded that neovascularization may be associated with tendon-related pain. This depiction of increased vascularity ranges from tissue blush to isolated new peritendinous and peribursal vessels.
Newman et al. [24]	Neovascularization was described as an increased number of discrete, visible small vessels to soft-tissue blush.	Authors concluded that these very small vessels (microvascular flow) can be studied ultrasonographically.
Abate et al. [12]	Neovascularization is present in Achilles, patella, elbow, fascia plantaris tendons in the chronic disease. There is a proliferation of new vessels inside the tendon.	Authors recognized the neovascularization process as a pathological phenomenon in the degenerative tissue.
Ohberg and Alfredson et al. [43]	Neovascularization was described in a tendon with advanced, degenerative alterations, and vessels in the Achilles tendons were seen through the entire widened part of the tendon. In the neovascularization described by authors, both arterial and venous blood flows were registered.	Authors stated that the neovascularization found in their investigation might have implications for the pathogenesis of chronic Achilles tendinopathy.
Fenwick et al. [2]	Neovascularization was described as an increased vascularity and present in healing tendon grafts, after acute tendon injury, in chronic tendinopathy.	Authors concluded that neovascularization is essential for the long-term survival of a graft. On the other hand, in cases of tissue regeneration after acute injury, it is usually a haphazard process. Finally, chronic tendinopathy may be associated with pain and the chronicity of tendon lesions.
Zabrzynski et al. [7]	Neovascularization was described as a chaotic expansion of new capillary vessels.	In the ageing of tendons, the neovascularization process is usually absent. Moreover, the neovascularization process is one of the most important components of tendinous tissue regeneration.
Ashraf et al. [44]	Neovascularization was presented as new vessel ingrowth in the synovium and at the osteochondral junction, penetrating into non-calcified cartilage and osteophytes.	The neovascularization process often appears simultaneously with the sensory nerve ingrowth. Moreover, it brings nerve fibers containing substance P and calcitonin gene-related peptide (CGRP), which are implicated in the unmyelinated burning pain described by patients with OA mediating sustained.
Xue et al. [45]	Neovascularization was defined as vessel growth mainly at the adhesion margin for less than one-third of the meniscus body ransverse diameter.	Authors concluded that the revascularization after meniscus transplantation is very important to the healing process. Moreover, they found that no significant vascular distribution was found at the free margin of the meniscus.

The experimental evidence that growth factors in platelets enhance the recruitment, proliferation, and differentiation of cells involved in tissue regeneration allowed for the widespread use of PRP in the therapy of tendinopathy [46]. The potential effect of PRP on neovessels has already been extensively studied in Achilles tendinopathy [5].

Based on these studies, it was suggested that the formation of neovessels is related to the release of VEGF as a potential angiogenetic trigger factor. De Vos et al. assessed the

role of PRP injection on neovascularization and the echogenicity of the Achilles tendon; however, there were no statistically significant differences between the groups [47].

In turn, Maia et al. presented an animal study showing the effect of PRP injections into an injured flexor tendon [47]. In the PRP-treated group, the flexor tendon was more organized with the proper arrangement of the collagen fibers and fibroblasts in the ECM. The numbers of fibroblasts and blood vessels did not differ between the groups. Similarly, Zabrzynski et al. showed that neovascularization was reduced in the areas of the non-collagenous chaotic matrix formation [21,48].

On the contrary, Kesikburun et al. at a 1-year follow-up after a PRP injection found no effect on improving quality of life, pain, disability, and shoulder range of motion compared to patients with a chronic rotator cuff tear who were treated only with an exercise program [49]. On the other hand, Finnoff et al. presented PRP injection as a safe and effective treatment for chronic recalcitrant tendinopathy. Authors found that 84% of subjects had an improvement in echotexture, 64% had a resolution of intratendinous calcifications, and 82% had a decrease in intratendinous neovascularity [50]. Additionally, Balasubramanian et al., in their systematic review about the clinical effects of PRP therapy in tendinopathy, found that PRP was most effective in patellar and lateral epicondylar tendinopathy [51]. Simultaneously, there was a lack of evidence to support the use of PRP in Achilles and rotator cuff tendinopathy. In turn, Zhang et al. revealed in their meta-analysis that PRP injection with eccentric training did not improve VISA-A scores, reduce tendon thickness, or color Doppler activity in patients with chronic Achilles tendinopathy compared with saline injection [52].

There is a huge discrepancy in clinical outcomes and effects after PRP injection treatment, and there is no sufficient evidence to prove the connection of PRP treatment and its effect on neovascularization. One of the main problems with PRP is the absence of standardization [53]. The large number and variability of the commercially available PRP systems lead to a lack of consistency among studies. The final product can differ between PRP systems. In addition, the content of growth factors can vary between the patients, even if the same PRP system is used. In addition, the potential of a placebo effect can explain the discrepancy in clinical outcomes of randomized, controlled trials.

3. Neovascularization in Meniscal Lesions and Its Therapeutic Potential

Menisci are a vital contributor to proper knee joint congruence and kinematics. Thus, it is suggested that the absence of the meniscus inevitably leads to cartilage lesion and the development of osteoarthritis [54]. Restoration of meniscal integrity is thought to be an essential step in joint preservation surgery. The role of menisci in the knee joint is complex. It is responsible for load transmission, shock absorption, proprioception, articular cartilage nutrition, lubrication, and protection [55–58]. Meniscal tissue consists of cells suspended in an ECM composed mainly of collagen (type 1), glycoproteins, proteoglycans, and elastin [44]. The disruption in collagen type 1 architecture with progressive loss of proteoglycans are signs of the meniscal degeneration [59]. There is a strong relationship between meniscus degeneration and articular cartilage damage, which inevitably leads to the development of osteoarthritis (OA) [60].

The meniscectomy in osteoarthritis (OA) can lead to a reduction in pain; however, the exact mechanisms are not yet established [44,61]. Day et al. indicated that the nerve fibers and endings were localized in the menisci with concomitant capillary vessels mainly in the outer third portion of the meniscus [62]. Moreover, some studies clearly showed the variations in vascularization and the innervation of the meniscus; however, it is uncertain what is responsible for this phenomenon [63].

The healing potential of the meniscus depends on the blood supply. Blood vessels mainly origin from the medial and lateral geniculate arteries. However, in the mature skeleton, only the peripheral 10–25% of the meniscus receives blood supply from vessels attached to the synovial membrane [45]. This area is called the red-red zone [56]. The inner 10–25% of the meniscus is called the white zone and is nourished by diffusion from the

synovial fluid. The transient central region of the meniscus is called the red-white region and has features of each zone. Former recommendation advised suturing menisci only in the red-red zone, but Barber-Westin et al. proved that the meniscus also has regenerative potential in the hypovascular zone, with an 86% rate of healed menisci in the red-white zone [64].

Ashraf et al. investigated the prevalence of vascular and neural ingrowth in OA [44]. The authors observed that in knee joints with more severe arthrosis, there was more abundant collagen degeneration in the outer third of the meniscus and these regions were more vascularized. Moreover, the calcitonin gene-related peptide (CGRP)-immunoreactive nerve profiles were identified alongside blood vessels. Again, it was commonly observed in the outer third part of the meniscus [44]. The inner region of the meniscus was mostly aneural [44]. These results suggest that neoangiogenesis and concomitant nerve ingrowth may contribute to pain in knee OA [44,65]. On the other hand, the neovascularization in the meniscus may be a regenerative response similar to the one observed in the tendinous tissue. The revascularization in the meniscus structure after transplantation is commonly observed and crucial to the healing process [45]. In the last decade, there has been a growing interest in using biological agents to enhance the healing of degenerative tissues in the knee joint [66–68]. The efficacy of PRP was examined in meniscal mechanisms under normal and post-traumatic inflammatory conditions in the New Zealand white rabbit model [69]. A reproducible defect on the meniscus was used to implant fibrin glue or PRP. The study showed that PRP treatment increases catabolic molecules, especially those related to inflammation, which may accelerate fibrosis instead of meniscal cartilage regeneration. In human randomized clinical trials, Kamiński et al. showed that PRP augmentation in suturing bucket-handle meniscal tears and trephination for degenerative meniscal tears are more effective than placebo [70,71]. However, Belk et al., in their systematic review, concluded that there is a limited number of high-quality studies comparing outcomes after meniscal repair with or without PRP augmentation [72].

Xue et al. revealed that, after meniscus transplantation, the meniscus body showed new vessel ingrowth mainly at the adhesion margin, while no significant vascular distribution was found at the free margin [45]. Moreover, blood circulation in vessels peaked after 8 weeks in the meniscus, mimicking the VEGF expression, which showed a progressive decrease with time, even though the vascular endothelial cells gradually increased over time. Moreover, there were no statistical differences in the various assessments between the allograft and autograft groups. The authors showed that hypervascular areas are associated with the meniscus attachment and adjoining regions can provide nutritional support for the meniscus body as well as a foundation for the reconstruction of the entire meniscus.

Clinical trials with PRP for tendinopathy and meniscal lesions were summarized in Table 2.

Table 2. Summarization of therapeutic area and clinical effects of PRP therapy.

Author	Year of Publication	Therapeutic Area	Therapeutic Effect	Sample Size	Control Group	Follow Up	Comments on Clinical Outcomes
de Vos et al. [46]	2010	Achilles tendon	NEUTRAL	54	Yes—Saline treated	24 weeks	The mean VISA-A score improved significantly after 24 weeks in the PRP group and in the placebo group. However, it was not significantly different between both groups.
Maia et al. [47]	2009	superficial digital flexor tendon in horses	Positive	6	Yes—Left limb	36 days	Differences ($p < 0.05$) between the groups were only observed in relation to fibroblastic density and tissue organization. The PRP-treated group showed better organization and parallelism of the collagen fibers and fibroblasts. PRP concentration = 407,500 ± 58,800) platelets/mL.
Kesikburun et al. [49]	2013	RCT	Neutral	40	Yes—Saline solution	1 year	There was no significant difference between the groups in Western Ontario Rotator Cuff index (WORC), Predictors of Shoulder Pain and Disability Index (SPADI), and Visual Analog Scale (VAS) scores at 1-year follow-up ($p = 0.174$, $p = 0.314$, and $p = 0.904$, respectively). PRP concentration = 1014.9 ± 3.402 × 10^5/mL.
Finnoff et al. [50]	2011	Various tendon (recalcintrant, advance and chronic tendinopathy)	Positive	51	No	14 months	A total of 4% of subjects had an improvement in echotexture, 64% had a resolution of intratendinous calcifications, and 82% had a decrease in intratendinous neovascularity. None of the variables analyzed in this study demonstrated a significant correlation with pain or functional outcome measures. PRP concentration = 1048.2 (107.0−1993.0).

Table 2. *Cont.*

Author	Year of Publication	Therapeutic Area	Therapeutic Effect	Sample Size	Control Group	Follow Up	Comments on Clinical Outcomes
Boesen et al. [73]	2017	Achilles tendon	Positive	60	Yes—Saline treatment or steroid (Depo Medrol) with saline treatment	24 weeks	Treatment with HVI or PRP in combination with eccentric training in chronic AT seems more effective in reducing pain, improving activity level, and reducing tendon thickness and intratendinous vascularity than eccentric training alone ($p < 0.01$). PRP concentration = 2.5 × approx.
de Jonge et al. [74]	2011	Achilles tendon	Neutral	54	Yes—Saline solution	1 year	This randomized controlled trial showed no clinical and ultrasonographic superiority of platelet-rich plasma injection over a placebo injection in chronic Achilles tendinopathy at 1 year combined with an eccentric training program.
Rha et al. [74]	2013	RCT	Positive	39	Yes—Dry needling	6 months	Statistically significant improvements in PRP vs. dry needling in SPADI. The Shoulder Pain and Disability Index (disability) and ROM at 6 months.
Vetrano et al. [75]	2013	Patellar tendon	Positive	46	Yes—ESWT	12 months	Statistically significant improvement in the PRP group vs. Extracorporeal shock wave therapy (ESWT) in VISA-P + VAS scores at 6 and 12 months, and Blazina scores at 12 months. Patient satisfaction was significantly better at 12 months in the PRP group.
Peerbooms et al. [76]	2010	Lateral Epicondyle tendinopathy	Positive	100	Yes—glucocorticoids (GKS)	1 year	Statistically significant improvements with PRP vs. corticosteroid at 26 and 52 weeks in VAS and The Disabilities of the Arm, Shoulder and Hand Score (DASH) scores: $p < 0.001$ both.

Table 2. *Cont.*

Author	Year of Publication	Therapeutic Area	Therapeutic Effect	Sample Size	Control Group	Follow Up	Comments on Clinical Outcomes
Creaney et al. [77]	2011	Lateral Epicondyle tendinopathy	Neutral	150	Yes—Autologous blood treatment	6 months	At 6 months, the authors observed a 66% success rate in the PRP group versus 72% in the Autologous blood injection group, p = NS. There was a higher rate of conversion to surgery in the ABI group (20%) versus the PRP group (10%). PRP concentration was 652 (581–722) platelets $\times 10^9$/L.
Lee et al. [69]	2016	Meniscus	Neutral/Negative	14	Yes	21 days	Local administration of PRP would lead to side effects for meniscal repair, owing to proteoglycan lysis via the upregulation of catabolic molecules and the increase in type I collagen, resulting in fibrous tissue formation, rather than meniscal cartilage. PLT concentration = 4 $\times 10^6$ platelets/µL.
Kaminski et al. [70]	2019	Meniscus	Positive	72	Yes—Only percutaneous trephination	24 months	The failure rate was significantly higher in the control group than in the PRP-augmented group (70% vs. 48%, p = 0.04). Kaplan–Meier analysis for arthroscopy-free survival showed a significant reduction in the number of performed arthroscopies in the PRP-augmented group. Our trial indicates that percutaneous meniscal trephination augmented with PRP results in a significant improvement in the rate of chronic meniscal tear healing, and this procedure decreases the necessity for arthroscopy in the future (8% vs. 28%, p = 0.032).

Table 2. *Cont.*

Author	Year of Publication	Therapeutic Area	Therapeutic Effect	Sample Size	Control Group	Follow Up	Comments on Clinical Outcomes
Kaminski et al. [71]	2018	Meniscus	Positive	37	Yes—Saline injection	42 months	After 18 weeks, the meniscus healing rate was significantly higher in the PRP-treated group than in the control group (85% vs. 47%, $p = 0.048$). The International Knee Documentation Committee (IKDC) score, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and Knee Injury and Osteoarthritis Outcome Score (KOOS) were significantly better in the PRP-treated group than in the control group. $p = 0.001$, $p = 0.002$ and $p < 0.05$ for all KOOS subgroups respectively.
Everhart et al. [78]	2019	Meniscus	Positive/Neutral	550	Yes	3 years	Among isolated meniscal repairs (20.3% failures at 3 years), PRP was independently associated with a lower risk of failure (aHR, 0.18; 95% CI, 0.03–0.59; $p = 0.002$), with no difference between PRP preparation systems ($p = 0.84$). PRP has a protective effect in terms of the risk of isolated meniscal repair failure over 3 years. In the setting of concomitant anterior cruciate ligament (ACL) reconstruction, PRP does not reduce the risk of meniscal repair failure.
Pujol et al. [79]	2015	Meniscus	Positive	34	Yes	24 months	MRI revealed five cases with the complete disappearance of any hyper-signal within the repaired meniscus in the PRP-treated group ($p < 0.01$). The PRP-treated group showed better outcomes in KOOS subgroups. ($p < 0.05$ for pain and sports parameters.)

4. Conclusions

The rate of tissue turnover is increased in tendinopathic tendons. The persisting hypoxia and anaerobic metabolism lead to the production of poorly organized but highly vascularized tissue. The tissue regeneration requires an abundant supply of oxygen and nutrients. The role of neovascularization in this field should be reconsidered. Detected neovascularization has no additional value for the diagnosis and clinical prognosis. Nevertheless, stabilization of the neovessels is important to achieve the healed tissue. The standardization of PRP systems has not yet been achieved, and clinical outcomes differed between clinical trials. Better knowledge of neovascularization processes is still needed for a future alternative therapeutic approach for the treatment of tendinopathy.

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